ISSN: 2564-6850
e-ISSN: 2564-7032

TÜRK CERRAHİ DERNEĞİ
1929
www.turkcer.org.tr

Turkish Journal of Surgery

VOLUME 40
ISSUE 3
SEPTEMBER 2024

www.turkjsurg.com

Turkish Journal of Surgery
Volume 40 • Issue 3 • September 2024 • Page 183-266

Turkish
Journal of Surgery

VOLUME 40
ISSUE 3
SEPTEMBER 2024

Published by Turkish Surgical Society.

Owner/Editorial Manager
Ahmet Serdar KARACA
(Owner on behalf of the Turkish Surgical Society)

Print ISSN 2564-6850
Elektronic ISSN 2564-7032

Contact
Turkish Journal of Surgery
Address: Koru Mah. Koru Sitesi, Ihlamur Cad. No: 26
06810 Çayyolu-Çankaya, Ankara, Türkiye
Phone: +90 (312) 241 99 90 **Fax:** +90 (312) 241 99 91
E-mail: editor@turkjsurg.com

Publishing House

bilimsel tıp yayınevi
www.bilimseltipyayinevi.com

Publishers
Osman ÇEVİK
General Coordinator
Ecz. İbrahim ÇEVİK
Assistant General Coordinator
Özlem ÖZTÜRK
Publication Coordinator
Elif GÜRPINAR
Redaction
Semanur PALA
Muhammed PEHLİVAN
Graphic Design
Mehmet DÜZENOĞLU

Contact
Bilimsel Tıp Yayınevi
Address : Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Türkiye
Phone : +90 (312) 426 47 47 • +90 (312) 466 23 11
Fax : +90 (312) 426 93 93
E-mail : bilimsel@bilimseltipyayinevi.com
Web : www.bilimseltipyayinevi.com

Publication Type: Periodical
Place of Printing: Step Dijital
İvedik Organize San. 1420. Cadde No: 58/1-2-3-4-5
Ostim-Yenimahalle/ANKARA
Phone: 0 (312) 395 85 71-72
Printing Date: 30 September 2024

Turkish
Journal of Surgery

EDITORIAL BOARD

AIMS AND SCOPE

Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of the Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication, and various manuscripts on medicine and surgery history and ethics, surgical education and the field of forensic medicine are included in the journal.

As a surgical journal, the Turkish Journal of Surgery covers all specialties, and its target audience includes scholars, practitioners, specialists and students from all specialties of surgery.

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

The Turkish Journal of Surgery is currently abstracted/indexed by PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Scopus and EBSCO.

Processing and publication are free of charge. No fees are requested from the authors at any point throughout the evaluation and publication process. All expenses of the journal are covered by the Turkish Surgical Society.

Manuscripts must be submitted via the online submission system, which is available at www.turkjsurg.com. Journal guidelines, technical information, and the required forms are available on the journal's web page.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Surgical Society, editors, editorial board, and/or publisher; thus, the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.turkjsurg.com.

The journal is printed on an acid-free paper.

Turkish Journal of Surgery
Address: Koru Mah. Koru Sitesi, Ihlamur Cad. No: 26
06810 Çayyolu, Ankara, Türkiye
Phone: +90 (312) 241 99 90
Fax: +90 (312) 241 99 91
E-mail: editor@turkjsurg.com

Publisher: Bilimsel Tıp Yayınevi
Address: Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Türkiye
Phone: +90 (312) 426 47 47 • +90 (312) 466 23 11
Fax: +90 (312) 426 93 93
E-mail: bilimsel@bilimseltipyayinevi.com
Web: www.bilimseltipyayinevi.com

Turkish
Journal of Surgery

INSTRUCTIONS TO AUTHORS

Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of the Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication, and various manuscripts on medicine and surgery history and ethics, surgical education and the field of forensic medicine are included in the journal.

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

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts submitted to another journal for evaluation but rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to the Turkish Journal of Surgery will go through a doubleblind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of the manuscripts submitted by the editors or the editorial board members of the journal. The Editor-in-Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement verifying that written informed consent of the patients and volunteers was obtained following a detailed explanation of the procedures should be included. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, name of the ethics committee, and the ethics committee approval number should also be stated in the Material and Methods section of the manuscript. It is the authors' responsibility to carefully protect patients' anonymity. For photographs that may reveal the identity of the patient, releases signed by the patient or his/herlegal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

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

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;
2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for other specific parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

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

Turkish Journal of Surgery requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.turkjsurg.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all responsibility for authorship during the submission and review stages of the manuscript.

The Turkish Journal of Surgery requires and encourages the authors and the individuals involved in the evaluation process of the submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to cases that cannot be resolved internally. The Editor-in-Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to the Turkish Journal of Surgery, authors accept to assign the copyright of their manuscript to the Turkish Surgical Society. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. Turkish Journal of Surgery requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.turkjsurg.com). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in the Turkish Journal of Surgery reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; thus, the editors, the editorial board, and the Publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

Manuscripts should be prepared in accordance with ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2017 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkjsurg.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process by the editorial office staff to ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

INSTRUCTIONS TO AUTHORS

during the initial submission. These forms are available for download at www.turkjsurg.com.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, which should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983; 7: 1489-93). Information on statistical analyses should be provided with a separate subheading under the Material and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Expert Opinions: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, Tables, Figures, Images, and other media are not included.

Review Articles: Reviews with high citation potential prepared by authors with extensive knowledge on a particular field and whose scientific background has already been proven by a high number of publications in the related field are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal, and reports on rare cases or conditions constituting challenges in diagnosis and treatment, those offering new therapies or revealing insight not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Video Articles: We do encourage the submission of the video articles which report interesting cases and technical methods.

The details of the review process are below.

- All videos will be peer reviewed.
- All videos will be published on the journals official Web site.
- Article length: It should not exceed 500 words.
- Reference Number: Not to exceed 5 references

Diagnosis, surgical technique and outcome should be summarized. All important steps and aspects of the surgery should be mentioned in the video. If it is a new surgical technique, appropriately labeled and cited video materials may be used. Authors can use a rare case they have encountered, a surgical technique, or videos using modern technological devices.

The following items must be provided:

- The file of the video written in Word format.
- A completed copy of the online broadcast consent form (form will be prepared and linked), together with completed copies of patient consent forms, if appropriate.
- All videos must contain an English narration.
- All videos should also be in the highest resolution possible, more details on accepted file types and resolution are available at this link (authors' video article submission guidelines; https://turkjsurg.com/video-article-guidelines).
- The duration of the videos should not exceed five minutes and the maximum file size should be 300Mb.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The article being commented on must be properly cited within this manuscript.

Human Subjects Research

All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s) and must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should be able to submit, upon request, a statement from the IRB or ethics committee indicating approval of the research. The Journal reserves the right to reject work believed to have not been conducted in a high ethical standard, even when formal approval has been obtained.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

INSTRUCTIONS TO AUTHORS

Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

Animal Research

All animal research must have approval from the authors' Institutional Animal Care and Use Committee (IACUC) or equivalent ethics committee(s), and the research must have been conducted according to applicable national and international guidelines. Approval must be received prior to beginning the research.

Manuscripts reporting animal research must state in the Methods section: The full name of the relevant ethics committee that approved the work, and the associated permit number(s). Where ethical approval is not required, the manuscript should include a clear statement of this and the reason why. The author should provide any relevant regulations under which the study is exempt from the requirement of approval.

Tables

Tables should be included in the main document, presented after the reference list, and numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in the USA) should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text and numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Only references cited in the text should be included in the reference list. The reference list must be numbered according to the order of mention of the references in the text. In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget - Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004. pp. 2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp. 1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Turkish Journal of Surgery

Address: Koru Mah. Koru Sitesi, Ihlamur Cad. No: 26
06810 Çayyolu, Ankara, Türkiye

Phone: +90 (312) 241 99 90

Fax: +90 (312) 241 99 91

E-mail: editor@turkjsurg.com

Publisher: Bilimsel Tıp Yayınevi

Address: Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Türkiye

Phone: +90 (312) 426 47 47 • +90 (312) 466 23 11

Fax: +90 (312) 426 93 93

E-mail: bilimsel@bilimseltipyayinevi.com

Web: www.bilimseltipyayinevi.com

Turkish
Journal of Surgery

CONTENTS

ORIGINAL ARTICLES

CASE SERIES

CASE REPORTS

Turkish
Journal of Surgery

FROM THE EDITOR'S DESK
Turk J Surg 2024; 40 (3): VIII
10.47717/turkjsurg.2024.20240301

Surgical education: Ensuring knowledge transfer to future generations

In the field of surgery, the transmission of knowledge and skills from one generation to the next is of paramount importance. Surgical education not only ensures the continuity of expertise but also facilitates the innovation and development of new techniques and procedures. However, in recent years, numerous challenges have emerged that threaten the effectiveness of surgical education.

Challenges in the current era: Pandemic and financial constraints

The recent global pandemic has undoubtedly disrupted all facets of healthcare, and surgical education has been no exception. While technology has offered some solutions, such as virtual surgical simulations, these tools cannot fully replicate the hands-on experience of real-time surgeries. For instance, a study by Ellison et al. emphasizes the severe reduction in clinical case volumes for residents during the pandemic, which has had a profound impact on their learning experiences (1).

Additionally, global financial issues within healthcare systems have further strained resources. Hospitals and educational institutions are facing budget cuts, leaving less funding available for training programs, research opportunities, and infrastructure development.

The role of scientific publishing in surgical education

Scientific publishing plays a critical role in the dissemination of new knowledge, advancements in surgical techniques, and outcomes of clinical trials. However, the current landscape of academic publishing is not without its problems. The rise of predatory publishing, where journals prioritize profit over quality, has become a serious concern. These journals often lack rigorous peer review processes, leading to the dissemination of unreliable or low-quality research.

At the same time, the criteria for academic advancement are constantly evolving, with an increasing emphasis on the quantity of publications rather than their quality (2). This places additional pressure on surgeons and researchers, who must navigate a publishing environment where the opportunities to conduct and disseminate meaningful research are dwindling. Limited time, funding, and access to reputable platforms all contribute to this growing challenge.

Looking forward: Addressing the gaps in surgical education

To address these issues, there is a need for systemic change. Healthcare institutions must prioritize investment in surgical education, ensuring that future generations of surgeons receive the training they need to succeed. Moreover, scientific publishing needs to uphold its integrity by fostering high-quality peer-reviewed work, while simultaneously providing equitable access to publishing opportunities for all researchers, regardless of financial constraints.

In conclusion, surgical education is at a critical moment. While the challenges are significant, so too are the opportunities for innovation and improvement. By addressing the systemic issues in education and publishing, we can ensure that the next generation of surgeons is equipped with the skills, knowledge, and integrity to advance the field of surgery.

Sincerely,

Kaya SARIBEYOĞLU

Editor-in-Chief
Turkish Journal of Surgery

REFERENCES

1. *Ellison EC, Spanknebel K, Stain SC, Shabahang MM, Matthews JB, Debas HT, et al. Impact of the COVID-19 pandemic on surgical training and learner well-being: Report of a survey of general surgery and other surgical specialty educators. J Am Coll Surg 2020; 231: 613-26. https://doi.org/10.1016/j.jamcollsurg.2020.08.766*
2. *Ioannidis JPA. Evidence-based medicine has been hijacked: A report to David Sackett. J Clin Epidemiol 2016; 73: 82-6. https://doi.org/10.1016/j.jclinepi.2016.02.012*

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 183-189

Ocular and the whole body radiation exposure during endoscopic retrograde cholangiopancreatography

Bahtiyar Muhammedoğlu[1], Mehmet Yasir Pektezel[2], Murat Ulaş[3], Sezgin Topuz[4], Emil Hüseyinoğlu[5]

[1] Department of Gastroenterological Surgery, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, Türkiye
[2] Clinic of Intensive Care Unit, Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Türkiye
[3] Department of Gastroenterological Surgery, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[4] Department of General Surgery, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, Türkiye
[5] Clinic of General Surgery, Bursa City Hospital, Bursa, Türkiye

ABSTRACT

Objective: This study aimed to analyze the average whole body radiation exposure, which changes significantly according to during endoscopic retrograde cholangiopancreatography (ERCP) difficulty and to determine whether an ocular protection device must be used by analyzing applied ocular radiation.

Material and Methods: Patients >18 years of age in whom an ERCP had been indicated were prospectively included in the study.

Results: A total of 1173 patients were included. Increased applied radiation dose significantly correlated with increased shot rate (Rho= 0.789, p< 0.001), ERCP duration (Rho= 0.487, p< 0.001), cost (Rho= 0.129, p< 0.001), and LOS (Rho= 0.109, p< 0.001). The whole body, skin, and eye radiation exposure doses were found to be lower than the recommended limit per year (20 mSv/year).

Conclusion: Limit of ocular radiation exposure during ERCP did not exceed the recommended annual limit (20 mSv/year), and it was also detected to be much lower than that. Therefore, the use of ocular visors is not recommended.

Keywords: Endoscopic retrograde cholangiopancreatography, radiation exposure, fluoroscopy duration

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a crucial diagnostic and treatment tool for hepatobiliary system disorders. However, a reliable procedure could not be achieved without using fluoroscopy. The radiation dose applied to the patients depends on many factors. The experience of the operator and technician, the features of the patient and fluoroscopy device, and the protective devices used are stated with regard to these factors. In some studies, the amount of radiation exposure has been found to be correlated with procedure type and fluoroscopy duration. Nevertheless, some factors related to long-term fluoroscopy have recently been described, but they cannot yet be confirmed (1). It was found that other staff were exposed to a lesser degree of radiation when compared to the operator with respect to radiation distance (2). However, the operator's exposure to radiation can still be considerably limited by using protective devices (2). Our aim was to analyze the average whole body radiation exposure, which changes significantly according to the ERCP difficulty, and to determine whether an ocular protection device must be used by analyzing applied ocular radiation.

MATERIAL and METHODS

Patients

Patients >18 years of age in whom an ERCP is indicated were prospectively included in the study between November 2019 and November 2022. Sedation was applied by an anesthesiologist via continuous monitoring. Demographics, additional diseases, and adverse events that occurred during the ERCP procedure were electronically recorded. A complete blood count (CBC) and comprehensive biochemistry tests were obtained both prior to and after the ERCP procedure. A

Cite this article as: Muhammedoğlu B, Pektezel MY, Ulaş M, Topuz S, Hüseyinoğlu E. Ocular and the whole body radiation exposure during endoscopic retrograde cholangiopancreatography. Turk J Surg 2024; 40 (3): 183-189.

Corresponding Author
Bahtiyar Muhammedoğlu
E-mail: baha197647@gmail.com

Received: 30.05.2024
Accepted: 22.08.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6461

pancreatitis prophylaxis was administered for all patients via intravenous Ringer lactate infusion and intramuscular non-steroid anti-inflammatory drug. Informed consent was obtained from all patients, and the whole data gathered were anonymized.

Procedure and Radiation Measurement

All procedures were performed by the same operator in the gastroenterological ERCP unit of the hospital. A lateral decubitus position was used. Advanced protective devices were used against radiation, including lead visors around the patient's table and upper to the C-arm and between the patient and the operator, other than routine lead aprons and thyroid shields.

Data regarding patients with respect to ampulla position, cannulation time, total procedure duration, procedure difficulty (easy-moderate-hard), type of periampullary diverticula, total number of fluoroscopic shots, total radiation dose, and adverse events were prospectively recorded. Dosimeters, including the whole body and ocular devices used by both the operator and two other staff, were periodically evaluated by a special organization (Radat Laboratory Services). A video-recorded C-arm fluoroscopy system producing 12.5 Hz pulses (BV Pulsera, Philips, Amsterdam, the Netherlands) was used in the study. Voltage and flow duration were automatically determined. An experienced technician applied the fluoroscopic shots according to the operator's requests. Cumulative radiation exposure was calculated and presented as mSv per hour. Our study was approved by the ethics board .

Statistical Analysis

All values are represented as mean ± standard deviation (SD), 95% confidence intervals (95% CI), percentages, medians with interquartile ranges (IQR) as appropriate. Distribution normality was analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests properly. Differences respecting ERCP difficulty were tested with one-way ANOVA or Kruskal-Wallis test appropriately. A p value of <0.05 was accepted as significant. All analyzes were calculated with Jamovi® (2.3.26), an open and free statistics program, provided for free.

RESULTS

A total of 1173 patients were included into the study. Mean age was 54 ± 18, 61 ± 19, and 65 ± 17 years in the easy, moderate, and hard ERCP groups, respectively (p= 0.023). Female rates were detected to be 23%, 34%, and 43% in separate three groups (p≤ 0.001). No clinically meaningful, albeit statistically significant, differences were found between groups (Table 1).

Table 1. Group features according to the difficulty in achieving ERCP

	Easy (n= 305)	Moderate (n= 418)	Hard (n= 450)	p	$P_{easy\text{-}moderate}$	$P_{easy\text{-}hard}$	$P_{moderate\text{-}hard}$
Sex (F), n (%)	110 (23)	166 (34)	206 (43)	**0.023**	0.579	**0.022**	0.169
Age* (year)	54 ± 18	61 ± 19	65 ± 17	**<0.001**	**<0.001**	**<0.001**	**<0.001**
CC, n (%)	2 (1)	10 (2)	31 (7)	**<0.001**	0.168	**<0.001**	**0.005**
Leakage, n (%)	4 (1)	6 (1)	10 (2)	0.554	0.989	0.635	0.665
Row ERCP, n (%)	1 (0.5)	12 (3)	71 (16)	**<0.001**	**0.030**	**<0.001**	**<0.001**
Diverticulum, n (%)	30 (10)	49 (12)	75 (17)	**0.014**	0.702	**0.021**	0.094
Stent impl., n (%)	34 (15)	74 (37)	77 (43)	**<0.001**	**<0.001**	**<0.001**	0.509
Sphincterotomy, n (%)	238 (78)	348 (83)	340 (76)	**0.019**	0.181	0.711	**0.014**
Sclerotherapy, n (%)	10 (3)	51 (12)	61 (14)	**<0.001**	**<0.001**	**<0.001**	0.823
WBC* (x10^3/cc)	6.2 ± 2.0	6.4 ± 2.1	6.8 ± 3.1	**0.020**	0.713	**0.017**	0.077
GGT* (U/L)	188 ± 175	220 ± 203	197 ± 212	0.062	0.059	0.809	0.222
Bil* (mg/dL)	0.67 ± 0.86	0.80 ± 1.1	1.1 ± 2.0	**<0.001**	0.318	**<0.001**	**0.021**
ALP* (U/L)	218 ± 163	262 ± 194	259 ± 205	**0.022**	**0.036**	0.058	0.980
ALT* (U/L)	88 ± 105	77 ± 78	54 ± 68	**<0.001**	0.325	**<0.001**	**<0.001**
AST* (U/L)	55 ± 72	49 ± 63	40 ± 42	**<0.001**	0.529	**0.003**	**0.026**
Amylase* (U/L)	68 ± 74	94 ± 201	70 ± 123	**0.049**	**0.039**	0.946	0.090
LOS* (day)	3 [2-5]	4 [2-6]	6 [3-9]	**<0.001**	**0.011**	**<0.001**	**<0.001**
Pre-cat, n (%)	4 (1)	20 (5)	102 (23)	**<0.001**	**0.027**	**<0.001**	**<0.001**
Duration* (min)	17 ± 5	25 ± 7	35 ± 13	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Shot*	15 [9-21]	22 [14-34]	29 [12-57]	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Radiation dose*	6.8 ± 5.7	11.2 ± 10.1	16.3 ± 17.8	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Cost* (₺)	2473 ± 1837	3657 ± 3598	6605 ± 12657	**<0.001**	**<0.001**	**<0.001**	**<0.001**

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Bil: Bilirubin, CC: Cholangiocarcinoma, F: Female, GGT: Gamma-glutamyl transferase, Impl: Implantation, LOS: Length of stay, Pre-cat: Pre-catheterisation, ₺: Turkish lira, WBC: White blood count.
*mean ± SD, ** median [IQR]. Bolds indicates statistical significance.

Table 2. Correlation matrix

		Radiation dose	Shot	Duration	LOS	Cost	Age
Radiation dose	**Rho**	-					
	p	-					
Shot	**Rho**	0.789*	-				
	p	**<0.001**	-				
Duration	**Rho**	0.487*	0.506*	-			
	p	**<0.001**	**<0.001**	-			
LOS	**Rho**	0.109*	0.094*	0.215*	-		
	p	**<0.001**	**0.002**	**<0.001**	-		
Cost	**Rho**	0.129*	0.073*	0.180*	0.693*	-	
	p	**<0.001**	**0.013**	**<0.001**	**<0.001**	-	
Age	**Rho**	0.056	0.132*	0.198*	0.108*	0.092*	-
	p	0.058	**<0.001**	**<0.001**	**<0.001**	**0.002**	-

LOS: Length of stay.
* Sign and bold indicates statistical significance.

According to results, it seemed that harder ERCP did not only mean the more accompanying cholangiocarcinoma, leakage, row ERCP, diverticulum, stent implantation rate, sphincterotomy, sclerotherapy but also increased LOS, pre-cat rate, ERCP duration, shot rate, total radiation dose, and the cost (Table 1). According to correlation analysis, increased applied radiation dose was significantly correlated with increased shot rate (Rho= 0.789, p< 0.001), ERCP duration (Rho= 0.487, p< 0.001), cost (Rho= 0.129, p< 0.001), and LOS (Rho= 0.109, p< 0.001) (Table 2, Figure 1). The whole body, skin, and eye radiation exposure doses were found to be lower than the recommended limit per year (20 mSv/year) (Figures 2, 3).

DISCUSSION

ERCP is a technical issue and depends on the operator's experience. Applied radiation during ERCP is multifactorial, and features of the operator and the patient, the type of the procedure, and other equipment may not be controlled. It is recommended that fluoroscopy duration be the shortest that could be achieved (1).

ERCP has also been performed recently via computed tomography (CT) technology. Although an ERCP via CT can facilitate the procedure in patients with hard ductal anatomy, it may elongate not only the duration of the procedure and the radiation but also require a contrast injection. A lower degree of radiation exposure has been detected in patients who have undergone a conventional ERCP procedure while compared to patients having an ERCP procedure via CT (2).

The eyes are a highly sensitive part of the human body, and radiation exposure may cause cataract formation (3). The minimum long-term exposure to trigger cataract formation is 2500 mSv (3). International guidelines recommend against exceeding a limit of 20 mSv/year for ocular radiation exposure (4). The radiation exposure of the operators working in high-volume centers (>200 procedures per year) and performing hard and complicated ERCP procedures must be cautiously assessed. Limitation by using lead-supported glasses might be logical in these circumstances (5).

Recent studies show the importance of radiation assessment. Although standard protection systems are routinely used for the skin, thyroid, and whole body against radiation exposure, knowledge about using ocular protection against radiation exposure is vague (6). Recently, it was shown that ocular cataractogenesis may be triggered by a lower radiation dose than previously considered (6). Radiation spread through fluoroscopy may cause cytotoxic cell damage in various tissues (7). Early reactions can occur in tissues with high metabolic demand, while late reactions take place in resistant tissues such as vessels and bones (8). On the other hand, immune system damage almost always occurs (8).

ERCP may be performed both in the supine and left lateral de cubitus (LDD) positions. It has been shown that ERCP performed in the LDD position is as safe as in the supine one (9). Ocular radiation exposure of the ERCP staff was found to be lower in the ERCP procedure performed in supine position while compared to in LDD position. The body thickness differences between two positions are accused of causing this phenomenon (7). Another study with patients who underwent an ERCP performed in the LDD position reported harder technical issues for operators who got used to performing ERCP in supine positions and more cardio-respiratory adverse events (3). Still, we consider the difficulty of the procedure to be more important than the body's thickness.

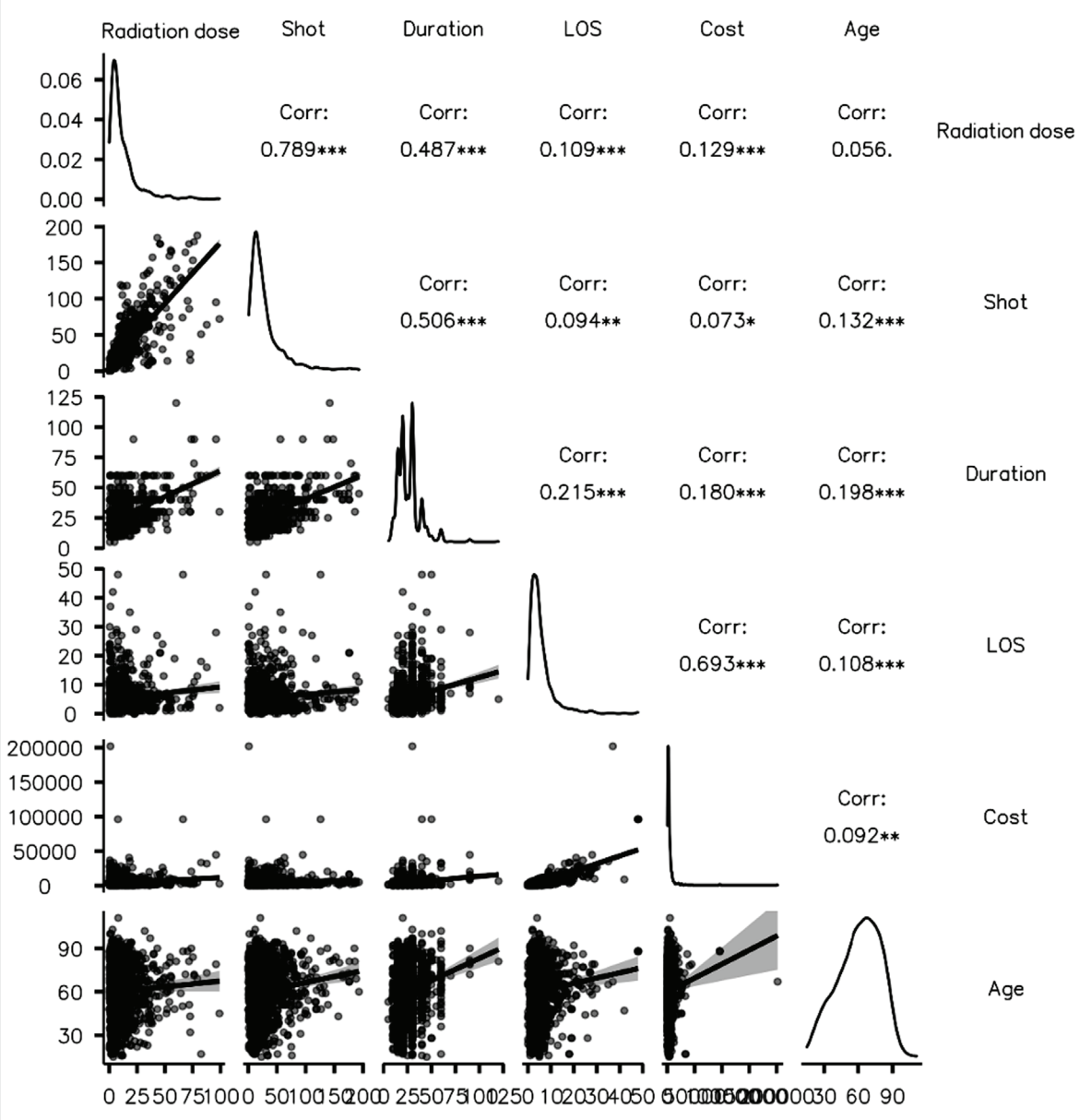

Figure 1. Correlation matrix depicting association among age, shot, duration, cost, and length of stay (LOS).

*p< 0.05, **p< 0.01, ***p< 0.001.

In the ERCP procedure, lead visors are mandatory for the operators; however, the use of the ocular protection devices is optional. In some studies, the duration of fluoroscopy (hour) to extend a recommended limit of ocular radiation exposure (10 mSv) was stated as 59.41 hours for operators and 88.17 hours for other staff (10). Then ocular protection devices have to be used by the operators in line with these results. However, according to our study, even the operators did not get close to the recommended level of the ocular radiation dose. Furthermore, it has been calculated that 100 times more ERCP procedures are needed to reach that limit.

Radiation dose exposure during ERCP is closely associated with fluoroscopy duration, and it may become longer in difficult cases (11). Another important factor is the experience of the operator and the technician (11). It is known that fluoroscopy's duration is shorter in the hands of experienced operators (11). Understanding the basics of radiation and using protective devices can help reduce stress on the team (12). Moreover, novel technologies provide features that might reduce radiation exposure. Still, the main factor preventing radiation exposure is a standard exposure time for ERCP (13).

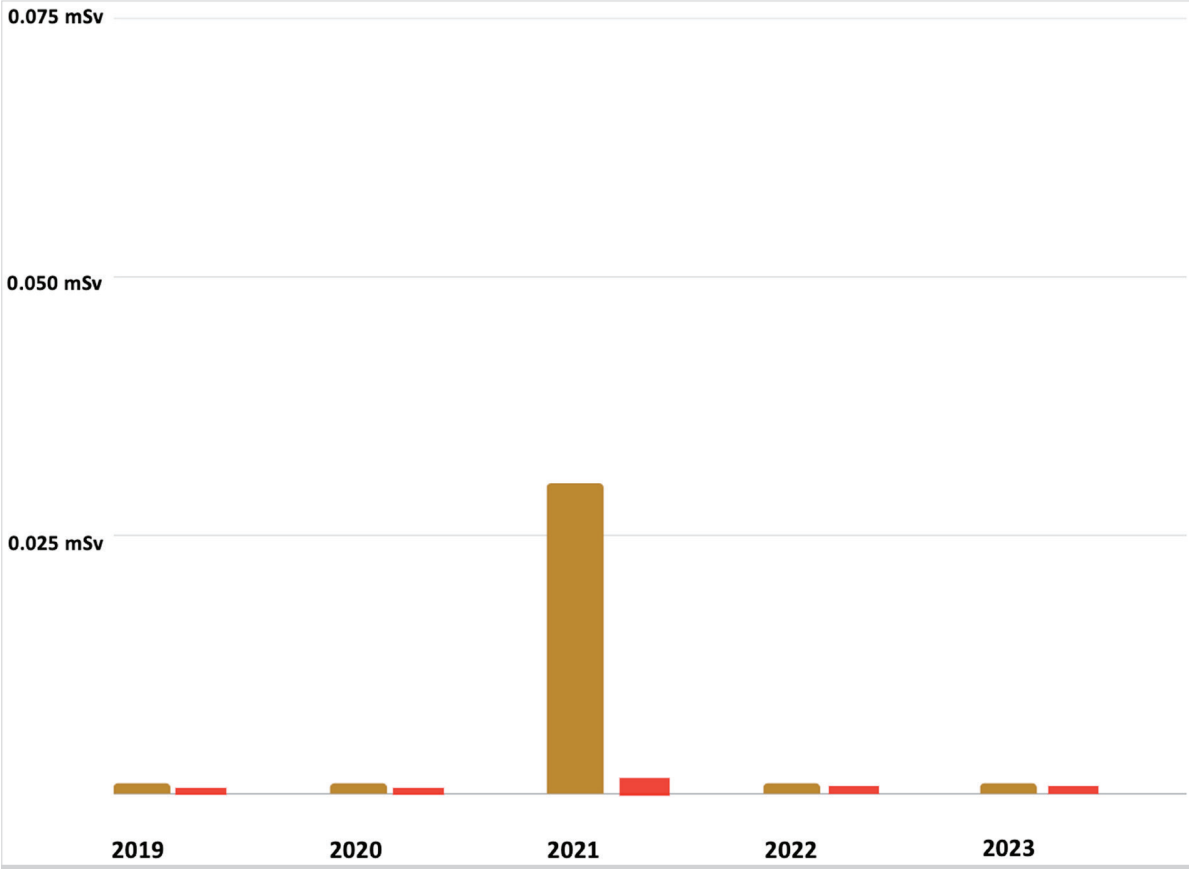

Figure 2. Eye radiation exposure through the years gone by for the operator (brown) and accompanying two nurses (red-mean value).
*A maximum of 20 mSv per year is the determined limit value according to provision of laws.

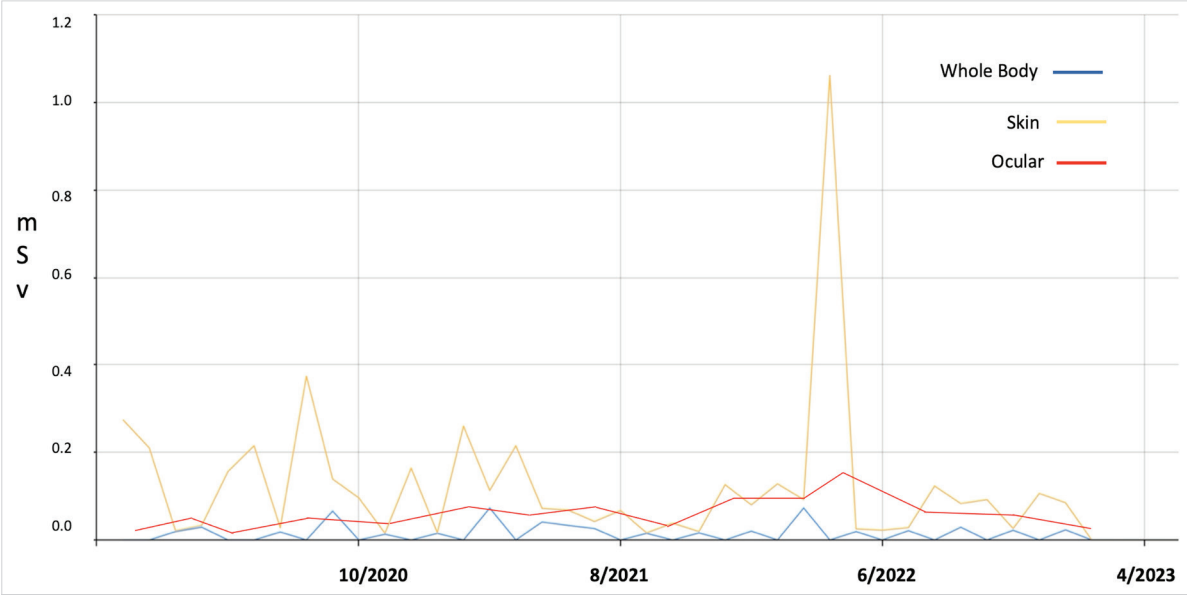

Figure 3. The whole body and skin radiation exposure through the years gone by for the operator (number before forward slash sign means the month of the year). Red line delineates the mean radiation exposure of two accompanying nurses (avarage of the whole body and skin radiation).
*A maximum of 20 mSv per year is the determined limit value according to provision of laws.

The radiation exposure of the staff working in an ERCP unit must be within acceptable limits. Unfortunately, some research has shown that staff might have be exposed to a higher level of radiation than that reported in the literature (14). Thus, the ERCP procedure's radiation doses and protective precautions are still a matter of debate. On the other hand, the radiation dose of patients for a diagnostic ERCP procedure is a mean of 14-26 Gy.cm^2, while it may increase to 67-89 Gy.cm^2 for a therapeutic procedure (15).

Indeed, there are also some studies investigating the radiation exposure of anesthesiologists. In a great number of studies, it has been shown that anesthesiologists, who were at least 1.5 meters away from the C-arm, did not expose themselves to radiation, or at least exposed themselves to only a minimal level of radiation (16). However, it has to be kept in mind that 1.5 meters of distance is the sensitivity limit of dosimeters. Understanding the basics of radiation and using protective devices can help reduce the possible harm to which the team might be exposed (16,17). In our hospital, working schedules are arranged in a shift formation that we consider another protective factor for the staff against radiation.

Although total body and thyroid lead visors are mandatory, the use of ocular protection devices is still a matter of debate. In fact, our prospective study highlights two important points. Does a standard body radiation dosimetry device provide reliable information regarding ocular radiation exposure, and what is the limit of fluoroscopy duration that makes it necessary to use an ocular protective device? According to our study, body radiation dosimetry results are in line with those of ocular devices, and almost 100 times more ERCP procedures than the current ERCP unit's work are needed to make an ocular protection device mandatory (Figures 2,3). This result also suggests a reevaluation to the recent guidelines.

The current study also has some limitations. To begin with, having only one center's experience makes our results not generalizable. However, considerable data, including more than a thousand patients, makes us believe it is clinically meaningful. Another point is that the only LDD position used in our study makes it impossible to compare our results with a supine position. Furthermore, the procedures were performed by a single experienced operator, hence results may vary according to the operators with different experiences. Lastly, we have analyzed only an 18-month duration, which limits our ability to comment on the chronic adverse events of the radiation exposure. It seems more advanced, structured prospective studies are needed.

CONCLUSION

Radiation exposure during ERCP is associated with fluoroscopy duration and the difficulty of the procedure. The exposure of radiation to the operators may be reduced significantly by using protective devices. In the current study, the ocular radiation limit did not only did exceed the recommended annual limit (20 mSv/year) but it was also detected to be much lower than that. Therefore, the use of ocular visors is not recommended.

Ethics Committee Approval: This study was obtained from Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 01, Date: 23.03.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - All of authors ; Design - All of authors; Supervision - All of authors; Data Collection and/or Processing - All of authors; Analysis and/or Interpretation - All of authors; Literature Search - All of authors; Writing Manuscript - All of authors; Critical Reviews - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Chen MY, Van Swearingen FL, Mitchell R, Ott DJ. Radiation exposure during ERCP: Effect of a protective shield. Gastrointest Endosc 1996; 43(1): 1-5. https://doi.org/10.1016/S0016-5107(96)70250-X*
2. *Taylor ER, Kramer B, Frye TP, Wang S, Schwartz BF, Kohler TS. Ocular radiation exposure in modern urological practice. J Urol 2013; 190(1): 139-43. https://doi.org/10.1016/j.juro.2013.01.081*
3. *Garg MS, Patel P, Blackwood M, Munigala S, Thakkar P, Field J, et al. Ocular radiation threshold projection based off of fluoroscopy time during ERCP. Am J Gastroenterol 2017; 112(5): 716-21. https://doi.org/10.1038/ajg.2016.540*
4. *Bhattacharjee A, Das PJ, Adhikari P, Marbaniang D, Pal P, Ray S, et al. Novel drug delivery systems for ocular therapy: With special reference to liposomal ocular delivery. Eur J Ophthalmol 2019; 29(1): 113-26. https://doi.org/10.1177/1120672118769776*
5. *Mekaroonkamol P, Keilin S. Editorial: ERCP-related radiation cataractogenesis: Is it time to be concerned? Am J Gastroenterol 2017; 112(5): 722-4. https://doi.org/10.1038/ajg.2017.100*
6. *Angsuwatcharakon P, Janjeurmat W, Krisanachinda A, Ridtitid W, Kongkam P, Rerknimitr R. The difference in ocular lens equivalent dose to ERCP personnel between prone and left lateral decubitus positions: a prospective randomized study. Endosc Int Open 2018; 6(8): E969-E74. https://doi.org/10.1055/a-0599-5917*
7. *Dorr W. Radiobiology of tissue reactions. Ann ICRP 2015; 44(1 Suppl): 58-68. https://doi.org/10.1177/0146645314560686*
8. *Park TY, Choi SH, Yang YJ, Shin SP, Bang CS, Suk KT, et al. The efficacy and safety of the left lateral position for endoscopic retrograde cholangiopancreatography. Saudi J Gastroenterol 2017; 23(5): 296-302. https://doi.org/10.4103/sjg.SJG_121_17*
9. *Terruzzi V, Radaelli F, Meucci G, Minoli G. Is the supine position as safe and effective as the prone position for endoscopic retrograde cholangiopancreatography? A prospective randomized study. Endoscopy 2005; 37(12): 1211-4. https://doi.org/10.1055/s-2005-870511*
10. *Sethi S, Barakat MT, Friedland S, Banerjee S. Radiation training, radiation protection, and fluoroscopy utilization practices among us therapeutic endoscopists. Dig Dis Sci 2019; 64(9): 2455-66. https://doi.org/10.1007/s10620-019-05564-z*

11. *Meisinger QC, Stahl CM, Andre MP, Kinney TB, Newton IG. Radiation protection for the fluoroscopy operator and staff. AJR Am J Roentgenol 2016; 207(4): 745-54. https://doi.org/10.2214/AJR.16.16556*
12. *Sun JG, Faulx AL. ERCP and fluoroscopy use: Is experience the difference? Gastrointest Endosc 2010; 72(1): 66-7. https://doi.org/10.1016/j.gie.2010.03.1116*
13. *Sulieman A, Elzaki M, Khalil M. Occupational exposure to staff during endoscopic retrograde cholangiopancreatography in Sudan. Radiat Prot Dosimetry 2011; 144(1-4): 530-3. https://doi.org/10.1093/rpd/ncq353*
14. *Takenaka M, Hosono M, Hayashi S, Nishida T, Kudo M. The radiation doses and radiation protection on the endoscopic retrograde cholangiopancreatography procedures. Br J Radiol 2021; 94(1126): 20210399. https://doi.org/10.1259/bjr.20210399*
15. *Rhea EB, Rogers TH, Riehl JT. Radiation safety for anaesthesia providers in the orthopaedic operating room. Anaesthesia 2016; 71(4): 455-61. https://doi.org/10.1111/anae.13400*
16. *Lee B, Kim MS, Eum D, Min KT. The radiation environment of anaesthesiologists in the endoscopic retrograde cholangiopancreatography room. Sci Rep 2019; 9(1): 9124. https://doi.org/10.1038/s41598-019-45610-4*
17. *Dagal A. Radiation safety for anesthesiologists. Curr Opin Anaesthesiol 2011; 24(4): 445-50. https://doi.org/10.1097/ACO.0b013e328347f984*

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 183-189

Endoskopik retrograd kolanjiyopankreotografi sırasında oküler ve tüm vücut radyasyon maruziyeti

Bahtiyar Muhammedoğlu[1], Mehmet Yasir Pektezel[2], Murat Ulaş[3], Sezgin Topuz[4], Emil Hüseyinoğlu[5]

[1] Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Gastroenterolojik Cerrahi Anabilim Dalı, Kahramanmaraş, Türkiye
[2] Kahramanmaraş Necip Fazıl Şehir Hastanesi, Yoğun Bakım Kliniği, Kahramanmaraş, Türkiye
[3] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Gastroenterolojik Cerrahi Anabilim Dalı, Eskisehir, Türkiye
[4] Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Kahramanmaraş, Türkiye
[5] Bursa Şehir Hastanesi, Genel Cerrahi Kliniği, Bursa, Türkiye

ÖZET

Giriş ve Amaç: Amaç, endoskopik retrograd kolanjiyopankreotografi (ERCP) zorluğuna göre önemli ölçüde değişen tüm vücut radyasyon maruziyetinin ortalamasını analiz etmek ve uygulanan oküler radyasyonu analiz ederek oküler koruma cihazı kullanılması gerekip gerekmediğini belirlemektir.

Gereç ve Yöntem: Endoskopik retrograd kolanjiyopankreotografi endikasyonu olan 18 yaş üstü hastalar prospektif olarak çalışmaya dahil edildi.

Bulgular: Çalışmaya toplam 1173 hasta dahil edildi. Artan uygulanan radyasyon dozu; artan radyografik çekim sayısı (Rho= 0,789, p< 0,001), ERCP süresi (Rho= 0,487, p< 0,001), maliyet (Rho= 0,129, p< 0,001) ve yatış süresi (Rho= 0,109, p< 0,001) ile anlamlı olarak ilişkilidir. Tüm vücut, cilt ve göz radyasyonuna maruz kalma dozlarının yıllık önerilen limitin (20 mSv/yıl) altında olduğu tespit edildi.

Sonuç: Endoskopik retrograd kolanjiyopankreotografi sırasında oküler radyasyona maruz kalma sınırının önerilen yıllık sınırı (20 mSv/yıl) aşmadığı gibi bunun çok altında olduğu tespit edildi. Bu nedenle göz vizörlerinin kullanılmaması önerilmektedir.

Anahtar Kelimeler: Endoskopik retrograd kolanjiyopankreatografi, radyasyon maruziyeti, floroskopi süresi

DOİ: 10.47717/turkjsurg.2024.6461

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 190-196

Liver biopsy in patients with gall stone disease and concomitant non-alcoholic fatty liver disease undergoing cholecystectomy: A prospective observational study

Aaron John[1], Utpal Anand[2], Tarun Kumar[3], Rohith Kodali[2], Kunal Parasar[2], Ramesh Kumar[4], Rajeev Priyadarshi[5], Basant Singh[2], Kislay Kant[2]

[1] Clinic of Gastrointestinal, HPB, Multi Organ Transplant Surgery, Rajagiri Hospital, Kochi, India
[2] Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Patna, India
[3] Department of Pathology, All India Institute of Medical Sciences, Patna, India
[4] Department of Medical Gastroenterology, All India Institute of Medical Sciences, Patna, India
[5] Department of Radiodiagnosis, All India Institute of Medical Sciences, Patna, India

ABSTRACT

Objective: Gallstone disease (GSD) and non-alcoholic fatty liver disease (NAFLD) share common risk factors. NAFLD can progress to non-alcoholic steatohepatitis (NASH), which may lead to severe liver conditions. This study aimed to assess the prevalence of NASH and associated factors in patients with GSD and fatty liver undergoing cholecystectomy.

Material and Methods: This prospective observational study was conducted from March 2021 to June 2023 and included 134 patients diagnosed with GSD and fatty liver based on preoperative ultrasound. Core liver biopsies were obtained during cholecystectomy. Preoperatively, clinical, anthropometric, demographic, biochemical variables, and FibroScan parameters were recorded.

Results: NASH was found in 21 (15.67%) patients, while 50 (37.31%) patients had probable NASH, and 63 (47.01%) had non-NASH scores. Metabolic syndrome was present in 63.6% of the patients. Univariate analysis revealed significant differences in AST and ALT values between the NASH and non-NASH groups. In multivariate analysis, AST was statistically significant (p= 0.041). Mean controlled attenuation parameter in patients with non-NASH was 219.40 ± 60.44 dB/m, and in patients with NASH, it was 265.48 ± 63.47 dB/m (p= 0.006). Fibrosis was present in 33 of the 82 slides examined, with 17 patients having grade 2 and two patients with grade 3 fibrosis.

Conclusion: The high prevalence of NASH among GSD patients highlights a significant public health issue, prompting consideration for liver biopsy in individuals with NAFLD and GSD undergoing laparoscopic cholecystectomy.

Keywords: Gallstone disease, NAFLD, NASH, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

INTRODUCTION

Symptomatic gallstone disease (GSD) stands as the most prevalent benign disorder of the gallbladder, with an incidence of up to 6% among Indian adults (1). Patients afflicted with GSD often exhibit a high prevalence of non-alcoholic fatty liver disease (NAFLD), characterized by significant fat deposition in hepatocytes (2). Cholesterol GSD shares several risk factors with NAFLD, notably age, obesity, diabetes mellitus, insulin resistance, hyperlipidemia, sedentary lifestyle, and metabolic syndrome (2-4). It remains uncertain whether NAFLD acts as a precursor to GSD, or if the presence of GSD signifies long-standing features of metabolic syndrome, thereby hastening the progression of NAFLD (5). NAFLD stands as the foremost cause of chronic liver disease and cryptogenic cirrhosis globally. Non-alcoholic steatohepatitis (NASH), encompassing 10%-20% of NAFLD cases, can advance to severe chronic liver disease, liver cirrhosis, and hepatocellular carcinoma (6).

As of today, non-alcoholic steatohepatitis (NASH) primarily relies on histological diagnosis due to the unreliability of non-invasive methods. Liver biopsy remains the gold standard for diagnosing and staging NAFLD. However, firm recommendations regarding when to perform a liver biopsy in NAFLD patients are lacking. In our present study, our objective was to estimate the prevalence of NASH in patients with symptomatic GSD and concomitant fatty liver diagnosed via US.

Cite this article as: John A, Anand U, Kumar T, Kodali R, Parasar K, Kumar R, et al. Liver biopsy in patients with gall stone disease and concomitant non-alcoholic fatty liver disease undergoing cholecystectomy: A prospective observational study. Turk J Surg 2024; 40 (3): 190-196.

Corresponding Author
Utpal Anand
E-mail: utpalanand2@gmail.com

Received: 20.06.2024
Accepted: 22.08.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6488

This insight could aid in determining whether liver biopsy should be routinely conducted during cholecystectomy to assess the severity of NAFLD in GSD patients with concurrent fatty liver. The diagnosis of NASH upon biopsy would offer sufficient grounds for recommending lifestyle modifications, controlling metabolic risk factors, and implementing long-term liver disease monitoring in these patients. Additionally, we aimed to identify clinical predictors of NASH within this population, potentially facilitating timely evaluation and intervention. Previous studies have primarily focused on general patient populations, whereas our study exclusively concentrated on individuals with fatty liver and GSD to ascertain both prevalence rates and predictors of NASH in such patients.

MATERIAL and METHODS

This prospective observational study was conducted on consecutive adult patients aged 18-70 years diagnosed with symptomatic GSD and fatty liver via ultrasound (US) undergoing cholecystectomy at a tertiary care center in Northeastern India from March 2021 to June 2023. Ethics approval was obtained from the Institutional Ethics Committee (AIIMS/Pat/IEC/PGTh/Jan20/09), and research approval was taken from the institutional research board (AIIMS/Pat/IRC/2020/PGTh/Jan20/09) on 01/03/2021. Patients positive for HBV and HCV, with a history of alcohol intake exceeding 20 g per day for females and 30 g per day for males, diagnosed with liver cirrhosis, autoimmune hepatitis, or other liver diseases, pregnant individuals, and those with a history of drug intake (including oral contraceptive pills, steroids, methotrexate, amiodarone, tamoxifen, highly active antiretroviral therapy, and chemotherapy agents) were excluded from the study. Written informed consent was obtained from all included patients, and the study was conducted in accordance with the declaration of Helsinki.

Demographic details, clinical history of comorbidities, and anthropometric parameters were recorded. All patients underwent blood investigations, including fasting blood sugar, glycated hemoglobin (HbA1c), liver function tests [bilirubin, albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), prothrombin time international normalized ratio (INR)], thyroid stimulating hormone (TSH), lipid profile [triglycerides (TG), cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL)], and serology for hepatitis B and C. Preoperatively, all patients underwent USG to document gallstones and assess the presence of fatty liver, as well as Fibroscan® (Echosens, Paris, France) for calculating controlled attenuation parameter (CAP).

Liver biopsies were performed during laparoscopic cholecystectomy using a 16 g × 20 cm, BARD Max-Core™ Core Biopsy Instrument (Arizona, USA) from the right lobe of the liver. Hematoxylin-eosin stained and Masson trichrome stained paraffin-embedded liver biopsy sections were examined and interpreted by a single experienced pathologist. Severity was assessed using the NAFLD activity score (NAS) as proposed by the clinical research network (7). A NAS score of less than three was categorized as non-NASH, 3-4 as borderline NASH, and five or more as NASH. Fibrosis was staged on a scale of zero to four according to the clinical research network (7).

The sample size was determined based on a survey by Monzon et al., which reported a 10.2% prevalence of NASH in adult patients with GSD (8). To achieve a 95% confidence level and a 5% absolute precision, the study required a sample size of 131 participants. Clinical demographic data collected were analyzed using descriptive statistics. Qualitative variables were presented as absolute [number, (n)] and relative [percentage, (%)] frequencies. Standard deviations, means, and frequencies for each group with categorical variables were calculated. Qualitative data between the groups were compared using Pearson's Chi-square test or Fisher's exact test as appropriate. Quantitative variables were analyzed using ANOVA for normally distributed data (confirmed by Shapiro-Wilk test) and equal variances (confirmed by Levene's test). Ordinal logistic regression analysis was adjusted for confounding variables to identify independent predictors of NASH in the entire study population. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for the Social Sciences, version 20, SPSS Inc., Chicago, IL, United States (SPSS) for Microsoft Windows.

RESULTS

Among the 550 patients initially evaluated for laparoscopic cholecystectomy, 150 patients with fatty liver on US who met the inclusion and exclusion criteria were enrolled in the study. A further 16 patients with inadequate liver tissue for quantifying fatty liver on liver biopsy were excluded from the final analysis.

The demographic details of the patients are summarized in Table 1. Mean age of the patients was 43.22 ± 11.54 years (range 20 - 72 years), with ninety (67.2%) of the study participants being female. Mean body mass index (BMI) was 26.53 ± 3.99 kg/m^2. Among all patients, 49 (36.6%) were obese, and 52 (38.8%) were overweight. Additionally, twenty patients (16.3%) were diabetic, 23 (17.2%) were hypertensive, 16 (11.9%) had hypothyroidism, and four had other comorbidities, including bronchial asthma and coronary artery disease. According to the International Diabetes Federation (IDF) consensus definition, metabolic syndrome was present in 63.6% of the study population (9).

Upon analysis of liver biopsy samples from 134 patients with fatty liver on preoperative US, NASH (i.e., NAS score≥ 5) was found in 21 (15.67%) patients with GSD. Fifty (37.31%) patients had probable NASH (i.e., NAS scores of 3 and 4), while sixty-three (47.01%) patients had non-NASH scores (i.e., NAS score≤ 2) (Table 2).

Table 1. Patient demographics

Category	Mean/Count	Standard Deviation/ Percentage
Age, years	43.22	11.54
Sex		
Male	44	32.8%
Female	90	67.2%
BMI, kg/m^2	26.53	3.99
BMI categories		
Normal (18.5-22.49)	20	14.9%
Overweight (22.5-27.49)	52	38.8%
Obese (>27.5)	49	36.6%
Comorbidity status	52	42.3%
Diabetes mellitus	20	16.3%
Hypertension	23	17.2%
Thyroid disease	16	11.9%
Other comorbidities	4	3.3%

BMI: Body mass index.

Table 2. Prevalence of NASH

Liver Biopsy	n= 134
Non-NASH	63 (47.01%)
Probable NASH	50 (37.31%)
NASH	21 (15.67%)

NASH: Non-alcoholic steatohepatitis.

Table 3. Prevalence of fibrosis

Grade	n
0	49
1a	2
1b	1
1c	11
2	17
3	2
4	0
Total	82

Masson trichrome staining was performed on 82 samples, revealing hepatic fibrosis in 33 of them, with 17 patients having stage 2 and two patients with grade 3 fibrosis. None of the patients had underlying cirrhosis (Table 3). Among patients with NASH, 23% exhibited significant hepatic fibrosis (F2 or higher).

A higher percentage of patients with NASH had metabolic syndrome (86.7%) although it did not achieve statistical significance as a risk factor for NASH (p= 0.114). NASH patients had higher AST levels (41.19 ± 20.53 IU/L) compared to non-NASH subjects (28.95 ± 12.66 IU/L) (p= 0.028). ALT levels in non-NASH subjects were 28.36 ± 17.88 IU/L, while in NASH subjects, they were 44.71 ± 27.92 IU/L (p= 0.047). The remaining biochemical parameters, such as ALP, albumin, INR, cholesterol, HDL, VLDL, LDL, triglycerides, FBS, HbA1c, and TSH, did not achieve statistical significance. CAP increased from 219.40 ± 60.44 dB/m in non-NASH subjects to 265.48 ± 63.47 dB/m in NASH patients (p= 0.006) (Table 4).

For multivariate analysis, the following variables were considered: age, sex, comorbidities, BMI, AST, ALT, INR, HDL, triglycerides, and CAP. In this model, only AST reached statistical significance (p= 0.041) (Table 5). No morbidity or mortality were reported secondary to intra-operative liver biopsy in any patient.

DISCUSSION

GSD and NAFLD share common risk and pathogenic factors, and several studies have reported a significant association between them. The clinical spectrum of NAFLD includes steatosis, NASH, fibrosis, and cirrhosis. Given the high prevalence of NAFLD in patients with GSD, our study aimed to determine the prevalence of NASH and identify contributing risk factors in patients with fatty liver undergoing cholecystectomy.

Our study found NASH in 21 (15.67%) out of 134 patients undergoing cholecystectomy with fatty liver detected on preoperative US. Fifty percent of the patients with NASH were obese, while 43.5% of the probable NASH group and 42.9% of the non-NASH group were obese. Univariate analysis revealed significant differences in AST, ALT, and CAP between the NASH and non-NASH groups (p= 0.028), (p= 0.008), and (p= 0.006), respectively. Multivariate analysis showed that only AST was significant (p= 0.041).

The prevalence of NAFLD varies depending on the diagnostic test and population studied. Indian data indicates a prevalence of NAFLD between 6.7%-55.1% in adults (10). The variation in prevalence results from different diagnostic methods such as US, magnetic resonance imaging, and biopsy. A meta-analysis has found the pooled odds ratio of NAFLD in patients with gallstone disease to be 1.55 (95% CI 1.31-1.82) (11). In studies on patients undergoing cholecystectomy, NAFLD has shown a prevalence of 35%-55% in persons with GSD (8,12-15). The prevalence of NASH varies from 6%-11% in patients undergoing cholecystectomy (8,14,16,17). However, these studies were conducted on a general cohort of patients undergoing cholecystectomy. Our study specifically targeted patients with a preoperative diagnosis of NAFLD on US, revealing a 15.67% prevalence of NASH in this population. This high prevalence justifies considering liver biopsy during cholecystectomy to detect NASH early and implement necessary interventions such as lifestyle modifications and treatment of metabolic comorbidities can help reduce the

Table 4. Characteristics of the patients with gallstones studied according to diagnosis on liver histology

Risk factors	Levels	Liver biopsy			p
		Non NASH (n= 63)	Probable NASH (n= 50)	NASH (n= 21)	
Age (in years)		41.35 ± 12.26	44.08 ± 10.51	46.76 ± 11.11	0.142
Sex	Male	18 (40.9%)	22 (50%)	4 (9.1%)	0.076
	Female	45 (50%)	28 (31.1%)	17 (18.9%)	
BMI (kg/m^2)		25.86 ± 4.11	27.34 ± 3.69	26.65 ± 4.15	0.169
BMI category	Normal	14 (23.7)	3 (6.5%)	3 (18.8%)	0.158
	Overweight	24 (35.6%)	23 (50%)	5 (31.3%)	
	Obese	21 (42.9%)	20 (43.5%)	8 (50%)	
Presence of comorbidity	Absent	39 (54.9%)	22 (31%)	10 (14.1%)	0.206
	Present	21 (40.4%)	24 (46.2%)	7 (13.5%)	
Metabolic syndrome	Absent	21 (42.9%)	17 (37%)	2 (13.3%)	0.114
	Present	28 (57.1%)	29 (53%)	13 (86.7%)	
Bilirubin (mg/dL)		0.73 ± 0.54	0.67 ± 0.42	0.63 ± 0.39	0.652
AST (IU/L)		28.95 ± 12.66	33.12 ± 14.75	41.19 ± 20.53	0.028
ALT (IU/L)		28.36 ± 17.88	39.78 ± 27.45	44.71 ± 27.92	0.008
ALP (IU/L)		92.18 ± 44.44	98.25 ± 46.44	88.76 ± 25.20	0.633
Albumin (g/dL)		4.00 ± 0.40	4.03 ± 0.39	3.90 ± 0.57	0.492
INR		0.99 ± 0.13	0.94 ± 0.08	0.93 ± 0.10	0.073
Cholesterol (mg/dL)		168.0 ± 29.9	172.2 ± 44.2	172.4 ± 50.3	0.832
HDL (mg/dL)		50.45 ± 40.25	42.85 ± 19.48	38.20 ± 10.19	0.212
VLDL (mg/dL)		32.56 ± 13.30	29.99 ± 15.49	34.05 ± 9.96	0.480
LDL (mg/dL)		93.50 ± 29.38	99.30 ± 36.40	93.10 ± 42.66	0.651
Triglycerides (mg/dL)		161.77 ± 62.7	149.38 ± 76.7	219.97 ± 251.3	0.077
FBS (mg/dL)		104.50 ± 25.5	105.50 ± 27.4	106.32 ± 16.5	0.958
HbA1c (%)		5.72 ± 0.85	5.72 ± 1.41	5.66 ± 0.59	0.974
TSH (m IU/L)		3.82 ± 2.42	3.42 ± 3.39	5.33 ± 10.15	0.319
CAP (dB/m)		219.40 ± 60.4	243.64 ± 59.7	265.48 ± 63.47	0.006

BMI: Body mass index, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio, HDL: High density lipoprotein, VLDL: Very low density lipoprotein, LDL: Low density lipoprotein, FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin, TSH: Thyroid stimulating harmone, CAP: Controlled attenuation parameter.

advanced liver disease burden in the population. We utilized a core liver biopsy instead of a wedge biopsy because fibrous septa from a subcapsular sample in a wedge biopsy may mimic cirrhosis and potentially overestimate the stage of liver disease (18). Previous studies have primarily employed wedge biopsies rather than core biopsies (13,15,16).

In patients with NAFLD, liver fibrosis plays a crucial role in overall morbidity and mortality. Our study revealed significant liver fibrosis in 23% of NASH subjects, although advanced fibrosis was rare, and none had compensated cirrhosis. These findings suggest that patients were likely identified during the relatively early phase of NAFLD progression. Typically, fibrosis progression in NAFLD is slow, with approximately seven years required for one stage of fibrosis to progress (19).

Obesity is a common risk factor for both NAFLD and GSD. Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. In studies conducted on patients undergoing cholecystectomy, some have found a statistically significant difference in BMI between the NASH and non-NASH groups (14,16). In contrast, other studies have reported no significant difference in BMI among NASH and non-NASH patients (17). The presence of 50% of the patients in the non-obese group might be attributed to the lower BMI in our population compared to other parts of the country. NAFLD has been reported in lean subjects residing in developing countries, suggesting that lean NAFLD may represent a distinct entity that could contribute to NAFLD in our population.

Table 5. Summary of ordinal regression analysis

Variable	Estimate (b)	Standard Error	p
Age	0.038	2.513	0.265
Sex	-0.354	0.460	0.442
BMI	0.060	0.054	0.270
Comorbidity	0.041	0.450	0.928
AST	0.050	0.024	0.041
ALT	0.004	0.015	0.792
INR	-2.108	1.858	0.257
HDL	-0.015	0.011	0.165
Triglycerides	0.001	0.002	0.688
CAP	0.003	0.004	0.416

BMI: Body mass index, AST: Aspartate transaminase, ALT: Alanine transaminase, INR: International normalized ratio, HDL: High density lipoprotein, CAP: Controlled attenuation parameter.

Metabolic syndrome is prevalent in patients with symptomatic gallstones, with a significant association with NAFLD. It remains unclear whether NAFLD serves as a precursor to GSD or if the presence of GSD indicates the presence of longstanding features of metabolic syndrome, potentially accelerating the progression of NAFLD. In our study, metabolic syndrome was present in 63.6% of NAFLD patients, with 20 patients (16.3%) diagnosed with diabetes mellitus and 23 (17.2%) with hypertension. A higher percentage of patients with NASH exhibited metabolic syndrome (86.7%) although it did not achieve statistical significance as a risk factor for NASH (p= 0.114). The prevalence of metabolic syndrome in the non-NASH group was 57.1%, and in the probable-NASH group, it was 53%. The close association between metabolic syndrome and GSD has led some researchers to propose GSD as another manifestation of metabolic syndrome (19). However, its role as a risk factor for NASH in our study did not reach statistical significance. Routine assessment of metabolic syndrome components is essential to mitigate NASH progression and liver-related complications.

Identifying subsets with NASH and liver fibrosis in NAFLD patients is crucial for disease management. While several non-invasive validated non-invasive markers for liver fibrosis such as AST/platelet ratio index, fibrosis-4 index, non-alcoholic fatty liver disease fibrosis score, BMI AST/ALT ratio, and diabetes score (BARD), exist for liver fibrosis, none reliably indicate the presence of NASH (20). In studies comparing NAFLD and NASH patients with normal controls based on liver biopsies, AST and ALT were found to correlate with the presence of NASH (15,21). In our univariate analysis, AST and ALT levels were significant in both NASH and non-NASH populations, with only AST showing independent association with NASH in the multivariate analysis.

High serum triglyceride levels and low serum HDL levels are commonly observed in patients with NAFLD (15,22-24). Our results were consistent with this observation although statistical significance was not achieved.

CAP is a valid method for the non-invasive detection and quantification of hepatic steatosis. Its measurement has been validated by multiple studies, and CAP scores have shown good correlation with hepatic steatosis observed on liver biopsies (25-28). In our study as well, CAP was significantly different between the NASH and non-NASH groups in the univariate analysis.

Liver biopsy during cholecystectomy was well-tolerated in our study, with no significant complications reported. This may be attributed to the fact that the liver biopsy procedure is performed under laparoscopic visualization, allowing for immediate coagulation of any bleeders using electrocautery. We can observe for any further bleeding from the biopsy site.

This study highlights the importance of screening for NASH in patients with GSD and fatty liver undergoing cholecystectomy. Liver biopsy emerges as a vital diagnostic tool to assess NASH and fibrosis presence and severity. Close monitoring of metabolic syndrome components is warranted to mitigate NASH progression and liver-related complications. Routine assessment of liver enzymes and evaluation of fibrosis status can aid in early detection and management strategies for patients with GSD and fatty liver undergoing cholecystectomy.

Our study had limitations, including being hospital-based and single-centered, posing a risk of referral bias. Additionally, as a cross-sectional study, causality cannot be determined. Our study group consisted of patients who were optimized for surgery; hence, the biochemical parameters obtained may reflect optimized rather than typical values found in the general population. Consequently, the prediction of risk factors may have been influenced. Nonetheless, our findings underscore the importance of considering liver biopsy in NAFLD patients with GSD undergoing cholecystectomy, particularly in those with elevated liver enzymes.

Ethics Committee Approval: This study was obtained from All India Institute of Medical Sciences Institutional Ethics Committee (Decision no: AIIMS/Pat/IEC/PGTh/Jan20/09 Date: 01.03.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - UA, RK, RP; Design - UA; Supervision - UA, RK, RP; Data Collection and/or Processing - AJ, RK, KP; Analysis and/or Interpretation - AJ, BS, KK; Literature Search - AJ, BS, KK; Writing Manuscript - AJ, BS, KK; Critical Reviews - AJ, RK, KP, RK, RP, BS, KK.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Khuroo MS, Mahajan R, Zargar SA, Javid G, Sapru S. Prevalence of biliary tract disease in India: A sonographic study in adult population in Kashmir. Gut 1989; 30(2): 201-5. https://doi.org/10.1136/gut.30.2.201*
2. *Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: The Dionysos nutrition and liver study. Hepatol Baltim Md 2005; 42(1): 44-52. https://doi.org/10.1002/hep.20734*
3. *Roesch-Dietlen F, Pérez-Morales A, Melo-Santisteban G, Díaz-Blanco F, Martínez-Fernández S, Martínez JA, et al. Frequency and clinical, biochemical and histological characteristics of nonalcoholic fatty liver disease in patients with gallstone disease. Cir Cir 2008; 76(1): 37-42.*
4. *Méndez-Sánchez N, Chavez-Tapia NC, Motola-Kuba D, Sanchez-Lara K, Ponciano-Rodríguez G, Baptista H, et al. Metabolic syndrome as a risk factor for gallstone disease. World J Gastroenterol WJG 2005; 11(11): 1653-7. https://doi.org/10.3748/wjg.v11.i11.1653*
5. *Ahmed MH, Ali A. Nonalcoholic fatty liver disease and cholesterol gallstones: Which comes first? Scand J Gastroenterol 2014; 49(5): 521-7. https://doi.org/10.3109/00365521.2014.894119*
6. *Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64(1): 73-84. https://doi.org/10.1002/hep.28431*
7. *Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatol Baltim Md 2005; 41(6): 1313-21. https://doi.org/10.1002/hep.20701*
8. *García-Monzón C, Vargas-Castrillón J, Porrero JL, Alonso MT, Bonachía O, Castillo MJ, et al. Prevalence and risk factors for biopsy-proven non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in a prospective cohort of adult patients with gallstones. Liver Int Off J Int Assoc Study Liver 2015; 35(8): 1983-91. https://doi.org/10.1111/liv.12813*
9. *Alberti KGMM, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet Lond Engl 2005; 366(9491): 1059-62. https://doi.org/10.1016/S0140-6736(05)67402-8*
10. *Shalimar, Elhence A, Bansal B, Gupta H, Anand A, Singh TP, et al. Prevalence of non-alcoholic fatty liver disease in India: A systematic review and meta-analysis. J Clin Exp Hepatol 2022; 12(3): 818-29. https://doi.org/10.1016/j.jceh.2021.11.010*
11. *Jaruvongvanich V, Sanguankeo A, Upala S. Significant association between gallstone disease and nonalcoholic fatty liver disease: A Systematic review and meta-analysis. Dig Dis Sci 2016; 61(8): 2389-96. https://doi.org/10.1007/s10620-016-4125-2*
12. *Yener O, Aksoy F, Demir M, Özçelik A, Erengül C. Gallstones associated with nonalcoholic steatohepatitis (NASH) and metabolic syndrome. Turk J Gastroenterol Off J Turk Soc Gastroenterol 2010; 21(4): 411-15. https://doi.org/10.4318/tjg.2010.0128*
13. *Singh K, Dahiya D, Kaman L, Das A. Prevalence of non-alcoholic fatty liver disease and hypercholesterolemia in patients with gallstone disease undergoing laparoscopic cholecystectomy. Pol Przegl Chir 2019; 92(1): 18-22. https://doi.org/10.5604/01.3001.0013.5660*
14. *Alsaif FA, Alqahtani SH, Alsadoon AM, Alswat KA, Abdo AA, Hassanain MM, et al. Prevalence of biopsy-proven nonalcoholic fatty liver among patients with gallstone disease. Saudi J Gastroenterol 2020; 26(4): 204-9. https://doi.org/10.4103/sjg.SJG_29_20*
15. *Ramos-De la Medina A, Remes-Troche JM, Roesch-Dietlen FB, Pérez-Morales AG, Martinez S, Cid-Juarez S. Routine liver biopsy to screen for nonalcoholic fatty liver disease (NAFLD) during cholecystectomy for gallstone disease: is it justified? J Gastrointest Surg Off J Soc Surg Aliment Tract 2008; 12(12): 2097-102; discussion 2102. https://doi.org/10.1007/s11605-008-0704-7*
16. *Hajong R, Dhal MR, Naku N, Kapa B. Incidence of nonalcoholic fatty liver disease in patients undergoing laparoscopic cholecystectomy. J Fam Med Prim Care 2018; 7(6): 1375-8. https://doi.org/10.4103/jfmpc.jfmpc_193_18*
17. *Naik A, Dahiya D, Duseja A, Kaman L. Prevalence and severity of nonalcoholic fatty liver disease in patients with gall stone disease. Sri Lanka J Surg 2020; 38: 31. https://doi.org/10.4038/sljs.v38i2.8659*
18. *Padoin AV, Mottin CC, Moretto M, Berleze D, Kupski C, Glock L, et al. A comparison of wedge and needle hepatic biopsy in open bariatric surgery. Obes Surg 2006; 16(2): 178-82. https://doi.org/10.1381/096089206775565159*
19. *Grundy SM. Cholesterol gallstones: A fellow traveler with metabolic syndrome? Am J Clin Nutr 2004; 80(1): 1-2. https://doi.org/10.1093/ajcn/80.1.1*
20. *Younes R, Caviglia GP, Govaere O, Rosso C, Armandi A, Sanavia T, et al. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. J Hepatol 2021; 75(4): 786-94. https://doi.org/10.1016/j.jhep.2021.05.008*
21. *Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: A prospective study. Gastroenterology 2011; 140(1): 124-31. https://doi.org/10.1053/j.gastro.2010.09.038*
22. *Nseir W, Shalata A, Marmor A, Assy N. Mechanisms linking nonalcoholic fatty liver disease with coronary artery disease. Dig Dis Sci 2011; 56(12): 3439-49. https://doi.org/10.1007/s10620-011-1767-y*
23. *Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007; 30(5): 1212-8. https://doi.org/10.2337/dc06-2247*
24. *Speliotes EK, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: The Framingham Heart Study. Hepatol Baltim Md 2010; 51(6): 1979-87. https://doi.org/10.1002/hep.23593*
25. *Vuppalanchi R, Siddiqui MS, Van Natta ML, Hallinan E, Brandman D, Kowdley K, et al. Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. Hepatol Baltim Md 2018; 67(1): 134-44. https://doi.org/10.1002/hep.29489*
26. *Ahn JM, Paik YH, Min SY, Cho JY, Sohn W, Sinn DH, et al. Relationship between controlled attenuation parameter and hepatic steatosis as assessed by ultrasound in alcoholic or nonalcoholic fatty liver disease. Gut Liver 2016; 10(2): 295-302. https://doi.org/10.5009/gnl15155*
27. *Chan WK, Nik Mustapha NR, Mahadeva S. Controlled attenuation parameter for the detection and quantification of hepatic steatosis in nonalcoholic fatty liver disease. J Gastroenterol Hepatol 2014; 29(7): 1470-6. https://doi.org/10.1111/jgh.12557*
28. *de Lédinghen V, Wong GL, Vergniol J, Chan HL, Hiriart JB, Chan AW, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2016; 31(4): 848-55. https://doi.org/10.1111/jgh.13219*

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 190-196

Kolesistektomi yapılan safra taşı hastalığı ve eşlik eden alkolik olmayan yağlı karaciğer hastalığı olan hastalarda karaciğer biyopsisi: Prospektif gözlemsel bir çalışma

Aaron John[1], Utpal Anand[2], Tarun Kumar[3], Rohith Kodali[2], Kunal Parasar[2], Ramesh Kumar[4], Rajeev Priyadarshi[5], Basant Singh[2], Kislay Kant[2]

[1] Rajagiri Hastanesi, Gastrointestinal, HPB, Çoklu Organ Nakli Cerrahisi Kliniği, Kochi, Hindistan
[2] Tüm Hindistan Tıp Bilimleri Enstitüsü, Cerrahi Gastroenteroloji Anabilim Dalı, Patna, Hindistan
[3] Tüm Hindistan Tıp Bilimleri Enstitüsü, Patoloji Anabilim Dalı, Patna, Hindistan
[4] Tüm Hindistan Tıp Bilimleri Enstitüsü, Tıbbi Gastroenteroloji Anabilim Dalı, Patna, Hindistan
[5] Tüm Hindistan Tıp Bilimleri Enstitüsü, Radyodiagnostik Anabilim Dalı, Patna, Hindistan

ÖZET

Giriş ve Amaç: Safra taşı hastalığı (STH) ve alkolik olmayan yağlı karaciğer hastalığı (AOYKH) ortak risk faktörlerini paylaşmaktadır. Alkolik olmayan yağlı karaciğer hastalığı, ciddi karaciğer rahatsızlıklarına yol açabilen alkol dışı steatohepatit (ADS)'ye ilerleyebilir. Bu çalışmada, kolesistektomi yapılan STH ve yağlı karaciğer hastalarında NASH prevalansını ve ilişkili faktörleri değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu prospektif gözlemsel çalışma Mart 2021-Haziran 2023 tarihleri arasında yürütülmüş ve preoperatif ultrasonografiye göre STH ve yağlı karaciğer tanısı koyulan 134 hasta dahil edilmiştir. Kolesistektomi sırasında kor karaciğer doku biyopsileri alınmıştır. Ameliyat öncesi klinik, antropometrik, demografik, biyokimyasal değişkenler ve FibroScan parametreleri kaydedilmiştir.

Bulgular: Hastaların 21'inde (%15,67) NASH, 50'sinde (%37,31) olası NASH ve 63'ünde (%47,01) NASH dışı skorlar saptandı. Hastaların %63,6'sında metabolik sendrom mevcuttu. Tek değişkenli analizde AST ve ALT değerleri NASH ve NASH olmayan gruplar arasında anlamlı farklılıklar göstermiştir. Çok değişkenli analizde, AST istatistiksel olarak anlamlıydı (p= 0,041). NASH olmayan hastalarda ortalama kontrollü zayıflama parametresi 219,40 ± 60,44 dB/m iken NASH olan hastalarda 265,48 ± 63,47 dB/m idi (p= 0,006). İncelenen 82 lamın 33'ünde fibrozis mevcuttu ve 17 hastada evre 2 ve iki hastada evre 3 fibrozis vardı.

Sonuç: Safra taşı hastalığı olan hastalar arasında NASH prevalansının yüksek olması, önemli bir halk sağlığı sorununa işaret etmekte ve laparoskopik kolesistektomi geçiren NAFLD ve STH'li bireylerde karaciğer biyopsisinin dikkate alınmasını gerektirmektedir.

Anahtar Kelimeler: Safra taşı hastalığı, NAFLD, NASH, alkolik olmayan yağlı karaciğer hastalığı, alkol dışı steatohepatit

DOİ: 10.47717/turkjsurg.2024.6488

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 197-203

The coexistence of gastrointestinal stromal tumors and malignancies: Our 10-year results

Yavuz Selim Angın, Cengiz Ceylan, Kutay Sağlam, Cemalettin Aydın

Department of General Surgery, İnönü University Faculty of Medicine, Malatya, Türkiye

ABSTRACT

Objective: Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors in the gastrointestinal system, occurring frequently after epithelial tumors. Although rare, secondary epithelial malignancies can be associated with GISTs. It was planned to conduct a retrospective cohort study evaluating the coexistence of GISTs with malignancies and their long-term outcomes through clinical and pathological findings.

Material and Methods: Demographic and clinicopathological data of 69 patients who underwent surgery for GIST between January 2011 and November 2021 were retrieved from the patient database. Variables between the groups with only GIST and those with a secondary malignancy alongside GIST were analyzed using the Chi-square test and Mann-Whitney U test. Long-term survival analyses were conducted using the Kaplan-Meier test. A p-value of <0.05 was considered statistically significant.

Results: Out of the 69 patients in our population, 40 (58%) were male, and the median age was 65 years (interquartile range= 56-75). GIST was the most commonly located in the stomach (59.4%), and nine (13%) patients had a secondary malignancy. Tumor size, smooth muscle antibody (SMA), and S100 antibody expression showed significant differences between the groups (p< 0.001, p= 0.015, p= 0.006). Shorter survival was observed in patients with GIST plus secondary malignancy (p= 0.005).

Conclusion: The incidence of other intraabdominal malignancies occurring alongside GISTs is more common than have been previously thought. While the presence of a secondary malignancy does not impact the overall survival (OS) in GISTs, it was observed that survival is dependent on the primary malignancy. Patients diagnosed with GISTs require thorough investigation and close monitoring for secondary malignancies.

Keywords: Gastrointestinal stromal tumors, synchron, clinicopathological, prognosis

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) originate from the interstitial Cajal cells (ICC) located in the intramuscular layer. Despite being the most common mesenchymal tumors, GISTs constitute only 1-2% of gastrointestinal system cancers (1). They are predominantly observed in individuals aged between 60-69 years and are rare in those below 40 years old. GISTs can occur anywhere in the gastrointestinal system from the esophagus to the anus. However, they are most frequently found in the stomach (2).

The diagnosis of GIST is established histologically in the presence of tyrosine-protein kinase kit (KIT) or cluster of differentiation 34 (CD34) positivity. If the tumor is negative for KIT, CD34, desmin, smooth muscle actin (SMA), and S-100 protein (S-100), additional tests such as discovered on gastrointestinal stromal tumor staining 1 (DOG1) or mutation analysis of the KIT or platelet-derived growth factor receptor-α (PDGFRA) genes are necessary (3).

GISTs are rare compared to epithelial malignancies in the gastrointestinal system, and the expected survival rate in this group is relatively better (4). Tumor aggressiveness is associated with Ki-67 score, mitotic index, tumor size, and localization (4,5). Additionally, GIST can coexist with epithelial malignancies. While it predominantly accompanies gastrointestinal system malignancies, it can also be observed in conjunction with prostate, breast, hematological malignancies, kidney, and lung cancers (6).

A retrospective cohort study was planned to investigate the clinicopathological differences and long-term (10 years) outcomes of GISTs accompanied by secondary malignancy, compared to GISTs alone.

Cite this article as: Angın YS, Ceylan C, Sağlam K, Aydın C. The coexistence of gastrointestinal stromal tumors and malignancies: Our 10-year results. Turk J Surg 2024; 40 (3): 197-203.

Corresponding Author
Yavuz Selim Angın
E-mail: dryavuz05@gmail.com

Received: 22.03.2024
Accepted: 29.08.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6389

MATERIAL and METHODS

Study Design and Patients Selection

Demographic and clinicopathological data, postoperative outcomes, and long-term follow-ups of 69 patients operated for GIST between 2011-2021 at our center were obtained from the patient database. The study was approved by the ethics committee. Approval number is 2023/5189.

Inclusion criteria:

- Operable GIST patients aged 18 and above, regardless of the presence of accompanying epithelial malignancy.

Exclusion criteria:

- Patients with distant metastasis.
- Unresectable and recurrent tumors.

Demographic information (age, sex), clinicopathological data (comorbidities, ASA scores, tumor size and localization, Ki-67 score, mitotic index, cluster of differentiation 117 (another name for the KIT protein) (CD117), CD34, DOG1, SMA, S100 statuses), postoperative complications [Clavien Dindo mild (1-2)/ severe (3-4)], the presence of a second primary malignancy, recurrence (localization), risk of GIST recurrence after surgery [National Institutes of Health (NIH) criteria], and overall survival data were retrieved from the patient database (7,8). All patients operated for GIST underwent preoperative thoraco-abdominal computed tomography (CT), endosonography (EUS), and if necessary, magnetic resonance imaging (MRI) for staging. To monitor patients during the follow-up period, we employed a rigorous imaging schedule, which included CT scans conducted every six months and annual PET scans to ensure any emerging malignancies were detected as early as possible. This protocol allowed for the timely identification of secondary malignancies that were not apparent at the time of the initial GIST diagnosis.

The population was divided into two groups: GIST with accompanying second primary malignancy and GIST alone.

Patient Management

Patients with suspected GIST based on radiological or endoscopic findings and having resectable tumors were operated. Those with accompanying secondary malignancies along with GIST received a pathological diagnosis in the preoperative period. Radical surgery was performed for patients with accompanying secondary malignancies. R0 resection was achieved for GIST cases. Disease staging was performed according to the American Joint Committee on Cancer (AJCC 8) criteria. After surgery, pathology reports were reevaluated, and appropriate patients received adjuvant therapy. All patients were scheduled for outpatient follow-ups every three months for the first two years postoperatively, followed by semiannual appointments for the next three years.

Statistical Analysis

Compliance of numerical data with normal distribution was controlled by Shapiro Wilk test. It was determined that none of the variables showed a normal distribution. Continuous variables were analyzed with the Mann-Whitney U test. Median and interquartile range (IQR) values of these variables were given. Chi-square analysis was performed for categorical variables. Surveillance analysis between groups was done with Kaplan-Meier.

RESULTS

Among the 69 patients who underwent surgery and were followed up due to GIST, median age was 65 years (range= 56-75), with 40 (58%) being male. Patients with more than two comorbidities accounted for 30.4% of the population, with the majority having ASA 1 (4.3%) and ASA 2 (60.9%) operative risk. The most common site of GIST localization was the stomach (59.4%), followed by the jejunum-ileum (21.7%). The presence of accompanying secondary malignancy was observed in nine patients (13%) (Table 1).

In our study, out of the nine patients diagnosed with gastrointestinal stromal tumors with additional malignancies, two malignancies were detected during the follow-up period after the initial GIST diagnosis. These secondary malignancies were identified 12 and 18 months following the GIST diagnosis. At the time of the initial GIST diagnosis, imaging methods, including computed tomography (CT) and positron emission tomography (PET) scans did not reveal the presence of these secondary tumors.

In the analyses conducted between the two groups, there were no statistical differences in terms of age, sex, comorbidity, histological type, mitotic index, and Ki-67 ($p> 0.05$). However, the tumor size in the group with secondary malignancy [3 cm (2-3)] was significantly smaller compared to the group with only GIST [8 (5-16)] ($p< 0.001$).

Following pathological examinations, there were no statistical differences between the groups in terms of CD117, CD34, and DOG1. However, there were statistically significant differences in SMA ($p= 0.015$) and S100 ($p= 0.006$) status (Table 2).

There were no statistically significant differences between the groups in terms of postoperative complications, length of hospital stay [seven days (5-10) vs. 10 days (7-15)], residual tumor classification [R1= 10 (16.7%) vs. 1 (11.1%)], recurrences [12 (20%) vs. 0 (0%)], and mortality [11 (18.3%) vs. 2 (22.2%)]. However, there was a statistically significant difference between the groups in terms of postoperative recurrence risk (NIH classification) ($p= 0.001$). In recurrence risk scoring, 63.3% of the patients in the GIST group were classified as high risk, whereas the majority of the patients in the GIST plus secondary malignancy group (55.6%) were classified as very low risk (Table 3).

Table 1. Demographic data and tumor locations of the population

Variables		Median	Count (%)
Age, year		65 (56-75)	
Sex	Male		40 (58%)
	Female		29 (42%)
Comorbidty	Absent		22 (31.9%)
	1-2		26 (37.7%)
	3≤		21(30.4%)
ASA	1		3 (4.3%)
	2		42 (60.9%)
	3		24 (34.8%)
Tumor localization	Stomach		41 (59.4%)
	Jejunum-ileum		15 (21.7%)
	Duodenum		2 (2.9%)
	Retroperitoneum		0 (0%)
	Colon		4 (5.8%)
	Rectum		0 (0%)
	Intesinal mesentery		5 (7.2%)
	Liver		1 (1.4%)
	Anal canal		1 (1.4%)
GIST plus secondary malignancy	Absent		60 (87%)
	Present		9 (13%)

ASA: American Society of Anesthesiologists, GIST: Gastrointestinal stromal tumor.

In the group of patients with secondary malignancies accompanying GIST, six out of nine patients were male. GIST, mostly originating from gastric localization, was present. Secondary malignancies in these patients included two colon cancers, two rectal cancers, two hepatocellular carcinomas (liver transplants had been performed before the diagnosis of GIST), one stomach cancer (synchronously detected gastric adenocarcinoma), one breast cancer (detected during follow-ups), and one lung cancer (diagnosed during follow-ups due to GIST) (Table 4).

Survey Analysis Results

The average follow-up period for patients was 47.4 months. During the follow-up period, mortality was observed in 13 patients (18.8%), and recurrence occurred in 12 patients (17.4%). Out of these recurrences, 9 (75%) were in the peritoneum, 2 (16.7%) were in the liver, and 1 (8.3%) was a local recurrence. In the group with only GIST, the average overall survival was 59.2 ± 4.98 months, whereas in the group with GIST plus secondary malignancy, it was 28.2 ± 6.08 months (p= 0.005) (Table 5, Figure 1).

DISCUSSION

In our study, consistent with the literature, GISTs (%13) are accompanied by secondary malignancies (mostly gastrointestinal malignancies) in long-term follow-ups. The occurrence of secondary malignancies accompanying GIST ranges from 4.5% to 33% (6,9,10). Moreover, a meta-analysis has revealed that secondary malignancies are predominantly derived from the gastrointestinal and genitourinary systems (9).

Studies supporting the association between epithelial tumors and GIST, as well as hypotheses attempting to explain this association, exist in the literature. Kawanowa and colleagues have reported microscopic GIST in 35% of the patients operated on for gastric adenocarcinoma (11). In an experimental study by Cohen and colleagues, simultaneous development of gastric cancer and leiomyosarcoma has been demonstrated using nitrosoguanidine and acetylsalicylic acid (12). Moreover, other hypotheses have focused on Helicobacter pylori-induced chronic gastritis and atrophic gastric mucosa as secondary factors, as well as the effects of chemotherapy and radiotherapy (13). Maiorana et al. have reported the potential of a single carcinogenic agent to affect two different tissues in the same organ, leading to the formation of different types of cancer (14). However, Ponti et al. have suggested the hereditary nature of a subset of GISTs negative for KIT and PDGFRA activation mutations, potentially contributing to a multineoplastic process (15). Nevertheless, the common factors and reasons for the tumorigenesis of both epithelial and mesenchymal-origin malignancies remain unproven in the present day.

Table 2. Analysis of the clinicopathological data of the groups

Variables		Only GIST		GIST Plus Seconder Malignancy		p
		Median (IQR)	n (%)	Median (IQR)	n (%)	
Age, year		65 (56-75)		68 (57-76)		0.742
Sex	Male		34 (56.7%)		6 (66.7%)	0.571
	Female		26 (43.3%)		3 (33.3%)	
ASA	1		1 (1.7%)		2 (22.3%)	**0.010**
	2		39 (65%)		3 (33.3%)	
	3		20 (33.3%)		4 (44.4%)	
Comorbidity	0		18 (30%)		4 (44.4%)	0.210
	1-2		25 (41.7%)		1 (11.2%)	
	3≤		17 (28.3%)		4 (44.4%)	
Histological type	Spindle-shaped		32 (53.3%)		4 (44.4%)	0.488
	Epithelioid		10 (16.7%)		3 (33.3%)	
	Mix		18 (30.0%)		2 (22.3%)	
Mitotic index		4 (1-14)		1 (1-10)		0.156
Ki-67		5 (2-10)		5 (2-10)		0.879
Tumor size, cm		8 (5-16)		3 (2-3)		**<0.001**
Tumor cut-off	<4		7 (11.7%)		7 (77.8%)	**<0.001**
	≥4		53 (88.3%)		2 (22.2%)	
SMA	Positive		39 (65%)		2 (22.2%)	**0.015**
S100	Positive		6 (10%)		4 (44.4%)	**0.006**
CD117	Positive		53 (88.3%)		8 (88.9%)	0.961
CD34	Positive		41 (69.5%)		9 (100%)	0.053
DOG1	Positive		47 (78.3%)		9 (100%)	0.121

IQR: Interquartile range, ASA: American Society of Anesthesiologists, KIT: Tyrosine-protein kinase kit, CD34: Cluster of differentiation 34, SMA: Smooth muscle actin, S-100: S-100 protein, CD117: Cluster of differentiation 117 (another name for the KIT protein), DOG1: Discovered on GIST-1.

In the literature, the majority of secondary malignancies originate from the gastrointestinal system, particularly the stomach (16-18). Similarly, in our study, six out of the nine tested patients had stomach-originated secondary malignancies. Another noteworthy point is that two of our patients underwent liver transplantation due to hepatocellular cancer. GISTs were incidentally detected during endoscopic examinations due to the close monitoring of these patients. Additionally, non-gastrointestinal cancers were observed in two patients.

In our group of patients with accompanying secondary malignancies, it was observed that the tumor size was statistically significantly smaller, with a low mitotic index, and consequently, a lower risk of tumor recurrence. A similar situation has also been demonstrated in the study conducted by Du et al. We believe that the reason for the smaller tumor size in patients with gastrointestinal system malignancies, either preoperatively synchronously or detected due to another malignancy while under observation, is early detection through the conducted screenings (18).

The most important markers for identifying GISTs are CD117 and CD34. Therefore, the majority of GISTs are positive for CD117 (>95%) and/or CD34 (40%) (19). The simultaneous detection of both CD117 and CD34 is a common feature in most patients. In our case series, there was no significant difference between the group with synchronous malignancy in terms of CD117 and CD34 and the group with only GIST. However, there was a significant difference between the two groups in terms of SMA (p= 0.033) and S100 (p= 0.045). While SMA was proportionally higher in the GIST-only group (65% vs. 22.2%), S100 was higher in the GIST plus secondary malignancy group (10% vs. 44.4%).

Although overall survival was lower in the GIST plus secondary malignancy group, we believe this is not due to GIST itself because of the low recurrence risks. Instead, it is likely that the

Table 3. Surgical and clinical follow-up outcomes of the groups in the postoperative period

		Only GIST		GIST Plus Secondary Malignancy		
Variables		**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**p**
Postoperative complication	CD 1-2	26 (44.8%)		1 (11.1%)		0.147
	CD 3-4	10 (17.2%)		3 (33.3%)		
Length of stay hospital, day			7 (5-10)		10 (7-15)	0.294
Resudual tumor classification	R0	50 (83.3%)		8 (88.9%)		0.671
	R1	10 (16.7%)		1 (11.1%)		
	R2	0 (0%)		0 (0%)		
NIH	Very low	4 (6.7%)		5 (55.6%)		**0.001**
	Low	6 (10%)		1 (11.1%)		
	Intermediate	12 (20%)		0 (0%)		
	High	38 (63.3%)		3 (33.3%)		
Postoperative chemotherapy	Absence	29 (48.3%)		3 (33.3%)		**<0.001**
	Imatinib	31 (51.7%)		0 (0%)		
	Adjuvant	0 (0%)		6 (66.7%)		
Recurrence		12 (20%)		0 (0%)		0.140
Recurrence localization	Absence	48 (80%)		9 (100%)		
	Peritoneum	9 (15%)		0 (0%)		
	Liver	2 (3.3%)		0 (0%)		
	Lung	0 (0%)		0 (0%)		
	Local recurrence	1 (1.7%)		0 (0%)		
Mortality		11 (18.3%)		2 (22.2%)		0.781

GIST: Gastrointestinal stromal tumor, CD: Clavien dindo classification, IQR: Interquartile range, NIH: National Institutes of Health.

Table 4. Clinical and pathological data of the patients with secondary malignancies accompanying GIST

No	Sex	Age (y)	Localization	TD (cm)	MI (x/50 hpf)	Localization	Follow-Up (Months)
1	F	57	Duodenum	3	1	Breast cancer (IDC)	DFS (36)
2	M	83	Stomach	3	1	Colon cancer	Death (12)
3	M	77	Stomach	11	10	Colon cancer	DFS (12)
4	M	50	Jejenum-Ileum	4	10	Lung cancer	Death (10)
5	M	57	Stomach	2	2	HCC (liver Tx)	DFS (24)
6	F	62	Stomach	2	1	HCC (liver Tx)	DFS (60)
7	M	69	Stomach	1	1	Gastric adenoca	DFS (24)
8	M	68	Jejenum-Ileum	2	13	Rectum cancer	DFS (15)
9	F	76	Stomach	3	1	Rectum cancer	DFS (24)

TD: Tumor diameter, MI: Mitotic index, IDC: Invasive ductal carcinoma, DFS: Disease free survival, HCC: Hepatocellular carcinoma.

secondary malignancy directly impacted the expected lifespan. Similar findings were observed in the study by Diamantis and colleagues, where there was no statistical difference in terms of expected lifespan between similar groups (p= 0.19) (20).

While our study provides valuable insights into the association between GISTs and secondary malignancies, several limitations should be acknowledged. First, the sample size is relatively small, which may limit the generalizability of our findings.

Table 5. Analysis of the overall survival rates of the groups

	Mean ± SD	95% CI	p
Only GIST	59.2 ± 4.98	49.56-68.91	**0.005**
GIST plus secondary malignancy	28.2 ± 6.08	16.28-40.10	
Overall	55.8 ± 4.59	46.79-64.80	

SD: Standart deviation, CI: Confidence interval, GIST: Gastrointestinal stromal tumor.

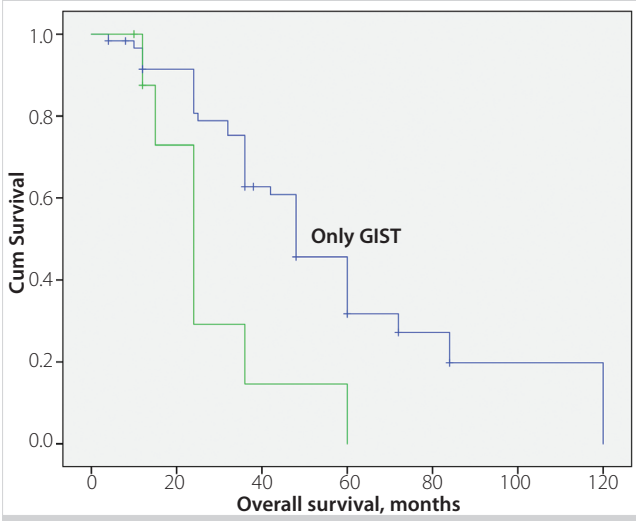

Figure 1. Overall survival rates of patients with only GIST and GIST plus secondary malignancy.

Larger studies with more diverse populations are needed to confirm these results. Second, the retrospective nature of our study may introduce selection bias, third, our study relies on data from a single institution, which may not reflect the broader population. Finally, the lack of longitudinal data limits our ability to assess long-term outcomes and recurrence rates beyond the study period. Future research should aim to address these limitations by including multicenter cohorts and longer follow-up durations.

CONCLUSION

Specifically, we will mention that our sample size is limited and that being a retrospective study may affect the generalizability of the results. Additionally, we recognize that a longer follow-up period and larger sample size would be necessary to fully assess. The frequency of secondary malignancies accompanying GIST is considerable. Furthermore, considering that in such cases the expected lifespan is determined by the presence of secondary malignancy, we recommend preoperative screening for gastrointestinal system malignancies in patients diagnosed with GIST.

Ethics Committee Approval: This study was approved by the İnönü University Scientific Research and Publication Ethics Board Health Sciences Non-Invasive Clinical Research Ethics Board (Decision no: 2023/5189, Date: 14.11.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - CA; Design - YSA; Supervision - CA; Data Collection and/or Processing - KS; Analysis and/or Interpretation - CC; Literature Search - KS; Writing Manuscript - YSA; Critical Reviews - CA.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152(5): 1259-69.*
2. *Mantese G. Gastrointestinal stromal tumor: Epidemiology, diagnosis, and treatment. Curr Opin Gastroenterol 2019; 35(6): 555-9. https://doi.org/10.1097/MOG.0000000000000584*
3. *West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol 2004 ;165(1): 107-13. https://doi.org/10.1016/S0002-9440(10)63279-8*
4. *Joensuu H, Eriksson M, Sundby Hall K, Reichardt A, Hermes B, Schütte J, et al. Survival outcomes associated with 3 years vs 1 year of adjuvant imatinib for patients with high-risk gastrointestinal stromal tumors: An analysis of a randomized clinical trial after 10-year follow-up. JAMA Oncol 2020; 6(8): 1241-6. https://doi.org/10.1001/jamaoncol.2020.2091*
5. *Joensuu H, Eriksson M, Sundby Hall K, Reichardt A, Hartmann JT, Pink D, et al. Adjuvant imatinib for high-risk GI stromal tumor: Analysis of a randomized trial. J Clin Oncol 2016; 34(3): 244-50. https://doi.org/10.1200/JCO.2015.62.9170*
6. *Agaimy A, Wünsch PH, Sobin LH, Lasota J, Miettinen M. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. Semin Diagn Pathol 2006; 23(2): 120-9. https://doi.org/10.1053/j.semdp.2006.09.004*
7. *Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008; 39(10): 1411-9. https://doi.org/10.1016/j.humpath.2008.06.025*
8. *Jang SH, Kwon JE, Kim JH, Lee JY, Kim SG, Kim JS, et al. Prediction of tumor recurrence in patients with non-gastric gastrointestinal stromal tumors following resection according to the modified National Institutes of Health criteria. Intest Res 2014; 12(3): 229-35. https://doi.org/10.5217/ir.2014.12.3.229*
9. *Diamantis A, Bouliaris K, Christodoulidis G, Vasdeki D, Perivoliotis K, Tepetes K. Gastrointestinal stromal tumors and synchronous intra-abdominal malignancies: Review of the literature. J BUON 2018; 23(6): 1573-9.*

10. Petrelli F, Tomasello G, Barni S, Varricchio A, Costanzo A, Rampulla V, et al. Risk of second primary tumors in GIST survivors: A systematic review and meta-analysis. Surg Oncol 2019; 29: 64-70. https://doi.org/10.1016/j.suronc.2019.03.001

11. Kawanowa K, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, Saito K, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006; 37(12): 1527-35. https://doi.org/10.1016/j.humpath.2006.07.002

12. Cohen A, Geller SA, Horowitz I, Toth LS, Werther JL. Experimental models for gastric leiomyosarcoma. The effects of N-methyl-N'-nitro-N-nitrosoguanidine in combination with stress, aspirin, or sodium taurocholate. Cancer 1984; 53(5): 1088-92. https://doi.org/10.1002/1097-0142(19840301)53:5<1088::AID-CNCR2820530512>3.0.CO;2-Y

13. Kaffes A, Hughes L, Hollinshead J, Katelaris P. Synchronous primary adenocarcinoma, mucosa-associated lymphoid tissue lymphoma and a stromal tumor in a Helicobacter pylori-infected stomach. J Gastroenterol Hepatol 2002; 17(9): 1033-6. https://doi.org/10.1046/j.1440-1746.2002.02649.x

14. Maiorana A, Fante R, Maria Cesinaro A, Adriana Fano R. Synchronous occurrence of epithelial and stromal tumors in the stomach: A report of 6 cases. Arch Pathol Lab Med 2000; 124(5): 682-6. https://doi.org/10.5858/2000-124-0682-SOOEAS

15. Ponti G, Luppi G, Martorana D, Rossi G, Losi L, Bertolini F, et al. Gastrointestinal stromal tumor and other primary metachronous or synchronous neoplasms as a suspicion criterion for syndromic setting. Oncol Rep 2010; 23(2): 437-44. https://doi.org/10.3892/or_00000653

16. Shen C, Chen H, Yin Y, Chen J, Han L, Zhang B, et al. Synchronous occurrence of gastrointestinal stromal tumors and other digestive tract malignancies in the elderly. Oncotarget 2015; 6(10): 8397-406. https://doi.org/10.18632/oncotarget.3108

17. Murphy JD, Ma GL, Baumgartner JM, Madlensky L, Burgoyne AM, Tang CM, et al. Increased risk of additional cancers among patients with gastrointestinal stromal tumors: A population-based study. Cancer 2015; 121(17): 2960-7. https://doi.org/10.1002/cncr.29434

18. Du J, Shen N, He HS, Fu XL, Wang JZ, Mao CZ. Synchronous gastrointestinal cancer and gastrointestinal stromal tumors: A single-institution experience. World J Surg Oncol 2016; 14: 130. https://doi.org/10.1186/s12957-016-0882-9

19. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): A review. Eur J Cancer 2002; 38 Suppl 5: S39-51. https://doi.org/10.1016/S0959-8049(02)80602-5

20. Diamantis A, Samara AA, Symeonidis D, Baloyiannis I, Vasdeki D, Tolia M, et al. Gastrointestinal stromal tumors (GISTs) and synchronous intra-abdominal malignancies: Case series of a single institution's experience. Oncotarget 2020; 11(52): 4813-21. https://doi.org/10.18632/oncotarget.27853

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 197-203

Gastrointestinal stromal tümörler ve malignitelerin birlikteliği: 10 yıllık sonuçlarımız

Yavuz Selim Angın, Cengiz Ceylan, Kutay Sağlam, Cemalettin Aydın

İnönü Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Malatya, Türkiye

ÖZET

Giriş ve Amaç: Gastrointestinal stromal tümör (GİST) gastrointestinal sistemde en sık görülen mezenkimal tümörlerden biridir ve sıklıkla epitelyal tümörlerden sonra ortaya çıkar. Nadir de olsa, ikincil epitelyal maligniteler GİST'lerle ilişkili olabilir. GİST'lerin malignitelerle birlikteliğini ve uzun dönem sonuçlarını, klinik ve patolojik bulgularla değerlendiren retrospektif bir kohort çalışması planlandı.

Gereç ve Yöntem: Ocak 2011 ve Kasım 2021 tarihleri arasında GİST nedeniyle ameliyat edilen 69 hastanın demografik ve klinikopatolojik verileri hasta veritabanından alındı. Sadece GİST olan ve GİST ile birlikte ikincil malignitesi olan gruplar arasındaki değişkenler ki-kare testi ve Mann-Whitney U testi kullanılarak analiz edildi. Uzun dönem sağkalım analizleri Kaplan-Meier testi kullanılarak yapıldı. p< 0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Popülasyonumuzdaki 69 hastanın 40'ı (%58) erkekti ve ortanca yaş 65 (çeyrekler arası aralık= 56-75) idi. GİST en sık mide yerleşimliydi (%59,4) ve dokuz hastada (%13) ikincil bir malignite vardı. Tümör boyutu, düz kas antikoru (SMA) ve S100 antikor ekspresyonu gruplar arasında anlamlı farklılıklar gösterdi (p< 0,001, p= 0,015, p= 0,006). GİST artı ikincil malignitesi olan hastalarda daha kısa sağkalım gözlendi (p= 0,005).

Sonuç: GİST ile birlikte diğer intraabdominal malignitelerin görülme sıklığı daha önce düşünülenden daha yaygındır. İkincil bir malignitenin varlığı GİST'lerde genel sağkalımı (OS) etkilemezken, sağkalımın birincil maligniteye bağlı olduğu gözlenmiştir. GİST tanısı konan hastaların ikincil maligniteler açısından kapsamlı bir şekilde araştırılması ve yakından izlenmesi gerekmektedir.

Anahtar Kelimeler: Gastrointestinal stromal tümörler, senkron, klinikopatolojik, prognoz

DOİ: 10.47717/turkjsurg.2024.6389

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 204-211

The role of ergonomics training and posture exercises in surgeons' musculoskeletal system disorders

Sevinç Külekçioğlu[1], Evren Dilektaşlı[2]

[1] Department of Physiotherapy, Mudanya University Faculty of Health Sciences, Bursa, Türkiye
[2] Department of General Surgery, İstinye University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: The surgeon needs to understand the risks involved in performing surgery with ergonomic errors. Although there are many barriers to ergonomic effectiveness, success begins with the surgeon's awareness, recognition of existing obstacles, and education. The main purpose of the study is to evaluate the effect of ergonomic training and posture exercises on the surgeon's pain, physical workload, psychological state, and quality of life to prevent musculoskeletal system disorders and extend career life.

Material and Methods: Surgeons who had completed at least one year in their profession, worked an average of 40 hours a week, had musculoskeletal pain in at least one area, and volunteered to participate in the study, regardless of gender and age, were included in the study. Researchers carried out the ergonomics training and exercise program individually by giving face-to-face training. Surgeons were asked to complete the physical workload questionnaire (PWQ), Beck depression index (BDI), and short form health survey (SF-36) before and one month after the study. Changes in visual analogue scale (VAS) and activities of daily living were recorded.

Results: Surgeons who received ergonomic training and exercise programs showed significant improvements in pain, physical workload, depression, and quality of life measurements.

Conclusion: To prevent fatigue and pain resulting from the accumulation of ergonomic flaws, surgeons should be trained and guided on proper posture and endurance, and encouraged to maintain a comfortable and natural posture.

Keywords: Surgeon, exercise, pain, posture, ergonomic, musculoskeletal system disorders

INTRODUCTION

Worldwide, 23-100% of surgeons in a range of subspecialties report musculoskeletal disorders (MSDs) brought on by poor workplace ergonomics (1,2). Regardless of expertise, this truth applies to all sorts of operations. In addition to mental acuity, attention, and precise movement application, the surgical procedures that surgeons do on a daily basis require them to maintain posture for minutes to hours with extended static effort (1,3). Because the surgical field is fundamentally dynamic and situations may change quickly, surgeons often choose suboptimal, ergonomically constrained postural positions to provide the best possible exposure and access to the surgical field. It is believed that these ergonomic issues result in pain, discomfort, and psychological issues (4,5). Surgeons also indicate that, off the job, MSD brought on by their jobs significantly impacts quality of life, interferes with social and sleep patterns, and makes them want to retire early (6,7). It is critical for the surgeon to realize the hazards of doing surgery with ergonomic mistakes, and although there are several barriers to ergonomic effectiveness, success starts with the surgeon's awareness, knowledge of existing barriers, and training (8). According to reports, as few as 9% of surgeons are aware of official ergonomic guidelines, and only 3% follow them on a regular basis (9). Despite the extensive literature on ergonomic issues, few research has proposed remedies to this problem (2,10,11).

The primary purpose of this study was to evaluate the effects of ergonomics training and posture exercises given to surgeons to prevent MSD and extend their career life on pain, physical workload, psychological state, and quality of life.

MATERIAL and METHODS

This prospective, cross-sectional study was conducted at İstinye University between 01/12/2023-01/02/2024, with the approval received from the Human

Cite this article as: Külekçioğlu S, Dilektaşlı E. The role of ergonomics training and posture exercises in surgeons' musculoskeletal system disorders. Turk J Surg 2024; 40 (3): 204-211.

Corresponding Author
Sevinç Külekçioğlu
E-mail: sevinckulek@gmail.com

Received: 16.04.2024
Accepted: 29.08.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6413

Research Ethics Committee of İstinye University. All procedures were performed in accordance with the principles of the World Medical Association Declaration of Helsinki. Thirty-seven surgeons, regardless of sex and age, who had at least one year of experience, worked an average of forty hours a week, and had musculoskeletal complaints in at least one area, were included in the study. After informing the surgeons who met the inclusion criteria about the study and its purpose, an informed consent form was obtained from those who agreed to participate in the study. Data were collected using survey forms developed based on previously published literature on postural ergonomics in the surgical field. Demographic information, areas where pain is felt, causes of pain, whether pain affects daily life, ergonomics awareness and training status, and visual analog scale (VAS) values in the region where they feel the pain most severely were questioned. The surgeons were asked to complete the physical workload questionnaire (PWQ), Beck depression index (BDI), and quality of life short form 36 (SF-36). Validation of the PWQ Turkish form used in our research was conducted by Kahraman et al. and, to our knowledge, it is the only self-report questionnaire used to evaluate physical workload in Türkiye. In addition to analyzing increased workload due to poor posture and intense effort in the workplace, it can also be used to prevent high-risk work-related tasks. PWQ contains nineteen items describing different work situations (12,13). Five items include trunk posture, three items include arm posture, five items include leg posture, and six items include weightlifting. Scoring is accomplished by summing the responses to each item to create a raw score. Final scores are calculated by dividing the raw score by the maximum possible score on the subscale and multiplying by one hundred.

The BDI, developed by Beck et al., was used to evaluate the psychological states of surgeons (14). The scale, which is used to determine the risk and susceptibility of depression in adults and to measure the severity of depression symptoms, does not diagnose the person with depression, but determines the person's depression level with a numerical data. The Turkish adaptation of the scale consisting of twenty-one items was made by Hisli (15). Each item in the scale is rated between zero and three points. The highest score is sixty-three, and the higher the score, the higher the person's depression level. The severity of depression is interpreted as 0-9= minimal, 10-16= mild, 17-29= moderate, and 30-63= severe.

We used the SF-36 short form survey to collect information about the patient's quality of life and health status (16). This survey evaluates eight sub-parameters: physical functioning (PF), physical role functioning (PRF), emotional role functioning (ERF), energy/vitality (VT), mental health (MH), social functionality (SF), bodily pain (BP) and general health (GH) perception. Each domain has a score ranging from 0 to 100%. Higher scores indicate higher levels of function and well-being. We evaluated the survey results by comparing them with Turkish norms (17).

Ergonomics training and an exercise program were given one-on-one by the physician in the form of face-to-face training. Simple and standardized ergonomic principles were taken from the literature and integrated into existing posture and strengthening exercise guides. The training procedure established regarding ideal working posture, correct monitor and table position, design of hand tools, and placement of equipment was applied to all surgeons. A standard exercise program was created, including neck (extensors, flexors, and rotators), shoulder (flexors, extensors), and upper and lower back (flexors, extensors, and rotators) muscle groups. Exercise training was given by explaining the parts of this program that could be done during surgery and outside of surgery in the work or home environment. Compliance with the program was checked, with checks made once a week. A brochure with images and descriptions was created and distributed to enable the surgeon to independently manage the program after training. After one month, they were asked to fill out the PWQ, BDI, and SF-36 questionnaires again, and the changes were recorded. It was questioned whether there were any changes in VAS and activities of daily living. Thirteen surgeons who did not comply with the procedure were excluded from the study.

Statistical Analysis

In calculating the sample size of this study, the power was determined to be at least 80%, and type-1 error was 5% for each variable. Shapiro-Wilk and Skewness-Kurtosis tests were used to check whether the continuous measurements in the study were distributed normally, and since the measurements were normally distributed, parametric tests were applied. Descriptive statistics for continuous variables in the study were expressed as mean, standard deviation, mean difference, number (n), and percentage (%). "Paired t-test" was used to compare the changes between "before and after" measurements. The McNemar test was calculated to determine the relationships between (before-after) ratios measured at various times in the same patients. In the calculations, the statistical significance level was taken as $p< 0.05$, and the SPSS (IBM SPSS for Windows, ver. 26) statistical package program was used for analyses.

RESULTS

Twenty-four surgeons from different surgical departments completed the study. Demographic characteristics are shown in Table 1, and the distribution of risk factors for MSD is shown in Table 2. Seventy percent of the surgeons stated that they had difficulty in daily life activities due to MSD, and 87.5% stated that ergonomic improvements needed to be made in the

Table 1. Demographic characteristics of the surgeons

		n	%
Sex	Female	6	25.0%
	Male	18	75.0%
		Mean	**SD**
	Age	49.17	8.83
	Height (cm)	173.25	6.77
	Weight (kg)	77.54	13.86

SD: Standard deviation, cm: Centimeter, kg: Kilogram.

Table 2. Risk factors of musculoskeletal symptoms among the study participants

	n	%
Bad position	21	87.5%
Bad posture	18	75.0%
Lean forward too much	14	58.3%
Standing for a long time	12	50.0%
Stand still	9	37.5%
Stress	7	29.2%
Temperature of the operating room environment	7	29.2%
Table height	7	29.2%
Used materials	7	25.0%
Insufficient equipment	6	20.8%
Monitor position	5	20.8%

operating room. Of the surgeons, 95.8% had not received any ergonomics training. The distribution of the regions with MSD before and after the study is shown in Table 3. After the program, the decrease in pain in the neck, back, and waist, which are the most frequently painful areas, was found to be statistically significant. Despite that, no statistically significant relationship was observed between the ratios of the patients' shoulder, leg, and hand variables measured at two separate times. Since the classifications of the patients' elbow, knee, hip, and foot variables, which were measured at two separate times, were not determined in some periods, the relationships between these variables could not be calculated. The changes in VAS, PWQ, BDI, and SF-36 values of the surgeons before and one month after the program are statistically significant and are shown in Table 4.

DISCUSSION

In our study, we evaluated the effects of ergonomic training and posture exercises on pain, physical workload, psychological state, and quality of life. Consistent with the literature, we found that MSDs are most commonly seen in the neck, upper back, and waist, and the most blamed factors are poor posture, inappropriate body positions, and working leaning forward for extended periods of time (1,2,10,11,18). The prevalence of MSD in surgeons also highlights the need for prevention. Ergonomics training is essential to protect surgeons from preventable, potentially career-changing, or even career-ending injuries. Although many surgeons seek medical treatment for MSD and modify their practices based on pain, they are not adequately trained. In studies, the rate of surgeons receiving ergonomics training varies between 1.5% and 16% (19-21). In our study, this rate was found to be 4.1%. Additionally, it has been reported that most surgeons receiving ergonomics training do not comply with these guidelines (9). In our study, it was determined that only half of the surgeons complied with the instructions. Forgetting and lack of time are the main reasons for not being able to adapt to the training program and exercises, which suggests that ergonomics and postural awareness should be the focus of surgical training from an early age. Poor posture can lead to muscle imbalances over time. It can cause one muscle group to repeatedly shorten and another muscle group to lengthen. In addition, no matter how many surgeons focus on ergonomics, posture problems will continue to occur in the operating room due to the nature of their work. In this context, exercises performed in and outside the operating room are thought to make a critical contribution to ergonomics to

Table 3. Distribution of pain regions

	n	%	*p
Neck 1	22	91.7%	.001
Neck 2	10	41.7%	
Upper back 1	21	87.5%	.016
Upper back 2	14	58.3%	
Back 1	10	41.7%	.008
Back 2	2	8.3%	
Shoulder 1	8	33.3%	.125
Shoulder 2	4	16.7%	
Leg 1	5	20.8%	.125
Leg 2	1	4.2%	
Hand 1	4	16.7%	.510
Hand 2	2	8.3%	
Elbow 1	2	8.3%	
Elbow 2			
Knee 1	1	4.2%	
Knee 2			
Hip 1	2	8.3%	
Hip 2			
Foot 1			
Foot 2			

prevent and reverse musculoskeletal problems. The exercises are aimed at improving postural imbalances, reducing musculoskeletal pain, and eliminating the negative impact of the operating room. Strength training and stretching exercise protocols have been proven to be effective in reducing neck, back, and waist pain (22-25). Training regimens have been shown to be effective in forward positioning of the head and straightening of the shoulders, which are common in surgeons (26-28,29). There are publications in the literature that reach the common conclusion that regular exercise reduces musculoskeletal pain (23-25,30,31). This claim is also supported in our study.

MSD is the leading cause of workforce loss (32,33). According to the current literature, the main risk factors are heavy lifting, bending the back or working with arms raised, repetitive movements, and vibration (34,35). Studies have shown that surgeons experience physical symptoms due to ergonomic problems, tilting their heads up or down more than 50° for half of the average surgery time, and working in awkward postures due to the nature of the operation (36,37). For these reasons, it is important to evaluate the physical workload in the workplace. In our study, we used PWQ to assess physical workload. To the best of our knowledge, PWQ is the only valid and reliable questionnaire available in Turkish to assess physical workload resulting from body posture and overexertion. Moreover, as far as we know, this is the first time it has been used in a study on the physical workload of surgeons. A significant improvement was detected in surgeons' PWQ scores before and after the training and exercise program, and this result is important in terms of drawing attention to the importance of ergonomics training and exercise programs to reduce the physical workload of surgeons.

It has long been known that doctors are at risk of developing several psychological conditions, such as burnout, stress, anxiety, and depression. The unique pressures of a surgical career, including long, unpredictable hours, the expectation of significant personal sacrifice, and dealing with life-or-death decisions daily, place surgeons at risk for psychological distress (38-40). Accumulated evidence from both observational studies and randomized controlled trials suggests that exercise reduces depressive symptoms and anxiety. In our study, the average Beck depression scale value before the program was 7.8, and the symptoms were found to be compatible with minimal depression. After the program, the mean value of the scale decreased significantly, and it was determined that mild depressive symptoms continued in only one surgeon, and the results were consistent with the literature (40-43).

Table 4. Comparison results of "before-after" values of measurements

	Mean	SD	Difference	t	*p
VAS 1	6.50	1.41	3.36	10.632	.001
VAS 2	3.10	1.48			
Beck 1	7.80	3.84	3.21	8.326	.001
Beck 2	4.60	2.75			
PWQ 1	16.60	6.34	5.51	6.412	.001
PWQ 2	11.10	4.37			
SF PF	73.75	19.46	-9.17	-4.011	.001
SF PF 2	82.90	14.06			
SF PRF	35.80	31.13	-26.74	-7.948	.001
SF PRF 2	62.50	27.58			
SF ERF	40.25	40.48	-18.01	-4.520	.001
SF ERF 2	58.25	31.46			
SF Energy	43.10	20.95	-13.29	-4.655	.001
SF Energy 2	57.25	17.94			
SF MH	55.00	18.57	-8.17	-3.099	.004
SF MH 2	63.20	13.62			
SF SF	49.50	22.87	-15.60	-5.704	.001
SF SF 2	65.10	20.49			
SF Pain	53.23	15.85	-16.48	-6.993	.001
SF Pain 2	69.70	17.11			
SF GS	52.80	20.03	-11.17	-5.376	.001
SF GS 2	63.40	16.68			

VAS: Visual analog scale, PWQ: Physical workload questionnaire, PF: Physical functioning, FRG: Physical role functioning, ERF: Emotional role functioning, MH: Mental health, SF: Social functionality, GS: General health.

The SF-36 is the most frequently used standardized scale with proven validity to evaluate quality of life (16,17). At baseline evaluation, surgeons reported moderate impairment on the physical role, bodily pain, physical role functioning, emotional role functioning, social functioning, mental health, and energy/vitality subscales; however, no impairment was detected at baseline assessments of physical functioning and general health.

This result shows that surgeons experience significant problems regarding their quality of life and personal health. A statistically significant increase was obtained in all parameters in the post-program evaluation. Physical role function, pain, and energy scores also reached the population average. Although the increases were significant, emotional role function, mental health, and social functioning scores were still below the average value. This result suggests that surgeons should also be supported in terms of mental health in addition to physical support programs (exercise and ergonomics training).

Ideally, formal, specialty-specific training in ergonomics, body mechanics, and posture should be provided at the assistant level. We predict that it is important to encourage surgeons to exercise, as well as to ensure that they continue their exercise habits for many years. It is important for surgeons to improve their working hours and make exercise a part of their lives, both for themselves and for their patients. This should be considered a public health problem; therefore, the surgeons and other members of society should be ensured to live together with sports throughout their lives. Thus, musculoskeletal pain, which has been shown to be the most common occupational disease in Europe, will decrease, and the frequency of the need to apply to health services will decrease.

The limitations of this study include the fact that the surgeons are from a single institution, the sample size is small, the follow-up period is short, the use of survey forms and the surgical sub-branches are not evaluated separately.

CONCLUSION

In conclusion, a significant improvement was shown in the pain, physical workload, depression, and quality of life measurement values of surgeons who were given ergonomics

training and exercise programs before and one month after the program. Surgeons should be encouraged to maintain a comfortable and natural body posture, trained, and directed to exercise for correct posture and endurance to avoid the fatigue and pain that accumulate from ergonomic errors. Future focus should be on specialty-specific ergonomics training, postural awareness training, and surgical expertise. We also think that ergonomic training should be accepted as a part of surgical training and that the ergonomic awareness of all individuals receiving surgical competence should be established at an early stage.

Ethics Committee Approval: The study was approved by the İstinye University Human Researches Ethics Committee (Decision no: 2023/09, Date: 06.11.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - ED, SK; Design - SK; Supervision - ED; Fundings - SK; Materials - SK; Data Collection and/or Processing - SK; Analysis and/or Interpretation - ED; Literature Search - SK; Writing Manuscript - SK; Critical Reviews - ED.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Epstein S, Sparer EH, Tran BN, Ruan QZ, Dennerlein JT, Singhal D, et al. Prevalence of work-related musculoskeletal disorders among surgeons and interventionalists: A systematic review and meta-analysis. JAMA Surg 2018; 21: 153-5. https://doi.org/10.1001/jamasurg.2017.4947*
2. *Catanzarite T, Tan-Kim J, Whitcomb EL, Menefee S. Ergonomics in surgery: A review. Female Pelvic Med Reconstr Surg 2018; 24(1): 1-12. https://doi.org/10.1097/SPV.0000000000000456*
3. *Szeto GP, Cheng SW, Poon JT, Ting AC, Tsang RC, Ho P. Surgeons' static posture and movement repetitions in open and laparoscopic surgery. J Surg Res 2012; 172(1): 19-31. https://doi.org/10.1016/j.jss.2011.08.004*
4. *Stucky CH, Cromwell KD, Voss RK, Chiang YJ, Woodman K, Lee JE, et al. Surgeon symptoms, strain, and selections: Systematic review and meta-analysis of surgical ergonomics. Ann Med Surg (Lond) 2018; 27: 1-8. https://doi.org/10.1016/j.amsu.2017.12.013*
5. *Voss RK, Chiang YJ, Cromwell KD, Urbauer DL, Lee JE, Cormier JN, et al. Do no harm, except to ourselves? A survey of symptoms and injuries in oncologic surgeons and pilot study of an intraoperative ergonomic intervention. J Am Coll Surg 2017; 224(1): 16-25.e1. https://doi.org/10.1016/j.jamcollsurg.2016.09.013*
6. *Howarth AL, Hallbeck S, Mahabir RC, Lemaine V, Evans GRD, Noland SS. Work-related musculoskeletal discomfort and injury in microsurgeons. J Reconstr Microsurg 2019; 35(5): 322-8. https://doi.org/10.1055/s-0038-1675177*
7. *Vaisbuch Y, Aaron KA, Moore JM, Vaughan J, Ma Y, Gupta R, et al. Ergonomic hazards in otolaryngology. Laryngoscope 2019; 129(2): 370-6. https://doi.org/10.1002/lary.27496*
8. *Horst N, Krokowicz P. Risk for the operator related to laparoscopic surgery and selected measures of their minimization. Pol Przegl Chir 2011; 83(06): 347-51. https://doi.org/10.2478/v10035-011-0054-0*
9. *Toffola ED, Rodigari A, Di Natali G, Ferrari S, Mazzacane B. Posture, and fatigue among surgeons in the operating room [in Italian] G Ital Med Lav Ergon 2009; 31(04): 414-18.*
10. *Lakhiani C, Fisher SM, Janhofer DE, Song DH. Ergonomics in microsurgery. J Surg Oncol 2018; 118: 840-4. https://doi.org/10.1002/jso.25197*
11. *Fisher SM, Teven CM, Song DH. Ergonomics in the operating room: The cervicospinal health of today's surgeons. Plast Reconstr Surg 2018; 142: 1380-7. https://doi.org/10.1097/PRS.0000000000004923*
12. *Kahraman T, Göz E, Genç A. Validity and reliability of the Turkish version of the Physical Workload Questionnaire. Work 2018; 59(2): 295-302. https://doi.org/10.3233/WOR-172670*
13. *Hollmann S, Klimmer F, Schmidt KH, Kylian H. Validation of a questionnaire for assessing physical workload. Scand J Work Environ Health 1999; 25: 105-14. https://doi.org/10.5271/sjweh.412*
14. *Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arc Gen Psychiatry 1961; 4: 561-71. https://doi.org/10.1001/archpsyc.1961.01710120031004*
15. *Hisli N. A reliability and validity study of Beck depression inventory in a university student sample. J Psychol 1989; 7: 3-13.*
16. *Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000; 25(24): 3130-9. https://doi.org/10.1097/00007632-200012150-00008*
17. *Demiral Y, Ergor G, Unal B, Semin S, Akvardar Y, Kivircik B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. BMC Public Health 2006: 6: 247. https://doi.org/10.1186/1471-2458-6-247*
18. *Khansa I, Khansa L, Westvik TS, Ahmad J, Lista F, Janis JE. Work-related musculoskeletal injuries in plastic surgeons in the United States, Canada, and Norway. Plast Reconstr Surg 2018; 141(1): 165-75. https://doi.org/10.1097/PRS.0000000000003961*
19. *Franasiak J, Ko EM, Kidd J, Secord AA, Bell M, Boggess JF, et al. Physical strain and urgent need for ergonomic training among gynecologic oncologists who perform minimally invasive surgery. Gynecol Oncol 2012; 126(3): 437-42. https://doi.org/10.1016/j.ygyno.2012.05.016*
20. *Wauben LS, Van Veelen MA, Gossot D, Goossens RH. Application of ergonomic guidelines during minimally invasive surgery: A questionnaire survey of 284 surgeons. Surg Endosc 2006; 20(8): 1268-74. https://doi.org/10.1007/s00464-005-0647-y*
21. *Epstein S, Tran BN, Capone AC, Ruan QZ, Fukudome EY, Ricci JA, et al. The current state of surgical ergonomics education in U.S. surgical training: A survey study. Ann Surg 2019; 269: 778-84. https://doi.org/10.1097/SLA.0000000000002592*
22. *Jay K, Jakobsen MD, Sundstrup E, Skotte JH, Jørgensen MB, Andersen CH, et al. Effects of kettlebell training on postural coordination and jump performance: A randomized controlled trial. J Strength Cond 2013; 27: 1202-9. https://doi.org/10.1519/JSC.0b013e318267a1aa*
23. *Booth J, Moseley GL, Schiltenwolf M, Cashin A, Davies M, Hübscher M. Exercise for chronic musculoskeletal pain: A biopsychosocial approach. Musculoskeletal Care 2017; 15: 413-21. https://doi.org/10.1002/msc.1191*
24. *Jakobsen MD, Sundstrup E, Brandt M, Jay K, Aagaard P, Andersen LL. Effect of workplace-versus home-based physical exercise on musculoskeletal pain among healthcare workers: A cluster randomized controlled trial. Scand J Work Environ Health 2015; 41: 153-63. https://doi.org/10.5271/sjweh.3479*

25. *Kim D, Cho M, Park Y, Yang Y. Effect of an exercise program for posture correction on musculoskeletal pain. J Phys Ther Sci 2015; 27: 1791-4. https://doi.org/10.1589/jpts.27.1791*
26. *Gupta BD, Aggarwal S, Gupta B, Gupta M, Gupta N. Effect of deep cervical flexor training vs. conventional isometric training on forward head posture, pain, neck disability index in dentists suffering from chronic neck pain. J Clin Diagn Res 2013; 7: 2261-4. https://doi.org/10.7860/JCDR/2013/6072.3487*
27. *Ruivo RM, Carita AI, Pezarat-Correia P. The effects of training and detraining after an 8 month resistance and stretching training program on forward head and protracted shoulder postures in adolescents: Randomized controlled study. Man Ther 2016; 21: 76-82. https://doi.org/10.1016/j.math.2015.05.001*
28. *Lynch SS, Thigpen CA, Mihalik JP, Prentice WE, Padua D. The effects of an exercise intervention on forward head and rounded shoulder postures in elite swimmers. Br J Sports Med 2010; 44: 376-81. https://doi.org/10.1136/bjsm.2009.066837*
29. *Adams SR, Hacker MR, McKinney JL, Elkadry EA, Rosenblatt PL. Musculoskeletal pain in gynecologic surgeons. J Minim Invasive Gynecol 2013; 20: 656-60. https://doi.org/10.1016/j.jmig.2013.04.013*
30. *Molina-Garcia P, Mora-Gonzalez J, Migueles JH, Rodriguez-Ayllon M, Esteban-Cornejo I, Cadenas-Sanchez C, et al. Effects of exercise on body posture, functional movement, and physical fitness in children with overweight/obesity. J Strength Cond Res 2020; 34: 2146-55. https://doi.org/10.1519/JSC.0000000000003655*
31. *Vranešić Hadžimehmedović D, Bajramović I, Likić S, Tabaković M, Imamović D. Effects of four-month exercise program on correction of body posture of persons with different visual impairment. J Anthr Sport Phys Educ 2018; 2: 15-8. https://doi.org/10.26773/jaspe.180403*
32. *Shanafelt TD, Sloan JA, Haberman TM. The well-being of physicians. Am J Med 2003; 114 (6): 513-9. https://doi.org/10.1016/S0002-9343(03)00117-7*
33. *Balch CM. Stress and burnout among surgeons. Arch Surg 2009; 144(4): 371. https://doi.org/10.1001/archsurg.2008.575*
34. *Choi KW, Zheutlin AB, Karlson RA, Wang MJ, Dunn EC, Stein MB, et al. Physical activity offsets genetic risk for incident depression assessed via electronic health records in a biobank cohort study. Depress Anxiety 2020; 37(2): 106-14. https://doi.org/10.1002/da.22967*
35. *Mayer J, Kraus T, Ochsmann E. Longitudinal evidence for the association between work-related physical exposures and neck and/or shoulder complaints: A systematic review. Int Arch Occup Environ Health 2012; 85(6): 587-603. https://doi.org/10.1007/s00420-011-0701-0*
36. *Fan X, Forsman M, Yang L, Lind CM, Magnus Kjellman M. Surgeons' physical workload in open surgery versus robot-assisted surgery and nonsurgical tasks. Surger Endos 2022; 36(11): 8178-94. https://doi.org/10.1007/s00464-022-09256-0*
37. *Arvidsson I, Dahlqvist C, Enquist H, Nordander C. Action levels for the prevention of work-related musculoskeletal disorders in the neck and upper extremities: A proposal. Ann Work Expo Health 2021; 65: 741-7. https://doi.org/10.1093/annweh/wxab012*
38. *Bang CK, Lund T, Labriola M, Villadsen E, Bültmann U. The fraction of long-term sickness absence attributable to work environmental factors: Prospective results from the Danish work environment cohort study. Occup Environ Med 2007; 64: 487-9. https://doi.org/10.1136/oem.2006.028563*
39. *Griffith LE, Shannon HS, Wells RP, Walter SD, Cole DC, Côté P, et al. Individual participant data meta-analysis of mechanical workplace risk factors and low back pain. Am J Public Health 2012; 102(2): 309-18. https://doi.org/10.2105/AJPH.2011.300343*
40. *Da Costa BR, Vieira ER. Risk factors for work-related musculoskeletal disorders: A systematic review of recent longitudinal studies. Am J Industrial Med 2010; 53: 285-323. https://doi.org/10.1002/ajim.20750*
41. *Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry 2016; 3(2): 171-8. https://doi.org/10.1016/S2215-0366(15)00505-2*
42. *Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, et al. Exercise for depression. Cochrane Database Syst Rev 2013; 2013(9): CD004366. https://doi.org/10.1002/14651858.CD004366.pub6*
43. *Josefsson T, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: Meta-analysis and systematic review. Scand J Med Sci Sports 2014; 24(2): 259-27. https://doi.org/10.1111/sms.12050*

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 204-211

Ergonomi eğitimi ve postür egzersizlerinin cerrahların kas iskelet sistemi rahatsızlıklarındaki rolü

Sevinç Külekçioğlu[1], Evren Dilektaşlı[2]

[1] Mudanya Üniversitesi Sağlık Bilimleri Fakültesi, Fizyoterapi Bölümü, Bursa, Türkiye
[2] İstinye Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Cerrahın ergonomik hatalarla ameliyat yapmanın içerdiği riskleri anlaması gerekir. Ergonomik etkinliğin önünde pek çok engel olsa da başarı, cerrahın farkındalığı, mevcut engelleri tanıması ve eğitimi ile başlar. Çalışmanın temel amacı kas-iskelet sistemi bozukluklarının önlenmesi ve kariyer ömrünün uzatılması için ergonomik antrenman ve postür egzersizlerinin cerrahın ağrısına, fiziksel iş yüküne, psikolojik durumuna ve yaşam kalitesine etkisini değerlendirmektir.

Gereç ve Yöntem: Cinsiyet ve yaş gözetmeksizin mesleğinde en az bir yılını tamamlamış, haftada ortalama 40 saat çalışan, en az bir bölgede kas-iskelet sistemi ağrısı olan, çalışmaya katılmaya gönüllü olan cerrahlar çalışmaya dahil edildi. Araştırmacılar ergonomi eğitimi ve egzersiz programını yüz yüze eğitim vererek bireysel olarak gerçekleştirdiler. Cerrahlardan çalışmadan önce ve çalışmadan bir ay sonra fiziksel iş yükü anketini (PWQ), Beck depresyon endeksini (BDI) ve kısa form sağlık anketini (SF-36) doldurmaları istendi. Görsel analog skala (VAS) ve günlük yaşam aktivitelerindeki değişiklikler kaydedildi.

Bulgular: Ergonomi eğitimi ve egzersiz programları alan cerrahların ağrı, fiziksel iş yükü, depresyon ve yaşam kalitesi ölçümlerinde anlamlı iyileşmeler görüldü.

Sonuç: Ergonomik kusurların birikmesinden kaynaklanan yorgunluk ve ağrıyı önlemek için cerrahlar, doğru duruş ve dayanıklılık konusunda eğitilmeli, yönlendirilmeli, rahat ve doğal bir duruş sürdürmeleri teşvik edilmelidir.

Anahtar Kelimeler: Cerrah, egzersiz, ağrı, duruş, ergonomik, kas-iskelet sistemi bozuklukları

DOİ: 10.47717/turkjsurg.2024.6413

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 212-218

Unveiling molecular clues: Exploring IFNγ, IL-10, and MMP7 blood levels in gastric carcinoma patients

Ajith Atul[1], Thirthar Palanivelu Elamurugan[1], Sundaramurthi Sudharsanan[1], Chellappa Vijayakumar[1], Gubbi Shamanna Sreenath[1], Vairappan Balasubramaniyan[2]

[1] Department of Surgery, Jawaharlal Institute of Postgraduation Medical Education and Research (JIPMER), Puducherry, India
[2] Department of Biochemistry, Jawaharlal Institute of Postgraduation Medical Education and Research (JIPMER), Puducherry, India

ABSTRACT

Objective: Gastric carcinoma is a leading cause of morbidity and mortality worldwide. Early detection can help reduce mortality rates. Biomarkers are being investigated globally for their potential in disease screening, monitoring, and follow-up in various cancers. However, currently, there is insufficient data on the role of biomarkers in gastric carcinoma.

Material and Methods: This single center case control study was conducted from June 2018 to March 2021 from South India. Blood samples were collected from 85 patients diagnosed with gastric carcinoma and 85 apparently healthy individuals serving as the control group. The samples were collected in a fasting state. The serum levels of biomarkers interferon gamma (IFNγ), interleukin 10 (IL-10), and matrix metalloproteinase 7 (MMP7) were measured using enzyme-linked immunosorbent assay (ELISA) and compared between the two groups. Additionally, the levels of biomarkers were compared within the gastric cancer group based on disease location, stage, and histotype.

Results: The serum levels of IFNγ and IL-10 were found to be significantly elevated in gastric carcinoma patients compared to the healthy control group. Both biomarkers exhibited high sensitivity and specificity in detecting carcinoma of the stomach. However, there was no significant difference in the serum level of MMP7 between gastric cancer patients and control group.

Conclusion: IFNγ and IL-10 show promise as potential molecular biomarkers for the detection of gastric carcinoma. Further, well designed studies, involving larger and more diverse populations matched for stage and histological types, are necessary to establish the screening and monitoring utility of these biomarkers in gastric carcinoma.

Keywords: Matrix metalloproteinase 7, interferon gamma, interleukin 10, enzyme-linked immunosorbent assay, gastric cancer, screening

INTRODUCTION

According to Global Cancer Statistics (GLOBACON) 2020, gastric cancer ranks as the fifth most common cancer worldwide and the fourth leading cause of cancer-related mortality. The current annual burden of gastric cancer amounts to approximately 1.1 million new cases per year and is expected to rise to 1.8 million per year by 2040 (1). However, the diagnosis of early-stage gastric carcinoma remains below 20% of cases, which results in poor prognosis and overall survival (2). To reduce disease burden, early detection and efficient monitoring of gastric carcinoma are crucial, necessitating the identification of novel screening, monitoring, and prognostic tools such as biomarkers.

The tumor microenvironment encompasses a variety of cells and inflammatory mediators, each exhibiting unique patterns in different tumors. These mediators can be detected and measured in peripheral plasma, offering potential for tumor detection and monitoring. Inflammatory molecules play a significant role in immune responses, chronic inflammation, tissue injury, and the development of cancer, invasion, and metastasis. The balance between pro-inflammatory and anti-inflammatory chemical mediators influence tumor growth (3).

Interferon gamma (IFNγ) is an important inflammatory mediator within the cancer microenvironment, released by invading immune cells. The role of IFNγ in gastric carcinogenesis remains controversial as it has been associated with both pro-carcinogenic and anti-carcinogenic properties (4). Interleukin 10 (IL-10) is an anti-inflammatory molecule produced by tumor infiltrating B lymphocytes, Th2 cells, macrophages, and tumor cells. Like IFNγ, IL-10 has been found to exhibit both tumor-supportive and tumor-inhibitory roles within the cancer microenvironment (5).

Cite this article as: Atul A, Elamurugan TP, Sudharsanan S, Vijayakumar C, Sreenath GS, Balasubramaniyan V. Unveiling molecular clues: Exploring IFNγ, IL-10, and MMP7 blood levels in gastric carcinoma patients. Turk J Surg 2024; 40 (3): 212-218.

Corresponding Author
Gubbi Shamanna Sreenath
E-mail: dr.sreenathgs@gmail.com

Received: 22.04.2024
Accepted: 29.08.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6421

Some recent studies, including one conducted by Shokrzadeh et. al., suggest that there may be an increase in serum levels of IL-10 and IFNγ, potentially indicating their usefulness as diagnostic markers for early detection of gastric carcinoma (6). Matrix metalloproteinase 7 (MMP7) is an enzyme known for its involvement in tumorigenesis, metastasis, and inflammatory processes through the remodeling of extracellular matrix components.

Limited studies have been conducted in the Indian subcontinent involving the serum levels of IFNγ, IL-10, and MMP7 in gastric carcinoma patients (7-11). The significance of these biomarkers in gastric carcinoma is yet to be confirmed with larger and more diverse populations. In this study, we assessed the circulating levels in blood of three important biomolecules IFNγ, IL-10, and MMP7 in gastric carcinoma patients and compared them with their levels in an apparently healthy control population.

MATERIAL and METHODS

The project received approval from the Institutional Ethics Committee in 2018, and the study was conducted from June 2018 to March 2021 in a tertiary care centre from South India.

Study Population and Sampling

The sample size was calculated using OPENEPI software for unmatched case-control studies with proportions, considering a 10% dropout rate, 80% power, and 95% confidence interval. Fasting blood samples were collected from 85 patients diagnosed with gastric carcinoma before treatment and 85 volunteers as controls. All participants were aged 18 years or older and provided informed consent to participate in the study. Venous blood samples of 5 mL were collected, centrifuged, and stored at -80°C until analysis.

Biomarker Analysis

The samples were processed using commercially available enzyme linked immunosorbent assay (ELISA) kits to assess the levels of the selected biomarkers, following the methodology provided in the respective user manuals. IL-10 levels were assessed using the Diaclone IL-10 ELISA kit. IFNγ levels were assessed using the fine test human IFNγ ELISA kit. MMP7 levels were assessed using the human matrix metalloproteinase-7 ELISA kit from Bioassay Technology Laboratories.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software version 20.0 for Windows. A few extreme outlier values were excluded from the study as they were due to ELISA well defects. Demographic data was compared and analysed using unpaired t-test for age and Chi-square test for gender. The serum levels of biomarkers were expressed in their respective quantitative units and compared using the Mann-Whitney U test. The variation of biomarkers based on the stage of the disease, location, and histology was calculated, and analysed using the Kruskal-Wallis and Mann-Whitney U tests.

RESULTS

A total of 170 participants were included (85 in each group) in the study. On comparing the mean age between the groups, it was found that there was a significant difference between age; however, the difference in proportion of sex between the groups was not significant. Half of the study patients presented with abdominal pain (Table 1). The statistical difference between the median values of IFNγ and IL-10 (not MMP7 levels) in these two groups were found to be significant ($p< 0.001$) (Table 2). Statistical significance of individual biomarker level difference between the stages of gastric carcinoma was found to be statistically insignificant (Table 3).

Table 1. Comparison of demographic data between gastric carcinoma patients cases and controls

Parameters		Cases, n= 85	Controls, n= 85	Significance* (p)
Age (years)	Mean	54.45	44.92	<0.001[a]
	Standard deviation	12.02	15.06	
Sex	Male (%)	64.7	52.9	0.07[b]
	Female (%)	35.3	47.1	
Symptoms	Presenting symptoms		Patients presented (%)	
	Abdominal pain		56.47	
	Vomiting		41.17	
	Distension		15.29	
	Hematemesis or melaena		5.8	
	Regurgitation		3.5	
	Others		18.82	

*p< 0.05 is considered significant; a: Unpaired t-test; b: Chi-square test.

Table 2. Comparison of biomarker levels in patients and controls

Biomarker	Cases M (IQR)	Control M (IQR)	p (*)
IFNγ (pg/mL)	9.6 (9.2-10.8)	6.4 (6.0-7.6)	<0.001
IL-10 (pg/mL)	12.1 (9.2-18.0)	3.9 (3.3-5)	<0.001
MMP7 (ng/mL)	0.7 (0.5-1.2)	0.8 (0.6-1.2)	0.188

*Statistical significance was determined by Mann-Whitney U test.
M (IQR): Median with inter quarter range.
IFNγ: Interferon gamma, IL-10: Interleukin 10, MMP7: Matrix metalloproteinase 7.

Table 3. Comparison of serum levels of biomarkers in different stages, locations and histotypes of gastric cancer

Parameters		IFNγ [M (IQR)] (pg/mL)	IL-10 [M (IQR)] (pg/mL)	MMP7 [M (IQR)] (pg/mL)
Stage	Early	11.42 (9.62 to 11.57)	13.8 (12.3 to 18.2)	1.21 (0.55 to 1.31)
	Locally advanced	9.6 (9.2 to 10.5)	11.2 (8.4 to 14.3)	0.73 (0.47 to 1.13)
	Metastatic	9.5 (9.2 to 9.8)	13.4 (9.1 to 17.8)	0.9 (0.43 to 1.29)
	P value[a]	0.75	0.46	0.88
Site	Proximal	9.3 (9.2 to 10.0)	10.4 (9.5 to 13.8)	0.7 (0.4 to 1)
	Distal	9.7 (9.2 to 10.8)	12.2 (9.3 to 15.8)	0.7 (0.5 to 1.1)
	Body	9.5 (9.1 to 10)	9.4 (5.3 to 13.3)	0.6 (0.3 to 0.7)
	P value[b]	0.5	0.22	0.33
Histology	Diffuse adenocarcinoma	9.5 (9.0 to 10.2)	11.3 (8.4 to 17.1)	0.85 (0.58 to 1.21)
	Intestinal adenocarcinoma	9.6 (9.2 to 10.8)	11.7 (9.3 to 14.8)	0.7 (0.38 to 1.16)
	p value[c]	0.39	0.69	0.08

M (IQR): Median with inter quarter range; a: Kruskal Wallis test; b: Kruskal Wallis test; c: Mann-Whitney U test. IFNγ: Interferon gamma, IL-10: Interleukin 10, MMP7: Matrix metalloproteinase 7.

It also showed the variation in serum levels of biomarkers according to the histology of gastric cancer. Statistical significance was not established when the biomarker values were compared between diffuse and intestinal types of adenocarcinoma. Other variants like GIST and lymphoma were not compared as their frequency in the data was too less to compare.

ROC Curve for Interleukin 10

A point of maximum sensitivity 86% (85.9%) and specificity 88% (88.2%) was selected as the cut-off point for IL-10 level, which corresponds to the serum level of 7.73 pg/mL and the area under curve was 0.9. This implied that IL-10 level at 7.73 pg/mL can classify the population into gastric carcinoma patients and healthy population with high accuracy (Figure 1).

ROC Plot for Interferon Gamma

A point of 95% (95.3%) sensitivity and 81% (81.2%) specificity was selected, which corresponds to serum level of 8.7 pg/mL as the cut off value and the area under curve was 0.9. This implied that IL-10 level at 8.7 pg/mL can classify population into gastric carcinoma patients and healthy population with high accuracy (Figure 2).

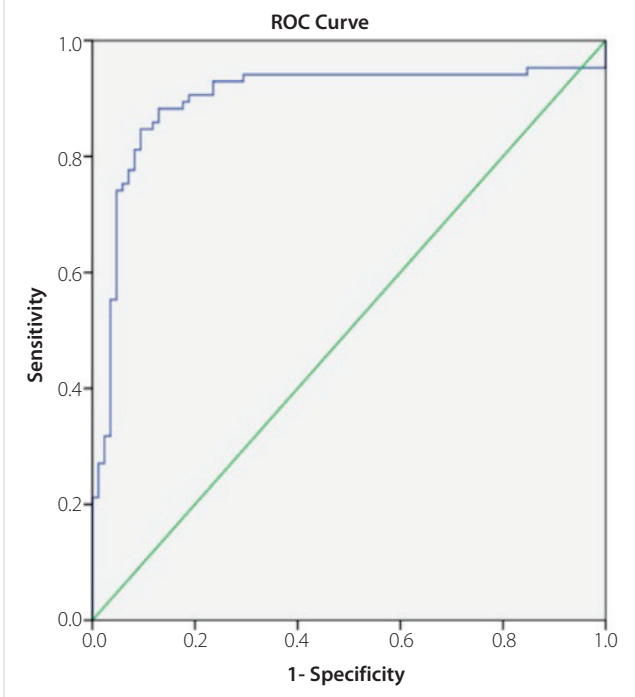

Figure 1. ROC curve for IL-10.

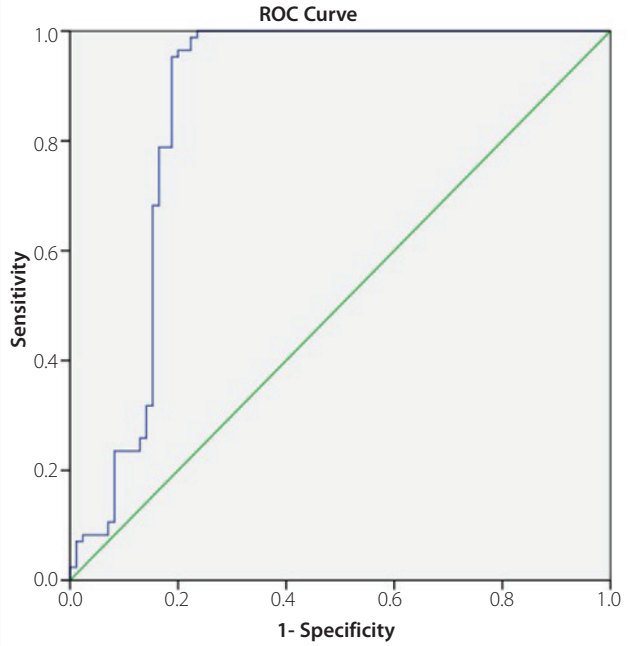

Figure 2. ROC curve for IFNγ.

DISCUSSION

Despite numerous research efforts and advancements, late-stage diagnosis remains a hindrance to the prognosis of gastric carcinoma in most cases. In developed countries like Japan and Korea, pre-emptive screening using upper gastrointestinal endoscopy has proven to enhance survival rates through early detection. However, the feasibility of implementing such screening programs on a day-to-day basis in developing countries is questionable. Ongoing studies aim to discover affordable and economical screening, diagnostic, monitoring, and prognostic tools for gastric carcinoma. Biomarkers play a crucial role in tumor management, overcoming the limitations of invasive, technically demanding, and expensive monitoring tools currently in use. Various biomarkers are being studied worldwide for their potential application in gastric carcinoma.

In our study, the average age of gastric carcinoma patients was found to be 54 years, which aligns with similar studies conducted in South India (average age of 60 years) and Eastern India (average age of 55 years) (8,9). The male-to-female ratio among gastric carcinoma patients in our study was 1.83:1. Comparable male predominance ratios have been observed in the northeastern population of India (2.16:1) and in other Indian studies (2:1) (10,11). A recent study reported a male predominance ratio of 2.2:1 worldwide for gastric carcinoma (12). Similar trends were observed in Korean patients younger than 45 years (13). This difference in sex difference may be attributed to the protective effects of female hormones as well as higher exposure to environmental agents like tobacco and alcohol in males (14,15).

Abdominal pain was the most common symptom reported by 56% of the gastric carcinoma patients in our study, followed by vomiting (41%), weight loss (10%), abdominal distension (15%), bleeding manifestations (6%), and regurgitation (3.5%). Similar studies have reported abdominal discomfort, pain, and anorexia as the most common presenting symptoms in gastric carcinoma patients (8,11).

Regarding tumor location, 15% of the patients in our study had proximal gastric cancer (fundus and cardia growths), 14% had cancer of the body of the stomach, and 71% had distal stomach carcinoma (antrum and pylorus growths). Other Indian studies have also shown that distal stomach is the most common location for gastric carcinoma (9,10). However, a Chinese analysis has reported a higher prevalence of gastric cardia tumors in their study population (16).

At presentation, 74% of the patients in our study had locally advanced gastric carcinoma, 20% had metastasis, and only 6% presented in the early stage. Similar findings have been reported by other studies, suggesting that late-stage presentation of gastric carcinoma is a common occurrence due to symptoms developing as the disease progresses and limited access to advanced healthcare and diagnostic tools in developing countries (10,16-18). Adenocarcinoma accounted for 92% of the gastric carcinoma cases in our study, with 41% classified as diffuse type and 59% as intestinal type. Other studies have also observed a higher frequency of intestinal type adenocarcinoma in gastric cancer patients (19,20). However, contrasting results have been reported in different populations, indicating that the prevalence of adenocarcinoma types may vary in different regions (21).

Helicobacter pylori and T cell inflammatory reactions can increase IFNγ in the gastric mucosa, leading to high serum IFNγ levels in gastric cancer patients (7,22,23). In our study, a significant rise in serum levels of IFNγ was observed in gastric carcinoma cases compared to controls. It is not clear if this increase is related to EBV or *H. pylori* infections (24,25). However, conflicting results have been reported by other studies, with some showing decreased levels of IFNγ in gastric cancer patients compared to healthy controls (26). Nonetheless, our study found a high sensitivity of 95% and specificity of 81% for IFNγ at a level of 8.7 pg/mL in differentiating gastric carcinoma patients from controls. Similarly, our study revealed higher serum levels of IL-10 in gastric carcinoma patients compared to controls. Similar trends have been reported by other studies emerging from India and other countries with average IL-10 levels ranging from 16-27 pg/mL in gastric carcinoma patients (6,23,27,28). A high sensitivity of 86% and specificity of 88% at a level of 8.7 pg/mL were observed for IL-10 in our study. The high sensitivity and specificity observed for IL-10 (86% sensitivity; 88% specificity) and IFNγ (95% sensitivity; 81%

specificity) support their utility in differentiating gastric carcinoma patients. This is in line with the proposed utility of IFNγ and IL-10 by Sánchez-Zauco et al. (22). Comparison of IL-10 and IFNγ values among different tumor locations, histological types, and stages of gastric carcinoma in our study did not yield statistically significant differences. However, further studies with larger sample sizes are needed to conclusively determine the significance of these biomarkers according to these variables.

MMP7 levels were analyzed in our study, but no significant relationship could be established between gastric carcinoma patients and controls. Contrasting results have been reported in other studies, with high MMP7 levels associated with poor prognosis in gastric carcinoma patients in some analyses (29-31). On the other hand, one study even observed immunonegative staining for MMP7 in majority of gastric cancer patients (32). Genetic polymorphism of the MMP7 gene and genotypic influences on its expression may contribute to the variability in results.

CONCLUSION

The introduction of novel biomarkers and the exploration of the tumor microenvironment have opened up a wide scope for early diagnosis and treatment approaches for numerous diseases, including gastric carcinoma. Our study has revealed higher serum levels of IFNγ and IL-10 in gastric carcinoma, suggesting the potential utility of these biomarkers for screening and monitoring gastric carcinoma patients. Further studies involving larger and more heterogeneous populations can help establish the effectiveness of these biomarkers in the management of gastric carcinoma.

Ethics Committee Approval: The study was approved by the Jawaharlal Institute of Postgraduate Medical Education Research Institutional Ethics Committee (Human Studies) (Decision no: JIP/IEC/2018/0215 Date: 23.05.2018).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - SGS; Design - AA, SGS; Materials - AA, CV, SS; Data Collection and/or Processing - AA; Analysis and/or Interpretation - TPE, BV; Literature Search - AA, CV, SS; Writing Manuscript - AA; Critical Reviews - SGS, BV, TPE.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was supported by Intramural Research Grant received from Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER).

REFERENCES

1. *Zhang X, Li M, Chen S, Hu J, Guo Q, Liu R, et al. Endoscopic screening in Asian countries is associated with reduced gastric cancer mortality: A meta-analysis and systematic review. Gastroenterology 2018; 155: 347-54.e9. https://doi: 10.1053/j.gastro.2018.04.026.*
2. *Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020-40: A population-based modelling study. E Clinical Medicine 2022; 47: 101404. https://doi.org/10.1016/j.eclinm.2022.101404*
3. *Căinap C, Nagy V, Gherman A, Cetean S, Laszlo I, Constantin AM, et al. Classic tumor markers in gastric cancer. Current standards and limitations. Clujul Med 2015; 88(2): 111-5. https://doi.org/10.15386/cjmed-409*
4. *Kumar S, Kumari N, Mittal RD, Mohindra S, Ghoshal UC. Association between pro-(IL-8) and anti-inflammatory (IL-10) cytokine variants and their serum levels and H. pylori-related gastric carcinogenesis in northern India. Meta Gene 2015; 6: 9-16. https://doi.org/10.1016/j.mgene.2015.07.008*
5. *Ni L, Lu J. Interferon gamma in cancer immunotherapy. Cancer Med 2018; 7: 4509-16. https://doi.org/10.1002/cam4.1700*
6. *Shokrzadeh M, Mohammadpour A, Hoseini V, Abediankenari S, Ghassemi-Barghi N, Tabari YS. Serum cytokine of il-2, il-10 and il-12 levels in patients with stomach adenocarcinoma. Arq Gastroenterol 2018; 55: 385-9. https://doi.org/10.1590/s0004-2803.201800000-83*
7. *Sánchez-Zauco N, Torres J, Gómez A, Camorlinga-Ponce M, Muñoz-Pérez L, Herrera-Goepfert R, et al. Circulating blood levels of IL-6, IFN-γ, and IL-10 as potential diagnostic biomarkers in gastric cancer: A controlled study. BMC Cancer 2017; 17: 384. https://doi.org/10.1186/s12885-017-3310-9*
8. *Matsuoka T, Yashiro M. Biomarkers of gastric cancer: Current topics and future perspective. World J Gastroenterol. 2018; 24(26): 2818-32. https://doi.org/10.3748/wjg.v24.i26.2818.*
9. *Saha AK, Maitra S, Hazra SC. Epidemiology of gastric cancer in the gangetic areas of west bengal. ISRN Gastroenterol 2013; 2013: 823483. https://doi.org/10.1155/2013/823483*
10. *Barad AK, Mandal SK, Harsha HS, Sharma BM, Singh TS. Gastric cancer-a clinicopathological study in a tertiary care centre of North-eastern India. J Gastrointest Oncol 2014; 5: 142-7.*
11. *Chand A, Malhotra P, Barall D, Singh S, Thapa G. Clinico-pathological presentation of gastric carcinoma and its relation to the anatomical site of occurrence among patients in the hilly state of Himachal Pradesh, India. Int Surg J 2019; 6: 2119-25. https://doi.org/10.18203/2349-2902.isj20192378*
12. *Rawla P, Barsouk A. Epidemiology of gastric cancer: Global trends, risk factors and prevention. Prz Gastroenterol 2019; 14: 26-38. https://doi.org/10.5114/pg.2018.80001*
13. *Chung HW, Noh SH, Lim JB. Analysis of demographic characteristics in 3242 young age gastric cancer patients in Korea. World J Gastroenterol 2010; 16: 256-63. https://doi.org/10.3748/wjg.v16.i2.256*
14. *Kim SM, Min BH, Lee J, An JY, Lee JH, Sohn TS, et al. Protective effects of female reproductive factors on lauren intestinal-type gastric adenocarcinoma. Yonsei Med J 2018; 59: 28-34. https://doi.org/10.3349/ymj.2018.59.1.28*
15. *Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. Eur J Cancer 2008; 44: 2397-403. https://doi.org/10.1016/j.ejca.2008.07.031*
16. *Sharma A, Radhakrishnan V. Gastric cancer in India. Indian J Med Paediatr Oncol 2011; 32(1): 12-6. https://doi.org/10.4103/0971-5851.81884*

17. Gong Y, Wang P, Zhu Z, Zhang J, Huang J, Xu H. Clinicopathological characteristics and prognosis of upper gastric cancer patients in China: A 32-Year single-center retrospective clinical study. Gastroenterol Res Pract 2019; 2019: 9248394. https://doi.org/10.1155/2019/9248394

18. Elmajjaoui S, Ismaili N, Zaidi H, Elkacemi H, Hassouni K, Kebdani T, et al. Epidemiological, clinical, pathological, and therapeutic aspects of gastric cancer in Morocco. Clin Cancer Inv J 2014; 3: 3. https://doi.org/10.4103/2278-0513.125770

19. Qiu MZ, Cai MY, Zhang DS, Wang ZQ, Wang DS, Li YH, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. J Transl Med 2013; 11: 58. https://doi.org/10.1186/1479-5876-11-58

20. Safaee A, Moghimi-Dehkordi B, Fatemi SR, Ghiasi S, Pourhoseingholi MA, Zali MR. Clinicopathological features of gastric cancer: A study based on cancer registry data. Iranian J Cancer Prev 2009; 2: 67-70.

21. Rana N, Gosain R, Lemini R, Wang C, Gabriel E, Mohammed T, et al. Socio-demographic disparities in gastric adenocarcinoma: A population-based study. Cancers (Basel) 2020; 12: 157. https://doi.org/10.3390/cancers12010157

22. Sánchez-Zauco N, Torres J, Gómez A, Camorlinga-Ponce M, Muñoz-Pérez L, Herrera-Goepfert R, et al. Circulating blood levels of IL-6, IFN-γ, and IL-10 as potential diagnostic biomarkers in gastric cancer: A controlled study. BMC Cancer 2017; 17: 384. https://doi.org/10.1186/s12885-017-3310-9

23. Epplein M, Xiang YB, Cai Q, Peek RM Jr, Li H, Correa P, et al. Circulating cytokines and gastric cancer risk. Cancer Causes Control 2013; 24: 2245-50. https://doi.org/10.1007/s10552-013-0284-z

24. Cárdenas-Mondragón MG, Torres J, Sánchez-Zauco N, Gómez-Delgado A, Camorlinga-Ponce M, Maldonado-Bernal C, et al. Elevated levels of interferon-γ are associated with high levels of Epstein-barr virus reactivation in patients with the intestinal type of gastric cancer. J Immunol Res 2017; 2017: 7069242. https://doi.org/10.1155/2017/7069242

25. Abdollahi H, Shams S, Zahedi MJ, Darvish Moghadam S, Hayatbakhsh MM, Jafarzadeh A. IL-10, TNF-α and IFN-γ levels in serum and stomach mucosa of helicobacter pylori-infected patients. Iran J Allergy Asthma Immunol 2011; 10: 267-71.

26. Zhao H, Dong N, Liu T, Zhang P, Zheng Y, Yang L, et al. Clinical significance of serum type III interferons in patients with gastric cancer. J Interferon Cytokine Res 2019; 39: 155-63. https://doi.org/10.1089/jir.2018.0119

27. Szaflarska A, Szczepanik A, Siedlar M, Czupryna A, Sierzega M, Popiela T, et al. Preoperative plasma level of IL-10 but not of proinflammatory cytokines is an independent prognostic factor in patients with gastric cancer. Antican Res 2009; 29: 5005-12.

28. Chen L, Shi Y, Zhu X, Guo W, Zhang M, Che Y, et al. IL 10 secreted by cancer associated macrophages regulates proliferation and invasion in gastric cancer cells via c Met/STAT3 signaling. Oncol Rep 2019; 42(2): 595-604. https://doi.org/10.3892/or.2019.7206

29. Soleyman-Jahi S, Nedjat S, Abdirad A, Hoorshad N, Heidari R, Zendehdel K. Prognostic significance of matrix metalloproteinase-7 in gastric cancer survival: A meta-analysis. PLoS One 2015; 10: e0122316. https://doi.org/10.1371/journal.pone.0122316

30. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: The Global Burden of Disease Study 1990-2016. Lancet Oncol 2018; 19: 1289-306.

31. Yeh YC, Sheu BS, Cheng HC, Wang YL, Yang HB, Wu JJ. Elevated serum matrix metalloproteinase-3 and -7 in H. pylori-related gastric cancer can be biomarkers correlating with a poor survival. Dig Dis Sci 2010; 55(6): 1649-57. https://doi.org/10.1007/s10620-009-0926-x

32. Koskensalo S, Mrena J, Wiksten JP, Nordling S, Kokkola A, Hagström J, et al. MMP-7 overexpression is an independent prognostic marker in gastric cancer. Tumour Biol 2010; 31: 149-55. https://doi.org/10.1007/s13277-010-0020-1

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 212-218

Moleküler ipuçlarının ortaya konulması: Mide karsinomu hastalarında IFNγ, IL-10 ve MMP7 kan düzeylerinin araştırılması

Ajith Atul[1], Thirthar Palanivelu Elamurugan[1], Sundaramurthi Sudharsanan[1], Chellappa Vijayakumar[1], Gubbi Shamanna Sreenath[1], Vairappan Balasubramaniyan[2]

[1] Jawaharlal Lisansüstü Tıp Eğitimi ve Araştırma Enstitüsü (JIPMER), Cerrahi Anabilim Dalı, Puducherry, Hindistan
[2] Jawaharlal Lisansüstü Tıp Eğitimi ve Araştırma Enstitüsü (JIPMER), Biyokimya Anabilim Dalı, Puducherry, Hindistan

ÖZET

Giriş ve Amaç: Mide karsinomu dünya çapında morbidite ve mortalitenin önde gelen nedenidir. Erken teşhis ölüm oranlarının azaltılmasına yardımcı olabilir. Biyobelirteçler, çeşitli kanserlerde hastalık taraması, izleme ve takipteki potansiyelleri açısından küresel olarak araştırılmaktadır. Ancak şu anda mide karsinomunda biyobelirteçlerin rolüne ilişkin yeterli veri bulunmamaktadır.

Gereç ve Yöntem: Bu tek merkezli vaka kontrol çalışması Haziran 2018'den Mart 2021'e kadar Güney Hindistan'da gerçekleştirildi. Mide kanseri tanısı alan 85 hastadan ve kontrol grubu olarak görev yapan sağlıklı görünen 85 kişiden kan örnekleri toplandı. Örnekler aç olarak toplandı. İnterferon gama (IFNy), interlökin 10 (IL-10) ve matriks metalloproteinaz 7 (MMP7) biyobelirteçlerinin serum seviyeleri, enzim bağlantılı immünosorbent tahlili (ELISA) kullanılarak ölçüldü ve iki grup arasında karşılaştırıldı. Ek olarak mide kanseri grubunda hastalığın lokasyonu, evresi ve histotipine göre biyobelirteçlerin seviyeleri karşılaştırıldı.

Bulgular: IFNy ve IL-10'un serum seviyelerinin mide karsinomu hastalarında sağlıklı kontrol grubuyla karşılaştırıldığında anlamlı derecede yüksek olduğu bulundu. Bu biyobelirteçlerin her ikisi de mide karsinomunun tespitinde yüksek hassasiyet ve spesifiklik sergiledi. Ancak mide kanseri hastaları ile kontrol grubu arasında serum MMP7 düzeyi açısından anlamlı bir fark yoktu.

Sonuç: IFNy ve IL-10, mide karsinomunun tespiti için potansiyel moleküler biyobelirteçler olarak ümit vericidir. Ayrıca, evre ve histolojik tiplere göre eşleştirilmiş daha büyük ve daha çeşitli popülasyonları içeren iyi tasarlanmış çalışmalar, bu biyobelirteçlerin mide karsinomunda tarama ve izleme yararlılığını belirlemek için gereklidir.

Anahtar Kelimeler: Matris metaloproteinaz 7, interferon gama, interlökin 10, enzime bağlı immünosorbent tahlili, mide kanseri, tarama

DOİ: 10.47717/turkjsurg.2024.6421

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 219-228

Surgical and survival outcomes of cytoreductive surgery alone or with perioperative intraperitoneal chemotherapy in high peritoneal cancer index

Metin Ercan[1], Mehmet Aziret[2], Kerem Karaman[2], Osman Köse[3], Volkan Öter[4], Hakan Yırgın[2], Ahmet Kaya[1], Yavuz Selim Kahraman[1], Elif Köse[5], Erdal Birol Bostancı[4], Orhan Ünal[6]

[1]Department of Surgical Oncology, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[2]Department of Gastroenterological Surgery, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[3]Department of Gynecological Oncology Surgery, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[4]Clinic of Gastroenterological Surgery, University of Health Sciences, Ankara City Hospital, Ankara, Türkiye
[5]Department of Public Health, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[6]Department of Gynecological Oncology Surgery, Yeditepe University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: The aim of this study was to examine the early surgical and long-term survival outcomes of cytoreductive surgery (CRS) alone and CRS plus perioperative intraperitoneal chemotherapy (IPC) in patients with peritoneal metastases (PM).

Material and Methods: CRS alone or CRS plus IPC was performed on 122 patients for various intraabdominal PMs. Patients were divided into two groups as PCI ≤19 and PCI >19 to compare early surgical outcomes.

Results: Among PM patients 70 (57.4%) were of non-ovarian and 52 (42.6%) were of ovarian origin. Of the patients 74 (60.7%) were in the peritoneal cancer index (PCI) ≤19 group and 48 (39.3%) were in the PCI >19 group. The complication ratio of PCI >19 group was higher than that of the PCI ≤19 group and median overall survival (OS) of PCI >19 group was lower than that of the PCI ≤19 group. Complete or nearly complete (CCR-0/CCR-1) resections rates were similar in both groups (95.9% in the PCI ≤19 group and 93.8% in the PCI >19 group). However, CCR-0 resection rate was found to be lower in the PCI >19 group compared to the PCI ≤19 group (60.8% vs. 39.6%) (p< 0.001).

Conclusion: CCR-0/CCR-1 resections can be achieved with CRS in most patients with PCI >19 score. It would be appropriate to consider CRS or CRS plus perioperative IPC for palliative purposes in selected patients with PCI >19 score.

Keywords: Peritoneal metastases, peritoneal cancer index, cytoreductive surgery, early post-operative intraperitoneal chemotherapy, hyperthermic intraperitoneal chemotherapy

INTRODUCTION

Peritoneal metastases (PM) is a disease characterized by the distribution of avascular tumor nodules in different diameters and numbers on peritoneal surfaces, and its prognosis is poor, especially in non-gynecological cancers (1). In recent years, cytoreductive surgery (CRS) plus perioperative, intraperitoneal chemotherapy (IPC) methods in PM of gastrointestinal and ovarian cancers have provided positive oncological results.

The most critical factors in selecting patients treated with CRS are the type of primary tumor, the volume and distribution of peritoneal disease, and the patient's performance status (2). As it is known, the parameters to be considered in the application of curative perioperative chemotherapy are the peritoneal cancer index (PCI) and the complete cytoreduction (CCR), which indicates the completion of cytoreduction. Some authors suggest prognostic cut-offs for PCI as <17 for colorectal PM, <7 for gastric PM, and <15 for ovarian PM (3-6). On the other hand, there is no specific PCI cut-off value for patients with pseudomyxoma peritonei (PMP) and long-term survival is not affected by the extent of the disease (7). Regardless of the origin of PM, the most important prognostic factor for survival is the removal of all visible tumor tissues with complete cytoreduction. The HIPEC or EPIC is eligible for patients undergoing complete (CCR-0) or nearly complete (CCR-1) resection (8,9).

Cite this article as: Ercan M, Aziret M, Karaman K, Köse O, Öter V, Yırgın H, et al. Surgical and survival outcomes of cytoreductive surgery alone or with perioperative intraperitoneal chemotherapy in high peritoneal cancer index. Turk J Surg 2024; 40 (3): 219-228

Corresponding Author
Volkan Öter
E-mail: otervolkan@gmail.com

Received: 29.05.2024
Accepted: 18.09.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6457

In the literature, it is emphasized that high PCI is associated with suboptimal cytoreduction, while the complication rates due to CRS are higher and survival outcomes are worse in patients. A study of colorectal cancer has shown that PCI >19 correlated with suboptimal cytoreduction and is associated with increased major morbidity and worse survival (10). Similarly, PCI ≥21 has been shown to be an independent predictor of high-grade complications after ovarian cancer surgery (11).

Additionally, since systemic chemotherapy cannot be started in cases of intestinal obstruction, surgical treatment is usually preferred. Averbach and Sugarbaker evaluated early post-operative IPC with CRS in patients with bowel obstruction due to recurrent intraabdominal cancer (12). The authors demonstrated that with aggressive treatment, favorable oncologic outcomes (three-year survival 32.7%) can be achieved with acceptable morbidity and mortality rates (55% and 7.14%, respectively).

In the light of these studies, we wanted to question the rationality of the treatment methods by revealing the early surgical and long-term survival results of CRS or CRS plus perioperative IPC in our patients with PMs with a high PCI (PCI >19).

MATERIAL and METHODS

Patients

Between 2011 and 2019, CRS alone or CRS plus IPC was performed on 122 patients for various intraabdominal PMs. The patients whose data were regularly recorded were analyzed retrospectively and were divided into two groups as PCI ≤19 and PCI >19.

Patient characteristics of the groups (origin of PMs, age, sex, BMI, clinical and radiological features), CCR-R resections (CCR-0, CCR-1, CCR-2), treatment modalities (CRS alone and SRC plus perioperative IPC), operative time, hospital stay, surgical procedures (organ resections and peritonectomies), early post-operative complications, and hospital mortality were compared. In the survival analysis, patients were categorized into two groups as non-ovarian and ovarian. Survival analysis was performed according to PCI scores [≤9, (10-19) and >19], CCR resections, and treatment modalities (CRS alone, CRS plus HIPEC, and CRS plus EPIC) in groups.

Peritoneal cancer index and complete cytoreduction scores

PCI scoring defined by Sugerbaker was used (15). Resections (completeness of cytoreduction) were classified as CCR-0, CCR-1, CCR-2. CCR-0 was defined as the absence of visible tumor tissue in the abdomen, CCR-1 residual tumor ≤2.5 mm, and CCR-2 residual tumor between 2.5 mm and 2.5 cm.

Patient selection criteria

All patients were discussed in detail in the multidisciplinary oncology council before the surgery and evaluated in terms of treatment planning. Imaging methods such as ultrasonography, computerized tomography, magnetic resonance imaging, and positron emission tomography were used to evaluate the extent of the disease in the pre-operative period. The selection criteria of the patients to be admitted to the CRS are listed below.

1- Performance status must be EGOG ≤2
2- Age >18
3- Absence serious medical histories (for example; severe cardiac or chronic obstructive pulmonary disease)
4- Nutritional status (albumine >2.5 ng/dL)
5- Absence of signs of extra-abdominal metastases
6- Absence of signs of biliary obstruction
7- No bulky involvement in the mesenteric root
8- Absence of bilateral hydroureteronephrosis

Surgical procedures

Laparotomy was performed with a median incision extending from the xiphoid to the pubis. Incision scars due to previous surgeries were removed and intraabdominal adhesions were separated by dissection. Except for PMP, only peritoneal areas infiltrated with tumor were removed in the dissection of the peritoneum. Routinely, after the resections, the abdomen was irrigated with a mixture of povidone-iodine and oxygenated water for one minute and then with 0.9% isotonic NaCl. HIPEC was not performed in patients who developed excessive blood loss and severe acidosis during the operation. After the HIPEC procedure was completed, the abdomen was re-opened and anastomoses were performed.

Organ resections and peritonectomy procedures were based on Paul H. Sugarbaker's procedures (13).

Perioperative intraperitoneal chemotherapy

In HIPEC for colorectal PM and PMP we used mitomycin C (15 mg/m^2, with 1.5% dextrose dialysis solution at 42 °C for 90 minutes) or oxaliplatin (360 mg/m^2, with 5% dextrose solution at 43 °C for 30-45 minutes). In HIPEC for gastric PM, PMP and ovarian PM we used cisplatin (50 mg/m^2, 1.5% dextrose dialysis solution at 42 °C for 90 minutes). In non-ovarian PM, 5-fluorouracil was used for EPIC (400-600 mg/m^2 with 50 meq $NaHCO_3$ and 1 liter of 5% dextrose). In ovarian PM, paclitaxel or cisplatin was used for EPIC. In EPIC, the drains were clamped for 23 hours after the chemotherapeutic agent was administered intraperitoneally. Then, the drains were opened for one hour and the chemotherapeutic agent was drained out of the abdomen. The EPIC procedure was reapplied in patients with good tolerance in the follow-up.

Post-operative approach

All patients were followed in the the intensive care unit after the operation. Post-operative bleeding was defined as more than 200 cc of blood coming from the drains. Post-operative mortality

was defined as mortality within the first month. Patients with CRS alone were transferred to medical oncology after recovery and were allowed to receive adjuvant chemotherapy regimens in the early period.

Statistical Analysis

Statistical analysis was achieved using the SPSS 21.0 software version. The variables were investigated using analytical methods (Kolmogorov-Smirnov test) to determine distribution. Descriptive analyses were introduced using means and standard deviations if the variables were normally distributed; medians and interquartile ranges were used if the variables were non-normally distributed. Categorical variables are specified as numbers and percentages. Pearson Chi-square test was used to compare categorical variables, and student's t test was used for pairwise comparison of normally distributed continuous variables.

The survival analysis of cancers according to treatment status, CC score, and PCI score was performed using the log-rank test. Chi-square test was used to compare categorical variables, and Mann-Whitney U test was used to compare non-normally distributed variables.

RESULTS

Among the PM patients 70 (57.4%) were of non-ovarian and 52 (42.6%) were of ovarian origin. Of the patients 74 (60.7%) were in the PCI ≤19 group and 48 (39.3%) were in the PCI >19 group. Male sex ratio was higher in the PCI >19 group than in the PCI ≤19 group. The origin of PMs with high PCI was colorectal cancer in the first place and ovarian cancer in the second place. A adverse clinical findings were found at a higher rate in the PCI >19 group. Especially bowel obstruction and hydroureteronephrosis were detected at a significantly higher rate in the PCI >19 group (p= 0.001, p= 0.041) (Table 1).

Table 1. Pre-operative patient characteristics

	PCI ≤19 (n= 74)	PCI >19 (n= 48)	p
Sex			
Female	58 (78.4%)	26 (54.2%)	**0.005**
Male	16 (21.6%)	22 (45.8%)	
Age (years), mean ± SD	54.18 ± 11.5	52.4 ± 13.7	0.431
BMI, mean ± SD	26.1 ± 5.5	25.4 ± 6.3	0.584
Origin of PM			
Colorectal	24 (32.4%)	23 (47.9%)	0.086
Appendiceal	3 (4.1%)	4 (8.3%)	0.321
Gastric	3 (4.1%)	4 (8.3%)	0.321
Mesothelioma	3 (4.1%)	2 (4.2%)	0.976
Pancreas	0	1 (2.1%)	0.212
GIST	1 (1.4%)	2 (4.2%)	0.327
Ovarian	40 (54.1%)	12 (25%)	**0.002**
Primary	37 (50%)	21 (43.7%)	0.596
Secondary*	37 (50%)	27 (56.3%)	0.499
Clinical and radiological findings			
Bowel obstruction	7 (9.5%)	16 (33.3%)	**0.001**
Ascites	30 (40.5%)	25 (52.1%)	0.211
Liver metastasis and/or			
Glisson capsule involvement	14 (18.9%)	16 (33.3%)	0.071
Mesenteric root involvement	1 (1.4%)	3 (6.3%)	0.550
Hydroureteronephrosis	7 (9.5%)	11 (22.9%)	**0.041**
5 cm >intraabdominal mass	34 (45.9%)	27 (56.2%)	0.266

BMI: Body mass index, PCI: Peritoneal cancer index, PM: Peritoneal metastasis, GIST: Gastrointestinal stromal tumor.

*Secondary: Peritoneal metastasis was detected after primary tumor surgery.

Table 2. Comparison of post-operative variables in PCI groups

	PCI ≤19 (n= 74)	PCI >19 (n= 48)	p
CCR score			
CCR-0	45 (60.8%)	19 (39.6%)	**<0.001**
CCR-1	26 (35.1%)	26 (54.2%)	**<0.001**
CCR-2	3 (4.1%)	3 (6.2%)	0.456
Treatment modalities			
CRS alone	37 (50.0%)	15 (31.2%)	0.060
IPC (HIPEC or EPIC)	37 (50.0%)	33 (68.8%)	0.058
Duration of surgery (minute), mean ± SD	391.9 ± 127.3	523.0 ± 159.9	**<0.001**
Duration of hospital stay (day), mean ± SD	16.9 ± 11.6	31.4 ± 24.1	**<0.001**
Follow up (mounth), mean ± SD	26.5 ± 15.1	12.8 ± 13.6	**<0.001**

PCI: Peritoneal cancer index, CCR: Complete cytoreduction, CRS: Cytoreductive surgery, EPIC: Early post-operative intraperitoneal chemotherapy, HIPEC: Hyperthermic intraperitoneal chemotherapy, SD: Standard deviation.

Seven appendicial tumors and two ovarian tumors were mucinous ascites, the others were non-mucinous. Primary surgery rate was (number of patients without previous abdominal surgery for cancer) 58 (47.5%), Recurrence rate was 64 (52.5%) (patients who had previously undergone abdominal surgery for cancer). All patients with recurrence had previously received different neoadjuvant and adjuvant chemotherapy regimens. All patients with primary recurrence underwent emergency surgery for obstruction and bleeding. In principle, neoadjuvant chemotherapy was administered except in cases where it was not needed. Adjuvant treatment is given between 4-6 months and neoadjuvant treatment between 8-12 months depending on the origin of the primary tumor. We use Folfox or Folfiri in colon cancer, Folfox or Folfiri in ovarian cancer Carboplatin and Flot combinations in gastric cancer as adjuvant and neoadjuvant chemotherapy regimens.

Complete or nearly complete (CCR-0/CCR-1) resections rates were similar in both groups (95.9% in the PCI ≤19 group and 93.8% in the PCI >19 group). However, the CCR-0 resection rate was found to be lower in the PCI >19 group compared to the PCI ≤19 group (60.8% vs. 39.6%) (p< 0.001). The rate of IPC was higher in the PCI >19 group (50% vs. 68.8%) (p= 0.058).

Mean duration of surgery time and the mean duration of hospital was significantly longer in the PCI >19 group than in the PCI >19 group (p< 0.001) (Table 2).

Comparison of complications

Surgical complications rates were very high in the PCI >19 group compared to the PCI ≤19 group (Table 3). The rates of reoperation (16.7% vs. 5.4%) and percutaneous intraabdominal abscess drainage (14.6% vs. 4.1%) were also significantly higher in the PCI >19 group than in the PCI ≤19 group (p= 0.042 and p= 0.038, respectively). Reasons for reoperation were bowel leakage in six patients, intraabdominal bleeding in four patients, and bladder/ureteral leakage in two patients. While hospital mortality rate was 12.5% in the PCI >19 group, there was no mortality in the PCI ≤19 group (p= 0.003).

Hospital mortality occurred in six patients. The causes of death

Table 3. Comparison of early post-operative complications and mortality in PCI groups

Complications	**PCI ≤19 (n= 74) n (%)**	**PCI >19 (n= 48) n (%)**	**p n (%)**
*Elevated AST-ALT levels	18 (24.3)	22 (45.8)	**0.014**
Acute renal failure	1 (1.4)	11 (22.9)	**<0.001**
Leukopenia	1 (1.4)	5 (10.4)	**0.037**
Wound site (seroma, dehiscence, infection)	20 (27.0)	27 (56.2)	**0.001**
Pulmonary (effusion, atelectasis, pneumonia)	13 (17.6)	20 (41.7)	**0.003**
Sepsis	4 (5.4)	16 (33.3)	**<0.001**
Intraabdominal bleeding	10 (13.5)	15 (31.2)	0.018
Intraabdominal fluid collection	7 (9.5)	14 (29.2)	**0.005**

Table 3. Comparison of early post-operative complications and mortality in PCI groups (continue)

Complications	PCI ≤19 (n= 74) n (%)	PCI >19 (n= 48) n (%)	p n (%)
Ileus	4 (5.4)	6 (12.5)	0.190
Bowel leakage	1 (1.4)	7 (14.6)	**0.006**
Urine leakage	1 (1.4)	6 (12.5)	**0.015**
Pancreatic leakage	0	5 (10.4)	**0.008**
Interventions for complications			
Re-operation	4 (5.4)	8 (16.7)	**0.042**
Percutaneous intraabdominal abscess drainage	3 (4.1)	7 (14.6)	**0.038**
Percutenous nephrostomy catheterization	2 (2.7)	3 (6.3)	0.346
Hospital mortality	0	6 (12.5)	**0.003**

ALT: Alanin aminotransferase, AST: Aspartat aminotransferase, PCI: Peritoneal cancer index.

of the patients were sepsis and pneumonia due to surgical complications.

Survival analysis

The follow-up period was 14.3 ± 9.5 months in the non-ovarian group and 20.5 ± 16.1 months in the ovarian group (p= 0.059). The survival distribution of non-ovarian and ovarian patients according to PCI score, CCR resections and treatment modalities is shown in Table 4. Median survival time of the patients with PC >19 in the non-ovarian and ovarian groups was similarly low (Table 4). Median survival time of patients with CCR-0 resection of non-ovarian and ovarian PMs was almost twice that of patients with CCR-1 resection (Table 4).

Although not statistically significant in either group, the best survival outcomes were achieved in patients who underwent CRS plus EPIC (Table 4).

DISCUSSION

CRS is an extensive surgical procedure that allows complete resection of all visible macroscopic peritoneal metastatic disease and treatment of residual microscopic peritoneal disease with perioperative IPC modalities. Most peritoneal surface malignancy treatment centers use HIPEC only, some use EPIC only, and others use both in turn.

The method of application of IPC may also vary according to cost conditions. We generally prefer to apply HIPEC, but due to perioperative instability, we may have to apply EPIC or alone CRS to some of our patients.

Patients to whom CRS plus IPC is applied are at risk of serious morbidity due to the possible side effects of both the complex surgical procedure and the drugs administered intraperitoneally (14). In this respect, identifying patients who will benefit from CRS plus IPC is extremely important from a prognostic point of view. Therefore, the authors proposed prognostic PCI score cut-off values for PMs of various origins (4-6,15-17). PCI ≥20 score, perihepatic region involvement and diffuse small bowel involvement were determined as risk factors in radiological prognostic evaluation in colorectal PM (18). Yan et al. have reported that the probability of suboptimal cytoreduction is 100% in the presence of a tumor >5 cm in the epigastric region and small intestine involvement and the probability of CCR is 94% in the absence of these findings, in the peritoneal mesothelioma study (19). Massive small bowel and mesenteric involvement and the presence of extensive hepatobiliary disease are negative predictive factors for cytoreduction, as emphasized in large-centered studies. However, it is not possible to exclude patients with bowel obstruction from cytoreduction, especially since they do not receive chemotherapy. In our study, approximately 40% of all patients had high PCI score. All negative clinical findings, especially bowel obstruction, liver metastasis and hydroureteronephrosis were found to be significantly higher in the PCI >19 group. As can be seen from these findings, a significant number of our patients were candidates for suboptimal cytoreduction. Despite this, in our study, complete or nearly CCR could be obtained with multiple organ resections and peritonectomy procedures in most (93.8%) patients with PCI >19. However, despite these extensive surgical procedures, the CCR-0 resection rate was significantly lower in the PCI >19 group than in the PCI ≤19 group (39.6% and 60.8%, respectively). Similarly, Yonemura et al. have reported in patients with colon cancer that, the rate of CCR decreased as the PCI score increased (20).

In a systematic review of morbidity and mortality of SRC plus HIPEC, mean mortality rate has reported as 2.9% (range 0-17%), and primary morbidity rate as 28.8% (0-52%). A multi-institutional study has reported a, reoperation rate of 14%, mortality rate due to SRC plus IPC as be 4.1% and the morbidity rate as 33.6% in non-ovarian peritoneal carcinomatosis (21).

Table 4. Distribution of the survival of non-ovarian and ovarian groups according to PCI scores, CCR resections and treatment modalities

	Number of patients (n)	**Mortality (n)**	**Overall survival (%)**	**Overall survival rates (%)**			**Overall survival time (months)**			
				6 months	1 year	3 years	Median ± Standard error	95% Confidence interval	Log-rank Chi-square/df	p
Non-ovarian	**70**	**33**	**52.9**	**75.3**	**59.4**	**41.8**	**24.0 ± 6.6**	**10.9 - 37.0**		
PCI (≤9)	16	2	87.5	100.0	90.9	81.8	31.6 ± 2.8	26.1 - 37.1	13.697/2	**0.001**
PCI (10-19)	18	9	50.0	88.9	76.9	41.1	26.8 ± 4.1	18.8 - 34.9		
PCI (>19)	36	22	38.9	58.0	36.7	24.1	13.4 ± 2.0	9.3 - 17.5		
CCR-0	35	10	71.4	96.9	83.4	60.8	32.5 ± 3.4	25.8 - 39.2		
CCR-1	29	17	41.4	82.8	71.3	24.1	18.8 ± 3.7	11.6 - 26.1	10.505/2	**0.005**
CCR-2	6	6	0	83.3	16.7	16.7	12.6 ± 5.0	2.7 - 25.5		
CRS alone	17	8	52.9	58.8	58.8	51.5	20.2 ± 3.8	12.7 - 27.7		
HIPEC	36	18	50.0	77.7	56.0	30.8	19.8 ± 2.7	14.5 - 25.2	0.990/2	0.610
EPIC	17	7	58.8	87.4	65.7	46.0	27.7 ± 4.9	18.0 - 37.3		
Ovarian	**52**	**16**	**69.2**	**82.1**	**74.8**	**60.4**	**38.4 ± 3.3**	**31.8 - 45.0**		
PCI (≤9)	17	2	88.2	100.0	86.5	50.0	50.1 ± 3.1	44.0 - 56.2	20.210/2	**<0.001**
PCI (10-19)	23	5	78.3	100.0	80.4	33.3	35.8 ± 3.4	28.9 - 42.6		
PCI (>19)	12	9	25.0	80.8	68.9	25.0	14.2 ± 4.9	4.6 - 23.8		
CCR-0	29	6	79.3	92.9	89.0	70.0	44.9 ± 3.6	37.8 - 51.9		
CCR-1	22	9	59.1	86.4	60.0	54.0	25.9 ± 4.2	17.6 - 34.3	10.456/2	**0.005**
CCR-2	1	1	0	0	0	0	2.0 ± 0	2.0 - 2.0		
CRS alone	36	9	75.0	79.8	76.2	69.8	32.7 ± 2.9	27.0 - 38.5		
HIPEC	4	4	0	50.0	50.0	0	17.0 ± 8.7	0 - 34.1	8.685/2	**0.013**
EPIC	12	3	75.0	100.0	77.8	64.8	39.3 ± 7.3	24.9 - 53.7		

PCI: Peritoneal cancer index, CCR: complete cytoreduction, CRS: Cytoreductive surgery, EPIC: Early post-operative intraperitoneal chemotherapy, HIPEC: Hyperthermic intraperitoneal chemotherapy.

The median OS of non-ovarian group with PCI <9 and PCI (10-19) score is higher than PCI score >19 (p= 0.001). The median OS of ovarian group with PCI <9 and PCI (10-19) score is higher than PCI score >19 (p< 0.001). The median OS in the non-ovarian and ovarian groups with a CCR-0 resection was much higher than the CCR-1 and CCR-2 resections (p= 0.005). The significant difference in overall survival on the treatment of ovarian PM is due to the fact that alone SRC and SRC plus EPIC procedures have more prolonged median OS than SRC plus HIPEC procedures (p= 0.001).

As demonstrated in the studies above, CRS plus perioperative IPC method is generally accepted as a surgical procedure with morbidity and mortality rates similar to those seen in any major abdominal surgery. Studies have shown that especially the increase in PCI is correlated with major morbidity. In a study on ovarian cancer, it has been found that high PCI (>24) caused an increase in complication rates (22). In another study, PCI ≥21 has been found to be an independent predictor of high-grade complications after ovarian cancer surgery (11). A study on colorectal cancer has confirmed that longer operative time (>540 minutes) and PCI >19 are independent risk factors for major morbidity (10). In our study, the mean duration of surgery time was significantly longer in the PCI >19 group (523 minutes vs. 391.9 minutes). We found that the morbidity and mortality rates after CRS were very high in the PCI >19 group compared to the PCI ≤19 group. Especially, intraabdominal bleeding, intraabdominal fluid collection bowel leakage, urine leakage, and pancreatic leakage were found to be quite high in the PCI >19 group. On the other hand, our results show that the incidence of post-operative complications in patients with PCI ≤19 is not significantly different from that seen in any major intraabdominal surgery.

Intestinal fistulase have been reported as the most important cause of morbidity in SRC plus perioperative IPC (22-24). In a study, the authors have reported that a high PCI score was the only independent risk factor for gastrointestinal complications in patients undergoing CRS plus IPC in multivariate analysis. In the study, it has been reported that the frequency of gastrointestinal complications was highly correlated with a PCI >30 score (25). In our study, we found a high rate of bowel leakage (8.6%) like the literature. However, one of these patients was in the PC ≤19 group and seven of them were in the PCI >19 group. In addition to intestinal fistulaes, urinary anastomotic leaks are complications that are difficult to manage. In the literature, it is stated that urological procedures increase the risk of major complications in CRS (26,27).

In our study, the hospital mortality rate was 12.5% in the PCI >19 group, while there was no mortality in the PCI ≤19 group. The causes of mortality of the patients were sepsis and pneumonia due to surgical complications. The rates of sepsis and pulmonary complications were found to be quite high, especially in the PCI >19 group (18.7 % and 41.7 %). Similarly, it is stated that the leading cause of death after CRS/HIPEC is sepsis and related respiratory complications (8,22).

In this study, the distribution of patients in the PCI groups (54% ovarian PM in PCI ≤19 and 48% colorectal PM in PCI >19) was not homogeneous. Therefore, it was thought that it would be more appropriate to perform survival analyzes in two separate groups (non-ovarian and ovarian) based on tumor origins. Analysis of survival in the groups was performed separately according to PCI scores [≤9, (10-19) and >19], CCR resections, and treatment modalities (CRS alone, CRS plus HIPEC, and CRS plus EPIC).

In our series, median survival time of the non-ovarian group was 31.6 months in the PCI ≤9 group, 26.8 months in the PCI (10-19) group and 13.4 months in the PCI >19 group. In colorectal carcinoma, Leonardo et al. have indicated that patients with high PCI (PCI >6) and significant nodal involvement (N2) may not benefit from the SRC plus HIPEC procedure (28). Weber et al. have reported that the median survival in patients with colon cancer was 33.2 months in patients with PCI ≤10, 12.1 months in patients with PCI (11-19) and the two-year overall survival was 89% with PCI ≤10 (29). Da silva and Sugarbaker have reported that patients with PCI of <20 had a median survival of 41 months compared with 16 months for patients with PCI >20 (17). The authors state that when PCI is greater than 20 in colorectal cancer, five-year survival rate is less than 10%, and that widespread disease becomes a relative contraindication for this combined therapy (6). In our series, non-ovarian PMs were heterogeneous, but the majority (approximately 2/3) were colorectal PMs. Therefore, it is seen that similar survival results have been obtained. In our series the median survival time of ovarian group was 50.1 months in the PCI <9 group, 35.8 months in the PCI (10-19) and 14.2 months in the PCI >19 group. In a study for ovarian cancer, PCI >10 in primary advanced ovarian cancer was positively associated with poor prognosis (6). A recent prospective study concluded that the PCI score is a reliable tool to help assess disease extent in patients with advanced epithelial ovarian cancer and may help predict complete surgical cytoreduction, but not as a predictor of death. In this study, the cut off value for over PC is PCI >13 (30). In our series, the survival of ovarian PM patients with PCI >19 was quite low. In fact, the median survival time of patients with PC >19 in the non-ovarian and ovarian groups was nearly identical.

In our study, one of the best prognostic factors for median OS was a CCR score as well as a low PCI score. Median survival time of the non-ovarian group was 32.5 months in CCR-0, 18.8 in months CCR-1 and 12.6 months in CCR-2. Three-year survival rates of the non-ovarian group was 60.8% in CCR-0, 24.1% in CCR-1 and 16.7% in CCR-2 (p= 0.005). Median survival time of non-ovarian PM patients with CCR-0 resection was almost twice that of patients with CCR-1 resection. We found that in non-ovarian PMs, the CCR-1 resection did not provide a significant long-term (three-years) survival advantage over the CCR-2 resection. Yonemura et al. have also reported the median survival time as 25.9 months and five-years overall survival 20% in patients who underwent CCR-0 resection and in 8.0 months and 9.9%, respectively with CCR-1 resection (20). In their study, CCR-0 resection and PCI ≤10 have been reported as independent favorable prognostic factors in multivariate analysis (20). Elias et al. have achieved a median survival of 33 months with CCR in 84% of patients with colorectal carcinoma. In multivariate analysis showed that CCR was one of the independent prognostic factors (8).

Median survival time in the ovarian group was 44.9 months in CCR-0, 25.9 months in CCR-1 and 2.0 months in CCR-2 (p= 0.005). Likewise, studies with ovarian cancer have emphasized that the survival benefit of R1 resection is low. Arjona-Sanchez A. have reported the mean PCI score of the patients as 15.8 and performed a CCR-0 score of 95% in their study (31). In the study, R1 cytoreduction was detected as a risk factor in multivariate analysis (31). Robella et al. have reported that the most important prognostic factor for survival was the completeness of cytoreduction (32). In their study, overall survival with CCR was 48 months. Similarly, CCR-0 resection was one of the most important prognostic factors affecting survival in our patients with ovarian PM. As with non-ovarian PMs, median survival time of ovarian PM patients with CCR-0 resection was almost twice that of patients with CCR-1 resection.

In the literature for PM due to gastric cancer, Yang et al. in a prospective randomized Phase III study, have reported median

survival as 6.5 months in the CRS group and 11 months in the CRS plus HIPEC group (33). In a recent phase three study for ovarian cancer, adding HIPEC to interval CRS in patients with stage III epithelial ovarian cancer resulted in longer recurrence-free survival and overall survival compared to surgery alone without increased side effects (34). A recent study has investigated the specific benefit of adding HIPEC to CRS in colorectal PM. The authors have reported overall survival of 41.7 months in the CRS plus HIPEC group and 41.2 months in the CRS alone group. The authors have underlined that adding HIPEC to CRS had no overall survival benefit (35). We performed CRS plus perioperative IPC (HIPEC or EPIC) in 50% of our patients with PCI ≤19 and 68.8% of our patients with PCI >19. CRS alone was applied to a significant proportion of patients in both groups. Overall in our study, it was observed that adding HIPEC to CRS in non-ovarian PMs did not provide a survival advantage over other treatment modalities. This may be due to the fact that most of the non-ovarian patients were of colorectal origin. On the other hand, the survival results of our patients who underwent CRS plus HIPEC for the ovarian PM group were poor. The reason for this may be the low number of patients who underwent CRS plus HIPEC in this group, as well as the fact that some of the patients died in the early post-operative period due to complications. In addition, it is clear in this series that alone CRS provided a remarkable survival in both groups.

The superiority of HIPEC and EPIC methods over each other is controversial in the literature. In the study on the method of IPC, Elias et al. have compared CRS and HIPEC/EPIC methods for complications and therapeutic outcomes in colorectal cancer (36). They have reported that HIPEC was better tolerated, had less morbidity and mortality, and provided a more prolonged survival. The same author, in a later study for colon PM, has shown that the use of HIPEC or EPIC did not have a statistically significant prognostic effect (8). Glehen et al. have shown that no significant difference in survival was observed between patients treated with intraperitoneal chemohyperthermia (IPCH) alone and EPIC alone or both, but survival outcomes were better with the combination (9).

The present study has some limitations. It is heterogeneous in terms of histopathological features and treatment modalities.

CONCLUSION

This study showed that a high rate of CCR-0/CCR-1 resections can be achieved with extensive CRS in patients with PCI >19.

However, this result was obtained with extensive surgery results in high post-operative morbidity and mortality. In both non-ovarian and ovarian groups, the CCR-1 resection provides approximately half the survival time of the CCR-0 resection. In the PCI >19 group, low CCR-0 resection rate and high CCR-1 resection rate also negatively affect long-term survival outcomes. In general, the best survival results are obtained in patients with a PCI ≤9 score and a CCR-0 resection. The survival time of patients who underwent EPIC in non-ovarian and ovarian PMs was relatively longer, but this was not statistically significant.

The results of this study showed that the application of CRS or CRS plus IPC treatment methods should be considered for palliative purposes in selected patients with PCI >19 score.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Sakarya University Faculty of Medicine (Decision no: E-71522473-050.01.04-83248-96, Date: 30.11.2021).

Peer-review: Extarnally peer-reviewed.

Author Contributions: Concept - ME, MA; Design - KK, ME; Supervision - OÜ, EBB; Materials - EK, OK, OÜ, EBB: Data Collection and/or Processing - MA, HY, YSK; Analysis and/or Interpretation - MA, KK; Literature Search - ME, VÖ, MA, OS; Writing Manuscript - ME, MA, VÖ; Critical Reviews - OÜ, EBB.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. *Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: Results of the EVOCAPE 1 multicentric prospective study. Cancer 2000; 88(2): 358-63. https://doi.org/10.1002/(SICI)1097-0142(20000115)88:2<358::AID-CNCR16>3.0.CO;2-O*
2. *Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: A consensus statement. Ann Surg Oncol 2007; 14(1): 128-33. https://doi.org/10.1245/s10434-006-9185-7*
3. *Goéré D, Souadka A, Faron M, Cloutier AS, Viana B, Honoré C, et al. Extent of colorectal peritoneal carcinomatosis: Attempt to define a threshold above which HIPEC does not offer survival benefit: A comparative study. Ann Surg Oncol 2015; 22: 2958-64. https://doi.org/10.1245/s10434-015-4387-5*
4. *Chia CS, You B, Decullier E, Vaudoyer D, Lorimier G, Abboud K, et al. Patients with peritoneal carcinomatosis from gastric cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: Is cure a possibility? Ann Surg Oncol 2016; 23: 1971-9. https://doi.org/10.1245/s10434-015-5081-3*
5. *Canbay E, Mizumoto A, Ichinose M, Ishibashi H, Sako S, Hirano M, et al. Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single specialized center in Japan. Ann Surg Oncol 2014; 21: 1147-52. https://doi.org/10.1245/s10434-013-3443-2*
6. *Llueca A, Escrig J, MUAPOS working group (Multidisciplinary unit of abdominal pelvic oncology surgery). Prognostic value of peritoneal cancer index in primary advanced ovarian cancer. Eur J Surg Oncol 2018; 44: 163-9. https://doi.org/10.1016/j.ejso.2017.11.003*

7. *Vaira M, Cioppa T, DE Marco G, Bing C, D'Amico S, D'Alessandro M, et al. Management of pseudomyxoma peritonei by cytoreduction+ HIPEC (hyperthermic intraperitoneal chemotherapy): Results analysis of a twelve-year experience. In Vivo 2009; 23: 639-44.*

8. *Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: Retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010; 28: 63-8. https://doi.org/10.1200/JCO.2009.23.9285*

9. *Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: A multi-institutional study. J Clin Oncol 2004; 24: 3284-92. https://doi.org/10.1200/JCO.2004.10.012*

10. *Baratti D, Kusamura S, Iusco D, Bonomi S, Grassi A, Virzì S, et al. Postoperative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: A two-center study of 101 patients. Dis Colon Rectum 2014; 57(7): 858-68. https://doi.org/10.1097/DCR.0000000000000149*

11. *Lomnytska M, Karlsson E, Jonsdottir B, Lejon AM, Stålberg K, Poromaa IS, et al. Peritoneal cancer index predicts severe complications after ovarian cancer surgery. Eur J Surg Oncol 2021; 47: 2915-24. https://doi.org/10.1016/j.ejso.2021.05.019*

12. *Averbach AM, Sugarbaker PH. Recurrent intraabdominal cancer with intestinal obstruction. Int Surg 1995; 80: 141-6.*

13. *Sugarbaker PH. Cytoreductive surgery using peritonectomy and visceral resections for peritoneal surface malignancy. Transl Gastrointest Cancer 2013; 2(2): 54-74*

14. *Valle SJ, Alzahrani NA, Liauw W, Sugarbaker PH, Bhatt A, Morris DL. Hyperthermic intraperitoneal chemotherapy (HIPEC) methodology, drugs and bidirectional chemotherapy. Indian J Surg Oncol 2016; 7: 152-9. https://doi.org/10.1007/s13193-016-0498-0*

15. *Benzaquen E, Wang Y, Wiseman S, Rosenfeld V, Sideris L, Dubé P, et al. Morbidity associated with the use of oxaliplatin versus mitomycin C in hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal or appendiceal origin: a multi-institutional comparative study. Can J Surg 2021; 64: E111. https://doi.org/10.1503/cjs.001619*

16. *Elias D, Blot F, El Otmany A, Antoun S, Lasser P, Boige V, et al. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. Cancer 2001; 92: 71-6. https://doi.org/10.1002/1097-0142(20010701)92:1<71::AID-CNCR1293>3.0.CO;2-9*

17. *da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg 2006; 203: 878-86. https://doi.org/10.1016/j.jamcollsurg.2006.08.024*

18. *Suzuki C, Wallgren H, Abraham-Nordling M, Palmer G. Preoperative CT-based predictive factors for resectability and medium-term overall survival in patients with peritoneal carcinomatosis from colorectal cancer. Clin Radiol 2018; 73: 756-e11. https://doi.org/10.1016/j.crad.2018.03.011*

19. *Yan TD, Haveric N, Carmignani CP, Chang D, Sugarbaker PH. Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. Cancer 2005; 103: 839-49. https://doi.org/10.1002/cncr.20836*

20. *Yonemura Y, Canbay E, Ishibashi H. Prognostic factors of peritoneal metastases from colorectal cancer following cytoreductive surgery and perioperative chemotherapy. Sci World J 2013; 2013: 978394. https://doi.org/10.1155/2013/978394*

21. *Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: A systematic review of morbidity and mortality. Ann Surg 2009; 249: 900-7. https://doi.org/10.1097/SLA.0b013e3181a45d86*

22. *Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: A multi-institutional study of 1290 patients. Cancer 2010; 116: 5608-18. https://doi.org/10.1002/cncr.25356*

23. *Jónsdóttir B, Lomnytska M, Poromaa IS, Silins I, Stålberg K. The peritoneal cancer index is a strong predictor of incomplete cytoreductive surgery in ovarian cancer. Ann Surg Oncol 2021; 28: 244-51. https://doi.org/10.1245/s10434-020-08649-6*

24. *Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003; 21: 3737-43. https://doi.org/10.1200/JCO.2003.04.187*

25. *Casado-Adam A, Alderman R, Stuart OA, Chang D, Sugarbaker PH. Gastrointestinal complications in 147 consecutive patients with peritoneal surface malignancy treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Int J Surg Oncol 2011; 2011: 468698. https://doi.org/10.1155/2011/468698*

26. *Braam HJ, van Oudheusden TR, de Hingh IH, Nienhuijs SW, Boerma D, Wiezer MJ, et al. Urological procedures in patients with peritoneal carcinomatosis of colorectal cancer treated with HIPEC: Morbidity and survival analysis. Anticancer Res 2015; 35: 295-300.*

27. *Lyon TD, Turner Ii RM, Nikonow TN, Wang L, Uy J, Ramalingam L, et al. Effect of a concomitant urologic procedure on outcomes following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. J Surg Oncol 2016; 113: 218-22. https://doi.org/10.1002/jso.24115*

28. *Solaini L, D'Acapito F, Passardi A, Framarini M, Tauceri F, Di Pietrantonio D, et al. Cytoreduction plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis in colorectal cancer patients: A single-center cohort study. World J Surg Oncol 2019; 17: 1-6. https://doi.org/10.1186/s12957-019-1602-z*

29. *Weber T, Roitman M, Link KH. Peritoneal carcinomatosis of colorectal origin: Results of cytoreductive surgery with peritonectomy and hyperthermic intraoperative chemotherapy. Chirurg 2013; 84: 130-2. https://doi.org/10.1007/s00104-012-2419-2*

30. *Elzarkaa AA, Shaalan W, Elemam D, Mansour H, Melis M, Malik E, et al. Peritoneal cancer index as a predictor of survival in advanced stage serous epithelial ovarian cancer: A prospective study. J Gynecol Oncol 2018; 29(4): e47. https://doi.org/10.3802/jgo.2018.29.e47*

31. *Arjona-Sanchez A, Rufián-Peña S. Progress in the management of primary and recurrent ovarian carcinomatosis with peritonectomy procedure and HIPEC in a high volume centre. Int J Hyperthermia 2017; 33: 554-61. https://doi.org/10.1080/02656736.2017.1278631*

32. *Robella M, Vaira M, Marsanic P, Mellano A, Borsano A, Cinquegrana A, et al. Treatment of peritoneal carcinomatosis from ovarian cancer by surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). Minerva Chir 2014; 69: 27-35.*

33. *Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: Final results of a phase III randomized clinical trial. Ann Surg Oncol 2011; 18: 1575-81. https://doi.org/10.1245/s10434-011-1631-5*

34. *van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Massuger, hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 2018; 378: 230-40. https://doi.org/10.1056/NEJMoa1708618*

35. *Quénet F, Elias D, Roca L, Goéré D, Ghouti L, Pocard M, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021; 22: 256-66. https://doi.org/10.1016/S1470-2045(20)30599-4*

36. *Elias D, Benizri E, Di Pietrantonio D, Menegon P, Malka D, Raynard B. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. Ann Surg Oncol 2007; 14: 509-14. https://doi.org/10.1245/s10434-006-9167-9*

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 219-228

Yüksek periton kanseri indeksinde tek başına veya perioperatif intraperitoneal kemoterapi ile birlikte sitoredüktif cerrahi ve sağkalım sonuçları

Metin Ercan[1], Mehmet Aziret[2], Kerem Karaman[2], Osman Köse[3], Volkan Öter[4], Hakan Yırgın[2], Ahmet Kaya[1], Yavuz Selim Kahraman[1], Elif Köse[5], Erdal Birol Bostancı[4], Orhan Ünal[6]

[1]Sakarya Üniversitesi Tıp Fakültesi, Cerrahi Onkoloji Anabilim Dalı, Sakarya, Türkiye
[2]Sakarya Üniversitesi Tıp Fakültesi, Gastroenterolojik Cerrahi Anabilim Dalı, Sakarya, Türkiye
[3]Sakarya Üniversitesi Tıp Fakültesi, Jinekolojik Onkoloji Cerrahisi Anabilim Dalı, Sakarya, Türkiye
[4]Sağlık Bilimleri Üniversitesi, Ankara Şehir Hastanesi, Gastroenterolojik Cerrahi Kliniği, Ankara, Türkiye
[5]Sakarya Üniversitesi Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, Sakarya, Türkiye
[6]Yeditepe Üniversitesi Tıp Fakültesi, Jinekolojik Onkoloji Cerrahisi Anabilim Dalı, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, peritoneal metastazlı (PM) hastalarda tek başına sitoredüktif cerrahi (CRS) ve CRS artı perioperatif intraperitoneal kemoterapinin (IPC) erken cerrahi ve uzun dönem sağkalım sonuçlarını incelemektir.

Gereç ve Yöntem: Çeşitli intraabdominal PM'ler için 122 hastaya tek başına CRS veya CRS + IPC uygulandı. Erken cerrahi sonuçları karşılaştırmak için hastalar peritoneal kanser endeksi (PCI) ≤19 ve PCI >19 olmak üzere iki gruba ayrıldı.

Bulgular: Peritoenal metastazlı hastalarının 70 (%57,4)'i non-ovaryan ve 52 (%42,6)'si over kökenliydi. Hastaların 74 (%60,7)'ü PCI ≤19 grubunda ve 48 (%39,3)'i PCI >19 grubundaydı. PCI >19 grubunun komplikasyon oranı PCI ≤19 grubundan daha yüksektir ve PCI >19 grubunun medyan genel sağkalımı (GS) PCI ≤19 grubundan daha düşüktü. Tam veya tama yakın (CCR-0/CCR-1) rezeksiyon oranları her iki grupta da benzerdi (PCI ≤19 grubunda %95,9 ve PCI >19 grubunda %93,8). Ancak CCR-0 rezeksiyon oranı PCI >19 grubunda PCI ≤19 grubuna kıyasla daha düşük bulunmuştur (%60,8'e karşı %39,6) (p< 0,001).

Sonuç: PCI >19 skoru olan hastaların çoğunda CRS ile CCR-0/CCR-1 rezeksiyonları elde edilebilir. PCI >19 skoru olan seçilmiş hastalarda palyatif amaçlar için CRS veya CRS + perioperatif IPC'yi düşünmek uygun olacaktır.

Anahtar Kelimeler: Peritoneal metastazlar, peritoneal kanser endeksi, sitoredüktif cerrahi, erken postoperatif intraperitoneal kemoterapi, hipertermik intraperitoneal kemoterapi

DOİ: 10.47717/turkjsurg.2024.6457

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 229-239

Comparison of surgical outcomes between shunt surgery and devascularization in non-cirrhotic portal hypertension

Saad Anwar, Kunal Parasar, Utpal Anand, Basant Singh, Kislay Kant, Rohith Kodali

Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Patna, India

ABSTRACT

Objective: Non-cirrhotic portal hypertension (NCPH) is the most common cause of portal hypertension and upper gastro-intestinal bleeding in children and adolescents in developing nations. It is characterized by features of portal hypertension with preserved liver function. Proximal splenorenal shunt (PSRS) and esophagogastric devascularization are the two most commonly performed surgeries for its management. The present study is aimed at comparison of surgical outcomes between these two procedures.

Material and Methods: Between April 2018 and March 2022, prospectively maintained data of consecutive NCPH cases who underwent surgical intervention was reviewed retrospectively. Cases were categorized into two groups- shunt surgery and devascularization. The pre-operative characteristics, peri-operative morbidity and long-term outcomes were compared between the groups.

Results: Of 112 cases who were treated during the study period, 54 cases which underwent surgery were included in the study. Of these, 20 cases underwent PSRS, and splenectomy and devascularization was performed in 34 cases. There was no difference in pre-operative variables between the two groups. Patients undergoing PSRS experienced longer duration of surgery (260 vs. 200 minutes, p< 0.001), and those in the devascularization group had significantly greater operative blood loss (350 vs. 455 ml, p< 0.001). Post-operative morbidity was comparable between the two groups. Hypersplenism was corrected in all cases and no cases reported rebleeding after median follow-up of 30 months. Three cases in each group developed features of portal biliopathy in follow up period.

Conclusion: Both PSRS and devascularization procedures have comparable efficacy and safety in the management of NCPH.

Keywords: Non-cirrhotic portal hypertension, extrahepatic portal venous obstruction, non-cirrhotic portal fibrosis, proximal spleno-renal shunt, devascularization

INTRODUCTION

The term "non-cirrhotic portal hypertension" (NCPH) includes a diverse group of vascular conditions with features of portal hypertension and relatively preserved liver function. NCPH is the commonest cause of portal hypertension and upper gastro-intestinal bleeding in children in developing nations (1). The two common pathologies leading to NCPH are non-cirrhotic portal fibrosis (NCPF)/idiopathic portal hypertension (IPH) and extrahepatic portal venous obstruction (EHPVO). Both conditions are characterized by the early development of features of portal hypertension (1). The etiology remains idiopathic in up to 70% of the patients (2). EHPVO and NCPF are differentiated from each other by the presence or absence of portal cavernoma formation, respectively (3).

The clinical features and management of EHPVO and NCPF share certain common characteristics. The commonest presentation of NCPH is variceal hemorrhage followed by symptomatic splenomegaly/and portal biliopathy (1). The primary focus of management in both of these conditions involves control of the acute episode of variceal bleeding first, followed by measures to prevent rebleeding (secondary prophylaxis) (2). Both for control of acute bleeding episode and secondary prophylaxis, endoscopic management in the form of endoscopic variceal ligation (EVL) or endoscopic sclerotherapy are the preferred modes of treatment (2). However, the re-bleeding rate following endotherapy is 17% and requires a long duration of regular follow-up (1). Moreover, endotherapy is not

Cite this article as: Anwar S, Parasar K, Anand U, Singh B, Kant K, Kodali R. Comparison of surgical outcomes between shunt surgery and devascularization in non-cirrhotic portal hypertension. Turk J Surg 2024; 40 (3): 229-239

Corresponding Author
Kunal Parasar
E-mail: kunal.parasar@gmail.com

Received: 23.05.2024
Accepted: 18.09.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6525

useful in symptomatic splenomegaly, hypersplenism, growth failure and portal biliopathy (4). Surgery is indicated in these conditions besides failure of endoscopic therapy (3). Non-selective porto-systemic shunts are the preferred surgical treatment option. Of these, proximal splenorenal shunt (PSRS) is the most common surgery performed (1).

Splenectomy with esophago-gastric devascularization is another effective way to treat variceal hemorrhage in NCPH and is indicated in situations where shunt surgery is not feasible due to unfavorable venous anatomy (5). The morbidity and rebleeding rate of devascularization procedures have been reported to be higher than those of shunt surgeries (6,7). However, the majority of these procedures were carried out for emergency management of uncontrolled variceal bleeding, leading to a higher rate of postoperative morbidity and mortality. There is also heterogeneity in the results of these procedures due to carrying out the procedure with or without esophageal transection (5,7). There are no studies comparing the outcomes of shunt surgery and devascularization procedure in the management of NCPH, especially in elective settings. The present study aimed at comparing the surgical outcome between shunt surgery and devascularization procedure in the management of NCPH.

MATERIAL and METHODS

Between April 2018 and March 2022, the prospectively maintained data of 112 consecutive patients with NCPH who were treated at a tertiary care institute in eastern India was reviewed retrospectively. Of these, 54 cases that underwent surgical intervention were included in the study. These cases were categorized into two groups based upon the type of surgery performed: shunt and devascularization groups (Figure 1). All cases were operated on an elective basis, and porto-systemic shunt surgery was the preferred mode of surgical intervention. Devascularization procedure was performed in situations where non-shuntable venous anatomy was identified either on preoperative imaging or as an intraoperative finding. Apart from these, devascularization was also carried out in NCPF with nodular liver. The two groups were compared in terms of surgical outcome and long-term follow-up. The study was conducted after prior approval of institutional research and ethical committee.

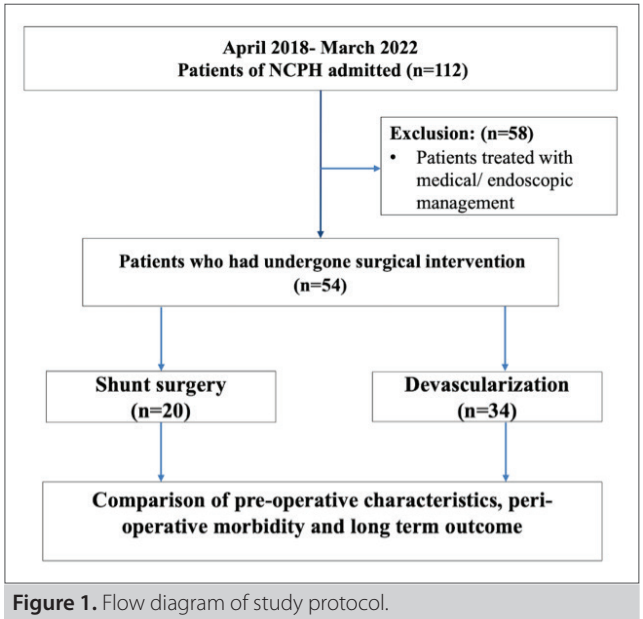

Figure 1. Flow diagram of study protocol.
NCPH: Non-cirrhotic portal hypertension.

The cases of NCPH were diagnosed as EHPVO or NCPF/IPH based upon doppler ultrasonographic or computed tomography porto-venography findings. Detailed pre-operative data of history and clinical examination findings were recorded. Pre-operative esophagogastroduodenoscopy was carried out in all cases, and esophageal varices were graded according to Baveno classification. Cases with active variceal bleeding, having grade 2 or 3 esophageal varices, or having red color signs were subjected to endoscopic variceal ligation or sclerotherapy. Indications of surgery were uncontrolled variceal bleeding on endotherapy, symptomatic hypersplenism/ splenomegaly, symptomatic portal biliopathy and growth retardation. During the initial phase of the study, we only performed transient elastography (fibroscan) in equivocal cases to differentiate between NCPF and child A cirrhosis. However, from July 2019 onward, it was regularly carried out in every case of NCPH. Hypersplenism was defined as cytopenias in any of cell lines associated with splenomegaly. Portal biliopathy (PB) or portal cavernoma cholangiopathy was defined as typical abnormalities of the biliary tract, including the gallbladder, cystic duct, and biliary ducts, in patients with portal hypertension.

Surgical Technique

Cases were planned for either shunt surgery (PSRS) or esophago-gastric devascularization with splenectomy, depending on the presence or absence of shuntable venous anatomy, respectively. For intended shunt surgery, cases were explored by either abdominal incision (reverse Makuchi incision or L-incision) or left thoracoabdominal (TA) incision, depending upon the surgeon's preference. The procedure begins with the opening of the lesser sac by division of gastrocolic omentum, identification, and ligation-in-continuity of the splenic artery over the superior border of pancreas. Complete mobilization of the spleen was achieved by the division of the splenic ligaments and collateral vessels along with them. On dissection of the splenic hilum, the splenic artery was ligated and divided, the splenic vein was clamped, and splenectomy completed. For PSRS, a length of 5-7 cm of splenic vein was dissected, and small tributaries were carefully ligated and divided. Exposure of

the left renal vein was done away from the renal hilum, and partial clamping was achieved by using Satinsky clamp. An end-to-side splenorenal shunt was performed using polypropylene 6-O double needle suture. In cases of pre-operatively identified non-shuntable venous anatomy, a left subcostal incision was utilized for the devascularization procedure. In this, devascularization of half of the lesser curvature and two-thirds of the greater curvature of the stomach was performed. Vessels along the lesser and greater curvature of the stomach, including short gastric, left gastroepiploic, and left gastric collaterals, were ligated. Retrogastric collaterals lying behind the gastro-esophageal junction were meticulously dissected and divided. Then, the lower 5-7 cm of esophagus was revascularized using a trans-hiatal approach without esophageal transection. Intra-operative core needle liver biopsy was taken in all cases for baseline liver histology. An abdominal drain was placed in all cases, and a left intercostal drain was placed when a thoraco-abdominal incision was used for surgery. The closure of incisions was carried out using delayed absorbable monofilament sutures (polydioxanone) in a continuous small-bites fashion. The bites were taken at a distance of 5 mm apart and about 5-9 mm from the wound edges.

The Clavien-Dindo (C-D) classification was utilized for classifying the post-operative complications. After discharge, the cases were followed at three-monthly intervals, which included history and clinical examination, laboratory investigations including complete blood counts, and liver function tests. Doppler ultrasonography of the abdomen was carried out six months post-operatively, and esophagogastroduodenoscopy was performed only when clinically indicated. A follow-up fibro-scan was also performed one year after the surgical procedure.

Statistical Analysis

For categorical variables, depending on the number of observations, Chi-square and Fisher's exact tests were applied to study the relations. Continuous variables were compared using the Student's t test for normally distributed data and the Mann-Whitney U test for non-parametric variables. Statistical significance was determined by applying a p-value of lower than 0.05. All the analyses were carried out using SPSS version 22.0 (SPSS Inc.).

RESULTS

The comparative analysis of pre-operative characteristics between the two groups is shown in the table (Table 1). Median age of the study population was 22.0 years (IQR= 15.5-28.5), and there was a slight female preponderance, as 28 (52%) of all cases were female. Participants in the shunt group had a lower age of onset of symptoms in comparison to devascularization group, and the majority of the cases underwent surgery in the second or third decade of life (Figure 2).

Of the total 54 cases, 45 (83.3%) were diagnosed as EHPVO, and the rest were NCPF (16.7%). The age of onset of symptoms was earlier in EHPVO than in NCPF (14.0 vs. 21.5 years). A history of bleeding and hypersplenism was present in 41 (76%) and 47 (87%) individuals, respectively.

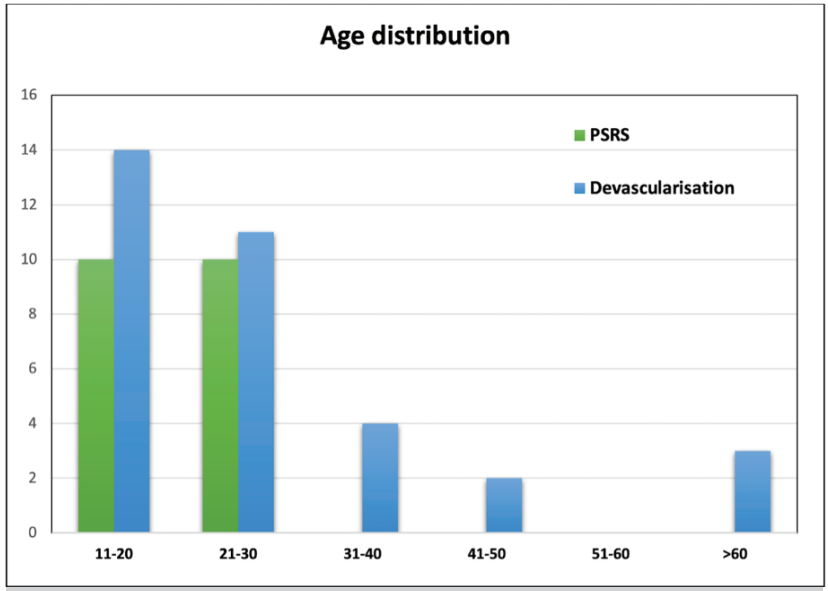

Figure 2. Comparison of age distribution of study subjects between the two groups. PSRS: Proximal spleno renal shunt.

Table 1. Comparison of pre-operative characteristics between two groups

Variable	Shunt	Devascularization	Total	p
Age (median, years)	20.0 (16.8-23.3)	23.0 (18.0-31.5)	22.0 (17.0-27.0)	0.119
Sex			0.181	
Male	12	14	26	
Female	08	20	28	
Duration of symptoms (mean, years)	5.11 ± 3.7	5.71 ± 2.4	5.49 ± 5.6	0.711
Age of onset (median, years)	14.0 (9.5-17.5)	18.0 (11.8-25.0)	16.0 (10.5-22.0)	0.089
Diagnosis				0.801
EHPVO	17	28	45	
NCPF	3	6	9	
Bleeder				0.232
Yes	17	24	41	
No	3	10	13	
Hypersplenism				0.733
Yes	17	30	47	
No	3	4	7	
EVL history				0.780
Yes	14	25	39	
No	6	9	15	
Number of EVL (median)	2.0 (1.0-3.0)	1.5 (1.0-3.0)	2.0 (1.0-3.0)	0.618
History of blood transfusion				0.842
Yes	13	23	36	
No	7	11	18	
Units of blood transfusion (median)	2.0 (1.0-4.0)	3.0 (0-4.0)	2.0 (0-4.0)	0.431
Esophageal varices				0.780
Present	19	29	48	
Absent	01	05	06	
Esophageal varices grade				0.439
Grade 1	04	06	10	
Grade 2	06	05	11	
Grade 3	09	18	27	
Portal hypertensive gastropathy				0.463
Present	11	22	33	
Absent	9	12	21	
Portal biliopathy				0.740
Symptomatic	01	03	04	
Asymptomatic	07	09	16	
Absent	12	22	34	
Grade of splenomegaly				0.426
Mild	0	2	2	
Moderate	7	7	14	
Gross	13	25	38	
Comorbidity				0.145
Present	0	5	5	
Absent	20	29	49	

Values are presented as number or mean ± standard deviation or median (inter quartile range).
EHPVO: Extra hepatic portal venous obstruction, NCPF: Non-cirrhotic portal fibrosis, EVL: Endoscopic variceal ligation.

A total of 39 (72%) cases underwent endotherapy (EVL) prior to surgery, with a comparatively higher number of median endotherapy sessions in the devascularization group (2.63 vs. 2.03). Esophageal varices were present in 48 (88.9%) cases, and half of the population had grade 3 esophageal varices. Features of clinical portal biliopathy were present in 20 (37%) cases. Of these, only four cases (7.5%) had symptomatic PB. A total of 38 (70.4%) cases had gross splenomegaly, with a mean splenic size of 20.4 ± 4.4 cm. Pre-operative characteristics were comparable between the two groups. Transient elastography was performed in 35/45 EHPVO and 6/9 NCPF cases, respectively. Mean liver stiffness (LS) in NCPF and EHPVO were (7.90 ± 1.17 kPa) and (4.61 ± 0.83 kPa), respectively.

The commonest indication of surgery in both groups was variceal hemorrhage, followed by symptomatic hypersplenism (Table 2). Three cases in devascularization and one case in the shunt group underwent surgery for symptomatic PB. Thrombosed spleno-portal axis (SPA) was evident in 14 (25.9%) cases, and all of these cases underwent devascularization. Median duration of the surgery was significantly higher in the shunt group (260 min) than the devascularization group (200 min) (p< 0.001). However, devascularization surgery was associated with significantly higher median blood loss (455 ml vs. 350 ml). No difference was found in other intra-operative parameters between the two groups.

Table 2. Comparison of intra-operative characteristics between two groups

Variable	Shunt	Devascularization	Total	p
Indication of surgery				0.676
Bleed	11	18	29	
Symptomatic hypersplenism (SH)	03	07	10	
Bleed + SH	05	04	09	
Portal biliopathy	01	03	04	
Splenomegaly	00	02	02	
Incision				<0.001
Abdominal	06	28	34	
Thoraco-abdominal (TA)	14	06	20	
Spleen size (cm)	20.2 ± 4.1	20.5 ± 4.5	20.4 ± 4.4	0.844
Splenic vein diameter (mm)	11.1 ± 2.75	12.5 ± 5.4	11.8 ± 4.4	0.371
Spleno-portal axis (SPA)				<0.001
Patent	20	20	40	
Thrombosed	0	14	14	
Spontaneous porto-systemic shunt				0.041
Present	02	12	14	
Absent	18	22	40	
Intra-operative blood transfusion				0.614
Yes	16	29	45	
No	04	05	09	
Pre-operative blood transfusion				0.273
Yes	01	05	06	
No	19	29	48	
Post-operative blood transfusion				0.801
Yes	03	06	09	
No	17	28	45	
Units of peri-operative BT	1.93 ± 1.3	2.86 ± 2.9	2.49 ± 2.4	0.274
Duration of surgery (min)[a]	260 (250-270)	200 (180-208)	210 (196-250)	<0.001
Blood loss (ml)[a]	350 (328-373)	455 (450-480)	445 (353-460)	<0.001

Values are presented as number or mean ± standard deviation or median (inter quartile range).

[a]Mann-Whitney U test, SH: Symptomatic hypersplenism, BT: Blood transfusion.

Overall, post-operative morbidity developed in 26 cases (48.1%). However, about two-thirds of these were C-D grade I and II (22 cases), and grade III and IV morbidities were reported in two and one cases, respectively (Table 3). One patient, who underwent surgery after failed endoscopic retrograde cholangiography (ERC) for PB with recurrent cholangitis, died in the post-operative period due to sepsis and multi-organ failure. The commonest morbidity was transient ascites, which developed in twenty-two cases (41%) and resolved through conservative management and pharmacotherapy in all the cases. No cases developed surgical site infection or wound dehiscence. There was no difference in the occurrence and grade of post-operative morbidity or length of hospital stay between the two groups. Liver histology was essentially normal in EHPVO cases while in NCPF, small portal vein branches were obliterated in all cases and nodular hyperplasia was evident in six (66.7%) cases.

Median duration of follow-up was 30 months (range= 24 to 66 months). Symptoms related to hypersplenism were corrected in all cases (Table 4). There was no reported re-bleeding episode in any of the cases during the follow-up. In 16/19 (84%) cases, a patent shunt was identified on Doppler ultrasonography. Three cases in each group developed symptomatic portal biliopathy during follow-up. Of these, two cases in the shunt group and three cases in the devascularization group presented with features of cholangitis. Two cases in each group required ERC-stenting, and one case in the shunt group underwent Roux-en-Y hepaticojejunostomy two years after the index surgery. We observed no significant change in liver stiffness on transient elastography at one year of follow-up. Mean LS value in NCPF and EHPVO were 7.97 ± 1.12 kPa (p= 0.187) and 4.75 ± 0.85 kPa (p= 0.477), respectively.

DISCUSSION

Porto-systemic shunt is the preferred surgical procedure in the management of NCPH. The most commonly performed shunt procedure is the PSRS (1). However, in the absence of shuntable venous anatomy, esophago-gastric devascularization procedures combined with splenectomy are employed (4).

Table 3. Comparison of post-operative morbidity between two groups

Variable	Shunt	Devascularization	Total	p
Overall morbidity				0.835
Present	10	16	26	
Absent	10	18	28	
Transient ascites				0.932
Present	08	14	22	
Absent	12	20	32	
Post-operative bleeding[a]				1.000
Present	01	03	04	
Absent	19	31	50	
Other morbidity[b a]				
Present	01	04	05	0.640
Absent	19	30	49	
Post-operative blood transfusion[a]				1.000
Yes	03	06	09	
No	17	28	45	
Clavien-Dindo grade[a]				0.606
Grade I	05	07	12	
Grade II	05	05	10	
Grade III	00	02	02	
Grade IV	00	01	01	
Grade V	01	00	01	
Hospital stay (median, days)	7 (5-10)	6 (4-22)	-	0.162

Values are presented as number or median (range)

[a]Fischer's exact test, [b]Includes pancreatic fistula (2), chest infections (2) and urinary tract infection (1).

Table 4. Comparison of follow-up results between two groups

Variable	Shunt	Devascularization	Total	p
Correction of hypersplenism				-
Yes	16	27	43	
No	0	0	0	
NA	3	7	10	
Rebleeding				-
Yes	0	0	0	
No	19	34	53	
Shunt thrombosis				
Yes	03	NA	-	-
No	16	NA		
Portal biliopathy				0.486
Yes	3	3	6	
No	16	31	47	
Cholangitis				0.885
Yes	2	3	5	
No	17	31	48	
Intervention for portal biliopathy				0.513
Conservative	1	1	2	
ERCP	1	2	3	
Surgery	1	0	1	
Mortality				-
Yes	0	0	0	
No	19	34	53	

Values are presented as number. ERCP: Endoscopic retrograde cholangiopancreatography, NA: Not applicable.

Even though there is ample literature on shunt surgery and selective devascularization, there is a paucity of literature comparing the two procedures. In the present study, we compared the surgical outcome between two main surgical procedures, namely shunt surgery (PSRS) and splenectomy with esophago-gastric devascularization. We demonstrated that the two procedures are safe and comparable for both short-term and long-term outcomes.

NCPH has been described as a disease of children and young adults. The median age of our study population at the time of surgical intervention was 22.0 years (range= 12-64), which is consistent with the previous studies (8-10). Median age of population at the symptom's onset was 16.0 years (range= 4-43). There is a difference of a decade in terms of the onset of symptoms in NCPF as compared to EHPVO, and generally, in EHPVO, symptoms appear in the first and second decade of life, while in NCPF they appear in the third or fourth decade (2,11). Our results were also in line with previous studies. The reported incidence of esophageal varices in EHPVO and NCPF is 80-90% (10-12). In accordance with previous studies, the commonest presentation of NCPH was recurrent variceal bleeding with failed endotherapy (10,11,13). About two-thirds and three-fourths of our cases required blood transfusions and endotherapy, respectively. Median number of endotherapy sessions in our study was 2.43 before undergoing surgery. Both of these conditions are associated with moderate or massive splenomegaly (10). The reported incidence of hypersplenism is comparatively higher in NCPH than cirrhosis of the liver, and it varies from 22% to 80% (14,15). Similar to our findings, most of the cases of hypersplenism are asymptomatic (14). A high incidence of hypersplenism in surgical patients may be explained by the fact that endotherapy does not treat hypersplenism, and such cases are more likely to be referred for surgical intervention. Portal biliopathy occurs in about 80-100% of cases of EHPVO and about 9-40% of cases of NCPF, and the majority of the cases (62-95%) remain asymptomatic (16). No difference was found between the two groups in terms of pre-operative characteristics, including patient demographics, symptomatology, and the presence of comorbidities.

NCPH treatment is primarily focused on the management of acute variceal bleeding and the prevention of rebleeding (secondary prophylaxis). Although endoscopic therapy is the preferred mode of treatment for NCPH, the indications of surgery included failed endotherapy, symptomatic hypersplenism, portal biliopathy, and growth retardation (1). Among these, the primary indication of surgery is a recurrent variceal bleed with failed endoscopic management (17). In accordance with previous studies, recurrent variceal bleeding with failed endotherapy was the most common indication for surgery in our study. Surgeries for symptomatic hypersplenism and portal biliopathy were indicated in 10 (18.5%) and 4 (7.4%) cases, respectively.

There was a difference in the type of incisions between the two groups, as all planned devascularization procedures were performed with abdominal incisions, while PSRS was performed with both abdominal and thoraco-abdominal (TA) approaches, depending upon the surgeon's preferences. The TA approach for devascularization was only used in situations where the plan of surgery was changed intra-operatively with the identification of non-shuntable venous anatomy. Since the cases with thrombosed SPA could not undergo PSRS, it was only present in the devascularization group. In the current study, spontaneous shunts were present in about 26% of the cases, which was higher than a previous study (10). However, other studies reported a non-shuntable venous anatomy due to the occurrence of splenic vein thrombosis in 35% to 69.2% of cases (5,18,19). The reason could be the delayed presentation after the onset of symptoms. There was no difference between the two groups in indications of surgery, splenic size, splenic vein diameter, or the or the need for peri-operative blood transfusions. Mean duration of surgery was significantly higher in the shunt surgery group (260 vs. 200 minutes), and intra-operative blood loss was significantly higher in the devascularization group (455 vs. 350 ml). Saluja et al. have compared PSRS with splenectomy alone in NCPF patients and reported a higher operative duration (215 vs. 95 min) and higher blood loss (375 vs. 200 ml) in the PSRS group (20). However, meaningful comparisons could not be drawn as the authors did not perform esophago-gastric devascularization along with splenectomy. Das et al. have reported a similar duration of shunt surgery (275.9 min), operative blood loss (365.6 ml), and mean duration of hospital stay (7.35 days) in shunt surgeries (21). Chattopadhyay et al. have compared the outcome of portal biliopathy in NCPH patients between PSRS and splenectomy and devascularization but did not provide intra-operative details (22).

In our study, about 48% of the total cases developed post-operative complications. Post-operative transient ascites was the most common morbidity and was present in 22 (84.6%) cases, which resulted in higher overall morbidity. Most of the complications were minor, and major complications (C-D grade ≥3) were evident only in four (7.4%) cases. The exact mechanism of post-operative ascites is unknown but a transient rise in portal pressure due to disruption of spontaneous shunts could be the possible mechanism. Das et al. have reported an overall complication rate of 20.8%, with minor complications in the majority of the cases Pal et al. have reported an operative mortality rate of 0.9%, and 3/114 cases required re-exploration for bleeding complications (21). The median hospital stay in their study was seven days (9). Similarly, in a previous study of 160 PSRS procedures in EHPVO, the authors have reported an elective mortality rate of 0.7% (23). Devascularization procedures were associated with higher post-operative complications owing to combined esophageal transection, including anastomotic leaks and delayed esophageal strictures. However, devascularization without esophageal transection has been found to be equally effective in controlling variceal bleeding but with a reduced rate of post-operative complications (5,7). The development of post-operative ascites in these cases could result in wound dehiscence and incisional hernia formation. The recommended technique of wound closure of elective laparotomies is by a "continuous small-bites suturing technique". In this, delayed absorbable suture materials are used, and bites are taken at only aponeurosis 5-9 mm away from the wound margins and distance from each bite is kept at 5 mm. This technique results in adequate tissue perfusion. Due to lack of quality evidence, European hernia society recommends the utilization of similar principles for non-midline incisions too (24). In our study, we observed no wound dehiscence or incisional hernia formation utilizing this method of abdominal wall closure.

Mesenterico-left portal vein bypass (rex-shunt) is regarded as the most physiological surgical option, but it is mostly feasible in young children, and comparative data with non-selective shunts is still lacking (3). Although, at present, porto-systemic shunts are the preferred surgical intervention in NCPH, devascularization is employed in situations where shunts are not possible owing to unfavorable venous anatomy, inadvertent venous injury, or venous thrombosis. Rebleeding rate after PSRS varies from 0.6% to 11% (9,15,21,23). Rebleeding rates of devascularization have been reported to be somewhat higher in older studies, i.e., 11%-17%; a newer study from India observed no rebleeding after a follow-up of 12-60 months (6,7,25). In our study, no patient in either arm reported a rebleeding episode after a median follow-up of 30 months. These favorable results could be because of meticulous esophago-gastric devascularization, which includes ligation of retrogastric and left gastric veins. An incomplete devascularization is known to increase re-bleeding rates substantially (26). The other reason could be a comparatively

shorter follow-up period, as a median bleed-free period of 45 months has been reported in a previous study (9). Similar to other studies, we observed resolution of hypersplenism in all cases (18,27). We observed one post-operative mortality in a case of EHPVO accompanied by portal biliopathy and recurrent cholangitis because of severe cholangitis, sepsis, and multi-organ failure. Up to 10% of individuals with PB may die because of various complications (2).

The shunt patency rate in EHPVO varies from 84% to 98% in different studies (14,15,21). However, a recent study from India questioned the long-term patency of shunts and reported a patency rate of 60% between one and five years after the procedure and observed a higher shunt patency in cases of NCPF (28). There are variable results of shunt obliteration in NCPF. Saluja et al. reported a shunt block in 6.25% of cases, while in another study from India, it was 25% (20,28). We observed patent shunts in 17/20 (85%) cases using clinical and doppler ultrasonography. We did not encounter any cases of encephalopathy in the follow-up period. Moreover, conditions specifically defined for NCPF after shunt surgery (myelopathy, encephalopathy, and nephropathy) were not observed in our study. Saluja et al. found hepatic encephalopathy in 12.5% of NCPF cases that underwent shunt surgery (20). Similarly, Pal et al. have reported a 13% incidence of post-shunt encephalopathy, and 9.7% of cases in their series developed post-shunt nephropathy (29). The authors have found shunt surgery effective in terms of variceal bleed control but questioned the feasibility of shunt surgery in NCPF due to its high long-term morbidity (45%) (29). We did not observe any of these complications, probably due to the selection of shunt surgery in very few NCPF cases and comparatively shorter duration of follow-up.

Chattopadhyay et al. have compared the outcomes of shunt surgery and devascularization in NCPH-associated portal biliopathy and found equal efficacy of both procedures in relieving PB (22). We also observed similar findings in our study. Shunt surgeries are known to decrease the portal pressure by diverting the portal blood and, hence, alleviate the symptoms of portal biliopathy. However, there are studies that have shown a reduction of portal blood flow by splenectomy in liver transplant cases (30). This was also observed in another study concerning NCPF, in which the authors found regression of varices after splenectomy alone in NCPF-associated PB (20). Therefore, splenectomy with devascularization is effective in relieving PB in NCPH and may be opted for in cases where shunt surgery is not possible. Six cases in the follow-up period developed PB (three in each group), and most of these cases responded to conservative (2) or ERC-stenting (3). One patient in the shunt group had recurrent cholangitis despite ERC intervention, was diagnosed as having biliary stricture, and required Roux-en-Y hepaticojejunostomy two years after the index surgery. Portal cavernoma of long duration exerts ischemic changes in bile ducts, resulting in biliary strictures that are not amenable to endoscopic therapy and often require surgical biliary bypass (31).

The role of liver biopsy is limited in the diagnosis of EHPVO and is only indicated when there is suspicion of chronic liver disease (1,32). However, in NCPF, it is required to rule out underlying cirrhosis and differentiate it from other causes of cirrhosis (1). An intraoperative liver biopsy is also recommended for documenting baseline liver histology for follow-up. Liver histology usually remains normal in patients with EHPVO (1). In accordance with the previous studies, an obliterative sclerosis of medium caliber portal vein branches was present in all cases, and there was no evidence of liver cirrhosis in NCPF (10). Transient elastography has emerged as a promising tool to differentiate NCPF from other causes of portal hypertension (33). A previous study from Spain has reported a significantly lower mean liver stiffness value in NCPF/IPH than cirrhosis but higher than in EHPVO (33). Similar findings have also been reported by another study from India (34). We also found a higher mean LS value in NCPF than EHPVO. A stable LS value at the one-year follow-up in our study also indicates that liver parenchyma is not involved in the pathogenesis of NCPH.

There are certain limitations to our study. Firstly, it is a retrospective and single-center study with an inherent risk of referral bias. Secondly, devascularization was carried out only in cases in which shunt surgery was not possible, and many of these cases had thrombosed SPA. The results should be interpreted cautiously, especially with regards to portal biliopathy, as devascularization may augment PB in cases with patent SPA. Lastly, we did not evaluate minimal hepatic encephalopathy. Nevertheless, this is the first study to compare the surgical outcomes between these two procedures on an elective basis. Most of the previous studies either performed a very small number of devascularization procedures in comparison to shunt surgeries or carried out them in emergency settings. Therefore, meaningful comparisons are difficult to interpret based on the findings of those studies.

In conclusion, both proximal spleno-renal shunt and devascularization procedures have comparable short-term and long-term outcomes in the management of non-cirrhotic portal hypertension. Although shunt surgery remains the preferred procedure when surgery is indicated, devascularization procedure is reasonably safe and should be performed when shunt surgery is not possible for various reasons.

Ethics Committee Approval: This study was obtained from All India Institute of Medical Sciences Patna-801507 Research Advisory Committee (Decision no: RD/AIIMS/PAT/2024/RAC/53, Date: 21.03.2024).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - KP, SA; Design - KP, SA; Supervision - KP, SA; Data Collection and/or Processing - KP, SA, KK; Analysis and/or Interpretation - KP, BNS; Literature Search - SA, RK; Writing Manuscript - SA, BNS, KK, RK; Critical Reviews - KP, UA.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Sarin SK, Khanna R. Non-cirrhotic portal hypertension. Clin Liver Dis 2014; 18(2): 451-76. https://doi.org/10.1016/j.cld.2014.01.009*
2. *Khanna R, Sarin SK. Non-cirrhotic portal hypertension - diagnosis and management. J Hepatol 2014; 60(2): 421-41. https://doi.org/10.1016/j.jhep.2013.08.013*
3. *Mangla V, Pal S, Sahni P. Surgery for non-cirrhotic portal hypertension: Current status. Tropic Gastroenterol 2017; 37(3): 152-5. https://doi.org/10.7869/tg.348*
4. *de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63(3): 743-52. https://doi.org/10.1016/j.jhep.2015.05.022*
5. *Johnson M, Rajendran S, Kannan TB, Jeswanth S, Ravichandran P, Surendran R. Transabdominal modified devascularization procedure with or without esophageal stapler transection - an operation adequate for effective control of a variceal bleed. Is esophageal stapler transection necessary?. World J Surg 2006; 30(8): 1507-18. https://doi.org/10.1007/s00268-005-0754-x*
6. *Mathur SK, Shah SR, Nagral SS, Soonawala ZF. Transabdominal extensive esophagogastric devascularization with gastroesophageal stapling for management of noncirrhotic portal hypertension: Long-term results. World J Surg 1999; 23(11): 1168-75. https://doi.org/10.1007/s002689900641*
7. *Goyal N, Singhal D, Gupta S, Soin AS, Nundy S. Transabdominal gastroesophageal devascularization without transection for bleeding varices: Results and indicators of prognosis. J Gastroenterol Hepatol 2007; 22(1): 47-50. https://doi.org/10.1111/j.1440-1746.2006.04330.x*
8. *Sarin SK, Gupta N, Jha SK, Agrawal A, Mishra SR, Sharma BC, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. Gastroenterology 2010; 139(4): 1238-45. https://doi.org/10.1053/j.gastro.2010.06.017*
9. *Pal S, Mangla V, Radhakrishna P, Sahni P, Pande GK, Acharya SK, et al. Surgery as primary prophylaxis from variceal bleeding in patients with extrahepatic portal venous obstruction. J Gastroenterol Hepatol 2013; 28(6): 1010-4. https://doi.org/10.1111/jgh.12123*
10. *Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): Experience with 151 patients and a review of the literature. J Gastroenterol Hepatol 2002; 17(1): 6-16. https://doi.org/10.1046/j.1440-1746.2002.02596.x*
11. *Weiss B, Shteyer E, Vivante A, Berkowitz D, Reif S, Weizman Z, et al. Etiology and long-term outcome of extrahepatic portal vein obstruction in children. World J Gastroenterol 2010; 16(39): 4968-72. https://doi.org/10.3748/wjg.v16.i39.4968*
12. *Pande C, Kumar A, Sarin SK. Non-cirrhotic portal fibrosis: A clinical profile of 366 patients: 439. ACG 2006; 101: S191. https://doi.org/10.14309/00000434-200609001-00439*
13. *Vakili C, Farahvash MJ, Bynum TE. "Endemic" idiopathic portal hypertension: Report on 32 patients with non-cirrhotic portal fibrosis. World J Surg 1992; 16(1): 118-24. https://doi.org/10.1007/BF02067126*
14. *Mitra SK, Kumar V, Datta DV, Rao PN, Sandhu K, Singh GK, et al. Extrahepatic portal hypertension: A review of 70 cases. J Pediatr Surg 1978; 13(1): 51-7. https://doi.org/10.1016/S0022-3468(78)80212-7*
15. *Orloff MJ, Orloff MS, Girard B, Orloff SL. Bleeding esophagogastric varices from extrahepatic portal hypertension: 40 years' experience with portal-systemic shunt. J American College Surgeons 2002; 194(6): 717-28. https://doi.org/10.1016/S1072-7515(02)01170-5*
16. *Chandra R, Kapoor D, Tharakan A, Chaudhary A, Sarin SK. Portal biliopathy. J Gastroenterol Hepatol 2001; 16(10): 1086-92. https://doi.org/10.1046/j.1440-1746.2001.02562.x*
17. *Sarin SK, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, et al. Consensus on extra-hepatic portal vein obstruction. Liver Int 2006; 26(5): 512-9. https://doi.org/10.1111/j.1478-3231.2006.01269.x*
18. *Koshy A, Bhasin DK, Kapur KK. Bleeding in extrahepatic portal vein obstruction. Indian J Gastroenterol 1984; 3(1): 13-4.*
19. *Orozco H, Takahashi T, Mercado MA, Prado E, Chan C. Surgical management of extrahepatic portal hypertension and variceal bleeding. World J Surg 1994; 18(2): 246-50. https://doi.org/10.1007/BF00294409*
20. *Saluja SS, Kumar A, Govind H, Varshney VK, Khullar R, Mishra PK. Splenectomy with endotherapy in non-cirrhotic portal fibrosis related portal hypertension: Can it be an alternative to proximal spleno-renal shunt? Ann Hepatobiliary Pancreat Surg 2020; 24(2): 168-73. https://doi.org/10.14701/ahbps.2020.24.2.168*
21. *Das S, Manadal TS, Das S, Biswas J, Gupta A, Mukherjee S, et al. Surgical outcome of extrahepatic portal venous obstruction: Audit from a tertiary referral centre in Eastern India. Ann Hepatobiliary Pancreat Surg 2023; 27(4): 350-65. https://doi.org/10.14701/ahbps.23-025*
22. *Chattopadhyay S, Govindasamy M, Singla P, Varma V, Mehta N, Kumaran V, et al. Portal biliopathy in patients with non-cirrhotic portal hypertension: Does the type of surgery affect outcome? HPB (Oxford) 2012; 14(7): 441-7. https://doi.org/10.1111/j.1477-2574.2012.00473.x*
23. *Prasad AS, Gupta S, Kohli V, Pande GK, Sahni P, Nundy S. Proximal splenorenal shunts for extrahepatic portal venous obstruction in children. Ann Surg 1994; 219(2): 193-6. https://doi.org/10.1097/00000658-199402000-00011*
24. *Deerenberg EB, Henriksen NA, Antoniou GA, Antoniou SA, Bramer WM, Fischer JP, et al. Updated guideline for closure of abdominal wall incisions from the European and American Hernia Societies. Br J Surg 2022; 109(12): 1239-50. https://doi.org/10.1093/bjs/znac302*
25. *Subhasis RC, Rajiv C, Kumar SA, Kumar AV, Kumar PA. Surgical treatment of massive splenomegaly and severe hypersplenism secondary to extrahepatic portal venous obstruction in children. Surg Today 2007; 37(1): 19-23. https://doi.org/10.1007/s00595-006-3333-3*
26. *Hassab MA. Gastro-esophageal decongestion and splenectomy GEDS (Hassab), in the management of bleeding varices. Review of literature. Int Surg 1998; 83(1): 38-41.*

27. *Rajalingam R, Javed A, Sharma D, Sakhuja P, Singh S, Nag HH, et al. Management of hypersplenism in non-cirrhotic portal hypertension: A surgical series. Hepatobiliary Pancreat Dis Int 2012; 11(2): 165-71. https://doi.org/10.1016/S1499-3872(12)60143-X*

28. *Mishra PK, Patil NS, Saluja S, Narang P, Solanki N, Varshney V. High patency of proximal splenorenal shunt: A myth or reality? - A prospective cohort study. Int J Surg 2016; 27: 82-7. https://doi.org/10.1016/j.ijsu.2015.12.071*

29. *Pal S, Radhakrishna P, Sahni P, Pande GK, Nundy S, Chattopadhyay TK. Prophylactic surgery in non-cirrhotic portal fibrosis: Is it worthwhile? Indian J Gastroenterol 2005; 24(6): 239-42.*

30. *Sato Y, Yamamoto S, Oya H, Nakatsuka H, Tsukahara A, Kobayashi T, et al. Splenectomy for reduction of excessive portal hypertension after adult living-related donor liver transplantation. Hepatogastroenterology 2002; 49(48): 1652-5.*

31. *Premkumar M, Dhiman RK. Portal cavernoma cholangiopathy: Indian perspective. Clin Liver Dis 2021; 18(3): 127-37. https://doi.org/10.1002/cld.1130*

32. *Flores-Calderón J, Morán-Villota S, Rouassant SH, Nares-Cisneros J, Zárate-Mondragón F, González-Ortiz B, et al. Guidelines for the diagnosis and treatment of extrahepatic portal vein obstruction (EHPVO) in children. Ann Hepatol 2013; 12: S3-24. https://doi.org/10.1016/S1665-2681(19)31403-6*

33. *Seijo S, Reverter E, Miquel R, Berzigotti A, Abraldes JG, Bosch J, et al. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. Digestive Liver Dis 2012; 44(10): 855-60. https://doi.org/10.1016/j.dld.2012.05.005*

34. *Sharma P, Agarwal R, Dhawan S, Bansal N, Singla V, Kumar A, et al. Transient elastography (Fibroscan) in patients with non-cirrhotic portal fibrosis. J Clin Exp Hepatol 2017; 7(3): 230-4. https://doi.org/10.1016/j.jceh.2017.03.002*

ORİJİNAL ÇALIŞMA-ÖZET

Turk J Surg 2024; 40 (3): 229-239

Sirotik olmayan portal hipertansiyonda şant cerrahisi ile devaskülarizasyon arasındaki cerrahi sonuçların karşılaştırılması

Saad Anwar, Kunal Parasar, Utpal Anand, Basant Singh, Kislay Kant, Rohith Kodali

[1]Tüm Hindistan Tıp Bilimleri Enstitüsü, Cerrahi Gastroenteroloji Anabilim Dalı, Patna, Hindistan

ÖZET

Giriş ve Amaç: Sirotik olmayan portal hipertansiyon (NCPH), gelişmekte olan ülkelerdeki çocuk ve ergenlerde portal hipertansiyon ve üst gastrointestinal kanamanın en yaygın nedenidir. Karaciğer fonksiyonu korunmuş portal hipertansiyon özellikleri ile karakterizedir. Proksimal splenorenal şant (PSRS) ve özofagogastrik devaskülarizasyon, bu durumun tedavisinde en sık kullanılan cerrahi tedavi yöntemleridir. Bu çalışma, bu iki prosedür arasındaki cerrahi sonuçların karşılaştırılmasını amaçlamaktadır.

Gereç ve Yöntem: Nisan 2018 - Mart 2022 tarihleri arasında cerrahi girişim uygulanan ardışık NCPH olgularının prospektif olarak tutulan verileri retrospektif olarak incelendi. Olgular şant cerrahisi ve devaskülarizasyon olmak üzere iki gruba ayrıldı. Gruplar arasında ameliyat öncesi özellikler, peri-operatif morbidite ve uzun vadeli sonuçlar karşılaştırıldı.

Bulgular: Çalışma süresi boyunca tedavi edilen 112 olgudan cerrahi uygulanan 54 olgu çalışmaya dahil edildi. Bunlardan 20 olguya PSRS, 34 olguya splenektomi ve devaskülarizasyon uygulandı. İki grup arasında ameliyat öncesi değişkenler açısından fark yoktu. Proksimal splenorenal şant uygulanan hastalarda daha uzun ameliyat süresi (260'a karşı 200 dakika, p< 0,001) ve devaskülarizasyon grubundakilerde anlamlı olarak daha fazla ameliyat kan kaybı (350'ye karşı 455 ml, p< 0,001) yaşandı. Ameliyat sonrası morbidite iki grup arasında karşılaştırılabilir düzeydeydi. Hipersplenizm tüm olgularda düzeltildi ve 30 aylık medyan takip sonrasında hiçbir olguda tekrarlayan kanama bildirilmedi. Her iki gruptaki üç olguda takip döneminde portal biliyopati özellikleri gelişti.

Sonuç: Hem PSRS hem de devaskülarizasyon prosedürleri NCPH tedavisinde karşılaştırılabilir etkinlik ve güvenliğe sahiptir.

Anahtar Kelimeler: Sirotik olmayan portal hipertansiyon, ekstrahepatik portal venöz obstrüksiyon, sirotik olmayan portal fibrozis, proksimal spleno-renal şant, devaskülarizasyon

DOİ: 10.47717/turkjsurg.2024.6525

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (3): 240-246

The relation between ABO blood groups and clinicopathologic characteristics of the patients with gastric adenocarcinomas

Süleyman Utku Çelik, Yasin Gülap, Mehmet Bahadır Demir, Şahin Kaymak, Rahman Şenocak

Clinic of General Surgery, Gülhane Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Objective: This study aimed to examine the association between blood groups and clinicopathological factors that could affect the prognosis of patients with gastric cancer.

Material and Methods: In this retrospective single-center study, patients with gastric adenocarcinoma were obtained from a prospectively maintained database. The association between blood groups and clinicopathologic characteristics including sex, age, tumor location, tumor size, tumor stage, metastatic lymph node ratio (MLR), lymphovascular invasion, and perineural invasion were analyzed.

Results: The study included 91 female and 221 male patients. The blood group distribution was A>O>B>AB both in the patients and healthy donors. Non-O blood types were more common in cancer patients than in healthy donors (p= 0.038). However, there was no significant association between sex, age, tumor location, tumor stage, lymph node status, lymphovascular invasion, and perineural involvement and blood groups. ≥7 lymph node involvement and MLR of >0.6 were significantly more common in patients with blood group A than in those with non-A blood groups (p= 0.034 and p= 0.018; respectively).

Conclusion: The findings of this study suggest that blood group A patients are associated with higher MLR and N3 involvement, so it is possible that these patients with gastric cancer have a poorer prognosis.

Keywords: ABO blood group, gastric cancer, outcome, pathologic characteristics

INTRODUCTION

Gastric cancer is a leading cause of cancer deaths worldwide. It is estimated that more than one million new cases of gastric cancer will occur annually, with approximately 750.000 of these cases resulting in death from the disease. Moreover, it is responsible for one in every 12 cancer-related deaths (1). Its prevalence among men is twice that of women (1,2).

The fact that the geographical distribution of gastric cancer shows a substantial variation suggests that there are numerous factors affecting its incidence, survival, and mortality (3). In addition to genetic predisposition, environmental factors and nutritional habits appear to have an important role in the development of gastric cancer. A diet high in salt, nitrite, or ultra-processed foods and fatty acids, as well as diets that are low in whole grains, seeds, fruit, and vegetables, has been linked to an elevated risk of gastric cancer (4). The association between Helicobacter pylori and gastric carcinoma is well-documented, with this microorganism accounting for approximately 90% of non-cardia gastric cancer (5).

ABO blood group antigens are complex carbohydrates expressed on red blood cells (RBCs) (6). These antigens have been the focus of many studies since their discovery. Although blood group antigens are markers on the surface of RBC membranes, they are highly expressed on lymphocytes, platelets, and the gastrointestinal mucosal epithelium (7). It has been suggested that the clinical use of the ABO blood-group system may be expanded beyond transfusion, immunohematology, and transplantation medicine (8). Aird et al. were the first to investigate the link between blood groups and gastric adenocarcinoma in an early-1950s study of almost 3.500 patients (9). The authors found that gastric

Cite this article as: Çelik SU, Gülap Y, Demir MB, Şahin K, Şenocak R. The relation between ABO blood groups and clinicopathologic characteristics of the patients with gastric adenocarcinomas. Turk J Surg 2024; 40 (3): 240-246.

Corresponding Author
Süleyman Utku Çelik
E-mail: s.utkucelik@hotmail.com

Received: 08.05.2024
Accepted: 24.09.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6434

cancer was more prevalent in patients with the blood group A, whereas the rate was lower among those with the O blood group compared to normal population. Since that time, numerous studies have been conducted to investigate the relation between blood groups and various types of cancer (10). It is currently believed that individuals with blood group A are at a higher risk of developing cancer than those with non-A blood groups. Conversely, those with blood group O are thought to be at a lower risk than those with non-O blood groups (11).

Although there is a well-established association between ABO blood groups and certain cancer characteristics, there has been a paucity of knowledge regarding the link between blood groups and the prognosis of these diseases, as well as the clinicopathologic features affecting the prognosis. In this study, we analyze the association between blood groups and the clinicopathologic characteristics that may influence the prognosis of patients with gastric adenocarcinomas. Additionally, the study presents a comparative analysis of the frequency of blood groups in patients with gastric cancer versus the general population.

MATERIAL and METHODS

Study population

Approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (approval no: 2024/178).

The study was conducted at a tertiary care hospital over the period of seven years from January 2017 and December 2023 and involved 312 patients with pathologically diagnosed gastric adenocarcinomas. Patients with gastric cancers other than adenocarcinomas and with Siewert type I-II cancers were excluded from the study. Patients with distant metastases (stage IV) were also not included since they were treated with chemotherapy instead of surgical resection (Figure 1). As a control group, 6.382 healthy blood donors who donated to the blood unit of the same hospital over the course of a year, between January 2017 and December 2018, were also enrolled.

Clinicopathological data

The standard agglutination test was used for the determination of the blood groups of the patients and the healthy controls. In addition, data on demographic features and pathological characteristics including tumor location, size, and differentiation degree, number of metastatic lymph nodes, tumor-node-metastasis (TNM) stage, metastatic lymph node ratio (MLR), lymphovascular invasion and perineural tumor invasion was obtained from the hospital database (12).

Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD) or median with range values, while categorical data were expressed as number (n) and percentage (%), depending on distribution assumptions. The differences in clinicopathologic characteristics between the blood groups were analyzed using chi-square or Fisher's exact test. All p values were two-sided, and the significance level was set at $p < 0.05$. Jamovi (version 2.5) software was used for data analyses (Sydney, Australia).

RESULTS

The study included 221 male patients (70.8%) and 91 female patients (29.2%), with a mean age of 66.2 ± 12.7 years. About half of the patients (n= 154, 49.4%) had blood group A, 89 (28.5%) had blood group O, 46 (14.7%) had blood group B, and 23 patients (7.4%) had blood group AB. Blood groups were

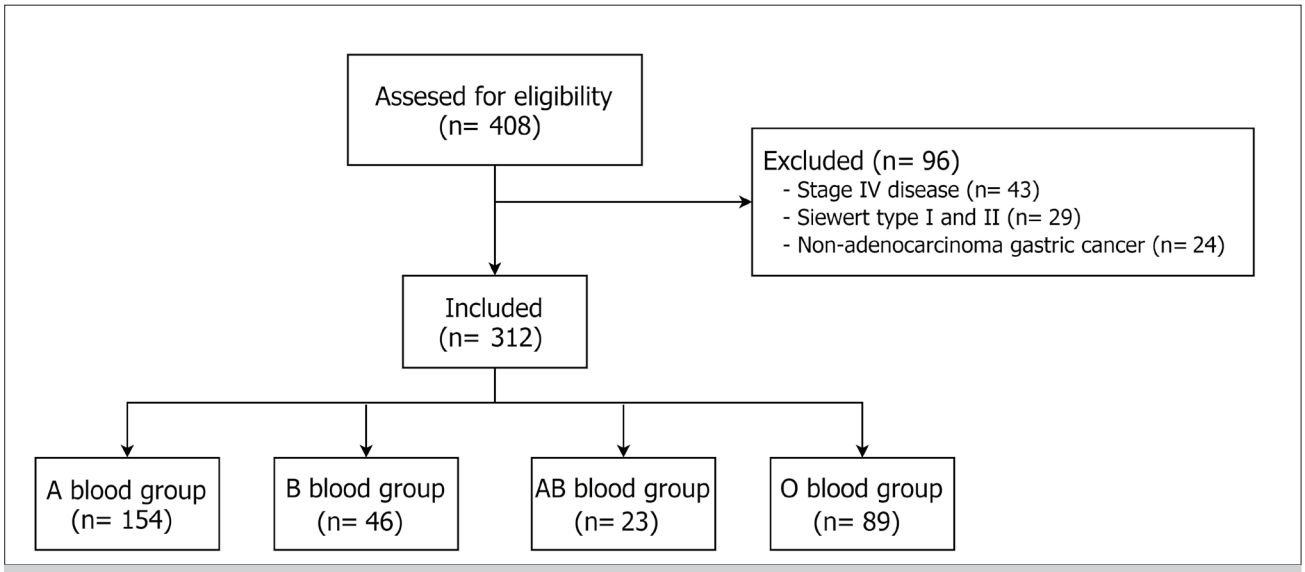

Figure 1. CONSORT flow diagram.

Table 1. The comparison of ABO blood distribution between patients and healthy donors

Groups	ABO blood types (%)						p*	p**	p***
	A	B	AB	O	non-A	non-O			
Healthy (n= 6382)	2859 (44.8)	942 (14.8)	397 (6.2)	2184 (34.2)	3523 (55.2)	4198 (65.8)	0.184	0.114	0.038
Gastric cancer (n= 312)	154 (49.4)	46 (14.7)	23 (7.4)	89 (28.5)	158 (50.6)	223 (71.5)			

p*, the comparison of ABO blood distribution between patients with gastric cancer and healthy donors; p**, differences between the blood group A and non-A blood group; p***, differences between the blood group O and non-O blood group.

similarly distributed between gastric cancer patients and healthy blood donors (p= 0.184). The order of frequency of blood groups was A>O>B>AB in both groups. Non-O blood groups were statistically more common in gastric cancer patients compared to healthy donors (71.5% vs. 65.8%, p= 0.038). However, when comparing the frequency of blood group A between the gastric cancer group and the healthy donor group, no significant difference was found (49.4% vs. 44.8%, p= 0.114) (Table 1).

The association between the blood groups and the clinicopathologic features of the patients with gastric adenocarcinomas is presented in Table 2. TNM stage I, II, and III patients were found to be 59 (18.9%), 65 (20.8%), and 188 (60.3%), respectively. No statistically significant difference was observed in sex (p= 0.885), age (p= 0.088), disease location (p= 0.270), size (p= 0.225), differentiation status (p= 0.144), stage (p= 0.097), lymph node involvement (p= 0.085), MLR (p= 0.084), and lymphovascular (p= 0.553) or perineural involvement (p= 0.159) between the blood groups.

In addition, regional metastatic lymph node involvement (N3) ≥7 and an MLR >0.6 were found to be significantly more common in the patients with blood group A than in those with blood group non-A (50.0% vs. 34.8%, p= 0.034 and 29.9% vs. 16.5%, p= 0.018; respectively). In addition, perineural invasion was more common in A blood groups than in non-A blood groups (39.6% vs. 29.7%, p= 0.067), but this difference was not statistically significant. However, our findings indicated that there was no statistically significant difference between patients with O blood type and those with non-O blood types regarding all clinicopathologic parameters (Table 2).

DISCUSSION

The relation between the ABO blood-group system and some tumors, systemic disorders (such as cardiovascular disease), and some infectious diseases has been known for many years

Table 2. Clinicopathological characteristics of the patients with gastric adenocarcinoma divided by different ABO blood groups

Groups	ABO blood types (%)						p*	p**	p***
	A (n= 154)	B (n= 46)	AB (n= 23)	O (n= 89)	non-A (n= 158)	non-O (n= 223)			
Sex							0.885	0.819	0.774
Male	110 (71.4)	34 (73.9)	15 (65.2)	62 (69.7)	111 (70.3)	159 (71.3)			
Female	44 (28.6)	12 (26.1)	8 (34.8)	27 (30.3)	47 (29.7)	64 (28.7)			
Age, years							0.107	0.061	0.959
<60	54 (35.1)	8 (17.4)	5 (21.7)	27 (30.3)	40 (25.3)	68 (30.5)			
≥60	100 (64.9)	38 (82.6)	18 (78.3)	62 (69.7)	118 (74.7)	155 (69.5)			
Tumor location							0.270	0.459	0.267
Upper	43 (27.9)	17 (37.0)	3 (13.1)	20 (22.5)	40 (25.3)	63 (28.2)			
Middle	50 (32.5)	15 (32.6)	9 (39.1)	38 (42.7)	62 (39.2)	74 (33.2)			
Lower	61 (39.6)	14 (30.4)	11 (47.8)	31 (34.8)	56 (35.5)	86 (38.6)			
Tumor size (cm)							0.225	0.931	0.199
<5	86 (55.8)	20 (43.5)	14 (60.9)	55 (61.8)	89 (56.3)	120 (53.8)			
≥5	68 (44.2)	26 (56.5)	9 (39.1)	34 (38.2)	69 (43.7)	103 (46.2)			
Differentiation status							0.144	0.271	0.803
Well	11 (7.1)	3 (6.5)	6 (26.1)	10 (11.2)	19 (12.0)	20 (9.0)			
Moderate	57 (37.0)	19 (41.3)	8 (34.8)	34 (38.2)	61 (38.6)	84 (37.7)			
Poor	86 (55.9)	24 (52.2)	9 (39.1)	45 (50.6)	78 (49.4)	119 (53.3)			

Table 2. Clinicopathological characteristics of the patients with gastric adenocarcinoma divided by different ABO blood groups (continue)

Groups	ABO blood types (%)						p*	p**	p***
	A (n= 154)	B (n= 46)	AB (n= 23)	O (n= 89)	non-A (n= 158)	non-O (n= 223)			
TNM stage[§]							0.097	0.177	0.067
I	28 (18.2)	7 (15.2)	8 (34.8)	16 (18.0)	31 (19.6)	43 (19.3)			
II	26 (16.9)	8 (17.4)	5 (21.7)	26 (29.2)	39 (24.7)	39 (17.5)			
III	100 (64.9)	31 (67.4)	10 (43.5)	47 (52.8)	88 (55.7)	141 (63.2)			
Lymph node metastasis							0.085	**0.034**	0.258
N0 (0)	38 (24.7)	11 (23.9)	11 (47.8)	27 (30.3)	49 (31.0)	60 (26.9)			
N1 (1-2)	22 (14.3)	5 (10.9)	3 (13.1)	16 (18.0)	24 (15.2)	30 (13.5)			
N2 (3-6)	17 (11.0)	11 (23.9)	3 (13.1)	16 (18.0)	30 (19.0)	31 (13.9)			
N3 (≥7)	77 (50.0)	19 (41.3)	6 (26.0)	30 (33.7)	55 (34.8)	102 (45.7)			
MLR							0.084	**0.018**	0.129
0	38 (24.6)	11 (23.9)	11 (47.8)	27 (30.3)	49 (31.0)	60 (26.9)			
>0-0.3	46 (29.9)	14 (30.4)	4 (17.4)	27 (30.3)	45 (28.5)	64 (28.7)			
>0.3-0.6	24 (15.6)	11 (23.9)	5 (21.8)	22 (24.8)	38 (24.0)	40 (17.9)			
>0.6	46 (29.9)	10 (21.8)	3 (13.0)	13 (14.6)	26 (16.5)	59 (26.5)			
Lymphovascular invasion							0.553	0.666	0.789
No	83 (53.9)	25 (54.3)	16 (69.6)	48 (53.9)	89 (56.3)	124 (55.6)			
Yes	71 (46.1)	21 (45.7)	7 (30.4)	41 (46.1)	69 (43.7)	99 (44.4)			
Perineural invasion							0.159	0.067	0.459
No	93 (60.4)	31 (67.4)	19 (82.6)	61 (68.5)	111 (70.3)	143 (64.1)			
Yes	61 (39.6)	15 (32.6)	4 (17.4)	28 (31.5)	47 (29.7)	80 (35.9)			

MLR: Metastatic lymph node ratio.
[§]AJCC Cancer Staging Manual, 8th edition.
p*, differences between the groups (A, B, AB, and O); p**, differences between the blood group A and non-A blood group; p***, differences between the blood group O and non-O blood group.

although discrepancies in the results of the studies in this field mean that trials in this issue are ongoing (6). Recent studies have suggested a potential association between blood group antigens and tumor oncogenesis, tumor dissemination, and survival in several forms of cancer (8). Aird et al. have shown an association between the blood group A and gastric carcinoma, and numerous later studies have confirmed this association, while numerous studies have been conducted to investigate the influence of blood group types on the prognosis and survival of individuals diagnosed with cancer (9-11,13,14). Nevertheless, the results are rather conflicting, even within the same kind of tumor.

In this study, we analyzed the link between blood groups and the clinicopathologic features that may have an impact on the prognosis of patients with gastric adenocarcinomas. There have been earlier studies investigating the association between blood groups and prognosis in gastric cancer although their results are inconsistent (15-17). As there are numerous factors affecting the prognosis of gastric cancer, we aimed to analyze the link between blood types and clinicopathological characteristics of gastric cancer rather than its prognosis. In line with other studies in the literature, the order of blood type frequencies were A> O> B> AB both in the patients and the healthy donors, and there was a male predominance in gastric cancer patients (16). In this study, non-O blood type was found to be more prevalent in patients with gastric cancer. Consistent with our findings, Zhang et al. have identified a lower gastric cancer risk (OR= 0.84) in patients with O blood group in their meta-analysis (11).

In earlier studies investigating the relation between the blood groups and gastric cancer survival, significant heterogeneity was present and different conclusions were documented. For instance, in a study investigating the link between blood types and clinicopathologic features of the patients with gastric cancer, the researchers have reported no significant association between blood groups regarding sex, tumor size, tumor stage,

degree of differentiation, and P53 expression. They have only reported that the subjects with blood group O were statistically significantly less likely to have angiolymphatic involvement than those with non-O blood groups (15). Furthermore, the expression of progestogen receptors, estrogen receptors, and carcinoembryonic antigen (CEA) was significantly higher in blood group A patients than in those with other blood groups. While there was no statistically significant difference between blood groups and survival, patients with blood group B had a longer survival than those with other blood groups. In another study, Xu et al. have analyzed the prognostic impact of the blood types in more than a thousand gastric cancer patients and reported that patients with blood group AB had a longer survival than those with non-AB blood groups ($p< 0.001$) (16). Furthermore, A blood group patients exhibited the poorest survival outcomes across all blood groups. In a study by Xiao et al., no significant difference has been found for the survival rates of patients across the four blood groups (17). The authors have also explored the prognostic impact of the blood types in gastric carcinoma patients with different preoperative CEA levels, and they have reported that among the patients with high preoperative CEA, the AB blood group was associated with longer survival than non-AB blood type.

Gastric cancer shows a significant geographic variation in incidence, and there are numerous factors that affect survival and mortality, with both genetic susceptibility and environmental triggers such as nutrition and infectious agents playing a crucial role in development, prognosis, and survival of gastric cancer (3-5). Tumor stage, lymph node status, MLR, tumor size and other histopathological tumor-related factors such as lymphatic, vascular or perineural invasion; tumor differentiation; and the Lauren classification are valuable prognostic factors in gastric cancer patients (18-21). Moreover, HER2 overexpression is considered to be a poor prognostic factor in patients with gastric cancer (22). When reviewing studies assessing prognostic features in gastric cancer specifically in relation with blood groups, tumor depth and stage, lymph node metastasis, blood group A, ER expression, and CEA elevation have been found as the most prominent factors (15-17). Considering the findings of above studies, there is a clear relationship between clinicopathological features and the prognosis of gastric cancer.

In the present study, among all clinicopathological features, seven or more regional lymph node involvement was more common in blood group A compared to non-A blood groups ($p= 0.034$) and patients with A blood group had a greater rate of MLR (>0.6) than those with the non-A blood groups ($p= 0.018$), while no relation was identified between the blood groups and patient demographics, tumor location, size, and stage, or lymphovascular invasion. Moreover, perineural invasion was more common in blood group A compared to non-A blood groups (39.6% vs. 29.7%, $p= 0.067$). According to these results, lymph node metastasis and MLR are significant prognostic indicators for gastric cancer patients undergoing radical D2 resection. Three staging systems have been used for decades to predict the prognosis of patients with gastric adenocarcinoma: Log odds of positive nodes (LODDS), nodal staging system, and MLR. When these systems compared with each other, the LODDS and MLR have exhibited a higher prognostic accuracy compared with TNM and nodal systems (23). A number of studies have employed a 0.2 to 0.3 cut-off for MLR, with the results indicating that a higher MLR is associated with a significantly lower survival rate and a higher recurrence for N3 disease (24-27). It is also a poor prognostic factor for stage III gastric cancer (28). In other words, an increased MLR in blood group A may indicate a worse prognosis in patients undergoing curative gastrectomy, given the large number of stage III patients in this study.

Studies have demonstrated a direct correlation between the ABO group genotype and the levels of inflammatory markers in the blood. This evidence suggests that blood-group antigens may influence the immune system response (29,30). Thus, ABO blood-group antigens and antibodies might have potential implications on tumor dissemination, angiogenesis, and lymphatic invasion. The results indicate a correlation between the ABO blood group and the predisposition to lymphatic invasion and tumorigenesis. Similarly, although a link between blood groups and the prognosis of gastric cancer could not be inferred, blood group A was associated with higher lymph node involvement.

The results indicate a correlation between the ABO blood group and a predisposition to lymphatic invasion and tumorigenesis.

Finally, there are several important limitations of this study that are noteworthy. First, the data comes from a retrospective single-center analysis; second, the high rate of advanced stage cancer limits its generalizability to every gastric cancer patient. Lastly, exclusion of stage IV patients can make tumor pathology biased and make findings not generalizable. In addition, the sample size of patients with AB blood group and B blood group was small, which could result in unsatisfactory statistical p values.

CONCLUSION

The relation between ABO blood groups and clinicopathological features and prognosis of gastric cancer has not been extensively studied. Although several studies have defined survival advantages for certain blood types, relevant studies are limited, and their results are inconclusive. The present study showed some association between the ABO blood groups and

clinicopathological characteristics in gastric cancer, especially with blood group A being associated with a higher MLR level and N3 involvement, estimating that patients having gastric adenocarcinoma with A blood group may have a worse prognosis. Although gastric carcinoma is more prevalent in patients with non-O blood groups, the relation between this blood type and tumor characteristics is relatively weak. There is need for further prospective multicenter studies with larger sample sizes to better define the influence of blood types on clinicopathological features and survival in gastric cancer.

Further prospective multicenter studies with larger sample sizes are needed to better define the influence of blood group on clinicopathological features and survival in gastric cancer.

Ethics Committee Approval: This study was obtained from University of Health Sciences Gülhane Scientific Research Ethics Committee (Decision no: 2024-178, Date: 24.04.2024).

Author Contributions: Concept - RŞ; Design - SUÇ, ŞK, RŞ; Supervision - RŞ; Fundings - SUÇ, RŞ; Materials - SUÇ, YG, MBD, ŞK, RŞ; Data Collection and/or Processing - SUÇ, YG, MBD, ŞK, RŞ; Analysis and/or Interpretation - SUÇ, ŞK, RŞ; Literature Review - SUÇ, YG, MBD, ŞK, RŞ; Writing Manuscript - SUÇ, YG, MBD, ŞK, RŞ; Critical Reviews - SUÇ, YG, MBD, ŞK, RŞ.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424. https://doi.org/10.3322/caac.21492*
2. *Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7-30. https://doi.org/10.3322/caac.21442*
3. *Carcas LP. Gastric cancer review. J Carcinog 2014; 13: 14. https://doi.org/10.4103/1477-3163.146506*
4. *Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: Descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014; 23: 700-13. https://doi.org/10.1158/1055-9965.EPI-13-1057*
5. *Moss SF. The clinical evidence linking Helicobacter pylori to gastric cancer. Cell Mol Gastroenterol Hepatol 2016; 3: 183-91. https://doi.org/10.1016/j.jcmgh.2016.12.001*
6. *Franchini M, Lippi G. The intriguing relationship between the ABO blood group, cardiovascular disease, and cancer. BMC Med 2015; 13: 7. https://doi.org/10.1186/s12916-014-0250-y*
7. *Eastlund T. The histo-blood group ABO system and tissue transplantation. Transfusion 1998; 38: 975-88. https://doi.org/10.1046/j.1537-2995.1998.381098440863.x*
8. *Franchini M, Liumbruno GM, Lippi G. The prognostic value of ABO blood group in cancer patients. Blood transfus 2016; 14: 434-40.*
9. *Aird I, Bentall HH, Roberts JA. A relationship between cancer of stomach and the ABO blood groups. Br Med J 1953; 1: 799-801. https://doi.org/10.1136/bmj.1.4814.799*
10. *Huang JY, Wang R, Gao YT, Yuan JM. ABO blood type and the risk of cancer - Findings from the Shanghai Cohort Study. PloS One 2017; 12: e0184295. https://doi.org/10.1371/journal.pone.0184295*
11. *Zhang BL, He N, Huang YB, Song FJ, Chen KX. ABO blood groups and risk of cancer: A systematic review and meta-analysis. Asian Pac J Cancer Prev 2014; 15: 4643-50. https://doi.org/10.7314/APJCP.2014.15.11.4643*
12. *Ajani JA, In H, Sano T, Gaspar LE, Erasmus JJ, Thang LH, et al. Stomach. In: Amin MB, editor. AJCC Cancer Staging Manual. 8th ed. Chicago: Springer Nature; 2017. pp 203-20.*
13. *Edgren G, Hjalgrim H, Rostgaard K, Norda R, Wikman A, Melbye M, et al. Risk of gastric cancer and peptic ulcers in relation to ABO blood type: A cohort study. Am J Epidemiol 2010; 172: 1280-5. https://doi.org/10.1093/aje/kwq299*
14. *Wang Z, Liu L, Ji J, Zhang J, Yan M, Zhang J, et al. ABO blood group system and gastric cancer: A case-control study and meta-analysis. Int J Mol Sci 2012; 13: 13308-21. https://doi.org/10.3390/ijms131013308*
15. *Qiu MZ, Zhang DS, Ruan DY, Luo HY, Wang ZQ, Zhou ZW, et al. A relationship between ABO blood groups and clinicopathologic characteristics of patients with gastric adenocarcinoma in China. Med Oncol 2011; 28(1): 268-73. https://doi.org/10.1007/s12032-010-9735-5*
16. *Xu YQ, Jiang TW, Cui YH, Zhao YL, Qiu LQ. Prognostic value of ABO blood group in patients with gastric cancer. J Surg Res 2016; 201: 188-95. https://doi.org/10.1016/j.jss.2015.10.039*
17. *Xiao S, Feng F, Sun L, Cai L, Liu Z, Liu S, et al. Blood type AB predicts promising prognosis in gastric cancer patients with positive preoperative serum CEA. Medicine 2017; 96: e8496. https://doi.org/10.1097/MD.0000000000008496*
18. *Park JM, Ryu WS, Kim JH, Park SS, Kim SJ, Kim CS, et al. Prognostic factors for advanced gastric cancer: stage-stratified analysis of patients who underwent curative resection. Cancer Res Treat 2006; 38: 13-8. https://doi.org/10.4143/crt.2006.38.1.13*
19. *Siewert JR, Böttcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: Ten-year results of the German Gastric Cancer Study. Ann Surg 1998; 228: 449-61. https://doi.org/10.1097/00000658-199810000-00002*
20. *Harrison JD, Fielding JW. Prognostic factors for gastric cancer influencing clinical practice. World J Surg 1995; 19: 496-500. https://doi.org/10.1007/BF00294709*
21. *Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N, Kitano S. Pathology and prognosis of gastric carcinoma: Well versus poorly differentiated type. Cancer 2000; 89: 1418-24. https://doi.org/10.1002/1097-0142(20001001)89:7<1418::AID-CNCR2>3.0.CO;2-A*
22. *Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008; 19: 1523-9. https://doi.org/10.1093/annonc/mdn169*
23. *Cao H, Tang Z, Yu Z, Wang Q, Li Z, Lu Q, et al. Comparison of the 8th union for international cancer control lymph node staging system for gastric cancer with two other lymph node staging systems. Oncol Lett 2019; 17: 1299-305. https://doi.org/10.3892/ol.2018.9694*
24. *Chen S, Zhao BW, Li YF, Feng XY, Sun XW, Li W, et al. The prognostic value of harvested lymph nodes and the metastatic lymph node ratio for gastric cancer patients: results of a study of 1,101 patients. PLoS One 2012; 7: e49424. https://doi.org/10.1371/journal.pone.0049424*
25. *Lee SR, Kim HO, Son BH, Shin JH, Yoo CH. Prognostic signifcance of the metastatic lymph node ratio in patients with gastric cancer. World J Surg 2012; 36: 1096-101. https://doi.org/10.1007/s00268-012-1520-5*

26. *Chen S, Zhao BW, Li YF, Feng XY, Sun XW, Li W, et al. Lymph node ratio is an independent prognostic factor in gastric cancer after curative resection (R0) regardless of the examined number of lymph nodes. Am J Clin Oncol 2013; 36: 325-30. https://doi.org/10.1097/COC.0b013e318246b4e9*

27. *Bilici A, Selcukbiricik F, Seker M, Oven BB, Olmez OF, Yildiz O, et al. Prognostic significance of metastatic lymph node ratio in patients with pN3 gastric cancer who underwent curative gastrectomy. Oncol Res Treat 2019; 42: 209-16. https://doi.org/10.1159/000496746*

28. *Chen Y, Li C, Du Y, Xu Q, Ying J, Luo C. Prognostic and predictive value of metastatic lymph node ratio in stage III gastric cancer after D2 nodal dissection. Oncotarget 2017; 8: 70841-6. https://doi.org/10.18632/oncotarget.19998*

29. *Paterson AD, Lopes-Virella MF, Waggott D, Boright AP, Hosseini SM, Carter RE, et al. Genome-wide association identifes the ABO blood group as a major locus associated with serum levels of soluble E-selectin. Arterioscler Thromb Vasc Biol 2009; 29: 1958-67. https://doi.org/10.1161/ATVBAHA.109.192971*

30. *Barbalic M, Dupuis J, Dehghan A, Bis JC, Hoogeveen RC, Schnabel RB, et al. Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. Hum Mol Genet 2010; 19: 1863-72. https://doi.org/10.1093/hmg/ddq061*

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (3): 240-246

Mide adenokarsinomlu hastaların ABO kan grupları ile klinikopatolojik özellikleri arasındaki ilişki

Süleyman Utku Çelik, Yasin Gülap, Mehmet Bahadır Demir, Şahin Kaymak, Rahman Şenocak

Gülhane Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışmada mide kanseri teşhisi konan hastaların prognozunu etkileyebilecek kan grupları ile klinikopatolojik faktörler arasındaki ilişkinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif tek merkezli çalışmada, mide adenokarsinomlu hastalar prospektif olarak tutulan bir veri tabanından elde edilmiştir. Kan grupları ile cinsiyet, yaş, tümör yeri, tümör boyutu, tümör evresi, metastatik lenf nodu oranı (mLNO), lenfovasküler invazyon ve perinöral invazyon gibi klinikopatolojik özellikler arasındaki ilişki analiz edildi.

Bulgular: Çalışmaya 91 kadın ve 221 erkek hasta dahil edildi. Kan grubu dağılımı hem hastalarda hem de sağlıklı donörlerde A> O> B> AB şeklindeydi. O kan grubu olmayan kanser hastalarında sağlıklı donörlere göre daha yaygındı (p= 0,038). Ancak cinsiyet, yaş, tümör yerleşim yeri, tümör evresi, lenf nodu metastazı, lenfovasküler invazyon, perinöral tutulum ve kan grupları arasında anlamlı bir ilişki bulunmadı. ≥7 lenf nodu tutulumu ve >0,6 mLNO, kan grubu A olan hastalarda kan grubu A olmayanlara göre anlamlı derecede daha fazlaydı (sırasıyla p= 0,034 ve p= 0,018).

Sonuç: Bu çalışmanın bulguları, kan grubu A olan hastaların daha yüksek mLNO ve N3 tutulumu ile ilişkili olduğunu ve dolayısıyla mide kanseri teşhisi olan bu hastaların daha kötü bir prognoza sahip olabileceğini göstermektedir.

Anahtar Kelimeler: ABO kan grubu, mide kanseri, patolojik özellikler, sonuç

DOİ: 10.47717/turkjsurg.2024.6434

CASE SERIES
Turk J Surg 2024; 40 (3): 247-255

Emphysematous liver abscess: Variable clinical presentations, management challenges and outcomes-a case series

Sukesh Kudumallige Sudhakara, Shiva Shiva, Ranjith Kumaran, Sheefali Chandra, Akshay Anand, Abhinav Arun Sonkar

Department of General Surgery, King George's Medical University, Lucknow, India

ABSTRACT

Emphysematous liver abscesses (ELAs), characterized by the presence of gas within the hepatic parenchyma, are an uncommon and potentially life-threatening entity. ELAs with clinical presentations mimicking hollow viscus perforation pose a diagnostic conundrum for clinicians. This series highlights the diagnostic challenges posed by such atypical presentations and emphasizes the importance of considering hepatic pathology in the differential diagnosis of pneumoperitoneum. Our objective is to provide a comprehensive analysis of the diverse clinical presentations, diagnostic challenges, and therapeutic strategies employed in managing this unique subset of liver abscesses.

Keywords: Emphysematous liver abscess, liver abscess, gas under diaphragm

INTRODUCTION

Emphysematous liver abscesses (ELAs) are also known as gas-forming pyogenic liver abscesses, with 76-85% occurring in patients with uncontrolled diabetes mellitus (1). Despite its infrequent occurrence, ELA poses a formidable clinical challenge due to its propensity for rapid deterioration and life-threatening complications. Complications are reported in as many as 92% of the cases, respiratory-related complications being the most common (2). The spectrum of clinical presentations ranges from subtle symptoms like fever and abdominal pain to dreaded complications like shock, making it a diagnostic challenge. Management of acute emphysematous liver abscess requires urgent external drainage of the abscess cavity, but pneumoperitoneum on radiological imaging can pose a serious diagnostic dilemma and can misguide surgeons, leading to unnecessary laparotomies. The evolving landscape of treatment options, encompassing medical therapy, percutaneous drainage, and surgical intervention, will be scrutinized in the context of individual cases, offering valuable insights into the optimal management strategies tailored to diverse clinical scenarios.

Case Reports

Case 1

A 22-year-old male with no comorbidities and a history of occasional alcohol intake presented with a history of on and off right upper quadrant pain for seven days with an associated low-grade fever. A chest radiograph (Figure 1A) done elsewhere showed gas under the right hemidiaphragm, suggestive of pneumoperitoneum. On examination, the patient was afebrile, hemodynamically stable, and showed no signs of peritonitis. Repeat chest radiographs revealed similar findings. Ultrasonography (USG) of the abdomen was suggestive of a liver abscess in the right lobe of the liver. Contrast enhanced computed tomography (CECT) of the abdomen and thorax (Figure 1B,C) revealed a hypodense space-occupying lesion with visible air fluid levels inside in the right lobe of the liver. Routine blood investigations were within normal limits, and external drainage via USG-guided pigtail catheter (PCD) insertion in the liver abscess cavity was done. Pus culture revealed the heavy growth of *Klebsiella pneumoniae*. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

Cite this article as: Kudumallige Sudhakara S, Shiva S, Kumaran R, Chandra S, Anand A, Sonkar AA. Emphysematous liver abscess: Variable clinical presentations, management challenges and outcomes-a case series. Turk J Surg 2024; 40 (3): 247-255.

Corresponding Author
Sukesh Kudumallige Sudhakara
E-mail: saisukeshks@gmail.com

Received: 09.05.2024
Accepted: 22.08.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6436

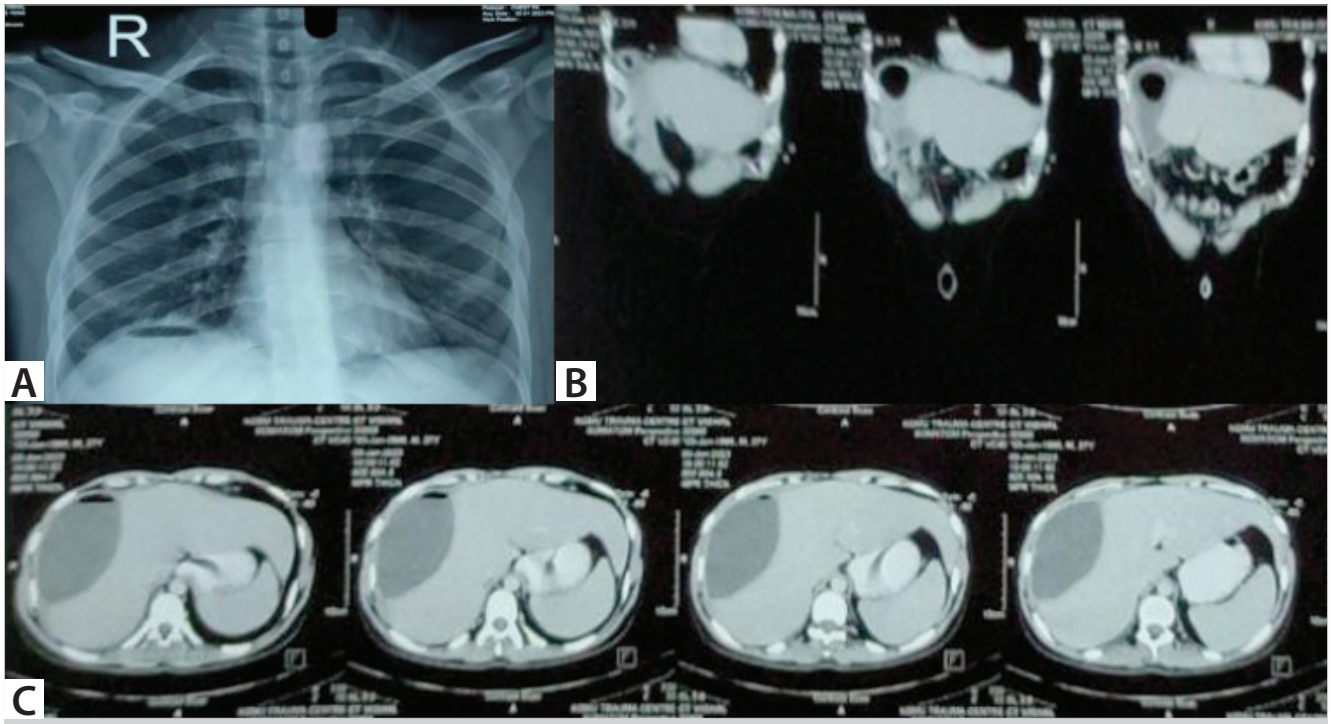

Figure 1. A. Chest radiograph showing pneumoperitoneum. **B,C.** CECT of the abdomen showing a hypodense space-occupying lesion with air specks and air-fluid levels.

Case 2

An 18-year-old heavy alcoholic and smoker male with no other comorbidities presented to the surgical emergency with complaints of severe abdominal pain, high-grade fever, and chills for seven days. On examination, the patient was febrile with tachycardia, hypotension, abdominal tenderness with guarding, and rigidity suggestive of peritonitis. An abdominal radiograph did not reveal any abnormalities. USG revealed multiple abscesses in the right lobe of the liver with no intra-abdominal collection. The patient's biochemical parameters were as follows: haemoglobin of eight, total leucocyte count of 28.000 with 85% polymorphocytes, platelet count of 35.000, urea of 180, creatinine of 3.8, INR of 3.7, and prothrombin time of 36. Liver function tests showed: total bilirubin= 3, alkaline phosphatase (ALP)= 400, SGOT= 120, and SGPT= 110, suggestive of multiorgan dysfunction syndrome. The patient was resuscitated, and CECT of the abdomen (Figure 2A, B) was done, which revealed multiple hypodense space-occupying lesions along with homogenous collection in the liver parenchyma, with specks of air noted inside the cavities in the right lobe of the liver, suggesting an emphysematous liver abscess. After initial resuscitation, the patient was managed by external drainage with multiple pigtail catheter insertions in the liver abscess cavity and empirical broad-spectrum antibiotics. Pus culture revealed *K. pneumoniae* as the causative agent. The patient's condition improved after drainage. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

Case 3

A 50-year-old diabetic female with poor glycaemic control presented with complaints of intermittent fever, chills, and right upper quadrant pain for 10 days. On examination, the patient was afebrile, hemodynamically stable, and tender in the right hypochondrium. Chest radiograph was suggestive of gas under the right hemidiaphragm and suggestive of pneumoperitoneum (Figure 3A). USG revealed two liver abscesses in the right lobe of the liver. The CECT of the abdomen was suggestive of two large hypodense spaces occupying lesions along with homogenous collection in the liver parenchyma, involving segments VIII, II, and III of the liver along with specks of air and visible air fluid levels inside the hypodense lesions (Figure 3B). The patient was managed by external drainage, pigtail catheter insertion in the liver abscess cavity, and glycaemic control. Pus culture was sterile. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow up.

Case 4

A 32-year-old male with a history of laparoscopic cholecystectomy a month prior presented with complaints of abdominal pain and intermittent fever for seven days. The patient was hemodynamically stable with localised tenderness

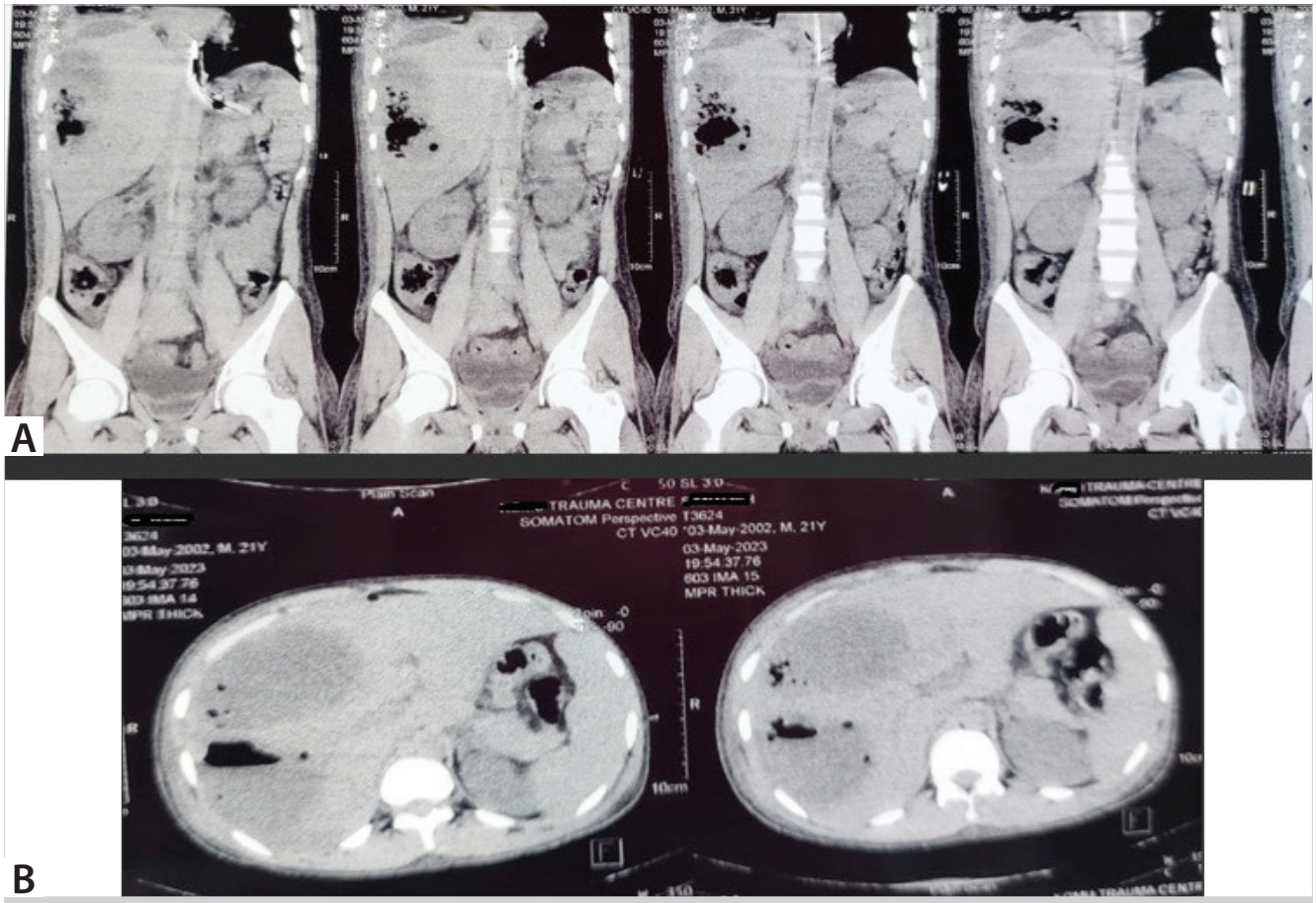

Figure 2. A,B. CECT of the abdomen showing multiple hypodense space-occupying lesions with air specks.

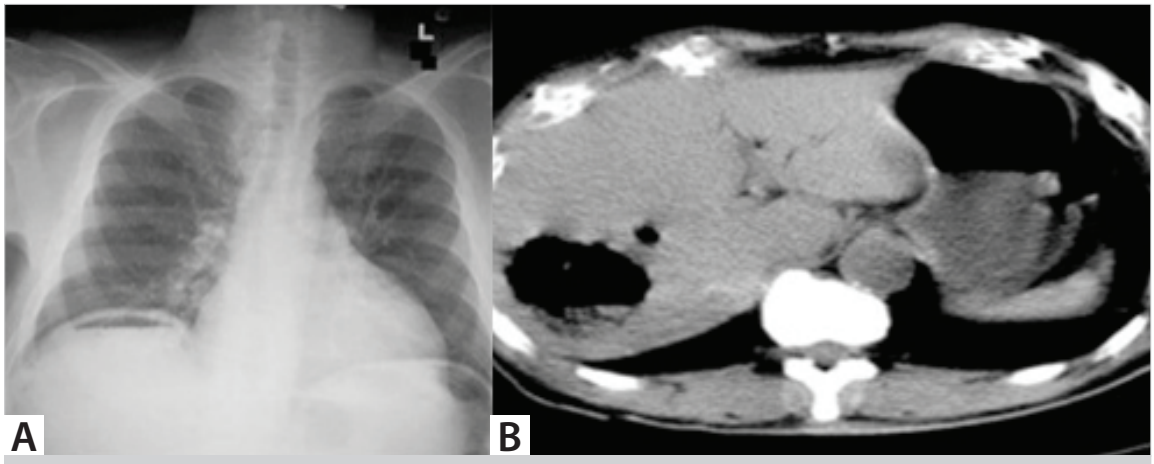

Figure 3. A. Chest radiograph showing pneumoperitoneum. **B.** CECT of the abdomen showing two large hypodense space occupying lesions with air specks and air-fluid levels.

in the right hypochondrium. Radiograph of the chest showed gas under the right dome of the diaphragm, suggestive of pneumoperitoneum, and USG showed a 400 mL hypoechoic lesion in segment seven of the liver, suggestive of a liver abscess (Figure 4A). The CECT of the abdomen showed a hypodense lesion with a speck of air in segment seven of the liver, suggesting an emphysematous liver abscess (Figure 4B,C). The patient was managed by external drainage, pigtail catheter insertion in the liver abscess cavity, and IV antibiotics. Pus culture was sterile. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

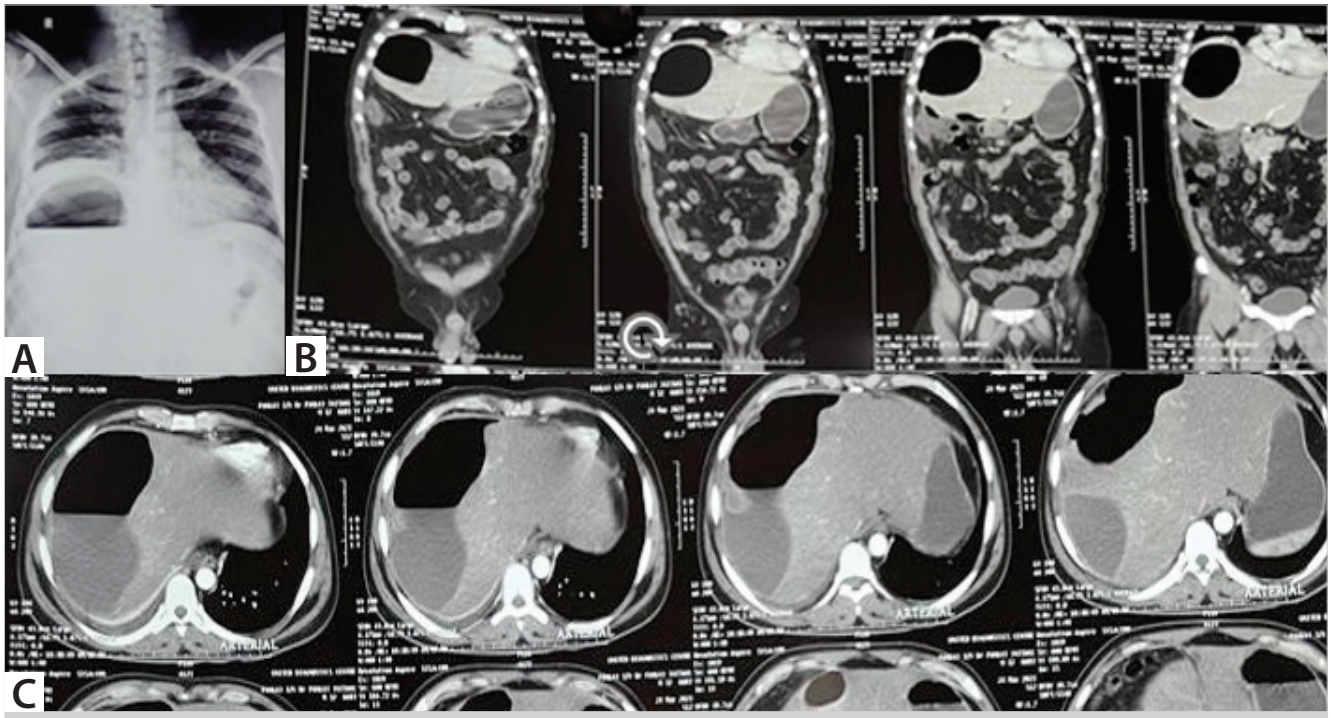

Figure 4. A. Chest radiograph showing pneumoperitoneum. **B,C.** CECT of the abdomen showing a hypodense space-occupying lesion with air speck.

Case 5

A 55-year-old chronic alcoholic male with no comorbidities presented with high-grade fever, abdominal distension, and right upper quadrant pain for one week. On examination, the patient was hemodynamically stable with a distended abdomen and right upper quadrant tenderness. USG revealed two liver abscess cavities, and CECT revealed a right lobe liver abscess along with an emphysematous left lobe abscess (Figure 5A,B). After initial resuscitation, the patient was managed by external drainage with pigtail catheter insertion in the liver abscess cavity, and cultures revealed *Klebsiella* spp. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

Case 6

A 54-year-old diabetic female with poor glycaemic control presented with upper abdominal pain and fever for one week. The patient was hemodynamically stable with right upper quadrant tenderness. USG was suggestive of emphysematous cholecystitis. Blood investigations showed hemoglobin= 6, total leukocyte count= 38.000, creatinine= 3, urea= 160, total bilirubin= 3.2, SGOT= 140, SGPT= 200, and alkaline phosphatase= 300. Non-contrast computed tomography of the abdomen showed a large liver abscess with emphysematous changes (Figures 6A,B). The patient was managed by external drainage with pigtail catheter insertion in the liver abscess cavity, glycaemic control, and broad-spectrum antibiotics. Pus culture

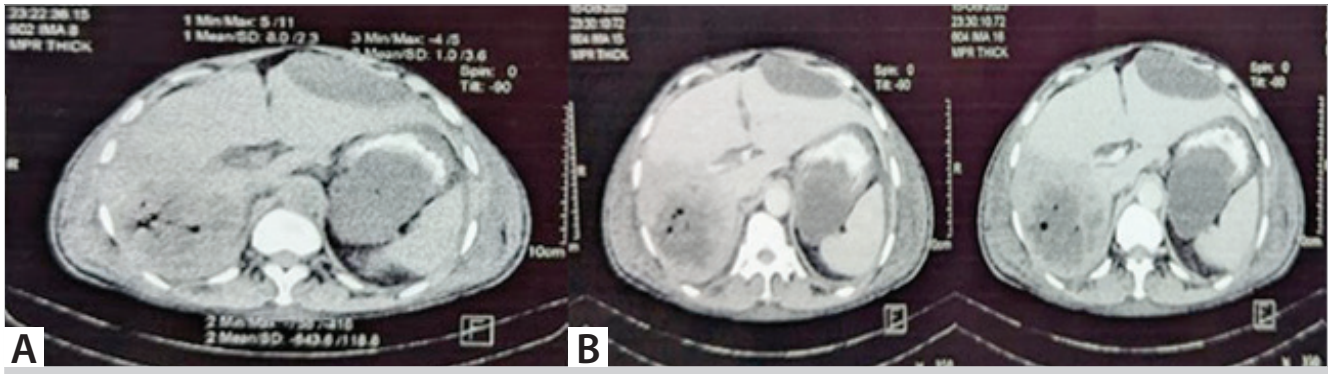

Figure 5. A,B. CECT showing a right lobe liver abscess and an emphysematous left liver lobe abscess.

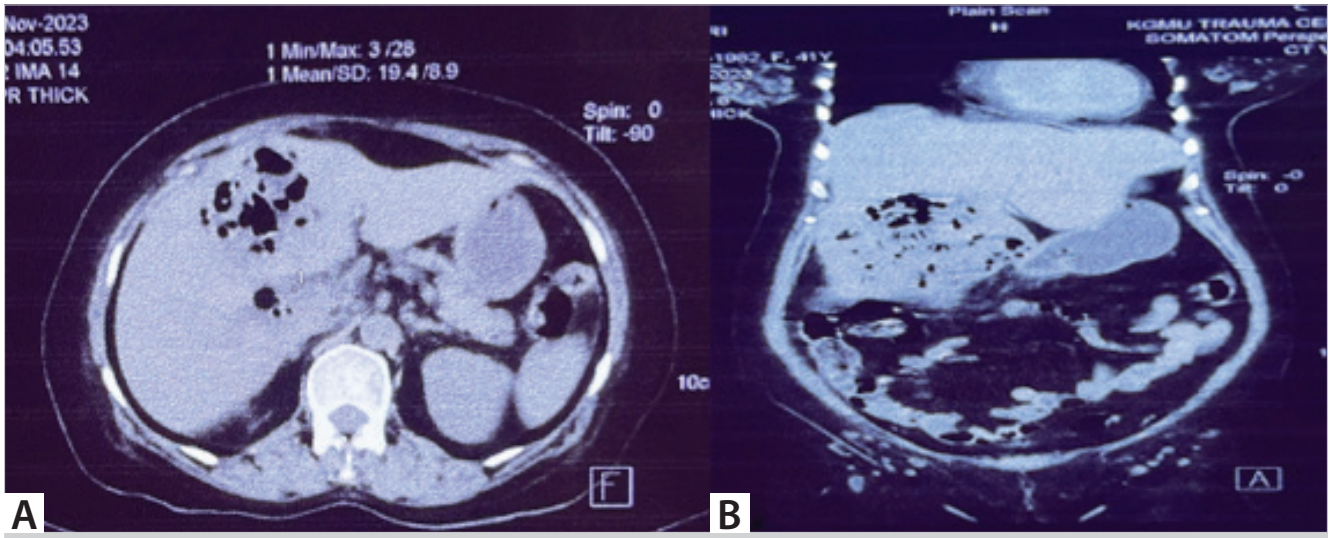

Figure 6. A,B. Non-contrast CT scan showing a large liver abscess with emphysematous changes.

revealed *Klebsiella* spp. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

Case 7

A 48-year-old alcoholic and diabetic male presented with complaints of high-grade fever, abdominal distension, and right upper quadrant pain for one week. On examination, the patient was hemodynamically stable with right upper quadrant tenderness. USG revealed a single liver abscess cavity, and CECT revealed a right lobe liver abscess with emphysematous changes and pleural effusion. After initial resuscitation, the patient was managed by external drainage with pigtail catheter insertion in the liver abscess cavity and glycaemic control (Figure 7A,B). Pus culture revealed *Escherichia coli* spp. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

Case 8

A 50-year-old chronic alcoholic male with no comorbidities presented with a high-grade fever and generalised pain in the abdomen for five days. On examination, the patient was hemodynamically stable with generalised peritonitis. Abdominal radiographs showed gas under the right dome of the diaphragm, suggestive of pneumoperitoneum; USG was suggestive of liver abscess (Figure 8A). CECT revealed a liver abscess with emphysematous changes and was managed by external drainage with pigtail catheter insertion in the liver abscess cavity (Figure 8A-C). Pus culture showed *E. coli* spp. The patient was discharged on oral antibiotics and was asymptomatic on three monthly follow ups.

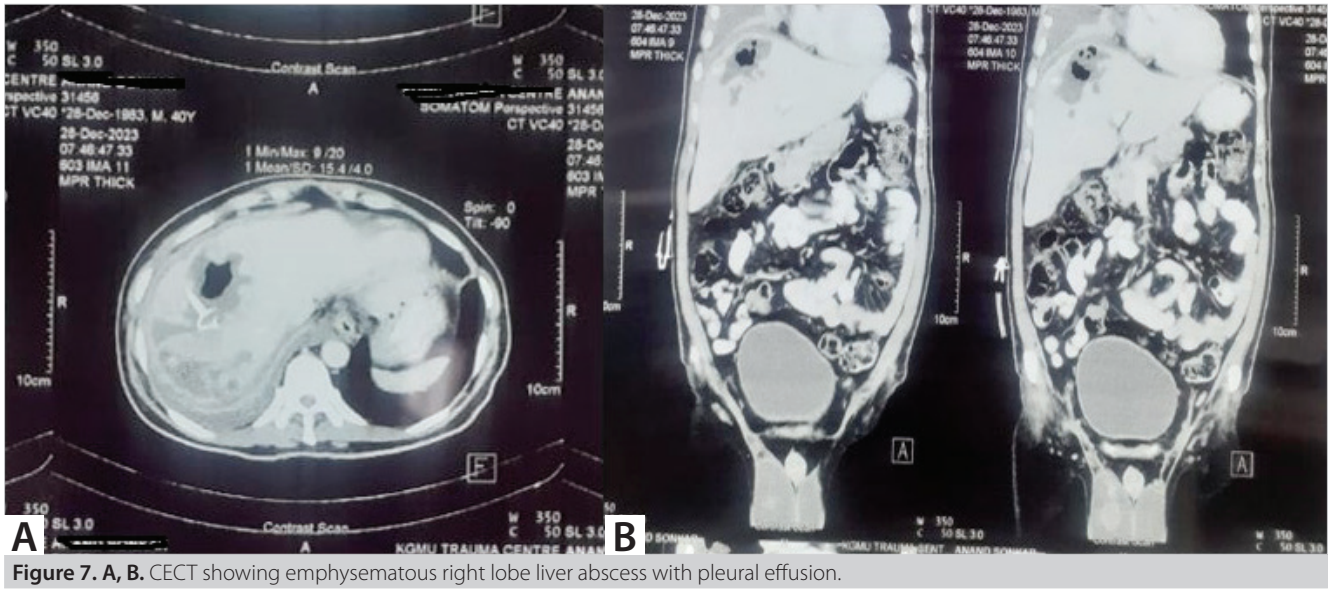

Figure 7. A, B. CECT showing emphysematous right lobe liver abscess with pleural effusion.

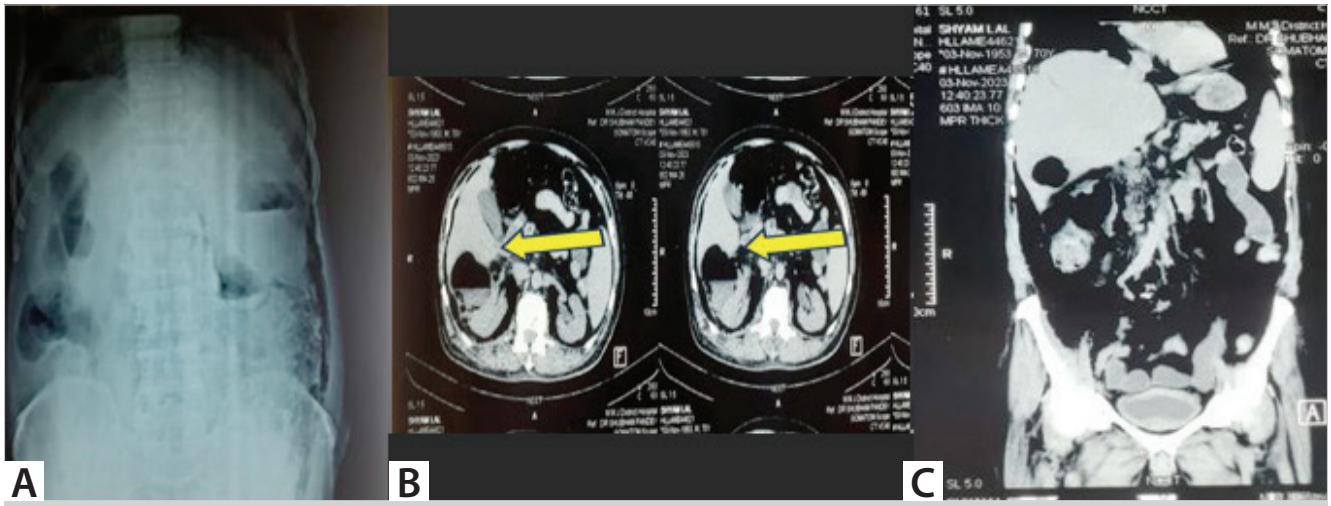

Figure 8. A. Chest radiograph showing pneumoperitoneum. **B,C.** CECT showing liver abscess with emphysematous changes.

DISCUSSION

ELAs are typically characterised by gas formation within the abscess cavity. 6-24% of all bacterial liver abscesses are emphysematous in nature, with the maximum incidence in Asia, particularly Taiwan (1). The most common pathogens are *K. pneumoniae* and *E. coli*, with *Klebsiella* accounting for 82% of cases (2). ELAs have a case fatality rate of 12-40% and a mortality rate of 27-37%, as compared to only 12% in non-gas-forming liver abscesses (3,4).

The clinical presentations vary from simple fever, malaise, pain in the abdomen, and respiratory difficulty to deadly complications like septic emboli, meningitis, endophthalmitis, or even shock (1). Yang et al. have reported hepatocellular damage in 57% of ELAs and 19% of non-gas-forming liver abscesses; similar findings were noted in our series, with all the patients having deranged ALP (5). Around 6% of the patients present with intrapleural or intraperitoneal rupture and features of peritonitis mimicking those of hollow viscus perforation (6). Diabetic patients might present with milder or no pain because of diabetic neuropathy, adding an additional layer of complexity and warranting careful assessment. A similar case of pneumoperitoneum because of a ruptured liver abscess has also been reported by Maliyakkal et al. (7).

The commonly identified risk factor is poor glycaemic control, as hyperglycaemia provides a favourable condition for gas formation via the mixed acid fermentation pathway of glucose, leading to the production of formic acid, which breaks down further into carbon dioxide and hydrogen by the action of formic hydrogenylase (3). ELAs are more prone to rupture due to mass tissue damage, gas formation, and impaired transport of gas and catabolic products away from the lesion because of diabetic microangiopathy, leading to gas accumulation and a rise in internal pressure (6).

Investigations usually show a raised total leukocyte count, alkaline phosphate, and liver enzymes, with or without coagulopathy. Abdominal USG, simple radiography, and other imaging techniques might prove to be helpful for diagnosis, but computed tomography is the diagnostic tool of choice for accurate detection of gas within the abscesses, along with abscess location, size, number, and associated complications. Differential diagnoses include subphrenic abscess, emphysematous cholecystitis, right renal abscess, perinephric abscess, hepatic flexure interposed between the diaphragm and liver, and partial abdominal heterotaxia. It is often difficult to differentiate ELAs from emphysematous hepatitis. Chromatographic analysis of the formed gas has shown nitrogen (N_2= 65.8 to 78.1%), oxygen (O_2= 1.2 to 7.3%), carbon dioxide (CO_2= 5.4 to 14.8%), and hydrogen (H_2= 9.0 to 18.3%) as constituents (3).

Treatment is mainly percutaneous abscess drainage, along with antibiotic therapy and glycaemic control, with a reported success rate of 94% (8). Surgery is indicated if peritonitis and rupture are suspected, and surgery as extensive as an emergency hepatectomy might be needed (9). The summary, blood parameters, and outcome of all patients are shown in Table 1, Table 2, and Table 3.

In our study, four hemodynamically stable patients with unremarkable clinical examinations were found to have gas under the right hemidiaphragm, which was a diagnostic dilemma. Such findings can easily misguide the surgeon to perform an unnecessary laparotomy, suspecting hollow viscus perforation, especially in low-resource settings where facilities for USG and CECT are not available, as reported by Pham et al. (10). Contrastingly, another patient with signs and symptoms of acute abdomen with multiorgan dysfunction had no gas under the right hemidiaphragm and was found to have ELAs, indicating the variability in the presentations of this rarer entity.

Table 1. Summary of all patients

Case no	Age/sex	Habits	Comorbidity	Symptoms	Examination	Blood parameters	X-ray	USG (Number and location)	CT	Pus culture
1.	22/M	Alcoholic	None	RUQ pain Fever	WNL	WNL	Gass under diaphragm	1 Right lobe	Single emphysematous abscess	*K. pneumoniae*
2.	18/M	Alcoholic Smoker	None	Generalised pain abdomen Fever Chills	Febrile, Hypotension peritonitis	MODS	WNL	Multiple Right lobe	Multiple liver abscess with emphysematous change	*K. pneumoniae*
3.	50/F	None	DM	RUQ pain Fever Chills	RUQ Tenderness	Elevated TLC	Gass under diaphragm	2 Right lobe	Two large emphysematous abscesses	Sterile
4.	32/M	None	None	RUQ pain Fever	RUQ Tenderness	Elevated TLC	Gass under diaphragm	1 Right lobe	Single emphysematous liver abscess	Sterile
5.	55/M	Alcoholic	None	Fever RUQ pain	RUQ Tenderness	Elevated TLC	WNL	2 Right and left lobe	Right lobe abscess with left lobe emphysematous abscess	*K. pneumoniae*
6.	54/F	None	DM	Fever RUQ pain	RUQ Tenderness	Elevated TLC	WNL	Emphysematous cholecystitis	Large liver abscess with emphysematous changes	*K. pneumoniae*
7.	48/M	Alcoholic	DM	Fever RUQ pain	RUQ Tenderness	Elevated TLC	WNL	1 Right lobe	Right emphysematous liver abscess with Pleural effusion	*E. coli*
8.	50/M	Alcoholic	DM	Fever RUQ pain	Peritonitis	Elevated TLC	Gass under diaphragm	1 Right lobe	Right emphysematous liver abscess with pleural effusion	*E. coli*

DM: Diabetes mellitus, WNL: Within normal limits, RUQ: Right upper quadrant, MODS: Multi organ dysfunction syndrome, M: Male, F: Female, *K. pneumoniae: Klebsiella pneumoniae, E. coli: Escherichia coli.*

Table 2. Blood parameters at admission

Case no	Hb	TLC	INR	Bilirubin	SGOT/SGPT	ALP	Urea	Creatinine	CRP	HBA1C	Lactate
1.	10.2	11000	1.1	0.8	60/55	120	40	0.8	2	5.2	3
2.	8	28000	3.7	3	120/110	400	180	3.8	65	5.6	6
3.	9.4	32000	1.2	2.4	80/65	200	64	1.2	28	10.4	2
4.	13	26000	1.24	4	110/75	180	68	0.8	15	6.2	2
5.	8.9	22000	1.8	2	80/55	160	120	2.2	8	5.4	1.8
6.	6	38000	3.2	2	140/200	300	160	3	55	8.8	4
7.	12	24600	2.2	1.2	60/45	140	70	1.8	15	9.2	3
8.	10.8	20800	2.6	1.4	50/45	150	72	1.1	10	10	3.8

Hb: Haemoglobin, TLC: Total leucocyte count, INR: International normalized ratio of prothrombin time, SGOT: Serum glutamyl ornithine transferase, SGPT: Serum glutamic pyruvate transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein, HBA1c: Glycosylated haemoglobin.

Table 3. Outcomes of all patients

Case no	Age/sex	Habits	Outcome	Total duration of PCD in-situ	Condition at three monthly follow up
1.	22/M	Alcoholic	Discharged to home	12 weeks	Stable
2.	18/M	Alcoholic/Smoker	Discharged to home	16 weeks	Stable
3.	50/F	None	Discharged to home	14 weeks	Stable
4.	32/M	None	Discharged to home	8 weeks	Stable
5.	55/M	Alcoholic	Discharged to home	10 weeks	Stable
6.	54/F	None	Discharged to home	6 weeks	Stable
7.	48/M	Alcoholic	Discharged to home	8 weeks	Stable
8.	50/M	Alcoholic	Discharged to home	16 weeks	Stable, required PCD reinsertion

PCD: Percutaneous drainage tube, M: Male, F: Female.

CONCLUSION

To conclude, heightened awareness among clinicians, radiologists, and surgeons regarding the potential for emphysematous liver abscess to mimic other acute abdominal emergencies is warranted. A comprehensive understanding of the varied clinical presentations, particularly distinguishing ELAs from hollow viscus perforations, and the incorporation of advanced imaging techniques like contrast-enhanced computed tomography are crucial for accurate and timely diagnosis, guiding appropriate therapeutic interventions, avoiding unnecessary laparotomies, and improving patient outcomes with less invasive modalities like percutaneous drainage.

Informed Consent: Informed consent was obtained from the all patients participating in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - All of authors; Design - SS, SKS, AA, AAS; Supervision - RK, SC, AA, AAS; Fundings; SC, SS, SKS, RK; Data Collection and/or Processing - SS, SKS, RK; Analysis and/or Interpretation - SS, SKS, AA, RK, SÇ; Literature Search - SS, SK, AA, SC; Writing Manuscript - SS, SKS, AA, AAS; Critical Reviews - AAS, AA, RK.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Hagiya H, Kuroe Y, Nojima H, Otani S, Sugiyama J, Naito H, et al. Emphysematous liver abscesses complicated by septic pulmonary emboli in patients with diabetes: Two cases. Intern Med 2013; 52(1): 141-5. https://doi.org/10.2169/internalmedicine.52.8737*
2. *Lee CJ, Han SY, Lee SW, Baek YH, Choi SR, Roh MH, et al. Clinical features of gas-forming liver abscesses: Comparison between diabetic and nondiabetic patients. Korean J Hepatol 2010; 16(2): 131. https://doi.org/10.3350/kjhep.2010.16.2.131*
3. *Lee HL, Lee HC, Guo HR, Ko WC, Chen KW. Clinical significance and mechanism of gas formation of pyogenic liver abscess due to Klebsiella pneumoniae. J Clin Microbiol 2004; 42(6): 2783-5. https://doi.org/10.1128/JCM.42.6.2783-2785.2004*
4. *Rahimian J, Wilson T, Oram V, Holzman RS. Pyogenic liver abscess: Recent trends in etiology and mortality. Clin Infect Dis 2004; 39(11): 1654-9. https://doi.org/10.1086/425616*
5. *Yang CC, Chen CY, Lin XZ, Chang TT, Shin JS, Lin CY. Pyogenic liver abscess in Taiwan: Emphasis on gas-forming liver abscess in diabetics. Am J Gastroenterol 1993; 88(11): 1911-5.*

6. *Chou FF. The comparison of clinical course and results of treatment between gas-forming and non-gas-forming pyogenic liver abscess. Arch of Surg 1995; 130(4): 401-5. https://doi.org/10.1001/archsurg.1995.01430040063012*

7. *Maliyakkal AM, Naushad VA, Al Mokdad OI, Hanana F, Basheer SM, Palaki JA. Gas under diaphragm: A rare case of ruptured liver abscess with gas forming organism. Cureus 2022; 14(1): e21672. https://doi.org/10.7759/cureus.21672*

8. *Wong W, Wong BCY, Hui CK, Ng M, Lai KC, Tso WK, et al. Pyogenic liver abscess: Retrospective analysis of 80 cases over a 10-year period. J Gastroenterol Hepatol 2002; 17(9): 1001-7. https://doi.org/10.1046/j.1440-1746.2002.02787.x*

9. *Shiba H, Aoki H, Misawa T, Kobayashi S, Saito R, Yanaga K. Pneumoperitoneum caused by ruptured gas-containing liver abscess. J Hepatobiliary Pancreat Surg 2007; 14(2): 210-1. https://doi.org/10.1007/s00534-006-1136-y*

10. *Pham Van T, Vu Ngoc S, Nguyen Hoang NA, Hoang Huu D, Dinh Duong TA. Ruptured liver abscess presenting as pneumoperitoneum caused by Klebsiella pneumoniae: A case report. BMC Surg 2020; 20(1): 228. https://doi.org/10.1186/s12893-020-00858-w*

OLGU SERİSİ-ÖZET
Turk J Surg 2024; 40 (3): 247-255

Amfizematöz karaciğer apseleri: Değişken klinik sunumlar, yönetim zorlukları ve sonuçlar-bir olgu serisi

Sukesh Kudumallige Sudhakara, Shiva Shiva, Ranjith Kumaran, Sheefali Chandra, Akshay Anand, Abhinav Arun Sonkar

King George's Tıp Üniversitesi, Genel Cerrahi Anabilim Dalı, Lucknow, Hindistan

ÖZET

Karaciğer parenkimi içinde gaz varlığı ile karakterize olan amfizematöz karaciğer apseleri (AKA) nadir görülen ve potansiyel olarak yaşamı tehdit eden bir durumdur. İçi boş organ perforasyonunu taklit eden klinik tablolara sahip AKA'lar klinisyenler için tanısal bir bilmece oluşturmaktadır. Bu seri, bu tür atipik sunumların yarattığı tanısal zorlukları ve pnömoperitoneumun ayırıcı tanısında hepatik patolojinin göz önünde bulundurulmasının önemini vurgulamaktadır. Bu çalışmanın amacı, karaciğer apselerinin bu benzersiz alt kümesinin yönetiminde kullanılan çeşitli klinik sunumların, tanısal zorlukların ve terapötik stratejilerin kapsamlı bir analizini sunmaktır.

Anahtar Kelimeler: Amfizematöz karaciğer apsesi, karaciğer apsesi, diyafram altında gaz

DOİ: 10.47717/turkjsurg.2024.6436

CASE SERIES
Turk J Surg 2024; 40 (3): 256-260

Tumor in the liver: Six inflammatory pseudotumor patients

Akile Zengin[1], Ahmet Murat Şendil[2], Yavuz Selim Angın[2], Barış Türker[3], Mehmet Kılıç[2], Murat Ulaş[1], Elif Gündoğdu[4], Deniz Arık[5]

[1]Department of Gastrointestinal Surgery, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[2]Department of General Surgery, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[3]Clinic of Gastrointestinal Surgery, Çanakkale Mehmet Akif Ersoy State Hospital, Çanakkale, Türkiye
[4]Department of Radiology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[5]Department of Pathology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye

ABSTRACT

Inflammatory pseudotumor (IPT) is a rare liver disease confused with liver tumors. It is a disease that should be known in the differential diagnosis for clinicians as the correct diagnosis of IPT will prevent unnecessary surgery. Demographic datas, diagnoses and imaging modalities of six patients with radiologically and/or histopathologically diagnosed hepatic IPT between 2016 and 2023 were retrospectively analyzed. Four out of six patients were female and median age was 57.5 (47-66). C-reactive protein was higher in four patients, and carbohydrate antigen 19.9 level was higher in one patient. We used magnetic resonance imaging (MRI) for diagnosis in five patients. Only in one patient computed tomography was enough for diagnosis. Tumor locations were segment 5 for two patients, segment 7-8 in two patients, segment 7 in one patient, and 8 in one patient. Liver biopsy was performed in five patients because it could not be distinguished from malignancy by imaging methods. Histopathological results of all these biopsies defined as IPT. Initial tumor median size was 31 (17-55) mm. Two patients were operated on. The first one underwent right hepatectomy due to a 2-fold increase in size within 11 months. The second one had a mass indistinguishable from hepatic adenoma by MRI and underwent nonanatomic resection. In one patient, IPT disappeared completely in the 18th month of follow-up period while it regressed in size in two patients. Two of our patients had a history of recurrent endoscopic retrograde cholangiopancreatography, which we noticed incidentally before IPT was diagnosed. IPTs are liver masses with low malignant potential and may shrink spontaneously during follow-up. We suspected that biliary tract interventions may be the cause of IPT.

Keywords: Inflammatory pseudotumor, hepatic mass, IgG4, biliary tract intervention

INTRODUCTION

Inflammatory pseudotumor (IPT) is a rare disease characterized by fibrosis and chronic infiltration of inflammatory cells (1). It may affect many organs including the biliary tract, lung, lymph nodes, pancreas, retroperitoneum and liver (2,3). IPT localized in the liver may be confused with liver tumors (1). In the etiology infections (mostly bacterial), immunology, allergy or malignancies are blamed (4). It has also been reported that there may be a relationship between immunoglobulin G4 (IgG4)-related sclerosing disease and IPT (5). It is mostly observed in men between the ages of 30-40 years, and its symptoms include nonspecific findings including fever, abdominal pain and weight loss (6). Computed tomography (CT) of the liver and magnetic resonance imaging (MRI) with liver-specific contrast are recommended for differential diagnosis (1) .

IPT has a good prognosis and it has been reported in the literature that spontaneous regression in tumor size may occur spontaneously or with anti-inflammatory drugs or steroid treatment (7). Since unnecessary surgery will be prevented with the correct diagnosis of IPT, it is a disease that should be known in the differential diagnosis for clinicians. Our aim was to raise awareness about this disease by sharing our clinical experience with you.

Cite this article as: Zengin A, Şendil AM, Angın YS, Türker B, Kılıç M, Ulaş M, et al. Tumor in the liver: Six pseudoinflammatory tumor patients. Turk J Surg 2024; 40 (3): 256-260.

Corresponding Author
Akile Zengin
E-mail: dr.akile.zengin@gmail.com

Received: 12.06.2024
Accepted: 18.09.2024
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2024.6479

MATERIAL and METHODS

This study was approved by the institutional review board (Approval number: 19). When the admissions to our clinic between 2016 and 2023 were analyzed retrospectively, we found that a total of six patients were diagnosed with IPT radiologically and/or histopathologically. Demographic data, diagnosis and screening parameters were analyzed retrospectively. Continuous variables were defined as median (range), and categorical data were defined as frequencies and percentages. Patients were followed up clinically and radiologically until March 2024.

RESULTS

Demographic and preoperative biochemical results of six patients are analyzed in Table 1. Four (66.6%) out of six patients were female and median age was 57.5 (47-66). White blood cell (normal level is between 4.4-12.6 x 10^3/Ul), and alpha fetoprotein (AFP) (normal level is between 0.5-5.8 IU/mL) levels were between normal values. C-reactive protein (CRP) (normal level is between 0-5 mg/L) was higher in four patients, and carbohydrate antigen (CA) 19.9 (normal level is between 0-27 U/mL) level was higher in one patient. Viral markers (hepatitis B, C, and anti-HIV) were between normal levels for all of the patients.

Diagnosis and follow-up outcomes are shown in Table 2. We used MRI for diagnosis in five patients. Only in one patient, CT was enough for diagnosis. Tumor locations were segment 5 for two patients, segment 7-8 in two patients, segment 7 in one patient, and 8 in one patient. Liver biopsy was performed in five patients because it could not be distinguished from malignancy by imaging methods. Histopathological results of all these biopsies were defined as IPT. The pathological results of three patients were related with IgG4. Anaplastic lymphoma kinase (ALK) was negative for five patients.

Table 1. Demographic data and preoperative biochemical test results of the patients

Patient Number	**1**	**2**	**3**	**4**	**5**	**6**
Gender	F	M	F	F	M	F
Age (year)	55	47	60	63	66	48
WBC (10^3/uL)	4.4	9.4	5	7.6	11.9	7.9
CRP (mg/L)	**13.8**	**76.6**	**14.6**	**22.8**	2.3	0.7
CA 19.9 level (U/mL)	2.9	9.48	0.6	4.43	**41.1**	-
AFP level (IU/mL)	4.2	-	1.86	1.69	3	-
Viral markers	N	N	N	N	N	N

F: Female, M: Male, WBC: White blood cell, AFP: Alpha fetoprotein, CRP: C-reactive protein, CA: Carbohydrate antigen, N: Normal.

Table 2. Diagnosis and follow-up outcomes of the patients

Patient Number	**1**	**2**	**3**	**4**	**5**	**6**
Imaging methods	CT	MRI	MRI	USG-MRI	MRI	MRI
Tumor location in the liver (segment)	5	5	7	7-8	8	7-8
Liver biopsy (+/-)	+	+	+	+	+	-
IgG4	-	+	-	-	+	+
ALK	-	-	NA	-	-	-
Initial tumor size (mm)	50	17	55	40	22	20
Tumor number (n)	1	1	1	1	1	1
O/F	F	F	F	F	O	O
Last tumor size (mm)	50	10	22	0	-	-
Follow up period (month)	12	33	4	18	11	6
Survival status	E	A	E	A	A	A

CT: Computed tomography, USG: Ultrasonography, MRI: Magnetic resonance imaging, IgG4: Immunoglobulin G4, ALK: Anaplastic lymphoma kinase, NA: Non-available, O: Operation, F: Follow up, A: Alive, E: Exitus.

Initial tumor median size was 31 (17-55) mm, and a tumor focus was detected in all patients using imaging methods. Two patients were operated. Patient 5 was diagnosed as IPT by preoperative liver biopsy but underwent right hepatectomy due to a 2-fold increase in size within 11 months. Patient 6 had a mass indistinguishable from hepatic adenoma by preoperative MRI and underwent nonanatomic resection.

In one patient, IPT disappeared completely in the 18th month of follow-up period while it regressed in size in two patients (Figure 1). One of the patients with tumor size regression died in the fourth month of follow-up period due to intracranial hemorrhage. One patient died in the 12th month of follow-up period because of heart failure; no progression in tumor size was noted during this 12-month follow-up period. The follow-up periods of the two patients who survived and did not have surgery were 33 month and 18 month, respectively.

Two of our patients had a history of recurrent endoscopic retrograde cholangiopancreatography (ERCP), which we noticed incidentally before IPT was diagnosed. Patient 1, who had pancreatic head malignancy, underwent preoperative ERCP three times. Postoperatively, three percutaneous transhepatic cholangiographies were performed, followed by the placement of a percutaneous biliary stent. A liver mass developed after the biliary tract interventions, and the pathological result was IPT. Patient 2 has a history of nine ERCP procedures performed over five years due to acute biliary pancreatitis.

DISCUSSION

IPT, also known as inflammatory myofibroblastic tumor and plasma cell granuloma, is a rare inflammatory soft tissue lesion (2). IPT is also known as inflammatory myofibrohistiocytic proliferation, fibrous histiocytoma, etc. in the literature (8). IPT usually affects the right lobe of the liver, but it has been rarely reported to be found in the spiegel lobe and hilar region or bilobar multifocal (6,9). IPT was localized in the right lobe in all of our patients in accordance with the literature. We thought that the reason of IPT for two patients may have been related to repeated biliary tract interventions. Similarly, our hypothesis is supported by a case series including three patients, in which it has been reported that biliary tract manipulation may be the cause of IPT (10).

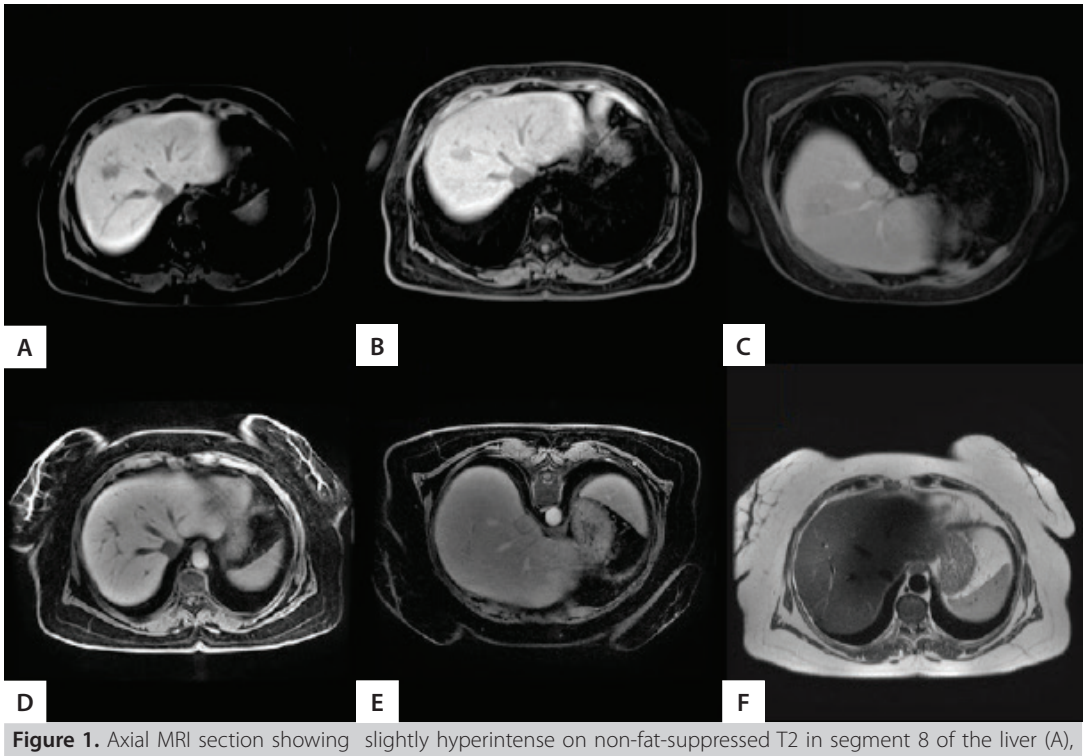

Figure 1. Axial MRI section showing slightly hyperintense on non-fat-suppressed T2 in segment 8 of the liver (A), hypointense on precontrast T1 (B), centrally stained in postcontrast portal phase images and becomes isointense with the parenchyma (C). In control imaging, the lesion has completely regressed. T2AG without fat suppression (D), post-contrast portal phase images (E) and hepatobiliary phase images (F).

Laboratory findings include leukocytosis, increased erythrocyte sedimentation rate and CRP, polyclonal hypergammaglobulinemia, and mildly elevated liver enzymes. AFP, one of the tumor markers, is mostly normal, whereas CA 19.9 has been found at high values in some patients (6). ALK overexpression is observed in 50% of patients with IPT, and positivity has been associated with high local recurrence and increased mortality (8).

Similar contrast enhancement patterns on CT and MRI can also be observed in other lesions such as atypical hepatocellular carcinoma, intrahepatic cholangiocarcinoma, metastatic tumors and abscesses (1). CT findings for IPT exhibit significant variability. The most frequently observed features are hypoattenuating, ill-defined masses with a range of contrast enhancement levels. Delayed enhancement, particularly in septal and peripheral regions, is noted and is believed to be associated with fibrous components (11). MRI reveals a variable presentation of these tumors; they are generally hypointense relative to skeletal muscle on T1-weighted images, hyperintense on T2-weighted images, and show heterogeneous enhancement after contrast material is administered (12). It has been reported that IPT should be suspected if Ig G4 is also positive in the presence of targetoid-like aspect of hepatic mass on MRI (4).

Nevertheless, because of uncertainty in the imaging diagnosis, histologic diagnosis is important to accurately diagnose IPT (8). It is known that the clinical course and prognosis of IPT are favorable with conservative treatment (1). While we diagnosed IPT in five patients with biopsy and followed four of them, right hepatectomy was performed in only one patient in consequence of of rapid growth. On histopathological examination, IPT is characterized by proliferation of fibroblasts or myofibroblasts and inflammatory cell infiltration consisting of lymphocytes and plasma cells (6,9). Two histologic forms have been reported for IPT in the liver. These are fibrohistiocytic and lymphoplasmocytic forms (13). Lymphoplasmocytic form has been associated with Ig G4. It has been reported that this form is mostly observed in the hepatic hilus (13). In the fibrohistiocytic form, the tumor is found as a mass located in the periphery of the liver (14).

It has been reported that spontaneous regression may occur with conservative treatments such as nonsteroidal antiinflammatory drugs after pathologic diagnosis (8). In a case series of three patients in the literature, spontaneous regression has been reported for liver localized IPT (7). Although the recurrence rate has been reported to be approximately 25%, it has also been reported that surgical procedure may be required (8). No conservative treatment was given to the patients in our study group, and no progression in the size of the mass was observed except in one patient and even regression was found.

CONCLUSION

IPTs are liver masses with low malignant potential and may shrink spontaneously during follow-up. As long as they are closely monitored with imaging methods and there is no suspicion of malignancy, there is no need for surgical intervention. Finally, we doubt that development of IPT may be associated with biliary tract interventions.

Ethics Committee Approval: This study was approved by the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee (Decision no: 19, Date: 21.03.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - MK, AZ; Design - MK; Supervision - MU, MK; Data Collection and/or Processing - All of authors; Analysis and/or Interpretation - AZ, MK; Literature Search - AZ; Writing Manuscript - AZ, EG; Critical Reviews - DA, BT.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Oh K, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, et al. Clinicopathological features and post-resection outcomes of inflammatory pseudotumor of the liver. Ann Hepatobiliary Pancreat Surg 2021; 25: 34-8. https://doi.org/10.14701/ahbps.2021.25.1.34*
2. *Zhang Z, Fu W, Wang M, Niu L, Liu B, Jiao Y, et al. IgG4-related inflammatory pseudotumor of the brain parenchyma: A case report and literature review. Acta Neurol Belg 2018; 118: 617-27. https://doi.org/10.1007/s13760-018-1027-4*
3. *Tublin ME, Moser AJ, Marsh JW, Gamblin TC. Biliary inflammatory pseudotumor: Imaging features in seven patients. Am J Roentgenol 2007; 188(1): W44-8. https://doi.org/10.2214/AJR.05.0985*
4. *Calistri L, Maraghelli D, Nardi C, Vidali S, Rastrelli V, Crocetti L, et al. Magnetic resonance imaging of inflammatory pseudotumor of the liver: A 2021 systematic literature update and series presentation. Abdom Radiol 2022; 47: 2795-810. https://doi.org/10.1007/s00261-022-03555-9*
5. *Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010; 7: 401-9. https://doi.org/10.1038/nrgastro.2010.81*
6. *Elpek GÖ. Inflammatory myofibroblastic tumor of the liver: A diagnostic challenge. J Clin Transl Hepatol 2014; 2: 53-7. https://doi.org/10.14218/JCTH.2013.00023*
7. *Yamaguchi J, Sakamoto Y, Sano T, Shimada K, Kosuge T. Spontaneous regression of inflammatory pseudotumor of the liver: Report of three cases. Surg Today 2007; 37: 525-9. https://doi.org/10.1007/s00595-006-3433-0*
8. *Kwag MH, Park JY, Jeong HW, Han JY, Lim JH, Kim YS, et al. Overlooked and challenging encounters inflammatory pseudotumors in the abdomen and pelvis: A pictorial essay. J Korean Soc Radiol 2020; 81: 1121-33. https://doi.org/10.3348/jksr.2019.0199*
9. *Puri Y, Lytras D, Luong TV, Fusai GK. Rare presentation of self-resolving multifocal inflammatory pseudo-tumour of liver. World J Clin Cases 2014; 2: 5-8. https://doi.org/10.12998/wjcc.v2.i1.5*

10. *Zhao J, Olino K, Low LE, Qiu S, Stevenson HL. Hepatic inflammatory pseudotumor: An important differential diagnosis in patients with a history of previous biliary procedures. ACG Case Rep J 2019; 6(1): e00015. https://doi.org/10.14309/crj.0000000000000015*

11. *Maheshwari E, Ram R, Pandey T, Bajaj G, Jambhekar K. Hepatic inflammatory pseudotumor - a diagnostic challenge: A case report and review of literature. J Gastrointestinal Abdominal Radiol 2019; 2(1): 45-8. https://doi.org/10.1055/s-0038-1676424*

12. *Narla LD, Newman B, Spottswood SS, Narla S, Kolli R. Inflammatory pseudotumor. Radiographics 2003; 23(3): 719-29. https://doi.org/10.1148/rg.233025073*

13. *Zen Y, Fujii T, Sato Y, Masuda S, Nakanuma Y. Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod Pathol 2007; 20: 884-94. https://doi.org/10.1038/modpathol.3800836*

14. *Hideshima K, Suzuki T, Oe S, Shinohara N, Matuhashi N, Ichii O, et al. IgG4-related hepatic inflammatory pseudotumor in a patient with serum IgG4-negative type 1 autoimmune pancreatitis. Clin J Gastroenterol 2023; 16: 895-900. https://doi.org/10.1007/s12328-023-01861-3*

OLGU SERİSİ-ÖZET
Turk J Surg 2024; 40 (3): 256-260

Karaciğerde tümör: Altı enflamatuvar psödotümör hastası

Akile Zengin[1], Ahmet Murat Şendil[2], Yavuz Selim Angın[2], Barış Türker[3], Mehmet Kılıç[2], Murat Ulaş[1], Elif Gündoğdu[4], Deniz Arık[5]

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Gastrointestinal Cerrahi Anabilim Dalı, Eskişehir, Türkiye
[2]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Eskişehir, Türkiye
[3]Çanakkale Mehmet Akif Ersoy Devlet Hastanesi, Gastrointestinal Kliniği, Çanakkale, Türkiye
[4]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Eskişehir, Türkiye
[5]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Eskişehir, Türkiye

ÖZET

Enflamatuvar psödotümör (EPT), karaciğer tümörleriyle karıştırılan nadir bir karaciğer hastalığıdır. Enflamatuvar psödotümörün doğru tanısı gereksiz cerrahiyi önleyeceğinden klinisyenler için ayırıcı tanıda bilinmesi gereken bir hastalıktır. 2016-2023 yılları arasında radyolojik ve/veya histopatolojik olarak hepatik EPT tanısı almış altı hastanın demografik verileri, tanıları ve görüntüleme yöntemleri retrospektif olarak analiz edildi. Altı hastanın dördü kadındı ve ortanca yaş 57,5'ti (47-66). C-reaktif protein dört hastada yüksekti ve karbohidrat antijeni 19,9 seviyesi bir hastada yüksekti. Beş hastada tanı için manyetik rezonans görüntüleme (MRG) kullanıldı. Sadece bir hastada tanı için bilgisayarlı tomografi yeterli oldu. Tümör yerleşimi iki hastada segment 5, iki hastada segment 7-8, bir hastada segment 7 ve bir hastada 8 idi. Beş hastaya görüntüleme yöntemleriyle maligniteden ayırt edilemediği için karaciğer biyopsisi yapıldı. Tüm bu biyopsilerin histopatolojik sonuçları EPT olarak tanımlandı. Başlangıçtaki tümör medyan boyutu 31 (17-55) mm idi. İki hasta ameliyat edildi. İlk hastaya 11 ay içinde tümör boyutunda iki kat artış olması nedeniyle sağ hepatektomi yapıldı. İkinci hastada MRG ile hepatik adenomdan ayırt edilemeyen bir kütle vardı ve anatomik olmayan rezeksiyon yapıldı. Bir hastada EPT, takip süresinin 18. ayında tamamen kaybolurken, iki hastada boyut olarak geriledi. Hastaların ikisinde EPT tanısı konulmadan önce tesadüfen fark edilen tekrarlayan endoskopik retrograd kolanjiyopankreatografi öyküsü vardı. Enflamatuvar psödotümörler düşük malignite potansiyeline sahip karaciğer kütleleridir ve takip sırasında kendiliğinden küçülebilmektedir. Safra yolu müdahalelerinin EPT'ye neden olabileceğinden şüphelenilmektedir.

Anahtar Kelimeler: Enflamatuvar psödotümör, karaciğerde kütle, IgG4, safra yolu girişimi

DOİ: 10.47717/turkjsurg.2024.6479

CASE REPORT
Turk J Surg 2024; 40 (3): 261-263

Primary neuroendocrine tumor of the perihilar bile duct: A case report

Mustafa Salış[1], Muhammed Kandemir[2], Elif Gündoğdu[3], İlter Özer[4], Bülent Ünal[5], Murat Ulaş[6]

[1] Clinic of General Surgery, University of Health Sciences, Eskişehir City Health Practice and Research Center, Eskişehir, Türkiye
[2] Clinic of General Surgery, Cizre Dr. Selahattin Cizrelioğlu State Hospital, Şırnak, Türkiye
[3] Department of Radiology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[4] Clinic of Gastrointestinal Surgery, Private Clinic, Ankara, Türkiye
[5] Department of General Surgery, İstanbul Aydın University Faculty of Medicine, İstanbul, Türkiye
[6] Department of General Surgery, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye

ABSTRACT

Neuroendocrine tumors (NETs) arising from extrahepatic bile ducts are very rare. We present a patient with perihilar NET who was operated on with a preoperative diagnosis of Klatskin tumor. A 58-year-old female patient was admitted with abdominal pain and jaundice. Laboratory data showed elevated serum bilirubin levels and liver function tests. Computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) findings were consistent with perihilar bile duct tumor. The patient was operated on with a diagnosis of Klatskin tumor. She underwent right hepatectomy, resection of the extrahepatic bile duct, portal lymphadenectomy and Roux-en-Y hepaticojejunostomy. The final pathologic examination of the resected specimen demonstrated a well differentiated neuroendocrine tumor (Grade 1). NETs originating from perihilar bile ducts are extremely rare, and preoperative definite diagnosis is very difficult. It should be kept in mind that NET may be one of the rare causes of perihilar bile duct obstruction.

Keywords: Neuroendocrine tumor, perihilar bile duct, resection

INTRODUCTION

Neuroendocrine tumors (NETs) can be found throughout the gastrointestinal tract and pancreas. However, NETs arising from extrahepatic bile duct are very rare. NETS arising from perihilar region is exceedingly rare with a few cases reported in the literature (1). Preoperative differential diagnosis of perihilar NET is difficult and in general, it is diagnosed with postoperative histopathologic evaluation of the resected specimen. We herein report a case of perihilar NET with a preoperative diagnosis of perihilar cholangiocarcinoma.

CASE REPORT

A 58-year-old female patient was admitted with abdominal pain and jaundice. Physical examination revealed only a mild tenderness on the right upper quadrant. Laboratory data showed elevated serum total and direct bilirubin levels (6.29/5.42 mg/dL) and liver function tests. Serum levels of CEA and CA19-9 were normal. The patient was referred to computed tomography (CT). Both right and left intrahepatic bile duct dilatation were revealed on contrast- enhanced abdominal CT and also a-two-cm diameter of an isodense mass was detected in the perihilar region (Figure 1). Magnetic resonance cholangiopancreatography (MRCP) was performed with a prediagnosis of perihilar cholangiocarcinoma. Dilated intrahepatic bile ducts, obstruction of common hepatic duct due to tumor mass and normal intrapancreatic distal common bile duct were seen on MRCP images (Figure 2). MRCP findings were consistent with perihilar bile duct tumor.

The patient was operated on with a diagnosis of perihilar cholangiocarcinoma (Klatskin tumor). She underwent right hepatectomy, excision of the caudate lobe, resection of the extrahepatic bile duct, regional lymphadenectomy and Roux-en hepaticojejunostomy. During the postoperative period, the patient developed collections and abscess in the operative field which were managed with percutaneous drainage procedures and prolonged antibiotic therapy. The patient was discharged after a postoperative course of 36 days.

Cite this article as: Salış M, Kandemir M, Gündoğdu E, Özer İ, Ünal B, Ulaş M. Primary neuroendocrine tumor of the perihilar bile duct: A case report. Turk J Surg 2024; 40 (3): 261-263.

Corresponding Author
Mustafa Salış
E-mail: salismustafa@gmail.com

Received: 26.08.2019
Accepted: 27.08.2020
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2022.4595

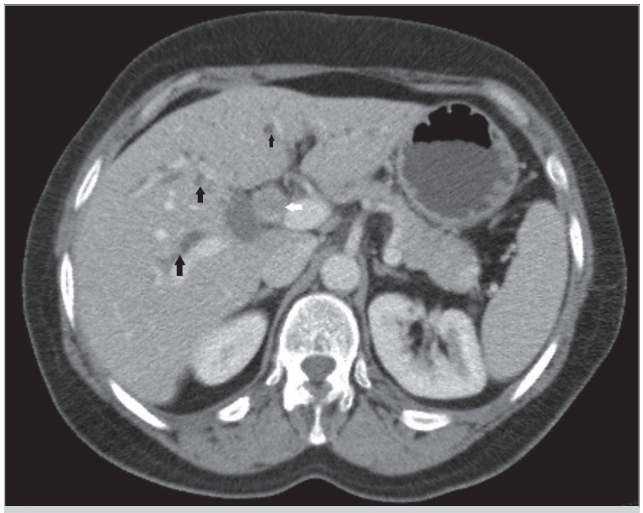

Figure 1. Contrast-enhanced axial CT image shows dilated left and right intrahepatic bile ducts (black arrows) and an isodense tumor mass (white arrow) localizated in common bile duct.

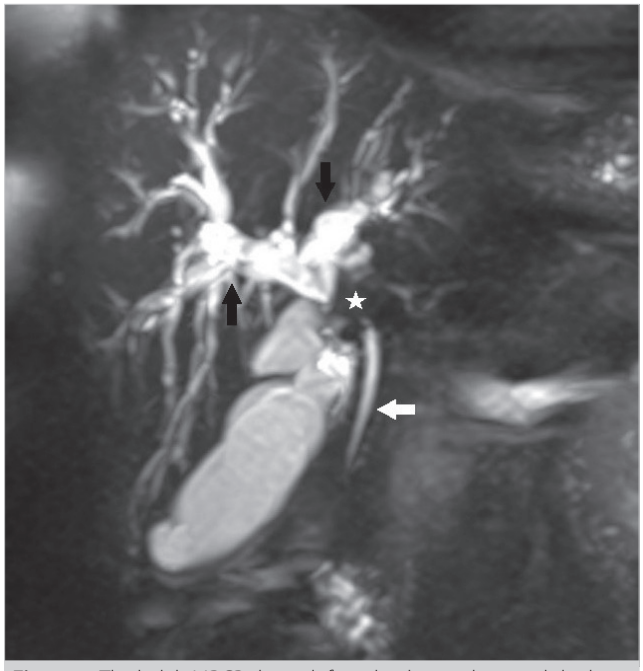

Figure 2. Thick slab MRCP shows left and right intrahepatic bile ducts dilatation (black arrows), perihilar extrahepatic bile duct tumor (star) and normal caliber of intrapancreatic terminal common bile duct.

The final pathologic examination of the resected specimen demonstrated a well differentiated (Grade 1) neuroendocrine tumor in accordance with the World Health organization (WHO) 2010 classification. The maximum diameter of the tumor was 1.2 cm. Proximal and distal surgical margins were free of tumor cells. However, there were tumor cells in the lateral margin and subepithelial stroma of the hepatic duct. There was only one metastatic local lymph node.

The patient did not receive any modality of adjuvant therapy. After a 15-month-follow-up period, the patient was doing well with normal physical examination findings and completely normal liver function tests. Ga67 PET BT showed no evidence of distant metastasis or local recurrence.

DISCUSSION

Neuroendocrine tumors are classified as as NET Grade 1 (G1), NET Grade 2 (G2), and neuroendocrine carcinoma (NEC) according to the 2010 WHO classification system (2). This paper presents a case of NET G1 arising from an extremely rare localization.

The precise diagnosis of perihiler NET is frequently not possible preoperatively. Differential diagnosis based on radiologic findings is difficult although BT reveals hypervascular, well-circumscribed lesions (3). The differential diagnosis includes cholangiocarcinoma, metastatic tumors and lymphoma (4). There are no specific hormonal symptoms and serum markers (3). Preoperative histopathologic diagnosis is usually not possible. Moreover, as the most frequent cause of malignant perihilar bile duct obstruction is adenocarcinoma, histopathologic diagnosis is not generally needed for resectable cases when a malignant obstruction is suspected. Therefore, the definite histopathologic diagnosis is generally possible after the evaluation of the resected specimen. In this case, our preoperative diagnosis was perihilar cholangiocarcinoma and the treatment plan was resection of the tumor.

Data regarding the optimal management and prognosis of these tumors are not sufficient in the literature. However, resection when technically possible should be performed as it is frequently impossible to distinguish NETs from cholangiocarcinomas. In addition, G1 and G2 NETs are slowly growing tumors and resection has been shown to be beneficial (5,6).

Surgery is the mainstay of treatment and should be considered in all patients if technically feasible in gastroenteropancreatic neuroendocrine tumors (GEP-NET). Curative surgical resection of the primary lesion should be performed in patients with localized GEP-NET (7).

In G1 and G2 NETs, curative intended surgery has been considered, even in patients with liver and/or lymph node metastases (8). Debulking surgery may also be performed for liver metastases in certain circumstances (8). In our patient, resection of the tumor with right hepatectomy and regional lymphadenectomy was performed as recommended in the literature (6-8).

As perihilar NETs are extremely rare, data regarding long-term follow-up of these tumors are lacking. However, as G1 and G2 NETs are slowly growing tumors, better survival when compared to perihilar cholangiocarcinoma may be expected. Similarly, our patient showed complete clinical and biochemical healing after a follow-up of 15 months.

CONCLUSION

In conclusion, NETs of the perihilar extrahepatic bile duct are extremely rare and are difficult to diagnose perioperatively. Surgical resection is the only therapy that offers a chance of cure. Perihilar NETs should be kept in mind in the differential diagnosis of a suspected perihilar malignant obstruction.

Informed Consent: Informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İÖ, MS, BÜ, EG; Design - MS, MK, İÖ, EG; Supervision - İÖ, BÜ, MU; Materials - MS, MK, EG; Data Collection and/or Processing - MS, EG, MU; Analysis and/or Interpretation - MS, İÖ, BÜ, MU; Literature Search - MS, İÖ, EG; Writing Manuscript - MS, İÖ, EG; Critical Reviews - İÖ, BÜ, MU.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Kihara Y, Yokomizo H, Urata T, Nagamine M, Hirata T. A case report of primary neuroendocrine carcinoma of the perihilar bile duct. BMC Surgery 2015; 15: 125. https://doi.org/10.1186/s12893-015-0116-z*
2. *Komminoth P, Arnold R, Capella C, Klimstra DS, Kloppel G, Rindi G, et al. Neuroendocrine neoplasms of the gallbladder and extrahepatic bile ducts. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). WHO Classification of Tumours of the Digestive System. Lyon, France: IARC Press; 2010. p. 274-6.*
3. *Hosoda K, Kobayashi A, Shimizu A, Kitagawa N, Ito T, Yamada A, et al. Neuroendocrine tumor of the common bile duct. Surgery 2016; 160: 525-6. https://doi.org/10.1016/j.surg.2016.01.001*
4. *Hoepfner L, White JA. Primary extrahepatic bile duct neuroendocrine tumor with obstructive jaundice masquerading as a Klatskin tumor. J Surg Case Rep 2017; 6: 1-3. https://doi.org/10.1093/jscr/rjx104*
5. *Michalopoulos N, Papavramidis TS, Karayannopoulou G, Pliakos I, Papavramidis ST, Kanellos I. Neuroendocrine tumors of extrahepatic biliary tract. Pathol Oncol Res 2014; 20: 765-75. https://doi.org/10.1007/s12253-014-9808-4*
6. *Ferrone CR, Tang LH, D'Angelica M, DeMatteo RP, Blumgart LH, Klimstra DS, et al. Extrahepatic bile duct carcinoid tumors: Malignant biliary obstruction with a good prognosis. J Am Coll Surg 2007; 205: 357-61. https://doi.org/10.1016/j.jamcollsurg.2007.02.076*
7. *Basuroy R, Srirajaskanthan R, Ramage JK. Neuroendocrine Tumors. Gastroenterol Clin North Am 2016; 45: 487-507. https://doi.org/10.1016/j.gtc.2016.04.007*
8. *Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. Vienna consensus conference participants. ENETS Consensus guidelines. Update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016; 103: 172-85. https://doi.org/10.1159/000443167*

OLGU SUNUMU-ÖZET
Turk J Surg 2024; 40 (3): 261-263

Safra yollarının primer nöroendokrin tümörü: Bir olgu sunumu

Mustafa Salış[1], Muhammed Kandemir[2], Elif Gündoğdu[3], İlter Özer[4], Bülent Ünal[5], Murat Ulaş[6]

[1] Sağlık Bilimleri Üniversitesi Eskişehir Şehir Sağlık, Uygulama ve Araştırma Merkezi, Genel Cerrahi Kliniği, Eskişehir, Türkiye
[2] Cizre Dr. Selahattin Cizrelioğlu Devlet Hastanesi, Genel Cerrahi Kliniği, Şırnak, Türkiye
[3] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Eskişehir, Türkiye
[4] Özel Klinik, Gastrointestinal Cerrahi Kliniği, Ankara, Türkiye
[5] İstanbul Aydın Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye
[6] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Eskişehir, Türkiye

ÖZET

Ekstrahepatik safra kanallarından kaynaklanan nöroendokrin tümörler (NET'ler) çok nadirdir. Preoperatif Klatskin tümör tanısı ile opere edilen perihiler NET'li bir hastayı sunuyoruz. Elli sekiz yaşında kadın hasta, karın ağrısı ve sarılık şikayeti ile başvurdu. Laboratuvar incelemesinde serum bilirubin düzeylerinde ve karaciğer fonksiyon testlerinde artış mevcuttu. Bilgisayarlı tomografi (BT) ve manyetik rezonans kolanjiyopankreatografi (MRCP) bulguları; perihiler safra kanalı tümörü ile uyumluydu. Hasta Klatskin tümör tanısı ile ameliyat edildi. Hastaya sağ hepatektomi, ekstrahepatik safra kanalı rezeksiyonu, portal lenfadenektomi ve Roux-en-Y hepatikojejunostomi yapıldı. Rezeke edilen numunenin patolojik incelemesinde, iyi farklılaşmış bir nöroendokrin tümör (evre 1) gösterildi. Perihiler safra kanallarından kaynaklanan NET'ler oldukça nadirdir ve preoperatif kesin tanı çok zordur. NET'in perihiler safra yolu tıkanıklığının nadir sebeplerinden biri olabileceği unutulmamalıdır.

Anahtar Kelimeler: Nöroendokrin tümör, perihiler safra yolu, rezeksiyon

DOİ: 10.47717/turkjsurg.2022.4595

CASE REPORT
Turk J Surg 2024; 40 (3): 264-266

A rare case of multiple gastric duplication cysts in an adult

Barış Zülfikaroğlu[1], Özgür Akgül[1], Mehmet Mahir Özmen[1,2,3]

[1] Clinic of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Türkiye
[2] Department of General Surgery, Istinye University Medical School, Istanbul, Türkiye
[3] Clinic of General Surgery, Ankara Liv Hospital, Ankara, Türkiye

ABSTRACT

Intestinal duplications are rare developmental anomalies that can occur anywhere along the gastrointestinal tract. Gastric duplication cysts are uncommon congenital anomalies and are rarely diagnosed in adults. However, diagnosis of the condition in an adult can be difficult as it is usually asymptomatic, or the symptoms are nonspecific. Here we report a rare case of symptomatic gastric duplication cysts in an adult who was treated successfully with surgical resection.

Keywords: Gastric duplication cyst, gastrointestinal duplication, adult, gastric surgery

INTRODUCTION

Intestinal duplications are rare developmental anomalies that can occur anywhere along the gastrointestinal tract. Intestinal duplications were originally described in 1941, by Ladd and Gross as having an attachment or adherence to some part of the gastrointestinal tract, the presence of a smooth muscle wall and a mucosal lining with one or more cell type of the gastrointestinal tract (1).

These malformations are believed to be congenital, formed before the differentiation of epithelial lining, and therefore named for the organ with which they are associated. Duplication cysts of the stomach represent four per cent of all alimentary tract duplications. Approximately 67 percent of gastric duplication cysts (GDCs) are identified within the first year of life. Duplication cysts in adults are generally asymptomatic and encountered as incidental findings at endoscopy or laparotomy (2).

GDCs are uncommon congenital anomalies and are rarely diagnosed in adults. Alimentary tract duplication cysts most frequent affect the ileum (35%), the esophagus (19%), the jejunum (10%), the stomach (9%) and the colon (7%) (3). In 35% of patients, GDCs co-exist with other congenital abnormalities such as annular or heterotopic pancreas, or vertebral anomalies such as spina bifida (3). On consideration of the fact that these cysts are usually asymptomatic or, in any case, have no specific signs and symptoms, diagnosis is frequently made post-operatively (3). Presentation in adults is uncommon as individuals with gastrointestinal duplication are usually asymptomatic or have nonspecific symptoms. A gastric duplication cyst can be complicated by intra cystic hemorrhage, ulceration, infection, mechanical obstruction, and rarely, malignancy (4).

Here we report a rare case of symptomatic GDC in an adult who was treated successfully with surgical resection.

CASE REPORT

A 19-year old female presented with a four-month history of intermittent epigastric discomfort associated with progressively increasing back and left upper quadrant abdominal pain. Review of systems revealed weight loss of approximately seven kg. Her past medical history and family history were not significant.

Cite this article as: Zülfikaroğlu B, Akgül Ö, Özmen MM. A rare case of multiple gastric duplication cysts in an adult. Turk J Surg 2024; 40 (3): 264-266.

Corresponding Author
Barış Zülfikaroğlu
E-mail: zbaris61@gmail.com

Received: 23.06.2020
Accepted: 27.08.2020
Available Online Date: 30.09.2024

DOI: 10.47717/turkjsurg.2022.4933

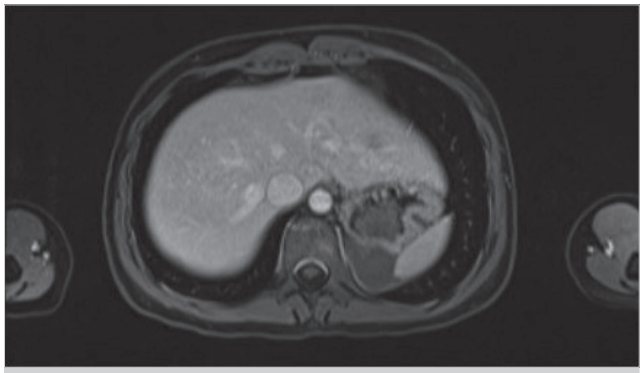

Figure 1. CT image shows a cystic lesion.

Ultrasonography demonstrated the presence of a 7 x 4 cm mass, posterior to the gastric fundus, well-defined cystic lesion located superior and anterior to the left kidney and the spleen medially.

Gastroscopy revealed a bulging deformity with extrinsic compression at the cardio-esophageal junction.

Magnetic resonance imaging (MRI) and computed tomograpghy (CT) scans of the abdomen confirmed 55 x 48 mm homogenous, septated cystic mass located posterior to the gastric fundus (Figure 1). The left kidney and spleen was clearly identified. To better evaluate the mass, patient underwent endoscopic ultrasonography that confirmed a hypoechoic mass with a slightly heterogeneous internal echo and regular margins located just below the gastroesophageal junction; the lesion measured about 5.5 x 5 cm and seemed to be contiguous to the fourth wall layer.

On exploratory laparotomy, there were two cystic masses measuring approximately 5 x 4 cm and 3 x 2 cm, which was slightly adherent to anterior wall of stomach close to the greater curvature (Figure 2). Totally excision of cystic masses without resection of stomach was performed for a presumed gastric duplication cyst.

Pathology confirmed a duplication cyst with gastric mucosa and no evidence of malignancy.

Patient's postoperative course was uneventful. She was discharged on the postoperative day four and she is doing well and symptomless six months post-operatively.

DISCUSSION

Gastric duplication cysts are uncommon developmental anomalies found primarily in children, being rarely diagnosed in adults. However, diagnosis of the condition in an adult can be difficult, as it is usually asymptomatic, or the symptoms are nonspecific, with vague abdominal pain. Continued secretion of enzymes and hydrochloric acid into the duplication cyst may result in gastric ulceration, perforation of the gastric ulcer and the formation of a fistula into adjacent organs, which can result in gastrointestinal hemorrhage (4). Laboratory investigations of gastric duplication cysts are usually unremarkable. Most gastric duplications are localized along the greater curvature. They may have a cystic or tubular configuration and may or may not communicate with the gastric lumen. Non-communicating cysts are more frequently encountered and can be identified as intramural defects with an irregular profile of the stomach at barium contrast radiography. Endoscopy may reveal a gastric mass with intact, erythematous or ulcerated overlying mucosa.

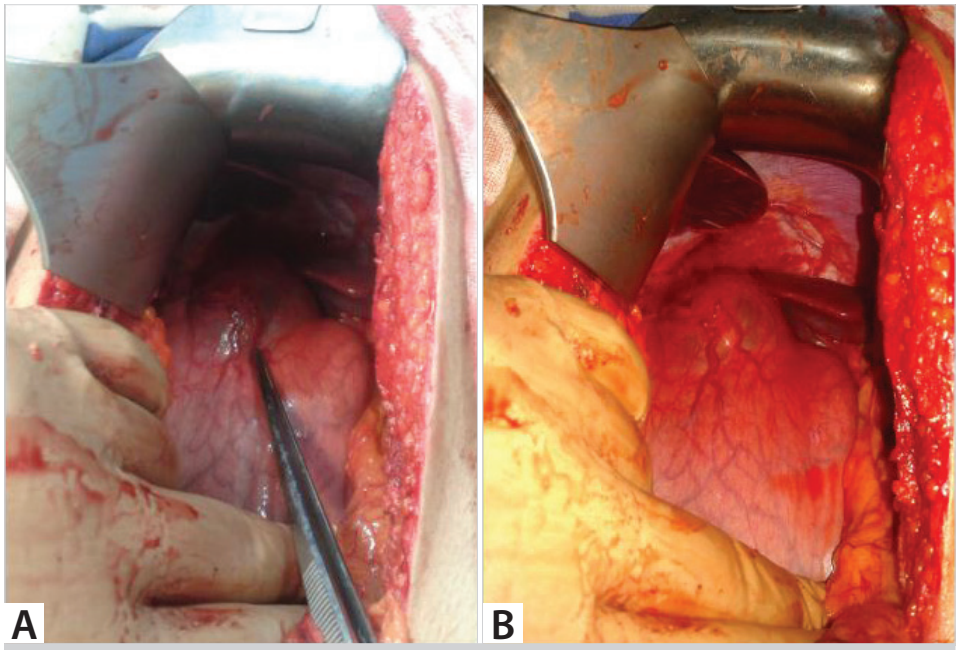

Figure 2. The pictures show duplication cysts.

CT and ultrasonography demonstrate the fluid content within the cyst, the former being the best method for studying such malformations and for establishing their size and connection with adjacent organs. Communicating cysts are extremely rare and easy to diagnose as they usually fill with barium during a barium swallow. CT may even reveal a double compartment stomach, directly visualizing the thickness of the duplication wall. The site of communication may also be located outside the stomach, in the duodenum or the esophagus (3).

Due to the risk of malignant transformation and other complications, treatment of GDC is surgical. Surgical excision is curative, provides symptomatic relief and prevents complications from the cyst. The basic principles of surgery are complete excision or else, depending on the localization, proximal or distal gastric resection may be performed.

Informed Consent: Informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - BZ, MMÖ; Design - BZ, ÖA; Supervision - MMÖ; Materials - BZ, ÖA; Data Collection and/or Processing - BZ, ÖA; Analysis and/or Interpretation - BZ, ÖA; Literature Search - BZ, ÖA; Writing Manuscript - BZ; Critical Reviews - MMÖ.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. *Jackson KL, Peche WJ, Rollins MD. An unusual presentation of a rectal duplication cyst. Int J Surg Case Rep 2012; 3(7): 314-5. https://doi.org/10.1016/j.ijscr.2012.03.015*
2. *Singh JP, Rajdeo H, Bhuta K, Savino JA. Gastric duplication cyst: Two case reports and review of the literature. Case Rep Surg 2013; 2013: 605059. https://doi.org/10.1155/2013/605059*
3. *Scatizzi M, Calistri M, Feroci F, Girardi LR, Moraldi L, Rubio CA, et al. Gastric duplication cyst in an adult: Case report. In Vivo 2005; 19(6): 975-8.*
4. *Lee LS, Ong HS. A rare case of two synchronous gastric duplication cysts in an adult. Singapore Med J 2013; 54(4): 91-2. https://doi.org/10.11622/smedj.2013090*

OLGU SUNUMU-ÖZET
Turk J Surg 2024; 40 (3): 264-266

Yetişkinlerde nadir görülen çoklu gastrik duplikasyon kisti: Olgu sunumu

Barış Zülfikaroğlu[1], Özgür Akgül[1], Mehmet Mahir Özmen[1,2,3]

[1] Ankara Numune Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Ankara, Türkiye
[2] İstinye Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye
[3] Liv Hastaneleri, Genel Cerrahi Kliniği, Ankara, Türkiye

ÖZET

Bağırsak duplikasyonları, gastrointestinal sistem boyunca herhangi bir yerde ortaya çıkabilecek nadir gelişimsel anomalilerdir. Gastrik duplikasyon kistleri nadir görülen konjenital anomalilerdir ve yetişkinlerde nadiren teşhis edilir. Bununla birlikte, bir yetişkinde durumun teşhisi zor olabilir çünkü genellikle asemptomatiktir veya semptomlar spesifik değildir. Burada cerrahi rezeksiyon ile başarılı bir şekilde tedavi edilen, yetişkinde nadir görülen semptomatik gastrik duplikasyon kisti olgusu sunulmaktadır.

Anahtar Kelimeler: Mide duplikasyon kisti, gastrointestinal duplikasyon, yetişkin, mide cerrahisi

DOİ: 10.47717/turkjsurg.2022.4933