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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.

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2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published; AND
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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.

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- Grant information and detailed information on the other sources of support,
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- 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.

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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.

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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).
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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

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

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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.

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.

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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)"

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

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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.

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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.

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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.

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Turkish
Journal of Surgery

CONTENTS

ORIGINAL ARTICLES

TECHNICAL REPORT

CASE REPORTS

Turkish
Journal of Surgery

FROM THE EDITOR'S DESK
Turk J Surg 2024; 40 (4): VIII
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A global journal with deep local roots: Turkish Journal of Surgery

Dear Readers of Turkish Journal of Surgery,

It is with great pleasure that we greet you in the final issue of 2024. The past year has witnessed both happy and extremely sad events around the world. As members of a profession that exists at the heart of society, it is inevitable that we are affected by such events. Our sincere hope is that the new year will bring peace and happiness to the world.

As communication between societies and cultures evolves, the resolution of global challenges becomes more feasible. Facilitating such communication is not only politically essential but also scientifically critical. One of the most vital components of scientific communication and the exchange of knowledge is scientific journals.

The Turkish Journal of Surgery (TJS) has concluded another year of extraordinary global engagement, with a steadily increasing presence in journal metrics and growing international interest. Each week, we are honored to receive submissions from diverse corners of the globe for consideration.

I would like to give you some interesting statistics about this issue. In 2024, of the 40 clinical studies we published, 25 (62.5%) originated from international institutions outside of Turkey. These contributions came from centers in the Americas (USA and Brazil), Europe (Germany, UK), Asia (Japan, Qatar, India), and Africa (Egypt, Libya, and Uganda). With this breadth of contributions, it would not be an exaggeration to describe TJS as a truly "**global journal**".

This success can be attributed to several key factors: the journal's strong scientific focus, unwavering commitment to ethical standards, a rapid and high-quality peer-review process, world-class visual production, and the free online availability of all published articles.

I would like to take this opportunity to express my gratitude to the entire editorial team, our reviewers, publishing and technology partners, and the Turkish Surgical Society. The Society has consistently protected the journal's editorial independence while offering unconditional support whenever needed. This collaborative effort has been instrumental in achieving sustainable and enduring success.

On behalf of the editorial team of TJS I wish for a Merry Christmas for our international readers and Happy New Year for all!

Again, we look forward to receiving your best studies in 2025!

Warm regards,

Kaya SARIBEYOĞLU
Editor-in-Chief
Turkish Journal of Surgery

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (4): 267-274

Surgical results of liver metastases of tumors other than colorectal-neuroendocrine: Is it really worth it or is it necessary?

Fuat Aksoy, Erhan Gökçe, Eyüp Anıl Balkan, Halit Ziya Dündar, Ekrem Kaya

Department of General Surgery, Bursa Uludağ University Faculty of Medicine, Bursa, Türkiye

ABSTRACT

Objective: It is known that surgical treatment is advantageous in terms of efficacy and survival in colorectal cancer and neuroendocrine tumor liver metastases. Our aim in this study was to determine the results of surgical treatment of non-colorectal (NCR), non-neuroendocrine tumor (NNET) liver metastases (LM).

Material and Methods: A total of 125 patients having NCR and NNET were included in the study. Demographic characteristics of the patients, histological features of the tumor, time from resection of the primary tumor to the first diagnosis of liver metastases, synchronous and metachronous presentations of hepatic metastases with primary malignancy, type of resection, postoperative complications, length of hospital stay, and survival were analyzed retrosepctively.

Results: Median follow-up time was 21 (1-132) months. Mean overall survival (OS) and mean proression free survival (PFS) were 29.86 ± 2.4 and 21.23 ± 2.1 months respectively. Most of the cases were LM of breast (n= 33, 26.4%), gastric (n= 25, 20.0%) and gastrointestinal stromal tumors (GIST) (n= 16, 12.8%). Interval from resection of primary tumor to the diagnosis of LM was 20.90 ± 28.9 (0-144) months. OS and DFS rates were found respectively as; 78% and 69% at one year, 45% and 38% at three years, 32% and 21% at five years and 3.2% and 1.6% at 10 years. Breast cancer liver metastases had the longest OS and PFS. Pancreatic cancer and gastric cancer group significantly have shorter OS than the other groups.

Conclusion: According to our data, the results are better in breast and GIST liver metastases, and the place of surgical treatment in pancreatic and malignant melanoma liver metastases is controversial.

Keywords: Liver metastases, non-colorectal, non-neuroendocrine

INTRODUCTION

It is well documented that surgical treatment of colorectal cancer liver metastases (CRC-LM), either resection or metastasectomy, has remarkable survival advantages. Therefore, almost all cases of CRC-LM may be candidates for liver surgery regardless of bi-lobar involvement or number and size of nodules (1). Recently, disease free and actual survival rates of CRC-LM get longer with staged hepatectomy, associated liver partition with portal vein ligation for staged hepatectomy (ALPPS procedure) and current chemotherapy modalities (2). Similarly, it has been reported that the surgical treatment of neuroendocrine tumor liver metastases (NET-LM) has been observed to be obviously beneficial on survival rates (3). In addition, liver transplantation can be considered as a treatment modality in NET-LM without extrahepatic disease (4). Considering the aforementioned surgical success, surgery has been preferred as a treatment modality in non-colorectal non -neuroendocrine tumor liver metastases (NCRNNET-LM) in recent years. Analyses of surgical results and survival rates of NCRNNET-LM are not clear due to the limited number of case series which have been reported until now. A few reports including beneficial results have been published (5). However, there are controversies in the recent data about the survival advantages of surgical treatment of some of the NCRNNET-LM including genitourinary, breast and some gastrointestinal tumors other than CRC-LM (6). In addition, a couple of case series including liver metastasectomy for solitary metastases due to very aggressive gastrointestinal tumors like pancreatic cancer have been published (7).

The aim, within the scope of this study, was to evaluate the surgical results and to investigate the effect on survival of NCRNNET-LM, except for CRC and NETs, whose surgical outcomes and survival effects are more clearly known.

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MATERIAL and METHODS

A total of 125 consecutive patients who underwent liver resection (major liver resection, metastasectomy, segmentectomy) because of NCRNNET-LM at a tertiary university hospital between 2003 and 2022 were identified, and the data were obtained from patient records retrospectively. An informed consent form was obtained from all patients. Patients were required to have at least one year of follow-up. Since there were no established resection criteria for the selection of the NCRNNET-LM, patients were evaluated in patient-by-patient manner by a team of oncologists, surgeons and radiologists. Patients having extra hepatic disease and other co-morbidities were excluded. Patients with direct hepatic invasion by extra hepatic primary tumor, cholangiocarcinoma and gall-bladder carcinoma even metachronous cases were also excluded. Negative surgical margins were required in all patients. Patients with positive surgical margins were also excluded from the study. Extrahepatic disease was detected by ultrasonography, computed tomography, magnetic resonance imaging and positron emission tomography. Routine biopsy was not performed in the preoperative period in patients with radiological evaluation of LM. Patients evaluated as having metastatic tumor from the pathology specimens were included in the study.

The demographic features of patients, tumor characteristics and stages, interval from resection of primary tumor to the initial diagnosis of LM, synchronous versus metachronous presentation of hepatic metastases with primary malignancy, type of resections (metastasectomy, segmentectomy or lobectomy), postoperative courses, preoperative and postoperative chemotherapy regimens, the treatment modalities applied in case of recurrence [re-resection and interventional radiological procedures such as trans arterial chemoembolization (TACE), radiofrequency ablation (RFA) and microwave ablation] and long term outcomes were recorded. For breast cancer LM, receptor status (estrogen, progesterone and HER2) were also evaluated. Surgical factors including resection type, simultaneous resection of primary tumor, other concomitant major extra hepatic procedures and resection margin status (microscopically negative R0, or positive R1 resections) were investigated. Major hepatectomy refers to resection of >2 segments, segmental resection refers to resection of 1-2 segments and metastasectomy refers to resection of metastatic nodule with negative margin or non-anatomic resection less than one segment or wedge resection. All the above mentioned surgical and nonsurgical factors thought to be related to overall (OS) and progression free survival (PFS) rates were statistically analyzed. This study was approved by the institutional review board of our institute (03.03.2015, 2015-5/9).

Operative mortality includes any deaths attributed to liver resection and all deaths within the 30 days after liver surgery. Deaths were ascertained by hospital records or official public records. For patients without evidence of disease, last date of any clinical correspondence was used to determine the length of progression free survival. Patients were categorized into six groups; Group 1: Breast cancer LM, Group 2: Gastric cancer LM, Group 3: Gastrointestinal stromal tumors (GIST) LM, Group 4: Pancreas cancer LM, Group 5: Genitourinary (GU) tumors LM and Group 6: Miscellaneous tumors (esophagus, melanoma, lung, peripheral nerve tumor, peritoneal mesothelioma, thyroid, adrenocortical) LM.

Statistical Analysis

Statistical analysis were done with SPSS 22 (IBM Corp, Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY9). Categorical variables were summarized with percentage. Variables were expressed as mean ± standard deviation or as median (minimum: maximum, range) values depending on whether the variable followed a normal distribution or not, using the Shapiro-Wilk normality test. The log-rank test was used to determine the difference between Kaplan-Meier curves for both OS and PFS time. Mean survival time was reported. To determine the prognostic factors that affected OS and PFS time, Cox proportional hazard regression analysis with backward selection procedure was performed after Kaplan-Meier analysis. Results were reported as hazard ratio with 95% confidence intervals (CI) and related p-values. Statistical significance was defined as $p< 0.05$.

RESULTS

There were 125 patients in the study period. Median age at the time of surgery was 58.42 years (range 26-86). The patients included were 56 (44.8%) males and 69 (55.2%) females. Most of the cases were LM of breast (n= 33, 26.4%), gastric (n= 25, 20.0%) and GIST (n= 16, 12.8%). Interval from resection of primary tumor to the diagnosis of liver metastases was 20.90 ± 28.9 (0-144) months. Mean number of metastases was observed to be 1.59 ± 1.0 (1-8) and mean diameter of the tumors was 3.9 ± 2.8 cm (1-18). Demographic data and other tumor characteristics are shown in Table 1. A total of 77 (61.6%) cases were metachronous and 48 (38.4%) were synchronous LM. The patients were categorized into six groups according to the type of primary tumor, and the distribution of the patients in each group is displayed in Table 2.

Operative Intervention

Major hepatectomy was performed in 20 (16.0%) cases and segmentectomy (n= 13, 10.4%) and metastasectomy (n= 92, 73.6%) were preferred in the remaining cases. Re-resection was performed in 9 (7.2%) patients when time interval between occurrence of two metastases was at least one year (breast 2, GIST 3, ovary 2, gastric 1 and lung 1).

Table 1. Demographic features of the patients	
Features	**n (125)**
Male/female (n)	56/69
Age (mean ± SD)	58.42 ± 10.78
Presentation (n)	
Synchronous	39
Metachronous	54
Tumor size (mean ± SD)	3.89 ± 2.8
Tumor number (mean ± SD)	1.59 ± 1.03
Interval (month)*	20.90 (0-144)
Resection type (n)	
Metastasectomy	92
Segmentectomy	13
Lobectomy	20
Re-operation (n)	9
*Median interval time from primary tumor surgery to diagnosis of liver metastasis. SD: Standart deviation.	

Table 2. Distribution of the patients according to the type ofprimary tumor					
Breast	**Gastric**	**GIST**	**Pancreas**	**GU (n= 16)**	**Miscellaneous (n= 17)**
33	25	16	11	Renal cell= 8	Lung= 3
				Ovarian= 9	Mesothelioma= 1
				Endometrium= 3	P. nerve= 1
					Thyroid= 1
					Melanoma= 6
					Adrenocortical=1
					Esophagus= 2
*GIST: Gastrointestinal stromal tumor, GU: Genitourinary tumors, P: Peripheral.					

Outcome

There were no operative mortality in this series and the mean length of hospital stay was 6 (2-70) days. Postoperative complications were developed in 13 (10.4%) cases. These were deep incisional surgical site infection in 4 (3.2%) of the cases, organ/space infection in 4 (3.2%) of the cases, anastomotic leakage in 2 (1.6%) of the cases (in concomitant surgery cases), bile leakage in 1 of the cases (0.8%) and iatrogenic small bowel perforation in one of the cases (0.8%). The median follow-up time was 21 (1-132) months.

Age, sex, re-resection, interventional radiologic treatment modalities, size and number of metastatic nodules, metastases interval and receptor status (for breast cancer liver metastases) were not determined as significant factors for both OS and PFS. Surgical margin status and chemotherapy after liver resection parameters were not available for statistical analysis due to insufficient sample size in each category. Factors associated with OS and PFS are shown in Table 3,4. LM from primary breast cancer had the longest OS and PFS. Pancreatic cancer, miscellaneous cancers and gastric cancer group significantly have shorter OS than the other groups. Tumor recurrence (metastases recurrence) was also found to be a significant risk factor for OS. The factors affecting OS were found to be type of primary tumor (pancreas group is the worst and breast cancer group is the best. p= 0.001), simultaneous surgical interventions with hepatectomy (p= 0.031) and development of surgical complications (p= 0.001) (Table 4). When all NCRNNE-LM patients were examined, the highest number of cases was breast cancer (33/125).

In terms of subgroup (breast, GIST, gastric, GU, pancreas and miscellaneous) analysis, there were not any factors shown to be associated with OS in all the groups except GIST. Univariate analysis revealed that patients having synchronous metastases had longer OS than those with metachronous metastases in

Table 3. Univariate analysis of the factors associated with survival for all cases

Features	n	Mean OS	p	Mean PFS	p
Type of primary tumor					
Breast	33	83.6 ± 13	*0.001*	56.8 ± 14	*0.008*
GIST	16	62 ± 12		32.5 ± 5	
GU	16	42.6 ± 7		31.6 ± 7	
Gastric	25	32.6 ± 7		34.6 ± 8	
Miscellaneous	17	24.65		15 ± 5	
Pancreas	11	12.3 ± 1.8		6.2 ± 1.1	
Synchronous/Metachronous					
Synchronous	48	41.9 ± 7	0.07	19.9 ± 3	0.02
Metachronous	77	61.5 ± 6		52.7 ± 9	
Concomitant procedures					
Yes	62	40.2 ± 7	*0.03*	21 ± 4	*0.01*
No	63	61.1 ± 8		51.1 ± 8	
Postoperative complications					
Yes	13	18.1 ± 5	*0.001*	18.2 ± 6	0.16
No	112	58.6 ± 5		43.3 ± 6	

GIST: Gastrointestinal stromal tumor, GU: Genitourinary cancer, OS: Overall survival (month), PFS: Progression-free survival (month).

Table 4. Cox proportional hazard regression analysis of the risk factors related OS and PFS

	OS		PFS	
Features	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Primary tumors				
Pancreas cancer	4.32 (1.3-13.7)	0.013		
Gastric cancer	4.08 (1.6-10.1)	0.003		
Recurrence	3.43 (1.6-7.1)	0.001		
Type of resection				
Metastasectomy			6 (1.4-25.1)	0.012
Segmentectomy			5.8 (1.8-29)	0.031

PFS is shorter in patients with metastasectomy and segmentectomy than lobectomy. OS is shorter in pancreas and gastric tumors with reference to breast cancer liver metastases, OS: Overall survival (month), PFS: Progression-free survival (month), CI: Confidence intervals, HR: Hazards ratio.

GIST cases (p< 0.03). On the other hand, lobectomy had more advantages on PFS as compared to metastasectomy in breast cancer LM cases (p= 0.01, HR= 8.41) (Table 4). Other risk factors were not found to be statistically significant for PFS in other groups. Receptor positivity (estrogen and progesterone) was also not found to be a statistically significant factor on OS and also PFS in breast cancer LM cases.

DISCUSSION

Liver is a quite eligible site for tumor cells to grow because of its specific type of blood flow which is provided by two different vascular systems including both portal system and arterial system. Therefore, it is not surprising that liver is the most commonly involved metastatic organ for all types of cancers. Liver metastases have been demonstrated in 58-79% of all the terminal period cancer patients and almost 85% of these have been found to be due to non-colorectal cancers in an autopsy study (8).

Although previously liver metastases were accepted to be one of the inoperability criteria, currently it is one of the main topics of hepatobiliary surgery. However, there are not enough multicenter, randomized controlled trials to build up a consensus about treatment algorithm of NCRNNET-LM. Most of the studies have been presenting data from single centers, retrospectively. Fortunately, the data in the literature is

increasing in accordance with the improvements in hepatobiliary surgery and oncology together with the opportunity of simultaneous usability of alternative treatment modalities with surgery. Liver resection for NCRNNET-LM rate is less than 10% of the all hepatic resections due to isolated metastases which are relatively rare. Surgical treatment indications for these kinds of tumors have been extended depending on the development of surgical technics and management in an acceptable mortality and morbidity rate. In a large sample sized multicentric study, it has been determined that five-year survival rate is more than 30% in adrenal, ovarian, breast and renal cancer LM, 15-30% in gastric, pancreas, melanoma and duodenal cancer and less than 15% in lung, esophagus, head and neck tumors (9). On the other hand, five-year survival rate after surgery of CRC-LM, which has been proven to be most advantageous for survival, is reported as 40%-70%. In our series, mean survival time was 37.4 ± 4.3 months and median survival time was 28 (21-45) months in 60 patients who underwent CRC-LM. Therefore, it is possible to infer that the results of present study are acceptable, satisfying and encouraging. Also, the complication rate reported in the present study is within the acceptable limits.

In the present study, the group with most patients was the breast cancer group. In breast cancer, metastatic liver disease is generally associated with disseminated disease and prognosis is poorer when compared to bone or other soft tissue metastases. Only 5-12% of patients were found to have isolated liver metastases. In our study, breast cancer LM group had the longest OS and PFS. Mean (median) OS and PFS were 83.6 and 56.8 months respectively. These results are comparable to other studies (9-11). In the present study, it was found that in patients who had undergone lobectomy because of primary breast cancer progression free survival period was longer. While progression free survival was 23.6 ± 5.1 months in metastasectomy group, it was observed to be 107.4 ± 22 months in lobectomy group. According to Cox regression analysis when metastasectomy was chosen as a resection method the risk of shorter survival periods was observed to be 8.4 times higher. Therefore, lobectomy should be always kept in mind as a treatment modality despite it is a major surgical procedure. Additionally, in patients who are not appropriate for surgical procedures, treatment modalities such as RFA and TACE can be used. In several studies investigating case series, interventional radiological procedures were shown to be used successfully in metastatic liver disease originating from breast cancer and median survival was reported between 30 and 60 months (12). Receptor positivity and good response to chemotherapy were found as factors related to longer survival in breast cancer LM in one study (13). However, the current study does not support these findings with a relatively small number of cases.

The role of surgical resection of gastric cancer (GC)-LM has always been debated. Resectable metastases without extrahepatic disease have been reported to be present in only 0.5-10% of patients (14). Solitary disease and well differentiated primary tumor were other factors found to be associated with long term survival (15). There is not a consensus about indications and patient selection criteria for hepatectomy (16). There are studies in the literature indicating that gastric cancer-LM that can be resected R0 and sometimes the use of RFA is safe and appropriate. In this figure, the median survival was determined as 48 months (17). In our study, after breast cancer, the second most common liver metastasis was observed in gastric cancer. Mean overall survival was 32 months. Accordingly, it was observed that the overall survival was statistically significantly prolonged especially in patients with solitary liver metastases who were removed as mastectomy, which was consistent with the literature (15,18,19).

Stage 4 pancreatic adenocarcinoma has a poor prognosis and five-year survival is nearly 1% (20). Although a significant increase in survival has been achieved with the development of medical treatments, surgical treatment is still an important treatment in terms of long-term survival (21). The value of synchronous metastasectomy in pancreas cancer was analyzed and median overall survival was observed as 10.7 months (7). Similarly, there were 11 primary pancreatic cancer cases in our study, and the lowest PFS durations (6.2 ± 1 months) and the worst prognosis (12.3 ± 1.8 months) were among these patients. Furthermore, in this study three-year survival rate was showed to be 0% and surgical treatment does not provide any advantages on survival in patients with stage four pancreas cancer. The benefit of surgical treatment for this group, which has the least survival compared to other groups, is also controversial.

For stage 4 renal cell carcinomas, one-year survival rate has been reported to be 10-15% previously. However, treatment in those cases is more successful currently. In a study analyzing 43 patients with metastatic liver disease due to renal cell carcinoma, who underwent curative hepatectomy, were evaluated. They found that one and three-year survival rates were 94.2 and 62.1%, retrospectively (22). The criteria that should be considered in patient selection can be sorted as such: Curative surgical interventions to have negative surgical margins, interval >24 months, tumor size <5 cm and eligibility for repetition of hepatectomy (23). In our study, isolated liver metastases are encountered quite rarely in gynecologic cancers since liver metastases are generally a part of general tumor dissemination (24). In liver metastases of ovarian cancer, hepatectomy can be applied securely. Survival is better in cases where involvement is through peritoneal seeding when

compared to hematogenous dissemination (23). The interval between the primary surgery (<24 months) and optimal secondary cytoreduction (residual disease of less than 1 cm) was found to be significantly associated with the longest survival periods in patients with liver resection during secondary cytoreduction (25). According to our data, OS was 42.6 ± 7.4 months and PFS was 31.6 ± 7.6 months for patients with LM due to GU malignancies. Although our survival times seem to be shorter when compared to the studies mentioned above, it may not be appropriate to make an inference based on data retrieved from such a heterogeneous patient group including renal cell carcinoma, endometrium and ovarian cancers.

In patient with LM due to malign melanoma survival is significantly poor and it was reported to be almost 15-20% (25,26). Contrary to cutaneous melanoma which primarily invades lymph nodes, in 95% of the metastatic uveal melanomas, liver metastases can be determined (27). In a study, similar survival periods have been observed in cutaneous and uveal melanoma cases (28). In our study, miscellaneous group including malign melanoma has the second worst survival rates following the GI group. According to our observations, laparoscopic exploration in case of LM due to malign melanoma gives more information about macroscopic features and subcapsular involvement because of staining pattern as compared to other tumor metastases.

In a study that investigated LM cases due to GIST, while median survival was found to be 53 months in patients given only imatinib, it was found to be 89 months in those who were given tyrosine kinase inhibitors (TKIs) in combination with liver resection (29). Likewise, concomitant therapy is suggested to be the therapy of choice by the Japanese study group (30). We found survivals following hepatic resections in combination with TKI therapy at first third and fifth years 76.2, 59.2 and 50.8 months respectively. Overall survival was shown to be 62.08 ± 12.9 months. We observed that the second-best OS and PFS periods following breast cancer were achieved in LM of GIST group.

In our study, re-resection was performed in seven patients when time interval between occurrence of two metastases was at least one year. Two of our patients with GIST are still being followed without recurrence for eight and 10 years. Although currently there is not a consensus about re-resection, surgical treatment modalities should be considered insistently in biologically good behaving tumors.

We can state as a limitation of our study the small sample size. However, this is an inexorable fact. In present study, since we share our experience in these relatively rare cases, we believe that this study could provide a contribution to the literature. However, larger sample sized more series are required to evaluate the effectiveness of surgical procedures in liver metastases of other cancers. On the other hand, the fact that it is a heterogeneous group study since it includes different tumor groups and biology is also limiting. However, we think that this study may be valuable in terms of sharing experience, as it appears that liver resection provides an advantage to survival in some tumor groups, while it may be unnecessary in others.

Ethics Committee Approval: This study was obtained from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 2015-5/19, Date: 03.03.2015).

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Kolorektal-nöroendokrin dışındaki tümörlerin karaciğer metastazlarının cerrahi sonuçları: Gerçekten değer mi, gerekli mi?

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ÖZET

Giriş ve Amaç: Kolorektal kanser ve nöroendokrin tümörlerin karaciğer metastazlarında cerrahi tedavinin etkinlik ve sağkalım açısından avantajlı olduğu bilinmektedir. Bu çalışmadaki amacımız primeri kolorektal veya nöroendokrin olmayan tümörlerin karaciğer metastazlarının cerrahi tedavisinin sonuçlarını belirlemektir.

Gereç ve Yöntem: Primeri kolorektal kanserli (KRK) veya nöroendokrin tümörlü (NET) olmayan karaciğer metastazlı toplam 125 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, tümörün histolojik özellikleri, primer tümörün rezeksiyonundan karaciğer metastazlarının ilk tanısına kadar geçen süre, karaciğer metastazlarının primer malignite ile eş zamanlı ve metakron ortaya çıkışı, rezeksiyon tipi, postoperatif komplikasyonlar, hastanede kalış süresi ve hayatta kalma analizi yapıldı.

Bulgular: Ortalama takip süresi 21 (1-132) ay idi. Ortalama sağkalım (OS) ve ortalama hastalıksız sağkalım (HS) sırasıyla 29,86 ± 2,4 ve 21,23 ± 2,1 aydı. Olguların primer tümörünün çoğunluğunu meme (n= 33, %26,4), mide (n= 25, %20) ve gastrointestinal stromal tümör (GİST) (n= 16, %12,8) oluşturmaktaydı. Primer tümörün rezeksiyonundan karaciğer metastazı tanısına kadar geçen süre 20,90 ± 28,9 (0-144) ay idi. OS ve HS oranları sırasıyla; bir yılda %78 ve %69, üç yılda %45 ve %38, beş yılda %32 ve %21 ve 10 yılda %3,2 ve %1,6 idi. Meme kanseri karaciğer metastazları en uzun OS ve HS'ye sahipti. Pankreas kanseri ve mide kanseri grubu diğer gruplara göre önemli ölçüde daha kısa OS'ye sahiptir.

Sonuç: Verilerimize göre meme ve GİST karaciğer metastazlarında sonuçlar daha iyi olup, pankreas ve malign melanom karaciğer metastazlarında cerrahi tedavinin yeri tartışmalıdır.

Anahtar Kelimeler: Karaciğer metastazları, kolorektal olmayan, nöroendokrin olmayan

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ORIGINAL ARTICLE
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The Gupta-Akami technique for percutaneous drainage of superficial liver abscess: An indigeneous economic method for low resources setups

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ABSTRACT

Objective: Liver abscesses, which are purulent cavities within the liver, pose significant health challenges, particularly in developing countries where treatment resources are limited. Despite advancements in imaging and drainage technologies, conventional methods such as pigtail catheters and surgical interventions are often financially prohibitive and inaccessible in low-resource settings. This study proposes Gupta-Akami technique, an indigenous and economically viable method for percutaneous drainage, utilizes simple, readily available materials and offers a potential solution for these settings.

Material and Methods: The study was conducted at a tertiary care hospital over a period of six months. It included 21 patients with liver abscesses meeting specific criteria (abscess volume >500 mL, intervening liver parenchyma <5 cm, and skin-to-abscess distance <10 cm).

Results: The average age of the patients was 45.6 years and there were more men than women. Most patients presented with fever and abdominal pain; nausea/vomiting was observed in the majority, and jaundice was noted in a few. Mean abscess volume was 890 mL. The procedure effectively drained over 87% of the abscess volume and only one patient requiring additional aspiration. Post-procedural pain decreased significantly from an average of 3.15 on a visual analog scale at 0 hours to 0.84 before discharge. The average hospital stay was 2.57 days. No complications or mortality were reported.

Conclusion: The Gupta-Akami technique demonstrates efficacy as a low-cost, accessible method for percutaneous drainage of liver abscesses in resource-limited settings. It offers a promising alternative to more expensive traditional methods, potentially improving patient outcomes and accessibility in low-resource environments.

Keywords: Liver abscess, metallic trocar, Ryle's tube, catheter drainage, economical method

Video link: https://turkjsurg.com/video/UCD-6563-v1.mp4

INTRODUCTION

Liver abscess is a common infection of the liver and gastro-intestinal tract in India caused by a bacterial, parasitic, or fungal infection (1). Every year, approximately 40-50 million people worldwide become infected, with developing countries accounting for the vast majority of infections. In endemic areas, infection rates exceed 5-10%, and in some cases can reach 55% (2,3). The highest prevalence is found in developing tropical countries, particularly in Mexico, India, Central and South America, and tropical Asia and Africa. In fact, India is reported to have the second highest incidence of liver abscess in the world (1).

Approximately 75% of hepatic abscesses in developed nations are caused by pyrogenic abscesses. While amoebic liver abscess accounts for two-thirds of liver abscesses in developing countries (4,5).

The treatment of a liver abscess is decided by its size, the patient's presentation, and comorbidities. Medical treatment with intravenous or oral antibiotics is usually sufficient for small abscesses; however, for large volume abscesses and in cases of sepsis, abscess drainage is required. A liver abscess can be drained via laparotomy or laparoscopic drainage (6-9). Percutaneous needle aspiration (PNA) or percutaneous catheter drainage (PCD) under image guidance ultrasonography or computarized tomography (USG or CT) is now preferred over surgical drainage due to lower morbidity and mortality, as well as a shorter hospital stay and earlier work (10-12).

McFadzean et al. described the percutaneous drainage method for liver abscess in Hong Kong in 1953 (13). PCD can bridge the gap between non-invasive and

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surgical intervention with minimally invasive, image-guided drainage (14,15). However, traditional drainage methods such as surgical interventions or pigtail catheters are often unavailable or too costly in low-resource settings. The Gupta-Akami technique, developed by Dr. Shardool Vikram Gupta and Dr. Kewecho Akami, is a low-cost, indigenous alternative that makes use of readily available materials and simplifies procedure steps. The purpose of this study was to examine the viability and effects of applying the Gupta-Akami technique in healthcare settings with limited resources.

MATERIAL and METHODS

This study was done at a tertiary care hospital over a period of six months (from October 2023 to March 2024). Given that the method is new and in its early stages, the authors developed patient selection and method application criteria based on safety and reproducibility while keeping in mind the fundamentals of percutaneous drainage as described in the literature (16). If the following criteria were met, all consenting adults with a liver abscess and no clinical or radiological signs of rupture were included.

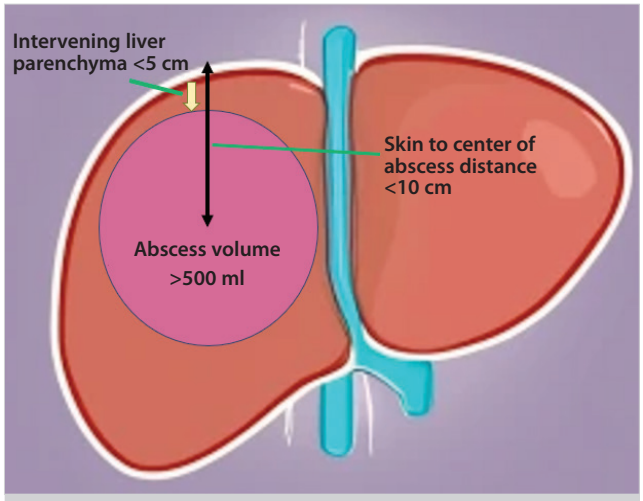

Figure 1. Pre-requisite characteristics of liver abscess kept for the technique.

The criteria of liver abscess were taken as: (Figure 1)

- Abscess volume> 500 mL
- Intervening liver parenchyma< 5 cm
- Skin to center abscess distance< 10 cm

Materials required for this technique are mentioned in the Table 1 and Figure 2 shows the material i.e. 5 mm laparoscopic trocar with ryles tube and pigtail also shown for comparison.

Surgical Technique

The patient is to be positioned supine. USG screening of liver abscess to assess the criteria set for procedure is done and then under USG guidance procedure is performed. The site for incision is marked and cleaned with betadine solution and draped to maintain sterility. 2% xylocaine, a local anesthetic, is infiltrated into the skin and deep up to the capsule of the liver to numb the area. A small incision of around 5 mm is made on the skin surface at the chosen site. The incision is dilated slightly using artery forceps to create a pathway for the trocar (Figures 3,4).

A 5 mm laparoscopic trocar is inserted percutaneously through the incision and guided into the abscess cavity under ultrasound guidance. A 10 cc syringe is attached to the trocar outlet, and fluid is aspirated to confirm that the trocar is indeed in the abscess cavity. The presence of fluid confirms correct placement. The obturator, which is the inner solid portion of the trocar, is then removed. A 14Fr Ryle's tube, a flexible tube used for drainage, is inserted through the trocar into the abscess cavity (Figure 5).

Once the Ryle's tube is in place, the trocar is carefully removed, leaving the Ryle's tube in position. The flow of pus through the Ryle's tube confirms that it is correctly positioned within the

Table 1. Materials and instruments required for the procedure

S.no.	Material Required	Rationale
1	5 mm laparoscopic trocar (metallic)	Multiple use; easy to sterilize
2	Injection xylocaine (1% or 2%)	For LA at site of incision
3	Surgical blade no. 11	For giving incision
4	Ryle's tube 14 Fr	Good caliber for drainage and can fit through the 5 mm port Easily available, low cost
5	2-0 silk suture	For fixing tube with skin
6	Drainage bag	For collecting pus
7	10 mL syringes	For giving LA, taking sample
8	Ultrasound machine	For evaluating abscess and guided drainage
9	Drape sheet, gauze pieces, betadine	For asepsis and dressing
10	Artery forceps	Dilating the incision site

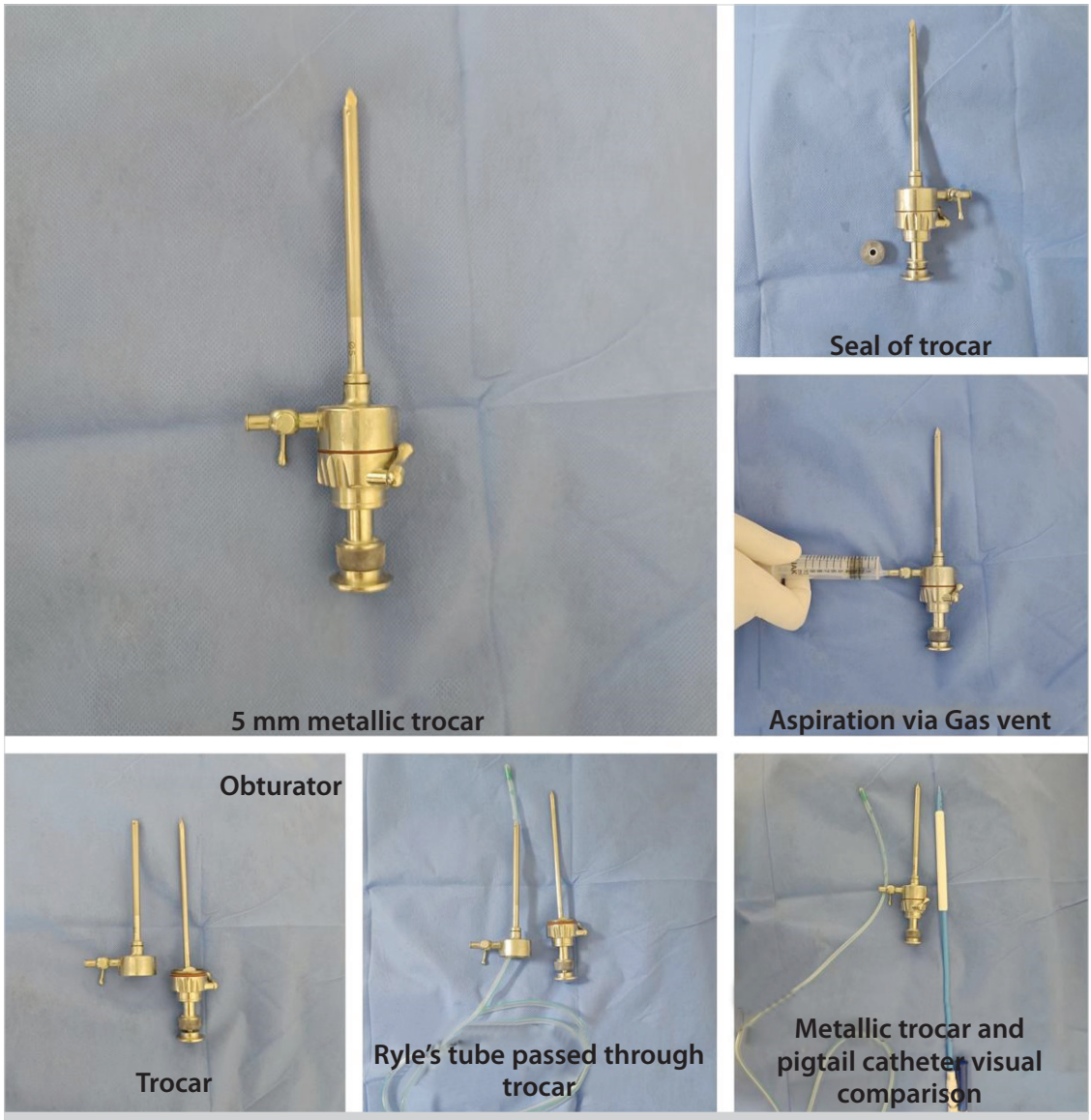

Figure 2. The laparoscopic metallic trocar and Ryle's tube required for insertion.

Figure 3. Ultrasound to assess the volume.

abscess cavity. This placement is also confirmed through ultrasound imaging. The Ryle's tube is then secured to the skin and adhesive dressing done to prevent movement and connected to a drainage bag or similar collection device to allow for gravity drainage of the pus (Figure 6).

During their hospital stay, the patients received intravenous broad-spectrum antibiotics as well as other supportive medications, and their vital signs and blood parameters were monitored. They were discharged after clinical symptoms were resolved or improved; sepsis was controlled, and the patient was allowed to start using oral medications. Follow up was done on out patient department basis for three months.

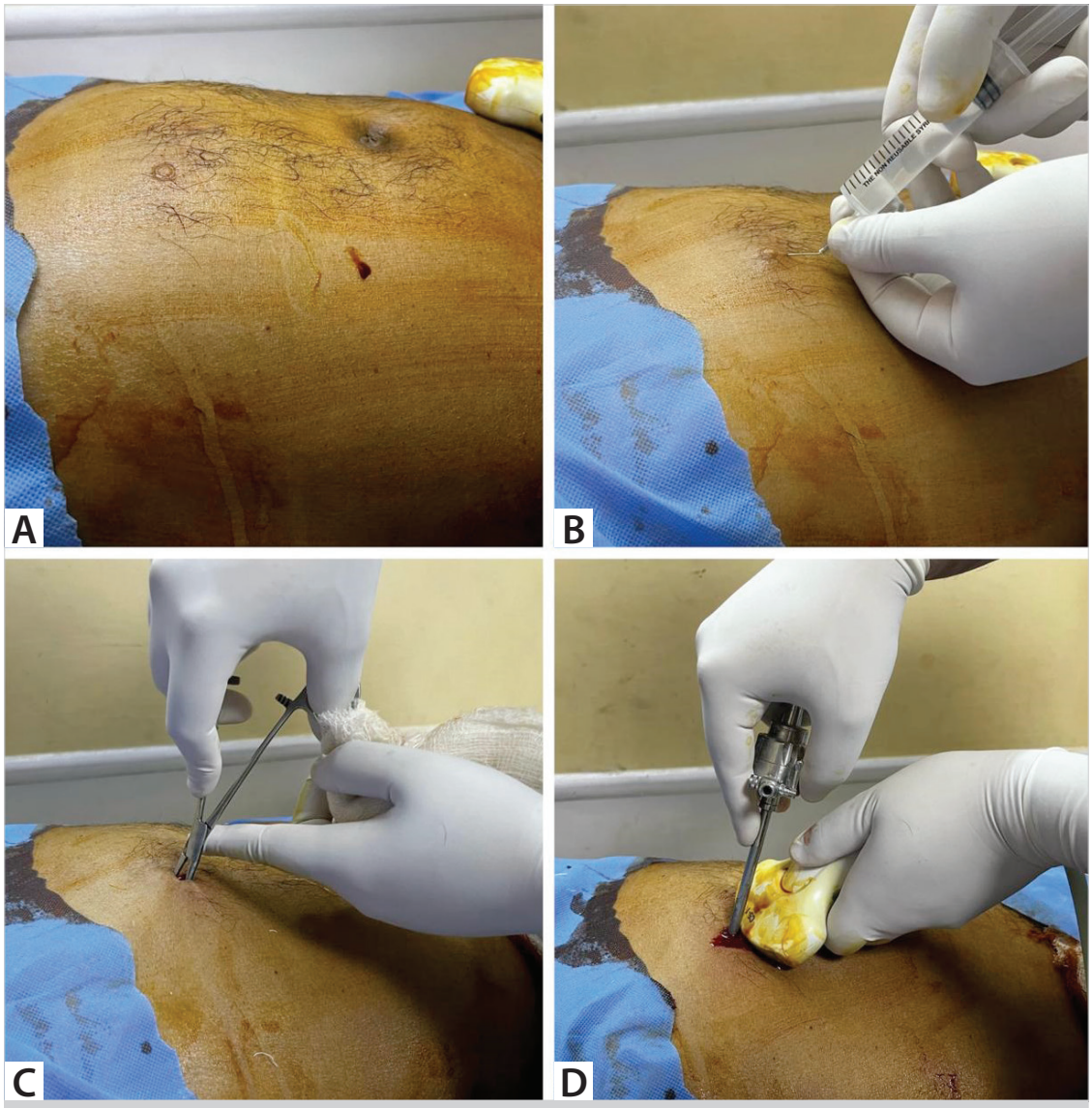

Figure 4. Steps for introduction of metallic trocar in liver abscess. **A.** Marking of incision site under USG guidance. **B.** 2% lignocaine, a local anesthetic, is infiltrated into the skin and deep to anesthetize the area. **C.** Small incision of around 5 mm is made on the skin surface and incision is dilated slightly using artery forceps to create a pathway for the trocar. **D.** Intoducing 5 mm metallic trocar under USG guidance.

RESULTS

During the study period, 79 patients were diagnosed with liver abscess, and 21 of them met the technique's pre-requisite criteria. Following informed consent, these 21 patients were included in the study, and their abscesses were drained using the Gupta-Akami technique. The study yielded the following results and observations.

The youngest patient in this study was 27 years old, and the oldest patient was 62 years old, with the study population having a mean age of 45.6 years. Most of the patients were between the ages of 40 and 50. There was a male sex preponderance of 18 patients versus three female patients. The clinical features observed in this study included fever, abdominal pain, nausea/vomiting, and jaundice. The most common symptoms were fever and abdominal pain, with only three patients showing jaundice. In the study population, 11 patients had no comorbidities, two had hepatitis B, and one had hepatitis C. Three patients had diabetes, two had hypertension, one had chronic kidney disease, and one had a history of coronary artery disease. In the study population, ten patients had a history of alcohol abuse and were chronic alcoholics.

According to the criteria established for our study, the procedure was performed on patients with a minimum abscess volume of 500 mL. The smallest liver abscess volume drained in this study

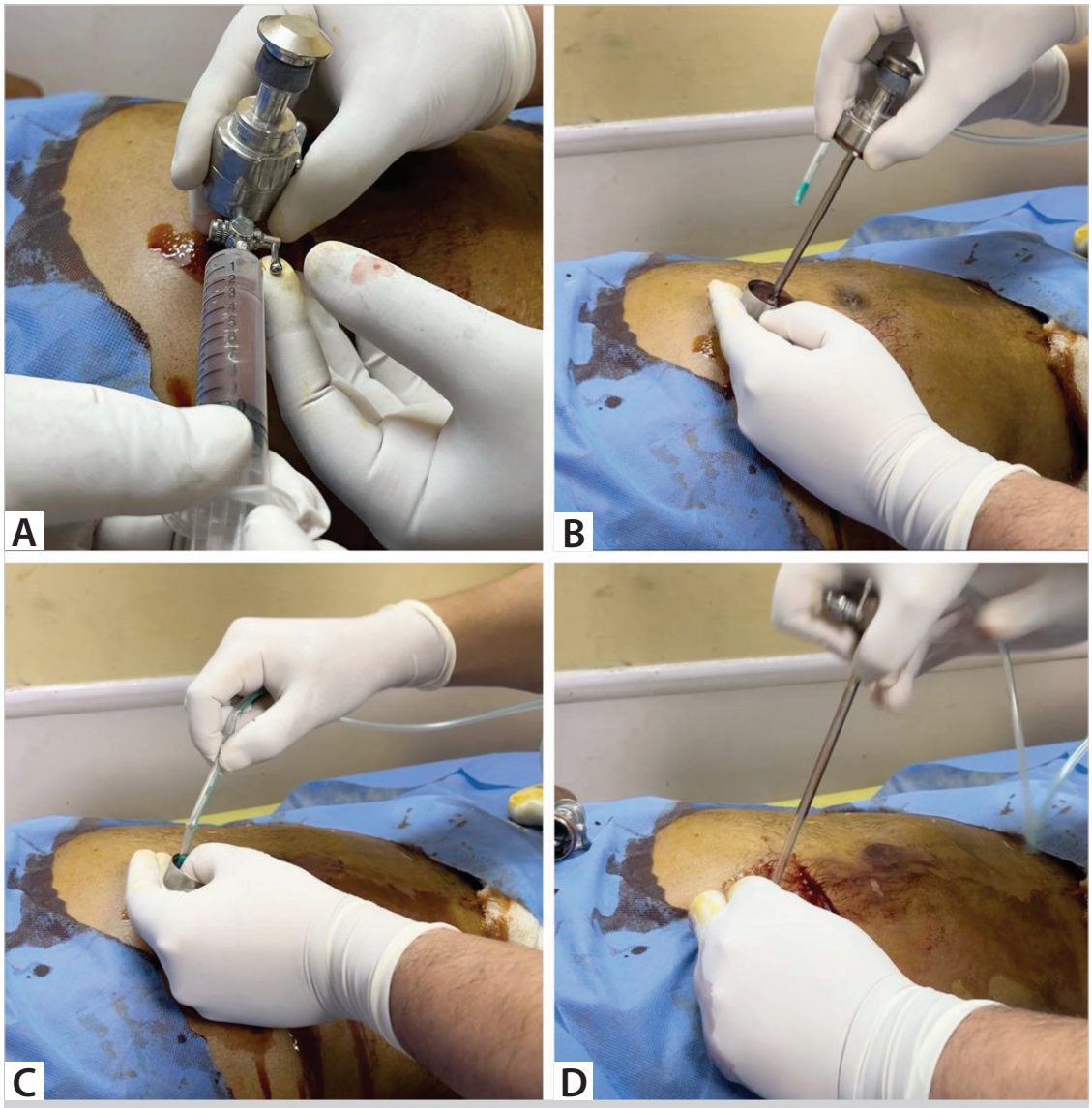

Figure 5. Steps for confirmation and inserting RT. **A.** Aspiration of pus through port to confirm entry inside abscess cavity. **B.** Removal of trocar from the port after entery into the abscess cavity. **C.** Passing the ryles tube through the trocar into abscess cavity. **D.** Removing the trocar after confirming the position of Ryle's tube in abscess cavity.

was 550 mL, while the largest abscess drained was 1.200 mL. The average liver abscess volume was 890 mL. The highest total leukocyte count (TLC) count observed in the study was 21.200/mL, while the lowest count was 8.300/mL. The average TLC count observed in the study was 12.706/mL.

On average, more than 87% of liver abscesses were drained after the drain was inserted, with only one patient requiring needle aspiration of pus later due to a separate cavity and non-resolution of symptoms. The study found no complications with the procedure, and there was no mortality.

Mean pain visual analog score after procedure at 0 hrs and 2 hrs was 3.15 (3-5) and after 24 hrs of procedure was 1.28 (1-3) and on before discharge of the patient was 0.84 (0-2). The average hospital stay was 2.57 days, with the longest stay being five days for one patient and the shortest being one day for one patient. Mean duration in reduction 50% cavity size in the study was 3.8 days (2-8 days).

DISCUSSION

Liver abscesses carry a high risk of sepsis and other serious health complications, potentially leading to high morbidity and mortality rates in patients. Patients with abscesses may become critically ill as a result of complications such as rupture into adjacent organs if not treated promptly. Radiologically guided interventions, such as percutaneous catheter drainage or percutaneous needle aspiration (PNA), in conjunction with antibiotic therapy, have proven to be highly effective in the

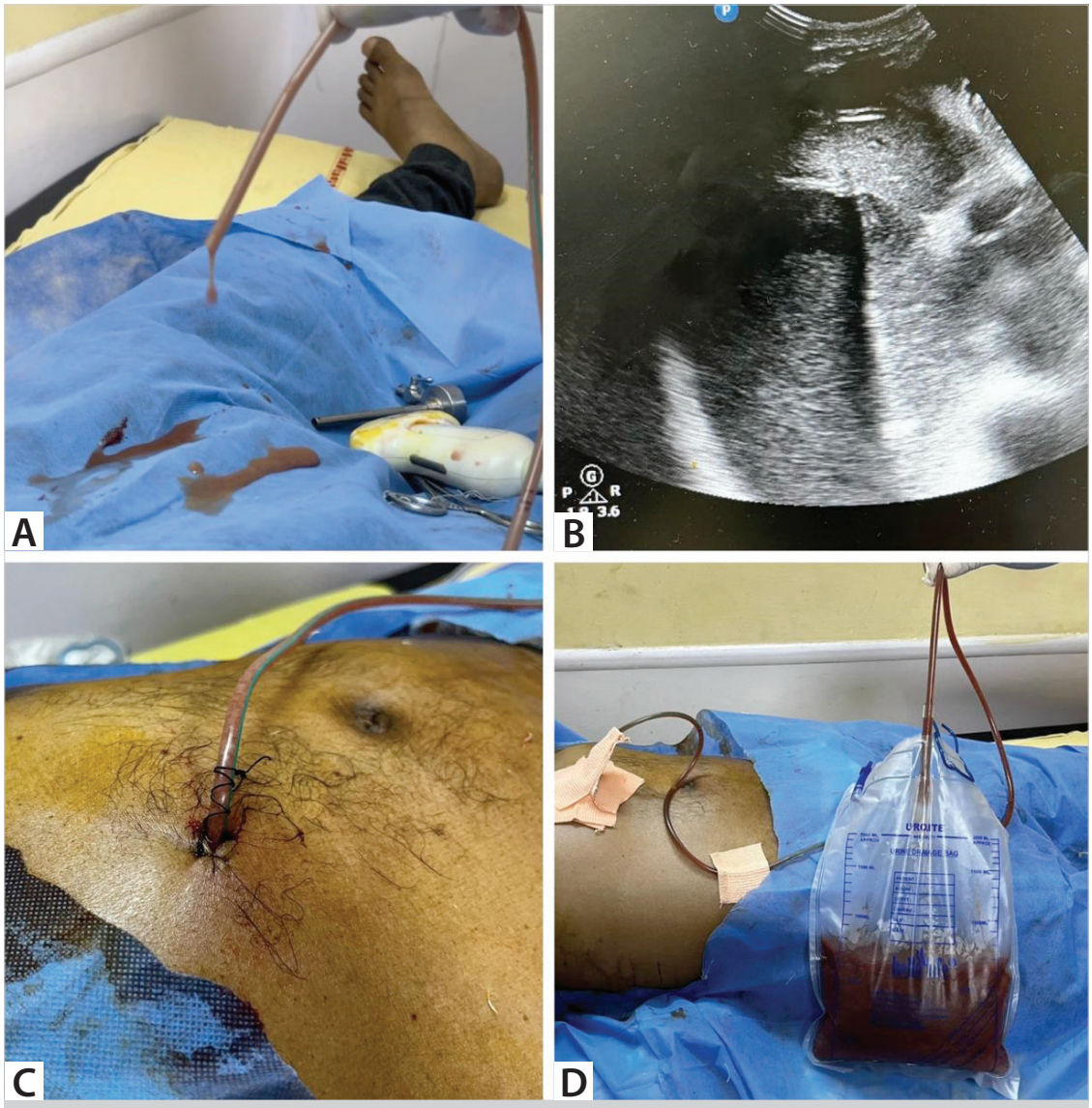

Figure 6. Confirmation and fixation of RT. **A.** Flow of pus through the Ryle's tube confirmed. **B.** Ryle's tube placement is also confirmed through ultrasound imaging. **C.** Fixation of Ryle's tube with skin. **D.** Pus drained via Ryle's tube after fixation.

treatment of liver abscesses, lowering morbidity and mortality rates (14,15,17). This approach has largely replaced surgical exploration, which is now used in very specific cases such as a ruptured liver abscess with peritonitis features.

The PCD has been preferred over the PNA due to the earlier resolution of the pus cavity and the fewer attempts required for proper pus drainage. The limiting factor for PCD is its availability and cost, particularly in settings catering to low-income populations with limited resources, which can sometimes force clinicians to resort to PNA or surgical methods due to the lack of commonly used pigtail catheters. This method has been developed to overcome this limiting factor because the materials used in our method, such as Ryle's tube, are relatively inexpensive and widely available in all wards, while the cost of a 5 mm trocar is significantly reduced due to its repeated use after sterilization.

As the principles of drainage are same i.e. putting a catheter or drain tube inside the abscess cavity to felicitate the drainage of pus, our method can be used in the setups where patients cannot afford to buy the pigtail catheters due to its cost or availability issues.

In this study involving 21 patients who met the criteria, we used our method for drainage of liver abscess and the results were at par with traditional PCD in terms of attempts required to drain the pus, hospital stay and complications. Additionally, it is common for small pigtail catheters to become blocked due to thick, viscous pus, requiring periodic flushing with

saline solution. However, this issue was not encountered in our case when using a 14Fr Ryle's tube.

We noted the time for 50% sonographic resolution of abscess cavities and that was also in concordance with the literature, which is around 3-9 days (18). The time required for complete sonographic resolution of abscess cavities following percutaneous treatment can vary widely, ranging from two weeks to nine months (19,20). However, total resolution may not always occur, and small residual cavities may persist for years, often resembling simple hepatic cysts (21).

The criteria which were set for this study for patient selection can be refined further by keeping the basic drainage principle in mind in studies with larger patient population.

The Gupta Akami technique holds promises as an economically acceptable alternative for percutaneous drainage of liver abscesses, especially in resource-limited settings. Its cost effectiveness, coupled with patient satisfaction and acceptability, underscores its potential to improve access to essential healthcare services and enhance the treatment outcomes for marginalized populations. However, further research is warranted to validate these findings and explore potential factors influencing patient preferences and healthcare utilization patterns.

CONCLUSION

Image-guided percutaneous drainage is extremely beneficial to critically ill patients, allowing for successful abscess drainage and sepsis control even when surgery is not an option due to deteriorating health. Our experience and research indicate that the Gupta-Akami technique has good economic viability and high patient satisfaction because it uses readily available materials and simplified procedural steps. Its affordability and acceptability can make it a viable option, especially for the economically disadvantaged. Continued research and application of this technique has the potential to reduce financial burdens and improve healthcare access for vulnerable populations.

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Ethics Committee Approval: The study was approved by the Atal Bihari Vajpayee Institute of Medical Sciences Ethics Committee (Decision no: TP (MD/MS) 31/2022 IEC/ABVIMS/RMLH, Date: 14.03.2023).

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Author Contributions: Concept - SVG, KA, LKB, AJ, NK; Design - All of authors; Supervision - All of authors; Data Collection and/or Processing - SVK, KA, SG, SB; Analysis and/or Interpretation - SVK, LKB, AJ, NK; Literature Search - SVK, LKB, AJ, NK; Writing Manuscript - SVK, KA, LKB, AJ; Critical Reviews - SVK, KA, LKB, AJ.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (4): 275-282

Yüzeysel karaciğer apsesinin perkütan drenajı için Gupta-Akami tekniği: Düşük mali kaynaklı kurulumlar için yerli ekonomik bir yöntem

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ÖZET

Giriş ve Amaç: Karaciğer apseleri, özellikle tedavi kaynaklarının sınırlı olduğu gelişmekte olan ülkelerde önemli sağlık sorunlarına yol açmaktadır. Görüntüleme ve drenaj teknolojilerindeki ilerlemelere rağmen, pigtail kateterler ve cerrahi müdahaleler gibi geleneksel yöntemler genellikle mali kaynakları kısıtlı kurumlarda kolay ulaşılabilir değildir. Bu çalışma, perkütan drenaj için yerel ve ekonomik olarak uygulanabilir bir yöntem olan Gupta-Akami tekniğini önermekte, basit, hazır malzemeler kullanmakta ve bu ortamlar için potansiyel bir çözüm sunmaktadır.

Gereç ve Yöntem: Çalışma üçüncü basamak bir hastanede altı aylık bir süre boyunca yürütülmüştür. Belirli kriterleri (apse hacmi >500 mL, araya giren karaciğer parankimi <5 cm ve cilt-apse mesafesi <10 cm) karşılayan karaciğer apseli 21 hasta çalışmaya dahil edildi.

Bulgular: Hastaların yaş ortalaması 45,6 olup, erkekler kadınlardan fazlaydı. Hastaların çoğu ateş ve karın ağrısı ile başvurdu; çoğunda bulantı/kusma ve az bir kısmında sarılık gözlendi. Ortalama apse hacmi 890 mL idi. İşlem apse hacminin %87'sinden fazlasını etkili bir şekilde boşalttı ve yalnızca bir hastada ek aspirasyon gerekti. İşlem sonrası ağrı, sıfırıncı saatte görsel analog skalada ortalama 3,15 iken taburcu olmadan önce 0,84'e düşmüştür. Ortalama hastanede kalış süresi 2,57 gündü. Herhangi bir komplikasyon veya mortalite bildirilmedi.

Sonuç: Gupta-Akami tekniği, kaynakların sınırlı olduğu ortamlarda karaciğer apselerinin perkütan drenajı için düşük maliyetli, erişilebilir bir yöntem olarak etkinliğini göstermektedir. Daha pahalı geleneksel yöntemlere umut verici bir alternatif sunarak, düşük kaynaklı ortamlarda hasta sonuçlarını ve erişilebilirliği potansiyel olarak iyileştirmektedir.

Anahtar Kelimeler: Karaciğer apsesi, metalik trokar, Ryle tüpü, kateter drenajı, ekonomik yöntem

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ORIGINAL ARTICLE
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Clinical significances of liver fibrotic markers in patients with cholangiocarcinoma after radical resections

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ABSTRACT

Objective: We examined the relation between several fibrotic markers reflecting liver parenchymal injury and conventional liver function or surgical outcomes in 67 patients with cholangiocarcinoma who underwent biliary drainage for obstructive jaundice followed by surgical resection.

Material and Methods: We examined conventional clinicopathological factors, six hepatic fibrosis parameters, including platelet count, hyaluronic acid, Mac-2 binding protein glycosylation isomer (M2BPGi), type IV collagen 7S, aspartate aminotransferase-to-platelet ratio index (APRI), and FIB-4 index before hepatectomy, and surgical outcomes or long-term prognosis.

Results: Obstructive jaundice was observed in 57% of the patients, a history of biliary diseases in 7.5%, and chronic hepatic injuries in 17.9%. M2BPGi was significantly higher in patients with obstructive jaundice as the primary sign ($p< 0.05$), the FIB-4 index was significantly correlated with patient age ($p< 0.01$), and serum hyaluronic acid and T4C7 levels were significantly increased in distal cholangiocarcinoma (CC). No markers were associated with the histological hepatic fibrotic index, tumor-related factors, or postoperative morbidities. Tumor relapse was observed in 37% of patients, and cancer-related death was observed in 25%. A higher FIB-4 index was significantly associated with shorter cancer-free survival ($p< 0.05$). Cox multivariate analysis showed that bilirubin levels, poor histological cancer differentiation, and absence of fibrotic markers were associated with cancer-free, cancer-specific overall, and overall survival.

Conclusion: Although a sufficient relation exists between these markers and elastographic or histological fibrotic indexes, the clinical significance of measuring conventional fibrotic markers might no longer be necessary in future studies.

Keywords: Cholangiocarcinoma, obstructive jaundice, fibrotic markers, liver dysfunction, surgical outcomes, patient prognosis

INTRODUCTION

In biliary tract carcinomas (BTC) with biliary obstruction and jaundice, the liver parenchyma or sinusoidal functions often show a macroscopically injured appearance, as black, dull, and fragile texture even after preoperative biliary drainage until the total bilirubin level is 2-3 mg/dL (1). This induces severe postoperative liver dysfunction and related biliary sepsis or hepatic failure (2,3) which are more unexpected based on the preoperative liver functional tests (2,3). In comparison with hepatocellular carcinoma (HCC) which has chronic background liver disease, rapid liver injury in BTC seems to be caused by different mechanisms. However, to date, it has been difficult to distinguish these different hepatic pathogeneses using conventional liver functional parameters such as indocyanine green (ICG) clearance test and liver scintigraphy (4).

Hepatic fibrosis is a significant potential factor among the impaired function causes of acute and chronic liver injury (5-10). Except for needle biopsy and resected specimen histology, representative direct liver fibrosis-associated surrogate markers in serum samples, such as type IV collagen hyaluronic acid (HA) and mac-2 binding protein glycosylation isomer (M2BPGi), have been investigated for decades (8-10). Furthermore, as non-invasive scoring systems based on liver functional parameters, decreased platelet count, increased aspartate aminotransferase-to-platelet ratio index (APRI), and FIB-4 index are often used to evaluate hepatic fibrosis and patient prognosis (9-11). These markers show not only the degree of fibrosis but also non-parenchymal cell or tissue damage of the liver, which is a useful surrogate marker of liver elastography (12). As previously reported, HA levels are well correlated with changes during liver failure after hepatectomy; M2BPGi is also a promising parameter for acute liver injury and a novel marker for assessing hepatic fibrosis that induces inflammatory cytokines

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and increases extracellular collagen or fibronectin levels (7,13). Bekki et al. have reported that stellate cells are a source of M2BPGi and that M2BPGi levels reflect the activation of these cells during acute liver fibrosis. To the best of our knowledge, the relation between these fibrotic markers and surgical outcomes in patients with BTC and obstructive jaundice has not been fully elucidated (14).

Therefore, we aimed to clarify which fibrotic markers are significantly related to postoperative lethal liver dysfunction. To achieve this aim, we collected data on fibrosis parameters and investigated the relation between conventional liver function or postoperative hepatic-related complications and these candidate markers in 67 patients with cholangiocarcinoma who underwent preoperative biliary drainage due to complete obstruction at a single academic cancer institute at the University of Miyazaki, Japan.

MATERIAL and METHODS

Patients

This study included 67 consecutive patients with BTC who were scheduled for surgery and admitted to the Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, University of Miyazaki Faculty of Medicine, Miyazaki, Japan for 7.5 years between April 2015 and September 2022. Patients with distant metastases or double cancer during surgery were excluded from the study. A radical hepatectomy was performed, and the hepatic tumors were completely resected without macroscopic exposure of the amputated sections to the remaining liver tissue. Before and after the primary treatment, serum tumor levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were measured as tumor markers of BTC every three months, and enhanced computed tomography (CT) of the liver was performed every six months after hepatectomy to monitor tumor recurrence. Mean follow-up period after hepatic resection in patients with cholangiocarcinoma (CC) who survived was 39 months (range, 12-86.5 months). This study adhered to the Declaration of Helsinki statement on the ethical principles for medical research involving human participants, including research on identifiable human materials and data. All the study protocols were approved by the Human Ethics Review Board of our institution (Approval number: O-1469; 22.12.2023). Patient agreement to participate in the study was obtained via an opt-out procedure for one month at the website and outpatient clinic of our institution. Anesthesia and patient data were retrieved from the the University of Miyazaki Hospital database.

Measurement of Tumor Markers and Histological Findings

Patient clinicopathological data were retrieved from the archives of our institute. At our hospital, the normal levels of CEA, CA19-9, and Duke pancreas II monoclonal antibody (DUPAN-II) were determined to be <5 ng/mL, <37 U/mL, and 150 U/mL, respectively. Elevated levels were defined as those that exceeded the normal levels. Tumor-related factors were compared with the histopathological findings of the resected specimen. For the clinicopathological assessment of biliary tract carcinomas, we used the general rules for clinical and pathological studies on cancer of primary liver cancer and the biliary tract cancer (15,16).

Measurement of Fibrotic Markers

Peripheral blood samples were collected from each patient early in the morning before surgery when the patient was stable. The blood samples were centrifuged at 3000 rpm for 15 min, and the obtained serum was stored at -80°C. HA was assayed using the sandwich binding protein assay by SRL Inc. (Tokyo, Japan) (7). The normal serum HA level reported by SRL Inc. is <50 ng/mL. M2BPGi levels were measured using a chemiluminescent enzyme immunoassay with anti-Wisteria floribunda agglutinin and anti-M2BP antibodies using a fully automated HSCL-2000i Immunoanalyzer (Sysmecs Co., Hyogo, Japan) (13). The cutoff value was set at <1 cutoff index (COI) according to the company's data. The serum 7S collagen concentration was measured using a type IV collagen 7S domain RIA kit (Diaiatron Co., Tokyo, Japan), which uses a polyclonal antibody against the 7S domain of type IV collagen isolated from the human placenta. The normal value was set at <8.0 ng/mL, according to company data. (17). The FIB-4 score was calculated as follows: age (years) × aspartate aminotransferase (AST) level (U/L)/platelet count (10^9/L) × alanine transaminase level (1/2 IU/L). According to the literature, the FIB-4 cutoff for fibrosis or cirrhosis (F3 and F4) is >3.25 (10). The APRI score was calculated by dividing the AST level by 30 (the upper limit of normal at our institute), multiplying it by 100, and dividing the total by the platelet count (11). We adopted the validated cutoff point with the presence of advanced fibrosis of 1.5, and a cutoff value of <0.5 predicted the absence of fibrosis. The histological fibrosis index was measured in some patients, following Knodell's method (18).

Statistical Analysis

Differences in categorical data between the groups and prevalence were assessed using the Chi-square test, Fisher's exact test, or Dunnett's multiple comparison test. Differences in continuous data between the groups were evaluated using Student's t-test or the Mann-Whitney test. Continuous data was expressed as mean ± standard deviation, and median with quartile (25%, 75%). The correlation coefficient was calculated and tested for the correlation relation by Pearson's test. Disease-free interval and overall survival were calculated using the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards

regression model. A two-tailed p value of <0.05 was considered significant. Statistical analyses were performed using the SAS software (Statistical Analysis System Inc., Cary, NC, USA).

RESULTS

Perioperative Parameters

Basic patient data were indicated as follows: The patients included 53 (79%) men and 14 (21%) women with a mean age of 71 ± 7.3 years [median 71 and (61, 75.8)] at the time of surgery. The tumor was located in the distal bile duct (Bd) in 24 patients, proximal bile duct in 14, both distal and proximal bile ducts (Bdp) in 12, and intrahepatic in 17. Obstructive jaundice was observed in 38 patients (57%), a history of biliary diseases in five (7.5%), chronic hepatic injuries in 12 (17.9%), diabetes in 20 (30%), smoking in 40 (59.7%), and other carcinomas in eight (11.9%). Mean levels of carcinoembryonic antigen (CEA) and cancer-antigen (CA) 19-9 were 6.3 ± 24 ng/mL (normal range: ≤5) and 4407 ± 32.735 ng/mL (normal range: ≤37) respectively, and median levels of these were 2.5 (1.7, 4.4) and 24 (7.5, 247), respectively. Preoperative liver functions showed that the mean and median ICGR15 were 10.3 ± 4.3 and 9.5% (6.6, 13.9), those of LHL15 were 0.94 ± 0.05 and 0.90 (0.90, 1.0), those of albumin level were 3.67 ± 0.59 and 3.69 mg/dL (3.42, 4.05), those of total cholesterol were 180 ± 58 and 176 mg/dL (152, 201), those of lymphocyte were 1461 ± 678 and 1320/mm^3 (974, 1816), those of CRP were 0.54 ± 0.72 and 0.24 mg/dL (0.10, 0.61), those of total bilirubin were 1.25 ± 2.28 and 0.70 mg/dL (0.6, 1.08), and those of prothrombin activity were 94 ± 20 and 91% (83, 103), respectively.

Operative procedures were pancreaticoduodenectomy (PD) in 34 patients (51%), partial or segmental hepatectomy in six (9%), hemihepatectomy with bile duct resection (BDR) in 26 (39%), and trisectionectomy with BDR in one. Combined resection of the hepatic artery in four (6%) patients, portal vein in one, and inferior vena cava in two. Macroscopic findings of the tumors were nodular in 24 patients (36%), flat in 23 (34%), papillary in 12 (18%), and mass-forming in 8 (12%). Mean and median tumor size was 4.0 ± 4.8 cm and 2.9 cm (2.1, 4.6), respectively. Histological differentiation was papillary in eight patients (12%), well in 23 (34%), moderate in 27 (41%), and poorly in nine (13%). The histological depth or extension of the tumor was Tis in two patients, T1 in eight (12%), T2 in 28 (42%), T3 in 27 (40%), and T4 in two. Histological vessel infiltration was positive in 12 patients (18%), which was portal veins in 11 patients (16%), and arteries in four (6%). Lymph node metastasis was observed in 18 patients (27%). Histological fibrosis was examined in 18 patients (27%), and the fibrotic grade was zero in seven, one in four, two in two, three in three, and four in two. Superficial extension >2 cm from the main tumor was observed in eight patients (12%). Surgical margin positivity was observed in eight patients (12%), including the hepatic duct side in six (9%), duodenal side in three (5%), and exposed margin in four (6%). Final tumor stage was I in 15 patients (22%), II in 39 (58%), III in seven (11%), and IV in six (9%). Curative resection was achieved in 59 patients (88%), and R1 in eight (12%). Postoperative complications of Clavien-Dindo III≤ were observed in 30 patients (45%) and mortality was nil. Adjuvant chemotherapy was not administered. Mean and median blood loss was 1202 ± 987 mL and 1010 mL (565, 1388), respectively, and those of operating time were 640 ± 655 minutes and 588 mL (491, 648), respectively. Postoperative complications were observed in 37 patients (55%), including hepatic failure in two, bile leakage in six (9%), pancreatic fistula in 14 (21%), uncontrolled ascites in nine (13%), and intra-abdominal abscess in 27 (40%).

Adjuvant chemotherapy was S-1 for six months in 19 patients (28%), gemcitabine and cisplatin for six months in one but nil in 47 patients (70%). Postoperative cancer recurrence was observed in 25 patients (37%), including the liver in eight, peritoneum in seven, lymph node in six, lung in four, local recurrence in two, and bone in one. Treatment for cancer recurrence included gemcitabine + cisplatin in 13 patients, gemcitabine + cisplatin + durvalumab in two, gemcitabine alone in one, gemcitabine +S-1 in one, and nil in 50 patients (75%). Mean and median cancer-free survival periods were 911 ± 610 and 809 days (380, 1257), respectively, and the overall survival periods were 1057 ± 580 and 924 days (575, 1446), respectively. A total of 37 patients (55%) were alive without cancer recurrence, ten (15%) were alive with cancer recurrence, 17 (2%) died due to cancer, and three (5%) died due to other causes.

The Relation Between Clinicopathological Parameters and Each Fibrotic Marker

With respect to fibrotic markers, mean and median hyaluronic acid (HA) levels were 139 ± 332 and 81 ng/mL (40, 123), those of platelet count were 25 x 10^4 ± 22 x 10^4 and 21 x 10^4/mm^3 (18 x 10^4, 25 x 10^4), those of M2BPGi level were 1.07 ± 0.54 and 1.00 C.O.I (0.71, 1.47), those of Type IV collagen 7S (T4C7) were 7.37 ± 5.61 and 5.5 ng/mL (5.03, 6.58), those of aspartate transaminase (AST) were 43 ± 77 and 25 IU/L (20, 35), those of alkaline phosphatase (ALP) were 455 ± 499 and 287 U/L (198, 405), those of APRI were 0.72 ± 1.46 and 0.40 (0.32, 0.61), and those of FIB-4 index were 4.09 ± 2.13 and 3.97 (2.38, 5.24), respectively. In 67 patients, relations of continuous data in each issue between the six types of fibrotic markers or scores and clinicopathological, surgical, and cancer recurrence after hepatectomy are shown in Table 1. In terms of patient demographics, M2BPGi was significantly higher in patients with obstructive jaundice as a primary sign ($p< 0.05$) but was not correlated with total bilirubin level just before surgery. The FIB-4 index significantly correlated with patient age ($p< 0.01$). With respect to tumor location, serum HA and T4C7 levels were significantly increased in distal CC (Bd) ($p< 0.01$). Although fibrotic markers were not associated with the histological fibrotic index, the number of patients examined was limited. Platelet count was significantly higher in

Table 1. Comparison of continuous parameters between fibrotic markers and clinicopathological parameters, surgical records, post-hepatectomy complications, and cancer recurrence in patients with cholangiocarcinoma (CC)

	Platelet Count (10^4/mL)	HA (ng/mL)	Type4 collagen 7S (ng/mL)	M2BPGi (COI)	APRI	FIB-4 Index
Demographics						
Sex, Male (n= 53)	21.6 ± 6.9	152 ± 366	7.7 ± 6.1	1.08 ± 0.58	0.75 ± 1.62	4.1 ± 2.2
Female (n= 14)	35.8 ± 45.6*	80 ± 57	5.9 ± 6.1	1.06 ± 0.78	0.61 ± 0.46	4.2 ± 2.1
Obstructive jaundice, no (n= 29)	28.8 ± 32.4	85 ± 52	6.4 ± 3.1	0.90 ± 0.46	0.53 ± 0.43	4.3 ± 2.1
Yes (n= 38)	22.2 ± 6.2	222 ± 527	8.7 ± 7.9	1.34 ± 0.62*	0.86 ± 1.90	4.0 ± 2.2
Chronic hepatitis, no (n= 55)	22.3 ± 24	169 ± 415	7.7 ± 6.9	1.11 ± 0.60	0.74 ± 1.60	4.0 ± 2.1
Yes (n= 12)	21.0 ± 6.7	88 ± 54	6.9 ± 3.5	1.02 ± 0.51	0.62 ± 0.39	4.7 ± 2.4
Diabetes, no (n= 47)	26.2 ± 25.8	76 ± 49	6.7 ± 5.6	1.04 ± 0.58	0.78 ± 1.71	4.1 ± 2.3
Yes (n= 20)	20.6 ± 6.2	334 ± 662	9.8 ± 5.5	1.17 ± 0.53	0.57 ± 0.37	4.0 ± 1.6
Tumor-factors						
Location, Bd (n= 24)	20.9 ± 6.6	1001 ± 1371**	25 ± 9.9**	1.99 ± 0.35	0.47 ± 0.37	4.3 ± 2.3
Bp (n= 14)	22.9 ± 9.3	79 ± 56	6.1 ± 1.6	1.16 ± 0.63	1.42 ± 0.35	4.6 ± 2.0
Bpd (n= 12)	22.0 ± 3.5	77 ± 11	5.2 ± 0.9	0.82± 0.50	0.61 ± 0.60	3.4 ± 1.5
ICC (n= 17)	32.8 ± 42	87 ± 51	6.4 ± 3.3	0.98 ± 0.45	0.58 ± 0.41	3.9 ± 1.3
Vascular involvement, no (n= 55)	25.1 ± 25	162 ± 416	8.1 ± 6.8	1.10 ± 0.60	0.76 ± 1.60	4.1 ± 2.2
Yes (n= 12)	21.8 ± 6.0	98 ± 58	6.1 ± 2.0	1.04 ± 0.50	0.55 ± 0.29	3.9 ± 2.0
Node metastasis, no (n= 49)	22.1 ±7.2	157 ± 373	6.9 ± 3.6	0.67 ± 0.48	1.07 ± 0.54	4.1 ± 1.8
Yes (n= 18)	31.2 ± 41	73 ± 31	9.5 ± 11	0.91 ± 0.55	1.07 ± 0.68	4.0 ± 2.9
Fibrotic stage, 0 (n= 7)	49.7 ± 63.4	55 ± 35	4.7 ± 0.8	0.69 ± 0.41	0.31 ± 0.14	2.9 ± 1.7
1 (n= 4)	24.8 ± 4.5	101 ± 48	5.6 ± 1.1	1.31 ± 0.44	0.91 ± 0.55	5.1 ± 3.3
2 (n= 2)	21.5 ± 3.5	79 ± 91	7.5 ± 1.0	1.16 ± 0.45	0.59 ± 0.32	3.2 ± 2.1
3 (n= 3)	16.7 ± 10.3	144 ± 23	11 ± 5.5	0.84 ± 0.14	0.78 ± 0.48	4.9 ± 2.5
4 (n= 2)	19.0 ± 2.8	129 ± 128	6.9 ± 2.4	1.23 ± 0.62	0.41 ± 0.05	4.8 ± 0.2
Macroscopic finding,						
Nodular (n= 24)	22 ± 7.1	78 ± 49	6.9 ± 3.8	1.03 ± 0.68	0.43 ± 0.27	4.6 ± 2.1
Mass-forming (n= 8)	45 ± 60*	95 ± 49	6.3 ± 1.9	1.12 ± 0.50	0.46 ± 0.28	5.7 ± 2.4
Flat or ulcerative (n= 23)	20 ± 4.2	275 ± 597	9.3 ± 9.0	1.16 ± 0.54	1.16 ± 2.41	4.2 ± 2.3
Papillary (n= 12)	26 ± 9.1	58 ± 43	5.8 ± 1.5	0.92 ± 0.58	0.25 ± 0.49	2.5 ± 1.6
Histological differentiation						
Papillary (n= 8)	26.4 ± 8.5	63 ± 4.8	5.3 ± 1.1	1.06 ± 0.58	0.50 ± 0.39	3.5 ± 1.8
Well (n= 23)	19.3 ± 4.2	89 ± 47	6.8 ± 3.7	1.14 ± 0.57	1.04 ± 2.39	4.9 ± 2.1
Moderately (n= 27)	28.6 ± 33.6	200 ± 491	8.5 ± 8.0	0.98 ± 0.59	0.62 ± 0.58	3.8 ± 2.2
Poorly (n= 9)	23.8 ± 6.8	118 ± 78	7.5 ± 2.3	1.34 ± 0.53	0.39 ± 0.16	3.3 ± 1.7
Tumor factor, ECC						
1 (n= 9)	22.8 ± 3.9	52 ± 12	5.6 ± 1.0	0.97 ± 0.62	0.44 ± 0.21	4.2 ± 1.3
2 (n= 21)	22.4 ± 8.6	68 ± 44	9.2 ± 9.3	1.12 ± 0.80	1.15 ± 2.53	4.7 ± 2.2
3 (n= 18)	20.4 ± 6.1	95 ± 60	8.4 ± 6.5	1.27 ± 0.53	0.49 ± 0.38	3.7 ± 2.2
4 (n= 2)	21.5 ± 2.2	61 ± 29	6.8 ± 2.1	1.44 ± 0.57	0.71 ± 0.28	2.2 ± 1.3
ICC						
1 (n= 1)	14	146	17.1	0.74	0.6	5.5
2 (n= 7)	21.6 ± 8.2	97 ± 55	5.7 ± 0.8	1.08 ± 0.62	0.70 ± 0.52	5.5 ± 2.3
3 (n= 9)	43.6 ± 56.2	73 ± 48	5.6 ± 2.1	0.92 ± 0.36	0.48 ± 0.38	2.5 ± 1.5
Postoperative complication						
No (n= 30)	28.1 ± 32.2	184 ± 448	7.0 ± 4.3	1.01 ± 0.45	0.48 ± 0.35	4.3± 2.6
Yes (n= 37)	21.6 ± 5.1	85 ± 46	7.8 ± 7.1	1.15 ± 0.68	0.92 ± 1.93	3.9 ± 1.7
CD≤ 2 (n= 12)	19.8 ± 5.0	81 ± 44	11.7 ± 11.4	1.24 ± 0.72	0.77 ± 0.71	4.5 ± 2.1
CD≥ 3 (n= 25)	225 ± 5.0	87 ± 48	5.6 ± 1.1	1.10 ± 0.69	0.98 ± 2.31	3.6 ± 1.5
Bile leakage, no (n= 31)	21.9 ± 5.0	92 ± 48	8.5 ± 7.9	1.17 ± 0.64	0.92 ± 2.08	3.8 ± 1.7
Yes (n= 6)	20.2 ± 6.2	64 ± 30	5.4 ± 0.4	1.22 ± 0.70	0.89 ± 0.82	4.1 ± 2.1
Pancreatic fistula, no (n= 23)	22.7 ± 5.0	79 ± 46	8.1 ± 8.0	0.85 ± 0.56	0.68 ± 0.57	3.8 ± 2.0
Yes (n= 14)	19.9 ± 5.0	107 ± 36	6.7 ± 2.8	0.97 ± 0.56	1.31 ± 3.07	4.0 ± 1.3
Long-term ascites, no (n= 28)	21.1 ± 5.1	74 ± 34	8.7 ± 8.8	0.97 ± 0.59	1.02 ± 2.20	3.9 ± 1.8
Yes (n= 9)	23.0 ± 5.0	107 ± 59	6.2 ± 1.5	1.51 ± 0.75	0.59 ± 0.37	4.0 ± 1.5
Intraabdominal abscess, no (n= 10)	20.9 ± 4.8	108 ± 89	6.0 ± 1.5	1.00 ± 0.53	0.68 ± 0.37	3.7 ± 1.7
Yes (n= 27)	21.9 ± 5.3	88 ± 35	8.8 ± 8.8	1.22 ± 0.75	1.00 ± 2.25	3.9 ± 1.8

Table 1. Comparison of continuous parameters between fibrotic markers and clinicopathological parameters, surgical records, post-hepatectomy complications, and cancer recurrence in patients with cholangiocarcinoma (CC) (continue)

	Platelet Count (10^4/mL)	HA (ng/mL)	Type4 collagen 7S (ng/mL)	M2BPGi (COI)	APRI	FIB-4 Index
Tumor recurrence,						
No (n= 42)	26.1 ± 27.3	86 ± 52	7.4 ± 6.5	1.18 ± 0.58	0.76 ± 1.80	4.5 ± 2.1
Yes (n= 25)	21.9 ± 6.4	231 ± 549	7.3 ± 3.9	0.88 ± 0.50	0.65 ± 0.54	3.3 ± 2.0
Prognosis, alive (n= 37)	26.4 ± 29.0	87 ± 52	7.6 ± 7.0	1.21 ± 0.61	0.80 ± 1.91	4.5 ± 2.1
Recurrent alive (n= 10)	23.6 ± 7.1	80 ± 55	6.4 ± 1.8	0.69 ± 0.29	0.44 ± 0.32	3.4 ± 2.3
Cancer death (n= 17)	21.9 ± 6.4	323 ± 722	7.7 ± 5.3	1.04 ± 0.57	0.72 ± 0.61	3.8 ± 0.8
Other death (n= 3)	19.0 ± 3.5	105 ± 63	7.5 ± 1.6	1.10 ± 0.43	0.64 ± 0.48	7.5 ± 2.0

The clinicopathological findings and TNM classification were based on the general rules for clinical and pathological studies on cancer of the biliary tract and primary liver cancer (15,16).
HA: Hyaluronic acid; M2BPGI: Mac-2 binding protein glycosylation isomer; APRI: Aspartate aminotransferase-to-platelet ratio.
n.s.: not significant with p-value >0.10, Wilcoxon test or Scheffe's multiple comparison test.
*p< 0.05, **p< 0.01

macroscopically mass-forming CC located in the liver or perihilar lesions (p< 0.05). No fibrotic markers were significantly different among other tumor-related factors, postoperative complications, or patient prognosis. Among the fibrotic parameters (Table 2), platelet count was negatively correlated with the FIB-4 index (p< 0.01), and T4C7 was positively correlated with the FIB-4 index (p< 0.05). HA was negatively correlated with serum albumin level and positively correlated with total bilirubin level (p< 0.01). The APRI was significantly associated with CRP and total bilirubin level (p< 0.01).

The Relation Between Preoperative Fibrotic Parameter Levels and Post-Hepatectomy Disease-Free and Overall Survival

Table 3 shows the cancer-free, overall, and cancer-specific overall rates, and the differences in each clinicopathological parameter of the entire CC. Tumor relapse was observed in 25 (37%) patients, and the one-, three- and five-year cancer-free survival rates were 77%, 64%, and 57%, respectively, with a median survival of 57 months. Cancer deaths occurred in 17 patients (25%), and the three-, five-, and seven-year overall

Table 2. Correlative relation between fibrotic markers in patients with cholangiocarcinoma (CC)

	Platelet Count (10^4/mL)	HA (ng/mL)	Type 4 Collagen 7S (ng/mL)	M2BPGi (COI)	APRI	FIB-4 Index
Correlations (r)						
Demographics						
Age	0.094	0.017	0.036	-0.019	0.149	0.312**
Tumor factors						
Tumor size	0.052	-0.052	-0.051	0.177	0.060	0.012
Carcinoembryonic antigen	0.046	-0.057	-0.0009	0.080	0.103	-0.010
Cancer antigen 19-9	0.029	-0.017	0.106	0.243	-0.029	0.174
Surgical records						
Blood loss	-0.038	0.144	0.192	-0.027	-0.015	-0.165
Fibrotic parameters						
Platelet count	-	-0.104	-0.179	-0.004	-0.100	-0.328**
HA	-0.104	-	0.306	0.250	0.146	0.012
Type IV collagen 7S	-0.179	0.306	-	0.067	-0.003	0.407*
M2BPGi	-0.0004	0.250	0.067	-	0.055	0.308
APRI	-0.100	0.146	-0.003	0.055	-	0.012
FIB-4 index	-0.328**	0.012	0.407*	0.308	0.012	-
Immuno-nutritional index and tumor marker						
Albumin	-0.008	-0.345**	0047	-0297**	-0.113	-0.109
Total cholesterol	0.007	-0.080	-0.002	-0.135	-0.075	-0.014
Lymphocyte count	-0.148	0.023	0.0003	0.152	-0.023	-0.007
C-reactive protein	-0.054	0.213	0.052	-0.020	0.439**	-0.099
Total bilirubin	-0.044	0.560**	0.199	-0.153	0.609**	-0.091
Prothrombin activity	0.048	-0.206	-0.103	-0.249	-0.058	-0.039

HA: Hyaluronic acid; M2BPGI: Mac-2 binding protein glycosylation isomer; APRI: Aspartate aminotransferase-to-platelet ratio.
*p< 0.05, **p< 0.01, Pearson correlation coefficient test.

Table 3. Relationship between fibrotic markers or parameters, and survivals in 67 patients with CC undergoing surgical resections using the log-rank test under Kaplan-Meier survival curves

	Cancer-Free Survival (years)	Significance p	Cancer-Specific Overall Survival (years)	Significance p	Overall Survival (years)	Significance p
	1 3 5		3 5 7		3 5 7	
Age, <70 (n= 49)	75 56 47	0.028	68 59 47	0.10	66 54 43	0.13
≥70 (n= 18)	89 83 83		89 89 -		81 81 -	
Sex, Male (n= 53)	72 61 56	0.29	73 73 53	0.92	68 64 48	0.63
Female (n= 14)	100 77 64		79 59 59		79 59 59	
Jaundice, no (n= 29)	72 68 68	0.44	82 82 82	0.20	79 79 79	0.16
Yes (n= 38)	82 61 48		67 57 38		68 68 32	
Chronic liver injury, no (n= 55)	78 64 59	0.87	68 68 51	0.13	64 60 45	0.08
Yes (n= 12)	75 66 50		100 67 67		100 67 67	
Diabetes, no (n= 47)	78 66 62	0.39	76 67 67	0.55	73 64 64	0.25
Yes (n= 20)	75 59 47		70 70 34		65 54 27	
Laboratory data						
Platelet count (10^4/mL), ≥15 (n= 60)	81 65 57	0.53	75 68 51	0.81	71 62 46	0.96
<15 (n= 7)	57 57 -		69 69 69		69 69 69	
HA (ng/mL), <100 (n= 29)†	82 66 51	0.61	79 63 42	0.34	79 56 38	0.59
≥100 (n= 18)	75 75 -		92 92 92		82 82 82	
Type IV collagen 7S (ng/mL), <5.5 (n= 44)†	79 69 60	0.56	72 62 0	0.20	72 62 0	0.73
≥5.5 (n= 15)	73 57 57		82 82 82		75 60 60	
M2BPGi (COI), <1 (n= 16)††	69 61 51	0.43	88 58 58	0.67	82 54 54	0.69
≥1 (n= 17)	88 74 55		77 77 0		77 64 0	
APRI, ≥0.56 (n= 14)	71 64 51	0.84	70 70 35	0.55	62 62 31	0.49
<0.56 (n= 53)	79 64 60		75 66 66		74 61 61	
FIB-4 index, <2.5 (n= 34)	88 81 76	0.012	68 68 45	0.49	63 56 38	0.36
≥2.5 (n= 33)	68 48 40		80 68 68		77 66 66	
Alkaline phosphatase (U/l), <450 (n= 48)	75 61 56	0.34	75 62 62	0.88	73 57 57	0.92
≥450 (n= 19)	84 73 63		73 73 48		67 67 44	
Albumin (g/dL), ≥4 (n= 19)	74 51 51	0.37	72 72 72	0.54	72 72 72	0.32
<4 (n= 48)	79 70 60		75 66 44		71 58 38	
Total cholesterol (mg/dL), ≥180 (n= 28)	85 63 56	0.81	65 43 43	0.28	65 43 43	0.63
<180 (n= 39)	72 64 59		82 82 61		74 70 52	
Lymphocyte (/mm^3), ≥1500 (n= 28)	82 71 61	0.48	79 79 40	0.53	79 70 35	0.49
<1500 (n= 39)	74 59 54		71 61 61		64 55 55	
Total bilirubin (mg/dL), <1 (n= 49)	86 69 63	0.040	80 80 53	0.058	78 74 49	0.053
≥1 (n= 18)	56 50 40		59 47 47		51 41 41	
Tumor-related factor						
CEA, <5 ng/mL (n= 55)	76 67 58	0.75	77 69 55	0.52	73 62 49	0.78
≥5 (n= 12)	83 52 52		63 63 -		64 64 -	
CA19-9, <37 U/L (n= 40)	78 64 57	0.89	78 78 59	0.47	77 69 52	0.55
≥37 (n= 27)	78 64 56		66 55 55		63 53 53	
Location, distal BD (n= 24)	66 57 57	0.39	69 69 69	0.68	59 59 59	0.51
Proximal (n= 14)	100 76 76		75 75 75		68 68 68	
Proximal to distal (n= 12)	83 75 50		71 71 0		71 54 0	
Intrahepatic (n= 17)	71 58 48		86 57 57		86 57 57	
Tumor size, <30 mm (n= 35)	74 56 50	0.16	74 59 59	0.72	66 53 53	0.55
≥30 mm (n= 32)	81 73 65		74 74 49		74 68 46	
Macroscopic finding, papillary (n= 12)	92 83 83	0.40	83 83 83	0.41	74 62 62	0.63
Nodular (n= 24)	75 61 -		62 62 -		63 63 -	
Flat, ulcerative (n= 23)	78 63 47		75 64 32		71 61 31	
Mass-forming (n= 8)	63 50 50		88 88 88		88 88 88	
Node metastasis, no (n= 49)	86 79 68	<0.001	84 75 60	0.009	79 67 53	0.036
Yes (n= 18)	56 25 -		40 40 -		41 41 -	
Vascular involvement, no (n= 55)	80 66 62	0.21	74 74 55	0.91	71 68 51	0.66
Yes (n= 12)	67 58 39		73 37 37		66 33 33	

Table 3. Relationship between fibrotic markers or parameters, and survivals in 67 patients with CC undergoing surgical resections using the log-rank test under Kaplan-Meier survival curves (continue)

	Cancer-Free Survival (years)			Significance p	Cancer-Specific Overall Survival (years)			Significance p	Overall Survival (years)			Significance p
	1	3	5		3	5	7		3	5	7	
Histological differentiation, papillary (n= 8)	100	88	-	0.006	88	88	88	0.14	88	66	66	0.41
Well (n= 23)	96	90	68		90	77	38		78	68	34	
Moderately (n= 27)	63	42	42		58	58	58		58	58	58	
Poorly (n= 9)	55	44	-		70	70	70		70	70	70	
Tumor factor, ECC t1 (n= 9)	100	100	-	0.0017	100	100	-	0.14	100	80	-	0.28
t2 (n= 21)	86	75	75		74	74	74		62	62	62	
t3 (n= 18)	61	42	-		50	50	50		50	50	50	
t4 (n= 2)	100	50	0		50	50	0		50	50	0	
ICC t1 (n= 1)	100	100	-		100	-	-		100	-	-	
t2 (n= 7)	71	71	-		100	100	-		100	100	-	
t3 (n= 9)	67	40	40		71	48	48		71	47	47	
Fibrotic stage, 0 (n= 7)[#]	71	57	29	0.41	85	43	-	0.82	86	43	-	0.63
1 (n= 4)	100	75	-		75	75	-		75	75	-	
2 (n= 2)	100	50	-		100	100	-		100	100	-	
3 (n= 3)	33	33	-		100	100	100		100	100	100	
4 (n=2)	100	-	-		100	100	-		50	50	-	
Superficial extension >2 cm, no (n= 59)	78	65	58	0.94	75	69	55	0.81	71	65	52	0.42
Yes (n= 8)	75	63	-		70	70	-		70	0	-	
Operation, PD (n= 34)	70	61	61	0.56	68	68	68	0.28	64	57	57	0.28
Hepatectomy (n= 33)	85	67	56	0.95	81	69	46	0.56	78	67	44	0.19
Limited resection (n= 3)	67	67	-		100	100	-		100	100	-	
Segmentectomy (n= 3)	100	50	-		100	100	-		100	100	-	
Hemihepatectomy (n= 27)	85	68	56		78	67	67		75	64	43	
Combined vascular resection												
Hepatic artery (n= 4)	75	-	-	0.65	0	-	-	0.18	0	-	-	0.21
IVC, PV (n= 2)	50	-	-		100	100	-		100	100	-	
Morbidity, C-D 0-2 (n= 37)	81	72	62	0.24	80	72	58	0.41	74	63	51	0.75
C-D 34 (n= 30)	73	53	53		62	62	-		62	62	-	
Hepatic failure (n= 2)	50	50	-	0.38	50	-	-	0.091	50	-	-	0.11
Bile leakage (n= 6)	67	25	25	0.039	42	42	-	0.013	42	42	-	0.023
Pancreatic fistula (n= 14)	72	72	72	0.0016	77	77	77	0.73	56	56	56	0.73
Prolonged ascites (n= 9)	89	51	51	0.67	77	70	56	0.43	72	63	51	0.61
Intraabdominal abscess (n= 9)	83	83	0	0.67	63	63	63	0.26	56	46	46	0.12
Blood loss, <1500 mL (n= 51)	100	100	0	0.87	85	77	58	0.00025	80	70	52	0.008
≥1500 mL (n= 16)	50	25	-		20	20	-		20	20	-	
Curability, R0 (n= 59)	76	63	60	0.97	75	68	68	0.31	72	63	63	0.12
R1 (n= 8)	88	77	0		73	73	0		63	63	0	
hm1 (n= 6)	83	83	0	0.87	83	83	0	0.61	83	83	0	0.70
dm1 (n= 3)	100	100	0	0.81	100	100	0	0.93	67	67	0	0.33
em1 (n= 4)	50	25	-	0.028	25	-	-	0.00029	25	-	-	0.0006
Adjuvant chemotherapy, no (n= 47)	89	76	70	0.0004	81	81	60	0.030	75	71	53	0.095
Yes (n= 20)	50	37	25		57	38	38		57	38	38	
Treatments for cancer recurrence, no (n= 50)	-			-	92	83	83	<0.0001	87	75	75	<0.0001
Yes (n= 17)[‡]	-				21	21	11		21	21	11	

The clinicopathological findings and TNM classification were based on the general rules for clinical and pathological studies on cancer of the biliary tract and primary liver cancer. (15,16)

C-D: Clavien-Dindo classification (40)

Cancer recurrence: None (n= 40, 61%); peritoneal dissemination (n= 7); liver (n= 8); lymph node (n= 6); local (n= 3); lung (n= 3); or bone (n= 1).

Prognosis: Survival without recurrence (n= 37, 55%), survival with CC recurrence (n= 10), death from CC (n= 17), and other related deaths (n= 3).

[#]n= 18, [†]n= 59, [††]n= 33.

[‡]: Gemcitabine alone (n= 1), gemcitabine plus CDDP (n= 14), durvalumab plus gemcitabine plus CDDP (n= 2).

survival rates were 74%, 68%, and 54%, respectively, with a median survival period of 64.7 months. With respect to fibrotic markers, lower T4C7 levels tended to be associated with a shorter cancer-specific overall survival period, but this was not statistically significant. A higher FIB-4 index was significantly associated with shorter cancer-free survival ($p< 0.05$). Other fibrotic markers were not significantly associated with survival. With respect to other laboratory parameters, a total bilirubin level over 1 mg/dL was significantly associated with shorter cancer-free survival, cancer-specific survival, and overall survival periods. Table 4 shows the results of Cox multivariate analysis using significant prognostic factors (p-value less than 0.20 identified by univariate analysis) with respect to CC-free and cancer-specific overall survival rates, including the candidate fibrotic parameters. A preoperative total bilirubin level over 1 mg/dL, lower histological differentiation, increased T-factors, postoperative bile leakage, and exposed margin positivity were independently associated with cancer-free

Table 4. Multivariate analysis of prognostic factors influencing cancer-free, cancer-specific and overall survival using Cox proportional hazard test in 67 patients with CC undergoing surgical resection

	Cancer-Free Survival		Cancer-Specific Overall Survival		Overall Survival	
Variables	**Rr* (95% CI)**	**p**	**Rr (95% CI)**	**p**	**Rr (95% CI)**	**p**
Age, <70 (n= 49)						
≥70 (n= 18)	0.18 (0.03-1.00)	0.050	0.11 (0.01-1.67)	0.11	0.25 (0.06-1.01)	0.056
Jaundice, no (n= 29)						
Yes (n= 38)			7.72 (1.31-45.6)	0.024	2.38 (0.86-6.59)	0.094
Chronic liver injury, no (n= 55)						
Yes (n= 12)			0.37 (0.03-4.30)	0.43	0.28 (0.03-2.66)	0.27
Type IV collagen 7S (ng/mL),<5.5 (n= 44)†						
≥5.5 (n= 15)			0.07 (0.01-1.29)	0.074		
FIB-4 index, <2.5 (n= 34)	0.85 (0.28-2.56)	0.78				
≥2.5 (n=33)						
Total bilirubin (mg/dL), <1 (n= 49)	4.85 (1.45-16.2)	0.011	8.38 (1.92-36.6)			
≥1 (n= 18)				0.005	3.14 (1.15-8.55)	0.025
Size of tumor (cm), <3 cm	2.78 (1.01-7.69)	0.048	1.55 (0.33-7.28)			
≥3 cm						
Lymph node metastasis, no (n= 49)	2.69 (0.87-8.30)	0.086	4.50 (0.88-23.0)			
Yes (n= 18)				0.58	2.18 (0.79-5.97)	0.13
Histological differentiation,						
Papillary, well (n= 31)	5.1 (1.58-16.5)	0.006	4.89 (0.82-29.2)			
Moderately, poorly (n= 36)				0.071		
Tumor factor, t1, t2 (n= 38)	6.03 (1.80-20.2)	0.004	1.05 (0.07-16.6)			
t3, t4 (n= 29)				0.082		
Operation, PD (n= 34)						
Hepatectomy (n= 33)					0.61 (0.21-1.83)	0.38
Combined vascular resection, no (n= 59)				0.97		
Yes (n= 8)						
Morbidity, C-D 0-2 (n= 37)						
C-D 34 (n= 30)						
Hepatic failure, yes (n= 2)				0.94	2.21 (0.21-23.2)	0.51
Bile leakage, yes (n= 6)	5.97 (1.36-26.1)	0.018	0.90 (0.05-14.9)	0.008	9.10 (1.55-53.3)	0.014
Pancreatic fistula, yes (n= 14)	0.52 (0.12-2.28)	0.39	29.31(2.44-352.6)			
Intraabdominal abscess, yes (n= 9)					1.02 (0.34-3.11)	0.97
Blood loss (mL), <1500 (n= 51)						
≥1500 (n= 16)			16.07(3.52-73.4)	0.003	6.02 (1.71-21.2)	0.005
Curability, R0 (n= 59)						
R1 (n= 8)						
em1 (n= 4)	3.89 (0.65-23.2)	0.14	10.76 (1.64-70.6)	0.013	4.41 (1.10-17.7)	0.037

Parameters less than p-value 0.20 by univariate analysis for patient survival, were selected for multivariable analysis.
The clinicopathological findings and TNM classification were based on the general rules for clinical and pathological studies on cancer of the biliary tract and primary liver cancer (15,16)
C-D: Clavien-Dindo classification (40),
RR: Risk ratio; CI: Confidence interval.
Cancer recurrence: None (n= 40, 61%); peritoneal dissemination (n= 7); liver (n= 8); lymph node (n= 6); local (n= 3); lung (n= 3); or bone (n= 1).
Prognosis: Survival without recurrence (n= 37, 55%), survival with CC recurrence (n= 10), death from CC (n= 17), and other related deaths (n= 3).

survival (p< 0.05), but no fibrotic markers were associated. The first signs of obstructive jaundice, higher total bilirubin level, postoperative bile leakage, increased blood loss over 1500 mL and exposed margin positivity were independently associated with cancer-specific overall survival (p< 0.05); however, no fibrotic markers were associated. Higher total bilirubin levels, postoperative bile leakage, increased blood loss over 1500 mL, and exposed margin positivity were independently associated with overall survival (p< 0.05), but no fibrotic markers were associated.

DISCUSSION

Specific CC tumor markers such as CEA or CA19-9 are commonly used for cancer diagnosis or tumor aggressiveness (19). According to the abovementioned data, our previous study showed that not only tumor-associated markers but also background liver dysfunction was significantly correlated with poor prognosis in patients with CC undergoing hepatectomy as well as previous reports (20). In patients with extrahepatic CC, particularly distal CC (Bd), obstructive jaundice is frequently observed, and the liver is functionally or macroscopically injured according to the degree of hyperbilirubinemia or a longer period of jaundice, even though adequate biliary drainage is performed until radical operation (1-3,21). During laparotomy, unexpected liver fragility due to liver injury caused by jaundice or background liver disease is often found, which might be associated with postoperative morbidity (22). We hypothesized that severe postoperative morbidity or increased blood loss might also be associated with patient survival in the primary author's previous study; therefore, we attempted to examine liver injury markers, including liver fibrotic markers, to clarify predictive non-tumorous parameters in patients with CC who underwent radical surgery in the present study. Fibrotic markers permitted by Japan's health insurance system at this stage were examined in our study (12).

We also reported that serum HA, a hepatic fibrosis marker, was associated with poor survival, reflecting non-parenchymal liver function, injury, or the risk of post-hepatectomy uncontrolled ascites in patients with chronic hepatitis or cirrhosis (6,7) HA or its protein complex are increased not only in cirrhotic patients but also in patients with HCC and liver malignancies. The mechanism underlying the relation between HA and tumor progression has not been fully clarified; however, physiological stress in the liver parenchyma may stimulate the production of liver-derived growth factors and induce subsequent tumor progression (23,24). The principal author previously reported a close relation between HA and prognosis in patients with HCC However, drug chemotherapy, minimally invasive surgery, and radiological interventions have dramatically improved (25). The prognostic factors for non-tumorous markers have changed over the last decade. Based on these results, it is hypothesized that increased liver fibrosis and related liver dysfunction or latent injury influence patient prognosis after hepatectomy. We also examined the relation between fibrotic markers and prognosis in patients with HCC who underwent hepatectomy in the last decade (unpublished data). Furthermore, the latent progression of remnant cancer cells or multiple carcinogenesis of the liver would also influence the prognosis of patients with hepatobiliary malignancies, including cholangiocarcinoma, through physiological stress (26).

In the present study, five fibrotic candidate parameters and platelet counts, which were routinely examined in patients who underwent hepatectomy but not pancreatectomy, were retrospectively examined in 67 consecutive patients with ICC and ECC, with a minimum follow-up period of one year after surgery, to clarify the relation between these parameters and patient prognosis. Concerning differences or correlations between them, platelet counts and FIB-4 index were significantly noted in each. In patients with HCC with chronic liver damage, platelet counts are closely associated with background liver disease progression; however, platelet counts do not differ between the stages of fibrosis. Despite the low number of patients in this series, platelet counts were not associated with liver damage caused by obstructive jaundice. In the formula for the FIB-4 index, the platelet count is the parameter denominator, and a negative correlation is reasonable when the transaminase levels are stable (10).

HA and type 4 collagen are thought to be specific parameters of general fibrosis, which are increased in patients with distal CC with the first onset of obstructive jaundice. Obstructive biliary congestion may have influenced the increase in the levels of these markers. However, in our study, only HA was significantly correlated with liver dysfunction such as hyperbilirubinemia and hypoalbuminemia. This result shows that obstructive jaundice may not always induce hepatic fibrosis, but increased damage to the endothelium of the hepatic sinusoid due to bile congestion is thought to be an important factor in this mechanism (27). Type IV collagen is common in various tumors, and a positive correlation between type IV collagen expression and tumor metastasis has been reported (28). Native type IV collagen induces epithelial-to-mesenchymal transition-like processes, cell migration, and invasion in MCF10A human mammary epithelial cells, which are suitable for HCC progression. However, T4C7 was not correlated with tumor-related factors; therefore, contrary to our expectations, it was not related to cancer-specific parameters (29). M2BPGi, a secreted glycoprotein present in the extracellular matrix of several organs, is a novel marker for assessing hepatic fibrosis and induction of inflammatory cytokines. According to a report by Bekki et al., the different mechanism as a fibrotic marker from HA or T4C7, is different

the hepatic stellate cell is a source of M2BPGi and the higher biological activities of M2BPGi are associated with the development of hepatocellular carcinoma (12,14). Recent reports have shown that M2BPGi is more strongly associated with liver fibrosis than with other serum markers; however, M2BPGi was not correlated with other fibrotic markers in this series. M2GPGi was associated only with obstructive jaundice and lower albuminemia (12). Although our preliminary data on patients who underwent hepatectomy showed that this marker was closely correlated with textbook outcomes, no such correlation was observed in the present study (13). This might be due to the inclusion of pancreatectomy, and the severity of preoperative obstructive jaundice might not have been associated with postoperative morbidities. The APRI and FIB-4 index were influenced by the degree of hepatocyte injury because the included parameters were transaminase levels, age, and platelet counts. However, these have recently been used to evaluate liver fibrosis in patients with chronic hepatic injuries, although the underlying mechanism has not been fully elucidated (10,11). Except for the correlation with platelet counts and T4C7, these indices were not associated with any parameters, including jaundice or postoperative morbidities, which would not be useful for subacute liver injury, such as obstructive jaundice due to CC.

Concerning cancer recurrence or patient survival in the present study, Steffani et al. reported that histological liver fibrosis is associated with poorer overall survival and higher recurrence rates in patients with CC (30). Contrary to our hypothesis, no fibrotic markers were significantly associated with long-term prognosis, owing to the impaired background liver in our results. Furthermore, in the univariate survival analysis in our study, preoperative obstructive jaundice and two fibrotic markers (T4C7 and FIB-4 index), tumor markers reflecting malignant behavior, and operative stress were significantly associated, as expected. Regarding cancer-free survival, known tumor-related parameters and operative curability are independent factors, whereas liver dysfunction and fibrosis are not, as seen on multivariate analysis (31,32). In order to examine non-cancerous survival due to liver damage caused by CC obstruction, both cancer-specific and overall survival rates were examined. Although the fibrotic parameters were not associated, preoperative jaundice and dominant bile leakage were independent prognostic factors. This shows that preoperative liver damage due to obstructive jaundice might influence the long-term prognosis, as previously reported (33). However, our results do not recommend fibrotic markers as independent biomarkers. In hepatectomy or PD operations, it is speculated that the risk of bile leakage always remains in patients with CC, in which cholangitis-induced liver damage could occur in any situation, but there is no evidence so far. Contrary to our hypothesis, fibrotic markers were not predictive of postoperative bile leakage or associated patient prognosis. Preoperative total bilirubin level alone is a candidate prognostic parameter; therefore, immediate preoperative biliary drainage and sufficient decrease of total bilirubin at the time of operation, even in PD for distal CC located in the Bd, is necessary, although the necessity of preoperative biliary drainage is controversial worldwide (1-5,34,35) Intraoperative blood loss was also an independent risk factor for overall and cancer-specific survival. Allogeneic blood transfusion remained a poor prognostic factor in our previous studies among patients with HCC undergoing hepatectomy (11,33). It has been speculated that liver injury, stress, and transfusion-induced immunodeficiency may occur (36,37).

The limitations were as follows:

1) This study was performed in a consecutive cohort with a relatively small number of participants (67 patients with both ICC and ECC);

2) We did not perform any elastography evaluation to detect the degree of hepatic fibrosis in all patients with CC, which is a more reliable and less invasive parameter for evaluating intrahepatic fibrosis and surgical outcomes (11). Candidate parameters are usually correlated with this in patients with chronic liver injuries; and, therefore, we scheduled elastographic exams preoperatively even in obstructive biliary carcinomas if clinical significances with candidate parameters were observed in the next step;

3) Classical histological fibrotic evaluation was not examined in all, particularly in patients with ECC. If there is a correlation between candidate fibrotic markers and histological fibrosis of the liver injured by obstructive jaundice, we might prospectively examine histological fibrosis as well as elastography in the next step. Due to health insurance or manpower limitations, further advanced examinations for histological liver injuries cannot be performed. In the present study, the histological mechanism of non-tumorous liver injuries caused by obstructive jaundice (biliary congestive liver injury) or carcinogenesis of ICC in the small hepatic ducts did not seem to be different from those in chronic viral hepatitis or steatosis in patients with HCC (38).

4) The relation between candidate markers, tumor-related factors, or surgery-related adverse results was not clearly observed, and these markers might not be produced by CC. However, the precise relations between these factors remain unclear. Another study showed that type IV collagen 7s was correlated with the degree of malignant behavior in HCC and similar results were not observed in CC in this study (39). Because of the above results and limitations, the relation between any patient prognosis was not significantly associated with candidate markers more than other known tumor- or

surgery-related factors influencing patient prognosis by multivariable analyses, contrary to our hypothesis. However, the clinical significance of these markers remains unclear.

CONCLUSION

We conducted a retrospective and consecutive analysis of the outcomes of 67 patients with ICC and ECC who underwent curative hepatectomy or pancreatectomy, including an analysis of the relation between six preoperative liver fibrosis or hepatic injury markers or conventional clinicopathological parameters, surgical outcomes, and patient prognosis. Among several fibrotic markers, M2BPGi was increased in patients with obstructive jaundice, serum HA and T4C7 were significantly increased in the distal CC (Bd), and no markers were significantly associated with tumor-related factors or postoperative complications. Although a higher FIB-4 index was significantly associated with shorter cancer-free survival, no candidate markers were independent prognostic markers for CC in multivariate analysis. Therefore, future studies might no longer be necessary.

Ethics Committee Approval: This study was approved by Chair of Research Institute Dean of University of Miyazaki Yoshitaka Hishikawa (Decision no: 0-1469, Date: 22.12.2023).

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ORİJİNAL ÇALIŞMA-ÖZET
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Kolanjiyokarsinomlu hastalarda radikal rezeksiyon sonrası karaciğer fibrotik belirteçlerinin klinik önemi

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ÖZET

Giriş ve Amaç: Obstrüktif sarılık nedeniyle biliyer drenaj ve ardından cerrahi rezeksiyon yapılan 67 kolanjiyokarsinomlu hastada karaciğer parenkim hasarını yansıtan çeşitli fibrotik belirteçler ile konvansiyonel karaciğer fonksiyonu veya cerrahi sonuçlar arasındaki ilişkiyi inceledik.

Gereç ve Yöntem: Konvansiyonel klinikopatolojik faktörleri, hepatektomi öncesi trombosit sayısı, hyalüronik asit, Mac-2 bağlayıcı protein glikozilasyon izomeri (M2BPGi), tip IV kollajen 7S, aspartat aminotransferaz-trombosit oranı indeksi (APRI) ve FIB-4 indeksi dahil olmak üzere altı hepatik fibrozis parametresini ve cerrahi sonuçları veya uzun dönem prognozu inceledik.

Bulgular: Hastaların %57'sinde obstrüktif sarılık, %7,5'inde safra yolu hastalığı öyküsü ve %17,9'unda kronik karaciğer yaralanması öyküsü gözlendi. Primer bulgu olarak obstrüktif sarılık olan hastalarda M2BPGi anlamlı olarak daha yüksekti ($p< 0,05$), FIB-4 indeksi hasta yaşı ile anlamlı olarak ilişkiliydi ($p< 0,01$) ve distal kolanjiyokarsinomda (CC) serum hyalüronik asit ve T4C7 düzeyleri anlamlı olarak artmıştı. Histolojik hepatik fibrotik indeks, tümörle ilişkili faktörler veya postoperatif morbiditeler ile ilişkili hiçbir belirteç yoktu. Hastaların %37'sinde tümör nüksü, %25'inde kansere bağlı ölüm gözlendi. Daha yüksek bir FIB-4 indeksi, daha kısa kansersiz sağkalım ile anlamlı olarak ilişkiliydi ($p< 0,05$). Cox çok değişkenli analizi, bilirubin düzeylerinin, zayıf histolojik kanser farklılaşmasının ve fibrotik belirteçlerin yokluğunun kansersiz, genel olarak kansere özgü ve genel sağkalım ile ilişkili olduğunu gösterdi.

Sonuç: Bu belirteçler ile elastografik veya histolojik fibrotik indeksler arasında yeterli bir ilişki olmasına rağmen, konvansiyonel fibrotik belirteçlerin ölçülmesinin klinik önemi gelecekteki çalışmalarda artık gerekli olmayabilir.

Anahtar Kelimeler: Kolanjiyokarsinom, obstrüktif sarılık, fibrotik belirteçler, karaciğer disfonksiyonu, cerrahi sonuçlar, hasta prognozu

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ORIGINAL ARTICLE
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The effect of preoperative vitamin D values on hypocalcemia after total thyroidectomy

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ABSTRACT

Objective: Hypocalcemia is a common complication following thyroidectomy. Vitamin D plays a critical role in calcium regulation. This study aimed to investigate the relation between preoperative vitamin D levels and postoperative hypocalcemia.

Material and Methods: We conducted a retrospective analysis of 899 patients who underwent total thyroidectomy at our center between 2015 and 2020 due to multinodular goiter, atypia of undetermined significance, follicular lesions, and follicular neoplasia. Patients were excluded if they had a history of thyroid surgery, Graves' disease, renal failure, incidental parathyroidectomy, or received calcium or vitamin D supplementation before surgery. The patients were divided into two groups based on their preoperative vitamin D levels: Group 1 (n= 240) with levels <10 ng/mL, and Group 2 (n= 659) with levels ≥10 ng/mL. Demographic characteristics and pre- and postoperative laboratory values were compared between the groups.

Results: The female-to-male ratio was 3.22, with an average vitamin D level of 18.94 ± 13.28 ng/mL. Vitamin D levels were significantly lower in women compared to men (p= 0.001). In Group 1, the rates of asymptomatic and symptomatic postoperative hypocalcemia were 17.1% and 6.7%, respectively; while in Group 2, these rates were 11.2% and 3.2% (p= 0.020). The average preoperative vitamin D level was 14.79 ± 9.4 ng/mL in patients who developed hypocalcemia and 19.12 ± 13.4 ng/mL in those who remained normocalcemic, with this difference being statistically significant (p= 0.026).

Conclusion: In our study, we found that preoperative vitamin D level below 10 ng/mL is associated with increased risk of hypocalcemia following thyroidectomy.

Keywords: Preoperative vitamin D, hypocalcemia, thyroidectomy

INTRODUCTION

Thyroidectomy is a common procedure for treating both benign and malignant thyroid diseases. A common complication of total thyroidectomy is hypocalcemia, which can be either asymptomatic or symptomatic. Hypocalcemia can pose significant risks to patient health and prolong hospital stays.

While most instances are temporary, permanent hypocalcemia necessitates lifelong calcium and vitamin D supplementation. Factors contributing to hypocalcemia include patient age, sex, preoperative levels of calcium, vitamin D, and parathyroid hormone (PTH), incidental parathyroidectomy, iatrogenic injury to parathyroid glands, Graves' disease, reoperation, surgical duration, and the weight of the resected specimen (1,2). Early prediction of hypocalcemia is crucial for timely intervention and reducing morbidity.

In this study, we retrospectively evaluated the demographic characteristics, laboratory results, postoperative hypocalcemia incidence, and intravenous calcium requirements of 899 patients who underwent total thyroidectomy performed by two senior endocrine surgeons. The patients were treated for multinodular goiter, atypia of undetermined significance, follicular lesion of undetermined significance, or follicular neoplasia. The aim was to investigate whether vitamin D levels can predict hypocalcemia.

MATERIAL and METHODS

We analyzed 899 patients who underwent total thyroidectomy between January 1, 2015, and December 30, 2020, for multinodular goiter, atypia of unknown significance, follicular lesion of unknown significance or follicular neoplasia according to the Bethesda classification. Patients with Graves' disease, primary hyperparathyroidism, renal insufficiency, central neck dissection, parathyroid reimplantation, or

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preoperative calcium or vitamin D replacement were excluded from the study. All surgeries were performed using capsular dissection technique and energy-based devices.

We recorded patients' demographic characteristics [age, sex, body mass index (BMI)], preoperative diagnosis, development of postoperative hypocalcemia, and intravenous calcium requirements by reviewing patient files. We documented preoperative levels of vitamin D, calcium, PTH, phosphorus, albumin, alkaline phosphatase (ALP), and creatinine, as well as postoperative levels of PTH, calcium, phosphorus, and albumin at 12 hours. Length of hospital stay and pathological diagnoses were also recorded and analyzed. Patients were divided into two groups based on their preoperative vitamin D levels: <10 ng/mL (Group 1, n= 240) and ≥10 ng/mL (Group 2, n= 659). Patients with vitamin D levels below 10 ng/mL were considered deficient. Corrected postoperative calcium values were calculated using the formula: Corrected calcium= measured calcium (mg/dL) + 0.8 × [4 - serum albumin (g/dL)].

Symptomatic hypocalcemia was defined by symptoms such as numbness around the mouth, muscle cramps, positive Chvostek or Trousseau signs, and cardiac arrhythmias following total thyroidectomy. Postoperative hypocalcemia was defined as a corrected calcium level below 8 mg/dL, regardless of symptoms. Patients with symptomatic hypocalcemia were treated with intravenous or oral calcium and oral calcitriol. The study was approved by the ethics committee of our institution, and informed consent was obtained from all participants (2018, Number: 4.8.21-153183).

Biochemical Analysis

Vitamin D levels were measured using high-performance liquid chromatography with an auto-analyzer (ZIVAK Technologies, Türkiye). Calcium, PTH, albumin, phosphorus, and ALP levels were measured using spectrophotometric and chemiluminescence methods with an auto-analyzer (Cobas 4000, Roche Diagnostic, Basel, Switzerland). The reference values in our laboratory were= serum calcium 8.2-10.2 mg/dL, vitamin D ≥30 ng/mL, PTH 15-65 pg/mL, albumin 3.5-5.2 g/dL, phosphorus 2.5-4.5 mg/dL, ALP 40-130 U/L, and creatinine 0.5-0.9 mg/dL.

Statistical Analysis

We used the number cruncher statistical system program for statistical analysis. Descriptive statistics (mean, standard deviation, median, frequency, percentage, minimum, maximum) were employed. Student's t-test was used for comparing normally distributed quantitative variables between two groups while Mann-Whitney U test was used for non-normally distributed variables. Paired t-test was used for comparing normally distributed variables within the groups, and Wilcoxon signed-ranks test was used for non-normally distributed variables. Pearson Chi-square test was used for categorical data. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 899 patients who underwent total thyroidectomy between January 1, 2015, and December 30, 2020. Severe vitamin D deficiency is defined as vitamin D level below 10 ng/mL. Group 1 had 240 patients with vitamin D levels <10 ng/mL, and Group 2 had 659 patients with vitamin D levels ≥10 ng/mL. The mean age, gender distribution, BMI, preoperative diagnosis, and postoperative pathology are detailed in Table 1. A significantly higher rate of low vitamin D levels was observed in females compared to males (p= 0.001) (Table 1).

In Group 1, there was a significant decline of 0.74 ± 0.46 mg/dL in postoperative calcium levels compared to preoperative levels (p= 0.001). Group 2 also experienced a significant decrease of 0.75 ± 0.52 mg/dL in postoperative calcium levels (p= 0.001) (Table 2). In addition, both groups experienced a significant decrease in postoperative albumin levels compared to preop-

Table 1. Demographic values of the study groups

		Group 1 (n= 240)	Group 2 (n= 659)	p
Age	mean ± sd	52.02 ± 12.48	53.29 ± 11.82	**[a]0.161**
Sex	Male	35 (14.6)	178 (27)	**[c]0.001****
	Female	205 (85.4)	481 (73)	
BMI	mean ± sd	28.14 ± 5.67	28.13 ± 5.38	**[b]0.551**
Hospital stay after surgery (day)	mean ± sd	1.07 ± 0.33	1.04 ± 0.21	**[b]0.306**
Preoperative diagnosis	AUS/FLUS	36 (15)	159 (24.1)	**[c]0.012***
	MNG	188 (78.3)	465 (70.6)	
	Follicular neoplasia	16 (6.7)	35 (5.3)	
Postoperative pathology	Benign	147 (61.3)	405 (61.5)	**[c]0.955**
	Malign	93 (38.8)	254 (38.5)	

[a]Student's t test. [b]Mann-Whitney U test, [c]Pearson Chi-square test.
*p< 0.05, **p< 0.01.
BMI: Body mass index.

erative levels (Group 1 0.29 ± 0.3 mg/dL, p= 0.001; Group 2 0.32 ± 0.33 units, p= 0.001).

Preoperative phosphorus levels were significantly higher in Group 2 (3.38 ± 0.51 mg/dL) compared to Group 1 (3.28 ± 0.55 mg/dL, p= 0.016). Group 2 had significantly higher preoperative serum creatinine levels compared to Group 1 (0.73 ± 0.17 mg/dL vs. 0.67 ± 0.15 mg/dL, p= 0.001).

Preoperative and postoperative PTH levels were significantly higher in Group 1 compared to Group 2 (p= 0.001). Group 1 exhibited a significant mean decrease of 21.73 ± 28.71 pg/mL in PTH levels postoperatively (p= 0.001) while Group 2 had a decrease of 16.47 ± 22.42 pg/mL (p= 0.001). The change in postoperative PTH levels was significantly greater in Group 1 compared to Group 2 (p= 0.020) (Table 2).

The incidence of asymptomatic and symptomatic hypocalcemia was lower in Group 2 compared to Group 1 (p= 0.020). There was no significant difference in the need for intravenous calcium supplementation between the groups (p> 0.05) (Table 2). Normocalcemic patients had a significant mean decline of 0.75 ± 0.5 mg/dL in postoperative calcium levels compared to preoperative levels (p= 0.001) while hypocalcemic patients had a decline of 0.93 ± 0.47 mg/dL (p= 0.001). The change in postoperative calcium levels was significantly greater in hypocalcemic cases compared to normocalcemic cases (p= 0.014) (Table 3). There was no significant difference in preoperative PTH values between the groups (p> 0.05). Postoperative PTH levels were significantly higher in normocalcemic cases compared to hypocalcemic cases (p= 0.001). Normocalcemic cases experienced a significant mean PTH decline of 17.19 ± 24.06 pg/mL (p= 0.001) while hypocalcemic cases had a decline of 33.64 ± 26.18 pg/mL (p= 0.001). The change in PTH levels was significantly greater in hypocalcemic cases (p= 0.001). Vitamin D levels were significantly higher in normocalcemic cases compared to hypocalcemic cases (p= 0.026). Postoperative hypocalcemia was observed in 12.79% of 899 patients. Of those 12.79%, 0.01% was permanent and 12.78% was transient hypocalcemia.

Table 2. Biochemical values of the study groups

		Group 1	Group 2	p
Preoperative calcium (mg/dL)	mean ± sd	9.35 ± 0.44	9.45 ± 0.41	**[a]0.001****
Postoperative calcium (mg/dL)	mean ± sd	8.61 ± 0.49	8.7 ± 0.48	**[a]0.017***
Preoperative PTH (pg/mL)	mean ± sd	61.48 ± 27.27	47.7 ± 17.98	**[b]0.001****
Postoperative PTH (pg/mL)	mean ± sd	39.75 ± 30.89	31.23 ± 21	**[b]0.001****
Preoperative ALP (U/L)	mean ± sd	75.5 ± 24.68	72.03 ± 28.38	**[b]0.023***
Hypocalcemia	Normocalcemia	199 (82.9)	585 (88.8)	**[c]0.020***
	Hypocalcemia	41 (17.1)	74 (11.2)	
Symptomatic hypocalcemia	Present	16 (6.7)	21 (3.2)	**[c]0.020***
	Absent	224 (93.3)	638 (96.8)	
Intravenous calcium requirement	Present	10 (4.2)	20 (3)	**[c]0.403**
	Absent	230 (95.8)	639 (97)	

[a]Student's t test, [b]Mann-Whitney U test, [c]Pearson Chi-square test, [d]Paired samples test, [e]Wilcoxon signed ranks test.
*p< 0.05, **p< 0.01.
PTH: Parathyroid hormone.

Table 3. Comparison of biochemical values based on calcium levels

		Normocalcemia	Hypocalcemia	p
Preoperative calcium (mg/dL)	mean ± sd	9.44 ± 0.42	9.2 ± 0.39	**[a]0.001****
Postoperative calcium (mg/dL)	mean ± sd	8.69 ± 0.48	8.28 ± 0.54	**[a]0.001****
Preoperative PTH (pg/mL)	mean ± sd	51.54 ± 21.73	47.62 ± 21.6	**[b]0.23**
Postoperative PTH (pg/mL)	mean ± sd	34.34 ± 24.22	13.98 ± 17.59	**[b]0.001****
Vitamin D (ng/mL)	mean ± sd	19.12 ± 13.4	14.79 ± 9.4	**[b]0.026***
Age	mean ± sd	53.2 ± 11.87	47.16 ± 13.7	**[a]0.003****
Sex	Male	198 (92.96)	15 (7.04)	**[c]0.002****
	Female	586 (85.42)	100 (14.57)	

[a]Student's t test, [b]Mann-Whitney U test, [c]Pearson Chi-square test, [d]Paired samples test, [e]Wilcoxon signed ranks test.
*p< 0.05, **p< 0.01.
PTH: Parathyroid hormone.

DISCUSSION

Our study indicates that low preoperative vitamin D levels may serve as a risk marker for postoperative hypocalcemia. Measuring and managing preoperative vitamin D levels could potentially enhance postoperative outcomes and reduce morbidity and costs.

One of the strengths of our study is that it was conducted on a large and comprehensive patient population. To our knowledge, there are no studies in the literature with a patient series as high as ours that evaluate the effect of vitamin D levels on the risk of hypocalcemia. Another strength is that we excluded patients with other risk factors that could cause hypocalcemia and standardized the impact of different surgical experience. However, a limitation of the study is its retrospective nature.

Hypocalcemia following thyroidectomy is a significant concern due to its impact on patient morbidity, extended follow-up requirements, and increased hospital costs. Permanent hypocalcemia, defined as lasting more than six months, can lead to lifelong calcium and vitamin D supplementation (3). The incidence of temporary hypocalcemia varies widely in the literature, ranging from 0.3% to 49%, while permanent hypocalcemia has been reported 0-13% (4). In our study, postoperative hypocalcemia was observed in 12.79% of 899 patients.

Several factors contribute to postoperative hypocalcemia, including injury or ischemia of the parathyroid glands, incidental parathyroidectomy, parathyroid reimplantation, female sex, Graves' disease, the surgeon's experience and technique, preoperative calcium and vitamin D levels, PTH levels, reoperation, and extensive neck dissection (1,5,6). A prospective study indicated that surgical technique is a major determinant of postoperative hypocalcemia (7). In our study, all thyroidectomies were performed by two experienced endocrine surgeons using a consistent technique.

Despite numerous studies investigating risk factors for postoperative hypocalcemia, the role of preoperative vitamin D deficiency remains controversial. Some studies support the link between vitamin D deficiency and hypocalcemia, while others do not (8-11). Vitamin D deficiency can exacerbate postoperative hypocalcemia because, in the presence of vitamin D deficiency, PTH compensates by increasing calcium reabsorption from bones and kidneys to maintain normocalcemia (12). However, when transient hypoparathyroidism occurs post-surgery, patients with vitamin D deficiency are more prone to hypocalcemia due to the loss of this compensatory mechanism (13). A study found that patients with preoperative vitamin D deficiency had a higher risk of hypocalcemia and elevated postoperative PTH levels compared to those with normal vitamin D levels (14). Conversely, another study suggested that preoperative PTH measurement could be misleading due to secondary hyperparathyroidism in patients with vitamin D deficiency (15).

Vitamin D deficiency is a prevalent issue in Türkiye (16,17). In our study, a cut-off value of 10 ng/mL for preoperative vitamin D was used. Severe vitamin D deficiency is encountered below this cut-off value. Using a lower cut-off value allows to examine the impact of severe deficiency on postoperative outcomes, providing insights into whether very low vitamin D levels are particularly predictive of hypocalcemia. Our study showed that patients with vitamin D levels <10 ng/mL had higher rates of biochemical and symptomatic hypocalcemia (17.1% and 6.7%, respectively) compared to those with levels ≥10 ng/mL (11.2% and 3.2%, respectively) (p= 0.020). This result demonstrates a significant effect of preoperative vitamin D levels on postoperative hypocalcemia. Similarly, in a prospective study of 166 patients with three groups based on their vitamin D levels: <10 ng/mL, 10-20 ng/mL, and >20 ng/mL, the study found postoperative hypocalcemia rates of 32%, 24%, and 13%, respectively, highlighting a significant association between vitamin D levels and postoperative hypocalcemia (14). In another study, vitamin D cut-off of <30 ng/mL significantly increased the risk of postoperative hypocalcemia (18). In our study, mean vitamin D level was 14.79 ± 9.4 ng/mL in hypocalcemic patients and 19.12 ± 13.4 ng/mL in normocalcemic patients, with a significant difference between these groups (p= 0.026; p< 0.05).

Although many studies support the association between low preoperative vitamin D levels and increased risk of postoperative hypocalcemia, some studies indicate no significant correlation between preoperative vitamin D levels and postoperative hypocalcemia (19-22). For example, a retrospective study has found no predictive value of preoperative vitamin D levels for postoperative hypocalcemia in benign thyroid conditions (23). One study has even suggested that low preoperative vitamin D levels might have a protective effect against hypocalcemia by inducing parathyroid hypertrophy and increased PTH secretion (24). Another study has concluded that PTH levels, rather than vitamin D levels, are the most accurate predictor of postoperative symptomatic hypocalcemia (10). Our study observed significant differences in postoperative calcium levels and hypocalcemia incidence (p= 0.017, p= 0.020), aligning with the literature.

A prospective study noted a significant decrease in pre- and postoperative PTH levels among those with vitamin D deficiency, suggesting that postoperative PTH levels were inadequate for predicting hypocalcemia (25). In our study, significant changes in preoperative and postoperative PTH levels were observed in vitamin D deficient patients (Group 1) compared to those with sufficient vitamin D levels (Group 2) (p= 0.001, p= 0.020). Postoperative PTH levels were lower in hypocalcemic patients, with a greater change compared to normocalcemic patients (p= 0.001). No significant relationship was found between preoperative PTH levels and hypocalcemia (p= 0.230). Other studies also demonstrate the association between postoperative PTH levels and hypocalcemia risk (25-27).

Our study revealed a significant sex difference, with a higher rate of vitamin D deficiency in women compared to men (p= 0.001). The incidence of hypocalcemia was also higher in females (14.6% vs. 7%, p= 0.002). Consistent with our findings, some studies show lower preoperative vitamin D levels and higher hypocalcemia rates in women (28). Additionally, female gender is often associated with increased risk of postoperative hypocalcemia (29,30).

Additionally, our study noted significant sex differences, with higher rates of vitamin D deficiency and postoperative hypocalcemia in women (p= 0.001; p= 0.002). This finding is consistent with some literature that reports lower preoperative vitamin D levels and higher hypocalcemia rates in women (28-30). Furthermore, we found that patients with postoperative hypocalcemia were significantly younger (p= 0.003) though no significant correlation between vitamin D levels and age was observed (p= 0.16).

We found that patients with postoperative hypocalcemia were significantly younger than those with normal calcium levels (p= 0.003) although no significant correlation was found between vitamin D levels and age (p= 0.16). One study reported that older patients had a higher mean age and a greater risk of postoperative hypocalcemia (28).

Although our study encompassed a wide patient population, there are conflicting findings in the literature regarding this topic. Further studies are needed to confirm and support our findings.

CONCLUSION

According to our data, preoperative vitamin D level below 10 ng/mL is associated with postoperative hypocalcemia.

Ethics Committee Approval: This study was approved by İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Decision no: 153183, Date: 04.08.2021).

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ORİJİNAL ÇALIŞMA-ÖZET
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Ameliyat öncesi D vitamini değerlerinin total tiroidektomi sonrasi hipokalsemi üzerine etkisi

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ÖZET

Giriş ve Amaç: Hipokalsemi, tiroidektomi ameliyatının sık görülen komplikasyonlarından biridir. D vitamini, kalsiyum homeostazında önemli bir role sahiptir. Çalışmamızda preoperatif D vitamini düzeyinin postoperatif hipokalsemi ile ilişkisini araştırmayı hedefledik.

Gereç ve Yöntemler: Merkezimizde 2015-2019 yılları arasında multinodüler guatr, önemi belirsiz atipi, önemi belirsiz foliküler lezyon ve foliküler neoplazi nedeniyle total tiroidektomi yapılan toplam 899 hasta retrospektif olarak tarandı. Graves hastalığı, böbrek yetersizliği tanısı olan, insidental paratiroidektomi saptanan, daha önce tiroid ameliyatı geçirenler ve preoperatif dönemde kalsiyum veya D vitamini takviyesi alan hastalar çalışma dışı bırakıldı. Hastalar preoperatif D vitamini değerlerine göre iki gruba ayrıldı. Grup 1 (n= 240); D vitamini <10 ng/mL olan hastalar ve Grup 2 (n= 659) ise D vitamini ≥10 ng/mL olarak oluşturuldu. Her iki gruptaki hastaların demografik özellikleri, preoperatif ve postoperatif laboratuvar değerleri ve hipokalsemi gelişme oranı karşılaştırıldı.

Bulgular: Kadın-erkek oranı 3,22 olarak izlendi. Ortalama D vitamini değeri 18,94 ± 13,28 ng/mL olarak tespit edildi. Kadınlarda D vitamini düzeyleri, erkeklere göre istatistiksel olarak anlamlı düzeyde düşük saptandı (p= 0,001). Grup 1'de postoperatif asemptomatik ve semptomatik hipokalsemi oranı sırasıyla %17,1 ve %6,7 iken, Grup 2'de bu oran sırasıyla %11,2 ve %3,2 olarak saptandı (p= 0,02). Hipokalsemik hastalarda, preoperatif D vitamini ortalaması 14,79 ± 9,4 ng/mL saptanmışken, normokalsemik hastalarda 19,12 ± 13,4 ng/mL olarak saptandı ve bu fark istatistiksel olarak anlamlı bulundu (p= 0,026).

Sonuç: Çalışmamızda, preoperatif vitamin D seviyesinin 10 ng/mL'nin altında olmasının tiroidektomi sonrası hipokalsemi riskini arttırdığı sonucuna vardık.

Anahtar Kelimeler: Preoperatif vitamin D, hipokalsemi, tiroidektomi

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ORIGINAL ARTICLE
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Effectiveness of clinical examination and radiological investigations in the success of selective non-operative management of abdominal gunshot injuries

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ABSTRACT

Objective: Non-operative management of abdominal gunshot injuries has become the standard care in the selected cases of modern surgery with an acceptable success rate to reduce the incidence of unnecessary laparotomies. In this study, an assessment was conducted to determine how the success of this form of management was impacted by physical examination and radiological investigation.

Material and Methods: This is a retrospective study that includes all consecutive penetrating abdominal gunshot wound patients who were admitted to the emergency department between February 2011 and December 2018. All patients with superficial gunshot wounds were excluded. The decision to perform a laparotomy on injured patients was the study's primary endpoint while the discharge of patients without surgery was its secondary endpoint.

Results: Of 429 torso gunshot wound patients, 411 were males. Average age was 29.5 years. Forty-one (9.5%) were initially treated by selective non-operative management. Five selective non-operative management patients underwent delayed laparotomy within 12 hours after admission without complication. In the end, 36 (88%) of the 41 patients were successfully treated without undergoing surgery, with only one patient developing pleural effusion and no mortality attributed to it. Of all injured patients, 45 (10.5%) patients had a negative laparotomy, with two of them subsequently developing an incisional hernia.

Conclusion: The success rate of non-operative management of torso gunshot injuries can be increased significantly in stable patients by adopting the strategy of repeated physical examinations alone or in conjunction with simultaneous radiological imaging.

Keywords: Gunshot, non-operative, abdomen, pelvis, torso

INTRODUCTION

Since the end of World War II in 1945 all Libyan government administrations have secured the state's monopoly on weapons, as well as the prohibition and criminalisation of arms trade, which has been reflected in the scarcity of the prevalence of gunshot injuries that were uncommon in the nation. This state of calm during the last sixty years in Libya has resulted in recent decades, in generations of surgeons lacking sufficient experience to deal with the casualties of war and gunshot injuries. Following that, the sudden change that occurred during the Libyan conflict after 2011 led to the widespread availability of weapons in the community and inexperienced hands in dealing with weapons, leading to an increased incidence of firearm-related violence (1).

Prior to 2011, abdominal blunt trauma in traffic accidents and abdominal penetrating injuries from stab wounds were common in the Libyan community. Therefore, good management of these cases has been advanced, whether by operative or later selective non-operative management in hemodynamically stable patients, and the absence of signs of peritonitis with a high success rate. The widespread use of weapons in the Libyan society led to the quick appearance of a new type of penetrating abdominal trauma, and a huge volume of abdominal gunshot cases started to become prevalent although limited experience in managing mass casualties such as in these cases was evident. Therefore,

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a clear effort has been made to improve the nation's capabilities and experience. Moreover, depending on the advice of experts and the conclusion of updated international literature, as well as in the present time, many studies have confirmed that gunshot injuries are common surgical cases, which have become a major and serious problem globally (2).

Mandatory laparotomies have historically been the standard treatment for abdominal gunshot wounds. Therefore, explorative laparotomies were initially performed to treat all abdominal gunshot wounds. It was previously believed that the majority of abdominal gunshot wounds were accompanied by serious organ injuries due to the fact that gunshots cause a significant amount of energy to be transmitted when they pass through body tissue (3). Later, because of the expansion of experiences due to exposure to a large volume of cases, it was discovered that not all abdominal gunshot wounds require surgical intervention. Correspondingly, in the late 1960s, Shaftan and McAlvanah proposed selective conservatism as an alternative option for treatment in selected patient (4,5). Recently, many studies have confirmed the effectiveness and safety of selective non-operative management in a large series of patients with gunshot abdominal injuries evaluated retrospectively and prospectively (6,7).

Abdominal gunshot injuries in patients who have a stable hemodynamic state without signs of peritonitis can be challenging to determine whether a patient needs an exploratory laparotomy or can wait while being closely monitored for conservative treatment. This is because all clinical signs are currently distorted, and many of these patients may still have tachycardia, even in the absence of bleeding due to anxiety and fear; they may have tenderness around the wound site, even in non-penetration of the peritoneal cavity. As with this particular case, there are several possible diagnostic options for the evaluation of the injured patient with the aim of confirming whether he requires explorative laparotomy or whether he is able to stay under conservative management to avoid unnecessary laparotomy, together with its complications (8-10). Additionally, the diagnostic modalities recognised that in order to improve the sensitivity and specificity of clinical judgment, it is important to include a series of physical examination, local wound exploration, diagnostic peritoneal lavage, ultrasound, computerized tomography, intravenous urography, and cystography in case of renal injury. Indeed, all these modalities can be used to carefully select patients for the selective non-operative management of abdominal gunshot injury.

In this study, an assessment was conducted to determine how the success of non-operative management of abdominal gunshot injuries was impacted by a series of physical examination and radiological investigation.

MATERIAL and METHODS

This is a retrospective study, which includes all consecutive patients who were admitted to the emergency room and had gunshot wounds to the anterior, posterior abdominal wall, flank, or pelvic walls in the period from February 2011 to December 2018. All unconscious patients and others with superficial non-penetrating gunshot wounds were excluded when they were confirmed by local wound exploration conducted under local anaesthetic (Table 1). The decision to perform a laparotomy on injured patients was the study's primary endpoint while the discharge of patients without surgery was its secondary endpoint. The strategy for applying a non-operative management group in fully conscious patients was based on a clinical examination backed by emergency bedside investigations, such as blood tests and abdominal ultrasounds at the time of admission. During this stage, patients are placed under careful observation for a minimum of 24 hours; the same team conducts clinical evaluations periodically over this time. After repeating the blood tests and abdominal ultrasound after 12 hours as part of a series of investigation, an abdominal computed tomography scan is requested before discharging or transferring patients to another specialty for further care.

Further, age, sex, blood pressure and heart rate at admission, initial signs of peritonitis, first haemoglobin, focused abdominal sonography in trauma scan, chest x-ray, computed tomography (CT) scan, time from admission to laparotomy, operative findings, type of surgical procedures, blood transfusion, intensive care unit, and hospital stay, and postoperative complication were the data collected for the study.

In statistical analysis, all continuous variables were expressed as mean ± standard deviation (SD) to evaluate the distribution of data; categorical data were expressed as frequency and percentage. Comparisons between the groups were made using the X^2 test or Fisher's exact test for categorical variables as appropriate. Statistical analyses were performed using the

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	
1	Penetrating abdominal gunshot wounds
2	Hemodynamically stable patients at admission time
3	Non peritonitis patients
Exclusion Criteria	
1	Polytrauma patients (Head injury, limb fractures)
2	Superficial non-penetrating gunshot wounds
3	Delayed admission (After 12 hours from injury)

SPSS v21 statistical software, and P values of less than 0.05 were considered statistically significant. Moreover, both unadjusted and adjusted logistic regression analyses were conducted to determine variables associated with a statistically significant study result. Initially, univariable analyses were conducted to identify factors.

In addition, informed consent was obtained, as the hospital is a teaching university hospital, and thus, written informed consent was routinely signed by all admitted patients or legally authorised representatives during the hospital stay and prior to the studies. This is imperative for all research in order to use patients' data and to be published in academic activities and research. Ethics approval was also received as the current study was approved by the Al-Jalaa Teaching Hospital, Benghazi University Institutional Review Board (IRB No. 264/2023).

Table 2. Types and numbers of organ injuries and performed operative procedures

	Organ	Procedure	No	Percent %
1	Diaphragm	Diaphragm primary repair with chest tube insertion	32	9.3%
2	Spleen	Splenectomy	33	9.6%
3	Stomach	Gastric wall primary repair	42	12.2%
4	Duodenum	Duodenal primary repair	8	2.3%
5	Liver	Topical liver parenchymal hemostasis	19	24.1%
		Liver parenchymal primary repair	29	
		Direct blood vessel ligation	17	
		Perihepatic packing	24	
		Non-anatomic liver resection	4	
6	Gall bladder	Cholecystectomy	12	3.4%
7	Pancreas	Pancreatic debridement	12	4.3%
		Distal pancreatectomy	3	
8	Small bowel	Small bowel primary repair	90	37.3%
		Small bowel resection and anastomosis	38	
9	Large bowel	Ascending colon primary repair	16	49.2%
		Ileocecal resection	2	
		Right hemicolectomy	40	
		Transverse colon primary repair	44	
		Transverse colon resection and anastomosis	9	
		Transvers loop colostomy	13	
		Descending colon primary repair	8	
		Sigmoid colon primary repair	14	
		Sigmoid colon resection and anastomosis	2	
		Sigmoid loop colostomy	10	
		Hartmann operation	11	
10	Kidney	Kidney primary repair	6	7.8%
		Nephrectomy	21	
11	Ureter	Ureter primary repair	2	2%
		Ureter anastomosis with DJ stent	5	
12	Abdominal blood vessels	Aorta primary repair	1	3.3%
		IVC primary repair	5	
		Superior mesenteric artery primary repair	3	
		Inferior mesenteric artery ligation	1	
		Inferior epigastric artery ligation	2	

Table 2. Types and numbers of organ injuries and performed operative procedures (continue)

	Organ	Procedure	No	Percent %
13	Rectum	Rectal primary repair	9	44.4%
		Rectal primary repair with proximal loop colostomy	19	
14	Urinary bladder	Urinary bladder primary repair	24	38%
15	Urethra	Urethral primary repair with suprapubic catheter insertion	5	7.9%
16	Anal canal	Anal canal debridement with proximal loop colostomy	7	11%
17	Pelvic blood vessels	External iliac artery primary repair	3	17.4%
		External iliac artery graft placement	2	
		External iliac artery end-to-end anastomosis	1	
		External iliac vein ligation	3	
		Internal iliac artery primary repair	1	
		Internal iliac artery ligation	2	
		Internal iliac vein ligation	1	

DJ: Double-J ureter stent, IVC: Inferior vena cava.

Table 3. Characteristics of delayed laparotomy patients

No	Age	Sex	Indication	Laparotomy Findings	Operation	Hospital Stays	Complication
1	22	Male	Late shock	Liver tear	Explorative laparotomy with primary repair	3 days	No
2	23	Male	Peritonitis	Small bowel sealed perforation	Explorative laparotomy with primary repair	5 days	No
3	34	Male	Peritonitis	Small bowel sealed perforation	Explorative laparotomy with primary repair	5 days	No
4	38	Male	Abdominal tenderness	Negative laparotomy	Explorative laparotomy	3 days	No
5	22	Male	Peritonitis	Liver tear & small bowel perforation	Explorative laparotomy with primary repair	6 days	No

RESULTS

During the study period from January 2011 to December 2018, 429 patients were admitted to the emergency department with abdominal gunshot injuries: 414 (96.5%) were males and 15 (3.5%) were females. Mean age was 28.7 years (range= 18-70 years). Three hundred and eighty-eight (90.4%) patients were treated by urgent explorative laparotomy, 343 were therapeutic and 45 were negative laparotomy. Table 2 shows details of the organ injuries and actual operative interventions performed. Negative laparotomy patients underwent the surgical procedure without a scan due to hemodynamic instability and abdominal tenderness that were associated with high suspicion of intra-abdominal organ injury, or omental evisceration; two patients suffering from these had an incisional hernia later. What is more, 41 (9.5%) patients who sustained penetrating abdominal gunshot wounds were included in the study.

Figure 1. Successful non-operative treatment for a patient with abdominal gunshot.
Dr. Salah Mansor, Al-Jalaa Hospital, Benghazi, Libya 2016.

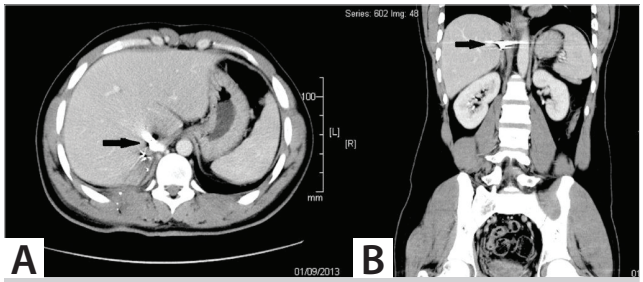

Figure 2. A. Axial and coronal **B.** Abdominal CT shows a gunshot bullet within the liver tissue.
Dr. Salah Mansor, Al-Jalaa Hospital, Benghazi, Libya 2013

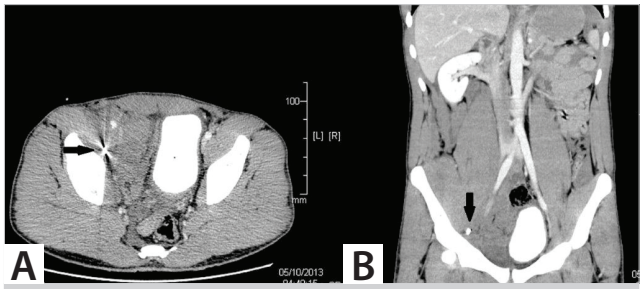

Figure 3. A. Axial and coronal **B.** Abdominal CT shows a pelvic gunshot bullet.
Dr. Salah Mansor, Al-Jalaa Hospital, Benghazi, Libya 2014

Thirty-nine (95%) were males and two (5%) were females. The average age was 30 years, with a range of 19 to 55 years, all of whom were treated by selective non-operative management; 36 of them were discharged home without complications, and only one patient who developed pleural effusion was treated conservatively; with no mortality was attributed to it. Further, five patients underwent delayed explorative laparotomy within twelve hours following admission due to the worsening of abdominal signs or in the presence of suspicious CT scan findings. Two patients had a delayed laparotomy because of hemodynamic instability brought on by continuous bleeding from a liver tear while three other patients had a CT scan that revealed small bowel perforation. The last patient underwent a negative laparotomy, and all patients without postoperative complications (Table 3).

DISCUSSION

Depending on the clinical presentation at the time of admission, gunshot injuries might present in three different scenarios. In the first scenario, patients require an immediate life-saving operation when they arrive at the emergency room. In this case, mortality rate can reach up to 90% due to massive bleeding from major blood vessel damage (11). Patients in the second scenario, who exhibit hypotension and peritonitis signs that are evident or evisceration, require an urgent exploratory laparotomy as a role of the golden hour in the management of trauma patients. The third scenario,

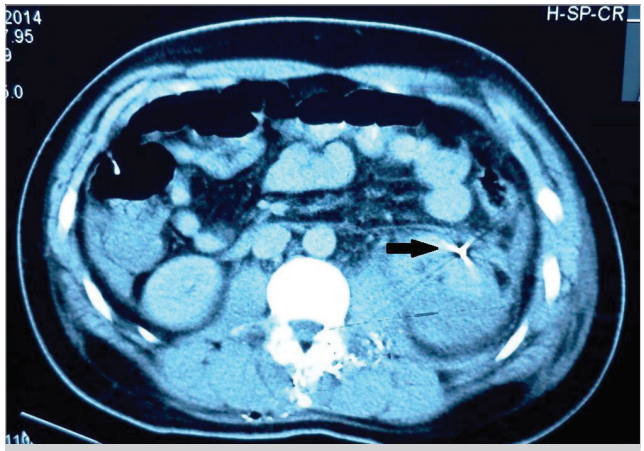

Figure 4. Axial Abdominal CT shows a gunshot bullet within the renal parenchyma.
Dr. Salah Mansor, Al-Jalaa Hospital, Benghazi, Libya 2014.

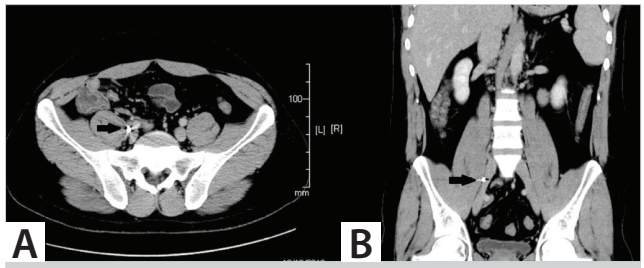

Figure 5. A. Axial and coronal **B.** Abdominal CT shows a posterior abdominal wall gunshot.
Dr. Salah Mansor, Al-Jalaa Hospital, Benghazi, Libya 2017.

which is the focus of the current study, consists of patients with abdominal gunshot injuries admitted with hemodynamic stability and blurred signs in abdominal examination, and such patients are good candidates for selective non-operative management (Figure 1).

Laparotomy is defined as therapeutic when there are intra-abdominal injuries that require to be repaired, while it is defined as negative or unnecessary when there are either no intra-abdominal injuries identified or those that require no repair, for example, non-expanding retroperitoneal hematoma. Comparatively, delayed laparotomy is laparotomy on a patient who has been initially selected for observation that subsequently presents a clear indication for surgery later, signalling a failure of non-operative management. Failure is caused by the progression of mild tenderness to more generalised abdominal pain accompanied by rises in white blood cell count and temperature, and an unexplained decrease in haematocrit or blood pressure is also taken into account in the context of the overall clinical picture. Overall, the management of patients suffering from penetrating abdominal wounds has undergone significant improvements in the last few decades in terms of both experience and procedures.

During the 20th century, routine laparotomy was mandatory for all patients with penetrating wounds of the abdomen, while exploratory laparotomies were a common surgical treatment used by most emergency surgeons worldwide to treat abdominal gunshot wounds (3,12). This was because they believed that there was a considerable intra-abdominal injury following abdominal gunshot wounds, and it is preferred to perform an explorative laparotomy to confirm or to roll out organ injury, due to blurred clinical indications, especially at the early period of injury (3,13,14). In accordance, Shaftan has concluded that some patients with penetrating abdominal trauma have no clear indication of explorative laparotomy and can be managed effectively and safely through close observation (4). This conclusion has been accepted and implemented quickly and smoothly in the abdominal stab wound cases and then established as the standard of care, while in regard to a gunshot injury, applying this conclusion is more challenging, as it requires great caution.

As routine, when a patient is received with an abdominal gunshot injury, after initial assessment and urgent resuscitation, if the patient is hemodynamically stable, clear urgent laparotomy indications are routinely ruled out, such as active bleeding, diffuse or localised abdominal tenderness, evisceration of intra-abdominal organs, leakage of intestinal content through the wound, shock with frank haematuria, hematemesis, and blood on rectal examination. If the patient exhibits none of these signs, he/she is placed under rigorous serial observation, before finishing the workup by requesting diagnostic tests, such as serial full blood counts, chest and abdomen x-rays, urgent abdominal ultrasound scan, and computed tomography scans if the ultrasound examination reveals a strong indication or suspicion. Other than avoiding an unnecessary operation, the conservative approach to managing abdominal gunshot injuries also aims to decrease post-operative complication rates, as well as shorten hospital stays (15,16).

There is no doubt that urgent exploratory laparotomies should be performed on patients with penetrating abdominal gunshot wounds if there are clear indications of hemodynamic instability, or if there is significant abdominal wall tenderness and guarding, even without performing additional diagnostic testing. The major challenge for surgeons is to make the right decision for patients who have none or who have minimal signs after penetrating abdominal gunshot injuries. Surgeons should use their own clinical experience and diagnostic modalities to decide which patients need explorative laparotomy and when patients should be operated on. As a gunshot injury can occur at any time of the day or night, and the patient will be received by an emergency team on duty, this situation may affect the success of the selective non-operative strategy in gunshot abdomen and may increase the rate of unnecessary laparotomies, while the goal of management strategy is to avoid these types of procedures. Also, as well as its complications, some international literature has concluded that the morbidity and mortality of unnecessary laparotomy for trauma patients have a significant rate (17).

In the assessment of abdominal gunshot victims who have hemodynamic stability, plain film radiographs have a limited role. X-rays of the chest and pelvis are frequently used to check for concomitant damage, which usually aids in determining exactly where the bullets were fired. If a mechanism for multisystem trauma is present then common findings include pneumoperitoneum, pneumothorax, haemothorax, and rib fractures. The sensitivity of the diagnostic peritoneal lavage (DPL) test for detecting injury in penetrating abdominal injury reaches 96% (18). Recently, the impact of new technology on the surgical field has been determined as the presence of modern computed tomography scanners providing high-resolution images with speed assessment of abdominal gunshots has led to the reduced frequency of DPL utilisation, and it has become very limited in very special situations.

The role of ultrasound scans in blunt abdominal injuries has been established with a high sensitivity of 81-88% and a specificity of 97-100% (19). It has also been possible to make use of its certain advantages in penetrating abdominal injuries, as during the initial assessment of a trauma patient, ultrasound waves can quickly identify and demonstrate the damage to solid organs, and easily detect free fluid in the peritoneal cavity (20,21). Ultrasound scan is known as a simple, fast, safe, cheap, and bedside non-invasive procedure although comparatively, it has a disadvantage because it is operator dependent, providing results based on the radiologist's skill, and is unable to rule out hollow viscus injury. What is more, Udobi et al. have confirmed that ultrasound scan is not as reliable as in blunt trauma and has a 15% negative laparotomy rate (21). Therefore, it should be combined with other diagnostic modalities to select the penetrating abdominal injury patients for the selective non-operative management group.

CT scan is one of the most important diagnostic modalities of investigation in gunshot patients. CT scans with intravenous and oral contrast are used to detect both solid and hollow viscus injuries. In hemodynamically stable patients, CT is considered a non-invasive rapid, and accurate diagnostic tool that helps to identify patients who might benefit from selective non-operative management with a high success rate as in patients suffering from isolated liver injury without active bleeding and no signs of bowel injury (Figure 2) (22-24). Some research on hemodynamically stable gunshot-injured patients concluded that abdominal CT with intravenous contrast has a

high sensitivity and specificity that reach 90.5% and 96%, respectively (25). This finding enables the possibility to believe that it is safe and feasible to observe stable abdominal gunshot patients using both serial physical examination and CT (Figure 2,3). In addition, if a patient with an abdominal gunshot injury, with the presence of gross haematuria, appeares to correlate with the presence of significant urological injuries, intravenous pyelograms continue to be the gold standard for assessing hemodynamically stable patients who are suspected of having urological injuries (26).

In comparison, Ramirez RM et al. have concluded that single contrast computed tomography successfully determined the need for operative intervention in hemodynamically stable patients with renal injury (Figure 4) (27). Indeed, it can quickly and accurately demonstrate the degree of injury, and shows the signs of per renal haemorrhage, as well as the extravasation of urine and vascular injuries. Moreover, it can detect any other adjacent organ injury in both the peritoneal cavity and retroperitoneal space (28). Due to the robust posterior abdominal wall muscles, back penetrating injuries have a less severe clinical outcome than the anterior abdominal wall, and as a result, in this instance, the contrast CT abdomen will aid in determining the location and severity of the injury (Figure 5) (29). In particular, one patient in the current study had a posterior abdominal wall gunshot injury that later developed into a low-output colo-cutaneous fistula. A contrast abdominal CT study confirmed this diagnosis, and the patient was then treated conservatively.

Finally, since gunshot injuries can happen at any time and the patients will be cared for by surgeons on duty, this scenario could have an impact on the effectiveness and success of the non-operative approach and raise the rate of unnecessary laparotomies. Therefore, surgeons have to make vital decisions for the appropriate selection among various diagnostic techniques for success in non-operative management and decreased rate of unnecessary laparotomy and its complication in torso gunshot wounds.

CONCLUSION

The success rate of non-operative management of abdominal gunshot injuries can be increased significantly in stable patients by adopting the strategy of repeated physical examinations alone or in conjunction with simultaneous radiological imaging.

Acknowledgments

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (4): 303-311

Abdominal ateşli silah yaralanmalarında seçici ameliyatsız tedavinin başarısında klinik muayene ve radyolojik incelemelerin etkinliği

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ÖZET

Giriş ve Amaç: Karın içi ateşli silah yaralanmalarının cerrahi olmayan yönetimi, gereksiz laparotomilerin sıklığını azaltmak için kabul edilebilir bir başarı oranıyla modern cerrahinin seçilmiş vakalarında bakım standardı haline gelmiştir. Bu çalışmada, bu yönetim biçiminin başarısının fiziksel muayene ve radyolojik incelemeden nasıl etkilendiğini belirlemek için bir değerlendirme yapılmıştır.

Gereç ve Yöntemler: Bu, Şubat 2011 ile Aralık 2018 arasında acil servise yatırılan ardışık tüm penetran abdominal ateşli silah yaralanması hastalarını içeren retrospektif bir çalışmadır. Yüzeysel ateşli silah yaralanması olan tüm hastalar hariç tutulmuştur. Yaralı hastalara laparotomi yapma kararı çalışmanın birincil son noktasıyken, hastaların ameliyat olmadan taburcu edilmesi ikincil son noktasıydı.

Bulgular: Dört yüz yirmi dokuz gövde ateşli silah yaralanması hastasından 411'i erkekti. Ortalama yaş 29,5'ti. Kırk bir'i (%9,5) başlangıçta seçici cerrahi olmayan tedavi ile tedavi edildi. Seçici cerrahi olmayan tedavi ile tedavi edilen beş hasta, komplikasyonsuz olarak hastaneye yatıştan sonraki 12 saat içinde gecikmiş laparotomiye girdi. Sonunda, 41 hastanın 36'sı (%88) ameliyata alınmadan başarılı bir şekilde tedavi edildi, sadece bir hastada plevral efüzyon gelişti ve buna bağlı ölüm olmadı. Yaralanan tüm hastalardan 45'inde (%10,5) negatif laparotomi yapıldı ve bunlardan ikisinde daha sonra insizyonel herni gelişti.

Sonuç: Gövde kurşun yaralanmalarının cerrahi olmayan tedavisinin başarı oranı, stabil hastalarda tek başına veya eş zamanlı radyolojik görüntülemeyle birlikte tekrarlanan fiziksel muayene stratejisinin benimsenmesiyle önemli ölçüde arttırılabilir.

Anahtar Kelimeler: Ateşli silah yaralanması, ameliyatsız, karın, pelvis, gövde

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ORIGINAL ARTICLE
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Comparative outcomes of blunt and penetrating diaphragmatic ruptures: A single trauma center study

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ABSTRACT

Objective: Diaphragma rupture is an insidious case following thoracoabdominal trauma with significant morbidity and mortality rates, if left untreated. Its symptoms might be masked by other associated injuries, which are often present, especially following blunt trauma. Modern imaging modalities might overlook a present diaphragmatic rupture. The real challenge, therefore, lies in diagnosis rather than treatment. To shed more light on this entity, we shared our experience in this regard.

Material and Methods: A total of 51 patients were enrolled in the study between January, 2008 and October, 2023, with a diagnosis of diaphragma rupture. Two groups were created, namely patients with blunt trauma (PwBT) and patients with penetrating trauma (PwPT). They were evaluated in terms of demographics, clinical and laboratory findings, trauma associated variables, mechanism of injury, accompanying injuries, imaging results, operative approaches and mortality rates.

Results: Mean age was 26 (22-33). 21.6% of the patients had blunt trauma. PwBT had significantly more extraabdominal site injuries and additional abdominal organ injuries ($p< 0.05$). Glasgow coma scale and calculated revised trauma score values were significantly lower and injury severity scores values were significantly higher in PwBT ($p< 0.05$). Significant thorax trauma accompanied 81.8% of PwBT and 40% of PwPT. Mortality was observed in 11.8% of the patients, with hemodynamic instability being the leading cause of death.

Conclusion: A trauma surgeon must exercise great caution not to overlook a diaphragma rupture following, especially, blunt thoracoabdominal trauma since it is both a consequence and reason of significantly increased mortality and morbidity rates. Future studies should focus on various aspects of both diagnosis and management of this entity, such as increasing the preoperative diagnosis accuracy and requirement of mesh usage during defect closure and optimal approach to especially right sided penetrating thoracoabdominal injuries.

Keywords: Thoracoabdominal trauma, diaphragma rupture, intrathoracic visceral herniation

INTRODUCTION

Diaphragmatic rupture (DR) following thoraco-abdominal trauma is both rare and insidious. DR occurs in less than 6% of patients with blunt thoraco-abdominal trauma and is often considered a marker of severe injury (1). It is frequently accompanied by additional abdominal organ injuries (AAOI), which usually prompt surgical evaluation. Consequently, DR may be overlooked at the time of admission, even with modern critical care and emergency protocols (2,3). In contrast, diaphragmatic injuries resulting from penetrating trauma are typically diagnosed via diagnostic laparoscopy, as recommended by current guidelines (4).

Until three decades ago, most patients with blunt abdominal trauma, suspected solid organ injuries, or a significant number of penetrating abdominal injuries underwent laparotomy (5,6). However, the modern approach to blunt abdominal trauma has shifted from emergency surgery to non-operative management, which has also contributed to DRs being overlooked, as they are often identified during surgical procedures (7). Unfortunately, missing a diagnosis of DR in both penetrating and blunt injuries can lead to significant morbidity and mortality, with reported mortality rates nearing 30%, particularly in cases involving hernia incarceration (8).

As a result, trauma surgeons must exercise great caution when evaluating patients with thoraco-abdominal trauma and interpreting their radiological images. Even advanced imaging techniques, such as computed tomography (CT), may initially fail to detect a DR (9). It is crucial for surgeons to be familiar with this life-threatening and potentially subtle clinical condition to prevent mortality. This study was therefore conducted to compare the clinical presentations of penetrating and

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blunt diaphragmatic injuries and to provide insights on the appropriate management of these trauma patients.

MATERIAL and METHODS

A total of 51 patients, admitted to our emergency department with either blunt or penetrating thoraco-abdominal trauma, and diagnosed with DR either upon admission or during surgery between January 2008 and October 2023, were enrolled in this study. Patient data were recorded daily, and a retrospective analysis was conducted specifically for this research. Ethics approval was obtained from our hospital's ethics committee (23.11.2023-B.10.1.TKH.4.34.H.GP.0.01/447).

The study participants were divided into two groups: Patients with blunt trauma (PwBT) and patients with penetrating trauma (PwPT). Data collected included demographics, mechanism of injury (MOI), presence of AAOIs and extra-abdominal site injuries (EASI), types of surgical procedures, mortality rates and causes, injury severity scores (ISS), calculated revised trauma scores (cRTS), Glasgow coma scales (GCS), hemoglobin (Hb) and white blood cell (WBC) counts, systolic blood pressure (SBP) and pulse rates, presence of pneumothorax, hemothorax, or hemopneumothorax, and the need for thoracotomy or tube thoracostomy. Radiological findings were also evaluated, including the percentage of preoperative diagnoses made using CT, diaphragmatic defect sizes, mesh applications during surgery, length of stay (LoS) in the intensive care unit (ICU), total hospital stay (THS), and the need for erythrocyte suspension (ES) transfusions.

Statistical Analysis

Statistical analysis was performed using SPSS software version 28.0 (IBM Corp, Released 2021. IBM SPSS Statistics for Windows, Version 28.0, Armonk, NY: IBM Corp). The distribution of variables was first assessed using the Kolmogorov-Smirnov test. Independent quantitative data were analyzed using unpaired t-tests, Kruskal-Wallis tests, ANOVA, and Mann-Whitney U tests, while dependent qualitative data were analyzed using the McNemar test. For independent qualitative data, Chi-square and Fisher's exact tests were employed. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 51 patients diagnosed with DR due to either blunt or penetrating thoraco-abdominal trauma were included in the study. Of these, 21.6% developed DR as a result of blunt trauma. Among 990 emergency admissions for blunt thoraco-abdominal trauma, 11 patients (1.1%) were diagnosed with DR. In comparison, out of 108 surgically evaluated cases of thoraco-abdominal stab wounds, 40 patients (37.1%) were found to have DR. Majority of the patients were males (96.1%) (Table 1),

Table 1. Demographics, trauma related pathologies, characteristics and interventions, follow-up characteristics

	Trauma			
Variables	**PwBT (n= 11)**	**PwPT (n= 40)**	**Total (n= 51)**	**p**
Age (year)	24.0 (20.0-32.2)	26.0 (22.5-32.5)	26 (22-33)	0.491
Male (%)	10 (90.9%)	39 (97.5)	49 (96.1%)	0.904
CT evaluation at admission (%)	3 (42.9%)	19 (47.5%)	22 (46.8%)	0.551
Additional abdominal organ injury (n)				**<0.001**
0	2 (18.2%)	34 (85.0%)	36 (70.6%)	
1	5 (45.5%)	2 (5.0%)	7 (13.7%)	
2	3 (27.3%)	4 (10.0%)	7 (13.7%)	
3	1 (9.1%)	0 (0.0%)	1 (2.0%)	
Extraabdominal site injury (n)				**<0.001**
0	1 (9.1%)	24 (60.0%)	39 (76.5%)	
1	5 (45.5%)	16 (40.0%)	7 (13.7%)	
2	3 (27.3%)	0 (0.0%)	3 (5.9%)	
3	2 (18.2%)	0 (0.0%)	2 (3.9%)	
Tube thoracostomy (%)	9 (81.8%)	16 (40.0%)	25 (49.0%)	**0.034**
Defect size (cm)	8.0 (7.0-11.0)	2.0 (1.0-2.0)	2.0 (1.5-4.8)	**<0.001**
ICU stay (day)	3.0 (1.0-11.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	**<0.001**
Total hospital stay (day)	4.0 (1.5-14.0)	4.0 (3.0-7.0)	4.0 (3.0-7.5)	0.917
Surgery at admission or during follow-up (%)	10 (90.9%)	40 (100.0%)	50 (98.0%)	0.485
Mortality (%)	5 (45.5%)	1 (2.5%)	6 (11.8%)	**0.001**

Data are presented as median (IQR) or n (%).
PwBT: Patients with blunt trauma, PwPT: Patients with penetrating trauma, CT: Computed tomography, ICU: Intensive care unit.

Table 2. Mechanism of injury in blunt trauma patients	
In-vehicle traffic accident	6 (54.5%)
Motorcycle accident	2 (18.2%)
Crush injury	2 (18.2%)
Bicycle accident	1 (9.1%)

and mean age was 26 years (22-33). No statistical differences were observed between the groups regarding these factors (p> 0.05).

In terms of MOI, the penetrating trauma group (PwPT) consisted solely of stab wounds. On the other hand, PwBT was comprised of six patients (63.6%) injured in vehicle traffic accidents, 2 (18.2%) in motorcycle accidents (MA), 2 (18.2%) due to crush injuries, and 1 (9.1%) from a bicycle accident (Table 2). Overall, 22 patients (46.8%) underwent CT evaluation before surgery. In PwPT, CT scans were primarily used to rule out concomitant injuries rather than to diagnose DR, and no patients in this group received a DR diagnosis at admission based on CT. However, CT was diagnostic for DR in three patients (27.3%) in the PwBT group, while another patient's findings were suspicious for left diaphragm elevation (Figures 1-3). DR was ultimately diagnosed in seven patients (63.6%) during surgery, which was performed for other life-threatening thoracoabdominal injuries in this group.

The majority of DR cases involved the left side in both groups (81.8% in Group 1 and 82.5% in Group 2). EASIs were observed in 10 patients (90.9%) in the PwBT group, with 6 (54.5%) having pelvic and extremity fractures, 4 (36.4%) with thoracic trauma, 3 (27.3%) with spinal trauma, 3 (27.3%) with cranial trauma, and 1 (9.1%) with maxillofacial injury (Table 3). In PwPT, 40.0% of patients had EASIs, all of which were thoracic injuries. The average number of EASIs was significantly higher in PwBT (p< 0.05). AAOIs were observed in 15 patients (29.4%), with PwBT having significantly more AAOIs (p< 0.05) (Table 4).

Mean Hb at admission was 14.2 g/dL (12.7-15.2), with the lowest mean Hb value during follow-up being 12.1 g/dL (8.2-12.9) (Table 5). Hb levels at admission were similar between the groups (p> 0.05); however, the lowest Hb values in PwBT were significantly lower than those in PwPT (p< 0.05). Mean WBC count at admission was 12.700/µL (8.730-16.250), with significantly higher WBC counts in PwBT (p< 0.05). Mean pulse rate and SBP at admission were 90 bpm (82.0-100.0) and 102 mmHg (88.0-110.0), respectively. SBP was similar between the groups (p> 0.05), but pulse rates were significantly higher in PwBT (p< 0.05).

Mean GCS, cRTS and ISS values at admission were 15.0 (13.0-15.0), 7.55 (7.84-6.81), and 14.0 (8.0-23.5), respectively. PwBT had significantly lower GCS and cRTS values and significantly higher ISS values (p< 0.05). Pneumothorax, hemothorax, and hemopneumothorax were observed in 6 (54.5%), 2 (18.2%), and 1

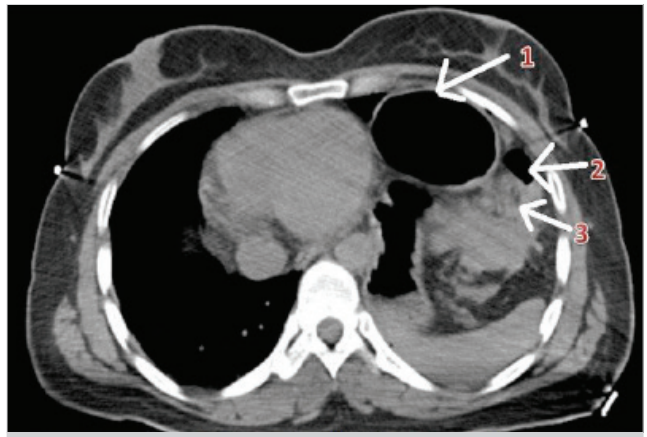

Figure 1. A 45-year-old female patient with left diaphragmatic stomach, colon and small bowel herniation following an in-vehicle traffic accident.

1: Stomach, 2: Colon, 3: Small bowel.

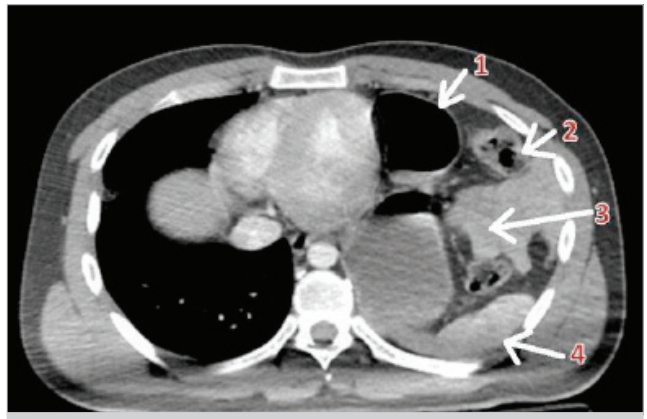

Figure 2. A 24-year-old male patient with left diaphragmatic stomach, colon, small boweland spleen herniation following an in-vehicle traffic accident.

1: Stomach, 2: Colon, 3: Small bowel, 4: Spleen.

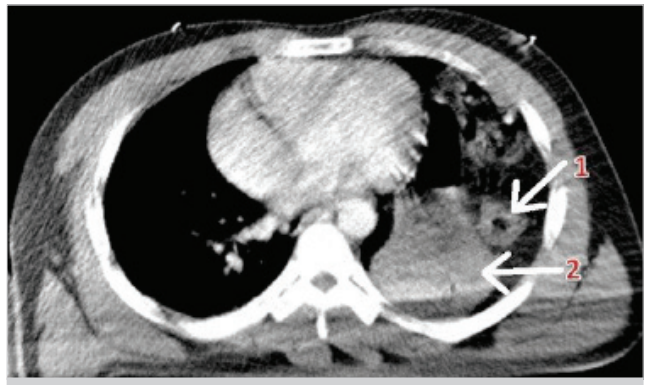

Figure 3. A 22-year-old male patient with left diaphragmatic stomach and colon herniation following an in-vehicle traffic accident.

1: Colon, 2: Stomach.

Table 3. Extra-abdominal site ınjury in blunt trauma patients	
	n
Pelvic and extremity fractures	6 (54.5%)
Thorax trauma	4 (36.4%)
Spinal trauma	3 (27.3%)
Cranial trauma	3 (27.3%)
Maxillofacial injury	1 (9.1%)

(9.1%) patients, respectively, in PwBT. In contrast, PwPT had 10 cases (25%) of hemopneumothorax and six cases (15%) of pneumothorax.

In the PwBT group, laparotomy was the most common surgical approach (72.7%), followed by thoracotomy (18.2%) and a combined approach (9.1%). In PwPT, 31 patients (77.5%) underwent laparoscopy, while nine patients (22.5%) required laparotomy. One PwPT patient had a missed diagnosis and was operated on six months after the initial injury. The average diaphragmatic defect size was 2.0 cm (1.5-4.8 cm), with significantly larger defects observed in PwBT ($p< 0.05$). Mesh repair was performed in two patients (3.8%), one from each group. All other defects were repaired primarily with non-absorbable sutures (98.1%). Tube thoracostomy was ultimately performed in 25 patients (49.0%), with PwBT having a significantly higher requirement for tube thoracostomy ($p< 0.05$).

Additional abdominal procedures (AAPs) were performed in seven patients (63.6%) in PwBT, including one case (9.1%) each of liver packing, hepatic vein ligation, right hemicolectomy, left hemicolectomy, small bowel resection and anastomosis, bladder repair, and orchiectomy. Similarly, seven AAPs were performed in PwPT, including two primary colon repairs (5.0%), two splenectomies (5.0%), one partial small bowel resection (2.5%), one primary small bowel repair (2.5%), and one distal pancreatectomy (2.5%).

Median ES transfusion requirement was 0.0 units (0.0-4.0), with significantly higher ES transfusion needs in PwBT ($p< 0.05$). The average THS and LoS in the ICU were 4.0 days (3.0-7.5) and 0.0 days (0.0-1.0), respectively, with PwBT showing a significantly longer ICU stay ($p< 0.05$). The overall mortality rate was 11.8%, with PwBT having significantly higher mortality ($p< 0.05$). Of the deaths, 83.3% were attributed to hemodynamic instability while the remaining 16.7% were due to severe head trauma.

Table 4. Additional abdominal organ injury			
	PwBT (n)	**PwPT (n)**	**Total (n)**
Liver	4 (18.2%)	1 (4.5%)	5 (22.7%)
Kidney	4 (18.2%)	0	4 (18.2%)
Small bowel	2 (9.1%)	2 (9.1%)	4 (18.2%)
Colon	2 (9.1%)	2 (9.1%)	4 (18.2%)
Spleen	0	4 (18.2%)	4 (18.2%)
Bladder	1 (4.5%)	0	1 (4.5%)
PwBT: Patients with blunt trauma, PwPT: Patients with penetrating trauma.			

Table 5. Clinical and laboratory findings along with trauma related scores				
	Trauma			
Variables	**PwBT (n= 11)**	**PwPT (n= 40)**	**Total (n= 51)**	**p**
Hemoglobin at admission (g/dL)	13.5 (10.7-14.8)	14.2 (12.9-15.4)	14.2 (12.7-15.2)	0.287
Minimum hemoglobin during follow-up (g/dL)	8.5 (7.1-10.2)	12.4 (9.5-13.0)	12.1 (8.2-12.9)	**0.002**
Leukocyte (10^3/µl) at admission	21300 (12850-23730)	11300 (8567-14050)	12700 (8730-16250)	**0.005**
Pulse at admission	110.0 (97.5-135.0)	89.0 (80.0-95.2)	90.0 (82.0-100.0)	**<0.001**
Systolic blood pressure (mmHg) at admission	110.0 (80.0-120.0)	101.0 (91.0-110.0)	102.0 (88.0-110.0)	0.628
GCS at admission	11.0 (7.0-15.0)	15.0 (14.0-15.0)	15.0 (13.0-15.0)	**0.014**
cRTS at admission	5.96 (4.61-7.47)	7.84 (7.18-7.84)	7.55 (7.84-6.81)	**<0.001**
ISS at admission	41.0 (31.5-45.5)	9.0 (6.0-15.2)	14.0 (8.0 to 23.5)	**<0.001**
ES transfusion (unit)	4.0 (2.0-8.0)	0.0 (0.0-2.0)	0.0 (0.0-4.0)	**<0.001**
Data are presented as median (IQR) or n (%) PwBT: Patients with blunt trauma, PwPT: Patients with penetrating trauma, GCS: Glasgow coma scale, cRTS: Calculated revised trauma score, ISS: Injury severity score, ES: Erythrocyte suspension.				

DISCUSSION

DR is a serious condition associated with significant morbidity and mortality if left untreated. Although many cases require only a straightforward defect closure using either non-absorbable separate or continuous sutures, diagnosing DR, especially following blunt trauma, poses a significant challenge for trauma surgeons. Not only can the symptoms be vague initially, but they are often overshadowed by more severe injuries. These vague symptoms can easily be masked by life-threatening conditions in blunt trauma patients, such as hemodynamically altering solid organ bleeding, signs of peritoneal irritation, or severe consciousness impairment due to head trauma. Additionally, even in the absence of peritoneal irritation, DR can be overlooked in PwPT. Given these challenges, trauma surgeons must exercise great caution and maintain a high degree of vigilance to avoid missing a DR diagnosis and its associated symptoms when evaluating patients with thoraco-abdominal trauma.

Our study group predominantly consisted of young male adults, a demographic pattern that aligns with current scientific evidence (10). The prevalence of DR observed in our study is also consistent with existing literature although some studies report higher rates of DR following blunt trauma (11,12). We believe that the inconsistency in these reports can be attributed to varying levels of clinical vigilance among centers and the time period during which the respective studies were conducted. With the advent of newer imaging modalities capable of better detecting occult DRs, it is possible that some centers may have previously overlooked a significant percentage of cases.

It is also plausible that we may have underestimated the incidence of DR in our study. Our actual numbers could be higher if we had applied the same level of clinical suspicion and vigilance during the earlier stages of data collection. On the other hand, the strict adherence to a laparoscopic evaluation protocol for penetrating injuries in our center resulted in favorable diagnostic outcomes. The literature indicates that the rate of missed diagnoses is less than 5% when patients undergo laparoscopic evaluation following penetrating thoracoabdominal trauma (13). Moreover, regarding the ratio of blunt to penetrating DR, geographical differences play a role in outcomes. Developing countries report up to three times more penetrating incidents compared to blunt trauma, which is consistent with our findings (14).

In our study, traffic accidents were the leading cause of blunt trauma-related DR, while stab wounds were the primary cause of penetrating trauma-related DR. These findings are consistent with the majority of contemporary studies (13,15). However, we believe that a more detailed discussion of the underlying mechanisms is warranted.

Blunt trauma to the thoracoabdominal region can cause DR through several mechanisms: shearing forces on a stretched diaphragm, muscular avulsion, burst-like rupture due to increased intra-abdominal pressure exceeding the diaphragm's capacity, or devitalization of a portion of the diaphragm, leading to delayed rupture (16). On the right side, the liver often absorbs some of the impact, making right-sided DR less common. When it does occur, it is usually associated with more severe trauma (17). For penetrating injuries, most cases result from violent assaults. Since the majority of assailants are right-handed, these injuries tend to affect the left side of the diaphragm (18). The distribution of DR based on location in both trauma groups in our study aligns with the patterns reported in the literature.

CT is the preferred imaging modality for evaluating patients with blunt thoracoabdominal trauma, provided they are hemodynamically stable (4,19). Given the severity of injuries that these patients may present with, it is unsurprising that nearly a quarter of our study group required emergency surgery without prior CT evaluation. The literature reports a detection rate of up to 70% for DR following blunt trauma using CT (4). However, our detection rates were significantly lower.

This discrepancy can be attributed to two primary factors. First, during the study period, improvements were made to our imaging equipment. Second, most patients were admitted to the emergency department during night shifts, when it was particularly challenging to obtain the expertise of a radiology specialist. While any physician can diagnose a large herniation into the thorax, the difficulty lies in recognizing more subtle signs, such as diaphragm discontinuity, the dangling diaphragm sign, diaphragm thickening, or the collar sign (20). A detailed review of each radiological sign is beyond the scope of this study.

The majority of PwBT presented with multiple accompanying injuries, either as EASI or AAOI. A significant percentage had associated thoracic trauma, and in cases of penetrating DR, thoracic injuries were the sole EASI. The literature similarly indicates that patients with DR following blunt trauma are often multitrauma patients, with the diagnosis of DR frequently made incidentally during surgery for another life-threatening injury (9). Stab wounds, in contrast, can easily damage both solid organs, such as the lungs and spleen, as well as the bowels, especially when multiple stab wounds are involved (21). Blunt trauma patients, on the other hand, frequently present with extremity fractures, thoracic injuries, and severe cranial trauma, all of which contribute to increased mortality and morbidity (22,23). In our study, AAOIs and EASIs were present in up to 90% of PwBT, highlighting the severity of the trauma. This high rate of associated injuries explains the increased complication rates, prolonged hospital stays, and the need for additional surgical interventions, such as thoracostomy tube placement.

Elevated WBC count at admission and the decrease in Hb levels in PwBT over time are expected findings, given the trauma setting and associated injuries. The average ES transfusion requirement in this group correlates with the severity of their injuries. GCS, cRTS and ISS findings further underscore the severity of trauma, as a significant portion of these patients presented to the emergency department with varying degrees of consciousness impairment. In the context of blunt DR, these findings align with existing literature (21). Stab wounds, on the other hand, typically result in less severe clinical outcomes compared to blunt trauma in the presence of a DR (24). Therefore, the observed statistical differences in these variables are both expected and consistent with the literature.

The literature suggests that the majority of DR cases following blunt thoracoabdominal trauma are treated via laparotomy, often followed by thoracotomy or a combined approach, as observed in our study (25). Some authors report high diagnostic and therapeutic success rates with laparoscopy (12). Given that hemodynamic instability typically necessitates emergent laparotomy, we anticipate that future studies will focus more on the role of laparoscopy in the evaluation of DR in less severe blunt thoracoabdominal trauma cases. In PwPT who are hemodynamically stable, diagnostic laparoscopy should be performed within 24 hours, regardless of the injury site. Contemporary evidence indicates significant rates of life-threatening DR even on the right side, making timely diagnosis critical (26,27).

Average defect sizes observed in our study are consistent with those reported in the literature. DR defect sizes following blunt trauma typically range from 5 cm to 15 cm while defects following penetrating injuries are generally smaller, often less than 5 cm (15,28). Currently, there is no strong evidence supporting or opposing the use of mesh during defect closure (12). In our study, two defect repairs were performed using polypropylene mesh, a decision based on the surgeon's preference and limited scientific evidence. We believe that future studies will offer further insight into the role of mesh in DR repair.

Mortality rates for all traumatic DRs range between 25% and 45%, with blunt trauma-associated DRs linked to higher mortality rates due to the severity of associated organ injuries (4,23). The mortality rate observed in PwBT in our study aligns with this literature while the mortality rate in PwPT was lower than what has been previously reported. We attribute this discrepancy to the inclusion of gunshot wounds in other studies, which we recognize as a major limitation of our study.

In addition to the previously mentioned limitation, this study has two other significant limitations. First, it has a retrospective design. Although much of the available trauma evidence in the literature comes from retrospective studies, certain issues-such as the need for mesh during diaphragmatic defect closure or the role of laparoscopy in evaluating the diaphragm after blunt trauma when radiological findings are inconclusive-may benefit from a prospective approach. Second, the size of our study group is modest. However, given the rarity of this clinical condition, any objective data contributed to the scientific literature are invaluable. We are pleased to have been able to add meaningful findings to the existing body of knowledge.

CONCLUSION

Traumatic DRs following blunt thoracoabdominal trauma are dangerous and insidious conditions, with high mortality and morbidity rates if left untreated. Even a slight clinical or radiological suspicion should prompt surgical evaluation. Future research should focus on factors contributing to increased mortality, improving preoperative diagnostic methods, the necessity of mesh during defect closure, and the role of early laparoscopic or thoracoscopic evaluation in hemodynamically stable patients with blunt DR.

Penetrating DRs, while generally less severe, are associated with excellent outcomes when managed appropriately. However, the optimal management strategies, including the use of thoracoscopy and the approach to right-sided penetrating injuries, remain areas of ongoing debate.

Ethics Committee Approval: This study was approved by İstanbul Health Sciences University, Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Decision no: B.10.1.TKH.4.34.H.GP.0.01/447 Date: 23.11.2023).

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

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Künt ve penetran diyafragma rüptürlerinin karşılaştırmalı sonuçları: Tek bir travma merkezi çalışması

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ÖZET

Giriş ve Amaç: Diyafram yaralanması torakoabdominal travmalarda sessiz seyredebilen ve tedavi edilmezse yüksek morbidite ve mortalite ile seyreden bir klinik tablodur. Özellikle künt travmayı takiben eşlik eden ek yaralanmalar tarafından semptomları baskılanabilir. Modern görüntüleme yöntemleri mevcut diyafram yaralanmasını atlayabilmektedirler. Bu nedenle asıl zorluk bu klinik tabloyu tedaviden ziyade tanı aşamasında oluşmaktadır. Bu klinik tabloya daha fazla açıklık getirebilmek amacı ile bu hususstaki tecrübemizi paylaştık.

Gereç ve Yöntemler: Ocak 2008 ve Ekim 2023 tarihleri arasında diyafram yaralanması tanısı almış toplam 51 hasta çalışmaya dahil edildi. Künt ve penetran yaralanma olmak üzere iki grup oluşturuldu. Hastalar demografik veriler, klinik ve laboratuvar bulguları, travma ilişkili skorlar, yaralanma mekanizmaları, görüntüleme sonuçları, eşlik eden yaralanmalar, cerrahi yaklaşımlar ve mortalite oranları yönünden değerlendirildi.

Bulgular: Ortalama yaş 26 (22-33) idi. Hastaların %21,6'sı künt travma grubundaydı. Ekstraabdominal yaralanmalar ve ek abdominal organ yaralanmaları birinci grupta istatistiksel olarak anlamlı yüksek bulundu ($p< 0,05$). Birinci grupta ortalama Glasgow koma skalası ve hesaplanmış revize travma skorları anlamlı düşük bulunurken ortalama travma şiddet skoru anlamlı yüksek bulundu ($p< 0,05$). Ciddi toraks travması birinci gruptaki hastaların %81,8'inde, ikinci gruptaki hastaların %40'ında mevcut idi. Hastaların %11,8'inde mortalite gözlendi ve en önemli ölüm sebebi hemodinamik instabilite olarak bulundu.

Sonuç: Bir travma cerrahı özellikle künt torakoabdominal travmalı bir hastayı değerlendirirken diyafram yaralanmasını atlamamak için dikkatli olmalıdır. Zira bu durum travma hastalarında önemli derecede artmış mortalite ve morbidite oranlarının hem sonucu hem de sebebidir. Gelecek çalışmalar ameliyat öncesi tanısal doğruluğun arttırılması, defekt kapatılmasında yama kullanılması, özellikle sağ taraflı penetran yaralanmalarda optimal yaklaşımın oluşturulması gibi bu klinik tabloların çeşitli yönlerini araştırmalıdır.

Anahtar Kelimeler: Torakoabdominal travma, diyafragma rüptürü, intratorasik visseral

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ORIGINAL ARTICLE
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The effect of cholecystectomy for symptomatic gall stone disease on hepatic steatosis using transabdominal ultrasonography: An observational prospective study

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ABSTRACT

Objective: Hepatic steatosis and gallstones are common in the general population, with risk factors being multifactorial. Experimental studies have shown that cholecystectomy increases hepatic steatosis and leads to non-alcoholic fatty liver disease (NAFLD). In order to evaluate this, the current study was carried out in the department of general surgery at a medical school, in the north of India.

Material and Methods: One hundred and three patients awaiting cholecystectomy were selected after written informed consent. Their baseline characteristics were captured preoperatively and thereafter followed at 3rd month with liver function test (LFT), lipid profile and ultrasound (USG) abdomen.

Results: Average age of the patients enrolled was 41.62 ± 13.62 years and mean body mass index (BMI) was 25.96 ± 1.73 kg/m^2. Total bilirubin (0.56 vs 0.76, p< 0.0001) and direct bilirubin (0.15 vs 0.27, p< 0.0001) decreased significantly post cholecystectomy as compared to preoperative values. Levels of serum glutamic-oxaloacetic transaminase (SGOT) (49.14 vs 34.98 IU/dL), serum glutamic-pyruvic transaminase (SGPT) (50.85 vs 35.46 IU/dL) and alkaline phosphatase (ALP) (101.16 vs 85.97 IU/dL) increased significantly post-surgery. Cholesterol values (146.28 vs 168.77 mg/dL), triglycerides (TGs) (119 vs 133.56 mg/dL), low density lipoprotein (LDL) (93.32 vs 113.05 mg/dL) and very low density lipoprotein (VLDL) (18.68 vs 27.45 mg/dL) decreased significantly while high density lipoprotein (HDL) (48.96 vs 42.42 mg/dL) increased significantly at three month follow-up. Prevalence of fatty liver increased post operatively with a rise in Grade 1 steatosis (75%). Severity of fatty liver increased with (8.73%) Grade 3 steatosis on USG post-surgery. Hence, new patients with formerly normal USG reports developed fatty liver and those with preexisting liver steatosis seemed to worsen.

Conclusion: The study concluded that the prevalence of fatty liver increased post-cholecystectomy. Lipid profile parameters improved favorably with a decline in total cholesterol, TG, LDL and VLDL versus increase in HDL. LFT parameters also changed significantly.

Keywords: Cholecystectomy, hepatic steatosis, liver function test, lipid profile, ultrasound abdomen

INTRODUCTION

Cholelithiasis is one of the most common diseases of the gastrointestinal tract, and patients often present with symptoms of biliary colic or sometimes with acute abdomen. Subsequently, cholecystectomy (laparoscopic) has become one of the most commonly performed surgical procedures worldwide (1). However, metabolic consequences following elective cholecystectomy have not been properly studied. Risk factors such as age, obesity and hyperlipidaemia are associated with cholelithiasis subsequently giving a solid argument for considering cholelithiasis as a part of metabolic syndrome. Metabolic syndrome is a multisystem disorder with diabetes, hypertension and central obesity as major components with insulin resistance suggested to be at the centre of it all (2). The gallbladder plays a major role in the regulation of bile storage and its enterohepatic circulation. With cholecystectomy, human body loses reservoir function of the gallbladder and hence, the bile gets continuously secreted into the gastrointestinal tract with subsequent shortening of enterohepatic circulation on bile acid pool ultimately exposing the liver to a higher flux of bile acids. Bile acids play a notable role in dietary lipid and cholesterol homeostasis. The gallbladder mucosa is metabolically active and is responsible for secreting and absorbing compounds to and from the bile, which are intricately associated with lipid metabolism (3). Following cholecystectomy, the body has to adapt to the altered milieu of lipid metabolism. Removal of the gallbladder eliminates the formation of cholesterol solid-plate crystals, which form in

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the gallbladder and are not able to be absorbed by the intestine. Therefore, cholecystectomy can increase the proportion of cholesterol that is reabsorbed and delivered to the liver, facilitating an increase in hepatic triglycerides concentration (4,5). Following the removal of the gallbladder, bile acid (BA)s are continuously secreted into the small intestine, and the BAs pool circulates faster, inducing increased cycling of the BA pool and thus expose the liver to a greater flux of BAs and the occurrence of metabolic derangements (6). Through this study, it was aimed to gain further insight into the metabolic changes in the body post cholecystectomy and to establish it as a risk factor for developing hepatic steatosis.

In order to find out the effect after cholecystectomy on hepatic steatosis, transabdominal ultrasound was done at three-month follow up along lipid profile and liver function test (LFT).

MATERIAL and METHODS

Study design and sample size: The present study was conducted as a prospective observational study among eligible patients undergoing cholecystectomy for chronic calculous cholecystitis from February 2023 to January 2024 in the department of general surgery at a medical school in the north of India. Written informed consent was obtained from all patients before inclusion into the study. The procedure was conducted in accordance with the Helsinki Declaration-2013. A total of 103 patients having symptomatic gallstone disease requiring cholecystectomy were enrolled in the study using convenience sampling method based on the patient load.

Inclusion and exclusion criteria: After getting approval from the Institutional Ethics Committee and written informed consent of the participants, a prospective observational study was conducted. Ultrasonography was the mainstay for preoperative diagnosis of gall stone disease and was performed by two experienced radiologists of the institute both in the preoperative period and postoperative follow-up. Patients aged 18-80 years having symptomatic gallbladder disease scheduled to undergo cholecystectomy were included in the study while patients who underwent cholecystectomy for cancer, with previous history of alcohol consumption, had pre-existing liver disease, had ischaemic cardiac or cerebrovascular disease, were on drugs causing steatosis (oestrogens, amiodarone, steroids, tamoxifen or lipid lowering agents), were affected by chronic viral hepatitis (HBsAg or HCV), were pregnant, had diabetes mellitus, and body mass index (BMI)> 30 kg/m^2 were excluded from the study.

Methods: The study involved screening of the patients presenting at the surgery outpatient department with symptoms of gallbladder stone disease. Initial assessment relied on detailed history-taking and physical examination to establish a provisional diagnosis. Confirmation of gall stone disease was subsequently achieved through transabdominal ultrasonography. Upon confirming cholelithiasis, patients willing to participate underwent a series of routine and specific investigations including preoperative lipid profile. Following completion of investigations and confirmation of diagnosis, patients underwent preanesthetic check-up to assess their fitness for surgery subsequent to which patients were scheduled for either laparoscopic or open cholecystectomy.

Preoperative preparation included nil per oral for six hours before surgery and administration of appropriate preanesthetic medications. During surgery, the extracted gallbladder was sent for histopathological examination. The patients were discharged in stable condition a day after surgery and were advised for routine follow-up in the outpatient department. At three months post-cholecystectomy, a visit was scheduled to evaluate hepatic steatosis using transabdominal ultrasound of the whole abdomen. Additionally, liver function tests and lipid profile were repeated at this visit. Findings from biochemical investigations and ultrasound scans were systematically recorded, analysed, and documented as per protocol.

RESULTS

Statistical Analysis

The data was compiled and analyzed using MS excel (R) office 365, GraphPad prism 8.4.2 and SPSS version 25. descriptive statistics were presented in the form of proportions/percentages for categorical variables, mean and standard deviation for continuous data variables. Fisher exact test/Chi-square test was used for the comparison of proportions (categorical variables). Continuous variables were analyzed using the Mann-Whitney U test/student's t test (independent group/unpaired data) and Wilcoxon sign rank test/paired t test (for paired data) based on the normality of the data. P value of <0.05 was considered significant.

A total of 103 patients with symptomatic gallstone disease were selected for the study after due screening and written informed consent. Demographic attributes and laboratory parameters of these participants along with abdominal ultrasound were captured in the preoperative period. All patients were followed up at three-month post-surgery with LFT, lipid profile and abdominal ultrasound. Demographic profile in terms of age and sex distribution, BMI and comorbidity is compiled in Table 1. Mean age of the patients undergoing cholecystectomy in our study was 41.62 ± 13.62 years, ranging from 18 to 80 years, with a median age of 40 years (IQR= 31.50-50 years). Most patients were below the age of 40 years (46.60%), followed by those aged 40-60 years (41.75%). Only 11% of the patients were aged 60 years and above. There was a significant female preponderance observed, comprising 88.35% of the study population. Mean BMI was 25.96 ± 1.73 kg/m^2,

Table 1. Demographic profile in terms of age, sex, BMI, comorbidity distribution

		Number	Percentage/Value
Age category	Below 40 years	48	46.60%
	40-60 years	43	41.75%
	More than 60 years	12	11.65%
Sex	Female	91	88.35%
	Male	12	11.65%
Body mass index (BMI)	Mean ± SD Range (Min-Max) Median (IQR)	-	25.96 ± 1.73 kg/m^2 21.80-29.60 kg/m^2 26.10 (24.80-27.30) kg/m^2
	<25 kg/m^2	24	23.3%
	25-30 kg/m^2	79	76.69 %
Comorbidity	Hypertension	16	15.5%
	Hyperthyroidism	20	19.41%
	Diabetes and CAD	Excluded as per exclusion criteria	
Indication	Chronic calculus cholecystitis	103	100%

ranging from 21.80 to 29.60 kg/m^2, with a median BMI of 26.10 kg/m^2. Patients with diabetes mellitus and coronary artery disease were excluded from the study. All patients who underwent cholecystectomy had chronic calculus cholecystitis. These patients had a normal hematological profile in the preoperative period (Table 2).

A comparison of LFT parameters, lipid profile and ultrasound (USG) grading of hepatic steatosis at three-month follow-up and preoperative levels revealed several significant changes and are shown in Table 3.

Total bilirubin levels (0.56 vs 0.76, p< 0.0001) and direct bilirubin levels (0.15 vs 0.27, p< 0.0001) were seen to decrease significantly in post cholecystectomy patients. Levels of serum glutamic-oxaloacetic transaminase (SGOT) (49.14 vs 34.98 IU/dL), SGPT (50.85 vs 35.46 IU/dL) and alkaline phosphatase (ALP) (101.16 vs 85.97 IU/dL) increased significantly in cholecystectomy patients. Total protein (7.71 vs 7.44, p= 0.0022) and S albumin levels (4.17 vs 3.89 mg/dL, p< 0.0001) level increased to statistically significant values (Figure 1).

In lipid profile test, it was seen that the levels of cholesterol (146.28 vs 168.77 mg/dL), triglycerides (119 vs 133.56 mg/dL), low density lipoprotein (LDL) (93.32 vs 113.05 mg/dL) and very low density lipoprotein (VLDL) (18.68 vs 27.45 mg/dL) were seen to decrease significantly while the levels of high density lipoprotein (HDL) (48.96 vs 42.42 mg/dL) were seen to increase significantly at the three-month follow-up suggesting a favorable impact on lipid profile after cholecystectomy (Figure 2).

Table 2. Summary of hematological parameters

	Parameters	Values
Hemoglobin (g/dL)	Mean ± SD	11.24 ± 0.84
	Range (Min-Max)	9.80-13.50
	Median (IQR)	11 (10.70-11.70)
TLC (cells/microL)	Mean ± SD	6.96 ± 1.40
	Range (Min-Max)	4.20-10.11
	Median (IQR)	6.90 (5.95-8.15)
Platelet count (cells/microL)	Mean ± SD	2.32 ± 0.41
	Range (Min-Max)	1.55-3.21
	Median (IQR)	2.22 (1.97-2.64)
INR	Mean ± SD	1.12 ± 0.01
	Range (Min-Max)	1.12-1.14
	Median (IQR)	1.12 (1.12-1.12)

Table 3. Liver function test, lipid profile parameters and usg grading for steatosis-pre op and post-op trend at three month

LFT	**Pre-Op**	**Post-Op**	**p**
Total Bilirubin (mg/dL)			
Mean ± SD	0.76 ± 0.26	0.56 ± 0.18	<0.0001
Median (IQR)	0.80 (0.60-0.90)	0.50 (0.40-0.65)	
Direct Bilirubin (mg/dL)			
Mean ± SD	0.27 ± 0.15	0.15 ± 0.06	<0.0001
Median (IQR)	0.21 (0.20-0.40)	0.15 (0.10-0.22)	
SGOT (U/L)			
Mean ± SD	34.98 ± 11.27	49.14 ± 10.95	<0.0001
Median (IQR)	36 (36-41)	50 (31-66)	
SGPT (U/L)			
Mean ± SD	35.46 ± 13.69	50.85 ± 12.37	<0.0001
Median (IQR)	34 (24-44)	50 (31.50-59)	
ALP (U/L)			
Mean ± SD	85.97 ± 22.44	101.16 ± 28.99	<0.0001
Median (IQR)	82 (68-98)	100 (77-108)	
Total Protein (g/dL)			
Mean ± SD	7.44 ± 0.74	7.71 ± 0.48	0.0022
Median (IQR)	7.60 (7-8)	7.80 (7.45-8)	
Albumin (g/dL)			
Mean ± SD	3.89 ± 0.47	4.17 ± 0.35	<0.0001
Median (IQR)	4 (3.80-4.10)	4.30 (4.10-4.40)	
Lipid Profile	**Pre-Op**	**Post-Op**	**p**
Cholesterol (mg/dL)			
Mean ± SD	168.77 ± 37.29	146.28 ± 21.94	<0.0001
Median (IQR)	169 (149-188.50)	150 (138.50-186.50)	
Triglycerides (mg/dL)			
Mean ± SD	133.56 ± 55.11	119.21 ± 50.71	0.0532
Median (IQR)	132 (96-155)	120 (114.50-127)	
HDL (mg/dL)			
Mean ± SD	42.42 ± 9.62	48.96 ± 9.05	<0.0001
Median (IQR)	42 (37-48)	50 (35-56)	
LDL (mg/dL)			
Mean ± SD	113.05 ± 34.37	93.32 ± 34.92	0.0001
Median (IQR)	112 (92-136)	93 (81-113)	
VLDL (mg/dL)			
Mean ± SD	27.45 ± 11.05	18.68 ± 10.40	<0.0001
Median (IQR)	28 (20-30)	19 (9-30.50)	
USG Findings	**Pre-Op**	**Post-Op**	**p**
Grade 1	33 (32.03%)	50 (48.54%)	<0.0001
Grade 2	10 (9.70%)	18 (48.54%)	
Grade 3	0	9 (8.73%)	
Normal	60 (58.25%)	26 (25.24%)	

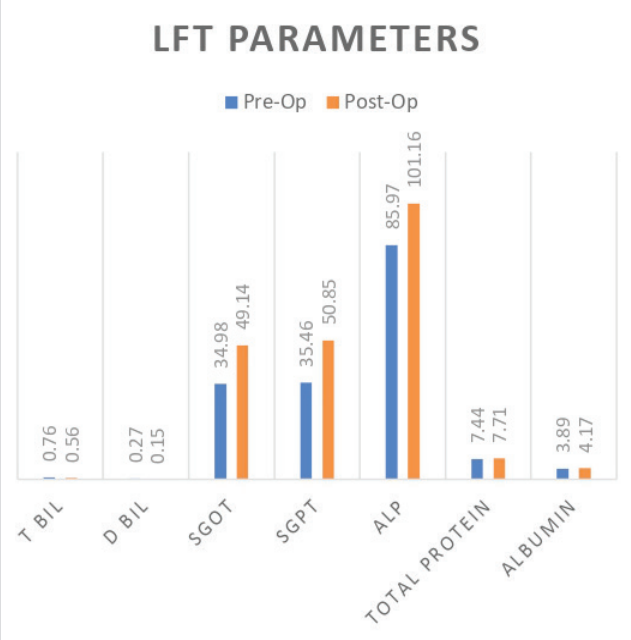

Figure 1. Liver function test parameteres. Pre op and post op trend.

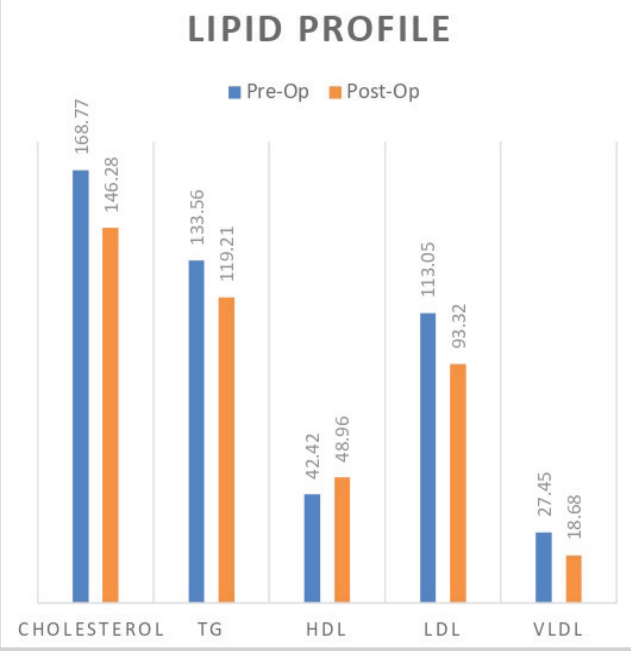

Figure 2. Lipid profile parameters.

The effect on liver steatosis post cholecystectomy was assessed using abdominal ultrasound, and it was found that the proportion of patients with Grade 1 fatty liver increased from 40% to 75%. Severity of fatty liver was also seen to increase, and about 8.73% patients developed grade three fatty liver at follow up, which suggests that patients with preoperative normal liver on abdominal ultrasound developed fatty liver and those with existing fatty liver seem to have worsening of liver steatosis.

DISCUSSION

Cholecystectomy has been shown in various studies to significantly decrease blood lipid levels in patients during subsequent follow-ups (4,5). Theoretically, this procedure leads to favourable impact on lipid profiles. These changes are attributed to enhancements in the secretion of phospholipids and bile acids into bile duct following cholecystectomy. Consequently, there is an increased frequency of bile acid circulation in the enterohepatic system, leading to greater excretion of lipids and thereby effectively reducing the total pool of bile acids. These physiological alterations contribute to the observed improvements in lipid metabolism and profiles post-cholecystectomy.

Multiple mechanisms have been postulated for the association between cholecystectomy and non-alcoholic fatty liver disease (NAFLD). It has been postulated that the basic underlying pathology is the increased responsibility of the liver to produce bile acids that help in digestion in the absence of the gallbladder storage. Wenzhu Yue et al. postulated that (6):

1. Removal of gallbladder eliminates formation of cholesterol solid-plate crystals which is not absorbed by intestine. Therefore, cholecystectomy can increase proportion of cholesterol reabsorbed and delivered to liver, facilitating an increase in hepatic triglycerides concentration.
2. Following cholecystectomy, bile acids are continuously secreted into duodenum, and BAs pool circulates faster, thus exposing liver to greater flux of BAs and occurrence of steatosis.
3. Cholecystectomy also removes the protective metabolic activity of gallbladder mucosa, which secrets fibroblast growth factor-19 that has a role in negative feedback regulation of BA synthesis and can inhibit hepatic fatty acid synthesis.

They showed that cholecystectomy was associated with a higher prevalence of NAFLD compared with gallstones among both centrally obese and non-centrally-obese subjects.

Profile of Patients Undergoing Laparoscopic Cholecystectomy

Aydın et al. reported a mean age of 49 ± 13 years in a similar study, with 75% of the patients being female, aligning closely with our observations. Nine patients (11%) in our study had diabetes and 14 (17%) were hypertensive, indicating comorbidities commonly associated with cholecystectomy candidates (7). Comparison with other studies reveals consistent findings.

Osman et al. noted a mean age of 46.5 ± 13.3 years among their cholecystectomy patients, slightly higher than our study. Their distribution showed 14.5% of patients being aged 30 years or younger, 43.6% being aged 31-50 years, and 41.8% being aged

over 50 years, reflecting a broader age range compared to our findings (8).

Ahi et al. both found a female predominance in their study populations, similar to ours. Gill et al. (2017) reported a female to male ratio of 1.7:1, while Ahi et al. highlighted that 52 out of 60 patients were female. These ratios underscore the consistent observation of gallbladder diseases being more prevalent in females (9).

Menezes et al. and Naila Ikram et al. also documented female predominance in their respective studies, reinforcing the demographic pattern observed in our study. Menezes et al. reported a mean age of 44.3 ± 14.4 years, with a majority falling within the 21-30 years age group (10,11). Naila Ikram et al. noted that 60% of their patients were female, with the highest percentage (31%) aged 31-40 years (11).

Investigational Parameters Trend

A comparison of LFT parameters at three-month follow-up and preoperative levels revealed several significant changes. Total bilirubin levels decreased from 0.76 to 0.56 mg/dL ($p< 0.0001$), and direct bilirubin levels decreased from 0.27 to 0.15 mg/dL ($p< 0.0001$) postoperatively. Conversely, levels of SGOT increased from 34.98 to 49.14 IU/dL, SGPT from 35.46 to 50.85 IU/dL, and ALP from 85.97 to 101.16 IU/dL, all showing significant increases. Total protein levels increased from 7.44 to 7.71 g/dL ($p= 0.0022$), and serum albumin levels increased from 3.89 to 4.17 mg/dL ($p< 0.0001$), both statistically significant changes.

Assessment of lipid profile parameters demonstrated significant improvements at the three-month follow-up post-cholecystectomy. Cholesterol levels decreased from 168.77 to 146.28 mg/dL, triglycerides from 133.56 to 119 mg/dL, LDL from 113.05 to 93.32 mg/dL, and VLDL from 27.45 to 18.68 mg/dL, all showing statistically significant decreases. HDL levels, on the other hand, increased from 42.42 to 48.96 mg/dL ($p< 0.0001$), and comparison with other studies supports these findings.

Menezes et al. observed significant reductions in total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides post-cholecystectomy, with a significant increase in HDL cholesterol levels (10). Similarly, Naila Ikram et al. reported statistically significant decreases in total cholesterol, LDL cholesterol, and triglycerides, along with a significant increase in HDL cholesterol post-surgery (11).

Contrary results were noted by Yue et al. who reported decreased bilirubin levels but elevated enzymes and Hajong et al. who found higher ALP levels but lower total cholesterol and LDL levels compared to our study (12,13). Osman et al. highlighted mixed changes in lipid profiles post-cholecystectomy, including varying trends in LDL and triglyceride levels over different postoperative periods (8).

Aydın et al. and Ahi et al. similarly documented significant reductions in total cholesterol and LDL cholesterol following cholecystectomy, with no significant changes in other liver enzymes or fasting glucose levels (7,9).

Radiological Parameters

Following cholecystectomy, there was a notable increase in the proportion of patients developing fatty liver disease during the postoperative period. The incidence of Grade 1 fatty liver increased from 40% to 75%, indicating both new occurrences and worsening severity among existing cases. Specifically, 8.73% of the patients were found to have Grade 3 fatty liver on ultrasound follow-up, highlighting a significant progression in hepatic steatosis.

Several studies corroborate these findings. De Luo et al. reported a 54% increased risk of nonalcoholic fatty liver disease (NAFLD), a 173% increased risk of cirrhosis, and a 46% increased risk of primary liver cancer associated with cholecystectomy (14). Jingting Lyu et al. similarly demonstrated a higher risk of postoperative NAFLD, particularly amplified in obese patients (15).

Yue et al. found significant correlations between hepatic steatosis index and fatty liver grade post-cholecystectomy, with notable proportions of patients experiencing worsening liver grades (6). Sanguankeo et al. observed a 1.56-fold increased risk of NAFLD following cholecystectomy, aligning with the increased incidence seen in our study (16).

Kwak MS et al. highlighted cholecystectomy as independently associated with NAFLD after adjusting for metabolic risk factors (17). Conversely, Wang et al. initially found a higher prevalence of fatty liver among those who underwent cholecystectomy, but this association became statistically insignificant after multivariate adjustment (1).

Hajong et al. noted higher metabolic risk factors in patients with non-alcoholic steatohepatosis among those undergoing cholecystectomy, suggesting routine liver biopsy may be warranted during surgery (13). Zin-Qin Xie et al. conducted a large-scale study linking cholecystectomy with substantially higher risks of liver fibrosis and cirrhosis, further underscoring the potential long- term consequences on liver health post-surgery (18).

In our study, the profile of patients undergoing laparoscopic cholecystectomy typically includes a relatively young age distribution with a significant female predominance, alongside comorbidities such as diabetes and hypertension. Postoperatively, there are notable improvements in lipid profiles but also an observed increase in fatty liver incidence and severity. These findings underscore the complex interplay between cholecystectomy, metabolic parameters, and liver health outcomes, necessitating ongoing monitoring and tailored management strategies for postoperative care.

Limitations

This study enrolled participants according to convenience sampling method, hence resulting in sampling bias where these participants cannot be considered representative of a larger group. Therefore, the key disadvantage can be lack of generalizability of the results on general population. Also, this study measures liver function test and lipid profiles along with the grading of fatty liver on ultrasound at the 3rd month of cholecystectomy. Therefore, it does not tell us about the trend over the time and cannot conclude causality. Hence, further studies involving random sampling technique, measuring lipid profile and LFT along with assessment on ultrasound with multiple scheduled intervals after surgery, and longer follow up are required to establish the effect of cholecystectomy over liver steatosis. Larger studies with multicentric study designs would be needed to further validate the findings.

CONCLUSION

The study was able to conclude that the prevalence of fatty liver disease (suggestive of NAFLD) and its severity were higher post cholecystectomy at 3rd month of follow up. It was observed that lipid profile parameters were favorable post cholecystectomy with a significant decrease in the total cholesterol, triglycerid (TG), LDL and VLDL and a significant increase in the HDL levels. In the liver function test, bilirubin levels decreased and hepatic enzymes levels were seen to increase significantly.

Ethics Committee Approval: This study was approved by Government Medical College and Hospital Institutional Ethics Committee (Decision no: GMCH/IEC/835/2022/197, Date: 29.11.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - UD; Design - RB; Supervision - RB; Materials - UD; Data Collection and/or Processing - UD; Analysis and/or Interpretation - RB; Literature Search - MS; Writing Manuscript - KA; Critical Reviews - RB, RS, NK, SG.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Semptomatik safra taşı hastalığı için kolesistektominin transabdominal ultrasonografi kullanılarak hepatik steatoz üzerine etkisi: Gözlemsel prospektif bir çalışma

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ÖZET

Giriş ve Amaç: Hepatik steatoz ve safra taşı genel popülasyonda yaygındır ve risk faktörleri multifaktöriyeldir. Deneysel çalışmalar kolesistektominin hepatik steatozu arttırdığını ve alkol dışı yağlı karaciğer hastalığına (NAFLD) yol açtığını göstermiştir. Bunu değerlendirmek amacıyla, bu çalışma Hindistan'ın kuzeyindeki bir tıp fakültesinin genel cerrahi bölümünde gerçekleştirilmiştir.

Gereç ve Yöntemler: Kolesistektomi bekleyen yüz üç hasta yazılı bilgilendirilmiş onamları alındıktan sonra seçilmişti. Ameliyat öncesi temel özellikleri kaydedildi ve daha sonra üçüncü ayda karaciğer fonksiyon testi (KFT), lipid profili ve karın ultrasonografisi (USG) ile takip edildi.

Bulgular: Çalışmaya dahil edilen hastaların yaş ortalaması 41,62 ± 13,62 yıl ve ortalama VKİ 25,96 ± 1,73 kg/m^2 idi. Toplam bilirubin (0,56 vs 0,76, p< 0,0001) ve direkt bilirubin (0,15 vs 0,27, p< 0,0001) kolesistektomi sonrası preoperatif değerlere göre anlamlı olarak azaldı. Serum glutamik oksaloasetik transaminaz (SGOT) (49,14 vs 34,98 IU/dL), SGPT (50,85 vs 35,46 IU/dL) ve ALP (101,16 vs 85,97 IU/dL) düzeyleri ameliyat sonrasında anlamlı olarak yükselmiştir. Kolesterol değerleri (146,28 vs 168,77 mg/dL), trigliseritler (TGs) (119 vs 133,56 mg/dL), düşük yoğunluklu lipoprotein (LDL) (93,32 vs 113,05 mg/dL) ve çok düşük yoğunluklu lipoprotein (VLDL) (18,68 vs 27,45 mg/dL) üç aylık takipte anlamlı şekilde azalırken yüksek yoğunluklu lipoprotein (HDL) (48,96 vs 42,42 mg/dL) anlamlı şekilde artmıştır. Yağlı karaciğer prevalansı ameliyat sonrasında artmış ve Grade 1 steatoz oranı yükselmiştir (%75). Karaciğer yağlanmasının şiddeti ameliyat sonrası USG'de Grade 3 yağlanma ile (%8,73) artmıştır. Dolayısıyla, daha önce normal USG raporları olan yeni hastalarda yağlı karaciğer geliştiği ve önceden var olan karaciğer yağlanması daha da kötüleştiği görüldü.

Sonuç: Çalışma, yağlı karaciğer prevalansının kolesistektomi sonrası arttığı sonucuna varmıştır. Lipid profili parametreleri toplam kolesterol, TG, LDL ve VLDL'de düşüş ve HDL'de artışla olumlu yönde iyileşmiştir. KFT parametreleri de önemli ölçüde değişmiştir.

Anahtar Kelimeler: Kolesistektomi, hepatik steatoz, karaciğer fonksiyon testi, lipid profili, karın ultrasonografisi

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ORIGINAL ARTICLE
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HER2 immunohistochemical expression and its association with clinicopathological features of gastric adenocarcinoma in Uganda

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ABSTRACT

Objective: Despite the remarkable improvement in gastric adenocarcinoma treatment modalities, the prognosis of gastric adenocarcinoma remains poor. The purpose of this study was to determine the prevalence of HER2 immunohistochemical expression and its association with clinicopathological features of patients with gastric adenocarcinoma.

Material and Methods: This was a cross-sectional study which was conducted at the department of pathology. A total of 86 formalin fixed paraffin embedded tissue blocks of the patients who were confirmed histologically with gastric adenocarcinoma from January 2009 to December 2019 were included in the analysis. Laboratory requisition form and patients' files were used to extract the clinical and pathological data of the cases. Immunohistochemistry to assess HER2 overexpression was done using monoclonal (SP3 clone) rabbit anti-HER2/neu (Thermo Fisher Scientific-USA). Chi-square statistical test was used to determine the association of the clinicopathological characteristics with HER2 expression. P< 0.05 was considered statistically significant.

Results: Mean age of the patients included in the study was 58.5 ± 14.3 years, and over half 54.7% (n= 47) of the patients were males. Poorly cohesive non-signet ring types contributed most (47.7%) (n= 41) of the cases, and diffuse/mixed histological subtypes were more prevalent (57%) (n= 49) subtypes. Poorly differentiated cases accounted for the majority (66.3%) (n= 57) of the cases. The prevalence of HER2 immunohistochemical expression was 8.1% (n= 7). None of the clinicopathological characteristics were associated with HER2 expression.

Conclusion: This study has shown almost every one in 10 patients with gastric adenocarcinoma may express HER2 when using immunohistochemistry test. However, the HER2 in this study was not associated with age, sex, tumor location, the nature of biopsy, histological subtypes, and tumor grade.

Keywords: Gastric adenocarcinoma, HER2 overexpression, prognosis, clinicopathological characteristics

INTRODUCTION

Gastric adenocarcinoma is the fifth most common malignancy globally accounting for 5.7% of all adenocarcinomas with an incidence of 11.4 per 100.000 population annually (1). It ranks third among the causes of adenocarcinoma-related deaths in both sexes worldwide, accounting for 8.2% of adenocarcinoma deaths with a rate of 8.45 per 100.000 population annually (1,2). There is a geographical variation in the incidence of gastric adenocarcinoma globally, and over 50% of the cases occur in developing countries (2,3). The highest incidence is in Eastern Asia, and the lowest in Central Africa (3). In Uganda, the incidence of gastric adenocarcinoma has increased by more than 11-fold from 0.8 per 100.000 population reported in the 1960s to nine per 100.000 population reported in 2014 (4,5). It is now one of the main causes of cancer-related deaths in Uganda with a mortality rate of 8.7 per 100.000 population (5). In most countries including Uganda, gastric adenocarcinoma is usually diagnosed at an advanced stage when curative surgical resection is no longer possible, which contributes to poor prognosis (6). Several poor prognostic factors such as diffuse histological subtype, high grade, and overexpression of proteins like human epidermal receptor 2 (HER2) among many others have been identified by independent studies (7,8).

HER2 protein, which is involved in various aspects of tumor cell biology, has previously been shown to be an independent poor prognostic factor in gastric adenocarcinoma (9). HER2 positive tumors behave more aggressively and have higher

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chances of recurrence than HER2 negative tumors (7,8). Moreover, HER2 protein overexpression in gastric adenocarcinoma is also considered a predictive biomarker for response to HER2 targeted therapy (7,10). The prognosis of HER2 positive gastric adenocarcinoma has been relatively improved by the use of the targeted therapies against HER2 (11). Nonetheless, a wide range of variation in the frequency of HER2 protein overexpression in gastric adenocarcinoma, ranging from 8% to 53.4%, which also with different populations, histological subtypes of gastric adenocarcinoma and tumor grade has been demonstrated by previous studies (12-14). The wide range of HER2 overexpression is attributed to many factors including geographical differences, tumor biology and heterogeneity, and methodological differences (14,15).

In Uganda, the prevalence of HER2 protein overexpression in gastric adenocarcinoma remains unknown. Therefore, this study aimed to determine the immunohistochemical expression of HER2 protein and its association with demographic and pathologic features of gastric adenocarcinoma.

MATERIAL and METHODS

Study Design and Setting

This was a cross-sectional study design which was conducted at the department pathology, Makerere College of Health Sciences (MakCHS) in Kampala, Uganda. The college is located in the same area with Mulago hospital. Therefore, the department of pathology receives most of samples from Mulago National Hospital and also from other health facilities which perform surgery mainly within the central region where Kampala is located. The department serves the roles of teaching, research, as well as offering diagnostic services for histological, cytological and autopsy services within Kampala, other parts of the country, and other areas of the neighboring countries such as Kenya, Rwanda, and Democratic Republic of Congo.

Study Population

The study analysed archived formalin-fixed paraffin-embedded (FFPE) tissue blocks of patients who were diagnosed with various histological types of gastric adenocarcinoma from January 2009 to December 2019. Laboratory requisition forms and patients' files were used to select the required cases. Cases with available clinical information and confirmed histological diagnosis and also available FFPE tissue blocks with good quality were retrieved and included in the study. However, cases with poorly fixed or processed FFPE tissue blocks, those with necrotic tissue blocks, cases with missing patients' files, and those with prior history of chemotherapy and/or radiotherapy al were excluded from the analysis.

Sample Size Estimation

The sample size was determined using the Kish Leslie formula in which the sample size was calculated as $n= Z^2 P (1-P)/e^2$; n= sample size, z= standard normal deviate at a 95% confidence interval corresponding to 1.96, and e= margin of error of 5% (16). The p= prevalence of HER2 protein overexpression in gastric adenocarcinomas was assumed to be 42.2% from a study done in Kenya (17). Therefore, $n= (1.96)^2 \times 0.422 (0.578)/(0.05)^2= 0.9370/0.0025= 374.81$. The possible population size for cases with gastric adenocarcinoma was estimated to be around 110. Therefore, the calculated sample size of approximately 375 was not possible which necessitated to apply the finite population correction formula so as to reduce the calculated sample size to an achievable sample size as follows: n= (calculated sample size x population size)/(calculated sample size) + (population size - 1). n= (374.81 x 110)/(374.81 + (110-1)). Therefore, n= 85.2. The obtained minimum sample size required for this study was approximately 86 (18).

Sampling Method

The required number of the cases were sampled using convenience sampling method, and all eligible number of FFPE tissue with confirmed histological diagnosis of gastric adenocarcinoma were retrieved consecutively from the archive of FFPE tissue blocks in the department of pathology. Retrieval of the FFPE tissue blocks was done by a laboratory technician using the inclusion criteria.

Haematoxylin and Eosin Staining

Each retrieved FFPE tissue block was processed and stained with haematoxylin and eosin (H,E) as it was previously done for re-confirmation of the previous diagnosis (19). Histological classification and grading of the tumors were done in accordance with the Lauren and World Health Organization 2010 report classification systems using an Olympus CX23 microscope (20,21). The evaluation of the microscopic tissue slides was done by two independent experienced pathologists.

Immunohistochemistry Staining

Immunohistochemistry (IHC) staining was performed to detect HER2 protein using a previously optimized protocol by a qualified technician (22). Monoclonal SP3 clone rabbit anti-HER2/neu (Thermo Fisher Scientific, USA) antibody was used. A known HER2 positive breast adenocarcinoma case was used as positive control while omitting the primary antibody served as the negative control. The percentage of tumor cells with HER2 positivity was recorded along with the strength of staining as done in a previous study (23). Tumors with score 0 or score 1+ in which there was no membranous staining or weak staining detected in only one part of the membrane were considered as negative. Cases with moderate or weak complete or basolateral membranous staining were regarded equivocal cases and were given score of 2+. Tumors with score 3+ in which there was strong complete or basolateral membranous staining were considered positive for HER2 protein. Background staining and

cytoplasmic staining were considered as nonspecific staining. Only complete or basolateral membranous staining was considered as true positive. The cut-off points of at least five cohesive, unequivocal tumor cells in endoscopic biopsies, and at least 10% of tumor cells in resection biopsies were used to evaluate HER2 over-expression.

Data Analysis

Data analysis was performed using STATA programme version 15.0. Continuous and categorical variables were presented in mean ± standard deviation and proportions, respectively. Pearson Chi-square statistical test was used to assess the association of the clinicopathological characteristics with HER2 immunohistochemical expression. $P< 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological Characteristics of the Patients

Table 1 presents the clinicopathological characteristics of the patients. Mean age of the patients with gastric adenocarcinoma was 58.5 ± 14.3 years, with an age range of 28-87 years. Majority of the patients (74.4%) (n= 64) were older than 50 years, and over half (54.7%) (n= 47) of the patients were males, and the male to female ratio was 1.2:1. Most of the cases of gastric adenocarcinoma (52.3%) (n= 45) were non-cardia tumors and endoscopic biopsies dominated the specimens (62.8%) (n= 58). Regarding Lauren and WHO classification of the cases, 57.0% (n= 49) and 47.7% (n= 41) were of diffuse type and poorly non-cohesive signet ring type, respectively. Majority (66.3%) (n= 57) of the tumors were poorly differentiated adenocarcinomas. Various histopathological variants of gastric adenocarcinoma are shown in Figure 1.

Age Distribution According to Sex of the Patients with Gastric Adenocarcinoma

The frequency of the gastric adenocarcinoma cases was not linear for both age and sex of the patients. There was a kind of trend to some extent, and there was an increase (35-39 years) and decrease (40-44 years) of the frequency of the cases with age and sex of the patients in the study. Moreover, at the age group of 55-59 years, there was a steep decrease (one case) in the fre-

Table 1. Clinicopathological characteristics of the patients included in the analysis (n= 86)

Variables	Frequency n (%)
Age (years)	
≤50 years	22 (25.6)
>50 years	64 (74.4)
Sex	
Male	47 (54.7)
Female	39 (45.3)
Tumor Location	
Cardia	4 (4.7)
Non-cardia	45 (52.3)
Not specified	37 (43.0)
Nature of Biopsy	
Endoscopic biopsy	54 (62.8)
Surgical biopsy	32 (37.2)
Tumor Grades	
Well differentiated	(16.3)
Moderately differentiated	(17.4)
Poorly differentiated	(66.3)
Lauren Classification	
Intestinal type	37 (43.0)
Diffuse type	49 (57.0)
World Health Organization 2010 Classification	
Mucinous	6 (7.0)
Papillary	8 (9.3)
Poorly cohesive signet ring	8 (9.3)
Tubular	23 (26.7)
Poorly non-cohesive signet ring	41 (47.7)
Tumor Grades	
Well differentiated	14 (16.3)
Moderately differentiated	15 (17.4)
Poorly differentiated	57 (66.3)

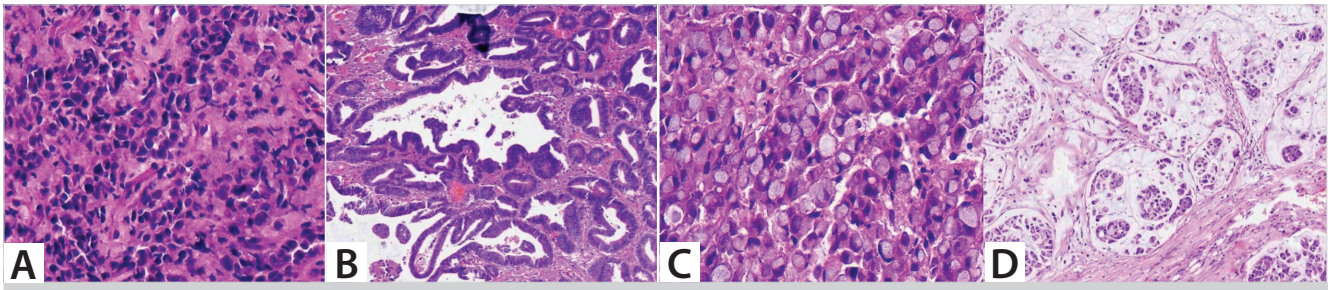

Figure 1. A. The above micrograph shows sheets of neoplastic epithelial cells with marked cytological atypia diffusely invading a desmoplastic stroma. **B.** Photomicrograph showing well differentiated papillary/intestinal adenocarcinoma under H&E stain (x100). **C.** Photomicrograph showing cohesive signet ring carcinoma under H&E stain (x400), and **D.** photomicrograph showing moderately differentiated mucinous/intestinal adenocarcinoma under H&E stain (x100).

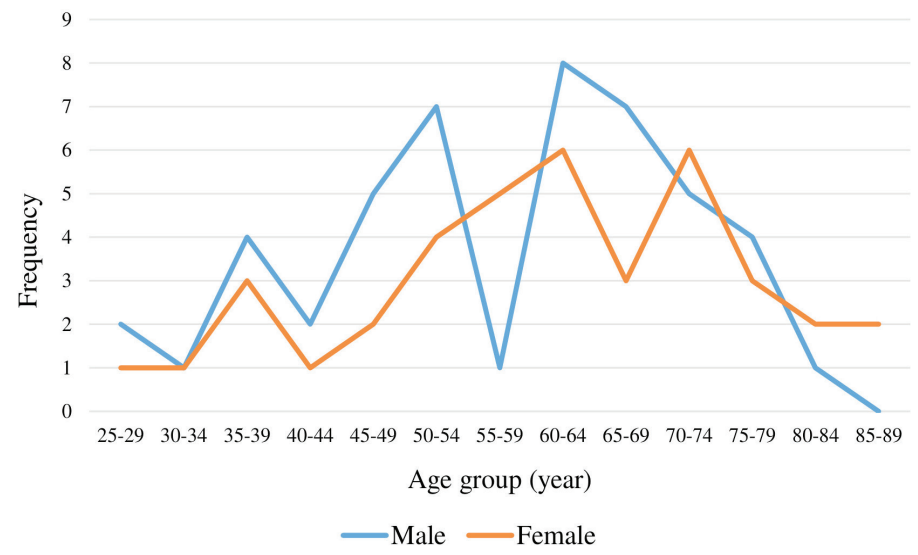

Figure 2. Age distribution according to sex of the patients with gastric adenocarcinoma.

quency of cases among males whereas a significant increase (five cases) in the frequency of cases among females was noticeable. Conversely, at the age group of 65-69 years, there was a decrease (three cases) in the frequency of cases among females whereas a significant increase (eight cases) in the frequency of cases among males was observed (Figure 2).

Prevalence of HER2 Immunohistochemical Overexpression

The variation of HER2 overexpression for the cases of gastric adenocarcinomas is presented in Figure 3. The prevalence of HER2 immunohistochemical overexpression was 8.1% (n= 7) (Figure 3a), all the other 91.9% (n= 79) of the cases were negative (both 0 and 1+ scores) (Figures 3b-d). There was intratumoral heterogeneity of HER2 over-expression in the current study, which occurred in 57% of cases. No equivocal cases were found in this series of tumors regarding HER2 expression.

Association of HER2 Overexpression with Clinicopathological Characteristics of the Patients

Table 2 shows the association of HER2 overexpression with clinicopathological characteristics. HER2 overexpression was higher in patients younger than or of 50 years of age (13.6%, 3/22), than in patients older than 50 years (6.3%, 4/64), although the difference was not statistically significant (p= 0.274). Four out of forty-seven (8.5%) gastric adenocarcinoma tumors from males overexpressed HER2 compared to 3/39 of tumors (7.7%) in females (p= 0.890). Tubular adenocarcinoma had the highest prevalence of HER2 positivity (17.4%, 4/23) compared to other histological subtypes, and we considered the difference was insignificant (p= 0.253). Considering Lauren classification, intestinal subtype of gastric adenocarcinomas had a higher rate of HER2 overexpression (13.5%, 5/37) than diffuse or mixed subtype (4.1%, 2/49), and the difference was also not statistically significant (p= 0.113). Regarding tumor grade, the moderately differentiated

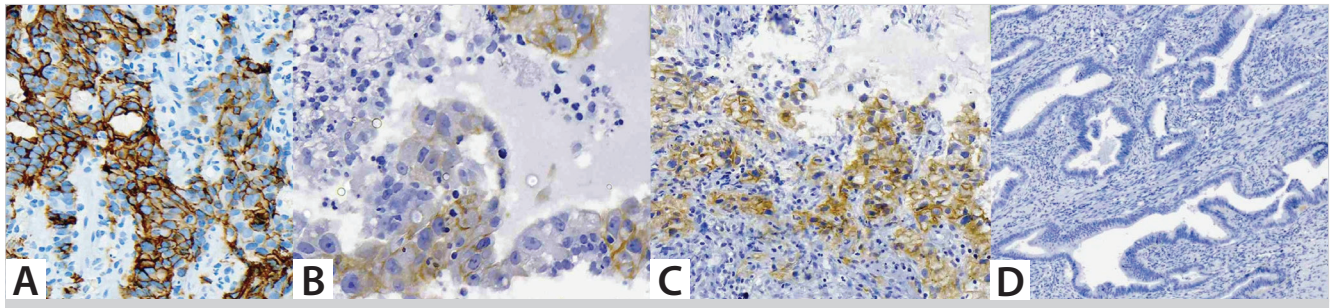

Figure 3. A. Photomicrograph showing HER2 positive score 3+ of a poorly cohesive non-signet ring adenocarcinoma case (HER2 immunohistochemistry antibody x400), **B.** photomicrograph showing HER2 negative score 1+ of a poorly cohesive non-signet ring adenocarcinoma case (HER2 immunohistochemistry antibody, x200), **C.** photomicrograph showing heterogeneous HER2 negative score 1+ in a poorly cohesive non-signet ring adenocarcinoma case (HER2 immunohistochemistry antibody, x200), and **D.** photomicrograph showing HER2 negative score 0 of a well differentiated tubular adenocarcinoma case (HER2 immunohistochemistry antibody, x100).

Table 2. Association of HER2 overexpression with clinicopathological characteristics of the patients

Variables	Positive n (%)	Negative n (%)	p
Age (years)			0.274
≤50 years	3 (13.6)	19 (86.4)	
>50 years	4 (6.3)	60 (93.8)	
Sex			0.890
Male	4 (8.5)	43 (91.5)	
Female	3 (7.7)	36 (92.3)	
Tumor Location			0.658
Cardia	0 (0)	4 (100)	
Non-cardia	3 (6.7)	42 (93.3)	
Not specified	4 (10.8)	33 (89.2)	
Nature of Biopsy			0.190
Endoscopic biopsy	6 (11.1)	48 (88.9)	
Surgical biopsy	1 (3.1)	31 (96.9)	
Histological Subtype (World Health Organization 2010)			0.253
Papillary	1 (12.5)	7 (87.5)	
Tubular	4 (17.4)	19 (82.6)	
Mucinous	0 (0%)	6 (100)	
Poorly cohesive signet ring	1 (12.5)	7 (87.5)	
Poorly cohesive non-signet ring	1 (2.4)	40 (97.6)	
Histological Subtype (Lauren)			0.113
Intestinal	5 (13.5)	32 (86.5)	
Diffuse/mixed	2 (4.1)	47 (95.9)	
Tumor Grades			0.720
Well-differentiated	1 (7.1)	13 (92.9)	
Moderately differentiated	2 (13.3)	13 (86.7)	
Poorly differentiated	4 (7.0)	53 (93.0)	

tumors had more HER2 protein overexpression (13.3%, 2/15) compared to either well differentiated (7.1%, 1/14,) or poorly differentiated cases (7.0%, 4/57) but the difference was not significant (p= 0.720). Also, the overexpression of HER2 protein was not associated with tumor location (p= 0.658) although all four tumors from the cardiac location were negative.

DISCUSSION

This study aimed to determine the prevalence of HER2 immunohistochemical overexpression among gastric adenocarcinoma cases and to establish its association with clinicopathological features of gastric adenocarcinoma. The prevalence of HER2 overexpression in gastric adenocarcinoma in the present study was 8.1% which is in agreement with previous studies (15,24). A wide range of HER2 immunohistochemical expression of 8%-53.4% among cases of gastric adenocarcinoma has been reported in previous studies (24,25).

The reasons for such a wide range of HER2 expression reported in previous studies and extended by the current study could be due to the nature of biopsies, type of antibody clone, scoring system, and tumor heterogeneity (14,26). Among these, tumor heterogeneity could be the leading factor contributing to the wide variation in HER2 prevalence. Previously, tumor heterogeneity of about 30% of tumor cells exhibiting reactivity or only focal staining of tumor cells in at least 30% of HER2 positive cases has been reported in gastric adenocarcinoma (27). Differences in sensitivity and specificity among the antibodies might have contributed to the variation of HER2 protein overexpression (28). Also, previous studies considered only cases with score 3+ as positive, similar to our study, which provided a positivity ranging from 6% to 10.5% (29,30). However, studies where tumors even with scores 2+ were considered positive reported relatively higher HER2 immunohistochemical overexpression rates. For instance, a study by Barros-Silva et al. showed 9.3% HER2 positivity after combining 3.9% which were

score 2+ cases and 5.5% for score 3+ cases (31). Likewise, Van Trung reported 11.7% of HER2 positivity after combining 6.9% which were score 2+ cases with 4.8% score 3+ cases (32).

The lack of association between HER2 immunohistochemical overexpression with all demographic and pathologic characteristics (age, sex, tumor site, grade, and histological subtype) in this study has also been reported in previous studies, though other studies have reported association of HER2 expression with some of the demographic and pathologic characteristics (33,34). This is likely because in the study of Li et al. it was also found that HER2 protein overexpression which is involved in tumor progression was not associated with age of the patients (35). Although the prevalence of HER2 expression was slightly higher in males compared to females, the difference was not statistically significant, similar to other studies (27,33,36,37). On the contrary, a study done in India found an association between HER2 overexpression and sex of the patients (27). The prevalence of HER2 immunohistochemical overexpression varied with WHO histological subtypes, in which tubular adenocarcinoma showed the highest HER2 overexpression, but the difference was not statistically significant, contrary to the findings in the previous studies (36,37). The intestinal subtype that was least frequent in the current study had a higher HER2 overexpression than the diffuse/mixed subtypes as reported by previous studies (36,38). This could partly explain the low prevalence of HER2 immunohistochemical overexpression in this study compared to previous studies which reported a higher proportion of the intestinal subtype of gastric adenocarcinoma than the diffuse/mixed subtypes (24,33,39). Unlike the finding in the current study, Kataoka et al. and Takehana et al. reported a positive association between histological type and HER2 expression (36,37).

Regarding association of tumor grade with HER2 expression, in this study, moderately differentiated adenocarcinomas showed a higher prevalence of HER2 positivity than poorly differentiated adenocarcinomas, though the difference was not significant similar to previous studies (27,36). However, some studies have shown an association between HER2 overexpression and tumor grade (36,40). This is probably due to the different antibody clones used for HER2 testing. Out of the seven cases with positive HER2 protein overexpression, three were non-cardia, while none of the cardia tumors showed reactivity. Compared with a previous study that showed a significant association between HER2 overexpression and tumor location, the current study is in agreement with another studies, which found no significant association (27,41). HER2 overexpression was more prevalent among endoscopic biopsy specimens (11.1%) than surgical biopsies (3.1%) This was consistent with the findings of previous studies (27,42), which also suggested that since small biopsy specimens fix much quicker than surgical biopsies with less ischemic time, antigens are preserved better resulting in higher positivity (41). Consistent with previous studies, there was no significant association between HER2 overexpression and nature of biopsy, probably because of the similarity of small sample size compared to some studies that showed significant association (27,41).

Study Limitations

We faced difficulty in obtaining a large number of FFPE tissue blocks from the tissue blocks repository due to poor storage despite the identification of potential cases from the laboratory requisition forms and patients' files. Incomplete information because of inadequately filled request forms with some important variables lacking like tumor location, incomplete clinical history on including a history of previous chemotherapy or radiotherapy contributed to failure to associate such factors with HER2 overexpression. Also, inappropriate tissue fixation might have affected antigen retrieval during IHC staining. Endoscopic biopsies contained one or two samples per patient which were not enough to represent the tumor.

CONCLUSION

The present study shows that almost one in 10 patients with gastric adenocarcinoma tumors in Uganda are more likely to have HER2 expression, and for that reason, they may benefit from targeted therapy that specifically targets inhibition of HER2. Moreover, HER2 immunohistochemical overexpression in this study was not significantly associated with age, sex, tumor location, nature of biopsy, histological subtype, and tumor grade. Larger scale prospective studies should be conducted to evaluate HER2 immunohistochemical overexpression in gastric adenocarcinoma cases in Uganda to obtain more generalizable results.

Ethics Committee Approval: This study was approved by Makerere University College of Health Sciences School of Biomedical Sciences Research and Ethics Committee (Decision no: SBS-713, Date: 30.01.2020).

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ORİJİNAL ÇALIŞMA-ÖZET
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HER2 immünohistokimyasal ekspresyonu ve Uganda'da mide kanserinin klinikopatolojik özellikleri ile ilişkisi

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ÖZET

Giriş ve Amaç: Mide kanseri tedavi modalitelerindeki kayda değer gelişmelere rağmen, gastrik adenokarsinomun prognozu kötü olmaya devam etmektedir. Bu çalışmanın amacı HER2 immünohistokimyasal ekspresyonunun prevalansını ve mide kanserli hastaların klinikopatolojik özellikleri ile ilişkisini belirlemektir.

Gereç ve Yöntemler: Bu çalışma patoloji bölümünde yürütülen kesitsel bir çalışmadır. Ocak 2009 ile Aralık 2019 tarihleri arasında histolojik olarak mide kanseri tanısı konmuş 86 hastanın formalin fikse parafine gömülü doku blokları analize dahil edildi. Olguların klinik ve patolojik verilerini elde etmek için laboratuvar talep formu ve hasta dosyaları kullanılmıştır. HER2 aşırı ekspresyonunu değerlendirmek için immünohistokimya monoklonal (SP3 klonu) tavşan anti-HER2/neu (Thermo Fisher Scientific-ABD) kullanılarak yapılmıştır. Klinikopatolojik özelliklerin HER2 ekspresyonu ile ilişkisini belirlemek için ki kare istatistiksel testi kullanılmıştır. P< 0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmaya dahil edilen hastaların ortalama yaşı 58,5 ± 14,3 yıldı ve hastaların yarısından fazlası (%54,7) (n= 47) erkekti. Olguların %47,7'sini (n= 41) kötü koheziv non-signet halka tipleri oluştururken, diffüz/karışık histolojik alt tipler %57 (n= 49) ile daha sık görülen alt tiplerdi. Kötü diferansiye vakalar vakaların %66,3'ünü (n= 57) oluşturmuştur. HER2 immünohistokimyasal ekspresyon prevalansı %8,1 (n= 7) idi. Klinikopatolojik özelliklerin hiçbiri HER2 ekspresyonu ile ilişkili değildi.

Sonuç: Bu çalışma, immünohistokimya testi kullanıldığında neredeyse her 10 mide kanserli hastadan birinin HER2 eksprese edebileceğini göstermiştir. Bununla birlikte, bu çalışmada HER2 yaş, cinsiyet, tümör yerleşimi, biyopsinin niteliği, histolojik alt tipler ve tümör derecesiyle ilişkili değildi.

Anahtar Kelimeler: Mide kanseri, HER2 aşırı ekspresyonu, prognoz, klinikopatolojik özellikler

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ORIGINAL ARTICLE
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Anal fissures in COVID-19 survivors: Incidence, risk factors, and outcomes

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ABSTRACT

Objective: In spite of COVID-19's typical presentation in the form of fever, cough, myalgia, and pneumonia, other gastrointestinal manifestations have been reported. Among the COVID-19 survivors, anal fissure has been documented. The aim of this study was to report the incidence of anal fissure among those patients, its possible risk factors and outcome.

Material and Methods: This is a retrospective cross-sectional study which was conducted on COVID-19 patients' who were diagnosed with anal fissure. Those who survived and were discharged home safely were contacted to pick up whether they suffered from any symptoms suggesting anal fissure, to identify the risk factors of anal fissure and their outcomes.

Results: A total of 176 COVID-19 patients were enrolled in this study. The incidence of anal fissure among all patients was 36.9%. Patients were categorized into two groups; fissure and non-fissure groups. No significant difference was noted in the demographic data apart from age, which was younger in the fissure group. The majority of anal fissures resolved spontaneously after patients recovered from the COVID-19 symptoms with no specific treatment (43.1%).

Conclusion: Anal fissure is quite a common problem in COVID-19 patients. Young and middle-aged patients are more vulnerable to develop anal fissure after COVID-19 infection.

Keywords: COVID-19, gastrointestinal symptoms, anal fissure, risk factors

INTRODUCTION

Anal fissure is one of the most common anorectal problems, which is a longitudinal tear or defect in the anal canal mucosa distal to the dentate line. It occurs more commonly in young adults with equal distribution in both sexes (1,2). It affects 15% of women after childbirth (3).

Anal fissure may be asymptomatic or may cause severe pain depending on the degree of anal sphincter spasm. Further, it may be associated with low volume rectal bleeding. Secondary constipation usually happens due to fear of pain during defecation. The fissure is usually located posteriorly in 85% of cases and anteriorly in 15% of cases (4).

After declaration of COVID-19 as a pandemic, nearly all countries were affected. Typical presentations included fever, cough, myalgia, fatigue and pneumonia (5,6). Gastrointestinal tract (GIT) symptoms such as diarrhea, nausea and vomiting were also reported (7-9). Interestingly, GIT symptoms were associated with severe form of COVID-19 infection with a higher rate of intensive care unit (ICU) admission when compared to those with respiratory symptoms only (10). Moreover, the COVID-19 virus was isolated from the stool sample of the infected people even after clearance of chest symptoms (11). As surgeons took part in the battle against COVID-19, we noticed many patients who developed anal fissures during or after recovery from COVID-19. The aim of this study was to report the incidence of anal fissure among COVID-19 patients, its possible risk factors, and outcome.

MATERIAL and METHODS

Study Design

This is a retrospective cross-sectional study which was conducted on patients diagnosed with COVID-19 infection who were admitted to a tertiary referral isolation hospital between September 2020 and November 2020.

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The study protocol was approved by the Institutional Review Board (IRB) (IRB No. R.21.07.1383) and was retrospectively registered in the clinical trials registry with registration number (NCT05736926). Consent has been taken from the participating patients in this study before the interview.

Eligibility Criteria

Our hospital is a tertiary referral center that admits COVID-19 patients who experienced any symptoms that suggests this infection and confirmed by polymerase chain reaction (PCR) positive nasal swab or with chest findings suggesting COVID-19 infection through computerized tomography (CT), according to the local protocol of the Egyptian Ministry of Health adapted from the World Health Organization (WHO) recommendation. Patients of both sexes aged between 20-70 years with or without associated co-morbidities who received treatment for COVID-19 infection who, were discharged home safely, and presented with anal fissure during the follow up were included. Patients who did not experience anal pain or anal fissure, and patients who died were excluded from this study.

Patient Interview

Patients were identified by checking the electronic medical records (EMR) during the study period, eligible patients were addressed and then contacted by telephone call to pick up whether they suffered from any symptoms of anal pain, difficulty in defecation suggesting anal fissure, to identify the risk factors for anal fissure development, their outcomes, and how they were managed. Three hundred and fifty patients deemed eligible, and 176 (50.3%) responded while 174 did not. We relied on the patients' history for the diagnosis of anal fissure due to the pandemic and limitations of clinical activities, as outpatient visits were not recommended at that time. Patients with symptoms suggested the diagnosis of anal fissure were further asked about the treatment they received and whether their symptoms improved or not (Figure 1).

Basic demographic data extracted were age, sex, and associated comorbidities. Disease related parameters were collected including respiratory symptoms, fever, loss of smell and/or taste sensation, GIT symptoms, infection severity, and the need for oxygen therapy. Additionally, the investigations that were done either laboratory or radiological were extracted.

Outcomes

The primary outcome was the incidence of anal fissure in confirmed COVID-19 patients. Secondary outcomes were risk factors that could be associated with anal fissure in COVID-19 patients, how they were managed, and the prognosis.

Statistical Analysis

Data were analyzed by SPSS (version 23, UK, Bristol). Continuous data was expressed as mean ± standard deviation (SD) or median and range based on normality. Categorical variables were expressed as number and percent. Student's t-test was used to process continuous data, whereas Fisher's exact test or Chi-square test were used for categorical variables. Risk factor analysis for anal fissure among COVID-19 survivors was assessed using binary logistic regression test. P values less than 0.05 were considered significant.

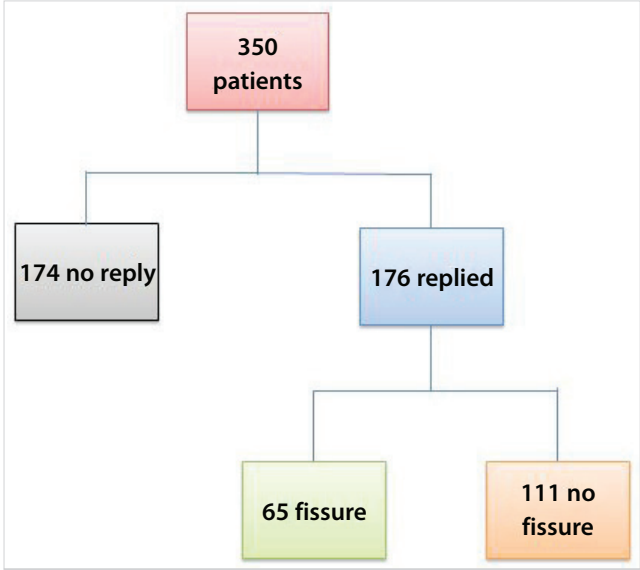

Figure 1. Patients' flow chart.

RESULTS

A total of 176 patients were enrolled in this study, among them 102 were males (58%) while 74 were females (42%). Median (IQR) age of patients was 53 (42-61).

As regard associated co-morbidities; 34.1% had hypertension, 29.6% had type II diabetes, 13.2% had chronic kidney disease, 11.9% had cardiac disease, and 6.8% had chronic liver disease. Regarding COVID-19 manifestations, the commonest symptoms were cough, fever and muscle fatigue, respectively. Median (IQR) oxygen (O_2) saturation was 90 (87-95). Based on route of O_2 supply, 39.2% received O_2 via mask with reservoir, 28.4% via O_2 mask, 6.3% via nasal cannula, while three patients (1.7%) via continuous positive air way pressure device (CPAP). Serum C reactive protein (CRP) was elevated with a median (IQR) of 30.8 (12-48). Median (IQR) hospital stay was 7 (2-12) days. The incidence of anal fissure was 36.9% among all admitted patients (Table 1).

In order to report possible risk factors, patients were further categorized into two groups; the first group included patients who developed anal fissure (n= 65) and the second group included patients who did not develop anal fissure (n= 111). The fissure group was significantly younger than the non-fissure group, with a median (IQR) age of [49 (41-59) versus 57 (44-65); p= 0.004]. No significant difference was noted between

Table 1 . Demographic data of all patients

Variables	Patients (n= 176)
Age (years) (Median + IQR)	53 (42-61)
Sex, n (%)	
Male	102 (57.9)
Female	74 (42.1)
Co-morbidities, n (%)	
Hypertension	60 (34.1)
Type II diabetes	52 (29.6)
Cardiac	21 (11.9)
Chronic liver disease	12 (6.8)
Chronic kidney disease	10 (13.2)
Neurological disease	9 (5.1)
Immunosuppressed	8 (4.6)
Taste loss, n (%)	20 (11.4)
Smell loss, n (%)	21 (11.9)
Muscle fatigue, n (%)	133 (75.6)
Cough, n (%)	156 (88.6)
Fever, n (%)	141 (80.1)
Diarrhea, n (%)	42 (23.9)
O_2 saturation (Median + IQR)	90 (87-95)
O_2 mask, n (%)	50 (28.4)
Nasal cannula, n (%)	11 (6.3)
Mask with reservoir, n (%)	69 (39.2)
CPAP, n (%)	3 (1.7)
Corticosteroids treatment, n (%)	130 (73.9)
Hospital stay (days) (Median + IQR)	7 (2-12)
Serum CRP (Median + IQR)	30.8 (12-48)
WBC count (Median + IQR)	9 (6.5-11.4)
Lymphocyte count (Median + IQR)	1.3 (1-1.8)
Anal fissure, n (%)	65 (36.9)

IQR: Interquartile range, CPAP: Continuous positive air way pressure, CRP: C-reactive protein, WBC: White blood cells.

both groups regarding sex. As regard associated comorbidities, no difference was detected apart from hypertension which was more prevalent in the non-fissure group (39.6% versus 24.6%; p= 0.042).

Neither group showed any significant difference in COVID-19 related parameters. Surprisingly, all patients did not experience constipation symptom even in the fissure group. Furthermore, median O_2 saturation in both groups did not reveal any significant difference (89% versus 90%) respectively. The number of patients who required O_2 mask was higher in the fissure group than in the non-fissure group; however, this was not significant (36.9% versus 23.4%; p= 0.055). There was no significant difference regarding the need of O_2 supply through nasal cannula, mask with reservoir or CPAP. Median (IQR) hospital stay for the fissure group was 6 (2-11) days, whereas in the non-fissure group was 8 (2-12) days. No significant difference was observed in serum CRP, white blood cell count or the differential lymphocytic count (Table 2).

Outcome of the Anal Fissure Group

Most of the patients' anal symptoms resolved spontaneously after they recovered from the COVID symptoms without receiving any treatment (43.1%). Four patients (6.2%) improved with medication and topical anal creams. Only one patient required surgery forchronic anal fissure. Five patients (7.7%) still have a tolerated anal pain; however, they refused further treatment. Five patients (7.7%) had anal fissure before COVID-19 infection and their symptoms became worsened after infection. Last, 22 patients (33.9%) did not respond to further questions on treatment outcome (Table 3).

DISCUSSION

In this retrospective cross-sectional study, the incidence of anal fissure was 36.9% among all admitted patients. The main presenting symptoms of COVID-19 disease were the usual respiratory symptoms in the form of dry cough with or without dyspnea (88.6%), fever (80.1%), and fatigue (75.6%) as most studies reported (6-9). Regarding GIT manifestation, the main presenting symptoms in our study were diarrhea (23.9%), anosmia (11.9%), and taste loss (11.4%). Some previous studies have found similar results to our study, that diarrhea was the commonest GIT presentation (3.8%-34%), followed by nausea or vomiting (3.9%-10.1%) and lastly abdominal pain (1.1%-2.2%) (12-14). In contrast to that, a study by Ungaro et al. have shown that anorexia was the commonest GIT manifestation (39.9%-50.2%) (15). In their study, Fang and his colleagues have attributed nearly half of their patients' symptoms of diarrhea to antiviral treatment (16). Additionally, Pan et al. have reported that GIT manifestations become worse with progression of the disease (17). Other rare GIT symptoms which have been reported were the GI bleeding and acute hemorrhagic colitis (18,19).

Mechanism of GIT Manifestation

Various reports have shown that COVID-19 virus uses the angiotensin converting enzyme II (ACE2) receptor as an entry to establish the infection. Moreover, ACE2 receptors are expressed by various tissues, including epithelial cells lining the GIT (20-24). Isolation of the RNA of the COVID-19 virus from the epithelial cells lining the GIT including the esophagus, stomach, duodenum and rectum has been reported. Moreover, presence of the virus itself in the intestinal cells can cause ileal and colonic dysfunction and hence the GIT manifestations (25,26). Another mechanism is that a host cell protein trans-membrane serine protease 2 which is present in the ileum and colon- helps in directing the virus to the host cells and so causing dysfunction (27,28). Thus, COVID-19 virus may cause digestive symptoms either by direct invasion into the target cells and/or immune-mediated tissue, or through inducing an end-organ injury (19,25). However, another theory suggested that the infection-induced respiratory complications, which lead to tissue hypoxia

Table 2. Demographic data of both groups

	Non fissure (n= 111)	Fissure (n= 65)	p
Age (Years) (Median + IQR)	**57 (44-65)**	49 (41-59)	**0.004**
Sex ratio n (%)			0.917
Male	64 (57.7)	38 (58.5)	
Female	47 (42.3)	27 (41.5)	
Co-morbidities, n (%)			
Hypertension	**44 (39.6)**	16 (24.6)	**0.042**
Type II diabetes	35 (31.5)	17 (26.2)	0.450
Cardiac	10 (9)	11 (16.9)	0.118
Chronic liver disease	9 (8.1)	3 (4.6)	0.375
Chronic kidney disease	5 (4.5)	5 (7.7)	0.378
Neurological	3 (2.7)	6 (9.2)	0.058
Immunosuppressed	4 (3.7)	4 (6.4)	0.429
Taste loss, n (%)	12 (10.8)	8 (12.3)	0.736
Smell loss, n (%)	13 (11.7)	8 (12.3)	0.906
Muscle fatigue, n (%)	87 (78.4)	46 (70.8)	0.257
Cough, n (%)	98 (88.3)	58 (89.2)	0.849
Fever, n (%)	91 (82)	50 (76.9)	0.417
Diarrhea, n (%)	28 (25.2)	14 (21.5)	0.580
O_2 saturation (Median + IQR)	90 (87-94)	89 (87-95)	0.973
O_2 mask, n (%)	26 (23.4)	24 (36.9)	0.055
Nasal cannula, n (%)	8 (7.2)	3 (4.6)	0.493
Mask with reservoir, n (%)	49 (44.1)	20 (30.8)	0.079
CPAP, n (%)	2 (1.8)	2 (3.1)	0.584
Corticosteroids treatment, n (%)	86 (77.5)	44 (67.7)	0.154
Hospital stay (days) (Median + IQR)	8 (2-12)	6 (2-11)	0.324
Serum CRP (Median + IQR)	34.4 (12-56.1)	24.4 (12-48)	0.498
WBC count (Median + IQR)	9.15 (6.4-11.2)	8.6 (6.5-11.6)	0.981
Lymphocyte count (Median + IQR)	1.27 (0.95-1.6)	1.4 (1.1-2)	0.071

IQR: Interquartile range, CPAP: Continuous positive air way pressure, CRP: C-reactive protein, WBC: White blood cells.

Table 3. Outcomes of anal fissure patients

Outcomes	Results
Still having anal pain	5 (7.7)
Resolved spontaneously	28 (43.1)
Improved with medications	4 (6.2)
Improved with surgery	1 (1.5)
No reply	22 (33.9)
History of previous fissure	5 (7.7)

Values are n (%).

causing cell injury and death, is the main cause of digestive symptoms. In favor of this hypothesis is the common use of corticosteroids, antibiotics and non-steroidal anti-inflammatory drugs for the treatment of tissue hypoxia in critically ill patients. Nevertheless, patients may develop drug induced diarrhea and other GIT manifestations after hospitalization (29). Histologically, the epithelium of the GIT showed lymphocytic and plasma cells infiltration with interstitial edema which was seen in the stomach, duodenum and rectum, while the esophagus showed patchy lymphocytic infiltration (29). Thus, presence of the virus in the rectum, or shedding of the viral RNA in stool of the infected people, its local inflammatory effect through tissue injury or ischemia can lead rectal or anal problems like anal fissure.

Median age of the people who suffered from anal fissure in our study was 49 years denoting that the middle age group is the commonest age of anal fissure presentation together with the young age people without any sex predominance (30). We also found that the fissure group needed more oxygen than the other group despite nearly equal O_2 saturation in both groups; however, this difference did not reach statistical significance. This may support the ischemic theory for anal fissure development. Another important notice was that the non-fissure group had a higher incidence of hypertension. This could explain that the use of antihypertensive medications in those patients could be protective against fissure.

We relied on the diagnosis of anal fissure among the studied group of patients on history via telephone calls because none of them visited our outpatient clinic to get examined to confirm the diagnosis due to limitation of clinical services during the pandemic. However, their main symptoms were severe anal pain and difficulty during defecation. Usually, anal fissure is diagnosed by inspection. It is considered acute if it has been present for less than six weeks, superficial, and having fresh clear mucosal edges, with little granulation tissue at its base. Whereas fissure is termed chronic if it has been present more than six weeks, having keratinized edges, skin tag, and if the fibers of the internal anal sphincter are visible (31,32).

Different treatment options are present for anal fissure. About 87% of acute anal fissures resolve with conservative treatment, while in chronic anal fissure, response to conservative management is reported in 50% of cases (33,34). Conservative management includes dietary habits modification, frequent sitz bath and local topical creams which cause relaxation of the internal sphincter, such as creams containing glyceryl trinitrate or calcium channel blockers together with local anesthetic (33,35). Several studies have reported the topical minoxidil cream in the treatment of anal fissure, which is a vasodilator agent, increases the blood supply to the fissure area hence promoting wound healing. It also causes smooth muscle hyperpolarization through activation of potassium channels and reduction of calcium influx through the calcium channels (36,37).

In the present study, 6.2% of our patients improved on conservative treatment, while 7.6% still have anal pain and are advised to seek medical advice at least to have some local medications. Nevertheless, 43.1% of our patients improved spontaneously without any treatment immediately after they recovered from COVID infection. Botulinum toxin injection in the internal anal sphincter has an important role as a chemical sphincterotomy and many studies have shown its efficacy in pain reduction with minor side effects (38). The last option which is reserved for chronic anal fissure is surgical treatment which entails lateral internal sphincterotomy, which is the gold standard treatment option for chronic anal fissure in comparison to non-surgical management (30). Only one patient in our study required surgical intervention because his pain became worse, and his fissure turned chronic without any response to medical treatment. He improved after surgery without any complications.

In relation to our study, Nakamura et al. have reported a case presented with restless, deep anal discomfort which worsens with rest, in spite of exclusion of anal fissure. They have reported it as restless anal syndrome which improved by clonazepam (39).

Anal Fissure Among COVID-19 Survivors and General Population

In our study, the incidence was 36.9% among all admitted patients. Middle aged group patients were the risky group. In contrast, anal fissure among general population is quite a common anal problem. About 10% of new patients visiting the colorectal outpatient clinics have anal fissure (40).

Moreover, in a population-based cohort study, the authors found the incidence of anal fissure in the United States, about 342.000 anal fissure cases each year with an average lifetime risk of 7.8% (41). In addition, anal fissure in the general population is more commonly seen in middle and young aged patients with equal sex distribution, which is similar to our results.

Study Limitations

This study has the following limitations: it is a retrospective one, with small sample size, and small response rate, so that we can't make solid evidence. However, to the best of our knowledge, this is the first study to report anal fissure problem following COVID-19 infection. Further studies with large sample size and more proof are needed to confirm this issue.

CONCLUSION

We observed an association between COVID-19 survivors and anal fissure development during or after recovery from the disease. However, this association has not been proven with conclusive evidence. Young and middle-aged people are more vulnerable. Anal fissure among COVID-19 patients' may improve with or without medical treatment and may require surgery in some chronic cases.

Ethics Committee Approval: This study was approved by Mansura University Mansura Faculty of Medicine Medical Research Ethics Committee Institutional Review Board (Decision no: R.21.07.1383, Date: 08.08.2021).

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ORİJİNAL ÇALIŞMA-ÖZET
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COVID-19'dan sağ kurtulanlarda anal fissürler: Görülme sıklığı, risk faktörleri ve sonuçlar

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ÖZET

Giriş ve Amaç: Ateş, öksürük, miyalji ve pnömoni gibi COVID-19'un tipik belirtileri yanında diğer gastrointestinal belirtiler de rapor edilmiştir. COVID-19'dan iyileşenler arasında anal fissür görülmektedir. Bu çalışmanın amacı bu hastalarda anal fissür görülme sıklığını, olası risk faktörlerini ve sonuçlarını bildirmektir.

Gereç ve Yöntemler: Bu, anal fissür tanısı alan COVID-19 hastaları üzerinde yapılmış, retrospektif kesitsel bir çalışmadır. Hayatta kalan ve güvenli bir şekilde evlerine taburcu edilen kişilerle temasa geçilerek anal fissürü düşündüren herhangi bir semptom olup olmadığı öğrenildi, anal fissürün risk faktörleri ve sonuçları belirlendi.

Bulgular: Bu çalışmaya toplam 176 COVID-19 hastası dahil edildi. Tüm hastalarda anal fissür görülme sıklığı %36,9 idi. Hastalar iki gruba ayrıldı; çatlak ve çatlak olmayan gruplar. Fissür grubunda yaşın daha küçük olması dışında demografik verilerde anlamlı bir farklılık görülmedi. Anal fissürlerin çoğunluğu, hastalar spesifik bir tedavi olmaksızın COVID-19 semptomlarından kurtulduktan sonra (%43,1) kendiliğinden düzeldi.

Sonuç: Anal fissür, COVID-19 hastalarında oldukça sık görülen bir sorundur. Genç ve orta yaşlı hastalar, COVID-19 enfeksiyonundan sonra anal fissür geliştirmeye daha yatkındır.

Anahtar Kelimeler: COVID-19, gastrointestinal semptomlar, anal fissür, risk faktörleri

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ORIGINAL ARTICLE
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The clinical presentation of Meckel's diverticulum: Eight years experience

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ABSTRACT

Objective: Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract. It is commonly encountered during surgical practice as the cause of the patient's presentation or as an incidental finding during other unrelated procedures. This study aimed to evaluate the frequency of Meckel's diverticulum in our clinical practice and to provide an adequate level of knowledge of the clinical and diagnostic features and the management of Meckel's diverticulum.

Material and Methods: We analyzed the medical records of all cases who were diagnosed with Meckel's diverticulum at our hospital for over eight years. Age, sex, presentation, diagnostic procedures, surgical techniques, and histopathology were reviewed and analyzed.

Results: A total of 104 patients were enrolled in our study. Mean age was 28.8 years, with male predominance in 92 (88.5%) patients. Symptomatic Meckel's diverticulum was detected in 80 (77%) patients and in 24 (23%) incidental findings. The most common emergency presentation was abdominal pain with 34 patients (42.5%), then intestinal obstruction with 20 patients (25%), bleeding per rectum with 12 patients (15%), acute abdomen with nine patients (11.3%), and intussusception with five patients (6.2%). Mean length of the Meckel's diverticulum was 4.3 centimeters. Small bowel resection was performed in 41 (45.1%) cases, stapled resection in 44 (48.3%), and ligated Meckel's base in 6 (6.4%). Ectopic gastric mucosa was the most common finding in histopathology in 30 (28.8%) patients.

Conclusion: Our study supports that the longer Meckel's diverticulum is, the more prone it is to developing complications, and stapler resection and small bowel resection are considered safe techniques, as well as resection of incidental Meckel's diverticulum, which does not increase the risk of morbidity.

Keywords: Meckel's diverticulum, gastrointestinal tract, small bowel resection

INTRODUCTION

Meckel's diverticulum (MD) is the most common congenital malformation of the gastrointestinal tract (1-3). It was described first in 1598 by Fabricius Hildanus, then by Levator in 1617 and Ruysch in 1730, but its name is derived from Johann Friedrich Meckel, who described its embryological and pathological features in 1809 (4-7). It is present in approximately 2-3% of the population and located on the antimesenteric border of the ileum, approximately 45-60 cm proximal to the ileocecal junction, and its length ranges from 3-5 cm in most of the patients (8). It is a true diverticulum, i.e., the walls contain all the three layers of the intestinal wall, and it has its own blood supply arising from the superior mesenteric artery (9). The mucosa of the diverticulum may contain heterotopic gastric mucosa (50%), pancreatic mucosa (5%), and less commonly colonic mucosa, endometriosis, or hepatobiliary tissue. These types of mucosae make it vulnerable to other complications such as hemorrhage, chronic peptic ulceration, and perforation (9).

It is commonly encountered during surgical practice as the cause of the patient's presentation or as an incidental finding during diagnostic imaging or surgical procedures (10). It generally remains silent, but some serious complications may occur, thus increasing its importance in clinical practice, such as bleeding, intussusception, intestinal obstruction, perforation, fistulas, or umbilical sinuses, and tumors (10,11). Bleeding is life-threatening in childhood, while intestinal obstruction is more common in adulthood (1,12,13).

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Preoperative diagnosis of a complicated MD can be challenging and is often difficult to establish because the clinical symptoms and imaging features of a complicated MD overlap with those of many other disorders that cause acute abdominal pain or gastrointestinal bleeding (14). Complications are more common in younger patients and decrease with advancing age (3). In this retrospective study, we aimed to evaluate the frequency of MD in our clinical practice and to provide an adequate level of knowledge of the clinical presentation and diagnostic features as well as the management of MD in all age groups.

MATERIAL and METHODS

Archive records of our surgical facilities from January 2015 to April 2023 were analyzed retrospectively. Files of patients with MD were reviewed. Age, sex, presenting symptoms, and preoperative diagnoses were recorded. Pediatric patient was defined as a patient younger than 14 years according to our hospital rules and an adult patient who is 14 years of age or older.

Symptomatic cases presenting with abdominal pain, gastrointestinal bleeding, intestinal obstruction, or intussusception, were evaluated with the preoperative diagnostic procedures used in each case, such as ultrasound, endoscopies, including capsules, computer tomography (CT), magnetic resonance imaging (MRI), CT, and MRI enterocolitis or Meckel's scan. The details of the management approach and surgical procedure, open or laparoscopic are shown in Figure 1. Intraoperative findings and types of MD resections were collected. Cases detected incidentally during another surgical procedure were classified as incidental findings or asymptomatic (Figure 2). Remarkably, in three cases, there was a traumatic penetration by a foreign body fish bone (Figure 3).

The indications and type of resection were evaluated. The length and base width of the diverticulum was collected from preoperative diagnostic imaging, an operative note, or a pathology report.

Hospital stay, mortality and morbidity rates were calculated for cases that underwent MD resection. Histopathology results were also retrieved to look for the presence of inflammation, ectopic tissue, or neoplastic changes within the diverticulum. Data are displayed in terms of frequency, mean, median, and standard deviations. Proportions are compared with the Chi-square test, and statistical calculations were done using the Statistical Package for Social Sciences (SPSS 25, IBM, USA).

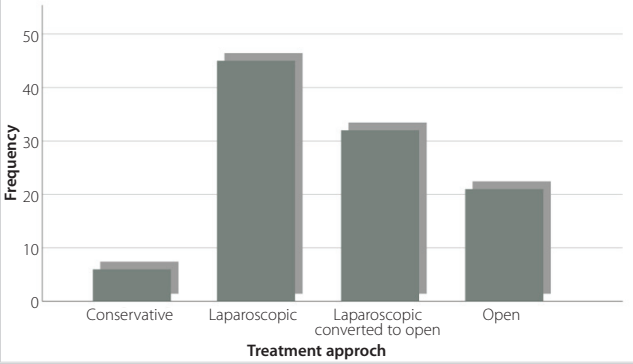

Figure 1. Types of management approaches and frequency of surgical procedures.

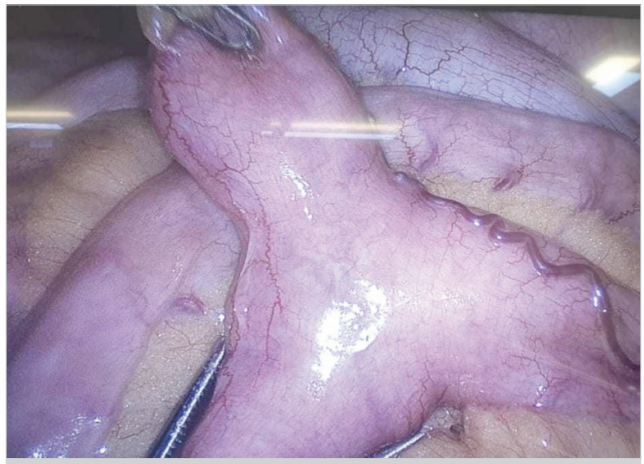

Figure 2. Meckel's diverticulum was discovered as an incidental finding in unrelated surgical procedures.

Figure 3. Perforation of Meckel's diverticulum by fish bone.

The authors declare that they have no conflict of interest, and the study was approved by the Institutional Review Board (IRB) (MRC-01-24-528).

RESULTS

A total of 104 patients were included in our study. Mean age of the involved patients was 28.87 years (ranging from one year to 70 years), with male predominance at 92 (88.5%) compared to 12 (11.5%) females. Mean age of the pediatric patients was 6.52 years, with 16 (76.2%) males and 5 (23.8%) females, while in the adult age group, mean age was 34.53 years, with 76 males (91.6%) and seven females (8.4%). Upon review of patient's files,

we found 80 (77%) patients presented with symptomatic MD, 67 (95%) were adults, and 13 (5%) were pediatrics, while in 24 (23%) cases, MD was found incidentally during unrelated surgical procedures (Figure 2). In symptomatic cases, the most common presenting symptom was abdominal pain in 34 (42.5%), followed by intestinal obstruction in 20 (25%), bleeding per rectum in 12 (15%), acute abdomen in 9 (11.3%), and intussusception in 5 (6.2%). There was a variation between adult and pediatric patients: abdominal pain was the most common finding in adult patients, 34 (50.7%), followed by intestinal obstruction, 17 (25.4%), and in pediatric patients, bleeding per rectum was the most common, 5 (38.5%), followed by intestinal obstruction, and intussusception, 3 (23.1%) for each.

Regarding the diagnostic tests used in our study, we found plain abdomen x-rays were done in 73 (70%) cases, ultrasonography in seven (6.7%) cases, CT scans in 75 (72.1%) cases, MRI enterocolitis in two (0.19%) cases, colonoscopy in eight (7.6%) cases, capsule endoscopy in two (0.19%) cases, and nuclear medicine (NM) scans in 11 (10.5%) cases. Preoperative pathological MD was diagnosed in 44 (56.2%) cases out of 80, 31 (38.7%) by CT scan, and seven (8.7%) by NM scan, three (3.7%) by US, two (2.5%) by MRI enterocolitis, and two (2.5%) by endoscopy capsule.

Ninety-eight (94.2%) patients underwent surgical procedures in this series; open approach was performed in 21 (21.4%) cases and laparoscopic in 77 (78.6%) cases, with conversion to open in 32 (41.5%) cases. Among the 80 symptomatic cases, 74 (92.5%) of them underwent surgical procedures with MD resection, and six (7.5%) patients were treated conservatively. Out of 74 operated-symptomatic patients, 38 (51.4%) underwent small bowel resection and anastomosis (SBR), 34 (45.9%) underwent stapler MD resection (SR), and two (2.7%) underwent ligated MD base. In 24 unrelated surgery procedures where the MD was found incidentally, 17 (70.8%) cases underwent MD resection, three (12.5%) cases by SBR technique, 10 (41.6%) cases by SR, and four (16.6%) cases by ligated MD base. Intraoperative findings in symptomatic MD as described in Table 1 showed normal MD in 12 cases (16.3%), intestinal obstruction due to the MD band in 20 (27%), inflamed MD in 19 (25.6%), perforated MD in 13 (17.5%), intussusception in 5 (6.8%), and mass formed by MD in 5 (6.8%).

Mean length of the diverticulum was 4.3 cm, and mean width was 2.4 cm. In operative cases, drain was used in 18 (18.4%) cases, with a mean duration of 6.27 days. Mean hospital stay was 8.1 days. Morbidity was recorded in eight (8.16%) cases, and four (4%) cases with wound infection, and four (4%) cases reoperated due to abdominal collection in one (1.02%) case, lower GIT bleeding in one (1.02%) case, wound dehiscence in one (1.02%) case, and a second look in one (1.02%) case. Mortality was recorded in one (1.02%) case.

Out of 91 resected Meckel's diverticula, they were sent for histopathological examination, which showed normal wall MD in 37 (40.6%), acute inflammation in the wall of the diverticulum in 31 (34.1%), chronic inflammation in 12 (13.2%), and perforated MD in 11 (12.1%). The absence of any abnormal mucosa was found in 47 cases (51.7%), and their presence was detected in 44 cases (48.3%); ectopic gastric mucosa was detected in 22 cases (24.2%), ectopic pancreatic mucosa in two cases (2.2%), ulcerated mucosa in 10 cases (10.9%), mixed gastric and pancreatic in three cases (3.3%), mixed gastric and ulcerated in four cases (4.4%), reactive lymphoid in two cases (2.2%), and the presence of follicular hyperplasia was detected in one case (1.1%).

Table 1. Clinical presentation, treatment approach, and operative findings of study cases

Symptoms	Treatment approach/No of cases		Operative finding/No of cases		No	%
Symptomatic Meckel's diverticulum						
Abdominal pain	Conservative Laparoscopic resection Laparoscopic to open surgery Open resection	6 15 8 2	Not operated Inflamed Meckel's diverticulum Phlegmon Perforated Meckel's diverticulum	6 19 5 4	34	32.6%
Acute abdomen	Laparoscopic resection Laparoscopic to open surgery Open resection	2 6 1	Perforated Meckel's diverticulum	9	9	8.6%
Bleeding per rectum	Laparoscopic resection Laparoscopic to open surgery Open resection	5 6 1	Congested Meckel's diverticulum	12	12	11.5%
Intestinal obstruction	Laparoscopic resection Laparoscopic to open surgery Open resection	9 9 7	Meckel's diverticulum band Intussusception	20 5	25	24%
Asymptomatic Meckel's diverticulum						
Incidental finding	Unrelated surgical procedures		Normal Meckel's diverticulum		24	23%

DISCUSSION

MD is considered the most common congenital malformation of the gastrointestinal tract, with an incidence rate around 2% (15). The lifetime risk for the development of complications related to MD is estimated to be around 4%, and the probability for the development of complications decreases with age (3,15-17). In our series, we found the commonest presentation was with abdominal pain in 34 patients (42.5%), while intestinal obstruction is the most common presenting symptom in adults, and the bleeding per rectum is the most common in pediatrics (1,12,13,15). Surgical resection is the main treatment for symptomatic MD, but there is still debate on asymptomatic cases (14). Ectopic gastric mucosa is predominant, and bleeding is mostly related to it, but not all ectopic gastric mucosa can cause bleeding (18,19).

With exceptions for patients presenting with symptoms of bleeding, a preoperative diagnosis of symptomatic MD is difficult and may be challenging (14,20). This is because the clinical and radiological findings resemble those of other acute abdominal conditions. Proper preoperative diagnosis was achieved in 45 patients (56.25%). In doubtful symptomatic cases, diagnostic laparoscopy was done, and it was a good option as both a diagnostic and therapeutic procedure (20). Most of the cases were operated laparoscopically with conversion to open in 29 patients (48.3%) cases. Conversion rate was nearly 50% due to limited visualization, difficult dissection, as documented in the operative note, and, to some extent, the surgeon's experience. When the length of MD (> or < 2 cm) was compared between symptomatic and asymptomatic patients, it was found that the length of MD in the symptomatic group was significantly longer than that in the asymptomatic (p value 0.0148), supporting the fact that longer diverticula are more likely to develop complications (9,15,18).

As the treatment of symptomatic Meckel's requires definitive surgical intervention, elective surgery is not recommended for cases where the MD is discovered incidentally on radiological imaging (14,18,21,22). Although there is agreement for prophylactic resection of incidentally discovered MD in young patients, it is still controversial in adult patients, and its removal is recommended only in the presence of risk factors such as male sex, age smaller than 45 years, the length of the MD greater than 2 cm, and the presence of a thick wall or fibrous band (18,21,22). The debate is between the risk of developing life-threatening complications post-prophylactic resection and the risk of future complications if unresected silent MD (23-25). A previous research has reported a 2% complication rate after MD resection over 20 years and a 6% lifetime risk of developing complicated MD presentations necessitating surgical management (26). So, they are arguing prophylactic resection if there are no contraindications like immunosuppression or hypoalbuminemia to avoid the risk of developing the future life-threatening presentation that is not decreasing with age (3,15,16,17,26). However, other literature does not share this view who found that the risk of postoperative complications after prophylactic resection is 5% and about 750 to 800 prophylactic resections would have to be done in order to save one life (27,28). Because of the lack of long-term follow-up, we cannot assess the late complications between patients with resected and non-resected MD. Therefore, it is essential to evaluate each case individually to determine whether to resect or not, taking into consideration the risk factors, the patient's condition, and the experience of the surgeons. In comparison of the complication rate post-MD resection in symptomatic and asymptomatic cases, it was found that the complication rate in symptomatic patients was higher than that in asymptomatic patients with statistical significance (p value 0.0144), and there was no difference in the complication rate between resected and non-resected MD in asymptomatic patients (p value 0.892), which supports that the resection of incidental MD, if indicated during an unrelated surgery procedure, does not increase the risk of postoperative complications (25).

The selection of the surgical procedure depends on the type of presentation, the character of the base of the diverticulum, its length, and the status of the adjacent ileum (9,15,29). In diverticula that are short and broad-based, the ectopic tissue may theoretically extend into the base and the ileum, with the potential for complications related to acid secretion and malignant transformation (9,15,29). Thus, the surgical objective is to resect all ectopic mucosa without increasing patient operative morbidity. Therefore, SBR with primary anastomosis is commonly performed and advisable over SR to ensure complete resection of any heterotopic mucosa or intestinal ulcer and to avoid the restriction of the bowel lumen (9,30). This study demonstrated that both SBR and SR techniques were safe in emergency and incidental settings using an open or laparoscopic approach based on surgeon preference. When comparing the complications presented in both techniques, no statistically significant difference was found (p value 0.396).

The resected samples of both symptomatic and asymptomatic MD were examined by histopathology. Normal MD was found in cases with resection of silent MD or intestinal obstruction caused by the MD band. There is agreement that ectopic gastric tissue is the commonest and the main cause of bleeding MD, which was our finding in this study as detected in 29 cases (65.9%) (2,31). The anticipated complication rate for Meckel's resection is approximately 5%, and the most common complications are surgical site infection, prolonged postoperative ileus, and anastomotic leak, which are expected for any small bowel surgery (11,16,18,25). Death related specifically to the resection of MD is rare, with an estimated incidence of 0.001% (27).

In our study, morbidity was recorded in 8 (8.16%) cases, we also recorded one death (1%) because of multiple co-morbidities and not directly related to MD complications.

CONCLUSION

Our study supports that the longer MD is, the more prone it is to cause complications, and stapler resection and small bowel resection are considered safe techniques, as well as resection of incidental MD, which doesn't increase the risk of morbidity.

Ethics Committee Approval: The study was approved by Hamad Medical Corporation Medical Research Center (Decision no: MRC-01-24-528, Date: 08.09.2024).

Peer-review: Externally peer-reviewed.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (4): 343-348

Meckel divertikülünün klinik görünümü: Sekiz yıllık deneyim

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ÖZET

Giriş ve Amaç: Meckel divertikülü gastrointestinal sistemin en sık görülen konjenital anomalisidir. Genellikle cerrahi uygulamalar sırasında hastanın başvurusunun nedeni olarak veya diğer işlemler sırasında tesadüfi bir bulgu olarak karşılaşılmaktadır. Klinik pratiğimizde Meckel divertikülü sıklığını değerlendirmek ve Meckel divertikülünün klinik ve tanısal özellikleri ile yönetimi hakkında yeterli düzeyde bilgi sağlamak amaçlanmıştır.

Gereç ve Yöntemler: Sekiz yılı aşkın süredir hastanemizde Meckel divertikülü tanısı konulan tüm vakaların tıbbi kayıtlarını inceledik. Yaş, cinsiyet, sunum, tanı prosedürleri, cerrahi teknikler ve histopatoloji gözden geçirildi ve analiz edildi.

Bulgular: Çalışmamıza toplam 104 hasta dahil edildi; ortalama yaş 28,8 olup 92 (%88,5) hastada erkek çoğunluktaydı. Hastaların 80'inde (%77) ve 24'ünde (%23) tesadüfi bulgularla semptomatik Meckel divertikülü tespit edildi. En sık görülen acil başvuru şekli karın ağrısı 34 (%42,5), bağırsak tıkanıklığı 20 (%25), rektum başına kanama 12 (%15), akut karın 9 (%11,3) ve invajinasyon 5 (%6,2) idi. Meckel divertikülü ortalama uzunluğu 4,3 santimetre idi. Olguların 41'ine (%45,1) ince bağırsak rezeksiyonu, 44'üne (%48,3) zımbalı rezeksiyon, 6'sına (%6,4) Meckel tabanı bağlandı. Histopatolojide 30 (%28,8) hastada en sık görülen bulgu ektopik mide mukozasıydı.

Sonuç: Çalışmamız, Meckel divertikülü ne kadar uzun olursa komplikasyon gelişme olasılığının da o kadar yüksek olduğunu, stapler rezeksiyonu ve ince bağırsak rezeksiyonunun güvenli teknikler olarak kabul edildiğini, ayrıca tesadüfen Meckel divertikülü rezeksiyonunun morbidite riskini arttırmadığını desteklemektedir.

Anahtar Kelimeler: Meckel divertikülü, gastrointestinal sistem, ince bağırsak rezeksiyonu

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TECHNICAL REPORT
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How we do it: Songket suture technique for lying half cone dog ear

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ABSTRACT

Dog ear deformities in wound closure can lead to cosmetic concerns and discomfort for patients, particularly when there is unequal wound length, resulting in lying half cone-type dog ears. Managing these deformities involves aligning the longer side with the shorter side without extending the wound. The Songket suture technique, implemented in a two-stage process, has shown effectiveness in addressing this issue, especially in patients undergoing modified radical mastectomy with a crescent incision that we have presented.

Keywords: Songket suture, lying half cone, dog ear deformity

INTRODUCTION

Dog ear was initially defined by Limberg as a cone-shaped deformation of wound tissue (1). Dog ear formation post-surgical wound closure is primarily associated with cosmetic concerns, although patients may also experience pain and discomfort. The development of dog ears is influenced by factors such as the form of the lesion, its location, and the skin's elasticity (2).

Borgess further categorizes dog ears into two types: the most common type of dog ear is a standing full cone caused by excess tissue at both margins of skin excision, typically occurring when the wound's length to width ratio is less than 3:1; and the lying half cone, due to excess tissue on one side only, forms asymmetrical elliptical lesions with a noticeable length discrepancy between the two sides of the ellipse (Figure 1,2) (1,3).

How We Do It

Standing full cone type dog ear occurs when the elliptical incision line is too short, the treatment is just to extend the elliptical incision to the point where the dog ear can be removed (1,3). Unequal wound length is the main issue affecting the development of lying half cone-type dog ears. The main purpose of management is to adjust the longer side to fit the shorter side. In order to fix lying half cone-type

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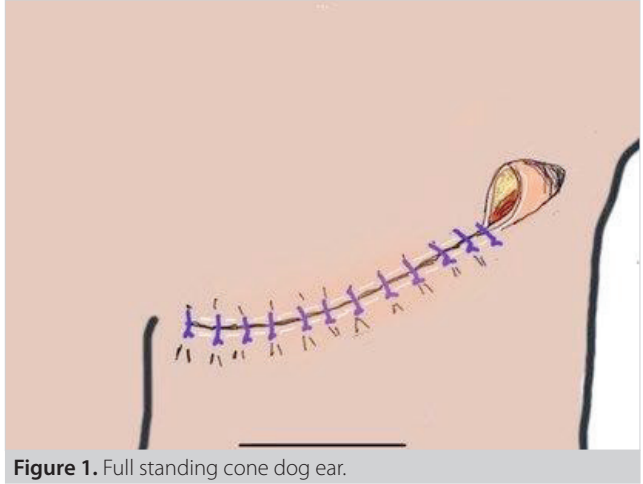

Figure 1. Full standing cone dog ear.

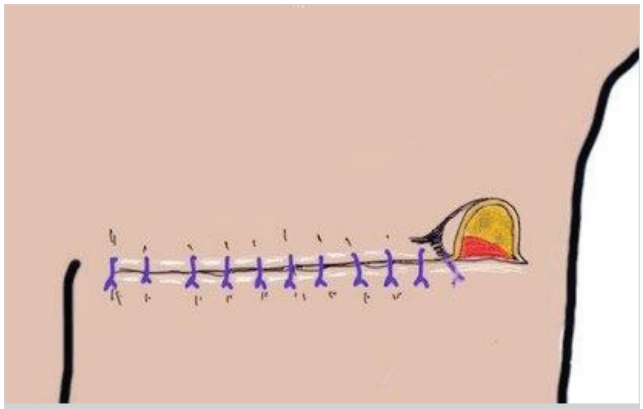

Figure 2. Half lying cone dog ear.

dog ears both functionally and attractively without extending the wound's length, we suggest using the Songket suture technique (4,5).

The stages of Songket suture technique are:

1. Rule of Halfs Pattern

The surgical wound closure technique relies on the rule of halfs pattern to prevent dog ear at the wound's end. It occurs by determining the starting point of the suture (key suture) in the middle of the shorter wound flap (minor curvature) and longer wound flap (mayor curvature) (Figure 3).

Once the initial key suture is formed, the remaining flaps of the major and minor curvature are used to establish the second and third key sutures, and so on, ensuring that there are no dog ears, as shown in Figure 4.

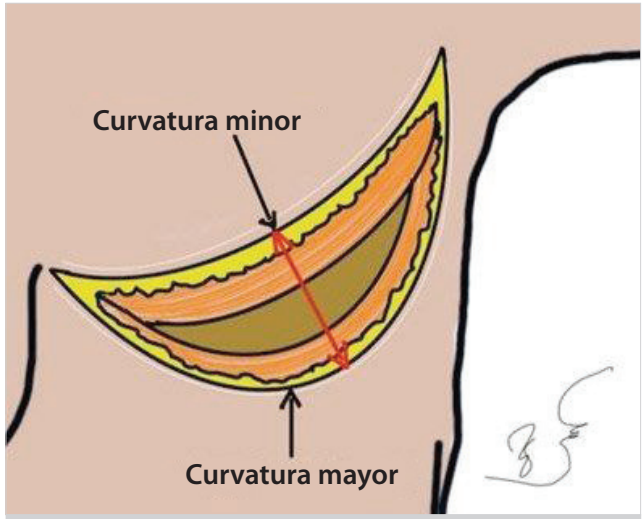

Figure 3. Mayor and minor curvature.

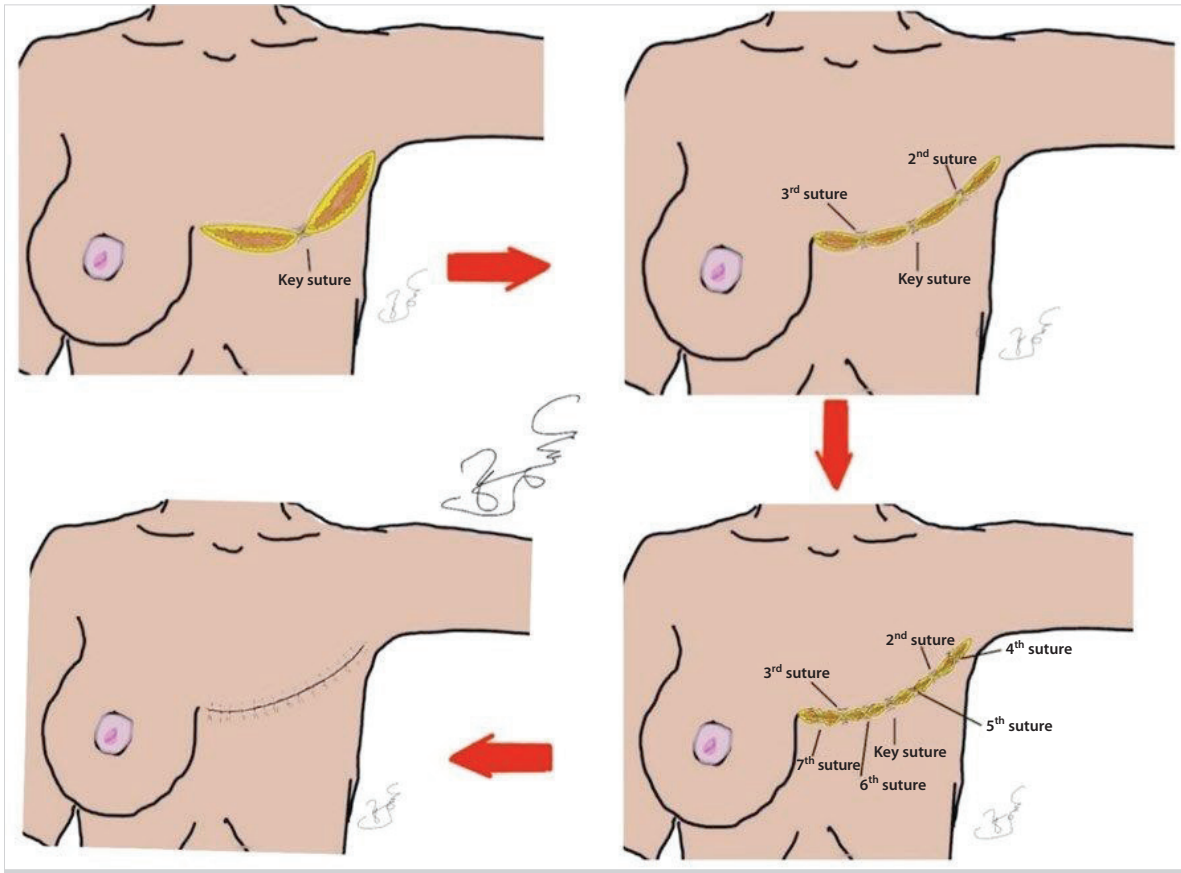

Figure 4. Rule of halfs pattern.

2. Buried Mixed Mattress Suture

The wound suturing technique used is buried mixed mattress suture, which is a combination of buried horizontal mattress on the major curvature and buried vertical mattress on the minor curvature (Figure 5,6).

We applied this Songket suture technique on patients who had undergone modified radical mastectomy (MRM) using cressent incision, as shown in Figure 7.

CONCLUSION

Addressing dog ear deformities necessitates a comprehensive approach that considers wound characteristics, patient anatomy, and cosmetic goals. Utilizing the Songket suture technique, surgeons can effectively manage dog ears and enhance postoperative patient satisfaction.

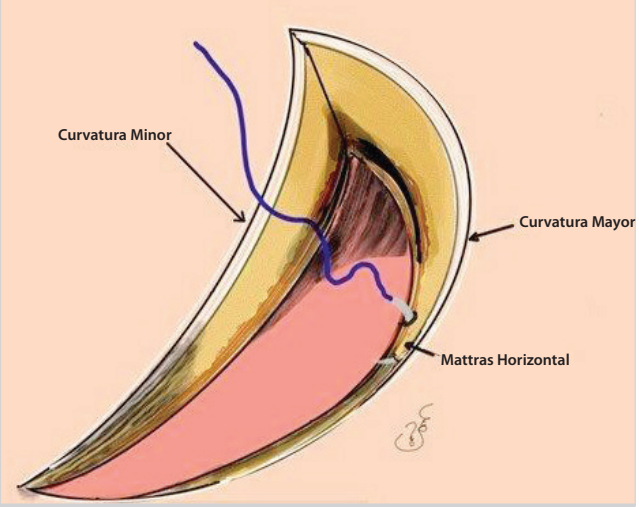

Figure 5. Buried horizontal mattres suture on the mayor curvature.

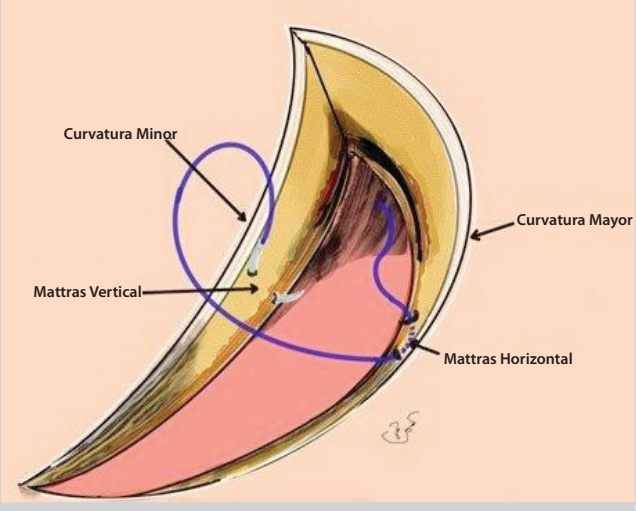

Figure 6. Buried vertical mattres suture on the minor curvature.

Figure 7. Result of Songket suture technique on patients whose performing MRM.

Peer-review: Externally peer-reviewed.

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

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TEKNİK SUNUM-ÖZET
Turk J Surg 2024; 40 (4): 349-352

Nasıl yapıyoruz? Yarım konik köpek kulağı deformitesinde Songket dikiş tekniği

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ÖZET

Yara kapanmasındaki köpek kulağı deformiteleri, özellikle eşit olmayan yara uzunluğu olduğunda, hastalar için kozmetik kaygılara ve rahatsızlığa yol açabilir, bu da yarım konik tipi köpek kulaklarına neden olur. Bu deformitelerin yönetimi, yarayı uzatmadan uzun tarafın kısa tarafla hizalanmasını içerir. İki aşamalı bir süreçte uygulanan Songket dikiş tekniği, özellikle sunduğumuz hilal insizyonlu modifiye radikal mastektomi geçiren hastalarda bu sorunu ele almada etkili olduğunu göstermiştir.

Anahtar Kelimeler: Songket dikişi, yarım konik, köpek kulağı deformitesi

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CASE REPORT
Turk J Surg 2024; 40 (4): 353-356

Osteosarcoma metastatic to the thyroid gland: A rare case report

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ABSTRACT

Sarcoma is rarely seen in the thyroid gland and it is difficult to differentiate it from anaplastic thyroid carcinoma. Extraosseus osteosarcoma, a rare malignant nonepithelial neoplasia, can be seen in the thyroid gland, breast, soft tissue, and intraabdominal organs. A 31-year-old woman with a previous history of osteosarcoma of distal femur was presented with a constantly growing mass in her neck accompanied with progressive shortness of breath and worsening dysphagia. On physical examination, a 4 x 5 cm firm mass was palpated in the left lobe of her thyroid gland. Seven years ago, during her pregnancy, she was diagnosed with osteosarcoma of the distal femur and she received chemotherapy and radiotherapy after medical abortion. A year after her initial diagnosis, she underwent surgery for osteosarcoma. Two years later, pulmonary metastasis was detected incidentally in her control computed tomography. She was operated for pulmonary metastasis since there was no remission after chemotherapy. When she presented to the clinic with a neck mass, her thyroid function tests were within the normal range. On computed tomography scan, a 2.5 cm calcified lesion in left lobe of her thyroid gland was detected. Fine-needle aspiration of the thyroid mass displayed numerous discohesive pleomorphic tumors cells identical to osteosarcoma cells seen on her previous knee biopsy specimen. On positron emission tomography, a 3 x 3 x 4.5 cm hypermetabolic lesion with pathologic 18F-FDG uptake on the left side of her neck in thyroid cartilage level was detected. A bilateral total thyroidectomy was performed. The patient was discharged without any complications.

Keywords: Osteosarcoma metastasis, thyroid gland, pathology, fine-needle aspiration, cytology

INTRODUCTION

Osteosarcoma is a high-grade malignant tumor arising from bone and producing osteoid (1). Primary osteosarcoma is most commonly encountered in the distal femur, proximal tibia, and proximal humerus (1). It is the most common primary skeletal malignancy in children and young adults (2).

In autopsy series, the incidence of metastasis to the thyroid gland ranges from 1.2% to 24% (3). But in the clinic, osteosarcoma metastasis is not very frequent. In both clinical and autopsy case series, renal cell carcinoma, breast, lung cancer are the most frequent primary tumor sites metastasizing to the thyroid gland. Although the thyroid gland is highly vascular, metastasis to this gland is infrequent (4). The rarity of metastasis to the thyroid gland is speculated to be due to high oxygen saturation and iodine content of thyroid gland and its fast blood flow (5).

CASE REPORT

A 31-year-old woman with a history of osteosarcoma of distal femur was presented with a constantly growing mass in her neck accompanied with progressive shortness of breath and worsening dysphagia in September 2019. In physical examination, a 4 x 5 cm firm mass was palpated in her left lobe of the thyroid gland.

In 2012 during her pregnancy, she was diagnosed with osteosarcoma around her right knee and had five sessions of chemotherapy and a month-long radiotherapy after medical abortion. A year after her initial diagnosis, she underwent surgery for osteosarcoma and in 2014 she had two prosthesis operations for her distal femur and proximal tibia. In 2015, pulmonary metastasis was detected incidentally on a routine computed tomography and she received chemotherapy. Failing to resolve, she underwent surgical treatment for pulmonary metastasis.

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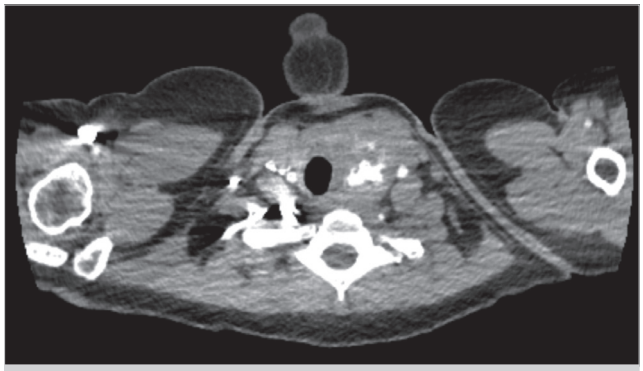

Figure 1. Computed tomography image of thyroid mass.

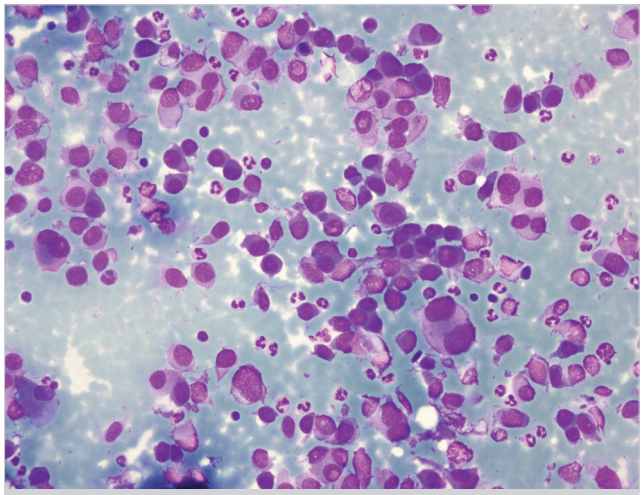

Figure 2. Fine needle aspiration biopsy hypercellular aspirates showing numerous discohesive tumor cells with intranuclear pseudoinclusions (×400, May Grünwald Giemsa).

When she presented to the clinic with a neck mass, her thyroid function tests were within the normal range. On computed tomography, a 2.5 cm calcified lesion in the left lobe of her thyroid gland was detected (Figure 1). The patient underwent ultrasound-guided fine-needle aspiration (FNA), which showed

Figure 3. Macroscopic examination, the tumor is gray- lobulated cut surface.

predominantly discohesive atypical pleomorphic tumor cells. In light of our patient's previous history, the FNA findings were most consistent with metastasis of osteosarcoma. (Figure 2). On positron emission tomography, a 3 x 3 x 4.5 cm hypermetabolic lesion with pathologic 18F-FDG uptake on the left side of her neck in thyroid cartilage level was detected (SUV_{max}= 12.7). Sutureless bilateral total thyroidectomy was performed with intraoperative neuromonitoring and the patient was discharged without any complication.

Serial sections through the left lobe of the thyroid showed gray lobulated firm mass surface with areas of necrosis and calcification. Chondroid appearance in peripheral zones was seen (Figure 3). Histopathological examination of the lesion revealed thyroid parenchyma with interstitial infiltrates of high-grade malignant neoplasm composed of polygonal cells and hyperchromatic nucleus presenting high mitotic index and necrotic areas and osteoid formation and confirmed osteosarcoma metastasis to the thyroid gland (Figure 4a, 4b).

Informed consent was taken from the patient.

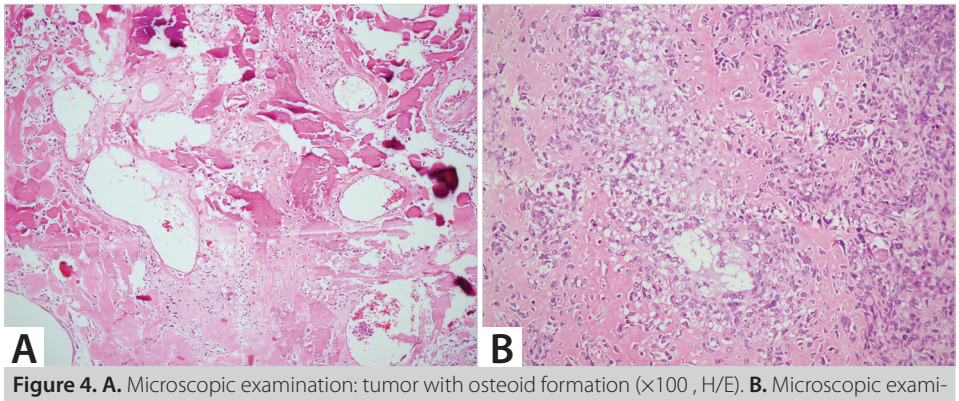

Figure 4. A. Microscopic examination: tumor with osteoid formation (×100 , H/E). **B.** Microscopic examination: High grade malignant neoplasm composed of polygonal cells of intermediate site and hypercromatic nucleus (×200, H/E).

DISCUSSION

Mesenchymal cells producing immature osteoid are the characteristic histopathologic feature of osteosarcoma. Similarly, pathologic examination of our specimen revealed interstitial infiltrates of high-grade malignant neoplasm and osteoid formation (2).

Most patients with metastasis to the thyroid gland remains asymptomatic unlike our case presenting with a growing mass accompanied by respiratory symptoms (4). In a study on 22 patients diagnosed with metastasis to the thyroid gland, 14 patients presented with palpable thyroid nodules similar to our case (6).

In a review article, 372 cases reported between 2000 and 2010 were analyzed (7). The mean age of the patients was found to be 59 years and the female to male ratio was found to be 1.4. The most frequently reported cancer metastatic to the thyroid gland was renal cell carcinoma followed by colorectal, lung, breast cancer. Only 4% of the reviewed cases were sarcomas. The interval between the initial diagnosis and metastasis was the longest with 75 months in sarcomas. For our case, this interval was almost seven years. In the same article, whether preexisting thyroid conditions such as primary thyroid neoplasm or benign thyroid conditions induce metastasis led to a controversy. Our case did not have any preexisting thyroid diseases. Also, most cases (87.6%) were euthyroid at the time of diagnosis of thyroid metastasis as our case (7).

Thyroid metastasis may be the initial evidence of diagnosis or recurrence of the primary tumor. The diagnosis was made through clinical complaints. Until proven otherwise in a patient with a history of a primary tumor, a thyroid mass should be treated as a metastatic lesion. In the review of Chung et al., it was shown that 24% of FNAs were incorrect (7). In another study, positive and negative predictive values of the fine-needle aspiration in metastasis to the thyroid gland were 89% and 93% respectively (8). A primary tumor and metastatic malignancy can be differentiated by immunohistochemical markers. Immunostaining of thyroid tumors is important in patients with a known malignancy and with appropriate immunohistochemical markers correct diagnosis can be made.

Without a history of osseus osteosarcoma, primary thyroid osteosarcoma may be kept in mind (9). It presents with an expanding lesion similar to our case. So it is clinically impossible to distinguish a primary thyroid cancer from metastasic neoplasm. FNA is a powerful tool in the diagnosis of metastatic malignancies of the thyroid. Kim et al. found patients with metastatic cancer to the thyroid diagnosed by FNA in a retrospective research (6).

In metastatic diseases, it is crucial to decide when to operate. Unnecessary surgery in patients with poor prognosis should be avoided (10). Total thyroidectomy or thyroid lobectomy is a mainstay of local treatment for metastasis of osteosarcoma (11). In a study, total thyroidectomy is favored since with lobectomy, there can be positive margins but total thyroidectomy seems to decrease recurrence (8). Total thyroidectomy both rules out the disease and treats the metastatic disease.

Survival after thyroidectomy depends on the primary tumor. Management of a metastatic patient depends on the primary tumor site, the extent of disease, metastasis to other sites, symptomatic patients. The extent of the disease and the stage of the primary tumor have a greater impact on survival (7).

Osteosarcoma metastasizes first to the lungs and it is the most common site of metastasis with more than 80% of initial metastases (11). Distant metastasis can occur in 25-30% of patients who were treated (11). The site and timing of the metastasis are crucial. While metastatic disease at presentation has a bad prognosis, patients with metastatic disease at least two years after the initial treatment have a better prognosis (1). Patients with longer disease-free survival have a better prognosis (1). Also, resectable metastatic osteosarcomas have better prognosis (1). In our case, the patient was diagnosed at a younger age, she had a disease-free period of two years till her first metastasis to lungs and four years of disease-free survival till her second metastasis to the thyroid gland. Both of the metastatic sites were resectable. Due to the site and timing of her disease, her prognosis seems to be better.

Resectable disease and the extent of the disease have an impact on survival. Treatment options should be selected carefully for each case considering metastasis site, tumor resectability, and duration between the initial diagnosis and metastasis (12).

CONCLUSION

In a patient with a prior history of malignancy presenting with a neck mass, a possible metastasis from the primary tumor site should be kept in mind.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - TÖ, LU; Design - TÖ; Supervision - ST; Materials - LU, TÖ; Data Collection and/or Processing - LU, SS; Analysis and/or Interpretation - İO, ST; Literature Search - SS; Writing Manuscript - SS, İO; Critical Reviews - ST, İO.

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.

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OLGU SUNUMU-ÖZET
Turk J Surg 2024; 40 (4): 353-356

Tiroid bezine osteosarkom metastazı: Nadir bir olgu

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ÖZET

Sarkom, tiroid bezinde nadir görülür ve anaplastik tiroid kanserinden ayırıcı tanısı zordur. Nadir epitelyal olmayan, malign neoplazi olan kemik dışı osteosarkom, tiroid bezinde, memede, yumuşak dokuda ve batın içi organlarda görülebilir. Daha önce distal femurda osteosarkom öyküsü olan 31 yaşındaki kadın hasta, nefes darlığı ve disfajiye neden olan boyunda büyüyen kitle ile başvurdu. Fizik muayenesinde tiroid bezinin sol lobunda 4 x 5 cm sert kütle palpe edildi. Hasta, yedi yıl önce gebelik döneminde distal femur osteosarkomu teşhisi almış, medikal abort sonrası kemoterapi ve radyoteapi almıştır. İlk tanısından bir yıl sonra, osteosarkom nedeniyle ameliyat edilmiş ve bundan iki yıl sonra çekilen kontrol tomografide insidental olarak akciğer metastazı tanısı almıştır. Kemoterapi sonrası remisyon gözlenmeyince akciğer metastazı nedeniyle ameliyat edilmiştir. Kliniğe boyunda kütleyle başvurduğunda tiroid fonksiyon testleri normaldi. Bilgisayarlı tomografide tiroid bezinin sol lobunda 2,5 cm kalsifiye lezyon izlenmiştir. Lezyonun ince iğne aspirasyonunda daha önceki diz biyopsisindeki osteosarkom hücrelerine benzeyen, çok sayıda diskoheziv pleomorfik hücreler saptanmıştır. Pozitron emisyon tomografisinde tiroid bezi sol lobunda 18F-FDG tutulumu olan, 3 x 3 x 4,5 cm hipermetabolik lezyon izlenmiştir. Yapılan bilateral total tiroidektomiyi takiben hasta komplikasyonsuz olarak taburcu edilmiştir.

Anahtar Kelimeler: Osteosarkom metastazı, tiroid bezi, patoloji, ince iğne aspirasyon, sitoloji

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CASE REPORT
Turk J Surg 2024; 40 (4): 357-360

First case of laparoscopic donor hepatectomy in Türkiye

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ABSTRACT

Living donor liver transplantation is an important treatment option in countries like ours where cadaver donors are insufficient. This surgery is a major operation for the donor as well as the recipient. We should minimize the damage to donors who come for organ donation in a healthy way and minimize the risks of such a major surgery. For this purpose, we have explained the details of the first laparoscopic donor hepatectomy surgery performed in our country.

Keywords: Live liver transplantation, donor hepatectomy, laparoscopy

INTRODUCTION

The advantages of laparoscopic surgery over open surgery such as smaller incision, less bleeding, faster recovery and faster return to normal life are well known. After the start of laparoscopic liver surgery 30 years ago, surgical techniques progressed to the first laparoscopic live donor liver transplantation (LDLT) in 2002 (1,2). Laparoscopic surgery is an effective way for the liver donors. Herein, we describe the details of the first laparoscopic living donor hepatectomy in Türkiye.

CASE REPORT

A 6-month-old (height 67.5 cm, weight 9.6 kg) boy suffering from biliary atresia was referred to our transplant center. The mother, a 30-year-old healthy person, volunteered to donate part of her liver. After a detailed evaluation was performed to rule out potential contraindications, living donation was accepted. Pre-donation workup for estimated graft weight was done with Myrian® Imaging Layer (Intrasense Company, Montpellier, France) and it was 200 g for the left lateral segment of liver. In the pre-operative imaging; the liver graft had a single left hepatic artery, a single ostium for the biliary ducts, and no anatomical variation in the left portal and hepatic veins were identified. The donor's consent for laparoscopic hepatectomy was obtained along with the approval of standard donor hepatectomy. And a pure laparoscopic left lateral sectionectomy was performed.

The Procedure

The donor was placed in supine and 30° reversed-Trendelenburg position with the surgeon standing between the patient's legs (Figure 1). Onset of surgery, 1.2 mg indocyanin green (ICG-Pulsion Medical Systems, Feldkirchen, Germany) dilated to 10 mL and was intravenously injected, thus allowing prompt visualization of the biliary duct. Of the five trocars (5/5/12/12/12 mm), 1 of 12 mm was inserted on the umblicus, 2 of 12 mm were inserted on the upper abdominal quadrants, and 2 of 5 mm were inserted lateral of upper abdominal quadrants (Figure 2). A 45° optical device (Karl Storz ICG fluorescent laparoscope, Tuttlingen, Germany) was used. The CO2 pressure was kept around 12 mmHg. The gallbladder was preserved. After a careful evaluation to search for anatomical landmarks, the falciform and the left triangular ligaments were divided with the Ligasure device (Covidien, USA) to

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Figure 1. Laparoscopic donor hepatectomy operation.

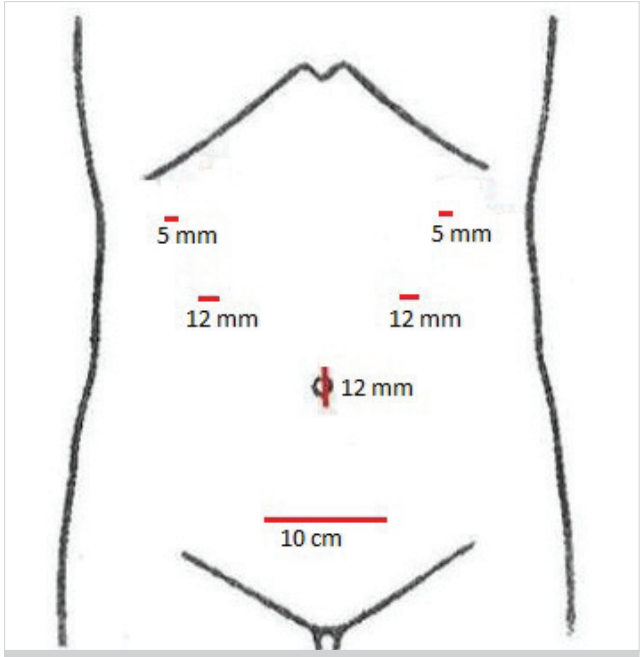

Figure 2. Placement of trocars.

release left lobe of liver and to find and tape the left hepatic vein. Thereafter, hilum dissection to expose, free and tape both the left hepatic artery and the left portal vein was done with hook. Caudate branches were sealed by Ligasure and hemoclips to maximize the length of the left portal vein. Parenchymal dissection was done using ultrasound dissector CUSA (Excel Valleylab, Integra, Ireland) along the right side of the falciform ligament. Low central venous pressure was used during parenchymal resection (<5 mmHg). Hemostasis and biliostasis of small vessels were made by bipolar electrocautery, Ligasure and using titanium clips. Once the dissection reached the hilar plate, the left biliary duct was clipped and cut under the negative fluorescence imaging guidance with straight laparoscopic scissors. The left hepatic vein was completely freed and taped at its confluence by cutting collaterals draining into the middle hepatic vein. A modified hanging maneuver was used during dissection with the CUSA. At this point, a Pfannenstiel incision was made, a 12 mm trocar was inserted to allow atraumatic harvesting of the graft via putting it into the endobag. The left lateral lobe was procured as follows: Hem-o-lock clip on the left hepatic artery, 30 mm Echelon Flex™ Staplers (Ethicon, USA) on the left portal vein and the left hepatic vein. After taking out the graft through the endobag with three minutes warm ischemia time, the graft (188 g) was flushed on the back table with 1 L of Belzer solution and the graft was prepared for transplantation. 3% hydrogen peroxide was sprayed on the liver cut surface to control bile leakage. After that, a silastic Jackson-Pratt (JP) drain under suction assured the drainage of the donor operative field (Figure 3). The total operative time of the donor surgery was 390 minutes. Liver transplantation was carried out with a total of five minutes donor warm ischemia time. The donor blood tests were normal except for a slight elevation in alanine aminotransferase (ALT) level. No blood transfusion is needed.

Figure 3. Postoperative insicision scars.

She was discharged on the fourth postoperative day (POD) after removing the JP drain. The donor was followed for two years with no complication.

Regarding the recipient, the early and late post-operative periods were uneventful.

DISCUSSION

Unfortunately, in the east, cadaveric organ donation is not sufficient for the treatment of liver diseases. In countries like ours, demand of organs are mostly provided by living donors, so LDLT has become a well-known treatment option for the patients with acute and chronic liver disease. With this surgery, a healthy person is exposed to a significant risk of morbidity and mortality for another person. Therefore donor surgery should be performed safely and possible complications should be minimized. It is essential that this risky situation is well understood by the donor. Laparoscopic donor hepatectomy surgery which should be performed by an experienced surgical team, providing less blood loss, earlier postop mobilization and oral intake, shorter hospital stay, and faster return to normal life (3).

In our case this life-saving procedure was performed for a pediatric patient from a living donor, who was a young and healthy mother. In important stages such as hepatic vein dissection and hilar dissection, it was possible to view the operative area from various angles with a magnified view, since the optical camera we use was 45°. In this way, the safety of the surgery is also increased. We used ICG to view the biliary tract. We were able to distinguish between the right and left bile duct very clearly and we were able to stay at a safe distance away from the right biliary tract while cutting the left bile duct and closing the stump. We used the technique of spraying 3% hydrogen peroxide on the cut surface, which is also described in the literature, in order to control possible bile leakage after parenchymal transection (4).

The duration of the operation is 390 minutes, and we think it will be shortened over time, considering the learning curve. Since there was no large incision in the upper abdomen after the surgery, pain was not a serious problem for our patient and she could tolerate breathing exercises very well. The patient, who had no problems in terms of mobilization and tolerating oral intake, could be discharged on the fourth POD. The patient did not require any peroperative or postoperative blood transfusions. And after two years, she is living her normal life and no complications have developed.

Living liver donors are generally young and healthy and care about cosmetic results. Although being a donor is not encouraged, there is a reality about the cosmetic advantage of laparoscopic surgery. In addition, it is obvious that by minimizing abdominal wall damage, the risk of complications such as incisional hernia and chronic wound pain is reduced (5,6).

Laparoscopic donor hepatectomy has been well validated for its safety and advantages. Nowadays, it has been pointed out that laparoscopic donor left lateral sectionectomy is considered the standard technique, and therefore, it has become a standard option recommended to donors in many experienced centers (7,8).

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

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Türkiye'deki ilk laparoskopik donör hepatektomi olgusu

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ÖZET

Canlı vericili karaciğer nakli bizimki gibi kadavra donörlerinin yetersiz kaldığı ülkelerde önemli bir tedavi seçeneğidir. Bu ameliyat, alıcı için olduğu kadar verici için de büyük bir ameliyattır. Sağlıklı bir şekilde organ bağışı için gelen donörlerin zararlarını en aza indirmeli ve böylesine büyük bir ameliyatın risklerini en aza indirmeliyiz. Bu amaçla, ülkemizde ilk kez gerçekleştirilen laparoskopik donör hepatektomi ameliyatının detaylarını anlattık.

Anahtar Kelimeler: Canlı vericili karaciğer nakli, donör hepatektomi, laparoskopi

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