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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.

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

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INSTRUCTIONS TO AUTHORS

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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.

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Manuscript Types

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- All videos will be peer reviewed.
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- 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:

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- All videos must contain an English narration.
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- The duration of the videos should not exceed five minutes and the maximum file size should be 300Mb.

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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 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.

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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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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.

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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.

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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.

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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.

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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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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.

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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.

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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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FROM THE EDITOR'S DESK
Turk J Surg 2022; 38 (4): IX
10.47717/turkjsurg.2022.20229008

Dear Readers of the Turkish Journal of Surgery,

I would like to start my words with sad news. We are saddened by the loss of Prof. Dr. Altan Tüzüner, a former president of the Turkish Surgical Association and a senior member of the editorial board of our journal. Prof. Tüzüner was a person who had great services to both the Turkish Surgical Association and our journal.

I wish condolences to his family and the Turkish surgical family.

In this December 2022 issue, you will have the chance to read very interesting studies. One of them is an important meta-analysis from India. Hernia surgery is an essential part of the daily routine of many surgeons in terms of daily patient load. Therefore I believe that the studies in hernia surgery bring very critical information for a significant number of readers. In this metaanalysis, Sinha et al. report whether a routine nerve detection has been performed during groin hernia surgery (1). It is a fact that revealing the nerve anatomy has a paramount importance in terms of postoperative pain. The interesting results of this meta-analysis show that this procedure is not regularly performed. I anticipate that the readers who are interested in hernia surgery will read this important meta-analysis with pleasure.

Another interesting study in this issue is about the gallbladder cancer. Gallbladder cancer is a relatively rare type of cancer and is known for its poor prognosis. In the last few decades, great advances have been made in the diagnosis and treatment of gallbladder cancer. Today, many patients are being diagnosed at an operable stage and more radical surgical procedures can be performed with improved liver surgery techniques. In addition to all these, many patients are referred to HPB surgery centers with -bad surprise- cancer diagnoses detected after cholecystectomy that had been performed for benign reasons. For all these reasons, studies on gallbladder cancer are very important. Uzun et al. report their experience on a large series of patients with gallbladder cancer (2). They are presenting the data on the long-term survival results, which is seldomly reported in the concerning literature. Therefore, I strongly recommend you to read this valuable study.

As of this issue, we are coming to the end of another publication year. In 2022, we were able to publish numerous important studies and I hope you had the chance to cite these articles in your works. On the other hand, I would like to remind you once again that our video article system as well as the instructions have been revised and technical facilities have been provided to the researchers who wish to send video articles to our journal. Turkish Journal of Surgery is an open access journal, and the published articles can be downloaded free of charge. In accordance with the publication policy of our journal, no fee is being charged for the submissions or accepted studies. Considering the current state of the scientific publishing worldwide, Turkish Journal of Surgery stands in a special place in this sense.

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

Best wishes,

Kaya SARIBEYOĞLU

Editor-in-Chief
Turkish Journal of Surgery

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ORIGINAL ARTICLE
Turk J Surg 2022; 38 (4): 315-326

Nerve identification in open inguinal hernioplasty: A meta-analysis

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ABSTRACT

Objective: In open inguinal hernioplasty, three inguinal nerves are encountered in the surgical field. It is advisable to identify these nerves as careful dissection reduces the chances of debilitating post-operative inguinodynia. Recognizing nerves during surgery can be challenging. Limited surgical studies have reported on the identification rates of all nerves. This study aimed to calculate the pooled prevalence of each nerve from these studies.

Material and Methods: We searched PubMed, CENTRAL, CINAHL, ClinicalTrials.gov and Research Square. We selected articles that reported on the prevalence of all three nerves during surgery. A meta-analysis was performed on the data from eight studies. IVhet model from the software MetaXL was used for preparing the forest plot. Subgroup analysis was performed to understand the cause of heterogeneity.

Results: The pooled prevalence rates for Ilioinguinal nerve (IIN), Iliohypogastric nerve (IHN), and genital branch of genitofemoral nerve (GB) were 84% (95% CI 67-97%), 71% (95% CI 51-89%) and 53% (95% CI 31-74%), respectively. On subgroup analysis, the identification rates were higher in single centre studies and studies with a single primary objective as nerve identification. The heterogeneity was significant in all pooled values, excluding the subgroup analysis of IHN identification rates in single-centre studies.

Conclusion: The pooled values indicate low identification rates for IHN and GB. Significant heterogeneity and large confidence intervals reduce the importance of these values as quality standards. Better results are observed in single-centre studies and studies which are focused on nerve identification.

Keywords: Hernioplasty, inguinal hernia, peripheral nerves

INTRODUCTION

Chronic inguinal pain is a known complication of groin hernia surgery. Mild to moderate inguinodynia is common, but some patients may experience severe pain (1). The etiology of pain is poorly understood, and injury to inguinal nerves may contribute to it (2,3). There is a need for meticulous dissection and identification of all inguinal nerves during surgery, which was first stressed by Amid 2004 from the Lichtenstein Institute (4). Subsequently, it was also endorsed by the European Hernia Society guidelines on the treatment of inguinal hernia and the international guidelines for groin hernia management (5,6).

Recognizing nerves during surgery can be challenging. Their numbers and positions vary, and one of the nerves (the genital branch of the genitofemoral nerve) is thin and inconspicuous. Studies have reported wide variations in nerve identification rates, making compliance with recommendations difficult. We need to calculate the pooled estimates from the available literature and search for the causes of variations, which will, in turn, increase our understanding of traditional hernioplasty surgery.

MATERIAL and METHODS

The study followed PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines (7,8).

Aim of the Study

The aim of the study was to calculate the pooled prevalence of nerve identification in open hernioplasty surgery and evaluate the effect of the study methodology on it. We also wanted to study the course of the nerves.

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Search Strategy

We searched the electronic database of PubMed/Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and Research Square in March 2022. The database of PubMed was searched with the following search strategies: Hernia, inguinal [Mesh] and peripheral nerves [Mesh], inguinal hernia [tiab] and nerves [tiab] and Lichtenstein repair [tiab]. We searched the database of CINAHL (EBSCO) with the following search strategy: inguinal hernia repair and inguinal nerves, keeping the search field optional. We searched the CENTRAL database with the terms inguinal hernia and inguinal nerves in the "title abstract keyword". We manually searched the references list of some of the review articles with the help of google scholar.

Inclusion and Exclusion Criteria

The articles on open inguinal hernia surgery that reported on all three inguinal nerves were included in the study. Prospective studies of all types (prospective comparative cohort, prospective non-comparative cohort and randomized controlled trials) were included. We excluded articles in which a report on any of the three inguinal nerves was missing.

Retrospective studies, case reports, editorials, conference proceedings and reviews were excluded. We excluded articles on ultrasound-guided nerve blocks or plane identification as they added bias to the objectives. The studies on cadavers, pediatric patients, and laparoscopic hernia surgeries were also excluded. The duplicates from the electronic search were removed manually.

Selection of Studies and Data Extraction

Based on inclusion and exclusion criteria, two authors, AB and PRT, independently identified the articles as included, excluded and uncertain. For uncertain articles, the full text was obtained and then reviewed. The consensus on included articles was reached through the involvement of author MKS.

Following Cochrane guidelines, a standard data collection sheet was prepared. The authors AB and MKS went through all the selected articles and collected data on the author, publication year, country, study type, sample size, objectives, methodology and results. The consensus was reached for any discrepancy in data by involving the author PRT.

Quality Assessment of the Included Studies

The included studies were separated into different types. Quality assessment of the randomized controlled trial was performed with software review Manager 5.4 (9). We assessed comparative cohort studies with the Newcastle Ottawa scale (NOS) and cohort studies without a comparison arm with JBI critical appraisal checklist for the case series (10,11). The authors AB and PRT independently performed quality assessment. The involvement of author MKS resolved any disputes.

Data Analysis

Data on nerve identification rates were extracted from the included studies. Binomial pooled prevalence was calculated, and forest plots were constructed using the Meta XL software. Statistical heterogeneity was measured with Cochrane's Q and I^2 statistics. The significance of heterogeneity was measured with the p-value. The funnel plots and the DOI plots were examined for asymmetry. We conducted a leave-one-out sensitivity analysis to understand the cause of heterogeneity. Subgroup analysis was conducted for objectives (single primary and multiple primaries) and the number of study centers (multi-centric and single center). An unweighted multiple regression analysis was conducted to identify the degree to which sample size, objectives and number of study centers were associated with nerve identification rates. SPSS 26.0 was used for regression analysis. The description of the course of the nerves was according to the source article.

RESULTS

The Outcome of Electronic Search

The PRISMA flow diagram of the study selection process is given in Figure 1. The initial search yielded 1214 articles, out of which 578 were duplicates, and 401 were ineligible for inclusion from titles/abstracts. The remaining 35 articles were searched for full text, and 32 articles were retrieved. Based on inclusion and exclusion criteria, the articles were further analyzed. After a careful review, only eight articles were selected for quantitative synthesis and systematic review (12-14).

Characteristics of the Included Studies

Characteristics of the included studies are presented in Table 1. The studies belonged to the period from 2006 to 2020. Two studies were from Brazil, and the remaining six were from Europe. The sample range was 29 to 973, with a median of 144. A total of 2118 surgical dissections were reported on nerve identification (15-22). The objectives of Lange 2009, Grossi 2015 and Mendes 2016 were centered on the intraoperative identification of the nerves only. There was more than one primary objective in other studies. The studies of Alfieri 2006, Lange 2009 and Sanders 2014 were multi-centric. Lange 2009 also studied the course of the nerves.

Qualitative Analysis of the Included Studies

Three comparative cohort studies, one randomized controlled trial and four non-comparative cohort studies were evaluated for quality. The result is presented in Table 2. All of the included studies were of good to excellent quality.

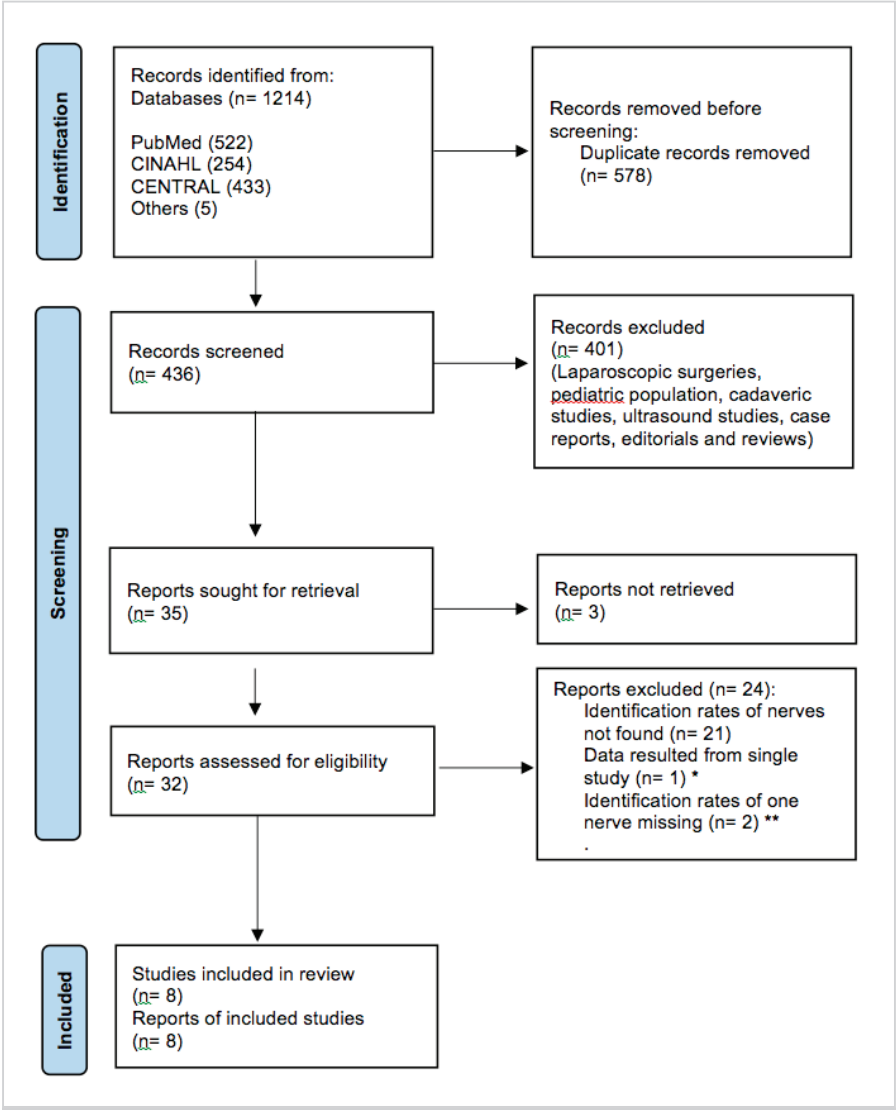


Figure 1. Flow diagram of the selection process of the studies.

*The studies of Smeds 2014 and Sanders 2014 were the result of a single trial. To avoid duplication of data we excluded the study of Smeds 2014. Smeds 2014 (12) also reported the results on a smaller sample size.

**The studies of Al-Dabbagh 2002 (13) and Emeksiz 2016 (14) were excluded as they reported identification and course of IIN and IHN only.

Meta-Analysis of Nerve Identification Rates

Ilioinguinal Nerve (IIN)

The forest plot of binomial pooled prevalence was constructed using the IVhet model (fixed effect, heterogeneity), as shown in Figure 2. In prevalence analysis, the IVhet model is preferred over the random effect model when the heterogeneity is significant, as seen in our study. It gives a more reliable coverage probability and exhibits lesser variance (23,24). We avoided the quality effect model as the methodology of included studies was heterogeneous (Table 2). The pooled prevalence rate of IIN was 84% (95% CI 67-97%). Statistical heterogeneity was significant (Cochrane's Q 228.21, I^2 97%, p< 0.001). On leave one out sensitivity analysis, the pooled prevalence varied from 81% to 91%. We analyzed the studies' funnel and DOI plots. We detected major asymmetry in these (Figure 3). An unweighted multiple regression analysis was performed with IIN identification rate as a dependent variable and sample size, centers of study and objectives as independent variables. We found that none of the independent variables significantly affected the outcome [model summary: R^2= 0.50, p= 0.37; coefficient: sample size (β= -0.19, p= 0.77), center (β= -0.59, p= 0.31), objective (β= 0.16, p= 0.75)].

Table 1. Characteristics of the included studies

Author year	Country	Type of study	Sample size	Objectives	Methodology	Results (excluding identification rates)
Alfieri 2006 (15)	Italy	Prospective cohort	973	To study the influence of nerve preservation vs division during hernioplasty	Surgeons at eleven centres were asked to report nerve identification and their preservation or division during the surgeries. They followed the patients for one year and wanted to study the chronic groin pain.	Non-identification of nerves or division of nerves was associated with chronic groin pain.
Bartlett 2007 (16)	UK	Prospective comparative cohort	172	Incidence of nerve division during the hernia surgery and its effect on pain	One hundred and seventy-two patients were operated. The pain scores in the groups with unidentified single nerve or divided single nerve or all identified and preserved nerves were recorded. They were compared for the differences.	Single nerve division during the hernia surgery is not associated with increased incidence of chronic groin pain.
Lange 2009 (17)	Netherlands	Prospective cohort	40	Feasibility of nerve recognizing Lichtenstein hernioplasty and measuring the extra time for it	Four experienced surgeons performed ten surgeries each at different centres. Nerve identification and the time taken for it was recorded.	Nerve recognizing Lichtenstein hernioplasty is feasible and non-time consuming. Major anatomical variations are uncommon.
Bischoff 2012 (18)	Denmark	Prospective comparative cohort	244	To study the effect of inguinal nerve identification on post-operative pain, sensory dysfunction and functional ability	Two surgeons performed the Lichtenstein inguinal hernioplasty and reported on nerve identification. After six months the outcome in patients were compared.	No difference in pain, sensory loss or functional outcome was observed in patients with or without nerve identification.
Sanders 2014 (19)	UK	Randomised controlled trial	507	Comparison of self-gripping mesh with suture fixation of mesh	Randomised controlled trial was performed at nine centres to study the pain scores at the time of discharge, seven days, three months and at one year. In one arm suture fixation was done and in another self-gripping mesh was employed. Identification of nerves was performed during the surgery.	Early post-operative pain at the time of discharge and at seven days was significantly less with self-griping mesh. No difference was observed for chronic pain at three months and at one year. Application of self-gripping mesh was less time consuming.
Grossi 2015 (20)	Brazil	Prospective cohort	38	Identification of three nerves during the surgery	After the surgery the data was entered as per the protocol of the study.	The identification rates were similar in emergency and the elective cases. The identification was difficult in recurrent cases.

Table 1. Characteristics of the included studies (continued)

Author year	Country	Type of study	Sample size	Objectives	Methodology	Results (excluding identification rates)
Mendes 2016 (21)	Brazil	Prospective comparative cohort	29	Neurotopographic adequacy of a transverse incision in Lichtenstein hernioplasty	Nerve identification in 29 inguinal hernia surgeries were compared with 10 groin dissections on cadavers. Transverse groin incision was used for surgery.	Nerve identification rates during hernia surgery on patients was comparable to groin dissections on cadavers.
Cirocchi 2020 (22)	Italy	Prospective cohort	115	Dermatome mapping test in inguinal hernia repair	One hundred and fifteen patients were followed for chronic postoperative neuropathic inguinal pain (CPIP). In the pre-operative period, the pain and its dermatomal distribution was recorded. Nerve identification was performed during the surgery. Post-operatively at sixth month, the CPIP and its dermatomal distribution was recorded. The effect of failure to identify nerves or its division on CPIP was evaluated.	CPIP is more prevalent when the nerves are not identified. It is more prevalent in the dermatome supplied by IIN and GB.

We performed the subgroup analysis of pooled prevalence for studies with a single primary objective vs studies with more than one primary objective and multicenter studies vs single center studies. The pooled prevalence in studies with a single primary objective was 0.88 (0.69-1.00). It was nearly the same in studies with more than one objective (0.84; 0.66-0.98) (Table 3A). The pooled prevalence in multicenter and single-center studies were 0.78 (0.58-0.95) and 0.95 (0.88-1.00), respectively (Table 3B).

Iliohypogastric Nerve (IHN)

The forest plot was constructed using the IVhet model (fixed effect, heterogeneity), as shown in Figure 2B. The pooled prevalence rate of IHN was 67% (95% CI 49-83%). Statistical heterogeneity was significant (Cochrane's Q 244.15, I2 97%, p< 0.001). On leave one out sensitivity analysis, the pooled prevalence varied from 69% to 79%. We analyzed the studies' funnel and DOI plots and detected major asymmetry. On multiple regression analysis, we found that none of the independent variables-sample size, centers of study and objectives significantly affected the IHN identification rates [model summary: R^2= 0.84, p= 0.14; coefficient: sample size (β= -0.55, p= 0.31), center (β= -0.13, p= 0.76), objective (β= 0.30, p= 0.46)].

On subgroup analysis, the pooled prevalence in studies with a single primary objective was 0.94 (0.85-1.00). It was 0.69 (0.49-0.88) in studies with more than one primary objective (Table 3A). The heterogeneity was not significant when two types of objectives were compared. This indicates that focused studies yield better identification rates for IHN. The pooled prevalence in multicenter and single-center studies were 0.54 (0.40-0.68) and 0.51 (0.12-0.90), respectively (Table 3B).

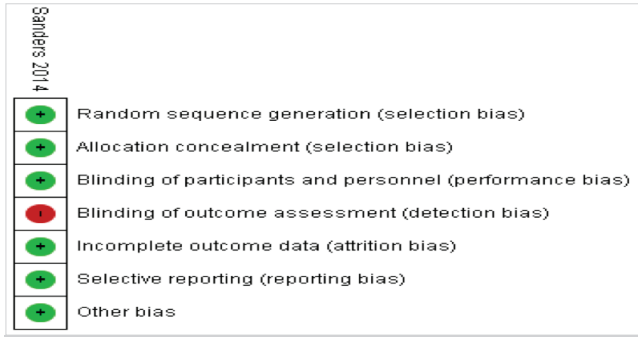
Genital Branch of Genitofemoral Nerve (GB)

The forest plot was constructed using the IVhet model (fixed effect, heterogeneity), as shown in the Figure 2C. The pooled prevalence rate of GB was 53% (95% CI 31-74%). Statistical heterogeneity was significant (Cochrane's Q 256.15, I2 97%, p< 0.001). The pooled prevalence varied from 49% to 57% on leave one out sensitivity analysis. We analyzed the studies' funnel and DOI plots and detected major asymmetry. On multiple regression analysis, we found that none of the independent variables-sample size, centers of study and objectives significantly affected the GB identification rates [model summary: R^2= 0.31, p= 0.64; coefficient: sample size (β= -0.26, p= 0.74), center (β= 0.27, p= 0.68), objective (β= -0.39, p= 0.53)].

On subgroup analysis, the pooled prevalence in studies with a single primary objective was 0.77 (0.52-0.97). It was 0.52 (0.30-0.73) in studies with more than one primary objective (Table 3A). The pooled prevalence in multicenter and single-center studies were 0.54 (0.40-0.68) and 0.51 (0.12-0.90), respectively (Table 3B).

Table 2. Quality assessment of the included articles

Quality assessment of comparative studies by Newcastle-Ottawa scale (NOS)										
	Selection				Comparability		Outcome			
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	Total quality score
Bartlett 2007	*	*	*	*	*	-	*	*	*	8
Bischoff 2012	*	*	*	*	-	-	*	*	-	6
Mendes 2016	*	*	*	*	*	*	*	*	*	9



Quality assessment of randomized controlled trial.

Studies with Nerve Identification as a Single Primary Objective vs Other Studies (Table 3A)

We found three articles where identifying nerves was the only primary objective. This subgroup included Lange 2009, Grossi 2015 and Mendes 2016. The sample size was small in each of the studies, with the largest being 40 in the study of Lange 2009. The identification rates were over 85% for all nerves except for IIN in Lange 2009 and GB in Grossi 2015 (75% and 52.6%, respectively). The pooled prevalence rates in this subgroup were 88%, 94% and 77% for IIN, IHN and GB, respectively. Heterogeneity was insignificant in the pooled value of IHN (p= 0.06) only. The identification rate of IHN was 94%, indicating a uniform identification in focused studies.

In five articles, there was more than one primary objective. This subgroup included Alfieri 2006, Bartlett 2007, Bischoff 2012, Sanders 2014 and Cirocchi 2020. The sample size ranged from 115 to 973. Alfieri 2006 reported poor identification rates for all nerves. Sanders 2014 reported low identification for IHN and GB (66.8% and 47.7%). Bischoff 2012 and Cirocchi 2020 observed a low prevalence of GB. The pooled prevalence in this subgroup was 84%, 69% and 52% for IIN, IHN and GB, respectively. Identification of IHN and GB was low by more than 20% compared to the other subgroup (94% & 77% vs 65% & 52%). The IIN rates differed only marginally in the two subgroups.

Multicenter vs Single Center Studies (Table 3B)

The studies of Alfieri 2006, Lange 2009 and Sanders 2014 were multi-centric. The sample size in the study of Lange 2009 was small. The other two studies were extensive. The nerve identification rate in single-center studies was 78%, 63% and 54% for IIN, IHN and GB, respectively. Heterogeneity was significant for all of the nerves.

Studies by Bartlett 2007, Bischoff 2012, Grossi 2015, and Mendes 2016 were conducted at a single center. The sample size ranged from 29 to 244. The pooled values for IIN, IHN and GB were 95%, 89% and 51%, respectively. More than a 20% increase in the identification of IIN and IHN was observed com-

Table 2. Quality assessment of the included articles

	Quality assessment of case series by JBI critical appraisal checklist									
Study	**Were there clear criteria for inclusion in the case series?**	**Was the condition measured in a standard, reliable way for all participants included in the case series?**	**Were valid methods used for identification of the condition for all participants included in the case series?**	**Did the case series have consecutive inclusion of participants?**	**Did the case series have complete inclusion of participants?**	**Was there clear reporting of the demographics of the participants in the study?**	**Was there clear reporting of clinical information of the participants?**	**Were the outcomes or follow up results of cases clearly reported?**	**Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?**	**Was statistical analysis appropriate?**
Alfieri 2006	YES	YES	NO	UNCLEAR	YES	YES	YES	YES	YES	YES
Lange 2009	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Grossi 2015	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Cirocchi 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES

pared to the other subgroup. However, the heterogeneity was significant for all nerves in this subgroup, as well.

Studies Detailing the Course of All Three Nerves During Surgery (Table 3C)

Lange et al. tried identifying the course of all three nerves during the surgery. The course of the nerves was recorded as standard anatomy or the variations. The surety of nerve identification was classified as: sure, probably sure, maybe, and probably not. They concluded that it is possible to identify IIN and IHN in most cases and significant anatomical variations are not observed. GB was difficult to recognize in at least 25% of the cases. The surgeons, in these cases, were unsure of the structure as a nerve or could not locate the blue vein near it. In an additional 12.5% (5/40) of the cases, they failed to identify it. They reported variations in the course of IIN in 15% (6/40) of the patients. Early branching over the spermatic cord was observed in these cases.

DISCUSSION

The pooled prevalence of IIN, IHN and GB was 81% (95% CI 64-96%), 67% (95% CI 49-83%) and 57% (95% CI 38-76%), respectively. There was significant heterogeneity in the pooled values. We evaluated a possible association of study sample size, centers of study and number of primary objectives with nerve identification rates but failed to find any. On subgroup analysis, poor identification rates of IIN were observed in multi-centric studies. A similar effect was seen on IHN in multi-centric studies and studies with more than one primary objective. GB was better recognized in studies with a single primary objective. The identification of IHN in studies with a single primary objective was the only subgroup where heterogeneity was not significant. These results indicate an acceptable good identification rate for IIN. The identification of IHN is adversely affected by the multicentricity and dilution in the focus of the study. The identification of GB is most difficult and probably unpredictable.

The anatomical location of inguinal nerves in the surgical field may explain some difficulties in their identification. The IIN lies on the spermatic cord. It may lie on the sac of an indirect (lateral) hernia or get displaced with the cord structures in a direct (medial) hernia. The nerve is frequently in the center of the surgical field, making identification easy. The IHN may be the most crucial regional nerve in respect to nerve entrapment during mesh fixation in open hernia repairs (25). It lies on the internal oblique muscle and its aponeurosis within the area of surgery. Its visualization needs retraction of the overlying external oblique aponeurosis. Its identification is difficult in comparison to IIN. Cirrochi 2018 also reported lower identification rates of IHN in their meta-analysis (26). The GB is thin compared to two other nerves and lies posteriorly in the spermatic cord. Its visualization requires

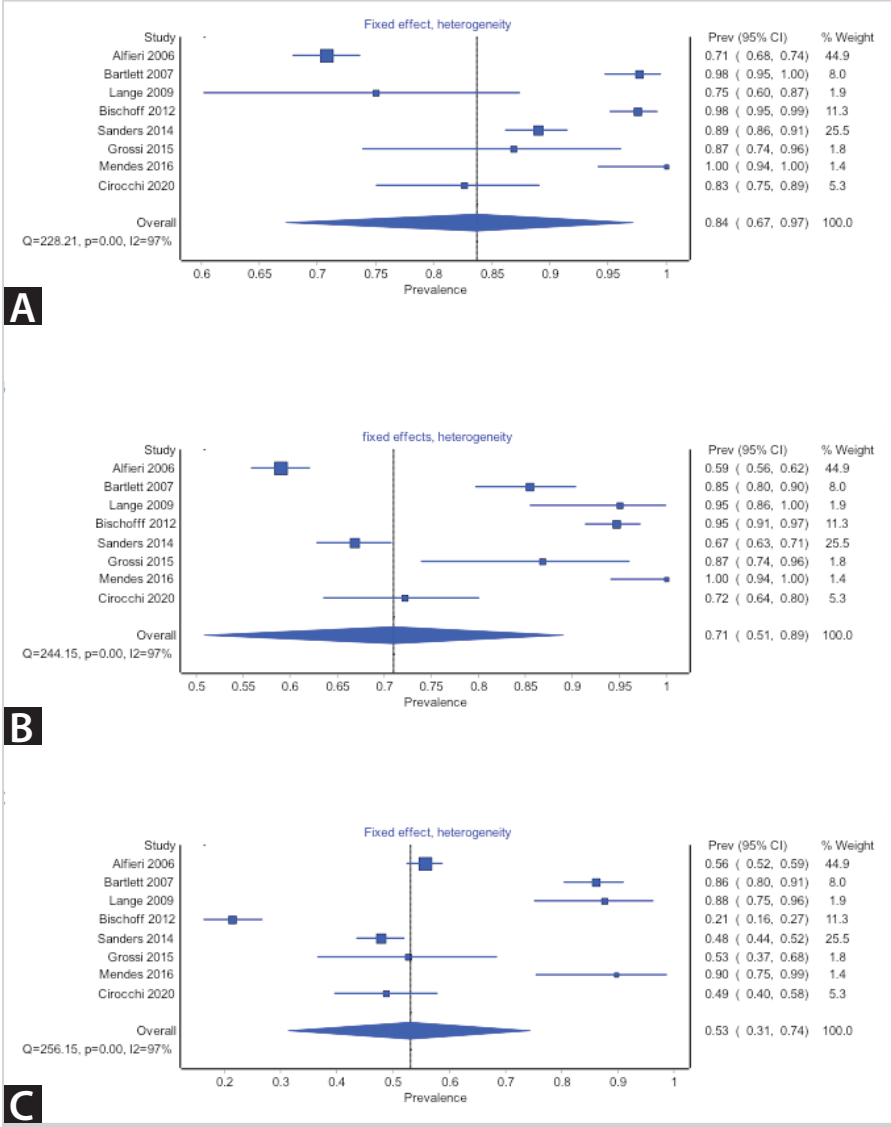


Figure 2. The forest plot of pooled prevalence under inverse variance heterogeneity model (IVhet model): **(A)** IIN, **(B)** IHN and **(C)** GB.

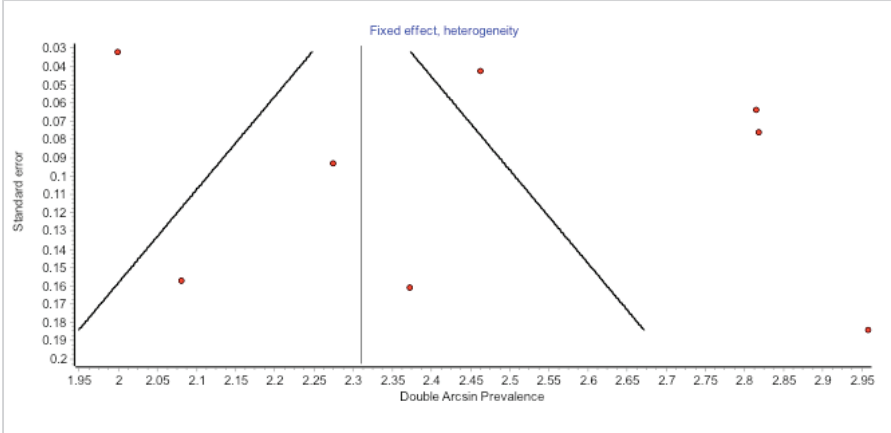


Figure 3. Funnel plot of the studies reporting IIN identification.

Table 3. The effect of study methodology on identification of nerves and description of the course of nerves

Table 3A. Studies with three nerve identification as single primary objective vs other studies

Studies with three nerve identification as single primary objective								
Author year	**Sample size**	**Identification rates (%)**			**Pooled prevalence (95% CI)**			
		IIN	**IHN**	**GB**		**IIN**	**IHN**	**GB**
Lange 2009	40	75	95	87.5	**IVhet model**	0.88 (0.69-1.00)	0.94 (0.85-1.00)	0.77 (0.52-0.97)
Grossi 2015	38	86.8	86.8	52.6				
Mendes 2016	29	100	100	89.7	**Q, P and I^2 statistics**	Q= 13.29 p< 0.01 I^2= 85%	Q= 5.74 p= 0.06 I^2= 65%	Q= 15.66 p< 0.01 I^2= 87%
Studies with three nerve identification not as single primary objective								
Alfieri 2006	973	70.8	59	55.6	**IVhet model**	0.84 (0.66-0.98)	0.69 (0.49-0.88)	0.52 (0.30-0.73)
Bartlett 2007	172	97.7	85.5	86				
Bischoff 2012	244	97.5	94.7	21.3				
Sanders 2014	557	89	66.8	46.8	**Q, P and I^2 statistics**	Q= 213.49 p< 0.01 I^2= 98%	Q= 193.02 p< 0.01 I^2= 98%	Q= 211.68 p< 0.01 I^2= 98%
Cirocchi 2020	115	82.6	72.2	48.7				

Table 3B. Nerve identification in multicentre vs single centre studies

Multi-centre studies								
Author year	**Sample size**	**Identification rates (%)**			**Pooled prevalence (95% CI)**			
		IIN	**IHN**	**GB**		**IIN**	**IHN**	**GB**
Alfieri 2006	973	70.8	59	55.6	**IVhet model**	0.78 (0.58-0.95)	0.63 (0.48-0.77)	0.54 (0.40-0.68)
Lange 2009	40	75	95	87.5				
Sanders 2014	557	89	66.8	47.7	**Q, P and I^2 statistics**	Q= 75.81 p< 0.01 I^2= 97%	Q= 36.78 p< 0.01 I^2= 95%	Q= 31.90 p< 0.01 I^2= 94%
Single centre studies								
Bartlett 2007	172	97.7	85.5	86	**IVhet model**	0.95 (0.88-1.00)	0.89 (0.77-0.98)	0.51 (0.12-0.90)
Bischoff 2012	244	97.5	94.7	21.3				
Grossi 2015	38	86.8	86.8	52.6				
Mendes 2016	29	100	100	89.7	**Q, P and I^2 statistics**	Q= 32.63 p< 0.01 I^2= 88%	Q= 41.81 p< 0.01 I^2= 90%	Q= 223.09 p< 0.01 I^2= 98%
Cirocchi 2020	115	82.6	72.2	48.7				

lifting and twisting of the cord. The difficult identification of GB is well-reported in the surgical literature (18,19,21,22).

The anatomical studies on cadavers report better identification of nerves. Cirrochi 2018 conducted a meta-analysis that included cadaveric and surgical studies. They have calculated 87% and 76.3% for IIN and IHN as the pooled prevalence. On subgroup analysis, the identification of IIN and IHN in cadavers was 98% and 99% (26), which indicates that the identification of nerves during surgery is more challenging than that on the cadavers. Multiple factors may play a role in this. The surgical field is blood-tinged, and the surgeon is more concerned about identifying and separating the hernia sac in the early steps. Lack of proper anatomical knowledge makes identifying the nerves in the inguinal region complex. This is especially true for IHN and GB, which are not in the center of the surgical field (27). The use of synthetic Mesh has made the surgery simple, and surgeons do not spare more time searching for a nerve.

Limited studies have reported the course of inguinal nerves during surgery. Lange 2009 found that the course of IHN was classical in all cases. They also said the course of IIN was classical

Table 3C. Study detailing the course of all three nerves (lange 2009)

Author	The standard anatomy	The details of variations observed
Lange 2009	IHN The nerve is horizontal and ventral to the internal oblique. It arises 2.4 (range 1.5-4.4) cm cranial to the internal ring and perforates the external oblique at 3.8 (range 2.5-5.5) cm cranial to the superficial ring. In 11%, it is inside IO and invisible. IIN The nerve is ventral and parallel to the spermatic cord. It runs dorsal to the external oblique. GB The nerve is found lying laterocaudally to the internal ring. It runs parallel to the cremasteric artery and vein called the 'blue line'.	IHN (38/40) All classical, and all identified as "for sure." IIN (30/40) 24 classical 6 branched over the spermatic cord All identified as "for sure." GB (35/40) Doubtful= 10 (probably sure= 3, May be= 5, Probably not= 2) Reasons for doubt 3= Not following blue line, 4= Structure might be vessel or muscle fibre 3= No reasons explained

in 75% of the cases. They could identify both these nerves in all cases (17). The course of IIN and IHN was also studied by Al-dabbagh 2002 and Emeksiz 2016. They reported the course as classical in only 50% of the cases. Their observations were based on a larger sample size (13,14). The anatomical studies on cadavers also report massive variation in the course of IHN and IIN (28,29).

The identification of GB is the most challenging. In the study by Cirrochi 2018, the pooled prevalence was 48.2% (26). Bischoff has identified this nerve in only 21.3% of the cases (18). This nerve runs close to the external spermatic vein and is called the blue vein. In case of difficulty, the nerve is presumed to be identified once the external spermatic vein is seen. This technique is seen in the study of Lange 2009 who identified GB in 35 out of 40 cases. They reported that they were unsure of the finding in at least 10 cases.

The values of pooled prevalence of the nerves are not suitable as the quality standard for hernia surgery. The presence of significant heterogeneity reduces the quality of pooled values. In our study, on subgroup analysis, better identification rates were observed for IIN and IHN in single-center studies. Further, in one subgroup with a single primary objective as nerve identification, heterogeneity was low for IHN identification. The pooled prevalence in this subgroup was 94%. This all suggests a possibility of better nerve identification with focused and motivated centers. Even if we use IIN as a quality standard, there is a probability of missing the nerve in 16% of the surgeries. The identification rates of the other two nerves, IHN and GB, are poor. We should continue identifying the nerves as this practice probably reduces the chances of debilitating chronic inguinodynia.

The objectives of our study were focused. We excluded studies on cadaveric dissection and studies that failed to report on all three nerves. The selected studies were recent, and their methodological quality was good to excellent. Nerve identification was the primary objective in all articles. The pooled findings indicate that higher identification rates of cadaveric studies are challenging to reproduce.

There are a few limitations of this study. The number of included studies was small, and they belonged to Europe or North America only. The study methodology was not uniform and included randomized controlled trials, prospective comparative cohort studies and prospective non-comparative cohort studies. Methodological quality assessment used three different tools. The detection of publication bias with funnel plot was unreliable as the number of included studies was less than ten (30). Due to the scarcity of data, we could not analyze the effect of some variables such as, body mass index, anthropometry and emergency surgery, on nerve identification rates.

More studies are needed that describe the course of inguinal nerves at the time of surgery. The studies should aim at simplifying the types of possible variation in the course of nerves. Further research is also needed to understand the feasibility of nerve identification in emergency surgeries.

CONCLUSION

This was a systematic review and meta-analysis of articles reporting the identification of all three inguinal nerves in open hernia surgery. The identification rates of none of the nerves were near 90% in the pooled estimates. It was even less in multi-centric studies and studies with more than one primary objective. The lowest identification rate was observed for the

genital branch of the genitofemoral nerve. A comprehensive description of the course of the nerves was not seen in most of the studies. Based on nerve identification rates from this pool of studies, it is difficult to suggest a benchmark for the quality assessment of hernia surgery.

Ethics Committee Approval: This study was approved by All India of Medical Sciences Bhubaneswar Intstitutional Ethics Committee (Reference no: T/IM-NF/Surg/21/148, Date: 07.02.2022).

Peer-review: Externally peer-reviewed.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Açık inguinal hernioplastide sinir tespiti: Bir meta-analiz

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ÖZET

Giriş ve Amaç: Açık inguinal hernioplastide cerrahi alanda üç kasık siniri ile karşılaşılır. Dikkatli diseksiyon, postoperatif kasık ağrısı riskini azalttığından, bu sinirlerin tanımlanması tavsiye edilir. Ameliyat sırasında sinirleri tanımak zor olabilir. Sınırlı sayıda cerrahi çalışma, tüm sinirlerin tanınma oranlarını bildirmiştir. Bu çalışmanın amacı, bahsi geçen çalışmalardaki her bir sinirin karma prevalansını hesaplamak ve sinirleri bulmanın ortalama olasılığını anlamak ve önemlerini analiz etmekti.

Gereç ve Yöntem: PubMed, CENTRAL, CINAHL, ClinicalTrials.gov ve Research Square veri tabanları tarandı. Ameliyat sırasında üç sinirin de prevalansını bildiren makaleler seçildi. Meta-analiz, sekiz çalışmadan elde edilen veriler üzerinde gerçekleştirildi. *Forest plot* hazırlamak için MetaXL yazılımından IVhet modeli kullanıldı. Heterojenliğin nedenini anlamak için alt grup analizi yapıldı.

Bulgular: İlioinguinal sinir (IIN), iliohipogastrik sinir (IHN) ve genitofemoral sinirin (GB) genital dalı için karma prevalans oranları sırasıyla %84 (%95 GA %67-97), %71 (%95 GA %51-89) ve %53 (%95 GA %3174) idi. Alt grup analizinde, tek merkezli çalışmalarda ve sinir tanımlaması gibi tek bir birincil amacı olan çalışmalarda tanımlama oranları daha yüksekti. Heterojenite, tek merkezli çalışmalarda IHN tanımlama oranlarının alt grup analizi hariç tüm karma değerlerde anlamlıydı.

Sonuç: Sonuçlar IHN ve GB için düşük tanımlama oranlarına işaret etmektedir. Belirgin heterojenlik ve geniş güven aralıkları, IHN ve GB'nin kalite standartları anlamında önemini azaltmaktadır. Tek merkezli ve sinir tanımlamaya odaklanan çalışmalarda daha iyi sonuçlar gözlenmektedir.

Anahtar Kelimeler: Hernioplasti, inguinal herni, periferik sinirler

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ORIGINAL ARTICLE
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Changes in vitamin D and calcium-phosphorus metabolism in patients with severe acute pancreatitis

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ABSTRACT

Objective: The problem of predicting the course of acute pancreatitis and early diagnosis of its complications remains unresolved. This study aimed to determine changes in vitamin D and calcium-phosphorus metabolism in patients with severe acute pancreatitis.

Material and Methods: There were examined 72 people divided into two groups as healthy persons (comparison group) - males and females without pathology of the gastrointestinal tract and any other conditions or diseases that could affect the state of calcium-phosphorus metabolism (n= 36) and patients with acute pancreatitis (main group, n= 36). In addition, in order to determine the prognostic criteria for the severity of the disease, patients in the main group were divided into two subgroups. The first subgroup included patients with severe disease (n= 18), the second (n= 18) - with mild and moderate disease.

Results: Serum calcium value was lower in patients with severe acute pancreatitis comparison to healthy persons: 2.18 (2.12; 2.34) vs 2.36 (2.31; 2.43) mmol/L (p< 0.0001), and the decrease of calcium levels was associated with an increase in the severity of acute pancreatitis. Therefore, hypocalcemia can be considered a reliable predictor of the severity of the disease. In patients with acute pancreatitis, the level of vitamin D was significantly low than in the healthy persons and was 13.8 (9.03; 21.34) and 28.4 (21.8; 32.3) ng/mL, respectively (p< 0.0001).

Conclusion: For patients with acute pancreatitis, serum vitamin D levels≤ 13.28 ng/mL can be considered as a significant predictor of severe disease (sensitivity 83.3%, specificity 94.4%) regardless of calcium level.

Keywords: Acute pancreatitis, vitamin D, calcium-phosphorus metabolism

INTRODUCTION

Acute pancreatitis is a polyetiological disease that remains one of the most pressing problems of modern medicine. According to the literature, more than 140 causes of this disease are known, most of which lead to a violation of the passage of pancreatic secretion. The leading factors in the occurrence of acute pancreatitis are alcohol abuse in 17-65% of cases, gallstone disease and pathology of the biliary system in 21-58% of cases, neoplasm or cicatricial stenosis of the large duodenal papilla, a intraductal or parenchymal neoplasia (1). Other causes include mechanical trauma to the pancreas (including iatrogenic damage), hypertriglyceridemia, tissue ischemia (atherosclerotic vascular disease), virsungolithiasis, chemotherapy (drug pancreatitis), hyperparathyroidism, and others (2).

The role of calcium in the genesis of acute pancreatitis remains debatable. It is known that calcium is a powerful release of peptides that stimulate the secretion of the pancreas, as well as intracellular secondary stimulators of the synthesis and secretion of pancreatic enzymes (3).

On the one hand, hypercalcemia in the case of prolonged hyperparathyroidism (4), genetic disorders or cancer (5) can cause the development of acute pancreatitis; however, currently, the detection of high calcium levels in patients with acute pancreatitis without concomitant pathology could explain the need to expand the diagnostic search and examination of the patient, in particular for hyperparathyroidism.

On the other hand, the development of multiple organ failure in acute pancreatitis leads to hypocalcemia (6), and several authors suggest considering the content of calcium in serum as a criterion for the severity of acute pancreatitis (7). One of the probable mechanisms of reducing serum calcium may be its accumulation in aci-

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nar cells, which explains the relationship between hypocalcemia and the severity of acute pancreatitis (8).

Another factor that is closely related to calcium and parathyroid hormone is vitamin D. Previously, it has been considered exclusively in terms of skeletal diseases; however, the discovery of receptors for vitamin D in various organs and tissues has indicated a much wider impact on the human body. Today, the role of vitamin D in the genesis of autoimmune, oncological, chronic inflammatory diseases, and etc. is being actively studied, and only isolated studies have found a link between vitamin D and acute pancreatitis (9).

A feature of acute pancreatitis is a high risk of complications with a mortality rate of 5.5%. In severe cases, this figure varies between 40-70% and is accompanied by a large number of clinical manifestations with options of unpredictable course (10). Therefore, accurate methods of diagnosing the nature of the pathomorphological process and the severity of multiorgan disorders are extremely important in order to identify them in a timely manner and provide adequate treatment.

It should be noted that many clinical prognostic markers of adverse course of acute pancreatitis have been proposed to date. In particular, the age of the patient and the timing of the onset of early multiple organ failure significantly affect mortality rate. Obesity is also an important risk factor for severe acute pancreatitis. The level of hematocrit at hospitalization ≥47%, which does not decrease during the day, is a predictor of necrotic pancreatitis. In addition, an increase in the concentration of C-reactive protein above 150 mg/L during the first 48 hours after admission to the hospital is a marker of severe prognosis of acute pancreatitis (11,12). However, the sensitivity and specificity of these indicators are low (13).

Thus, despite the progress of modern surgical science, the problem of predicting the course of acute pancreatitis and early diagnosis of its complications remains unresolved and requires further development, finding new diagnostic markers, taking into account various pathogenetic factors of the disease.

This study aimed to determine changes in vitamin D and calcium-phosphorus metabolism in patients with severe acute pancreatitis.

MATERIAL and METHODS

The study was conducted by the staff of the Department of Surgery No: 2 Bogomolets National Medical University. All patients were examined between January and December 2021 and signed informed consent to participate in this study and/or treatment at the clinic. Approval for this study was granted by the Local Commission on Bioethical Expertise and Ethics of Scientific Research at the Bogomolets National Medical University (Decision No: 5/3, Date: 17.12.2020).

Study Design

Seventy-two patients aged 26-83 years were examined and divided into two groups as healthy persons (comparison group) - males and females without gastrointestinal pathology and any other conditions or diseases that could affect the state of calcium-phosphorus metabolism (n= 36) and patients with acute pancreatitis (main group, n= 36). Patients of the comparison group were examined on an outpatient basis. All patients of the main group were hospitalized at the clinic of the Department of Surgery No: 2. According to the etiological factor, acute pancreatitis of alcoholic etiology occurred in 24 (66.7%) patients and biliary pancreatitis in 12 (33.3%) patients. Patients in the two groups did not differ significantly in age and sex (Table 1). In addition, in order to determine the prognostic criteria for the severity of the disease, patients in the main group were divided into two subgroups. The first subgroup included patients with severe acute pancreatitis (n= 18) and the second (n= 18) with mild and moderate course of acute pancreatitis.

Table 1. Demographic and clinical characteristic of the patients

Demographic data	Healthy subjects (n= 36)	Patients with acute pancreatitis (n= 36)	p
Sex			
Male	31 (86.1%)	30 (83.3%)	>0.05
Female	5 (13.9%)	6 (16.7%)	>0.05
Age (year)	51.8 ± 17.8	51.2 ± 18.1	>0.05
Etiological factors:			
Alcoholic		24 (66.7%)	
Biliary		12 (33.3%)	
Severity of acute pancreatitis:			
Mild and moderate		18 (50%)	
Severe		18 (50%)	

Blood sampling in patients of the comparison group was performed on an empty stomach and patients in the main group, it was performed during hospitalization before infusion therapy. Determination of total calcium, albumin, total phosphorus, alkaline phosphatase in serum was performed on a biochemical automatic analyzer A15 (BioSystems, Italy). The level of albumin-adjusted calcium was determined by the following formula: Adjusted calcium (mmol/L)= total Ca (mmol/L) + 0.02 [40 - serum albumin (g/L)]. Determination of vitamin D (25(OH) D) and parathyroid hormone was performed using the electrochemiluminescent method on the Sobas analyzer (Roche Diagnostics, Germany).

Patient Selection

The diagnosis of acute pancreatitis in patients of the main group was established by the presence of two of the following three criteria: clinical (upper abdominal pain), laboratory (serum amylase or lipase level 3 times higher than the maximum normal value), imaging (CT, MRI, Ultrasound) criteria. The study used the classification proposed by the Acute Pancreatitis Classification Working Group and the International Association of Pancreatology/American Pancreatic Association in 2012 (14). The severity of the course was determined using the APACHE II scale (severe course - 8 points or more). The diagnosis of mild acute pancreatitis was established in the absence of reliable signs of pancreatic necrosis based on a typical set of clinical and laboratory data, moderate in the presence of transient multiorgan failure or local/systemic complications without organ failure, and severe in in the presence of persistent multiorgan failure.

Exclusion criteria for both groups were any chronic disease affecting calcium-phosphorus metabolism, mental illness, recent surgery, glucocorticoids, calcium or vitamin D for three months before enrollment.

Statistical Analysis

Normality of data distribution was determined by the Shapiro-Wilk test. The difference between the groups was established using Student's t-test for independent samples and Mann-Whitney U test. Differences in sample distribution were assessed using the χ^2 test criterion. Correlation analysis was performed using Pearson correlation for parametric and Spearman correlation for nonparametric data distribution. The relation between the indicators was determined using ROC analysis. The results were presented as mean values and their standard deviation (M ± SD) in the case of parametric distribution and as median and quartile [Me (Q1; Q3)] in the case of non-parametric data distribution. Differences between indicators were considered significant at $p< 0.05$.

Statistical analysis was performed using Statistica 10, IBM SSPS Advanced Statistics 22.0 and MEDCALC® (open source internet resource, https://www.medcalc.org/calc/).

RESULTS

Changes in vitamin D and calcium-phosphorus metabolism in the individuals of both groups are shown in Table 2. Significantly lower levels of albumin, total and albumin-corrected calcium were also reported, but parathyroid hormone levels did not differ significantly and alkaline phosphatase levels were significantly higher.

Decreased albumin levels and increased alkaline phosphatase are known as direct laboratory manifestations of acute pancreatitis. The decrease in serum total calcium in albumin-bound form is also due to a decrease in albumin. Therefore, in patients with acute pancreatitis, it is necessary to determine albumin-corrected calcium, an indicator that takes into account the content of albumin. Because albumin-corrected calcium was normal in patients with pancreatitis, no increase in parathyroid hormone levels was expected, as would be expected with true hypocalcemia.

Significant changes were also found in total calcium and albumin and in the content of albumin-adjusted calcium and other indicators of calcium-phosphorus metabolism (alkaline phosphatase, phosphorus, parathyroid hormone) significantly did not differ (Table 3).

The decrease in total calcium can be considered a criterion for the severity of acute pancreatitis, but a significant decrease in albumin content leads to the retention of albumin-corrected

Table 2. Vitamin D and calcium-phosphorus metabolism indices in healthy subjects and patients with acute pancreatitis

Indices	Range	Healthy subjects (n= 36)	Patients with acute pancreatitis (n= 36)	p
Total calcium, mmol/L	2.15-2.58	2.36 (2.31; 2.43)	2.18 (2.12; 2.34)	<0.0001
Albumin, g/L	35-50	43.2 (40.1; 45.6)	32.6 (27.2; 35.6)	<0.0001
Albumin-adjusted calcium, mmol/L	2.15-2.58	2.37 (2.31; 2.43)	2.34 (2.21; 2.42)	0.35
Alkaline phosphatase, U/L	26-117	76.6 (63.7; 91.0)	127.5 (102.5; 147.8)	<0.0001
Vitamin D, ng/mL	30-50	28.4 (21.8; 32.3)	13.8 (9.03;21.34)	<0.0001
Parathyroid hormone, pg/mL	15.0-65.0	46.3 (39.5; 55.9)	39.3 (20.6;56.2)	0.06
Phosphorus, mmol/L	0.81-1.45	1.17 (1.01; 1.27)	1.07 (0.8;1.4)	0.39

Table 3. Calcium-phosphorus metabolism indices in patients with acute pancreatitis

Indices	Severe acute pancreatitis (n= 18)	Mild and moderate acute pancreatitis (n= 18)	p
Total calcium, mmol/L	2.13 (2.09; 2.18)	2.33 (2.17; 2.41)	<0.001
Albumin, g/L	29.9 (25.8; 31.5)	34.2 (32.9; 37,2)	<0.05
Albumin-adjusted calcium, mmol/L	2.31 (2.19; 2.38)	2.39 (2.32; 2.44)	0.09
Alkaline phosphatase, U/L	131.9 (101.2; 157.6)	119.1 (103.4; 133.9)	0.23
Vitamin D, ng/mL	9.17 (7.38; 12.10)	20.4 (15.1; 24.1)	<0.0001
Parathyroid hormone, pg/mL	41.7 (33.2; 46.9)	24.1 (17,6; 73.1)	0.86
Phosphorus, mmol/L	1.11 (0.9;1.34)	0.95 (0.72; 1.46)	0.49

calcium within normative values, and therefore, patients do not develop the clinic of hypocalcemia and do not increase the content of parathyroid hormone. This should be taken into account when deciding on additional calcium intake in such patients.

Significantly lower levels of vitamin D in patients with severe acute pancreatitis are currently unclear. The possible connection with both calcium metabolism and the inflammatory process is discussed.

The content of total calcium (Figure 1) and vitamin D (Figure 2) was also analyzed according to the severity of acute pancreatitis according to the APACHE II scale.

The study found that a decrease in total calcium levels is associated with an increase in the severity of acute pancreatitis, but the relation between disease severity and vitamin D content is closer.

No association was found between calcium and vitamin D, indicating the independence of these predictors.

In our opinion, the decrease in the level of total calcium in serum may be due to both a decrease in the level of albumin and the impregnation of calcium with damaged cells and is not associated with changes in phosphorus-calcium metabolism.

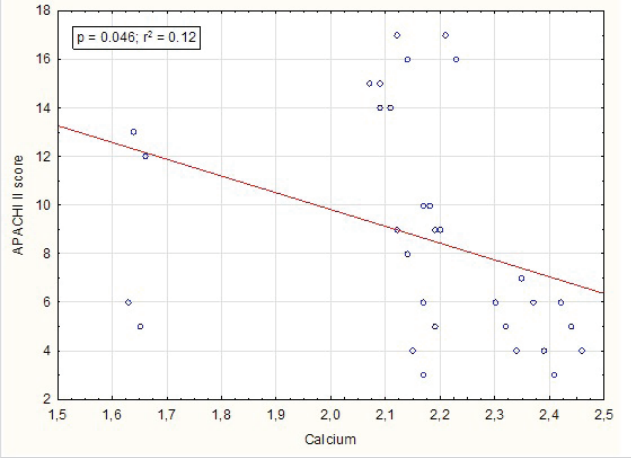

Figure 1. The association between total calcium levels and the severity of acute pancreatitis.

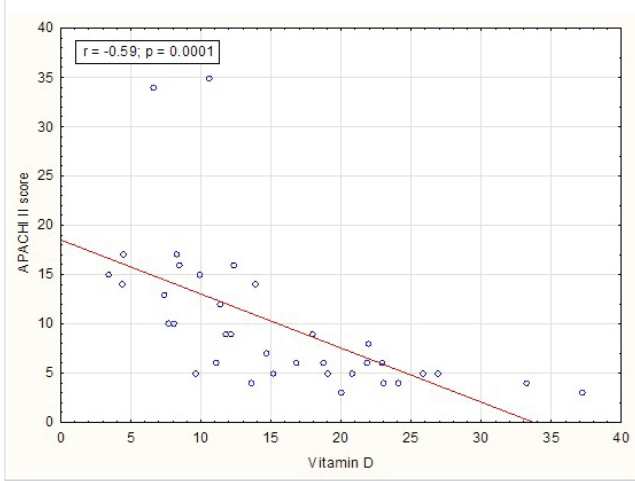

Figure 2. The association between vitamin D levels and the severity of acute pancreatitis.

That is why a link was not found between calcium and vitamin D and parathyroid hormone. The decrease in calcium and vitamin D in these patients depends on the severity of acute pancreatitis.

The next step in the study was to set a threshold value for serum vitamin D that can be used as a criterion for predicting the severity of acute pancreatitis. For this purpose, ROC analysis was used (Figure 3).

According to the results of the analysis, the area under the ROC curve (AUROC) was 0.907 (95% CI= 0.807-0.99; p= 0.001), the cut-off point corresponded to 13.28 ng/mL, Youden index was 0.667, that is for patients with acute pancreatitis, serum vitamin D level ≤13.28 ng/mL can be considered as a significant predictor of severe course (sensitivity 83.3%, specificity 94.4%).

Currently, there are different classifications of vitamin D conditions in the world with different points of difference. Different recommendations define the proposed cut-off points, and no consensus has been reached so far. Therefore, we defined our own cut-off point as a criterion for the severe course of acute pancreatitis.

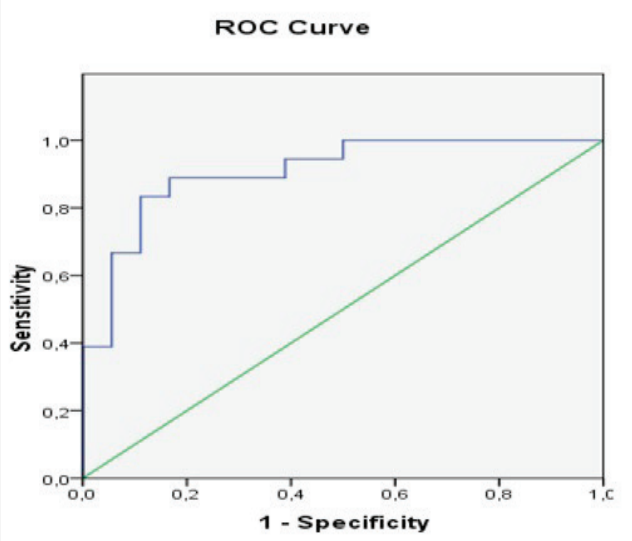

Figure 3. ROC curve for vitamin D levels in predicting the severity of acute pancreatitis.

DISCUSSION

In recent years, the place of the universal trigger in the occurrence of acute pancreatitis is given to the growth in the cytoplasm of the acinar cell content of free calcium ions and, consequently, changes in the nature of the calcium signal at its apical pole (15). To date, it is believed that the physiological stimulus causes a series of calcium oscillations. For many cell types, including acinar cells, an increase in calcium concentration is a trigger for exocytosis of proteins and enzymes (16). It is proven that most of the etiological factors that cause acute pancreatitis (alcohol, hypoxia, hypercalcemia, hyperlipidemia, some pharmacological drugs) also contribute to abnormally high fluctuations in calcium levels (17). Therefore, we can assume that in acute pancreatitis, calcium is a common trigger for various etiological factors that trigger the pathological process.

However, according to the literature, a decrease in serum calcium below 1.97 mmol/L is a criterion for multiorgan failure as a complication of acute pancreatitis (sensitivity 89.7%, specificity 74.8%) (18).

In our study, hypocalcemia was significantly more common in people with severe acute pancreatitis, and a decrease in calcium levels was associated with an increase in APACHE II scores, so hypocalcemia should be considered a predictor of severe disease.

Although new data, which have recently been published, suggest a possible link between vitamin D deficiency and an increased risk of acute and chronic disease, only a few studies with acute pancreatitis have been found, which do not contain reliable evidence of such a connection (19). According to the results of our study, it was found that the content of vitamin D was lower in patients with acute pancreatitis. It is unclear whether low level vitamin D is a predictor or consequence of acute pancreatitis. On the one hand, pancreatic cells have the ability to extrarenal synthesis of 1.25 (OH) 2D regulated by CYP27B1 and in the case of an aggressive inflammatory process, can affect the level of vitamin D, on the other hand, the most common causes of acute pancreatitis (alcoholism and gallstone disease) can be caused by vitamin D deficiency due to lifestyle changes and reduced insolation and eating disorders.

The treatment of patients with acute pancreatitis remains a difficult task due to the variety of clinical manifestations, the difficulty of timely early diagnosis of complications and prediction of the course of the disease. Thus, patients with acute pancreatitis of mild and moderate severity are hospitalized in the surgical department, while patients with severe disease require comprehensive treatment in the intensive care unit. Timely assessment of the severity of acute pancreatitis in patients with hospitalization is an important component of diagnosis and comprehensive treatment of this pathology, so the use of scales and markers that predict the severity of the disease and determine the degree of inflammation significantly affects the end results of comprehensive treatment. Thus, in order to predict the course of acute pancreatitis, many systems for assessing the severity of patients have been developed and implemented in clinical practice, among which the most common are the Ranson scale and APACHE II. It should be noted that the sensitivity and specificity of these scales in predicting the development of severe acute pancreatitis is 88.6% and 70.4% and 91.4% and 92.6%, respectively (20). In addition, such scales are quite complex and cumbersome for use in clinical practice.

These changes in vitamin D in the serum of patients with acute pancreatitis necessitate their monitoring, starting from the stage of hospitalization in order to early predict the severity of the disease and prevent its fatal complications. The sensitivity and specificity of the serum vitamin D content ≤13.28 ng/mL as a predictor of severe acute pancreatitis was 83.3% and 94.4% respectively.

Like any other study, our study also has limitations. It should be noted that there are many factors that determine the severity of acute pancreatitis. In this study, we did not analyze other factors, but found only a correlation between the level of vitamin D in the serum of patients and the severity of acute pancreatitis, which can be considered as a relation rather than a causal relation/prediction, especially since the sample size is small to test any hypothesis. Therefore, we agree that a much more detailed analysis is needed to test the hypothesis that "vitamin D is a predictor of severe acute pancreatitis." It was a one-center study with its own limitations.

CONCLUSION

Serum calcium value was lower in patients with severe acute pancreatitis when compared to healthy persons: 2.18 (2.12; 2.34) vs 2.36 (2.31; 2.43) mmol/L (p< 0.0001), and the decrease of calcium levels was associated with an increase in the severity of acute pancreatitis, therefore, hypocalcemia can be considered a reliable predictor of the severity of the disease. In patients with acute pancreatitis, the level of vitamin D was significantly low compared to that of healthy persons and was 13.8 (9.03;21.34) and 28.4 (21.8; 32.3) ng/mL respectively (p< 0.0001). For patients with acute pancreatitis, serum vitamin D levels ≤13.28 ng/mL can be considered a significant predictor of severe disease (sensitivity 83.3%, specificity 94.4%) regardless of calcium level.

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ORİJİNAL ÇALIŞMA-ÖZET
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Ağır akut pankreatitli hastalarda D vitamini ve kalsiyum- fosfor matebolizmasındaki değişiklikler

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ÖZET

Giriş ve Amaç: Akut pankreatitin seyrini tahmin etme ve komplikasyonlarının erken teşhisi sorunları çözülmemiştir. Bu çalışma, şiddetli akut pankreatitli hastalarda D vitamini ve kalsiyum-fosfor metabolizmasındaki değişiklikleri belirlemeyi amaçladı.

Gereç ve Yöntem: İki gruba ayrılan 72 kişi incelendi: Birinci grup (karşılaştırma grubu) gastrointestinal sistem patolojisi olmayan ve kalsiyum-fosfor metobolizmasının durumunu etkileyebilecek diğer koşullar veya hastalıkları olmayan erkek ve kadınlardan (n= 36) ve ikinci grup (ana grup) akut pakreatitli hastalardan oluştu (n= 36). Ayrıca hastalığın şiddetine yönelik prognostik kriterlerin belirlenmesi amacıyla ana gruptaki hastalar iki alt gruba ayrıldı. Birinci alt grup, şiddetli hastalığı olan (n= 18), ikinci hafif ve orta hastalığı olan hastalar içerdi.

Bulgular: Şiddetli akut pankreatitli hastalarda sağlıklı kişilerle karşılaştırıldığında serum kalsiyum değeri daha düşüktü: 2,18 (2,12; 2,34) ve 2,36 (2,31; 2,43) mmol/L (p< 0,0001) ve kalsiyum düzeylerindeki azalma, akut pankreatitin şiddetinin artması ile ilişkiliydi. Bu nedenle hipokalsemi, hastalığın şiddetinin güvenilir bir göstergesi olarak kabul edilebilir. Akut pankreatitli hastalarda D vitamini düzeyi sağlıklı kişilere göre anlamlı derecede düşüktü ve sırasıyla 13,8 (9,03; 21,34) ve 28,4 (21,8; 32,3) ng/mL idi (p< 0,0001).

Sonuç: Akut pankreatitli hastalarda serum D vitamini düzeyleri ≤13,28 ng/mL, kalsiyum düzeyinden bağımsız olarak ciddi hastalığın (duyarlılık 83,3%, özgüllük 94,4%) anlamlı bir öngördürücüsü olarak kabul edilebilir.

Anahtar Kelimeler: Akut pankreatit, D vitamini, kalsiyum fosfor metabolizması

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Long-term results and prognostic factors after surgical treatment for gallbladder cancer

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ABSTRACT

Objective: Gallbladder cancer is relatively rare and traditionally regarded as having poor prognosis. There is controversy about the effects of clinicopathological features and different surgical techniques on prognosis. The aim of this study was to investigate the effects of clinicopathological characteristics of the patients with surgically treated gallbladder cancer on long-term survival.

Material and Methods: We retrospectively analyzed the database of gallbladder cancer patients treated at our clinic between January 2003 and March 2021.

Results: Of 101 evaluated cases, 37 were inoperable. Twelve patients were determined unresectable based on surgical findings. Resection with curative intent was performed in 52 patients. The one-, three-, five-, and 10-year survival rates were 68.9%, 51.9%, 43.6%, and 43.6%, respectively. Median survival was 36.6 months. On univariate analysis, poor prognostic factors were determined as advanced age; high carbohydrate antigen 19-9 and carcinoembryonic antigen levels; non-incidental diagnosis; intraoperative incidental diagnosis; jaundice; adjacent organ/structure resection; grade 3 tumors; lymphovascular invasion; and high T, N1 or N2, M1, and high AJCC stages. Sex, IVb/V segmentectomy instead of wedge resection, perineural invasion, tumor location, number of resected lymph nodes, and extended lymphadenectomy did not significantly affect overall survival. On multivariate analysis, only high AJCC stages, grade 3 tumors, high carcinoembryonic antigen levels, and advanced age were independent predictors of poor prognosis.

Conclusion: Treatment planning and clinical decision-making for gallbladder cancer requires individualized prognostic assessment along with standard anatomical staging and other confirmed prognostic factors.

Keywords: Biliary tract surgical procedures, gallbladder neoplasm, prognostic factors, survival

INTRODUCTION

Gallbladder cancer (GBC) is relatively rare form of cancer with a worldwide incidence of less than 2/100.000 people (1). Surgical resection is the only treatment with curative potential, and success depends on the biology of the tumor and the completeness of the resection (2). However, there is controversy about the effects of clinicopathological features and different surgical techniques on prognosis. The evaluation of such variables predicted to affect prognosis and long-term survival outcomes may provide valuable data, which can be used to develop effective survival prediction models, allowing individual evaluation beyond standard anatomical staging and possibly affecting treatment algorithms. This single-center retrospective study on GBC patients treated with surgery aimed to determine prognostic factors by evaluating long-term survival outcomes.

MATERIAL and METHODS

We retrospectively analyzed the hospital database for GBC patients treated and followed up in our tertiary referral surgery center between January 2003 and March 2021. Approval for the study was obtained from the institutional ethics committee of the University of Health Sciences Haydarpaşa Numune Training and Research Hospital 2021/65).

Patients and Surgical Approach

Patients who were inoperable at presentation due to unresectable or metastatic disease were referred for supportive care and palliative treatment. Patients who

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were considered operable at the initial workup were operated on after being prepared for curative surgical treatment. The American Joint Committee on Cancer Staging (AJCC) 8th Edition Manual was used for the patients' clinical and pathological staging (3). While simple cholecystectomy was considered sufficient for Tis and T1a cases, radical cholecystectomy was required for more advanced cases. While standard radical cholecystectomy was sufficient in most cases for curative R0 resection, some advanced cases required extended resection. Patients were then evaluated in a multidisciplinary manner and referred for postoperative adjuvant treatment when necessary.

Statistical Analysis

Data analysis was performed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Categorical data were expressed as numbers (n) and percentages (%), and quantitative data as mean ± standard deviation (SD) and median (interquartile range, 25th-75th percentiles). Shapiro-Wilk test was used to investigate whether the normal distribution assumption was met. Mean differences between the groups were compared using Student's t-test. In all 2 × 2 contingency tables used to compare categorical variables, the continuity corrected $\chi 2$ test was used when one or more of the cells had an expected frequency of 5-25; Fisher's exact test, ≤5. In all R × C contingency tables used to compare categorical variables, Fisher Freeman Halton test was used when one quarter or more of the cells had an expected frequency of ≤5. Kaplan-Meier survival analysis via the log-rank test was used to determine whether categorical variables had a statistically significant effect on prognosis [i.e., recurrence-free and overall survival (OS)]. Cumulative one-, three-, five-, and 10-year survival rates, mean expected duration of life, and 95% confidence intervals (CIs) were computed. Kaplan-Meier survival curves were generated using STATA 16.1 (Stata Corp., College Station, TX, USA). Whether the potential factors had a statistically significant effect on prognosis was investigated using univariate Cox's proportional hazard regression models. Multiple Cox's proportional hazard regression models via the backward stepwise elimination procedure were obtained to determine the best independent predictors that affected prognosis. Any variable (except for those with missing values) whose univariable test had a p-value <0.25 was accepted as a candidate for the multivariable model. Hazard ratios (HR) and 95% CIs for each independent variable were also calculated. P values <0.05 were considered statistically significant.

RESULTS

Of the 101 GBC patients, 37 patients (36.6%) were deemed inoperable at baseline and referred for palliative treatment and supportive care, while the other 64 (63.4%) were operable. Inoperable and operable patient groups were comparable in terms of age and sex. Mean age was 64.6 ± 13.5 years (64.7 ± 15.4 years for inoperable and 64.6 ± 12.4 years for operable group, p= 0.986). Sixty-three patients (62.4%) were females (62.2% of inoperable and 62.5% of operable group, p> 0.999).

Twelve of the 64 operable patients were determined unresectable based on surgical findings and received only palliative surgery or exploration. The other 52 patients underwent resection with curative intent. R0 resection was achieved in 50 patients, but in the other two patients, surgical margin was reported as R1 on final pathology. Among 52 patients, a total of 20 patients received adjuvant therapy (chemotherapy, n= 15; chemoradiotherapy, n= 5). However, due to the diversity of therapy protocols and treatment centers, prognostic effect of adjuvant therapy was not evaluated in this study.

Twenty-nine of the patients in the operable group (45.3%) were incidentally diagnosed during cholecystectomy performed due to cholelithiasis and/or a polyp [incidental GBC (IGBC)]: Five (17.2%) intraoperatively versus 24 (82.8%) during postoperative pathological evaluation. Thirty-five patients (54.7%) undergoing surgery with a preoperative diagnosis of GBC constituted the non-incidental (non-IGBC) group.

The most frequent symptom in the operable group was abdominal pain [n= 58 (90.6%)], 52 (81.3%) had gallbladder stones, and 15 (23.4%) had jaundice at admission. Table 1 and Table 2 show descriptive statistics of serum tumor markers and surgical procedures, and pathological characteristics, respectively.

Seven of the operated patients (10.9%) died postoperatively in the hospital. Median follow-up time for 57 patients included in the survival analysis was 29.8 months (interquartile range, 2.3-198.4). Recurrence occurred in 23 patients (40.4%) after curative resection. Median recurrence-free survival (RFS) was not statistically computable, while the one-, three-, five-, and 10-year RFS rates were 68.5%, 52.1%, 49.2%, and 49.2%, respectively.

Table 3 shows cumulative one-, three-, five-, and 10-year survival rates and the overall median and mean life expectancy according to operable or inoperable status, curative or non-curative surgery, IGBC or non-IGBC, absence or presence of jaundice, and AJCC 8th ed. stages. Kaplan-Meier survival curves are shown for IGBC versus non-IGBC (Figure 1) and AJCC stages (Figure 2A-D).

When the IGBC and non-IGBC groups were compared, no statistically significant difference was observed in terms of mean age, sex distribution, jaundice, curative or non-curative operation rates, N and M stage, perineural invasion (PNI), or grade (p> 0.05). In contrast, T stage, lymphovascular invasion (LVI) incidence, AJCC stage, and mortality incidence in the non-IGBC group were significantly higher than in the IGBC group (p< 0.05) (Table 4).

When different categorical variables that may affect prognosis were evaluated by univariate statistical analyses, mortality rate

Table 1. Serum tumor markers in operable patients and the surgical procedures applied

	n= 64 (%) or mean (95% CI)
Serum CA19-9 (U/mL)	20.3 (6.6-125.5)
Serum CEA (U/mL)	2.84 (1.71-7.67)
Type of surgery	
Curative (R0)	50 (78.1%)
Non-curative	14 (21.9%)
R1	2
Palliative or explorative surgery	12
Surgical procedure details	
Procedures with curative intent	52 (81.3%)
Simple cholecystectomy (LC/open)	4 (6.3%)
Standard radical cholecystectomy	38 (59.4%)
Hepatic wedge resection	7
Segment IVb/V segmentectomy	31
Extended radical resection	10 (15.6%)
Hepatopancreatoduodenectomy	6
Right hepatic trisectionectomy	1
Right hepatectomy plus segment IVb segmentectomy	1
Central hepatectomy	1
Segment IVb/V plus segment VI segmentectomy	1
Palliative or explorative surgery	12 (18.8%)
Simple cholecystectomy (LC/open)	6
Gastrojejunostomy	2
Explorative laparoscopy or laparotomy	4
Liver resection plus en bloc adjacent organ or structure resection	29 (45.3%)
EHBD resection	20 (31.3%)
Duodenum wedge resection	11 (17.2%)
Colon wedge or segmental resection	9 (14.1%)
Right hepatic artery	4 (6.3%)
Portal vein	3 (4.7%)
Others (Distal gastrectomy, omentum, abdominal wall and small intestine segmental resections)	9 (14.1%)
Lymphadenectomy	
No	14 (21.9%)
Standard dissection	38 (59.4%)
Standard dissection plus paraaortic dissection	12 (18.8%)
Total number of lymph nodes	8.0 (4.0-13.0)

CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, LC: Laparoscopic cholecystectomy, EHBD: Extrahepatic bile duct.

increased in direct proportion with advanced age (≥60 years), high serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels, non-IGBC versus IGBC, intraoperative versus postoperative incidental diagnosis, presence of jaundice, non-curative surgery, resection of adjacent organ or structure, grade 3 versus grade 1-2 tumors, presence of LVI, high T, stage N1 or N2 instead of N0, stage M1, and high AJCC stage ($p< 0.05$) (Table 5).

All variables with values of $p< 0.25$ on univariate statistical analyses were included in the multivariate Cox proportional hazards regression model. The following most determinant factors for OS were determined via the backward stepwise elimination procedure: High AJCC stage, grade 3 tumor, elevated serum CEA level, and advanced age (Table 6).

DISCUSSION

Median survival of the patients on whom we performed curative resection was 36.6 months, and their five-year survival rate was 51.9%; in contrast, in the group that underwent non-curative surgery, median survival was 7.2 months, and no patients survived five years later ($p< 0.001$). These suggest that

Table 2. Pathological characteristics of operable patients

	n= 64 (%)
Location	
Fundus	17 (27.0%)
Corpus	27 (42.9%)
Neck	4 (6.3%)
Multiple	3 (4.8%)
Diffuse	12 (19.0%)
Histologic type	
Adenocarcinoma	58 (90.6%)
Squamous cell	2 (3.1%)
Carcinosarcoma	1 (1.6%)
Neuroendocrine	3 (4.7%)
Grade	
1-2	46 (75.4%)
3	15 (24.6%)
AJCC 8th ed. stage	
0-I	6 (9.4%)
II	12 (18.8%)
III	14 (21.9%)
IV	32 (50.0%)
T stage	
T_{is}-T_{1a}	4 (6.3%)
T_{1b}-T_2	21 (32.8%)
T_3-T_4	39 (60.9%)
N stage*	
N_0	24 (50.0%)
N_1-N_2	24 (50.0%)
M stage	
M_0	47 (73.4%)
M_1	17 (26.6%)
LVI	
Absent	23 (40.4%)
Present	34 (59.6%)
PNI	
Absent	23 (40.4%)
Present	34 (59.6%)

AJCC 8th ed.: American Joint Committee on Cancer 8th edition, LVI: Lymphovascular invasion, PNI: Perineural invasion.
*NX was excluded from the calculation.

curative resection is a prerequisite for the treatment of GBC, as demonstrated in many other series (4-9). Herein, simple cholecystectomy was considered sufficient for curative resection in Tis and T1a cases, while radical resection was performed in T1b and more advanced cases. This practice was consistent with the Guidelines of the National Comprehensive Cancer Network recommendations and the Expert Consensus Statement derived from the Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/American Society of Clinical Oncology (ASCO) Consensus Conference (10,11). When the effects of AJCC stage and the T, N, and M stages on survival were evaluated separately, the negative effect of a high AJCC stage, high T stage, N1 or N2 stage, or M1 stage on survival was demonstrated in the univariate analysis, whereas only a high AJCC stage was an independent factor with a negative effect on survival in the multivariate analysis. These results were consistent with those of previous studies that revealed AJCC stage as the strongest prognostic factor (4-6). In our series, the high number of stage T3-T4, N1-N2, and M1 patients was noteworthy, while 50% of the patients had stage IV disease. Median survival of stage IV patients was 8.1 months, their one-year survival rate was 36%, and their three-, five-, and 10-year survival rates were 10.7%. In the Nagoya series, which is considered one of the main series in the surgical treatment of stage IV patients, median survival has been found as 9.6 months and three-, five-, and 10-year survival rates as 19%, 12%, and 10%, respectively (12). To provide a chance of survival for such advanced GBC cases, surgical treatment may be recommended if R0 resection is possible (13).

An estimated 25-50% of GBC patients present with jaundice. It has been found that the chance of resectability is lower and the incidence of metastatic disease and locally advanced disease is higher in jaundiced patients than in those without jaundice. In addition, when curative resection is performed, morbidity and mortality rates are higher and median survival is lower. As such, some studies have suggested that jaundice is a relative contraindication for resection (2,14). Mishra et al. have demonstrated that jaundice is an independent negative predictor of resectability; however, it is not an independent prognostic factor for post-resection survival (14). In our series, 23.4% of the patients had jaundice, among whom R0 curative resection was achieved in 80%. All patients required extrahepatic bile duct (EHBD) resection, and three patients needed hepatopancreatoduodenectomy (HPD) to achieve R0 resection. Mortality rate for these patients was 16.6%, median survival was 7.6 months. These results are significantly worse than those of the patients without jaundice. While jaundice was a negative prognostic factor in the univariate analyses, it was not an independent factor in the multivariate analysis for this group, which mostly consisted of stage IV patients.

Here, six HPD procedures were performed to achieve R0 curative resection: Two patients died during the postoperative period in the hospital, three died in the first year, and one remained alive at month 64. The cause of mortality was intraabdominal sepsis due to pancreaticojejunal anastomotic leakage. There were an insufficient number of HPD cases for analysis in our series; however, the literature demonstrates mortality rates

Table 3. Kaplan-Meier survival analyses of overall survival via log-rank test

	n	Cumulative survival rates				Expected duration of life		Log-rank	p
		One-year	Three-year	Five-year	10-year	Median (95% CI)	Mean (95% CI)		
Groups								51.408	**<0.001**
Operable	57	61.4	42.2	35.5	35.5	25.7 (9.2-42.2)	76.8 (53.6-100.1)		
Inoperable	37	5.4	N/A	N/A	N/A	3.0 (1.7-4.3)	4.6 (3.2-5.9)		
Operation								13.633	**<0.001**
Curative	45	68.9	51.9	43.6	43.6	36.6 (7.1-66.1)	92.5 (65.8-119.3)		
Non-curative	12	33.3	N/A	N/A	N/A	7.2 (3.7-10.8)	9.1 (5.9-12.5)		
Diagnosis								6.905	**0.009**
Incidental	29	75.9	57.4	49.2	49.2	N/A	106.5 (72.2-140.8)		
Non-incidental	28	46.4	26.0	21.6	21.6	8.3 (2.1-14.6)	48.9 (20.8-77.0)		
Jaundice								10.568	**<0.001**
Absent	44	70.5	51.1	45.2	45.2	44.7 (0.0-117.4)	94.3 (67.0-121.6)		
Present	13	30.8	10.3	N/A	N/A	7.7 (3.4-12.0)	13.8 (6.8-20.8)		
AJCC 8th ed. stage								25.181	**<0.001**
0-I	6	100.0	100.0	100.0	100.0	N/A	N/A		
II	12	100.0	75.0	75.0	75.0	N/A	154.4 (111.2-197.6)		
III	14	57.1	34.3	12.9	12.9	15.1 (1.5-28.8)	27.5 (13.2-41.7)		
IV	25	36.0	10.7	10.7	10.7	8.1 (6.3-9.9)	29.7 (6.3-53.1)		
T stage								18.620	**<0.001**
T_{is}-T_{1a}	4	100.0	100.0	100.0	100.0	N/A	N/A		
T_{1b}-T_2	19	94.7	67.4	56.1	56.1	N/A	121.2 (80.8-161.5)		
T_3-T_4	34	38.2	19.9	14.9	14.9	8.1 (7.1-9.1)	37.9 (14.7-61.1)		
N stage*								12.079	**<0.001**
N_0	23	87.0	67.9	67.9	67.9	181.6 (0.0-391.7)	134.2 (99.0-169.4)		
N_1-N_2	19	47.4	21.3	14.2	14.2	9.3 (0.0-20.7)	23.0 (10.9-35.2)		
M stage								6.304	**0.012**
M_0	43	69.8	49.7	40.8	40.8	33.3 (6.5-60.0)	91.2 (63.0-119.2)		
M_1	14	35.7	19.0	19.0	19.0	7.2 (1.7-12.7)	41.7 (2.4-81.0)		

AJCC 8th ed.: American Joint Commission on Cancer 8th edition, CI: Confidence interval, N/A: Not applicable.
*NX was excluded from the calculation.

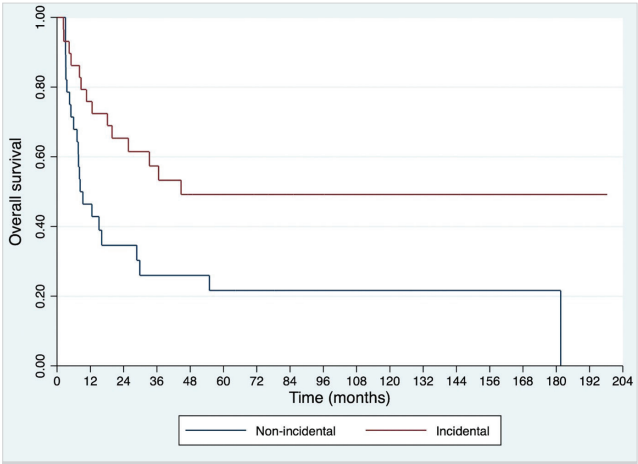

Figure 1. Kaplan-Meier survival curves of overall survival of patients with incidental versus non-incidental gallbladder cancer (p= 0.009).

of 0-60% and five-year survival rates of 0-39.8% were reported after HPD for advanced GBC cases (13).

In our series, another extended radical resection method was major hepatectomy; however, the low number and diversity prevented statistical evaluation. In standard radical cholecystectomy, the most common hepatic resection method was segment IVb/V resection. Although this resection method tended to lead to longer OS than wedge resection, the difference was not statistically significant. Segment IVb/V resection, which was previously recommended considering that potential micrometastases to this region through the venous drainage of the gallbladder by segment IVb/V resection would be also resected, provided no survival advantage over wedge resection; therefore, recommendations of Expert Consensus Statement derived from the AHPBA/SSAT/SSO/ASCO Consensus Conference and version 3 of the Clinical Practice Guidelines for the Management of Biliary Tract Cancers of the Japanese Society of Hepato-Biliary-Pancreatic Surgery have proposed that gallbladder bed resection would be sufficient provided that negative surgical margins are achieved (11,15-17). In 29 (45.3%) of our cases, combined en bloc adjacent organ or struc-

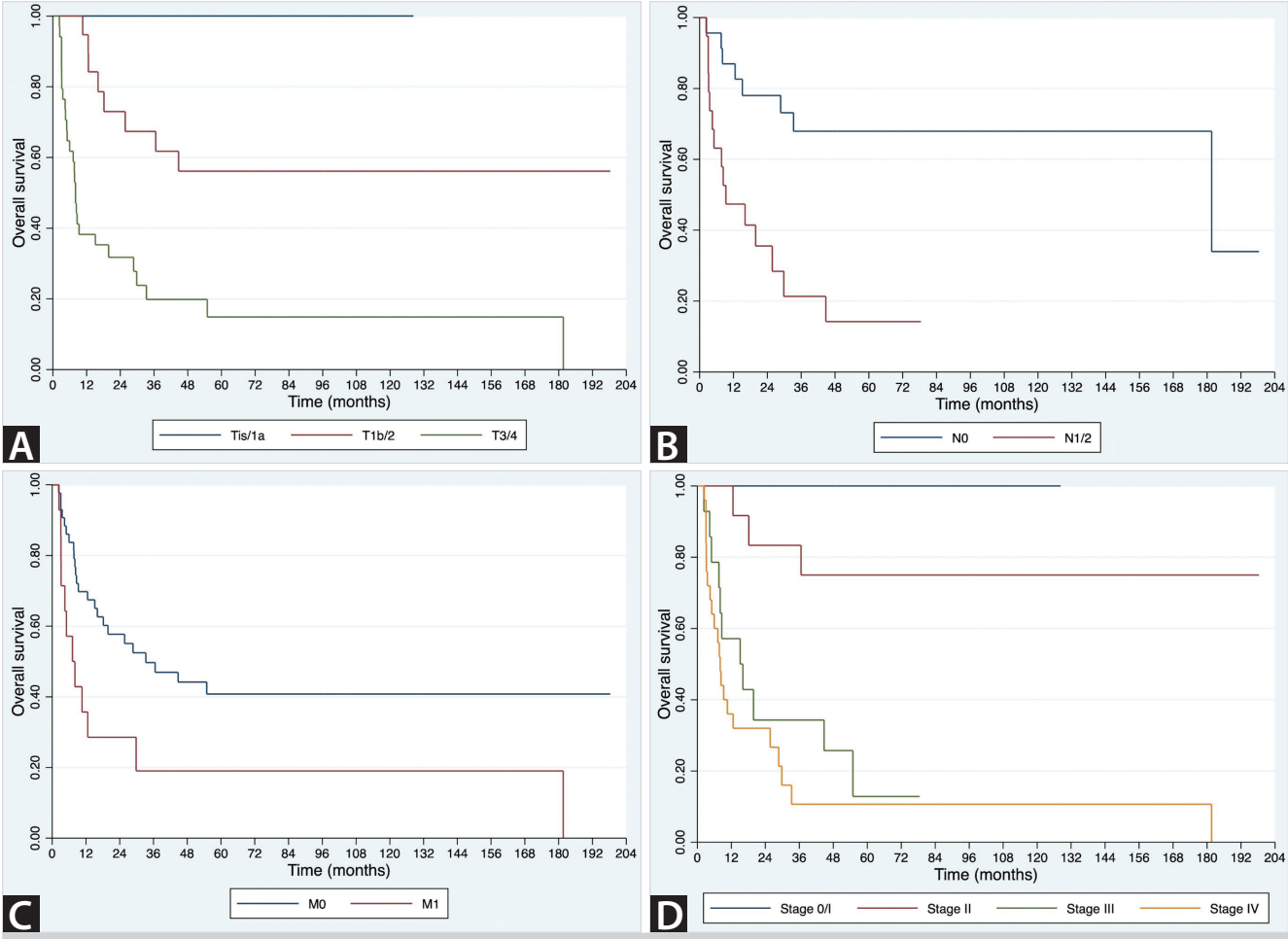

Figure 2. Kaplan-Meier survival curve of overall survival according to T stage (p< 0.001) **(A)**, N stage (p< 0.001) **(B)**, M stage (p= 0.012) **(C)**, and American Joint Commission on Cancer stage (p< 0.001) **(D)**.

Table 4. Patients' demographic and clinical characteristics of incidental versus non-incidental groups

	Incidental (n= 29) n (%) or mean ± SD	Non-incidental (n= 35) n (%) or mean ± SD	p
Age	63.1 ± 12.1	65.9 ± 12.6	**0.365†**
Female sex	18 (62.1%)	22 (62.9%)	**>0.999‡**
Jaundice	3 (10.3%)	12 (34.3%)	**0.051‡**
Curative operation	24 (82.8%)	26 (74.3%)	**0.608‡**
T stage			**0.002¶**
T_{is}-T_{1a}	3 (10.3%)	1 (2.9%)	
T_{1b}-T_2	15 (51.7%)	6 (17.1%)	
T_3-T_4	11 (38.0%)	28 (80.0%)	
N stage*			**0.143‡**
N_0	13 (65.0%)	11 (39.3%)	
N_1-N_2	7 (35.0%)	17 (60.7%)	
M stage			**0.210‡**
M_0	24 (82.8%)	23 (65.7%)	
M_1	5 (17.2%)	12 (34.3%)	
LVI			**0.013‡**
Absent	16 (59.3%)	7 (23.3%)	
Present	11 (40.7%)	23 (76.7%)	
PNI			**0.159‡**
Absent	14 (51.9%)	9 (30.0%)	
Present	13 (48.1%)	21 (70.0%)	
Grade			**0.060‡**
1-2	24 (88.9%)	22 (64.7%)	
3	3 (11.1%)	12 (35.3%)	
AJCC 8th ed. stage			**0.002¶**
0-I	4 (13.8%)	2 (5.7%)	
II	10 (34.5%)	2 (5.7%)	
III	7 (24.1%)	7 (20.0%)	
IV	8 (27.6%)	24 (68.6%)	
Mortality	0 (0.0%)	7 (20.0%)	**0.013¥**

†Student's t test, ‡Continuity-corrected $\chi 2$ test, ¶Fisher Freeman Halton test, ¥Fisher's exact test.

SD: Standard deviation, LVI: Lymphovascular invasion, PNI: Perineural invasion, AJCC 8th ed.: American Joint Committee on Cancer 8th edition.

*NX was excluded from the calculation.

ture resections other than HPD were also needed for R0 resection. The most common ones were EHBD resection in 20 cases, duodenal wedge resection in 11, and colon wedge or segmental resection in nine. In the univariate analysis, OS was significantly poor in the group subjected to en bloc adjacent organ or structure resection (p= 0.012). This may have been due to the more aggressive tumor characteristics in the EHBD resection group compared to the non-resected group as reported by Choi et al (18).

It is recommended that a minimum of six lymph nodes be resected to ensure sufficient staging in the lymphadenectomy part of radical cholecystectomy for GBC (10,11). Some studies have asserted that the number of lymph nodes resected during lymphadenectomy affects both staging and survival (19,20). In our study, a mean eight lymph nodes were resected for each patient, and the number of resected lymph nodes did not have a significant effect on OS. In their study comparing standard regional lymphadenectomy with extended regional lymphadenectomy including paraaortic lymphadenectomy, Wang et al. have reported that the latter provided significantly higher survival in patients with nodal positive stage III and IV disease without distant metastases (21). In our study, the survival effect

Table 5. Univariate Cox proportional hazard regression analysis of overall survival

	HR	95% CI for HR		Wald	p
		Lower limit	Upper limit		
Age ≥60 years	2.685	1.220	5.909	6.026	**0.014**
Female sex	1.168	0.591	2.309	0.199	0.656
Serum CA19-9*	1.013	1.0003	1.026	4.011	**0.045**
Serum CEA	1.020	1.009	1.030	13.584	**<0.001**
Non-incidental diagnosis	2.411	1.225	4.748	6.482	**0.011**
Intraoperative versus postoperative diagnosis	3.734	1.158	12.038	4.865	**0.027**
Jaundice	3.126	1.515	6.451	9.512	**0.002**
Non-curative operation	3.929	1.794	8.605	11.703	**<0.001**
Wedge resection versus segment IVb/V	2.395	0.923	6.210	3.226	0.072
Adjacent organ or structure resection	2.343	1.202	4.570	6.246	**0.012**
Grade 3 versus grade 1-2	3.376	1.671	6.820	11.504	**<0.001**
LVI	3.235	1.485	7.046	8.740	**0.003**
PNI	2.005	0.958	4.197	3.407	0.065
Location					
Corpus	1.689	0.727	3.924	1.486	0.223
Neck	0.901	0.190	4.266	0.017	0.896
Multiple	N/A	-	-	-	-
Diffuse	1.969	0.754	5.138	1.915	0.166
Total number of lymph nodes	0.990	0.952	1.029	0.280	0.597
Standard plus paraaortic lymphadenectomy	0.727	0.274	1.928	0.411	0.521
AJCC 8th ed. stage	2.696	1.740	4.177	19.708	**<0.001**
T stage	4.376	2.066	9.267	14.866	**<0.001**
N stage	4.456	1.784	11.128	10.239	**<0.001**
M stage	2.408	1.187	4.886	5.926	**0.015**

CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, LVI: Lymphovascular invasion, PNI: Perineural invasion, AJCC 8th ed.: American Joint Committee on Cancer 8th edition, CI: Confidence interval, HR: Hazard ratio, N/A: Not applicable.

*The effect of every 100-unit increase in carbohydrate antigen 19-9 level on overall survival.

Less than 60 years for age, male factor, incidental diagnosis, postoperative diagnosis, curative operation, the resection of segment IVb/V, Grade 1-2, location in the fundus, standard lymphadenectomy, M0 for M stage and the absence of jaundice, adjacent organ or structure resection, LVI, and PNI were taken considered as reference category. The measurements of serum CA 19-9, serum CEA and total number of lymph nodes were taken into the model as continuous variables. On the other hand, AJCC 8th ed. stage, T stage and N stage were treated as ordinal variables.

Table 6. Results of multivariate Cox proportional hazards regression model via the backward stepwise elimination procedure for determining predictors affecting overall survival

	HR	95% CI for HR		p
		Lower limit	Upper limit	
Age≥ 60 years	4.506	1.127	18.023	**0.033**
Serum CEA*	1.041	1.005	1.078	**0.023**
Grade 3 versus grade 1-2	5.144	1.641	16.127	**0.005**
AJCC 8th ed. Stage**	2.568	1.354	4.870	**0.004**

CEA: Carcinoembryonic antigen, AJCC: American Joint Commission on Cancer 8th edition, CI: Confidence interval, HR: Hazard ratio.

Less than 60 years for age, and Grade 1-2 were taken as reference category.

*Effect of each 1-unit increase in serum CEA on overall survival

**Effect of each 1-step (e.g., Stage 2 vs 3 or Stage 3 vs 4 etc.) increase in AJCC stage on overall survival.

of extended regional lymphadenectomy was evaluated without any discrimination of stages due to the insufficient number of cases, and no significant effect on survival was found.

Advanced patient age and high tumor grade have been shown to be independent poor prognostic factors reducing OS in the literature (22,23). We also found that being ≥60 years of age and having grade 3 tumor were independent factors that reduced OS. Ouchi et al. have found that LVI and PNI, in addition to high tumor grade, were significantly associated with lower survival (24). Choi et al. have shown that LVI was an independent prognostic factor for OS; however, they did not find the effect of PNI to be significant (18). In our series, LVI significantly shortened OS; however, although such a trend was detected for PNI, it was not significant.

Univariate and multivariate analyses revealed that high serum CA19-9 and CEA levels were significantly associated with poor prognosis in resectable GBC, suggesting that they can be used as independent prognostic markers (25). In the present study, both were significantly associated with poor prognosis on the univariate analysis, whereas only CEA was an independent factor on the multivariate analysis.

IGBC has a better prognosis overall than does non-IGBC, which may result from its tendency to be detected at earlier stages (5,6). In our series, IGBC cases comprised 45.3% of all cases, and the incidence of advanced T stage, advanced AJCC stage, and LVI was significantly higher in non-IGBC patients. The incidence of jaundice, N stage, M stage, grade 3, and PNI also tended to be higher, but the difference was not statistically significant. In the univariate analysis of survival of patients with non-IGBC and IGBC, non-IGBC was a predictor of poor prognosis and was not an independent factor in the multivariate analysis. Patients with IGBC who were diagnosed intraoperatively and underwent radical resection simultaneously had significantly worse survival than those who were diagnosed postoperatively and underwent radical resection as a secondary operation. These results were similar to those reported by Schauer et al. (5) and He et al (26). He et al. have suggested that this may have been because the postoperative diagnostic group was subjected to a more comprehensive preoperative radiographic evaluation and underwent higher quality surgical procedures (26).

The present study has some limitations. First, it is a retrospective study, which carries an inherent risk of selection bias. Second, it includes data from a single center and a relatively low number of patients, precluding subgroup assessments.

CONCLUSION

In conclusion, individualized prognostic assessment is necessary in the treatment of GBC. Well-established prognostic factors whose effects have been confirmed along with standard anatomical staging may be of benefit in treatment planning and clinical decision-making.

Ethics Committee Approval: Approval for the study was obtained from Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Protocol number: 2021/65, Approval date: 02.15.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – All of authors; Design – All of authors; Supervision – All of authors; Fundings - MAU; Materials - MAU, AG; Data Collection and/ or Processing – MAU, MT, SAK, AG; Analysis and/or Interpretation – All of authors; Literature Search – All of authors; Writing Manuscript – All of authors; Critical Reviews – All of authors.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2022; 38 (4): 334-344

Safra kesesi kanserinin cerrahi tedavisi sonrasında uzun dönem sonuçlar ve prognostik faktörler

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ÖZET

Giriş ve Amaç: Safra kesesi kanseri nispeten nadir olup, geleneksel olarak kötü bir prognoza sahip olduğu kabul edilir. Klinikopatolojik özelliklerin ve farklı cerrahi tekniklerin prognoza etkileri konusunda tartışmalar mevcuttur. Bu çalışmanın amacı, cerrahi olarak tedavi edilen safra kesesi kanserli hastaların klinikopatolojik özelliklerinin uzun dönem sağkalımları üzerine etkilerini araştırmaktır.

Gereç ve Yöntem: Kliniğimizde Ocak 2003 ile Mart 2021 tarihleri arasında tedavi edilen safra kesesi kanseri hastalarının veri tabanını geriye dönük olarak analiz ettik.

Bulgular: Değerlendirilen 101 vakanın 37'si inoperabl idi. On iki hasta cerrahi bulgulara göre anrezektabl olarak saptandı. Elli iki hastaya küratif amaçlı rezeksiyon yapıldı. bir, üç, beş ve 10 yıllık sağkalım oranları sırasıyla %68,9, %51,9, %43,6 ve %43,6 idi. Medyan sağkalım 36,6 aydı. Tek değişkenli analizde; ileri yaş, yüksek karbonhidrat antijeni 19-9 ve karsinoembriyonik antijen seviyeleri, non-insidental tanı, insidental vakalarda intraoperatif tanı, sarılık, komşu organ/yapı rezeksiyonu, *grade* 3 tümörler, lenfovasküler invazyon, yüksek T, N1 veya N2, M1 ve yüksek AJCC evreleri kötü prognostik faktörler olarak bulundu. Cinsiyet, *wedge* rezeksiyon yerine IVb/V segmentektomi yapılması, perinöral invazyon, tümör lokasyonu, çıkarılan lenf nodu sayısı ve genişletilmiş lenfadenektomi genel sağkalımı anlamlı olarak etkilemedi. Çok değişkenli analizde, sadece yüksek AJCC evreleri, *grade* 3 tümörler, yüksek karsinoembriyonik antijen seviyeleri ve ileri yaş kötü prognozun bağımsız öngörücüleriydi.

Sonuç: Safra kesesi kanseri için tedavi planlaması ve klinik karar verme, standart anatomik evreleme ve diğer doğrulanmış prognostik faktörlerle birlikte bireyselleştirilmiş bir prognostik değerlendirme gerektirir.

Anahtar Kelimeler: Safra yolu cerrahi prosedürler, safra kesesi neoplazmı, prognostik faktörler, sağkalım

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ORIGINAL ARTICLE
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What has changed in the last 20 years in the postoperative specimen findings of the papillary thyroid cancer cases? A retrospective analysis

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ABSTRACT

Objective: In this study, it was aimed to investigate the changes in surgical approaches and histopathological evaluation of the tumor according to years of patients who were operated on with the diagnosis of thyroid papillary cancer (PTC) in our center in the last 20 years.

Material and Methods: The records of the cases who underwent thyroidectomy in our department were divided into four groups of five years each and analyzed retrospectively. Demographic characteristics, surgical procedures, presence of chronic lymphocytic thyroiditis, histopathological features of tumour and hospital stay of the cases in the groups were evaluated. Based on tumor size, PTCs were classified into five subgroups. PTCs of 10 (mm) or less were accepted as papillary thyroid microcarcinoma (PTMC).

Results: There was a significant increase in PTC and multifocal tumors in the groups over the years ($p< 0.001$). There was a significant increase between the groups in the presence of chronic lymphocytic thyroiditis ($p< 0.001$). In contrast, the total number of metastatic lymph nodes ($p= 0.486$) and the largest metastatic lymph node size were similar between the groups ($p> 0.999$). In our study, it was observed that there was a significant increase over the years in both the total/near-total thyroidectomy cases and the number of cases with a postoperative hospital stay of one day ($p< 0.001$).

Conclusion: In the present study, it was found that papillary cancer sizes decreased gradually and the frequency of papillary microcarcinoma increased gradually in last 20 years. Also, a significant increase was detected in the rates of total/near-total thyroidectomy and lateral neck dissection over the years.

Keywords: Papillary thyroid carcinoma, papillary thyroid microcarcinoma, multifocal tumor, tumor size

INTRODUCTION

Thyroid cancer is the most common type of endocrine cancer accounting for 3% of all cancers and 0.4% of cancer-related mortality in 2019 in the USA (1). According to the data of the Turkish Public Healthcare Institution published in 2014, it was reported that thyroid cancer is the ninth most common cancer in men and the second in women. Also, it is the most common cancer type in women between the ages of 15-24 (2). However, it is cancer that has had the fastest increasing incidence in the world in the last 30 years. In the USA, the annual incidence increased from 4.9 per 100.000 in 1975 to 14.3 per 100.000 in 2009 (3), and almost all of this change was associated with increased incidence of papillary thyroid cancer (PTC) (4). Needle biopsy histopathological evaluations used in the past in the diagnosis of thyroid cancer have changed, and novel classifications are now used, and in this respect, more conservative surgical approaches are preferred in selected cases.

A relation was reported in a meta-analysis conducted in Korea in 2018 among Hashimoto's thyroiditis and multifocal papillary cancer in patients with PTC (5). In their study, Karakoç et al. have reported that 31.95% of PTCs were microcarcinomas and 46.15% of the patients underwent modified neck dissection (6). It was reported in the consensus decisions published by the European Society of Endocrine Surgeons in 2013 that age was not a risk factor for multifocality, but it had prognostic significance, and the prognostic importance of bilateral multifocal papillary thyroid cancer was emphasized. However, it was shown as an opposing opinion that multifocality has little or no prognostic significance in thyroid papillary microcarcinomas (7).

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In the present study, the changes in surgical approaches and histopathological evaluations of the tumor over the years were investigated in patients who were operated on in our center with the diagnosis of thyroid papillary cancer in the last 20 years.

MATERIAL and METHODS

The records of the cases who underwent thyroidectomy and/or neck dissection in Bursa Uludağ University General Surgery Endocrine Surgery Department during 20 years between January 1999 and December 2018 were reviewed retrospectively by scanning electronic (Avicenna "TM"/MIAMed "TM") and written archives. Ethics committee approval was received from Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee with the decision number of 2020-14/12. It was found that a total of 3580 cases were operated on for thyroidectomy, and nine out of 777 cases that were diagnosed with PTC over the age of 18 included in the study were excluded because of missing data. The cases under the age of 18 were not included in the study. Although neck dissection was performed along with thyroid surgery or thyroidectomy in a total of 726 cases, it was observed that only neck dissection was performed in 42 cases.

The cases were divided into four groups of five years in the 20 years between 1999-2018. These groups were; Group I (1999-2003), Group II (2004-2008), Group III (2009-2013), and Group IV (2014-2018). Demographic characteristics, surgical procedures for thyroid and lymph node dissection, tumor size, multifocality, number of foci, presence of chronic lymphocytic thyroiditis, capsule invasion, vascular invasion, extrathyroidal spread, and hospital stay of the cases in the groups were evaluated. Extrathyroidal spread was examined as muscle invasion, trachea invasion, and surrounding soft tissue invasion. The presence and number of metastatic lymph nodes and the long size of the largest metastatic lymph node were also recorded. The length of hospital stay was noted as one day, two days, three days, four days, and five or more days.

When the tumor size was considered, PTCs were classified into five subgroups as below 10 mm, 11-20 mm, 21-30 mm, 31-40 mm, and over 40 mm. PTC of 10 (mm) or less was accepted as papillary thyroid microcarcinoma (PTMC) and were divided into two subgroups of 5 millimeters (mm) and less and 6-10 mm.

Statistical analyzes of the present study were performed using IBM SPSS.21 Program. Normal distribution of the data was evaluated with Kolmogorov-Smirnov test. Data that were not distributed normally were expressed as median (minimum-maximum). Kruskal Wallis Test was used in the analysis of numerical data, and Pearson Chi-square test and Fisher's exact test were used in the analyses of the categorical data. $p< 0.05$ was considered statistically significant.

RESULTS

When all of the patients who underwent thyroidectomy were compared with the patients who were diagnosed with PTC after thyroidectomy, there was an increase in the rate of PTCs ($p< 0.001$) (Table 1). In subgroup analysis, an increase was detected in all subgroups except for Group I and Group II ($p< 0.001$), and the highest rate was found in Group IV.

Female sex was generally dominant (78% of the cases). However, no significant differences were detected in the evaluation of age ($p= 0.168$) and sex ($p= 0.177$) among the groups (Table 1).

Significant increases were detected in the evaluation among the groups in multifocal PTCs over the years ($p< 0.001$) (Table 1), and this rate was the highest in Group IV. In the group analyses, the increase between Group I and IV ($p= 0.002$) and Group III and IV ($p< 0.001$) was found to be statistically significant. This difference was not significant in other group analyzes. In unifocal tumors, the tumor size tended to decrease in the analysis among the groups ($p< 0.001$) The smallest tumor sizes were in Group IV, and the largest tumor sizes were in Group I (Table 1).

Significant differences were detected in the evaluations of the total tumor size among the groups ($p< 0.001$) (Table 1). This difference tended to decrease in general; however, there was an increase in Group III when compared to previous years. Tumor size was the smallest in Group IV when compared to all groups.

In histopathological evaluations, the presence of Hashimoto's thyroiditis increased over the years among the groups ($p< 0.001$). No significant differences were detected in the evaluations of the presence of metastatic lymph nodes among the groups ($p= 0.706$), and there were no significant differences in the evaluation of capsule invasion, vascular invasion, and extrathyroidal spread among the groups ($p= 0.056$, $p= 0.240$, $p= 0.534$, respectively) (Table 1).

In the comparisons of the surgical procedures regarding the thyroid, a significant increase was detected in total/near-total thyroidectomy ($p< 0.001$) and a significant decrease in subtotal thyroidectomy ($p< 0.001$) in correlation with this, and Group III and Group IV subtotal thyroidectomy procedure was not carried out in the study. However, no significant differences were detected among the other types of surgeries (Table 2).

Significant differences were detected among the central neck dissection groups ($p= 0.002$), and the highest rate was in Group II and decreased in the following groups. Lateral neck dissection had an increasing trend among the groups ($p< 0.001$). It was found that it was applied at the highest rates in Group IV (Table 2).

Table 1. Demographic characteristics of the patients with PTCs and histopathological features of the tumor (n= 726)

	Group I	Group II	Group III	Group IV	Total	p
Non-PTC Thyroidectomy, n (%)	706 (91)	749 (91)	882 (76)	517 (58)	2854 (80)	<0.001[b]
PTC, n (%)	71 (9)	69 (9)	246 (24)	340 (42)	726 (20)	
Age (min-max)	48 (21-84)	45 (18-80)	50 (18-90)	49 (19-78)	49 (18-90)	0.168[a]
Female sex, n (%)	48 (67)	55 (80)	194 (79)	269 (77)	566 (78)	0.177[b]
PTMC, n (%)	30 (42)	25 (36)	110 (45)	197 (58)	362 (50)	<0.001[b]
Multifocal PTC, n (%)	14 (20)	23 (33)	57 (23)	134 (39)	228 (31)	<0.001[b]
Single-focus tumors, n (%)	57(80)	46 (67)	189 (77)	206 (61)	496	<0.001[b]
Single-focus tumors-size, mm median (min-max)	15 (2-55)	12 (2-50)	12 (1-140)	8 (1-75)	10 (1-140)	<0.001[a]
Total tumor size, mm Median (min-max)	15 (2-155)	13 (2-70)	14.5 (1-140)	11 (1-135)	12 (1-155)	<0.001[a]
Hashimoto's Thyroiditis, n (%)	13 (18)	13 (19)	85 (35)	168 (49)	279 (38)	<0.001[b]
Metastatic LN presence, n (%)	9 (13)	9 (13)	28 (11)	50 (15)	96 (13)	0,706[b]
Capsule invasion, n (%)	15 (21)	14 (20)	75 (31)	73 (22)	177 (24)	0.056[b]
Vascular invasion, n (%)	5 (7)	3 (4)	18 (7)	13 (4)	39 (5)	0.240[c]
Extra thyroidal invasion, n (%)	8 (11)	7 (10)	29 (12)	51 (15)	95 (13)	0.534[b]

[a]: Kruskal Wallis test, [b]: Pearson Chi-square test, [c]: Fisher's exact test.

Table 2. Subgroup analysis of the surgical procedures and postoperative hospitalization durations

	Group I	Group II	Group III	Group IV	Total	p
Surgical procedures, n (%)						
Total/near-total thyroidectomy	48 (68)	53 (77)	203 (83)	305 (90)	615 (85)	<0.001[b]
Subtotal thyroidectomy	11 (16)	6 (9)	0 (0)	0 (0)	11 (2)	<0.001[b]
Hemithyroidectomy-lobectomy	7 (10)	5 (7)	27 (11)	22 (7)	61 (8)	0.253[b]
Completion thyroidectomy	4 (6)	4 (6)	16 (7)	13 (4)	37 (5)	0.454[b]
Biopsy	1 (1)	1 (1)	0 (0)	0 (0)	2 (3)	0.037[b]
Neck dissection	n= 3	n= 25	n= 55	n= 54	n= 137	
Central, n (%)	1 (33)	18 (72)	25 (46)	15 (28)	59 (43)	0.002[b]
Thyroidectomy	1	18	23	15	57	
No thyroidectomy	0	0	2	0	2	
Lateral, n (%)	0 (0)	7 (28)	26 (47)	37 (69)	70 (51)	<0.001[b]
Thyroidectomy	0	3	10	23	36	
No thyroidectomy	0	4	16	14	34	
LN excision, n (%)	2 (67)	0 (0)	4 (7)	2 (4)	8 (6)	0.009[b]
Thyroidectomy	2	0	0	0	2	
No thyroidectomy	0	0	4	2	6	

[a]: Kruskal Wallis test, [b]: Pearson Chi-square test, [c]: Fisher's exact test.

When the cases with postoperative hospital stays of one day were examined among the groups, it was found that there was a significant change over the years (p< 0.001). When subgroup analyzes were made, significant increases were detected between Group I and Group II (p= 0.002), Group I and Group III (p< 0.001), and Group I and Group IV (p= 0.002); however, a significant decrease was observed between Group III and Group IV (p= 0.014). When the patients who had hospitalization periods of ≥4 days were analyzed among the groups, it was observed that there was a significant decrease over the years (Figure 1).

Significant variations were detected among the groups in PTC dimensions of ≤10 mm and >10 mm PTC, and this change tended to increase in tumors of ≤10 mm and tended to decrease in tumors of >10 mm (p< 0.001). In subgroup analysis of PTMCs, increased incidence of tumors below ≤5 mm was detected in recent years (p< 0.01, p< 0.016, respectively) (Table 3).

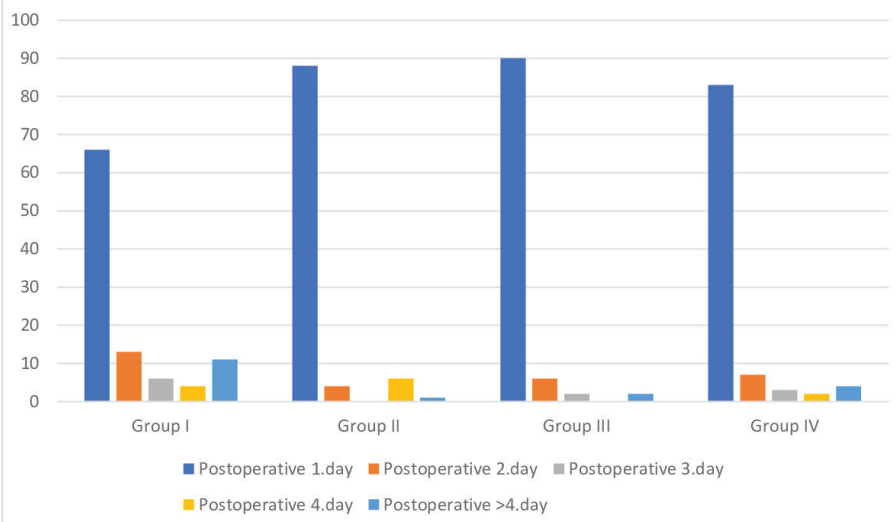

Figure 1. The change of hospitalization days among the groups.

Table 3. Intragroup comparisons of the tumor sizes in PTMC cases

	Group I	Group II	Group III	Group IV	p
≤10 mm, n (%)	30 (42)	25 (36)	110 (45)	197 (58)	<0.001[b]
≤5 mm, n (%)	13 (43)	6 (24)	47 (43)	102 (52)	0.045[b]
6-10 mm, n (%)	17 (57)	19 (76)	63 (57)	95 (48)	0.045[b]
>10 mm, n (%)	41 (58)	44 (64)	136 (55)	143 (42)	<0.001[b]
11-20 mm, n (%)	19 (46)	29 (66)	71 (52)	92 (64)	0.054[b]
21-30 mm, n (%)	12 (29)	10 (23)	31 (23)	28 (20)	<0.001[b]
31-40 mm, n (%)	5 (12)	4 (9)	23 (17)	10 (7)	0.173[b]
>40 mm, n (%)	5 (12)	1 (2)	11 (8)	13 (9)	0.016[c]

[b]: Pearson's Chi-square test, [c]: Fisher's exact test.

In general, metastatic lymph was detected in 13% of the cases and this did not differ among the groups (p= 0.706) (Table 1). The presence of multifocal PTC or the detection of Hashimoto's thyroiditis did not change the presence of metastatic lymph nodes, and no significant differences were detected among the groups (0.917 and p= 0.615, respectively) (Table 4).

The comparison of PTMK characteristics among the groups is given in Table 5. The incidence of PTMC tended to increase over the years (p< 0.001) and was at the highest level in Group IV. In group analyses, significant increases were detected in the comparison of Group IV with all groups (p= 0.016, p= 0.001, p= 0.002, respectively). Although multifocal PTMC appeared more frequently over the years, no statistically significant differences were detected (p= 0.052). When compared in terms of the number of foci, no significant differences were detected among the groups of 2-focal and 3-focal PTMK. Significant

Table 4. The characteristics of the cases with metastatic lymph nodes and intragroup comparisons

	Group I	Group II	Group III	Group IV	p
Number of metastatic LN Median (min-max)	2 (1-7)	2 (1-18)	5 (1-24)	3 (1-27)	0.486[a]
The largest MLN size Median (min-max)	12 (2-30)	15 (3-30)	14 (2-85)	12 (2-45)	>0.999[a]
Multifocal PTC, n (%)	2 (14)	5 (22)	9 (16)	24 (18)	0.917[c]
Hashimoto's thyroiditis, n (%)	0 (0)	2 (15)	12 (14)	24 (14)	0.615[c]

[a]: Kruskal Wallis test, [c]: Fisher's exact test.

Table 5. Intragroup comparison of PTMC characteristics

	Group I	Group II	Group III	Group IV	p
n (%)	30 (42)	25 (36)	110 (44)	197 (58)	<0.001[b]
Multifocal PTK	6 (20)	6 (24)	24 (22)	69 (35)	0.052[b]
Number of foci (mean)	2.3	3.1	2.3	2.4	
2	5 (83)	2 (33)	19 (79)	43 (62)	0.127[c]
3	0	1 (17)	4 (17)	23 (33)	0.186[c]
4	1 (17)	3 (50)	1 (4)	3 (5)	0.006[c]
Capsule invasion	3 (10)	1 (4)	19 (17)	32 (16)	0.088[b]
Vascular invasion	0	2 (8)	0	3 (2)	0.056[c]
Non-tumor spread	0 (0)	2 (8)	6 (1)	15 (1)	
Muscle tissue invasion	0	0	0	2	0.419[c]
Trachea invasion	0	2	1	2	
Lipomatosis tissue inv.	0	0	5	11	
Presence of metastatic LN	2 (7)	1 (4)	4 (4)	10 (5)	0.877[c]
Hashimoto's thyroiditis	5 (17)	5 (20)	35 (32)	98 (50)	<0.001[b]

[b]: Pearson's Chi-square test, [c]: Fisher's exact test.

Table 6. Intragroup comparison of papillary thyroid carcinoma characteristics over 10 mm

	Group I	Group II	Group III	Group IV	p
n (%)	41 (58)	44 (64)	136 (55)	143 (42)	<0.001[b]
Multifocal	8 (20)	17 (39)	33 (24)	65 (46)	<0.001[b]
Number of foci* (mean)	2.3	2.6	2.6	2.6	
2	6 (75)	8 (47)	19 (58)	34 (52)	0.585[c]
3	2 (25)	8 (47)	9 (27)	20 (31)	0.594[b]
4	0	1 (6)	5 (15)	11 (17)	0.607[c]
Capsule invasion	12 (29)	13 (30)	56 (41)	41 (29)	0.125[b]
Vascular invasion	5 (12)	1 (2)	18 (13)	10 (7)	0.094[c]
Non-tumor spread	8 (20)	5 (11)	23 (17)	36 (32)	
Muscle tissue invasion	5	1	6	3	<0.001
Trachea invasion	0	3	5	0	
Lipomatosis tissue inv.	3	1	12	33	
Presence of metastatic LN	7 (17)	8 (18)	24 (18)	39 (27)	0.14[b]
Hashimoto's thyroiditis	8 (16)	8 (20)	50 (37)	70 (49)	<0.001[b]

[b]: Pearson's Chi-square test, [c]: Fisher's exact test.

decreases were detected in 4-focal tumors in the last 10 years when compared to previous years (p= 0.006). When the presence of non-tumor extension (p= 0.056), capsule invasion (p= 0.088), and vascular invasion (p= 0.056) was evaluated, no significant differences were detected. No differences were detected among the groups in terms of the presence of metastatic lymph nodes (p= 0.877). However, when the association of Hashimoto's thyroiditis was evaluated, significant increases were detected, especially in recent years (p< 0.001).

The features of >10 mm PTKs are given in Table 6. Although the number of PTC cases >10 mm tended to decrease in recent years (p< 0.001), this difference was detected among Group IV and other groups (Group I versus Group IV (p= 0.016), Group II and Group IV (p= 0.001), and Group III and Group IV (p= 0.002). However, multifocal tumors were found at the highest levels in Group IV, and there was a difference among the groups (p< 0.001). It was seen that it was highest in Group IV and included the last years. When compared in terms of the number of foci, no differences were detected among the groups. No significant differences were detected when the presence of capsule invasion (p= 0.125) and vascular invasion (p= 0.094) were evaluated. Significant differences were detected among

the groups in the evaluation of non-tumor spread, and Group IV had the highest rate (p< 0.001). In subgroup analysis, the increase between Groups II and IV (p= 0.009) and Groups III and IV (p= 0.006) was significant. No differences were detected in the analysis of the presence of metastatic lymph nodes among the groups (p= 0.188). There was a significant change (p< 0.001), which tended to increase towards the last years in the groups when separated by years.

DISCUSSION

It has been reported that there was an annual increase rate of 3% in the USA as the third fastest-growing cancer type. Similar patterns of increase have been reported in Canada, Australia, and Western Europe (5-8). The increased incidence rate of papillary thyroid cancer may represent an increasing number of diagnoses, either from a true increase in disease or from increased diagnostic investigation methods. Especially with the widespread use of ultrasonography, fine-needle aspiration biopsy, and non-thyroid imaging, more hidden and small thyroid nodules are detected and investigated (9). There has been an increase in recent years by approximately 3% a year in the number of patients diagnosed with PTC, with the increasing share of these newly diagnosed tumors of lesions smaller than 1 cm. Papillary thyroid microcarcinoma (PTMC) is defined as PTC tumors smaller than 1 cm. It is a subtype of PTK. PTMC also accounts for 39% of thyroid cancers in the USA. In the present study, the incidence of thyroid papillary cancer was found to have increased in recent years. PTMC constituted 42-58% of the cases according to the years in the study groups. The increase in the incidence of both PTC and PTMK was found to be significant especially in recent years.

Although sex did not differ at significant levels among the groups, female sex was more dominant than the male sex in all groups. The mean age of papillary thyroid cancer incidence was between 45 and 50, and the age range was similar in all groups.

Multifocality, which is considered a poor prognostic factor, has been reported in the literature as 18-87% in different case series (10). In our series, it varied between 20% and 39%. Especially, the incidence of multifocal PTC has increased significantly over the years. It is considered that thinner cross-sectional examination of pathology specimens is more effective in detecting small multifocal foci causing an increased number of multifocal tumors. In recent studies, the incidence of multifocal PTMC has been reported as 13.47% and 36.18% in all PTMCs. In our series, it varied between 20% and 35% according to years, and the rate of multifocal PTMC has increased in recent years. Especially, more multifocality was detected in lesions >1 cm when compared to PTMC. This remarkable increase in multifocality over the years is correlated with increasing total thyroidectomy in the present study. In the literature, in another study investigating multifocality in PTC, although multifocality has been found to be more common in tumors >1 cm and lymph node metastasis has been detected more frequently in multifocal tumors, only mixed-type pathology has been found to be significant in multifocality in multivariate analyses. In the present study, no relations were detected between lymph node metastasis and multifocality. However, in a meta-analysis, the prognostic importance of multifocality has been emphasized in thyroid cancers, and it has been found that it is highly associated with lymph node metastasis and extrathyroidal spread (11).

Multifocality was found to have increased in both PTCs and PTMCs over the years in the present study. However, this increase in multifocality was significant in tumors >1 cm. Although the number of four-focal tumors decreased at significant levels over the years in PTCs (p= 0.006), the opposite was true in PTCs >10 mm. Although not significant, an increase was detected in four-focal pathologies in these tumors. In a retrospective study published by Ning et al. in 2014, an increase was detected in aggressive tumor features such as lymph node metastasis and extrathyroidal spread, and a poor prognosis was reported as the number of foci increased (12).

It was observed that the tumor size decreased significantly over the years in unifocal PTCs and multifocal PTCs; however, the rate of detection of metastatic LN, capsule invasion, vascular invasion, and extrathyroidal spread did not change. Although tumor size decreased, histopathological aggressiveness of the tumor did not change. Especially in PTCs >10 mm, non-tumor spread was significantly higher than in PTMCs. These findings suggest that the smaller size of cases with PTC in our series might be a result of the increased use of USI in the approach to thyroid nodules.

The discussions about Hashimoto's thyroiditis were first published by Dailey et al. in 1955 and have kept their up-to-date status since then (13). The relation between chronic lymphocytic thyroiditis and PTC continues to increase. The effect of Hashimoto's Thyroiditis on lymph node metastasis is found at lower rates in patients with PTC (5). In the present study, no significant relations were detected on the lymph node. However, we think that the increased incidence of Hashimoto's association in both PTMCs and pathologies of PTCs may have caused earlier diagnosis of patients followed up more closely because of the known relation between chronic lymphocytic thyroiditis and PTC. For this reason, the increasing incidence of Hashimoto's thyroiditis over the years may have caused the detection of smaller tumors in patients who were under close follow-up, which enabled more patients to be diagnosed with PTMC.

It is very difficult to diagnose PTC variants with FNAB. The diagnoses of subtypes with poor prognoses can be made in definitive pathology reports. Performing total/near-total thyroidectomy facilitates the follow-up of any recurrence in thyroglobulin

levels and I^{131} scans. In a study comparing the definitive pathology report after bilateral subtotal thyroidectomy procedure and morbidity of patients undergoing completion thyroidectomy and those undergoing total thyroidectomy, it has been found that recurrent nerve injury and hypocalcemia were more common in completion thyroidectomy (7). The identification of PMTCs has caused the introduction of conservative surgical procedures in selected patients with thyroid cancers and to guide the lobectomy procedure in unifocal PMTCs. However, as stated in a previous meta-analysis, the false-negative rate of the benign diagnosis of the contralateral nodule in a case with unifocal PTMC has been found to be 23% (14). Risk factors for contralateral malignancy in unifocal PMTCs with contralateral negative thyroid nodules are multifocality of primary carcinomas, capsular invasion, and Hashimoto's thyroiditis (14). In our study, it was observed that there was a change in the types of surgeries performed over the years. It is noteworthy that subtotal thyroidectomy decreased significantly over the years and even, it was not performed in the last two groups, and total/near-total thyroidectomy increased at significant levels. No differences were detected among the groups in lobectomies. The fact that the cases found in the present study had more multifocal and Hashimoto associations over the years appears to be the reason for the increased total/near-total thyroidectomy procedure in thyroid surgery. In the study published by Karakoc et al. in 2009, although the incidence of thyroid malignancy associated with the increased rate of papillary thyroid cancer increased after 2000, a significant increase was also detected in total thyroidectomies (6).

Although no significant changes were detected in LN metastasis in the present study, central neck dissection was used widely in surgical procedures in groups including the first years; however, it has gradually decreased in recent years. The reason for this is to avoid the morbidities that may be brought by the changes in the guidelines and unnecessary central dissection in recent years. In the present study, prophylactic lymph node metastasis was not performed if it was not proven by FNAB. As the tumor size decreased, the increase in lateral neck dissections suggests that the tumors take a more aggressive progression; however, the relation between tumor size and lymph node metastasis is controversial in the literature. On the other hand, in Betül et al.'s study, extrathyroidal spread, lymphovascular invasion, capsule invasion, and multifocal tumor have been evaluated as relevant risk factors for lymph node metastasis (15). Although the tumor size decreased in the present study, the multifocality increased, which may have caused the presence of metastatic lymph nodes to remain unchanged.

It was observed that the length of hospital stay after thyroidectomy was significantly shortened over the years. Although the one-day length of stay increased especially in recent years, the significant decrease in hospitalizations of ≥4 days can be explained by the morbidity in central neck dissections, which were applied more frequently in previous years.

The number of tumors of 10 mm or less increased in cases with PTC over the years; however, it gradually decreased over the years in tumors over 10 mm. Especially in tumors larger than 2 cm, there was a significant decrease over the years. Although this increase in smaller tumor diameter can be explained histopathologically by the pathologists who took thinner sections, decreased case counts with larger tumor diameters along with the increased rate of papillary cancer can be explained by the use of more precise criteria in ultrasonographic examinations in the guidelines.

CONCLUSION

In the present study, when the pathology specimens of thyroid papillary cancer cases were examined over 20 years, it was found that the papillary cancer sizes decreased gradually and the frequency of papillary microcarcinoma increased gradually. In addition, a significant increase was detected in the rates of total/near-total thyroidectomy and lateral neck dissection over the years when the operations on the cases were compared.

Ethics Committee Approval: This study was approved by Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 2020-14/12, Date: 19.08.2020).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – TK; Supervision – TK, SK; Materials - Data Collection and/ or Processing – TK, BB; Analysis and/or Interpretation – BB, PT, SK; Literature Search – PT; Writing Manuscript – BB, PT; Critical Reviews – PT, SK.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2022; 38 (4): 345-352

Papiller tiroid kanserli olguların ameliyat sonrası spesimen bulgularında son 20 yılda neler değişti? Retrospektif analiz

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ÖZET

Giriş ve Amaç: Bu çalışmada, merkezimizde son 20 yılda tiroid papiller kanseri (PTK) tanısı ile opere edilen hastaların yıllara göre cerrahi yaklaşımlarındaki ve tümörün histopatolojik değerlendirmesindeki değişiklikler araştırıldı.

Gereç ve Yöntem: Bölümümüzde tiroidektomi yapılan olguların kayıtları her biri beşer yıllık dört gruba ayrılarak geriye dönük olarak incelendi. Gruplardaki olguların demografik özellikleri, cerrahi prosedürler, eşlik eden kronik lenfositik tiroidit varlığı, tümörün histopatolojik özellikleri ve hastanede kalış süreleri değerlendirildi. Tümör boyutuna göre PTK'lar beş alt gruba ayrıldı. 10 (mm) ve altındaki PTK'lar papiller tiroid mikrokarsinomu (PTMC) olarak kabul edildi.

Bulgular: Yıllar içinde gruplarda PTK ve multifokal tümörlerde anlamlı artış vardı (p< 0,001). Eşlik eden kronik lenfositik tiroidit varlığında gruplar arasında anlamlı artış vardı (p< 0,001). Buna karşılık, toplam metastatik lenf nodu sayısı (p= 0,486) ve en büyük metastatik lenf nodu büyüklüğü gruplar arasında benzerdi (p> 0,999). Çalışmamızda hem total/total tiroidektomi olgularında hem de postoperatif hastanede kalış süresi bir gün olan olgu sayısında yıllar içinde anlamlı artış olduğu gözlendi (p< 0,001).

Sonuç: Bu çalışmada, son 20 yılda papiller kanser boyutlarının giderek azaldığı ve papiller mikrokarsinom sıklığının giderek arttığı bulunmuştur. Ayrıca, yıllar içinde total/total tiroidektomi ve lateral boyun diseksiyonu oranlarında anlamlı bir artış tespit edildi.

Anahtar Kelimeler: Papiller tiroid karsinom, papiller tiroid mikrokarsinom, multifokal tümör, tümör boyutu

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ORIGINAL ARTICLE
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Current status of laparoscopic surgery usage in Türkiye: A middle-income country

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ABSTRACT

Objective: This study aimed to determine the usage status of laparoscopic procedures in general surgical practice in Türkiye, which is a sample of middle-income countries.

Material and Methods: The questionnaire was sent to general surgeons, gastrointestinal surgeons, and surgical oncologists who have completed their residency training and are actively working in university, public or private hospitals. Demographic data, laparoscopy training and the period of education, the rate of laparoscopy use, the type and volume of laparoscopic surgical procedures, their views on the advantages and disadvantages of laparoscopic surgery, and the reasons for preferring laparoscopy were determined with a 30-item questionnaire.

Results: Two hundred and forty-four questionnaires from 55 different cities of Türkiye were evaluated. The responders were mainly males, younger surgeons (F/M= 11.1/88.9 % and 30-39 y/o), and graduated from the university hospital residence program (56.6%). Laparoscopic training was frequently taken during residency (77.5%) in the younger age group, while the elderly participants mostly received additional training after specialization (91.7%). Laparoscopic surgery was mostly not available in public hospitals for advanced procedures ($p< 0.0001$) but was available for cholecystectomy and appendectomy operations (p= NS). However, participants working in university hospitals mostly stated that the laparoscopic approach was the first choice for advanced procedures.

Conclusion: The results of this study showed that the surgeons working in MICs spent strong effort to use laparoscopy in daily practice, especially in university and high-volume hospitals. However, inappropriate education, cost of laparoscopic equipment, healthcare policies, and some cultural and social barriers might have negatively impacted the widespread use of laparoscopic surgery and its usage in daily practice in MICs such as Türkiye.

Keywords: Laparoscopy, laparoscopy training, questionnaire, residency

INTRODUCTION

The use of laparoscopy in general surgery operations has been a revolutionary innovation. The first laparoscopic surgeries have been applied in cholecystectomy, appendectomy, and reflux surgery. After demonstrating the safety and efficacy of laparoscopic approaches with randomized controlled studies, the use of laparoscopy for other surgical procedures has become more widespread (1-3).

The advantages of laparoscopic surgery have led to an increase in their popularity. Nevertheless, despite all the advantages, laparoscopic surgery has not yet found its place in standard surgical training system, especially in middle-income countries (MICs) such as Türkiye. The World Bank defines countries whose gross national income per capita is between 1045 and 12.746 dollars as middle-income countries (4). As of year 2021, with gross national income per capita income of 9586 dollars, Türkiye has been classified as a middle-income country according to the World Bank (https://data.worldbank.org/country/tr). Adoption of laparoscopic surgery in MICs remains sporadic and marginal due to various reasons. Some of the reasons are directly related to the healthcare system while others might be financially driven, such as inadequately trained personnel, lack of equipment, and reimbursement policies of health insurance or social security. Moreover, the cost of initial setup, maintenance of laparoscopic surgery equipment, and the cost of disposable laparoscopic instruments have been noted as critical inhibitory factors for the maintenance of laparoscopic surgery in MICs (5-6). Furthermore, the scarcity of laparoscopic masters and heterogeneity in the use of laparoscopic surgical methods among centers are the biggest obstacles for emerging surgeons to receive standard laparoscopic surgery training.

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In contrast, increasing patient demands, industrial pressure, the popularity of surgeons using the laparoscopic technique as the first choice, and secondary benefits gained from this cause make surgeons feel under pressure to perform laparoscopy. Furthermore, this situation led to be more often sharing the advantages of laparoscopy than the disadvantages in MICs. Because of all of these reasons, surgeons working in MICs are making great efforts to use new technologies such as laparoscopic surgery, including laparoscopic cholecystectomies, appendicectomies, and diagnostic laparoscopies. These procedures are well established and performed routinely in university or high-volume public or private hospitals in MICs (6-9).

To date, there is no study on the tendency of surgeons' usage of laparoscopy in their clinical practice in Türkiye, which leads to creating laparoscopic strategies and policies under the low-evidence data. Today, there is no evidence-based data on surgeons tending to prefer laparoscopic surgery as the first choice and in which operations laparoscopy is preferred more frequently in Türkiye.

This study aimed to investigate the current status of laparoscopic surgery and underline reasons such as educational, hospital, general healthcare system by sharing the survey results on laparoscopic surgery usage experiences and usage purposes of general surgeons working in Türkiye.

MATERIAL and METHODS

For the study, a questionnaire was prepared by the Mersin University Faculty of Medicine, Department of General Surgery and Surgical Oncology. The questionnaire was sent to general surgeons, gastrointestinal surgeons, and surgical oncologist who have completed their general surgery residency training and are actively working in university, public or private hospitals. Mersin University Clinical Research Ethics Committee approved this study with the number 2019/528.

A pilot study was conducted to optimize the questionnaire before sending it to surgeons. The questionnaire was applied to 10 surgeons working at Mersin University Medical Faculty Hospital, and the questions were modified to reach the final version, and then an online survey was created via Google Documents with the question patterns optimized as a result of the pilot study.

We reached to the members of the Turkish Society of Surgery, or Turkish Society of Colon and Rectum Surgery, or the Turkish Society for Surgical Oncology by mail between June 1, 2019, and October 31, 2019. In addition, closed groups formed by Surgeons were also utilized using social media to reach general surgeons. In addition, survey participation link was sent to general surgeons who are members of the Turkish Society of Surgery 35th weekly bulletin published on August 26, 2019. Finally, after the link in the 44th-weekly bulletin, data collection was terminated on October 31, 2019. The data of the surveys were collected anonymously to ensure confidentiality.

The questionnaire was sent to 2647 surgeons, and 312 of these people filled out the questionnaire. Questionnaires filled by residents who were continuing their general surgery residency training and general surgery specialists who were not actively working were excluded from the study. As a result, 244 questionnaires were evaluated after the participants were excluded from the study.

We applied a 30-item questionnaire to the participants on demographic data, the laparoscopy training they received and the period of education, the number of monthly operations and the rate of laparoscopy use in their operations, the type and volume of laparoscopic surgical procedures, their views on the advantages and disadvantages of laparoscopic surgery, and the reasons for preferring laparoscopy.

Statistical Analysis

In data analysis, mean, median, and standard deviation, minimum and maximum values of the features, frequency, and percentage values were used when defining categorical variables. Chi-square test statistics were used to evaluate the relation between categorical variables. Statistical significance level of the data was taken as $p< 0.05$. The www.e-picos.com New York software and the MedCalc statistical package program were used to evaluate the data.

RESULTS

A total of 244 questionnaires from 55 of 81 different cities of Türkiye were evaluated. Most of the participants were from İstanbul with 56 surgeons, 2nd was from Ankara with 22, and the 3rd was from İzmir with 15 surgeons, which is correlated with a living population in these cities. There were 27 (11.1%) females and 217 (88.9%) males. Age was divided into five categories as 20-29 years, 30-39 years, 40-49 years, 50-59 years, and over 60 years. One hundred and eleven surgeons were in the 30-39 age group, 76 surgeons were in 40-49, 45 surgeons were in 50-59,

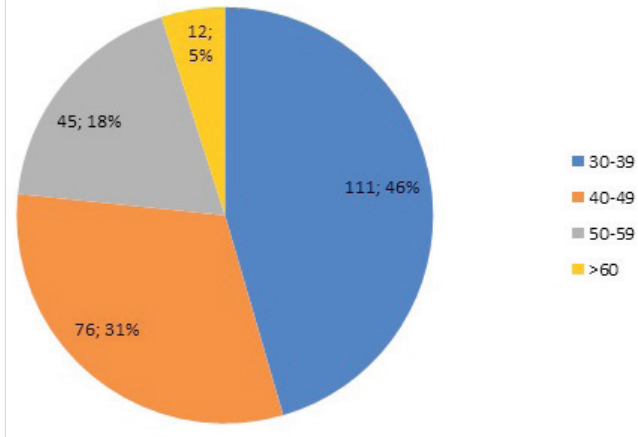

Figure 1. Age distribution of participants.

and 12 surgeons were in the over than 60 years age group. These are summarized in Figure 1. While 138 (56.6%) of the participants had their general surgery residency from a university hospital, the remaining 106 (43.4%) had their residency from a training and research hospital (Figure 2). In addition, 64 participants were in university hospitals, 51 participants in Training and Research or City Hospital, which is a high bed volume hospital, 87 participants were in public hospitals, and 42 participants were in private hospitals (Figure 3). Seventy-two (30%) participants had academic carrier (32 of them were professors, 21 were associate professors, and 19 were assistant professors) (Figure 4). Most of the participants were general surgeons without sub-specialty, but 26 (11%) participants were surgical oncologists, 15 (6%) were gastrointestinal surgeons, and 7 (%3) were in other general surgery sub-specialties (Figure 5). However, 168 (68.8%) surgeons declared that they had special interest in colorectal surgery, 94 (38.5%) in hepatobiliary surgery, 80 (32.7%) in breast-endocrine surgery, 54 (22.1%) in emergency and trauma surgery, and 65 (26.6%) in bariatric surgery. While 11 of the participants stated that they did not prefer laparoscopy in their daily practice, four of them stated that they could not use laparoscopy due to technical possibilities of the institution where they worked. It was determined that the remaining participants actively applied laparoscopic surgery. The reason for preferring laparoscopy in their operations was the advantage of the laparoscopy technique over laparotomy in 129 (53%), the preference of the surgeon in 90 (37%), the patient's demand in 16 (6%), and psychological and co-worker pressure in nine (4%) of the participants (Figure 6). It was determined that there was no statistically significant difference according to the age groups of the participants in the case of preferring laparoscopy and the reason for preference (p= 0.35, p= 0.16, respectively) (Table 1).

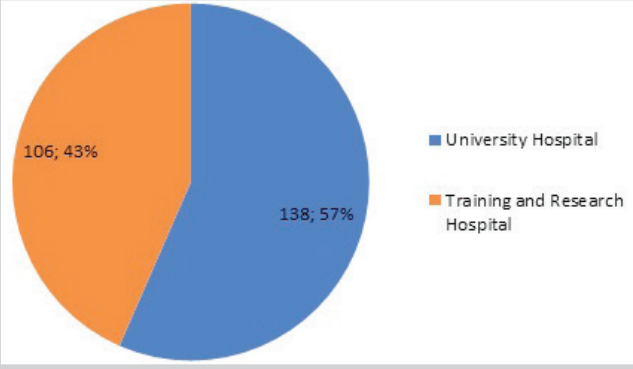

Figure 2. Participants residency institution.

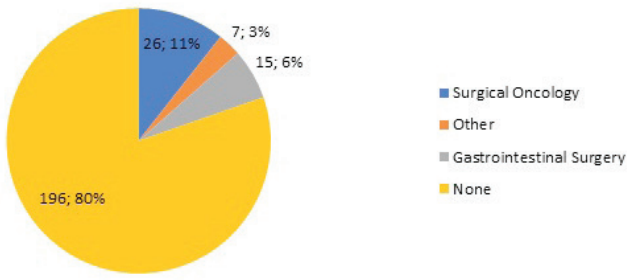

Figure 3. Sub-branch status of participants.

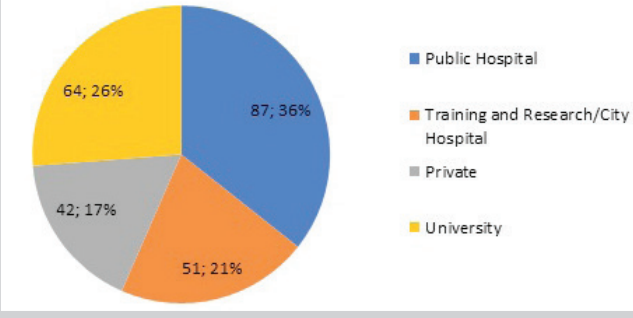

Figure 4. Institution of participants.

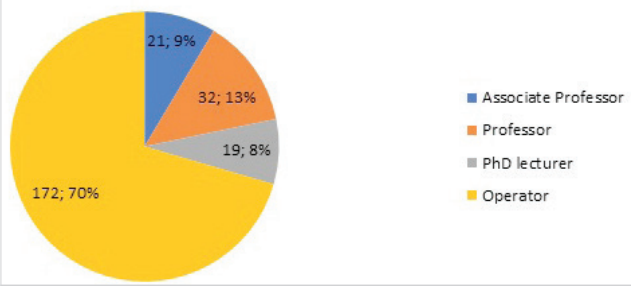

Figure 5. Academic titles of participants.

One hundred and forty-four surgeons revealed that their laparoscopic training had been in their general surgery residency (86 of them 30-39, 43 of them 40-49, and 15 of them 50-59 years old), whereas 61 surgeons needed additional training after their residency (24 surgeons 30-39, 22 surgeons 40-49, 14 surgeons 50-59, and 1surgeon over 60 years old), and in 37 surgeons, laparoscopic training or experiences were totally in post-residency (one surgeon 30-39, 10 surgeons 40-49, 15 surgeons 50-59, and 11 surgeons were over 60 years old). Laparoscopy training was determined to have been taken more frequently in the younger age group during general surgery training (77.5), and the elderly participants mostly received additional training

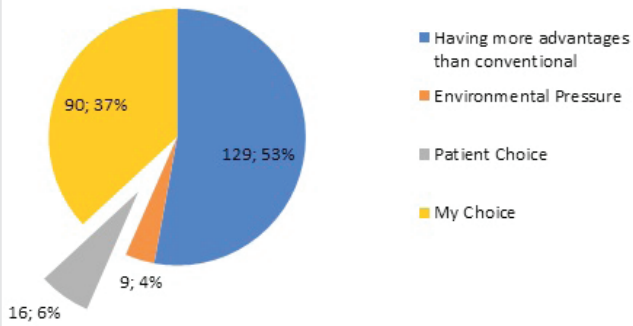

Figure 6. Reason of choosing laparoscopy.

Table 1. Participants' laparoscopy preference status, reason and time of training by age groups

n= 244	30-39 n= 111	40-49 n= 76	50-59 n= 45	≥60 age n= 12	p
Do You Prefer Laparoscopy?					
Yes	107 (96.4)	74 (97.4)	41 (91.1)	11 (91.7)	0.35
No	4 (3.6)	2 (2.6)	4 (8.9)	1 (8.3)	
Reason					
Patients' Choice	7 (6.3)	6 (7.9)	3 (6.8)	-	0.16
My choice	44 (39.6)	27 (35.5)	11 (25)	6 (50)	
Having more advantages than conventional	57 (51.4)	42 (55.3)	25 (56.8)	5 (41.7)	
Environmental Pressure	3 (2.7)	1 (1.3)	5 (11.4)	-	
Laparoscopy Training Time					
During residency and afterwards	24 (21.6)	22 (29.3)	14 (31.8)	1 (8.3)	**<0.0001**
After Residency	1 (0.09)	10 (13.3)	15 (34.1)	11 (91.7)	
During Residency	86 (77.5)	43 (57.3)	15 (34.1)	-	

after specialization (91.7%). There was a statistically significant difference between age groups according to the time of receiving laparoscopy training (p< 0.0001) (Table 1).

Procedures preferred laparoscopically as a first choice, or institutional facilities for laparoscopy are summarized in Table 2.

Twenty-eight (11.4%) of the participants stated that they had the technical possibility of robot-assisted surgery in the health institution they work. A total of 15 participants (6.1%) stated that they could perform robot-assisted surgery, while 11 of these people had robot-assisted surgery in the hospital where they worked.

The most common answer for conversion to open approaches was "inadequate exploration" with 202 (82.79%) participants. Other reasons for conversion were perioperative complications, bleeding, prolonged operation time, insufficient experience, technical inadequacy, and team incompatibility.

Laparoscopic operations were mostly unavailable in state hospitals for inguinal hernia, bariatric surgery, colorectal malignancy, benign colorectal procedures, upper gastrointestinal benign procedures, hiatal hernia, upper gastrointestinal malignancy, splenectomy, adrenalectomy, and diagnostic laparoscopy, but were available in other institutions (p< 0.0001). On the other hand, no statistical difference was found in terms of the technical possibilities of the institutions for performing cholecystectomy and appendectomy operations (p= 0.29, p= 0.21, respectively) (Table 3).

A statistically significant difference was found between the candidate of the first choice for laparoscopy and the institutions for advanced procedures such as inguinal hernia, colorectal malignancy, benign colorectal procedures, upper gastrointestinal benign procedures, and upper gastrointestinal malig-

Table 2. The procedures that the participants prefer to perform laparoscopy, the adequacy of technical possibilities and the procedures for which they think laparoscopy should be the first choice

n= 244	Laparoscopy Preferred Procedure	(%)	Technical Adequacy	(%)	Laparoscopy First Choice	(%)
Cholecystectomy	240	98.3	242	99.1	244	100.0
Appendectomy	217	88.9	234	95.9	207	84.8
Inguinal Hernia	117	47.9	175	71.7	112	45.9
Bariatric Surgery	91	37.3	153	62.7	195	79.9
Colorectal Malignancy	101	41.3	159	65.1	120	49.1
Benign Colorectal Procedures	85	34.8	140	57.3	122	50.0
Upper GIS* Benign Procedures	86	35.2	139	56.9	123	50.4
Hiatal Hernia	131	53.6	169	69.2	196	80.3
Upper GIS* Malignancy	52	21.3	123	50.4	72	29.5
Splenektomy/Surrenalectomy	109	44.6	158	64.7	165	67.6
Diagnostic	183	75.0	193	79.1	173	70.9

*GIS: Gastrointestinal system.

Table 3. Rates of laparoscopic operations that can be performed according to the technical possibilities of the institutions and rates of operations for which laparoscopy is considered to be the first choice according to the institutions worked

	Groups by Institution				
n= 244	Public Hospital n= 83 n (%)	Training and Research/ City Hospital n= 51 n (%)	Private Hospital n= 43 n (%)	University Hospital n= 64 n (%)	p
Procedures that can be performed in institutions					
Cholecystectomy	83 (100)	50 (98)	43 (100)	64 (100)	0.29
Appendectomy	77 (92.8)	48 (94.1)	41 (95.3)	64 (100)	0.21
Inguinal Hernia	33 (39.8)	43 (84.7)	34 (79.1)	58 (90.6)	**<0.0001**
Bariatric Surgery	14 (16.9)	41 (80.4)	36 (83.7)	57 (89.1)	**<0.0001**
Colorectal Malignancy	24 (28.9)	45 (88.2)	29 (67.4)	56 (87.5)	**<0.0001**
Benign Colorectal Procedures	15 (18.1)	40 (78.4)	26 (60.5)	54 (84.4)	**<0.0001**
Upper GIS Benign Procedures	19 (22.9)	37 (72.5)	26 (60.5)	55 (85.9)	**<0.0001**
Hiatal Hernia	26 (31.3)	42 (82.4)	33 (76.7)	62 (96.9)	**<0.0001**
Upper GIS Malignancy	14 (16.9)	34 (66.7)	22 (51.2)	51 (79.7)	**<0.0001**
Splenectomy/Surrenalectomy	24 (28.9)	41 (80.4)	29 (67.4)	60 (93.8)	**<0.0001**
Diagnostic	52 (62.7)	45 (88.2)	30 (69.8)	59 (92.2)	**<0.0001**
Procedures where Laparoscopy should be first choice					
Cholecystectomy	86 (100)	50 (98)	42 (97.7)	64 (100)	0.35
Appendectomy	65 (75.6)	42 (82.4)	36 (83.7)	57 (89.1)	0.20
Inguinal Hernia	27 (31.4)	23 (45.1)	24 (55.8)	35 (54.7)	**0.01**
Bariatric Surgery	61 (70.9)	40 (78.4)	33 (76.7)	57 (89.1)	0.07
Colorectal Malignancy	31 (36)	25 (49)	18 (41.9)	42 (65.6)	**0.004**
Benign Colorectal Procedures	28 (32.6)	27 (52.9)	19 (44.2)	43 (67.2)	**<0.0001**
Upper GIS Benign Procedures	33 (38.4)	24 (47.1)	20 (46.5)	43 (67.2)	**0.006**
Hiatal Hernia	63 (73.3)	43 (84.3)	34 (79.1)	52 (81.3)	0.43
Upper GIS Malignancy	19 (22.1)	8 (15.7)	9 (20.9)	29 (45.3)	**0.001**
Splenektomy/Surrenalectomy	47 (54.7)	35 (68.7)	23 (53.5)	52 (81.3)	**0.003**
Diagnostic	56 (65.1)	36 (70.6)	25 (58.1)	47 (73.4)	0.37

nancy, splenectomy, and adrenalectomy operations ($p< 0.05$). Participants working in university hospitals mostly stated that the laparoscopic approach was the first choice in these types of surgeries compared to other groups (Table 3).

Laparoscopic Appendectomy and diagnostic laparoscopy were preferred more frequently in the younger group than the older groups ($p< 0.05$), but there was no statistically significant difference for other procedures (p= NS). In addition, younger surgeons preferred laparoscopy as a first choice for cholecystectomy, appendectomy, bariatric surgery, upper GI benign interventions, hiatal hernia, diagnostic laparoscopy, splenectomy, and adrenalectomy ($p< 0.05$) (Table 4).

DISCUSSION

Laparoscopy has been used in general surgical practice for more than 20 years and is becoming more commonly used. Especially for some surgical procedures, laparoscopy has become the gold standard (10-12). Laparoscopic procedures are preferred for reducing postoperative pain, hospital stay, and rapid return to work (13-15).

Laparoscopic approach is preferred for numerous surgical procedures in high-income countries (HICs), while it is still not available in many middle income countries (MICs) due to the high cost of purchasing and maintaining the equipment and the lack of trained surgeons (16). Equipment costs are not the only limit for implementing laparoscopy in MICs. Indeed, healthcare policy, difficulties, inappropriate training, lack of dry and wet lab facilities, and unaffordable trained specialists play a role in limiting the laparoscopic approach (17). Moreover, in many MICs, it is difficult to promote new ideas in surgery, not only among patients but also among local surgeons, due to cultural and social barriers (6).

Table 4. Rates of performing a procedure laparoscopically according to age. Rates of operations for which laparoscopy is considered to be the first choice according to age

n= 244	Groups by age				p
	30-39 n= 111 n (%)	40-49 n= 76 n (%)	50-59 n= 45 n (%)	≥60 n= 12 n (%)	
Procedures that you perform laparoscopy					
Cholecystectomy	106 (95.5)	74 (97.4)	44 (100)	12 (100)	0.43
Appendectomy	106 (95.5)	63 (82.9)	34 (77.3)	10 (83.3)	**0.006**
Inguinal Hernia	43 (38.7)	36 (47.4)	24 (54.5)	6 (50)	0.29
Bariatric Surgery	39 (35.1)	31 (40.8)	14 (31.8)	7 (58.3)	0.33
Colorectal Malignancy	37 (33.3)	37 (48.7)	17 (38.6)	6 (50)	0.17
Benign Colorectal Procedures	28 (25.2)	29 (38.2)	17 (38.6)	5 (41.7)	0.17
Upper GIS Benign Procedures	31 (27.9)	29 (38.2)	15 (34.1)	4 (33.3)	0.53
Hiatal Hernia	49 (44.1)	42 (55.3)	25 (56.8)	7 (58.3)	0.32
Upper GIS Malignancy	17 (15.3)	23 (30.3)	10 (22.7)	2 (16.7)	0.1
Splenektomy/Surrenalectomy	51 (45.9)	29 (38.2)	21 (47.7)	6 (50)	0.65
Diagnostic	91 (82)	45 (59.2)	29 (65.9)	9 (75)	**0.006**
Procedures where Laparoscopy should be first choice					
Cholecystectomy	111 (100)	76 (100)	45 (100)	10 (83.3)	**<0.0001**
Appendectomy	99 (89.2)	58 (76.3)	36 (80)	7 (58.3)	**0.02**
Inguinal Hernia	54 (48.6)	27 (35.5)	23 (51.1)	5 (41.7)	0.25
Bariatric Surgery	104 (93.7)	44 (57.9)	36 (80)	7 (58.3)	**<0.0001**
Colorectal Malignancy	61 (55)	34 (44.7)	16 (35.6)	5 (41.7)	0.14
Benign Colorectal Procedures	58 (52.3)	39 (51.3)	18 (40)	2 (16.7)	0.07
Upper GIS Benign Procedures	68 (61.3)	32 (42.1)	18 (40)	2 (16.7)	**0.002**
Hiatal Hernia	96 (86.5)	49 (64.5)	40 (88.9)	7 (58.3)	**<0.0001**
Upper GIS Malignancy	36 (32.4)	19 (25)	9 (20)	1 (8.3)	0.17
Splenectomy/Surrenalectomy	86 (77.5)	41 (53.9)	26 (57.8)	4 (33.3)	**<0.0001**
Diagnostic	84 (75.7)	42 (55.3)	32 (71.2)	6 (50)	**0.01**

The results of this study showed that the participating surgeons preferred laparoscopic methods in their practice more than the rest of the country. According to the general health insurance official figures, only 8.9% of all colorectal operations have been performed laparoscopically (The data of Social Security Institution of Türkiye), while approximately 1/3 of the surgeons who answered the questionnaire preferred laparoscopic surgery for colorectal illness. This situation can be interpreted as surgeons who prefer laparoscopic surgery in their daily practices are more enthusiastic to answer the questionnaire due to their self-confidence. The participating surgeons were mostly working in reference hospitals. This situation also led to the calculation that the preference for laparoscopy is much higher than the country's official figures. On the other hand, these results can be interpreted as showing the willingness of surgeons in MICs to use high technology/laparoscopy, which is very promising for the future and encourages surgeons to train and prepare the infrastructure for laparoscopy.

Twenty years ago, laparoscopy training was needed in addition to conventional surgical residency for general surgeons, as the use of laparoscopy was relatively new. Moreover, as part of their continuing professional development, some surgeons from MICs travel to centers in HICs to gain more laparoscopic experience (18). On the other hand, it is also known that laparoscopy is not suitable for old surgical learning technique. Under this traditional model, some local surgeons in MICs have acquired and developed laparoscopic abilities in an unstructured way. This has the potential for unsafe practices being learned by surgeons in training (16). Now, education for laparoscopy technical skills has been initiated in surgical residency programs in some high-volume centers. This might explain why younger surgeons prefer laparoscopic surgery more than older surgeons

because this study revealed that laparoscopy would be used more frequently and as the first choice by young surgeons.

There was a statistically significant difference between the age groups of the participants in the way they received laparoscopy training. The reason for this is that surgeons over the age of 50 did not have laparoscopy applications when they received general surgery residency. Interestingly, 21.6% of the surgeons aged 30-39 and 29.3% of the surgeons aged 40-49 felt the need for additional post-residency training for laparoscopy. Despite the increasing popularity and application areas of laparoscopy, it shows that laparoscopy training still has not taken its place in general surgery residency.

The advantages of laparoscopy are scaling up with the increase in the frequency of use, the development of the surgeon's laparoscopic experience, and the developing technological opportunities. As a result of the patient's request and developing surgery, the surgeon is directed to prefer laparoscopy instead of conventional procedures (19). There are many reasons for the preference of laparoscopic operation for the surgeons or the patients. These are less pain in the postoperative period, early mobilization, reduced hospital stay, loss of workforce, and cost. In addition, the surgeon makes a wider exploration in the abdomen with laparoscopy. Additional surgical interventions that may be required can be performed more easily in the same session (20). In our study, the most preferred reason for laparoscopy was its advantage over conventional (53%) and the surgeon's own request (37%). The low preference of non-surgical factors such as the effort to catch up with surgical developments (4%) and patient request (6%) revealed that general surgeons of all age groups had a high interest in laparoscopy, despite all of the impossibilities in Türkiye.

The devices used in laparoscopy are gradually developing (21). Advancing technology makes laparoscopic surgery more advantageous than conventional surgery. As a result of the close relationship between the laparoscopy technique and the developing technology, the rapid progress in technology also provides an opportunity for the development of the laparoscopic technique. However, in order to perform laparoscopy, it is necessary to have laparoscopy devices and an experienced operating room team, especially the surgeon who can use these devices. The cost of the devices and the training of the surgical team are very costly for MICs, especially in public and hospitals located far from the metropolis, limiting the widespread use of laparoscopy.

While the technical adequacy of institutions for basic laparoscopic surgeries such as cholecystectomy and appendectomy is 99.1% and 95.9%, respectively, the technical adequacy for advanced laparoscopic surgeries such as colorectal malignancy and upper GI malignancy interventions is 65.1% and 50.4%, respectively. While surgeries that require basic laparoscopic skills are performed in most hospitals in our country, advanced laparoscopy operations are performed only in comprehensive hospitals.

The rate of surgery preferred to be performed laparoscopically is lower than the adequacy of the available technical adequacy of institutions for the same procedure. In addition, it is seen that these surgeons perform fewer laparoscopic procedures than the procedures that they consider laparoscopy as the first choice. The rate of those who think that laparoscopy should be the first choice in hiatal hernia repair is 80%, while the rate of those who have technical adequacy in laparoscopic hiatal hernia repair is 69.2%, and the rate of those who perform this surgery laparoscopically is 53.6%. In other words, we think that the participants wanted to use the laparoscopy technique, but they had technical inadequacies in practice.

With advancing technology, new instruments such as vessel sealing energy devices and endoscopic staplers have been added to the surgeon's inventory in laparoscopic surgery applications. Thus, the rate of conversion to conventional surgery in laparoscopy has gradually decreased. New laparoscopic instruments allow both the laparoscopic application of more advanced procedures and the laparoscopic repair of existing iatrogenic damages without converting conventional surgery (22). While the rate of conversion was 8.5% in low-volume surgeons at laparoscopic cholecystectomy, the rate of conversion was found to be 4.5% in high-volume surgeons with more than 100 cholecystectomy experience (23).

The most common answer that forces participants to convert to conventional surgery is stated as "inadequate exploration" by 202 participants (82.7%). De Nereetot Babberich et al. (24) have found inadequate exploration as the most common reason for converting conventional surgery to laparoscopic colorectal cancer surgery. Other common reasons for converting to conventional surgery are "complications" (69.2%) and "bleeding" (56.9%). Conversion due to bleeding is most common in organ surgeries with a rich vascular structure, such as the stomach (25). The fact that "technical inadequacy" was preferred by 114 surgeons (46.7%) as the reason for switching to conventional surgery reveals that some institutions in our country still do not have sufficient technical equipment and trained staff to perform laparoscopic surgery. One of the three surgeons participating in the questionnaire stated that they do not have an adequate operating room for advanced surgical practices. Other preferred reasons for converting to conventional surgery were inability of the patient to tolerate laparoscopy (47.9%), team incompatibility (32.7%), prolonged case duration (30.7%), and insufficient experience (28.2%).

The operations that can be performed with basic laparoscopy skills and a simple technical infrastructure have been identified as appendectomy, cholecystectomy, and diagnostic laparosco-

py (15). The technical adequacy for basic laparoscopy procedures such as appendectomy and cholecystectomy were sufficient in institutions where participants were working. Acute appendicitis and cholecystitis are urgent diseases that have a higher incidence than other diseases and require surgery in a shorter time (10-15). Most hospital facilities are adequate to provide basic laparoscopy services. However, adequate technical facilities are available in comprehensive hospitals for advanced surgical procedures that require experienced staff and equipment to ensure efficient use of available resources.

Evaluation about which procedures participants prefer to perform laparoscopically, according to the age groups of the participants revealed that there are proportionally higher rates of laparoscopy application in younger age groups. However, this difference could not be statistically significant except for appendectomy and diagnostic laparoscopy. The reason for the statistical difference in appendectomy was the high preference rate of 95.5% between the ages of 30-39. The reason for the statistical difference in diagnostic laparoscopy was the low rate of preference of 25% in surgeons aged 60 and over.

There was a statistically significant difference between age groups in cholecystectomy, appendectomy, bariatric surgery, upper gastrointestinal benign interventions, hiatal hernia, splenectomy/adrenalectomy, and diagnostic laparoscopy procedures when asked about in which surgeries laparoscopy should be the first choice. This difference is due to the fact that young surgeons want to benefit from the advantages of laparoscopy, respond to patient requests, and apply advancement in surgery.

CONCLUSION

There is neither standardization in routine practice nor in the education of laparoscopic surgery for general surgeons in Türkiye. Turkish general surgeons have a high desire to perform laparoscopy, but unfortunately, this request may not match with daily practice, such as the numbers in the procedures, especially in advanced laparoscopy. It is necessary to standardize laparoscopy training, encourage and spread mentor/mentee educations, adopt or revise the healthcare system for laparoscopy funding strategies, and provide laparoscopic basement equipment in Türkiye, such as a sample for MICs.

Ethics Committee Approval: This study was approved by Mersin University Rectorate Clinical Research Ethics Committee (Decision no: 528, Date: 04.12.2019).

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ORİJİNAL ÇALIŞMA-ÖZET
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Türkiye'de laparoskopik cerrahinin mevcut durumu: Orta gelirli bir ülke örneği

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ÖZET

Giriş ve Amaç: Bu çalışma, orta gelirli ülkeler (MİK) örneklemi olan Türkiye'de genel cerrahi pratiğinde laparoskopik prosedürlerin kullanım durumunu belirlemeyi amaçlamıştır.

Gereç ve Yöntem: Anket, uzmanlık eğitimini tamamlamış, üniversite, kamu veya özel hastanelerde aktif olarak görev yapan genel cerrahlar, gastrointestinal cerrahlar ve cerrahi onkologlara gönderilmiştir. Demografik veriler, laparoskopi eğitimi ve eğitim süresi, laparoskopi kullanım oranı, laparoskopik cerrahi işlemlerin türü ve hacmi, laparoskopik cerrahinin avantaj ve dezavantajlarına ilişkin görüşleri ve laparoskopiyi tercih etme nedenleri 30 soruluk bir anket ile belirlendi.

Bulgular: Türkiye'nin 55 farklı ilinden gelen 244 anket değerlendirildi. Yanıt verenler çoğunlukla erkek, genç cerrahlardı (K/E= 11,1/88,9 ve 30-39 yaş) ve üniversite hastanesi asistanlık yapmıştı (%56,6). Laparoskopik eğitim genç yaş grubunda sıklıkla asistanlık döneminde (%77,5) alınırken, ileri yaştaki katılımcılar çoğunlukla uzmanlık sonrası (%91,7) ek eğitim almıştı. Laparoskopik cerrahi ileri işlemler için çoğunlukla kamu hastanelerinde mevcut değildi (p< 0,0001), ancak kolesistektomi ve apendektomi ameliyatları için mevcuttu (p= NS). Üniversite hastanelerinde çalışan katılımcılar daha çok ileri işlemler için laparoskopik yaklaşımın ilk tercih olduğunu belirtmişlerdir.

Sonuç: Bu çalışmanın sonuçları, MİK'lerde çalışan cerrahların, özellikle üniversite ve yüksek hacimli hastanelerde laparoskopiyi günlük pratikte kullanmak için yoğun çaba harcadıklarını göstermiştir. Ancak uygun olmayan eğitim, laparoskopik ekipman maliyeti, sağlık politikaları ve bazı kültürel ve sosyal engeller, Türkiye gibi MİK'lerde laparoskopik cerrahinin yaygınlaşmasını ve günlük pratikte kullanımını olumsuz etkilemektedir.

Anahtar Kelimeler: Laparoskopi, laparoskopi eğitimi, anket, uzmanlık

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ORIGINAL ARTICLE
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Gastro-intestinal stromal tumor (GIST): Experience from a tertiary care center in a low resource country

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ABSTRACT

Objective: The aim of this retrospective study was to review the overall survival (OS) and disease-free survival (DFS) of GISTs treated surgically at our center over the past decade.

Material and Methods: We undertook a 12-year retrospective review of our experience in treating this condition with a focus on long-term outcomes of treated patients in a resource-constrained environment. Incomplete follow-up information continues to be a major problem with studies conducted in low resource settings, and in order to overcome this, we undertook telephonic contact with patients or their relatives to get the necessary information about their clinical status.

Results: Fifty-seven patients with GIST underwent surgical resection during this period of time. The stomach was the most common organ involved in the disease, with 74% of the patients. Surgical resection was the main treatment approach, with R0 resection possible in 88%. Nine percent of the patients were given Imatinib as neoadjuvant treatment and 61% were offered the same, as adjuvant therapy. The duration of adjuvant treatment changed from one year to three years over the study period. Pathological risk assessment categorized the patients as Stage I, 33%; Stage II, 19%; Stage III, 39%; and Stage IV, 9%. Of the 40 patients who were at least three years from surgery, 35 were traceable giving an 87.5%, overall three-year survival. Thirty-one patients (77.5%) were confirmed to be disease-free at three years.

Conclusion: This is the first report of mid-long-term outcomes of the multimodality treatment of GIST from Pakistan. Upfront surgery continues to be the main modality. OS & DFS in resource-poor environments can be similar to those seen in a better-structured healthcare setting.

Keywords: Survival, gastro intestinal stromal tumor, surgery

INTRODUCTION

Gastrointestinal stromal tumors (GISTs), albeit rare, are the most common mesenchymal tumor of the gastrointestinal (GI) tract (1). They account for 1-2% of GI tumors (2) with an incidence of approximately 10-15 per million population per year (3). GISTs originate from the malignant transformation of the interstitial cells of Cajal and c-KIT positive cells of neuroendocrine origin that control gut motility (4). They are most commonly found in the stomach (60%) and proximal portions of the small intestine (30%); however, any portion of the GI tract may be affected. Occasionally, they may originate in extra-gastrointestinal sites such as the omentum, mesentery and peritoneum (2,3,5). GISTs have been categorized into very low, low, intermediate and high-risk tumors, with location, size and mitotic activity acting as predictors of recurrence and metastatic potential (6-8). Eighty to eighty-five percent of GISTs are localized when diagnosed (5,9). While lymph node metastases are rare, intra-abdominal and liver metastasis are not (10).

Gastro-intestinal stromal tumors are generally resistant to the effects of traditional chemo and radio-therapy and till a couple of decades ago, surgical removal was the only treatment option (2,11). Introduction of targeted therapy in the form of Tyrosine kinase inhibitors (TKIs) in the early 2000s revolutionized the treatment options (12-14). TKIs have been shown to increase median progression free survival and overall survival in both adjuvant and neo-adjuvant settings (10,15,16).

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We conducted a retrospective study to review overall survival (OS) and disease-free survival (DFS) of GISTs treated surgically at our center over the past decade. We also reviewed the association of OS and DFS with clinic-pathological features of GIST and its management. To the best of our understanding, there has been no publication with long term survival information on surgically treated GISTs from our geographical locale.

MATERIAL and METHODS

This is an ambi-directional cohort study, in which the assessment of exposure status was determined retrospectively from the records, and the outcomes of overall survival (OS) and disease-free survival (DFS) were assessed prospectively. All patients with GIST diagnosed on histopathology and having undergone surgery, from 1st January 2007 to 31st December 2019, were eligible for inclusion.

Patients with prior history of malignancies or incomplete records were excluded. A total of 57 patients were included in this study. The collected data included patients' age, sex, clinical presentations, radiological investigations, laboratory findings, pathological findings, tumor characteristics (mitotic rate, immuno-histochemical analysis etc.), surgical procedures, and perioperative complications.

For overall survival (OS) and disease-free survival (DFS) at three years, patients who were at least three years from surgery, till 31st December 2016, (n= 40) were included. Recurrence and survival data were recorded from clinical records during the follow up period.

In cases of incomplete information, individual patients or close relatives were telephoned using contact details provided on admission to update their current status. After obtaining informed consent, inquiries were made regarding disease status, whether or not the patient was still alive, and if deceased, what the cause of death was. At least three calls were made, at different time intervals, before a patient was labelled "lost to follow-up".

When evaluating three-year overall survival (OS), 35 of the 40 patients were included, as survival data could not be obtained for the remaining five. In the case of three-year disease free survival (DFS), 31 patients out of 40 were included for analysis as no recurrence data was available for six patients while the remaining three had Stage IV disease at presentation.

Approval from the Ethics Review Committee (ERC) was obtained before data collection, with ERC# 2020-5026-11860. Data was entered and analyzed using SPSS version-21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Quantitative (continuous) variables were expressed using descriptive statistics such as mean ± SD and median (IQR). Qualitative variables were reported as percentages. Survival analysis was performed with Kaplan-Meier methods, while differences in survival between the groups was assessed with log-rank tests. P value less than 0.05 was considered significant.

RESULTS

A total of 57 patients with GIST underwent surgical resection during the study period. There were 34 (60%) males and 23 (40%) females with a median age of 61 years. Thirty-four (60%) patients had associated comorbidities. Majority of the patients, 47 (82%), were admitted electively for surgery. Most patients had clinical symptoms or signs that led to the diagnosis with GI bleeding in 28 (49%), abdominal pain in 23 (40%) and weight loss in 11 (19%) of the patients making up the commonest.

Table 1 summarizes patients' characteristics. Stomach was the most common organ involved (n= 42, 74%) followed by the small intestine (n= 9, 16%). Mean tumor size was 8 cm (+/-SD 5 cm). On microscopy, mitotic rate per 50 high power fields (HPF) was less than 5 in 32 (56%) patients and more than 5 per 50 HPF in 25 (44%) patients.

Spindle cell type was the commonest histological variant, seen in 45 (79%) tumors. On immunohistochemical analysis, CD 17 positivity was seen in 48 (84%), CD 34 positivity in 44 (77%) and DOG 1 positivity in 32 (56%) patients. Pathological risk assignment placed 18 (32%) patients in very low to low risk, nine (16%) in intermediate and 28 (49%) patients in high-risk category, whereas, two (3.5%) patients did not have viable tumor in final histopathology because of neo-adjuvant treatment.

On final staging, 19 (33%) patients were in Stage I, 11 (19%) in Stage II, 22 (39%) in Stage III and five in Stage IV. Table 2 summarizes tumor characteristics.

Upfront surgery was the main stay of treatment for 52 (90%) patients. Five patients (8.7%) were offered neo-adjuvant treatment with first line tyrosine kinase inhibitor (TKI), Imatinib.

Table 1. Patients' characteristics (n= 57)

Patients' characteristics		
Age	Median (IQR)	61 (53-70)
Sex	Male	34 (59.6%)
	Female	23 (40.4%)
Co-morbidities	Yes	34 (59.6%)
Mode of admission	Elective	47 (82.5%
	Emergency	10 (17.5%)
Reason for presentation	Incidental	9 (15.8%)
	Symptoms	48 (84.2%)
Symptoms	Pain	23 (40.4%)
	Bleeding	28 (49.1%)
	Weight loss	11 (19.3%)
	Others	4 (7%)

Table 2. Tumor characteristics		
Tumor characteristics		
Site	Stomach	42 (73.68%)
	Small intestine	9 (15.8%)
	Rectum	2 (3.5%)
	Other	4 (7%)
Size	Mean	8.06 (5.3)
Mitotic rate (HPF/50)	≤5	32 (56%)
	>5	25 (44%)
Immunohistochemical analysis	CD 17	48 (84.2%)
	CD 34	44 (77.2%)
	DOG 1	32 (56.1%)
Risk assessment	Very low	3 (5.3%)
	Low	15 (26.3%)
	Intermediate	9 (15.8%)
	High	28 (49.1)
	Not documented	2 (3.5%)
Final stage	I	19 (33.33%)
	II	11 (19.29%)
	III	22 (38.59%)
	IV	5 (8.8%)

Thirty-five patients (61%) received adjuvant treatment following surgery with the same drug. The duration of adjuvant therapy changed overtime from one year in the initial few years to three years at present.

An R0 resection was possible in 50 patients (88%). Mean duration of surgery was 144 minutes. Median length of hospital stay was eight days (7-9 days). Eleven patients (19%) had postoperative complications. There was one 30-day mortality. Early surgical outcomes are presented in Table 3.

Table 3. Surgical outcomes of GIST resection		
Surgical outcomes of GIST resection		
Duration of surgery (mins)	Mean	144 (SD 80)
Length of stay (days)	Median	8 (7-9)
Margin	RO	50 (88%)
	R1	7 (12%)
Post-operative complication	Yes	11 (19%)
Complications	SSI	5 (9%)
	Intra-abdominal collection	2 (3.5%)
	Other	4 (7%)
30-day mortality	Yes	1 (1%)
SSI: Surgical site infection.		

Three-year overall survival was 92%, whereas, three-year DFS was 87% in the study population. On univariate analysis, age, sex, comorbidities, chief complaints, organ involved, risk category, stage at presentation, adjuvant or neo-adjuvant chemotherapy, and negative resection margin were not found to be significant for three-year OS&DFS.

A total of eight patients (14%) died by the end of the study period, with four due to disease progression, three due to unrelated medical conditions, and one due to postoperative complications. At the end of the study period, 10 patients (17.5%) were known to be living with recurrence.

DISCUSSION

This study aimed to present short and long-term outcomes for surgically treated localized GISTs managed at a single tertiary care center. Reports on clinicopathological features and treatment undertaken have been published before from our geographical area (17-20); to the best of our understanding, this is the first report that presents long term outcomes of treatment by actively tracing patients lost to routine follow up.

We included 57 patients based on our selection criteria over a 12-year period. Median age at presentation was 61 (IQR 53-70) years, which correlates well with international literature (21). A male preponderance (60%) noted in our study was in contrast to international epidemiological review (3), the reasons for which is unclear; however, it could be related to the relatively small sample size of the study group. Stomach was the most commonly involved organ, followed by the small intestine and rectum, and these findings were in concordance with other studies (21,22). In our study, 16% of the tumors were identified incidentally, the rest presenting with clinical symptoms. Gastrointestinal bleeding was the most common symptom followed by pain (19,23,24).

Mean resected tumor size was 8 cm, and the predominant histological subtype was spindle cell type, followed by epithelioid and mixed type. Fifty-six percent of the tumors showed a mitotic rate per 50 high power fields (HPF) of less than 5. Immunohistochemistry showed gene expressions of CD117 and CD34 to be 84% and 77% respectively, these results were consistent with the international literature (19,22,24).

Upfront surgery was the main modality of treatment. Five patients received neo-adjuvant treatment and 35 (61%) received adjuvant therapy with Imatinib. The choice and duration of systemic therapy was variable in our patients ranging from 6-36 months, which was influenced by oncology recommendations and also patients' ability to tolerate and afford potentially expensive treatment.

Our study showed a three-year OS of 92%. Survival data for treated GISTs has tended to be variable in different studies (10,25,26).

Due to the inconsistent biological behavior of these tumors, clinical risk factors like, age, tumor size, mitotic rate, site of tumor, adjuvant treatment, and negative resection margin have been used to develop prognostic models to predict the relative risk of recurrence and metastasis (6,22,26-28). These can be used to identify patients suitable for targeted therapy. Sixty-three percent of our cohort received adjuvant Imatinib treatment. Our study was unable to identify any statistically significant factors affecting OS.

Three-year disease-free survival in our patients was noted to be 87%. A weakness of our follow up methodology was reliance on telephonic interaction for disease recurrence. In developing countries with weak health care infrastructure, quality tertiary medical care is often provided by the private sector and is expensive as a result. In addition, tertiary medical centers are few and far between, it is not unusual for patients with major illness to have to travel long distances for treatment. With medical insurance almost nonexistent, these patients usually have to self-fund the cost of both travel and treatment, a combination that can be financially exhausting. Following successful surgical treatments, patients at times do not have the resources for prolonged follow up and tend to drop out, especially if asymptomatic. With wide availability of mobile phone connectivity, we decided on this approach, considering it better than not having follow up data.

There has been a paradigm shift in the management of GIST in last two decades due to the addition of targeted therapy with tyrosine kinase inhibitors (TKI). In our 12-year study duration, TKI usage was initially in the adjuvant setting but more recently has been used in the neo-adjuvant role as well. Duration of adjuvant treatment has been changing, with initial one-year treatment to three-year at present.

CONCLUSION

We present the first report of mid and long-term outcomes for the multimodality treatment of gastrointestinal stromal tumors (GIST) from Pakistan. Due to the inadequately developed medical coverage, most patients present with locally advanced tumor. Upfront surgery continues to be the main treatment approach. Availability of TKI in the neoadjuvant and adjuvant setting has increased treatment options. Despite advanced disease and limited resources, our survival outcomes are comparable with other studies. This concludes that overall and disease-free survival in resource-poor environments can be similar to those seen in better structured health care settings.

Ethics Committee Approval: This study was approved by The Aga Khan University Ethics Review Committee with effect from 22.08.2020.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – TS, IP; Design – TS, JA, AF; Supervision – TS, IP, FS; Data Collection and/ or Processing – TS, JA, AF; Analysis and/or Interpretation – TS, NS, FS; Literature Search – TS, BP, JA; Writing Manuscript – TS, BP, FS, NS, AF; Critical Reviews – TS, IP, FS, AF, NS, IP.

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ORİJİNAL ÇALIŞMA-ÖZET
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Gastrointestinal stromal tümör (GIST): Düşük kaynaklara sahip bir ülkede üçüncü basamak bir merkezin deneyimi

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ÖZET

Giriş ve Amaç: Bu retrospektif çalışmanın amacı, son on yılda merkezimizde cerrahi olarak tedavi edilen GİST'lerin genel sağkalımını (OS) ve hastalıksız sağkalımını (DFS) gözden geçirmekti.

Gereç ve Yöntem: Kaynakların kısıtlı olduğu bir ortamda tedavi edilmiş hastaların uzun dönem tedavi sonuçlarını, 12 yıllık bir geriye dönük incelemeyle araştırdık. Eksik takip bilgileri, kısıtlı kaynakların olduğu ortamlarda yürütülen çalışmalarda halen önemli bir sorundur ve bunu aşmak amacıyla hasta veya yakınları ile telefon görüşmesi yaparak klinik durumları hakkında bilgi aldık.

Bulgular: Bu süre zarfında GİST'li 57 hastaya cerrahi rezeksiyon uygulandı. Mide, hastaların %74'ü ile hastalığa en sık tutulan organdı. Ana tedavi yaklaşımı cerrahi rezeksiyondu ve %88 oranında R0 rezeksiyon mümkün oldu. Hastaların %9'una neoadjuvan tedavi olarak İmatinib verildi ve %61'ine aynı adjuvan tedavi önerildi. Adjuvan tedavi süresi, çalışma süresi boyunca bir yıldan üç yıla değişiklik gösterdi. Patolojik risk değerlendirmesi hastaları Evre I, %33; Evre II, %19; Evre III, %39 ve Evre IV, %9 olarak kategorize etti. Ameliyatın üzerinden en az üç yıl geçmiş olan 40 hastadan 35'i izlenebilir durumdaydı ve toplamda %87,5'lik bir üç yıllık sağkalım sağladı. Otuz bir hastanın (%77,5) üç yılda hastalıksız olduğu bulundu.

Sonuç: Bu çalışma, Pakistan'dan GIST'in multimodalite tedavisi için orta-uzun vadeli sonuçların sunulduğu ilk rapordur. Primer cerrahi ana modalite olmaya devam etmektedir. Kaynak sıkıntısı yaşayan ortamlarda OS ve DFS, daha iyi yapılandırılmış bir sağlık hizmeti ortamında görülenlere benzer olabilir.

Anahtar Kelimeler: Sağkalım, gastrointestinal stromal tümör, cerrahi

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ORIGINAL ARTICLE
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Protective effect of intraluminal fecal diverting device against colonic wall erosion induced by wrapping bands: A post-hoc pathological analysis

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ABSTRACT

Objective: Materials wrapping the bowel elicits tissue erosion gradually. We experienced several bowel wall erosions with no serious clinical consequences in our two previous animal experiments aimed at the safety and efficacy of the COLO-BT developed for intra-luminal fecal diversion. We tried to find out why the erosion is safe by investigating histologic changes of the tissue.

Material and Methods: Tissue slides at the COLO-BT fixing area from the subjects which had COLO-BT over three weeks acquired from our two previous animal experiments were reviewed. For the classification of the histologic change, microscopic findings were classified for six stages (from minimal change of stage 1 to severe change of stage 6).

Results: A total of 26 slides of 45 subjects were reviewed in this study. Five subjects (19.2%) had stage 6 histological change; three of stage 1 (11.5%), four of stage 2 (15.4%), six of stage 3 (23.1%), three of stage 4 (11.5%), and five of stage 5 (19.2%). All subjects which had a stage 6 histologic change survived. The phenomenon from which the back of the band is passed through is replaced by a relatively stable tissue layer due to fibrosis of the necrotic cells in the stage 6 histologic change.

Conclusion: We found that thanks to the sealing effect of the newly replaced layer, no leakage of the intestinal content occurs even if perforation by erosion develops according to this histologic tissue evaluation.

Keywords: Colonic wall erosion, foreign body, mesh, COLO-BT

INTRODUCTION

Traditionally, several materials have been surgically implanted to treat the human body permanently or temporarily. For example, foreign materials are used in gastric banding procedures in the management of morbid obesity. Despite the established safety of gastric banding procedures, newly placed foreign materials may cause complications. During the gastric banding procedure, the pressure induced by the wrapping of the stomach with the banding material may damage the stomach wall. These damages include gastric wall erosion, ulcers, necrosis, and perforation although the incidence has been reported to be <5% (1,2). Patients experiencing these complications require emergent surgery to avoid poor outcomes.

Recently, the development of intraluminal fecal diverting devices has garnered the attention of researchers due to its ability to avoid stoma after proctectomy. These devices, e.g., CG-100™ and Colovac™ (Colospan), require intraluminal and/or extraluminal fixation using foreign materials to maintain the device location in the colon for several days or weeks to protect the anastomotic site (3-5). Preliminary animal and human studies regarding these devices have reported positive results (3-9); however, concerns regarding the clinical and histological changes of the colonic wall which is the device fixing site by foreign materials remain, similar to gastric banding.

Our group developed a new type of intraluminal fecal diverting device named, COLO-BT (previously reported name as fecal diverting device, FDD, tentatively). The efficacy and safety of this device as a substitution for dysfunctional stoma have been reported in our previous studies (6-9). In these studies, several cases of colon-

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ic wall erosion have been observed in both the animal and clinical studies; however, none developed severe complications requiring further intervention. Considering these results, we realized the need to investigate the histological changes in colonic wall erosive lesions caused by foreign materials.

Therefore, this study aimed to investigate the histologic changes in erosive lesions of the colonic wall by reviewing the slides of our two previous animal experiments.

MATERIAL and METHODS

In order to evaluate the efficacy and safety of COLO-BT, we previously conducted two animal experiments in mongrel dogs (6,7). All dogs were euthanized at the end of the study period, and macroscopic findings were recorded. In cases of premature deaths, the specimen was obtained the day the dogs died. After macroscopic investigations, tissues were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E) in several sections. Specifics of the COLO-BT procedure and experimental design have been described in our previous animal studies (6,7).

Since the maintenance period of COLO-BT was more than three weeks, slides from subjects unable to maintain the device or that died before three weeks were excluded. In one animal study, all 30 subjects were applied with the COLO-BT device and 16 remained alive for over three weeks (7). In the other animal study, which was designed as a randomized controlled study, 15 were applied with the COLO-BT among 30 subjects and 10 remained maintaining the COLO-BT and alive for over three weeks (6). Therefore, histological slides from 26 dogs that maintained their COLO-BT over three weeks were included in this study (Table 1).

Tissue slides fixated between the mesh band and colonic wall from these two animal studies were reviewed. All tissue slides were retrospectively reviewed by an experienced pathologist (MJ Gu) and discussed with three surgeons.

The histological changes were classified as follows:

Table 1. COLO-BT maintenance period in two previous animal experiments

	Studies	
	Kim et al. (7) (n= 30)	Kang et al. (6) (n= 15)
<1 week*	5*	3**
1-3 weeks	9	2
>3 weeks	16	10

*Four of the five dogs died within 1 week.
**all died within 1 week.

Stage 1. Mesh material enclosed by a thick fibrotic capsule was found in the serosa or subserosa. Inflammation was sparse (Figure 1).

Stage 2. A well-demarcated fibrotic nodule containing mesh was impinging upon the outer longitudinal muscle. Acute and chronic inflammatory cell infiltration was observed in the fibrotic capsule (Figure 2).

Stage 3. The mesh penetrated the inner circular muscle and the muscularis propria. Fibrosis formation was observed more posteriorly compared to internally (Figure 3).

Stage 4. The mesh was located in the inner muscle and submucosa. The external area was surrounded by mature fibrosis with neovascularization. Inflammation was sparse (Figure 4).

Stage 5. Mesh was found from the mucosa to the subserosa and surrounded by fibrotic tissue without tears or perforations (Figure 5).

Stage 6. Formation of a deep ulcer and exposure of the mesh in the lumen while being surrounded by the fibrotic capsule (Figure 6).

No animal sacrifices were required for this study, and approval from the Institutional Animal Care and Use Committee (IACUC) was waived.

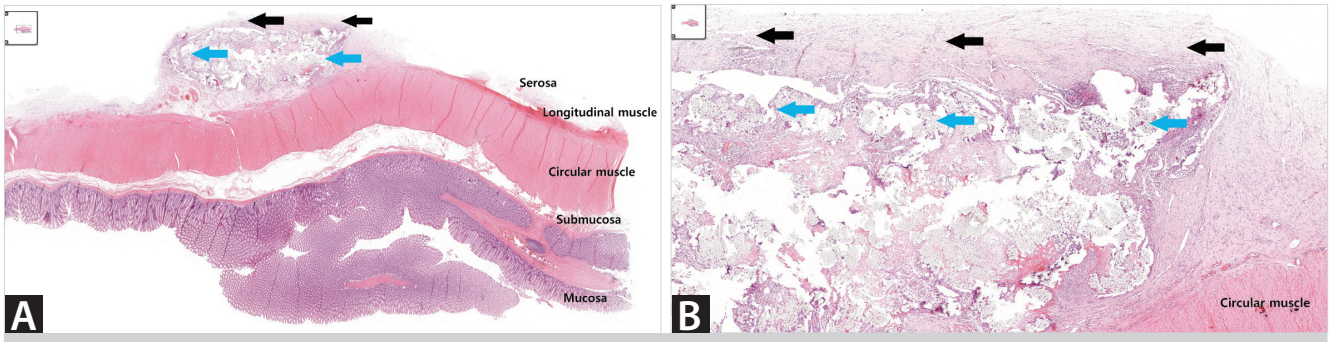

Figure 1. Stage 1. Mesh material was found in the serosa or subserosa enclosed by a thick fibrotic capsule. Inflammation is sparse. H&E stain, **(A)** x 40 **(B)** x 100. Black arrow, fibroblast; blue arrow, mesh materials.

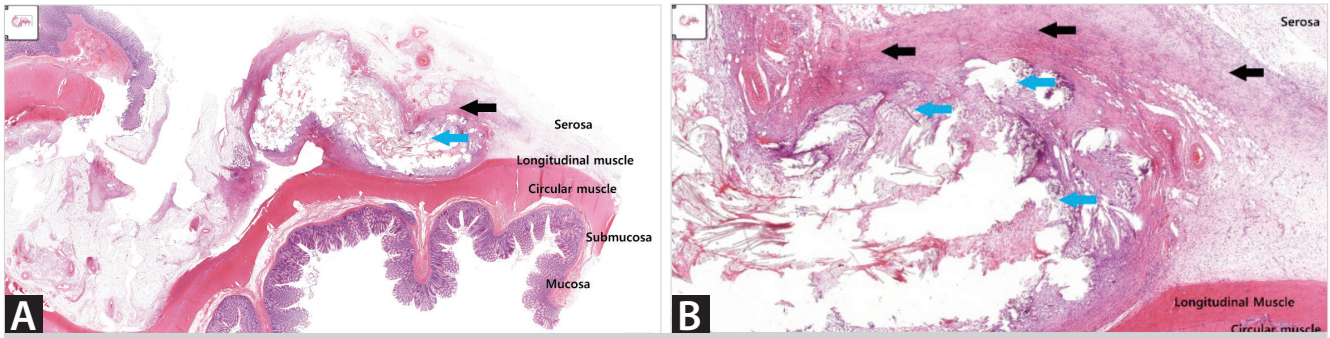

Figure 2. Stage 2. Well demarcated fibrotic nodule containing mesh was impinging upon the outer longitudinal muscle. Acute and chronic inflammatory cells infiltration was seen in the fibrotic capsule. H&E stain, **(A)** x 40 **(B)** x 100. Black arrow, fibroblast; blue arrow, mesh materials.

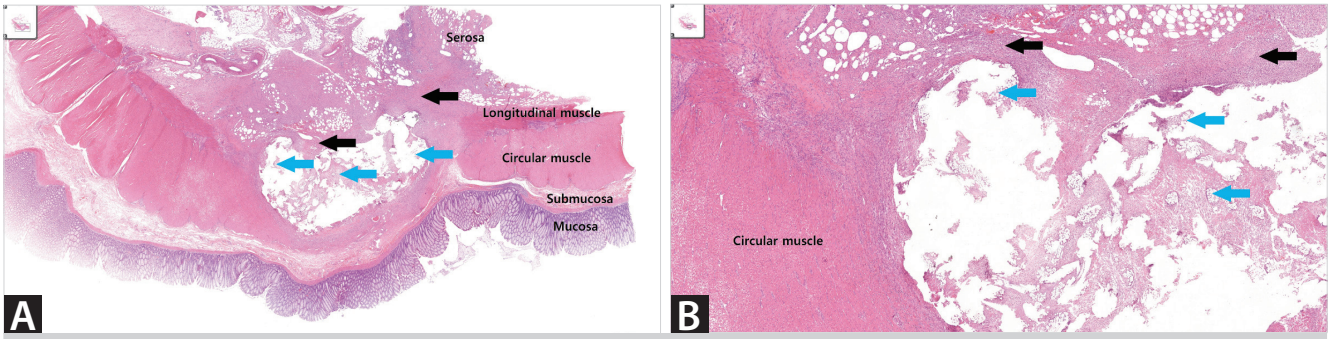

Figure 3. Stage 3. The mesh was penetrating the inner circular muscle and muscularis propria. Fibrotic formation of collagen fibers was observed more in the posterior side compared to the internal area. H&E stain, **(A)** x 40 **(B)** x 100. Black arrow, fibroblast; blue arrow, mesh materials.

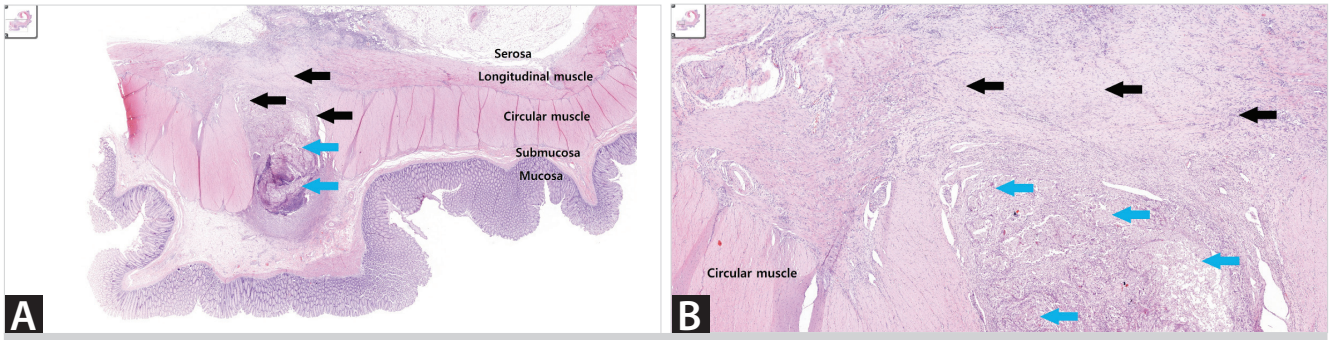

Figure 4. Stage 4. Mesh located in the inner muscle and submucosa. The external area was completely surrounded by mature fibrosis with neovascularization. Inflammation is sparse. H&E stain, **(A)** x 40 **(B)** x 100. Black arrow, fibroblast; blue arrow, mesh materials.

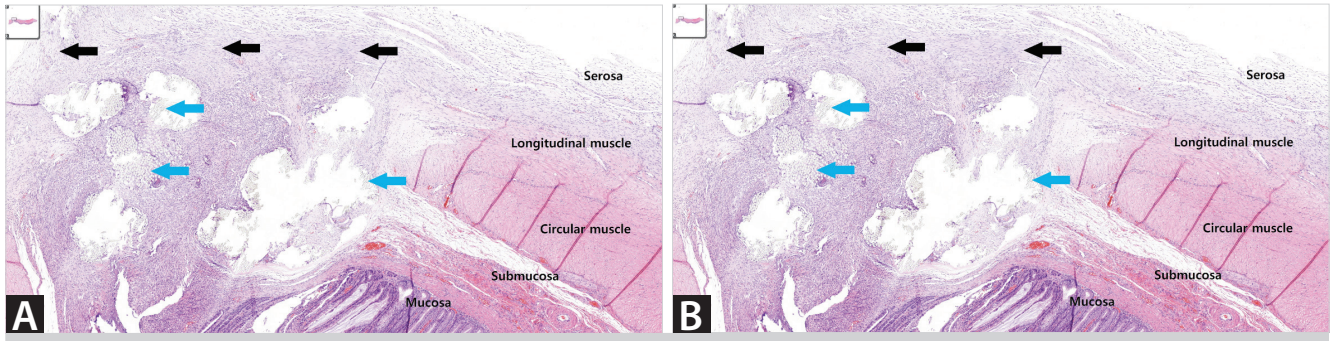

Figure 5. Stage 5. Mesh was found from the mucosa to subserosa and surrounded by fibrotic tissue without tear or perforation. H&E stain, **(A)** x 40 **(B)**x 100. Black arrow, fibroblast; blue arrow, mesh materials.

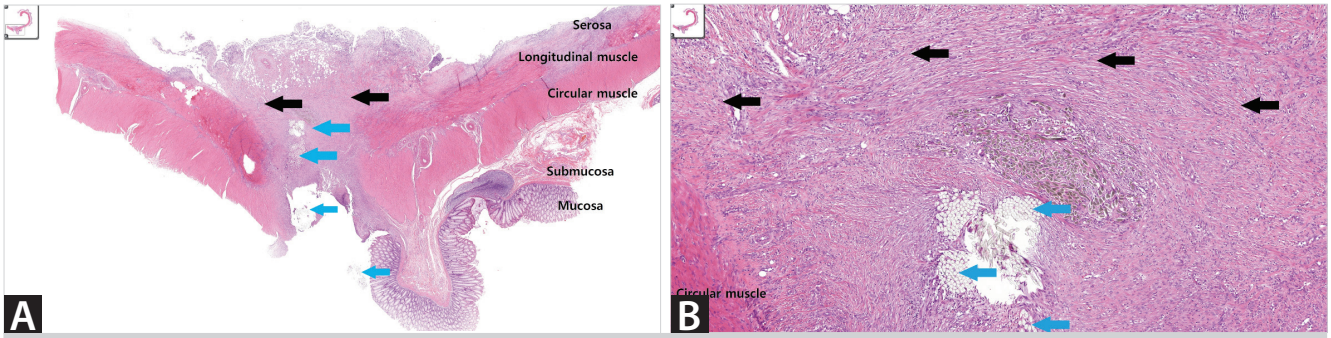

Figure 6. Stage 6. Deep ulcer was formed and mesh was exposed in the lumen, but mesh was still well surrounded. H&E stain, **(A)** x 40 **(B)** x 100. Black arrow, fibroblast; blue arrow, mesh materials.

Table 2. Stages of histologic change

	n= 26 (n, %)	Survival, %
Stage 1	3 (11.5)	100
Stage 2	4 (15.4)	100
Stage 3	6 (23.1)	100
Stage 4	3 (11.5)	100
Stage 5	5 (19.2)	100
Stage 6	5 (19.2)	100

RESULTS

Each of the two previous studies included 16 and 10 dogs. Among the 16 dogs, stage 6 histological changes were observed in three dogs at the band fixed site. Others were classified into stage 1 (n= 2), stage 2 (n= 2), stage 3 (n= 4), stage 4 (n= 2), and stage 5 (n= 3). Among the 10 dogs, stage 6 histological changes were observed in two dogs at the band fixed site. Others were classified into stage 1 (n= 1), stage 2 (n= 2), stage 3 (n= 2), stage 4 (n= 1), and stage 5 (n= 2).

Overall, five dogs (19.2%) from a total of 26 that maintained COLO-BT over three weeks, demonstrated stage 6 histological changes. However, not all subjects experienced local or systemic sepsis due to severe histological changes (Table 2). Additionally, fibrotic changes in stage six dogs were observed; particularly, the replacement of the posterior of the band by a relatively stable tissue layer.

DISCUSSION

Several intraluminal fecal diverting devices have been developed as substitutes for temporary stoma. Maintenance of the colonic wall without developing severe complications is an important issue for these devices. To affix the device in the colonic lumen, a suturing method has been applied to the mucosal and submucosal layers. However, this method has been found to have a high failure rate in maintaining the device causing impaired healing of the anastomotic site due to tissue necrosis (10,11). Therefore, extra- and/or intraluminal pressure is inevitable to affix an intraluminal fecal diverting device in the colonic lumen. However, persistent and excessive wall pressure causes complications such as wall ischemia, necrosis, or perforation. Therefore, an appropriate amount of pressure is necessary to maintain the device in the colonic lumen while avoiding complications.

COLO-BT is composed of two fixation systems: an extra-balloon system for intraluminal fixation and an extra-luminal mesh band.

In this review of two animal studies, we found that 19.2% of the experimental subjects demonstrated stage 6, severe histological changes, deep ulcerations and luminal mesh exposure at COLO-BT fixing area. Despite this severity, it is emphasized that none of the dogs developed systemic sepsis or death.

Implanting foreign substances for temporary or permanent management of certain diseases is necessary. However, foreign body implants may cause pressure injury by impinging upon adjacent organs. A representative procedure that causes pressure by a foreign body is gastric banding for morbid obesity. However, advancements in gastric banding procedures have caused a decrease in the incidence of pressure injuries (12). Research regarding colonic erosions due to wrap bands is limited; therefore, we reviewed other situations related to gastrointestinal wall erosion, particularly regarding gastric banding for morbid obesity.

The mechanism for the histological changes of gastric wall erosion due to mesh has been recognized. In summary, early erosive changes occur soon after the procedure; thereafter, the physiologic movement of the stomach causes stronger shearing forces between the mesh and the gastric wall. Constant repetition of this process can cause gastric wall perforation (13,14). Another mechanism is related to the immune response. The immune response produces chronic inflammation causing tissue fibrosis, contraction, and subsequent erosion (15,16). Gastrointestinal wall erosion can cause serious clinical symptoms and problems. Therefore, most gastric wall erosions have been treated endoscopically and/or surgically through the removal or replacement of the wrap band (17,18).

Our hypothesis regarding the histological changes induced by the fixation of the COLO-BT to the colonic wall is similar to the mechanisms for gastric wall erosion due to wrap-banding; particularly, injured tissue repair is caused by scar formation. Injury to a tissue, such as muscle (which has limited regenerative capacity), induces inflammation, which clears any dead cells and microbes. The formation of vascularized granulation tissue and deposition of extracellular matrix for scar formation follows inflammation (19).

COLO-BT causes alternating intermittent minimal and increased peristalsis. This variation in peristaltic movement pushes the colonic wall to the mesh material generating pressure that causes tissue damage to the colonic wall. In most cases, the pressure on the colonic wall is immediately resolved preventing lasting damages to the colonic wall. However, constant pressure causes tissue injury. In patients who underwent COLO-BT procedure, these changes occurred over a long period of time; therefore, immediate colonic wall perforation caused by rapid tissue necrosis was not observed. Tissue damage, which progresses slowly due to intermittent pressure, is repaired by fibrotic scar tissue in the posterior direction of the mesh. This blocks the movement of intestinal contents to the outside of the intestine. Therefore, no severe complications were observed even when intestinal wall erosion occurred.

Even in stage 6 dogs, we found no serious complications related to the histological changes of the COLO-BT fixing site. Similar results were found in our previous clinical studies; however, histological examinations are yet to be performed (8,9). In these two clinical studies, 10% of the patients experienced colonic wall erosions similar to the stage 5-6 histological changes in this study; however, no severe co-morbidities related to COLO-BT fixing site was found in all studies. All patients who exhibited colonic wall erosion at the COLO-BT fixing site were managed conservatively or thru observation only; despite this, none experienced clinical problems during the two-year follow-up (20). Our hypothesis of the mechanism related to this result is as follows:

1. Increases in the intermittent pressure of the band causes tissue cell necrosis.

2. Pressure causes inflammation, cell necrosis, fibrosis, and other phenomena in necrotic tissues.

3. The posterior side of the band is replaced by a relatively stable tissue layer due to fibrosis of the necrotic cells.

4. This newly replaced layer seals the intestinal contents preventing leakage even if perforation by erosion occurs.

The maintenance of the appropriate pressure between the colonic wall and wrap band is the most essential to prevent severe histological changes of the colonic wall. Inadequate pressure causes easy detachment of the COLO-BT; on the other hand, excess pressure leads to colonic wall necrosis. In our previous studies, we applied an automatic tension measuring instrument (ATMI, JSR Medical Inc., Daegu, Korea) to measure the band length for wrapping the colonic wall with appropriate pressure (7,8)

In addition, absorbable mesh use helps in preventing the severe histologic change of the colonic wall. In our animal studies, a non-absorbable mesh band was used because an appropriate absorbable mesh was yet to be developed. In our clinical studies, we used an absorbable mesh band (NEOSORB MESH®, Samyang Biopham. Co. Daejeon, Korea), with a half-life of six weeks (8). Therefore, the pressure due to the mesh band was relieved after six weeks.

This study has several limitations. First, the results originated from previous studies. Histological examinations at the COLO-BT fixed site were not designed in the previous animal studies since COLO-BT was a newly developed device; no information or similar studies were available to refer to. Therefore, most of the studies used research regarding gastric banding procedures as reference. Moreover, we decided not to conduct a prospective study since it requires further euthanizing of animals and slides from our previous animal studies were available. Second, histological changes over time were not evaluated due to the retrospective nature of the study. Instead, we described various changes occurring in the colon wall after maintaining the COLO-BT for more than three weeks. We believe that this is important because COLO-BT should be maintained for approximately three weeks for effective fecal bypass from an anastomotic site. Furthermore, the type of study is not feasible for humans. Therefore, the results of this study may not be consistent with clinical results. However, similar results may be anticipated due to the absence of symptoms and similarities in the morphological and histological changes observed in the past clinical and current studies, respectively.

In summary, from our two previous animal experiments, we found that 19.2% of the subjects who maintained COLO-BT for more than three weeks demonstrated severe histological changes at the COLO-BT fixing site. However, no clinical complications due to histological changes were observed. We hypothesize that the sealing effect of the newly replaced layer prevented the leakage of intestinal content even in dogs with perforation due to erosion, as demonstrated by histological evaluation.

Ethics Committee Approval: It is only a retrospective review of the histological slides obtained from two previous animal studies, which were already published in peer-reviewed journals. Thus, a new ethical approval was not obligatory.

Peer-review: Externally peer-reviewed.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Sarıcı bantların neden olduğu kolonik duvar erozyonuna karşı intralüminal fekal yönlendirici cihazının koruyucu etkisi: Post-hoc patolojik bir analiz

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ÖZET

Giriş ve Amaç: Bağırsakları saran malzemeler yavaş yavaş doku erozyonuna neden olur. Lümen içi fekal saptırma için geliştirilen COLO-BT'nin güvenliğini ve etkinliğini amaçlayan önceki iki hayvan deneyimizde ciddi klinik sonuçları olmayan birkaç bağırsak duvarı erozyonu yaşadık. Dokudaki histolojik değişiklikleri inceleyerek erozyonun neden güvenli olduğunu bulmaya çalıştık.

Gereç ve Yöntem: Önceki iki hayvan deneyimizden elde edilen COLO-BT'ye üç hafta boyunca sahip olan deneklerden COLO-BT sabitleme alanındaki doku slaytları gözden geçirildi. Histolojik değişikliğin sınıflandırılması için, mikroskopik bulgular altı evre için sınıflandırıldı (1. evredeki minimal değişiklikten 6. evredeki şiddetli değişikliğe kadar).

Bulgular: Bu çalışmada toplam 45 denek arasından toplam 26 slayt incelendi. Beş denekte (%19,2) altıncı evre histolojik değişiklik vardı; üçü 1. evre (%11,5), dördü 2. evre (%15,4), altısı 3. evre (%23,1), üçü 4. evre (%11,5) ve beşi de 5. evredeydi (%19,2). 6. evre histolojik değişikliği olan tüm denekler hayatta kaldı. Sarıcı bandın arka tarafa geçişiyle ortaya çıkan durum, 6. evre histolojik değişiklikteki nekrotik hücrelerin yerini alan fibrozisin oluşturduğu görece stabil bir doku katmanıyla desteklendi.

Sonuç: Bu histolojik doku değerlendirmesine göre, yeni değiştirilen tabakanın sızdırmazlık etkisinden dolayı, erozyon ile perforasyon meydana gelse bile, bağırsak içeriğinde sızıntı olmadığını bulduk.

Anahtar Kelimeler: Kolonik duvar erozyonu, yabancı cisim, yama, COLO-BT

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ORIGINAL ARTICLE
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Preoperative scoring system validation and analysis of associated risk factors in predicting difficult laparoscopic cholecystectomy in patients with acute calculous cholecystitis: A prospective observational study

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ABSTRACT

Objective: Today laparoscopic cholecystectomy (LC) is the treatment of choice for acute cholecystitis. However, the presence of severe inflammation makes it challenging for the surgeons to accurately recognize the Calot's triangle which increases the risk of intraoperative complications. The aim of this study was to explore the validity of a scoring system used to predict difficult LC and to analyse the risk factors associated with difficult cholecystectomy in the setting of acute calculous cholecystitis.

Material and Methods: An observational study was conducted between December 2018 and December 2020 among 132 patients diagnosed with acute cholecystitis, who underwent laparoscopic cholecystectomy. A scoring system by Randhawa et al. was used preoperatively for all of these patients to predict difficult LC, which was correlated to intraoperative difficulties in actual surgery. Data were analysed using the SPSS version 26.0.

Results: Mean age was 43.63 ± 13.37, with almost equal representation from both sexes. History of previous attacks of cholecystitis, impacted stone, thickness of GB wall were statistically significant in calculating preoperative difficulty of laparoscopic cholecystectomy. The scoring system had a sensitivity and specificity of 82.6% and 63.5%, respectively. The conversion rate to open cholecystectomy was 6.9%.

Conclusion: Analysing the significant risk factors before operating in the presence of an inflamed gallbladder can reduce the overall mortality and morbidity. An accurate preoperative scoring system will enable the operating surgeon to be well prepared with adequate resources and time. The patient attenders can also be counselled regarding the risk involved beforehand.

Keywords: Laparoscopy, cholecystectomy, risk factors, cholecystitis

INTRODUCTION

Gallstones are hardened deposits of the bile that is formed within the gallbladder and varies in size and shape (1). When an imbalance in the chemical constituents of the bile occurs, it leads to the precipitation of one or more of the components resulting in the formation of gallstones. Gallstones are becoming common and are seen in all age groups, with incidence gradually increasing with age and about a quarter of women developing it above the age of 60. In most cases, they are asymptomatic, and only about 10% will show symptoms within five years of diagnosis. Hence, the risk of developing symptomatic cholelithiasis is close to 2.0-2.6%/year, which is quite low (2). Acute calculous cholecystitis (ACC) constitutes around one-third of all surgical emergencies at the hospital. According to the study conducted by World Society of Emergency Surgery (WSES), ACC is the second most common source of complicated intra-abdominal infection (18.5%). The main cause, biliary stones, is seen in about 6.5% and 10.5% of men and women, respectively (3).

After its implementation in 1987 by P. Mouret, laparoscopic cholecystectomy (LC) has become the treatment of choice in managing symptomatic gallstone diseases. The advantages of LC are well defined relative to open cholecystectomy and includes less postoperative pain, shorter ileus, earlier diet and sooner discharge from hospital (4-9). However, LC remains a highly demanding technical procedure which can lead to dramatic complications, especially when the surgeon is faced with serious inflammation that obscures the calot's triangle during emergency LC in the setting of acute cholecystitis which causes increased operative time, high con-

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version rate and common bile duct injuries with other postoperative complications. Many factors can make a laparoscopic cholecystectomy complicated, which includes old age, male sex, fever and previous symptomatic episodes, obesity, prior gastro-intestinal surgery, prior symptomatic cholecystitis and some ultrasonographic findings, such as distended gallbladder (GB) with a thick wall, collection around the gallbladder fossa and an impacted stone (10). The difference between emergency and scheduled LC, however, is not adequate to accurately predict operational problems, which improves the risk of surgery and encourages dissolution of the staff and the operating theatre (11).

In order to classify high risk treatments, a preoperative predictive statistical score for operating complexity is significant and may be effective in enhancing patient and attenders counselling, maximizing pre-operative preparation, and recognizing high risk patients and training them beforehand. A significant feature of the preparation of laparoscopic surgery is the preoperative estimation of the possibility of conversion or operating difficulties. High Risk patients can be notified beforehand with aid of detailed prediction, and the operating team will have a chance to be cautious. Surgeons will also get an insight about the procedure so that they can properly ready the team for surgery. Prolonged hospitalization with intensive postoperative care should be scheduled for patients with a high-risk score. From time to time, numerous ranking methodologies have been proposed using various standards adding to the debate. Due to some difficult conditions that exist during laparoscopic cholecystectomy in acute cholecystitis, the following study is designed to consider the challenges faced in the operating room and determine the risk factors of a difficult laparoscopic cholecystectomy in the picture of acute cholecystitis using a scoring system devised previously.

MATERIAL and METHODS

Study Design and Participants

A prospective observational study was conducted between the period of December 2018 and December 2020 for all patients who were diagnosed with acute cholecystitis on the basis of clinical, laboratory and ultrasound findings and presented to the surgery out-patient department or to the emergency department and underwent laparoscopic cholecystectomy during the study period of two years. Patients with bile duct stones, pregnant/pediatric patients, patients in cholangitis, patients in cardiac failure and patients in whom laparoscopic cholecystectomy was performed with other laparoscopic intervention in the same setting; were excluded from this study. The sample size for our study was calculated based on a study by Brodsky A et al. in which the reported proportion of patients having complications (infection, adhesion, bleed, bile duct injury) in laparoscopic cholecystectomy in the background of acute cholecystitis is 17% (12). Using this as an estimated proportion of patients with complications in acute cholecystitis at a relative precision of 6.5% and at 95% confidence level, we estimated that the minimum sample size required for our study would be 130 patients.

Study Tools and Data Collection

The recruited patients were categorized into mild, moderate, and severe cholecystitis based on Tokyo guidelines 2018 (TG 2018) (13). TG 2018 diagnostic criteria for acute cholecystitis includes: 1. Local signs of inflammation; right upper quadrant mass/pain/tenderness (Murphy's sign), 2. Systemic signs of inflammation; fever, elevated CRP, elevated white blood cell (WBC) count and 3. Ultrasound findings; thick gallbladder wall (>4 mm), gallbladder size, debris echo, ultrasound murphy's sign, pericholecystic fluid (13). Based on these TG 2018 criteria, patients were divided into:

1. Grade I (Mild) cholecystitis; Grade I can be defined as acute cholecystitis in healthy patients. These patients present without organ dysfunction and mild inflammatory changes in the gallbladder.
2. Grade II (Moderate) cholecystitis; can include any one among- elevated WBC counts (>18.000), positive Murphy's sign, prolonged duration of symptom onset (>72 hrs), marked local signs of inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
3. Grade III (Severe) cholecystitis; cardiac failure (hypotension requiring ionotropic supports), neurological dysfunction, pulmonary dysfunction (PaO_2/FiO_2 ratio> 300), kidney injury (oliguria and creatinine> 2 mg/dL), hepatic failure (PT-inr> 1.5), thrombocytopenia< 100.000.

Data were collected as per the designed case record form (CRF). A patient information sheet containing the study rationale, noting strict voluntary participation was provided. After providing consent, the participant was interviewed for the study. The following data were collected in the structured case record form.

1. Socio-Demographic Characteristics: Patient initials, age, sex.
2. Patient Clinical Characteristics: BMI, previous episodes of cholecystitis, presence of abdominal scar, palpable gallbladder, wall thickness, collection, impacted stone, conversion of operative procedure.

All patients diagnosed with acute calculous cholecystitis who were admitted were kept Nil per oral until the surgery and started on Injection Cefuroxime 1.5 gm iv Q12H with adequate analgesia every sixth hourly. Their pulse rate, blood pressure and saturation were monitored at regular intervals and progress noted. All routine blood investigations like total count, differential count, renal function test and liver function tests were sent. Clotting parameters were also noted. The patients were also

given detailed information regarding their condition, plan of surgery, duration of hospital stay for approximate number of days. They were also informed regarding their participation in the study, and informed consent was taken. The complications of laparoscopic cholecystectomy such as bleeding, risk of bile duct injury causing bile leak, iatrogenic bowel injury, need for drain placement, possibility of conversion to an open cholecystectomy procedure were also explained to the patient and the attenders in a language understood by them. A scoring system employed by Randhawa et al. was used for all the patients admitted after due permissions were obtained (Table 1) (14). The patients were given a score at the time of admission based on the history, clinical findings and the ultrasonographic findings. The patients were then divided into easy, difficult, and very difficult based on their scores pre-operatively (Table 2). The patients were given a pre-operative score based on the above table with a total score of 15.

All surgeons in the hospital were involved in the surgery. All of the patients were operated on within seven days of presentation of the symptoms. Surgery was performed using carbon dioxide pneumoperitoneum with a pressure of 12 mmHg and with two 5 mm, two 10 mm standard ports. The surgery was started after the induction of anaesthesia. The pre-operative checklist protocol was strictly followed. The time taken from first port incision until the last port closure was documented. All intraoperative events including the duration of surgery, gall bladder appearance, bile leakage, spilled gallstones, common bile duct injury, conversion and the number of blood transfusions were also noted in case of haemorrhage. Based upon the events intra-operatively, surgery was also classified into easy, difficult, and very difficult grades. Intraoperative assessment was then compared with the preoperative predictive score to determine the usefulness of the preoperative predictive score: 1) Easy was where the time taken was less than sixty minutes, 2) Difficult was where the time taken was between sixty to one hundred and twenty minutes or with bile spillage or with common bile duct injury, 3) Very difficult was where the time taken was more than one hundred and twenty minutes or the surgical procedure was converted to open cholecystectomy (Table 3).

Table 1. Preoperative score parameters-total maximum score 15

Parameters			**Maximum Score**
Age	<50 years (0)	>50 years (1)	1
Sex	Female (0)	Male (1)	1
Previous attacks of cholecystitis	No (0)	Yes (4)	4
BMI	<25 (0)	25-27.5 (1)> 27.5 (2)	2
Abdominal scar	No (0)	Infra-umbilical (1)	
supra-umbilical (2)	2		
Palpable gallbladder	No (0)	Yes (1)	1
GB wall thickness	Thin (0)	Thick> 4 mm (2)	2
Pericholecystic collection	No (0)	Yes (1)	1
Impacted stone	No (0)	Yes (1)	1

Table 2. Preoperative prediction of difficulty levels according to the scoring system

Scores	**Preoperative difficulty level**
0-5	Easy
6-10	Difficult
11-15	Very difficult

Table 3. Intraoperative difficulty level classification of the patients

Intraoperative Difficulty Level	**Basis**
Easy	Easy was where the time taken is less than sixty minutes.
Difficult	Difficult was where the time taken was between sixty to one twenty minutes or with bile spillage or with common bile duct injury.
Very difficult	Very difficult was where the time taken was more than one twenty minutes or the surgical procedure was converted to an open cholecystectomy.

Statistical Analysis

The collected data were extracted into Microsoft Excel 2020 and coded for analysing using SPSS 26.0. Proportions, mean, and standard deviation were calculated to describe the data. Univariate analyses were performed to study the association between demographic factors and outcome variables, using, chi-square test, ANOVA test and independent sample t test, as appropriate. Significant variables from univariate analysis were put into the multivariate model and analysed via multivariate logistic regression. A p-value of less than or equal to 0.05 was considered significant for all purposes.

Ethics Consideration

Ethics approval for the study was obtained from the institutional ethics committee of the hospital to which the researchers are affiliated (IEC no: 390/2018). Informed consent was obtained from each participant prior to participation in the study.

RESULTS

Mean age of 132 patients included in this study was 43.63 ± 13.37 years. There was almost equal representation from both sexes in this study, with males (48.1) and females (51.9). According to Tokyo Guidelines, 102 patients belonged to Grade 1, 24 patients to Grade 2 and six patients belonged to Grade 3.

Clinical parameters used to calculate the preoperative score are depicted in Table 4. Most patients did not report previous attacks of cholecystitis (60.3), had normal BMI (67.2), had no abdominal scar (64.1). In the setting of acute cholecystitis, a palpable gallbladder was found only in 5.3% of the patients in this study. Ultrasonographic study findings showed most of the patients had thick GB walls (57.3), without any collection (88.5) and without the presence of any stone (82.3). The conversion rate from laparoscopic cholecystectomy to open cholecystectomy was 6.9%. Out of the nine converted patients, five patients had dense adhesions, one patient had suspected CBD injury, two patients had suspected bowel injury and one patient had gangrenous cholecystitis.

On scoring the surgeries preoperatively, 47.3% cases were evaluated to be easy while 52.7% were difficult/very difficult surgeries. On intraoperative assessment of the surgery, 64.9% of the surgeries were easy while 35.1% were difficult. Based on comparison of pre-operative outcome, the sensitivity of intra-operative outcome was 82.6% and specificity was 63.5% (Table 5).

Multivariate analysis comparing intraoperative difficulty with associated risk factors depicted that only three variables (previous attacks of cholecystitis, thick GB wall and an impacted stone) were statistically significant in predicting preoperative difficulty (Table 6).

Table 4. Patient parameters for preoperative score assessment

Patient parameter (n= 132)	Summary statistics n (%)
Age	
≤50	93 (70.2)
>50	39 (29.8)
Sex	
Female	69 (51.9)
Male	63 (48.1)
Previous attacks of cholecystitis	
No	80 (60.3)
Yes	52 (39.7)
BMI	
<25	89 (67.4)
25-27.5	30(22.9)
>27.5	13 (9.8)
Abdominal scar	
No	85 (64.1)
Infraumbilical	42 (32.1)
Supraumbilical	5 (6.6)
Palpable gallbladder	
No	124 (94.7)
Yes	8 (5.3)
Wall thickness	
Thin (<4 mm)	57 (42.7)
Thick (≥4 mm)	75 (57.3)
Pericholecystic collection	
No	116 (88.5)
Yes	16 (11.5)
Impacted stone	
No	108 (82.3)
Yes	23 (17.7)
Conversion	
No	123 (93.1)
Yes	9 (6.9)

DISCUSSION

Cholecystectomy is the procedure to remove the gallbladder as a result of stone or inflammation. Today, laparoscopic cholecystectomy has become the gold standard for the management of acute cholecystitis (15). It provides many advantages over open surgery, such as minimal postoperative pain, good cosmesis, short hospital stays and fast recovery. However, 2-15 % of the patients undergoing LC are converted to open cholecystectomy

Table 5. Comparison between preoperative and intraoperative difficulty assessment

	No of cases easy on surgery n (%)	No of cases difficult/very difficult on surgery n (%)	X_2	p
No of cases easy on preoperative evaluation	55 (41.2)	8 (6.1)	25.49	<0.001
No of cases difficult/very difficult on preoperative evaluation	31 (23.7)	38 (29.0)		

Table 6. Univariate and multivariate analyses of intraoperative outcome with risk factors

Risk factors	Intraoperative outcome n (%)		Unadjusted odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)	p
	Easy (n= 86)	Difficult/very difficult (n= 46)				
Age (years)						
≤50	64 (74.4)	29 (63.0)	Reference	0.09	Reference	0.16
>50	22 (25.5)	17 (37.0)	1.96 (0.91, 4.23)		2.04 (0.76, 5.51)	
Sex						
Female	45 (52.3)	24 (52.1)	Reference	0.75	Reference	0.81
Male	41 (47.7)	22 (47.9)	1.13 (0.55, 2.31)		0.90 (0.37, 2.16)	
Previous attacks of cholecystitis						
No	64 (74.4)	16 (34.7)	Reference	<0.001	Reference	**0.01**
Yes	22 (25.6)	30 (65.3)	6.30 (2.86, 13.87)		3.34 (1.33, 8.35)	
BMI						
<25	56 (65.1)	33 (71.7)	Reference		Reference	
25-27.5	18 (20.9)	12 (26.0)	1.34 (0.58, 3.12)	0.50	1.65 (0.57, 4.78)	0.36
>27.5	12 (13.9)	1 (0.3)	0.15 (0.02, 1.17)	0.07	0.39 (0.04, 3.68)	0.41
Abdominal scar						
No	56 (65.1)	29 (63)	Reference		Reference	
Infraumbilical	25 (29.0)	17 (37.0)	1.36 (0.63, 2.92)	0.57	1.15 (0.43, 3.05)	0.60
Supraumbilical	5 (5.8)	0 (0)	0.50 (0.05, 4.69)	0.43	0.19 (0.01, 5.76)	0.78
Palpable gallbladder						
No	83 (96.5)	41 (89.1)	Reference	0.06	Reference	0.16
Yes	3 (3.5)	5 (10.9)	5.06 (0.94, 27.21)		4.93 (0.54, 44.79)	
Wall thickness						
Thin (<4 mm)	50 (58.1)	7 (15.2)	Reference	<0.001	Reference	**0.002**
Thick (≥4 mm)	36 (41.8)	39 (84.7)	9.52 (3.64, 24.89)		6.15 (1.99, 19.04)	
Impacted stone						
No	84 (97.6)	24 (52.1)	Reference	0.001	Reference	**0.04**
Yes	2 (2.3)	22 (47.9)	12.91 (2.88, 57.82)		7.52 (1.13, 50.03)	
Collection						
No	79 (91.8)	37 (80.4)	Reference	0.04	Reference	0.76
Yes	7 (8.2)	9 (19.6)	3.20 (1.06, 9.66)		1.26 (0.30, 5.24)	

due to various difficulties encountered during the procedure (15). The difficulty in cholecystitis is due to adhesions present around at the Calot's triangle, history of upper abdominal surgery, acutely inflamed and gangrenous gallbladder, gallbladder empyema, Mirizzi's syndrome, previous cholecystostomy, and cholecystogastric/duodenal fistula (16).

The complications of laparoscopic cholecystectomy are haemorrhage, gallbladder perforation causing biliary leakage, bile

duct injury, subhepatic collection, biliary fistula, surgical site infection, hematoma formation (17). Preoperative and intraoperative factors, such as male sex, old age, body mass index (BMI), history of abdominal surgery, leucocytosis and ultrasonographical findings like distension of the gallbladder, thick gallbladder lining, impacted stone, and pericholecystic fluid collection are the risk factors that make laparoscopic cholecystectomy technically difficult and time consuming (18). The controversy surrounding the timing of laparoscopic cholecystectomy continues all over the world. In this study, patients were operated within three days of presentation, which is in accordance with Tokyo guidelines 2018. In our study, we compared the perioperative and intraoperative risk factors which predict a difficult cholecystectomy in the setting of acute cholecystitis. In this study, laparoscopic surgery was conducted in 132 patients, and the risk factors of a difficult gallbladder were analysed.

Old age is considered as a significant risk factor to predict difficult laparoscopic cholecystectomy in various studies (18). In this study, age was not a significant risk factor. This is probably because of the low sample size of our study. Sex is known to be an important risk factor for difficult surgery (18). However, in this study, sex did not play any major role in the surgery. Patients with history of previous episodes of cholecystitis have been previously reported to have difficult laparoscopic cholecystectomy (19). In this study, similarly, patients with past cholecystitis attack history had difficult LC. This can be probably explained by the presence of dense adhesions at the Calot's triangle and gallbladder fossa due to repeated episodes of inflammation. Clinical findings such as BMI, abdominal scar, and palpable gallbladder have been shown to be significant risk factors in the prediction of operative difficulties (19). However, in this study, palpable gallbladder was not a significant risk factor for a difficult LC. Body mass index (BMI) and abdominal scar in this study were not associated with difficulty at surgery which was in similarity with other studies (15). Increased gallbladder thickness was another significant risk factor which helps to predict difficult laparoscopic cholecystectomy because it limits the extent of anatomical definition and makes dissection difficult from the gallbladder bed and due to distorted Calot's triangle. In this study, gallbladder wall thickness≥ 4 mm was also a risk factor making LC difficult intra-operatively. Stone impacted at the neck of the gallbladder is an important risk factor. Impacted stone causes distension of the gallbladder making it difficult to grasp and making dissection difficult similar to the thickened gallbladder (15). This risk factor was also significant in our study.

CONCLUSION

Our study concluded that gallbladder wall thickness, impacted stone and previous attacks of cholecystitis were significant risk factors in predicting difficult laparoscopic cholecystectomy in the setting of acute calculous cholecystitis. Hence, by analysing these risk factors, overall mortality and morbidity while operating in the presence of inflamed gallbladder can be reduced. Preoperative scoring system also helps the operating surgeon and team to be well prepared with adequate resources and time and the patient attenders along with patient can also be counselled regarding the risk involved beforehand.

Limitations of the Study

One of the limitations of this study was its sample size. A small sample size may have influenced non-significant relationship between few variables. Second, the participation of surgeons with different levels of expertise in this study may have indirectly placed a bias on measuring intraoperative difficulty in surgery. Even with few limitations, this study is among a few novel studies to successfully explore the validity of a preoperative scoring system to predict difficult laparoscopic cholecystectomy in the setting of acute cholecystitis. However, a prospective study with larger sample size may help us to better assess and validate this scoring system.

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of St. Johns Medical College and Hospital, and informed consent was obtained from all the participants prior to participation in the study (IEC 390/2018).

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2022; 38 (4): ???-???

Akut taşlı kolesistitli hastalarda zor laparoskopik kolesistektomiyi öngörmede ilişkili risk faktörlerinin analizi ve preoperatif skorlama sistemi validasyonu: Prospektif gözlemsel bir çalışma

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ÖZET

Giriş ve Amaç: Günümüzde laparoskopik kolesistektomi (LK), akut kolesistit için tercih edilen tedavi yöntemidir. Ancak, şiddetli enflamasyonun varlığı, cerrahların intraoperatif komplikasyon riskini artıran Calot üçgenini doğru bir şekilde tanımasını zorlaştırır. Çalışmamızın amacı, zor LK'yi tahmin etmek için kullanılan bir puanlama sisteminin geçerliliğini araştırmak ve akut taşlı kolesistit ortamında zor kolesistektomi ile ilişkili risk faktörlerini analiz etmekti.

Gereç ve Yöntem: Aralık 2018 ile Aralık 2020 arasında akut kolesistit tanısı alan ve laparoskopik kolesistektomi yapılan 132 hasta üzerinde gözlemsel bir çalışma yapılmıştır. Gerçek cerrahideki intraoperatif zorluklarla ilişkili olan zor LK'yi tahmin etmek için tüm bu hastalara preoperatif olarak Randhawa ve arkadaşları tarafından geliştirilen bir skorlama sistemi kullanıldı. Veriler SPSS versiyon 26.0 kullanılarak analiz edildi.

Bulgular: Ortalama yaş 43,63 ± 13,37 idi ve her iki cinsiyet neredeyse eşitti. Laparoskopik kolesistektominin preoperatif zorluğunun hesaplanmasında önceki kolesistit ataklarının öyküsü, gömülü taş, safra kesesi duvar kalınlığı istatistiksel olarak anlamlıydı. Puanlama sistemi sırasıyla %82,6 ve %63,5 duyarlılık ve özgüllüğe sahipti. Açık kolesistektomiye geçiş oranı %6,9 idi.

Sonuç: İltihaplı bir safra kesesi varlığında ameliyattan önce önemli risk faktörlerinin analiz edilmesi genel mortalite ve morbiditeyi azaltabilir. Doğru bir preoperatif skorlama sistemi, ameliyatı yapan cerrahın yeterli kaynak ve zaman ile iyi hazırlanmasını sağlayacaktır. Hasta refakatçileriyle önceden ilgili risk konusunda da istişare edilebilir.

Anahtar Kelimeler: Laparoskopi, kolesistektomi, risk faktörleri, kolesistik

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ORIGINAL ARTICLE
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Selective approach to arterial ligation in radical sigmoid colon cancer surgery with D3 lymph node dissection: A multicenter comparative study

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ABSTRACT

Objective: Radical surgery for sigmoid colon cancer is commonly performed with complete mesocolic excision (CME) and apical lymph node dissection, reached by central vascular ligation (CVL) of the inferior mesenteric artery (IMA) and associated extended left colon resection. However, IMA branches can be ligated selectively according to tumor location with D3 lymph node dissection (LND), economic segmental colon resection and tumor-specific mesocolon excision (TSME) if IMA is skeletonized. This study aimed to compare left hemicolectomy with CME and CVL and segmental colon resection with selective vascular ligation (SVL) and D3 LND.

Material and Methods: Patients (n= 217) treated with D3 LND for adenocarcinoma of the sigmoid colon between January 2013 and January 2020 were included in the study. The approach to vessel ligation, colon resection and mesocolon excision was based on tumor location in the study group, while in the comparison group, left hemicolectomy with routine CVL was performed. Survival rates were estimated as the primary endpoints of the study. Long- and short-term surgery-related outcomes were evaluated as the secondary endpoints of the study.

Results: The studied approach to the IMA branch ligation was associated with a statistically significant decrease in intraoperative complication rates (2 vs 4, p= 0.024), operative procedure length (225.56 ± 80.356 vs 330.69 ± 175.488, p< 0.001), and severe postoperative morbidity (6.2% vs 19.1%, p= 0.017). Meanwhile, the number of examined lymph nodes significantly increased (35.67 vs 26.69 per specimen, p< 0.001). There were no statistically significant differences in survival rates.

Conclusion: Selective IMA branch ligation and TSME resulted in better intraoperative and postoperative outcomes with no difference in survival rates.

Keywords: Colon cancer, complete mesocolon excision, D3 lymph node dissection, central vascular ligation, inferior mesenteric artery, sigmoid colon

INTRODUCTION

According to the principles of complete mesocolon excision (CME), described by Hohenberger et al., sigmoid colon cancer should be treated with central vascular ligation (CVL) of the inferior mesenteric artery (IMA) to reach apical lymph node dissection (1). According to Japanese guidelines, segmental resections for sigmoid colon cancer are performed within longitudinally spread borders: 5 cm (N1 zone) and 10 cm (N2 zone). This zonation is based on the pattern of lymph node metastasis distribution (2). This approach to resection margin identification is described as a 'cm-rule' (3). If the 'cm-rule' is followed and D3 lymph node dissection is performed in respect to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019, vessel preservation can be considered for segmental resections if IMA is unsealed from the mesocolon (4,5). The left colic artery (LCA) is commonly saved in distal sigmoid colon cancer surgical treatment and has been shown to be superior to D3 lymph node dissection with high vascular ligation (6). Preservation of the superior rectal artery (SRA) is also possible for proximal sigmoid colon resection (4). In this technique, tumor-specific mesocolon excision (TSME) is performed.

This study aimed to compare a segmental colonic resection with TSME, selective approach to the ligation of the inferior mesenteric artery with D3 LND and left hemicolectomy with complete mesocolon excision, central vascular ligation and apical lymph node dissection in terms of early and late postoperative complications, outcomes and survival rates.

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MATERIAL and METHODS

Study Design

This was a two-center retrospective comparative study of consecutive patients treated for sigmoid colon cancer between January 2013 and January 2020.

Patients at one center (Moscow, Russia) underwent segmental colon resection with 10 cm resection margins in proximal and distal directions from the tumor according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 (7). Selective IMA branches ligation with D3 lymph node dissection [(selective vascular ligation (SVL)] was reached by skeletonization of IMA. Patients at the other center (Malatya, Türkiye) were treated with left hemicolectomy, central vascular ligation and apical lymph node dissection according to the principles of complete mesocolon excision [central vascular ligation (CVL)] and included in the comparison group.

Inclusion criteria were as follows: 1) tumor of the sigmoid colon, confirmed intraoperatively; 2) radical elective surgery; 3) adenocarcinoma of the sigmoid colon, confirmed by pathomorphology; and 4) D3 lymph node dissection.

Exclusion criteria were as follows: 1) multiple primary tumors, 2) urgent surgical treatment without radical intent, 3) obstructive sigmoid colon resection, and 4) colorectal cancer caused by germline mutations or inflammatory bowel disease.

The last follow-up assessment was conducted in January 2022. The primary endpoints of the study were overall, progression-free, and cancer-specific survival rates.

The secondary endpoints included: 1) operative outcomes, such as blood loss volume, duration of surgery, intraoperative complication rates, and number of examined and metastatic lymph nodes, 2) long-term surgical outcomes, including anastomotic leakage and anastomotic stricture rates.

Approach to Tumor Location Identification

Tumor location was confirmed by intraoperative revision. The tumor was considered in the descending colon if it was located in the part of the colon, fixed to the left wall of the abdomen by Toldt's fascia. If the tumor was in the mobile part of the colon, not fixed by Toldt's fascia-it was considered in sigmoid colon.

The tumor was supposed to be in the middle third of the sigmoid colon if both resection margins were within the sigmoid colon. If the proximal resection margin was within the descending colon, while the distal resection margin was within the sigmoid colon, the tumor was considered in the proximal third. If the distal resection margin was within the upper rectum, the tumor was considered in the distal part of sigmoid colon.

Surgical Approach

In the SVL group, left segmental resection, sigmoid colon resection, or anterior rectal resection with D3 lymph node dissection was performed. The IMA was unsealed from the surrounding mesocolic tissue to preserve the vessels outside the resection margins (Figure 1). If the tumor was in the upper third of the sigmoid colon, the distal resection margin was above the promontorium-the SRA was preserved in those cases, while the IMA was skeletonized and sigmoid branches were ligated in the same way described by Kobayashi et al. (4,5) (Figure 2a). The LCA was ligated if it supplied the descending colon at the level of the proximal resection line. Otherwise, both LCA and SRA were preserved.

The SRA was ligated if the distal resection line was below the promontorium, i.e., sigmoid colon resection with anterior rectal resection was performed. In those cases, the LCA was preserved (Figure 2b).

If resection of the sigmoid colon for middle third tumors was managed, both the LCA and SRA were spared (Figure 2c). The root of IMA was exposed to guarantee the excision of lymph nodes from the group № 253-the D3 LND was performed.

In the CVL group, left hemicolectomy with CME was performed (1). The IMA was ligated at the root based on the principles suggested by Hohenberger. In these procedures, the proximal resection margin was at the splenic flexure, while the distal resection margin in the upper third of the rectum. The apical lymph node dissection was guaranteed by high IMA ligation at the level of its outflow from the aorta. The aorta sidewall was exposed while the length of IMA stump was no longer than 1 cm in length.

In both groups, anastomosis was performed by double-stapling technique in end-to-end or side-to-end fashion.

Specimen Processing

The photograph of unfixed, unopened specimen was made along the metric scale prior to formaline fixation. Lymph node dissection from the mesocolon tissue was performed by the assisting surgeon. The mesocolon tissue along the inferior mesenteric artery branches was dissected for lymph node excision and grouped according to lymph node classification described in the JSCCR guidelines 2019 for the treatment of colorectal cancer (7). The specimen was characterized using a standardized pathology report for colorectal cancer (8).

Statistical Analysis

Categorical variables were presented as absolute counts and percentages for the whole sample and were compared using Pearson's chi-square or Fisher's exact test, as appropriate.

Continuous data were presented as mean ± standard error and interquartile range. Non-normally distributed data were compared using the Mann-Whitney U test. Five-year survival rates were estimated with the Kaplan-Meier method.

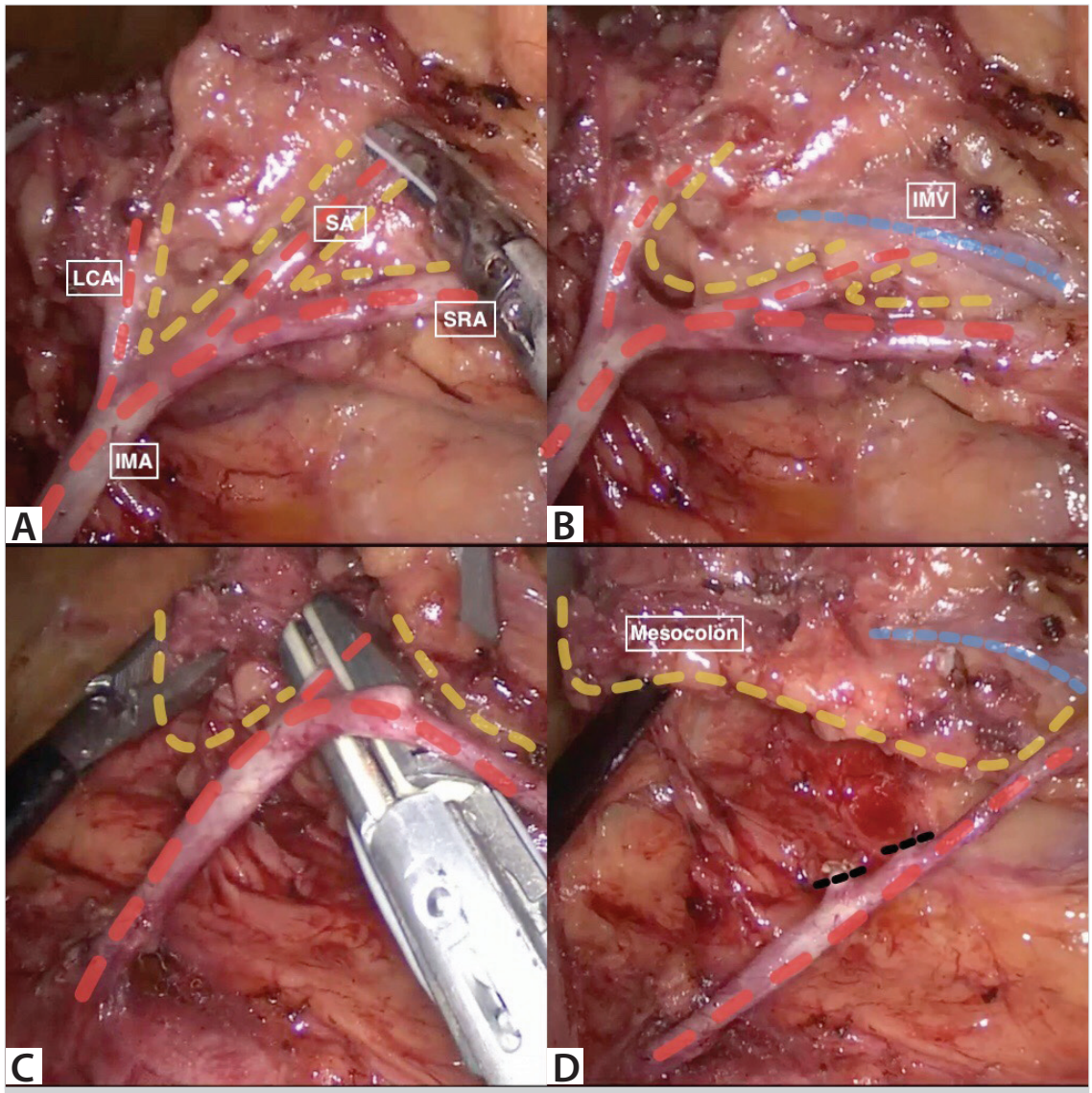

Figure 1. Skeletonization of inferior mesenteric artery (IMA): **A.** Skeletonization of sigmoid artery (SA), **B.** Final view of skeletonization, **C.** Ligation of left colic artery (LCA) with ultrasound device harmonic ACE, **D.** LCA and SA are coagulated red dotted line.

RESULTS

This retrospective study included 217 consecutive patients treated for sigmoid colon cancer at the Clinic for Coloproctology and Minimally Invasive Surgery (Moscow, Russia): Nineteen patients were excluded because of D2 lymph node dissection, six patients were excluded because of multiple primary cancer, and 28 patients did not match the criteria of inclusion because of obstructive sigmoid colon resection, extended left colectomy, or anterior rectal resection. As a result, 164 patients were included in the study. Finally, three patients were lost to follow-up. Overall, 161 patients were included in this study.

The CVL database included 50 patients treated for sigmoid colon cancer, two patients had primary multiple cancers. One patient was excluded because of obstructive sigmoid colon resection. Finally, 47 patients met the inclusion criteria.

There were no inter-group differences in clinicopathological characteristics, such as age, body mass index (BMI), tumor stage, and differentiation ($p > 0.05$; Table 1).

In the CVL group, left hemicolectomy with splenic flexure mobilization was performed in all cases because of high ligation of IMA. In the SVL group, segmental left colon resection for proximal sigmoid cancer was performed in 10 cases (6.1%), sigmoid colon resection-in 83 cases (51.5%), sigmoid colon and anterior rectal resection-in 68 cases (32.9%). In 22 cases (13.7 %), anastomosis formation demanded splenic flexure mobilization.

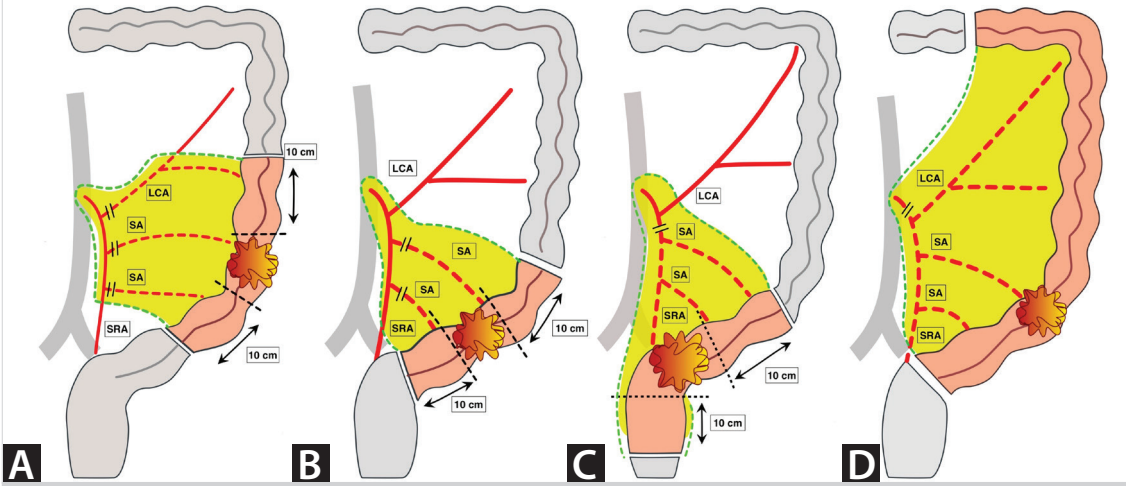

Figure 2. A. Left segmental resection for proximal sigmoid colon cancer, **B.** Sigmoid colon resection for medially located sigmoid colon cancer, **C.** Sigmoid colon and anterior rectal resection for distal sigmoid colon cancer, **D.** Left hemicolectomy for sigmoid colon cancer.

LCA: Left colic artery, SA: Sigmoid artery, SRA: Superior rectal artery.

Table 1. Clinico-morphological characteristics of the patients

Characteristic	Selective IMA branch ligation, n= 161	High IMA ligation, n= 47	p
Age (years), mean ± SD (IQR)	64.5 ± 10.821 (38-87)	58.9 ± 9.675 (36-79)	0.269
Sex, n (%)			
Male	74 (46.0)	21 (44.7)	
Female	87 (54.0)	26 (55.3)	0.872
BMI, mean ± SD (IQR)	26.33 ± 4.287 (17-38)	28.07 ± 3.746 (20-49)	0.075
AJCC stage, n (%)			0.692
Stage 1	16 (9.8)	2 (4.3)	
Stage 2	52 (31.9)	14 (29.8)	
Stage 3	70 (42.9)	21 (44.7)	
Stage 4	25 (15.3)	10 (21.3)	
pT stage, n (%)			0.231
Tis	2 (1.2)	0 (0.0)	
T1	8 (5.0)	0 (0.0)	
T2	16 (9.9)	3 (6.4)	
T3	113 (70.2)	33 (70.2)	
T4	22 (13.7)	11 (23.4)	
pN stage, n (%)			0.475
N0	71 (44.1)	18 (38.3)	
N1	41 (25.5)	16 (34.0)	
N2	49 (30.4)	13 (27.7)	
cM stage, n (%)			0.375
M0	138 (84.7)	37 (78.7)	
M1	25 (15.3)	10 (21.3)	
Tumor differentiation, n (%)			0.202
G1	34 (21.8)	9 (19.1)	
G2	82 (52.6)	32 (68.1)	
G3	3 (1.9)	0 (0.0)	
Mucinous	37 (23.7)	6 (12.8)	

SD: Standard deviation, IQR: Interquartile range , n: Number, AJCC: American Joint Committee on Cancer, BMI: Body mass index, G: Grade, Tis: T in situ.

Table 2. Surgery-related characteristics

Characteristic	Selective IMA branch ligation, n= 161	High IMA ligation, n= 47	p
Approach, n (%)			
Open	58 (36.2)	3 (6.4)	<0.001
Laparoscopic	81 (49.7)	44 (93.6)	
Robotic	22 (14.1)	0 (0.0)	
Operative time (min), mean ± SD (IQR)	225.56 ± 80.356 (130-490)	330.69 ± 175.488 (120-720)	<0.001
Blood loss (mL), mean ± SD (IQR)	98.25 ± 97.57 (10-300)	183.45 ± 248.471 (10-1000)	0.300
Surgically important intraoperative complications, n (%)	2 (1.2)	4 (8.5)	0.024
Ureter injury	0	1	
Anastomotic air leakage	1	1	
Proximal resection margin extension due to ischemia	0	1	
Bowel deserosation	0	1	
Superior rectal artery trauma	1	0	
Overall number of examined LN, mean ± SD (IQR)	35.67 ± 18.509 (1-135)	26.69 ± 14.455 (4-57)	<0.001
Overall mts of LN among N+, mean ± SD (IQR)	7.13 ± 8.482 (1-46)	5.34 ± 7.745 (1-42)	0.205

SD: Standard deviation, IQR: Interquartile range, n: Number, LN: Lymph nodes.

The operative time was significantly lower in SVL even though the robot-assisted approach was used in the study group (225.56 vs 330.69, p< 0.001).

Intraoperative complications were observed less often in the SVL group than in the CVL group (p= 0.024) (Table 2). However, only two complications were associated with surgical technique.

There was one case of SRA trauma during IMA skeletonization in the SVL group. The SRA was ligated below LCA debranching-only LCA was preserved in this case. There was no significant blood loss associated with the SRA trauma. Blood loss in the SVL group was lower than in the CVL group but not statistically significant. There was one case of proximal resection margin extension due to ischemia in the CVL group. That complication may have been caused by high ligation of IMA (Table 2).

Postoperative complication rate, such as ileus, lymphorrhea, and wound site complications were lower in the SVL group than in the CVL group (p= 0.095; Table 3).

Severe complications (grade III and IV by the Clavien-Dindo classification) were more common in CVL than in SVL patients (6.2% vs 19.1%, p= 0.023). All patients survived beyond the first 30 days (Table 3).

Anastomotic leakage occurred less frequently in the SVL group than in the CVL group [five cases (3.1%) vs three cases (6.4%), p= 0.382; Table 3]. Colorectal anastomosis stricture was observed in one case in the SVL group, while it happened in five cases in CVL (0.6% vs 10.6%, p= 0.002) (Table 4).

The number of examined lymph nodes was significantly higher in the SVL group than in the CVL group (35.67 vs 26.69 lymph nodes per specimen, p< 0.001), while the number of metastatic lymph nodes was comparable in both groups (Table 2).

Survival Rates

The follow-up period did not differ between the groups (p= 0.698). The overall, cancer-specific and progression-free survival rates were comparable in both groups (Table 4). In this

Table 3. Short-term postoperative results

Characteristic	Selective IMA branches ligation, n= 161	High ligation of the IMA, n= 47	p
Postoperative hospital stay (days), mean ± SD (IQR)	10.667 (4-37)	9.207 (4-37)	0.062
Postoperative morbidity, n (%)			
Clavien-Dindo I-II	17 (10.6)	4 (8.5)	0.790
Clavien-Dindo III-IV	10 (6.2)	9 (19.1)	0.017
Anastomotic leakage, n (%)	5 (3.1)	3 (6.4)	0.382
Short-term postoperative complications, n (%)	27 (16.6)	13 (27.7)	0.095

SD: Standard deviation, IQR: Interquartile range, n: Number.

Table 4. Long-term postoperative data

Characteristic	Selective IMA branches ligation, n= 161	High ligation of the IMA, n= 47	p
Neoadjuvant chemotherapy, n (%)	2 (1.2)	2 (4.3)	0.217
Postoperative chemotherapy	64 (39.8)	32 (68.1)	0.001
Anastomotic stricture, n (%)	1 (0.6)	5 (10.6)	0.002
5-year overall survival	93.3	93.6	0.802
5-year progression free survival	81.6	85.1	0.237
5-year cancer-specific survival	93.3	91.5	0.976
Follow-up	38.55 ± 16.27 (5-87)	37.22 ± 12.36 (3-85)	0.698

IMA: Inferior mesenteric artery, n: Number.

study, vessel preservation based on tumor location did not affect overall (Figure 3), progression-free (Figure 4), or cancer-specific survival rates (Figure 5).

DISCUSSION

There are two accepted approaches to radical sigmoid colon cancer treatment. Complete mesocolic excision with IMA ligation at the root (within 1 cm below its debranching point) allows the excision of the colon with the tumor within its fascial envelope and removal of lymph nodes at the root of IMA (1,8). Central ligation of the IMA demands extended colon resection, reached by the proximal resection line in the descending or transverse colon, and the distal resection line-in the upper rectum.

Meanwhile, the Japanese guidelines are based on the 10 cm rule that considers dominant arteries, supplying the tumor and horizontal spread of metastasis in the lymphatic system. D3 lymph node dissection (i.e., excision of the lymph nodes from group № 253) should be performed for T3 tumors and may be

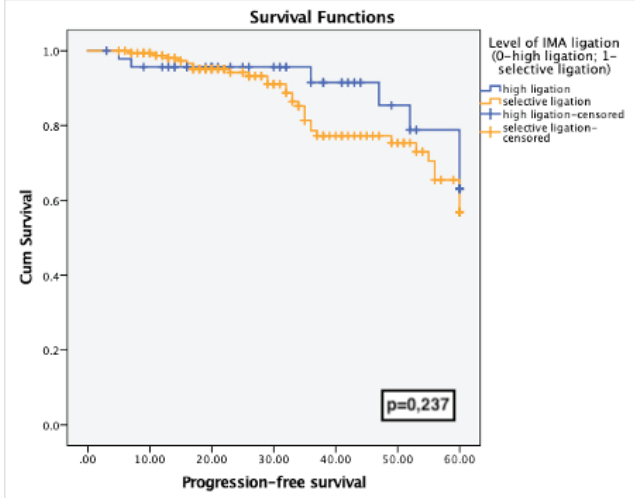

Figure 4. Progression-free survival in high-ligation and selective ligation groups.

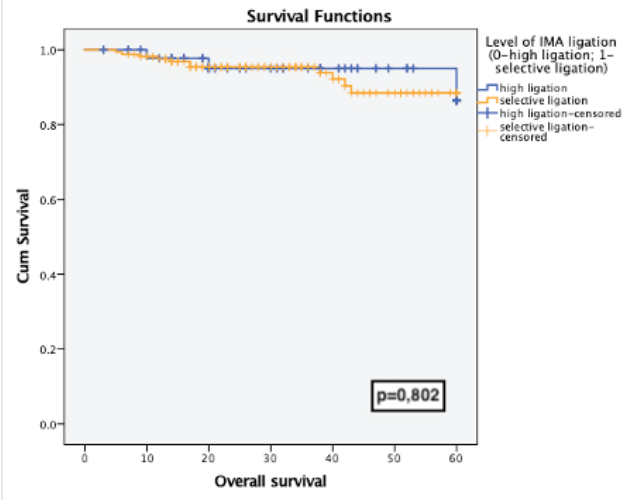

Figure 3. Overall survival rates in selective ligation and high ligation groups.

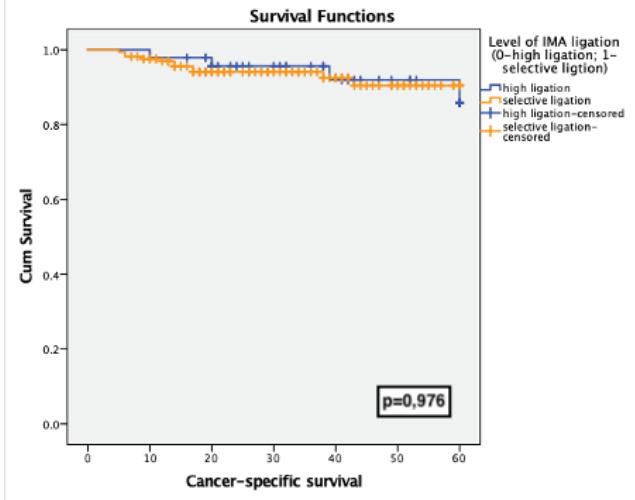

Figure 5. Cancer-specific survival rates in selective ligation and high-ligation groups.

considered for T2 tumors (3,7). A meta-analysis by Nerad et al. has reported the diagnostic odds ratio of computer tomography (CT) scanning as 20.6% [95% confidence interval (CI), 10.2-41.5] for tumor invasion and 4.8% (95% CI, 2.5-9.4) for nodal involvement (9). Thus, CT is not relevant enough in colon cancer staging. Therefore, in our study, all patients with any risk of nodal involvement or tumor invasion into the muscular layer underwent D3 lymph node dissection.

The Japanese guidelines provide no recommendation on the IMA ligation level. They state that for tumors located above the promontorium, the colon should be cut 10 cm proximally and distally away from the tumor (2). From this perspective, the LCA and SRA may be spared if their basins are outside the resection margins.

Kobayashi et al. have demonstrated a technique for laparoscopic IMA skeletonization, which involves dissection of the IMA and its branches from the mesocolon, exposing the arterial wall up to the adventitial layer. D3 lymph node dissection and tumor-specific mesocolon excision within resection margins can be performed in such contexts (4,5).

In our study, we preserved the SRA if the distal resection margin was above the promontorium level. LCA was preserved if the proximal resection line was in the proximal third of the sigmoid colon or descending colon. This approach allowed to avoid unnecessary resection of the colon in the proximal and distal directions; therefore, 1) splenic flexure mobilization was not performed routinely in distal tumor cases, and 2) the anal-side marginal artery could be preserved (10). The mesocolon associated with the feeding vessel was excised.

Splenic flexure mobilization has been shown to 1) add time to surgery with no decrease in anastomotic leakage rate and 2) increase intraoperative risk (11).

Selective ligation with TSME resulted in less need for splenic flexure mobilization. Concurrently, the rate of intraoperative complications was lower in patients with selective ligation than in their counterparts and the operative time and blood loss were significantly shorter, which may be due to reduced demand for splenic flexure mobilization.

Open surgery was more common in the study group, which may have been due to 1) the higher number of surgeons with different learning curves, performing the surgical procedure, 2) the amount of cases was mostly three times bigger in the study group than in the comparison group, 3) more fragile elderly patients in the study group.

According to the American Society of Colon and Rectal Surgeons, high ligation is performed at the root of the IMA, whereas low ligation is performed after LCA debranching. Therefore, the excision of lymph nodes from group № 253 is not performed in the latter approach. Kanemitsu et al. have demonstrated a survival benefit associated with high ligation, which can be due to the completeness of lymph node dissection, rather than the level of IMA ligation (12). Recently, Akagi et al. have demonstrated survival benefit in D3 lymph node dissection with left colic artery preservation (6).

According to a recent meta-analysis, the anastomotic leakage rate is reduced if LCA is preserved in the sigmoid colon and rectal cancer treatment (13). Moreover, it is associated with a better quality of life in terms of continence and sexual and urinary function in the postoperative period (14). However, there is lack of data on survival rates in SRA preservation for proximal sigmoid colon tumors. If a significant length of the distal sigmoid colon can be left with no decrease in radicality, than SRA may be preserved in respect to distal marginal artery supply (10). In the study by Wakahara et al., SRA preservation did not affect three-year relapse-free survival rates, lymph node harvest, blood loss volume, or other relevant outcomes. However, the patients were not grouped according to level of lymph node dissection, and for all of them LCA was preserved (15).

A meta-analysis by Yang et al. has revealed no differences in anastomotic leakage frequencies, lymph node harvest, or survival rates between groups undergoing high and low ligation of the IMA (16). On the contrary, the meta-analysis by Zeng et al. has demonstrated that the risk of anastomotic leakage increases in the group with patients who had undergone high ligation of the inferior mesenteric artery (17). There was no statistically significant difference in the anastomotic leakage rates in our study, although they tended to decrease if the IMA branches were preserved. However, anastomotic strictures were more common in the CLG group.

Low ligation is routinely performed with D2 lymph node dissection, in contrast to high ligation, which includes apical lymph node harvest. Kanemitsu et al. have shown that high ligation coupled with D3 lymph node dissection leads to increased survival rates (12). The mean percentage of apical lymph node involvement in oncological processes has been reported in the range of 3-6% (18,19). Moreover, D3 lymph node dissection allows for better staging, as it leads to skip metastasis determination. Alici et al. have reported apical lymph node metastasis in 5.8% of patients, including 1.9% with skip metastasis (19).

Central ligation at the root of the IMA results in a higher lymph node yield, which corresponds to higher survival rates (20). Herein, we demonstrated that IMA branch preservation and TSME with D3 lymph node dissection resulted in higher lymph node yield, while the approach to pathomorphological specimen extraction and analysis was standardized in both groups.

However, the applicability of selective IMA branch ligation in open and minimally invasive surgery is very limited, as selective ligation of colic arteries is a technically advanced procedure, which demands IMA refinement to perform D3 lymph node

dissection (21). It is advantageous in patients with high BMI and distorted complex anatomy. Thorough understanding of IMA anatomy is needed for this approach (22).

This comparative study showed that the studied approach is feasible in routine surgical practice as it is associated with a shorter operative time with no increase in blood loss, a lower rate of intraoperative complications, and comparable frequency of anastomotic leakage, relative to those associated with the standard approach. The rates of anastomotic strictures in the late postoperative period were significantly lower in the SVL group, which benefit the quality of life. The studied approach is not inferior to the compared approach in terms of survival rates.

Study Limitations

This study has some limitations. First, it was a retrospective study, and the sample sizes were unequal. The comparison group was three times smaller than the study group. These factors may have affected the obtained results. Prospective studies are required to validate these findings. This study gives a way to randomized clinical trial.

CONCLUSION

Skeletonization allows for D3 lymph node dissection and preservation of the IMA, leading to high lymph node yield and low rates of postoperative morbidity, anastomotic leakage, and anastomotic strictures. Preoperative identification of the tumor location and feeding vessel features can help plan selective ligation and segmental resections.

Survival outcomes were comparable in both groups. Sigmoid colon cancer can be treated surgically in a more tailored manner, based on tumor location and IMA anatomy, including selective ligation of its branches.

Statements and Declarations

Written informed consent was obtained from all patients for study participation and publication of obtained images and data. The study was approved by the ethics committee of the WMA and adhered to the Declaration of Helsinki 1964 (updated in 2013).

Ethics Committee Approval: This study was approved by Sechenov University Institutional Review Board (Registration no: SU300585, Date: 08.08.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SE, AZ, PT; Design – SE, AZ; Supervision – SE, PT; Fundings – SE, CK; Materials – SE, CK, PT; Data Collection and/ or Processing – AZ, AM, AA, YB; Analysis and/or Interpretation – AZ, SE, AM; Literature Search – AZ; Writing Manuscript – AZ, SE; Critical Reviews – AZ, SE, CK.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2022; 38 (4): 382-390

D3-lenf nodu diseksiyonu ile radikal sigmoid kolon kanseri cerrahisinde arteriyel ligasyona selektif yaklaşım: Çok merkezli karşılaştırmalı bir çalışma

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ÖZET

Giriş ve Amaç: Sigmoid kolon kanseri için radikal cerrahi, genellikle, inferior mezenterik arterin (IMA) santral vasküler ligasyonu (CVL) ve buna bağlı genişletilmiş sol kolon rezeksiyonu ile ulaşılan tam mezokolik eksizyon (CME) ve apikal lenf nodu diseksiyonu ile gerçekleştirilir. Ancak İMA iskeletleştirilmiş ise D3 lenf nodu diseksiyonu (LND), ekonomik segmental kolon rezeksiyonu ve tümöre özgü mezokolon eksizyonu (TSME) ile İMA dalları tümör yerleşimine göre seçici olarak bağlanabilir. Bu çalışma, KME ve CVL ile sol hemikolektomi ile selektif vasküler ligasyon (SVL) ve D3 LND ile ekonomik kolon rezeksiyonunu karşılaştırmayı amaçladı.

Gereç ve Yöntem: Ocak 2013 ile Ocak 2020 arasında sigmoid kolon adenokarsinomu nedeniyle D3 LND ile tedavi edilen hastalar (n= 217) çalışmaya dahil edildi. Çalışma grubunda damar ligasyonu, kolon rezeksiyonu ve mezokolon eksizyonuna yaklaşım tümörün yerleşimine göre belirlenirken, karşılaştırma grubunda rutin CVL ile birlikte sol hemikolektomi uygulandı. Hayatta kalma oranları, çalışmanın primer son noktası olarak ele alındı. Ameliyatla ilgili uzun ve kısa vadeli sonuçlar, çalışmanın sekonder son noktaları olarak değerlendirildi.

Bulgular: IMA dal ligasyonuna yönelik çalışılan yaklaşım, intraoperatif komplikasyon oranlarında (2'ye karşı 4, p= 0,024), ameliyat prosedür uzunluğunda (225,56 ± 80,356'ya karşı 330,69 ± 175,488, p< 0,001) ve ciddi postoperatif morbiditede istatistiksel olarak anlamlı bir azalma ile ilişkilendirildi. (%6,2-19,1, p= 0,017). Bu arada, incelenen lenf nodlarının sayısı önemli ölçüde arttı (örnek başına 35,67'ye karşı 26,69, p< 0,001). Sağkalım oranlarında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Seçici IMA dal ligasyonu ve TSME, sağkalım oranlarında hiçbir fark olmaksızın daha iyi intraoperatif ve postoperatif sonuçlara yol açtı.

Anahtar Kelimeler: Kolon kanseri, komplet mezokolon eksizyonu, D3 lenf nodu diseksiyonu, santral vasküler ligasyon, inferiyor mezenterik arter, sigmoid kolon

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ORIGINAL ARTICLE
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Validation of the adapted clavien dindo in trauma (ACDiT) scale to grade management related complications at a level I trauma center

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ABSTRACT

Objective: Complications during trauma management are the main factor responsible for the overall increase in treatment cost. There are very few grading systems to measure the burden of complications in trauma patients. A prospective study was conducted using the Adapted Clavien Dindo in Trauma (ACDiT) scale, with the primary aim of validating it at our center. As a secondary aim, it was also wanted to measure the mortality burden among our admitted patients.

Material and Methods: The study was conducted at a dedicated trauma center. All patients with acute injuries, who were admitted, were included. An initial treatment plan was made within 24 hours of admission. Any deviation from this was recorded and graded according to the ACDiT. The grading was correlated with hospital-free days and ICU-free days within 30 days.

Results: A total of 505 patients were included in this study, with a mean age of 31 years. The most common mechanism of injury was road traffic injury, with a median ISS and NISS of 13 and 14, respectively. Two hundred and forty-eight out of 505 patients had some grade of complication as determined by the ACDiT scale. Hospital-free days (13.5 vs. 25; p< 0.001) were significantly lower in patients with complications than those without complications, and so were ICU-free days (29 vs. 30; p< 0.001). Significant differences were also observed when comparing mean hospital free and ICU free days across various ACDiT grades. Overall mortality of the population was 8.3 %, the majority of whom were hypotensive on arrival and required ICU care.

Conclusion: We successfully validated the ACDiT scale at our center. We recommend using this scale to objectively measure in-hospital complications and improve trauma management quality. ACDiT scale should be one of the data points in any trauma database/registry.

Keywords: Morbidity, trauma, quality improvement, outcome assessment

INTRODUCTION

Trauma is a complex entity involving multiple systems, which affect the injured person's anatomy and physiology. According to the trauma registry established by the Australia India Trauma Systems Collaboration (AITSC) Project, in-hospital trauma mortality rate in urban trauma centers of India is 12.4% (1).

There is increasing evidence that trauma care involves a substantial financial burden, both on the patient and the government/insurance companies. As per a study done at a Level I trauma center in India in 2011, the mean cost of trauma care per admission was around USD 1900 (2). The severity of injury, length of stay in the intensive care unit (ICU) and hospital, surgical interventions, and transfusion requirements are significant drivers of the total costs incurred (3). Complications occurring during management tend to increase all these parameters, thus analyzing them would help us to better the quality and bring down the cost of treatment.

Even if we strictly adhere to the best practices and patient safety guidelines, trauma management complications cannot be avoided (4). Though non-mortality complications are far more common than mortality, the latter is the only parameter measured and used as a quality indicator. A grading system to measure morbidity would help us compare our outcomes with other centers and improve our quality of care.

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Several attempts have been made since the 1990s to classify surgical complications. Surgical Complication Outcome (SCOUT) score, Clavien Dindo grading system, Memorial Sloan Kettering (MSKCC) severity grading system, and the Accordion severity classification of postoperative complications are a notable few (5-8). None of them, except the Clavien Dindo grading system, have gained widespread acceptance, but that too only in elective surgeries.

Naumann et al., in their multicentric study, have described a novel "adapted Clavien-Dindo in trauma (ACDiT) scale" which encompasses all aspects of trauma management, especially non-operative treatment (9). We found that this scale is the only grading system explicitly designed for this purpose. Though few studies have validated this scale, all of them have been conducted in high-income countries (HICs). Validation of the ACDiT in low- and middle-income countries (LMICs), which lack similar organized trauma systems like the HICs, would help in determining whether it can be used for trauma quality improvement and trauma outcomes research on a global level.

A prospective study was performed using the ACDiT scale (Table 1) with the primary aim of grading the complications at our center. We thus examined this grading system's validity in an LMIC. Measurement of the mortality burden among our patients was a secondary aim.

MATERIAL and METHODS

Study Design

A prospective single-center observational study was undertaken over 12 months (January 2018 to December 2018).

Place of Study

The study was conducted at a level I trauma center of an LMIC in the division of trauma surgery & critical care.

Inclusion Criteria

All adult (age≥18 years) patients with acute injuries admitted under the Division of Trauma Surgery and Critical Care were included in the study.

Exclusion Criteria

Patients with any kind of known malignancy (including treatment completed/undergoing treatment) or any known co-morbidities were excluded from the study. Referred patients treated for more than 24 hours in other health care facilities and pregnant/lactating women were also excluded.

Methodology

Our trauma center has an annual emergency department (ED) footfall of about 75.000 injured patients. All these patients are triaged and resuscitated as per standard advanced trauma life support (ATLS) protocols. Most of them are discharged after primary treatment, and around ten percent are admitted.

Admission primarily occurs under any of the three departments, trauma surgery & critical care, orthopedics and neurosurgery. Patients admitted under trauma surgery & critical care are generally acutely injured patients involving one or more systems, isolated thoracic and abdominal injuries, extremity, vascular, and extensive soft tissue injuries. The average annual admission in this department is around 1300.

Table 1. The adapted clavien dindo in trauma (ACDiT) scale (adopted from Naumann et al.) (9)

Grades	Complications
I	Any deviation from the clinical course expected during the initial management plan without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. The allowed therapeutic regimens include antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections that were opened at the bedside.
II	Complications that require pharmacological treatment with drugs other than those allowed for Grade I complications. Unexpected blood product transfusions after hemostasis were deemed to be achieved*, and total parenteral nutrition (unless specified as part of original management) are also included.
III	Complications that require unplanned surgical, endoscopic or radiological interventions**. a. without general anesthesia b. with general anesthesia
IV	Life-threatening complications that require unplanned readmission or extension of stay in the critical care unit (including high dependency) beyond what was initially expected. This includes new organ failure other than the primarily injured organ. a. single organ dysfunction b. multi-organ dysfunction
V	Death a. No active treatment or escalation (patient kept comfortable) b. Actively treated patient

*Blood transfusions used for initial resuscitation are not included; **Relook surgeries as part of damage control are not considered as unplanned.

Every patient's clinical and epidemiological data were recorded in a preformed data set by a dedicated floor nurse and later transferred to an electronic database. When documenting the mechanism of injuries, fall from height, industrial and agricultural accidents were clubbed together as accidental/unintentional injuries. Hypotensive on arrival has been defined as an initial systolic blood pressure <90 mmHg.

Upon admission, the seriousness of injuries [based on the Injury Severity Score (ISS), New Injury Severity Score (NISS), Revised Trauma Score (RTS), Glasgow Coma Scale (GCS)] and the primary survey findings determine where the patient is transferred from the emergency department. they are either shifted to the operation room (OR) or the ward or ICU/high dependency unit (HDU).

The trauma surgery consultant in charge examined these patients to formulate a complete plan of treatment. It included: any upfront damage control procedure, expected surgeries, planned radiological interventions, and non-operative management. The so decided "initial treatment plan" was written down and attached to the patient's treatment file within 24 hours of admission. Patients were followed up daily (by the resident and the consultant in charge), and clinical parameters were recorded on preformed datasets until the time of patient discharge or death.

Any deviation from the initial treatment plan was prospectively recorded and graded according to the ACDiT. The resident in charge did it after a discussion with the consultant in charge. These recorded deviations were reviewed at the time of the patient's death/discharge, or at 30 days, whichever was earlier. If there were multiple grades of complications, only the highest grade was considered for final analysis. Patients, who were initially planned for non-operative management but ended up getting operated on, were considered to have a complication. Supplementary Table 1 depicts a few case-based examples of the complications to which this grading system was applied.

Hospital-free days and ICU-free days within 30 days were calculated for all patients for correlation with the ACDiT grades.

This study was approved by the institutional ethics committee (All India Institute of Medical Sciences, New Delhi, India) with the reference number IECPG-458/29.11.2017 with effect from 29.11.2017.

Data Analysis

Data was analyzed using SPSS version 21, IBM Inc., and STATA 14. Descriptive statistics such as median and interquartile range were calculated. Chi-square test was used for frequency analysis. The level of statistical significance was set at a p-value less than 0.05. Normality was determined by rule of thumb and was found to be not normally distributed in all grades. Jonckheere-Terpstra test was used to compare hospital free days and ICU free days across the ACDiT grades, and Tukey's HSD was used for pairwise comparison.

RESULTS

During the study period, 73.245 patients visited the ED, out of whom a total of 1207 patients were admitted under trauma surgery & critical care. Out of this, 87 patients did not fit the age criteria (≥18 years), and 453 were referred cases having undergone treatment elsewhere for >24 hours. A total of 99 patients were excluded for having known co-morbidities (Hypertension, COPD, chronic kidney disease, and hypothyroidism). Sixteen patients were either pregnant or lactating, and another 47 patients had known malignancies. After excluding all these patients, we recruited a total of 505 patients for our study.

Of the patients, 49.1% (248 of 505) had some complications and were assigned an ACDiT grade, as depicted in Table 2. As per the study protocol, the rest of the patients (257/505) did not have any complications. When looking at individual grades, Grade I (15.6%) and Grade II (9.3%) constituted the maximum, followed by Grade III (8.2%) and IV (7.7%). Demographic characteristics of the total patient population are summarized in Table 3. Mean age was 31 years with a male preponderance of 88 percent. Median ISS, NISS and GCS were 13, 14 and 15 respectively with a mean RTS of 7.52. The most common mechanism of injury was road traffic injury (63%), followed by accidental/unintentional injuries (including falls) (15%). Blunt assault (8%) was more common than penetrating assault (6%). Median time gap between the injury and arrival at the ED was six hours.

Complications: Table 4 depicts the comparison among patients having or not having complications. ISS, NISS, and Revised Trauma Score were found to be less severe in patients without any complications. A total of 159 (31.5%) patients were hypotensive on arrival and a vast majority of them had complications (124 out of 159). Patients who presented to the ED with a heart rate of more than 100/minutes were also prone to complications.

Management strategy: Of the total of 505 patients, 230 (45.54%) were initially planned for non-operative management. Table 5 depicts the differences in demographic characteristics and outcomes among patients in which the Initial management plan was operative or non-operative.

Comparison between the ACDiT grade and outcomes: Median hospital stay for the entire study population was eight (5-13) days. Among the patients requiring ICU care, median ICU stay was 9 (2.25-15) days. Hospital-free days (13.5 vs. 25; $p< 0.001$) were significantly lower in patients with complications than those without complications, and so were ICU-free days (29 vs. 30; $p< 0.001$). A strong association was also observed between an increase in the grade of ACDiT and a decrease in the hospital-free and ICU-free days.

Supplementary Table 1. Examples of some cases, their complications, the interventions done and the subsequent ACDiT grades assigned

Age/Sex	Mechanism	ISS	Injuries	Management	Complication	Intervention	Grade
45/M	RTI (Pedestrian hit by 4-wheeler)	25	Multiple rib fractures, Pneumothorax, Splenic injury in hemorrhagic shock	ICD, Operative management with splenectomy	Superficial skin infection	Opening of skin sutures and dressing	I
39/M	Blunt assault with rods and sticks	13	Bilateral rib fractures	Non operative management	Missed injury-fracture of distal phalanx of thumb	Required splinting of the finger when injury was detected just before discharge	I
29/F	Multiple penetrating assault to abdomen (Stab injury)	9	Multiple small bowel perforations, mesenteric injury with bleeding	Damage control surgery followed by mesh laparostomy	Enteroatmospheric fistula	Required unplanned TPN	II
46/M	RTI (2-wheeler rider hit by 4-wheeler)	9	Blunt trauma abdomen with pneumoperitoneum due to small bowel perforation	Operative management and repair of bowel perforation	Postoperatively developed urinary tract infection	Treated with urine culture-based antibiotics	II
59/M	RTI (2-wheeler rider hit by 4-wheeler)	13	Hemothorax, multiple bilateral rib fractures multiple transverse process fractures	Bilateral ICD, Non operative management	Iatrogenic pneumothorax during removal of ICD	Reinsertion under LA	IIIa
34/M	Railway associated injury	16	Crush injury left lower limb, without involvement of knee joint	Below knee amputation with primary closure of stump	Wound infection with sepsis	Revision amputation (above knee amputation) under RA	IIIa
44/M	RTI (Pedestrian run over by 4-wheeler)	25	Hemodynamically stable pelvic fractures, no bowel injury on initial CT	Non operative management	Delayed sigmoid colon gangrene	Exploratory laparotomy under GA	IIIb
25/F	RTI (Passenger in an autorickshaw which overturned)	25	Subarachnoid hemorrhage; subdural hemorrhage, multiple rib and spinal fractures; pulmonary contusion	Non operative management	Sepsis	Extended stay in ICU	IVa
35/F	Gunshot injury chest	25	Penetrating injury to lungs with massive hemothorax	Thoracotomy with non-anatomical lung resection	Multiorgan failure	Prolonged ICU stay for 21 days, followed by recovery and discharge	IVb
44/M	Penetrating assault to head, face, chest (Gunshot injury)	50	Severe head injury, facial injury	Non operative management (Palliative)	Patient became brain dead	Palliative management till physiological death	Va
24/M	RTI (Pedestrian hit by 4-wheeler)	34	Subdural hematoma, blunt thoracic injury, liver injury	Decompressive craniectomy, ICD for hemopneumothorax	Patient had a sudden cardiac death in postoperative ICU	Active management till death	Vb

RTI: Road traffic injury, ICD: Intercostal chest drain, TPN: Total parenteral nutrition, LA: Local anesthesia, RA: Regional anesthesia, GA: General anesthesia.

Table 2. Distribution of the patients according to the adapted Clavien Dindo in trauma (ACDiT) scale				
Total number of patients (n)	505			
No complications, n (%)	257 (50.9)			
ACDiT complications, n (%)	Grade I	79 (15.6)		
	Grade II	47 (9.3)		
	Grade III	41(8.1)	A	31 (6.1)
			B	10 (2)
	Grade IV	39 (7.7)	A	33 (6.5)
			B	6 (1.2)
	Grade V	42 (8.3)	A	3 (0.6)
			B	39 (7.7)

Significant differences were observed in mean Hospital free days and ICU free days between various ACDiT grades when compared using the Jonckheere-Terpstra test ($p< 0.001$), i.e., the mean number of hospital-free days and ICU-free days were found to be more among subjects with a lower grade of ACDiT complications (Figures 1A and 1B).

Mortality: Of the 505 patients, 8.3% (42 of 505) died and were categorized as Grade V complications. Among these 42 mortalities, 35 were hypotensive on arrival, 40 needed ICU care, and 29 patients required upfront surgery.

DISCUSSION

Our study depicts the association of ACDiT grades of complications with the total stay in the hospital or the ICU for a trauma patient. It thus proves the applicability of this scale in an LMIC to measure the complications occurring during trauma management.

Epidemiological parameters in the present study are in concordance with similar studies done in LMICs. Among these studies, mean age has been found around 30 years, with 80-90 % of males being injured. The severity of the injuries (as depicted by the mean ISS, NISS, and RTS) is also comparable (10-12). This trend among LMICs is, however, different from HICs, as evident from US-based studies (mean age 43.3 years, male 62.6%) (13)

In our study, when considering the injury mechanism, road traffic injuries (RTIs) were the majority, contributing 64.2% of the total, which is similar to other LMICs (11,12). Accidental/unintentional injuries (15.2% of total) were mostly due to falls from height, a common injury mechanism in our country (10). However, in the US, falls constitute a more significant proportion (36.9%), mostly due to the elderly population more prone to falls related to age or co-morbidities (13).

In trauma, be it blunt or penetrating, severe hemorrhage is associated with increased mortality risk, more extended hospital stays, and higher costs (14). The majority of hypotensive patients on arrival (bleeding being the most common cause) ended up with a higher ACDiT grade of complication. Again, there were 42 mortalities, out of which 35 (83.3%) were hypotensive on arrival on presentation.

Patients with a heart rate >100/minute at presentation to the ED had more complications. The literature states that in patients who present after moderate to severe trauma, the lowest mortality is observed when admission heart rate (AHR) is between 70 and 89 (15). Similarly, the complication rate was much more in patients presenting to the ED with acidosis on initial ABG. We already know that persistent acidosis is a cause of mortality in trauma (15). pH, initial lactate, lactate clearance, and base deficit are excellent indicators of shock and resuscitation, as well as predictors of complications and mortality (16). In a study from California involving a group of severely injured trauma patients, the degree of metabolic acidosis at the time of admission has identified those patients with the highest probability of developing acute lung injury (17).

In 2017, Naumann et al. first proposed a novel grading system for complications during trauma management (9). Compared to this multicentric ambispective index study by Naumann et al., ours was a prospective single center-based study. When considering the individual grades of complications, it was observed that our study had a higher number of Grade I complications (16% vs. 4%) and fewer Grade V complications (8% vs. 13%) than the index study. It can be explained by the fact that our study population consisted of fewer ICU admitted patients. In the index study, those patients who had complications had shorter hospital-free and ICU-free days than patients who did not have complications, (11 vs. 18 days; $p= 0.006$) and (10 vs. 28; $p< 0.001$) respectively. Similar was the distribution of hospital-free days (13.5 vs. 25; $p< 0.001$) and ICU-free days (29 vs. 30; $p< 0.001$), with versus without complications, in our study. In both studies, increasing ACDiT grades were strongly associated with decreasing hospital free days and ICU-free days (Figures 1A and 1B).

Table 3. Demographic characteristics, ED presentation and outcomes of the entire patient population

Patient characteristics		**All patients (n= 505)**
Age, (Mean, SD)		31.09 (14.78)
Male, n (%)		447 (88.5)
Trauma scores	ISS (Median, IQR)	13 (9-22)
	NISS (Median, IQR)	14 (9-24)
	RTS (Mean, SD)	7.52 (0.93)
	GCS (Median, IQR)	15 (15-15)
Mechanism of injury, n (%)	Road traffic injury	318 (62.9)
	Blunt assault	40 (7.9)
	Accidental/Unintentional	77 (15.2)
	Penetrating assault low velocity	15 (3)
	Penetrating assault high velocity	13 (2.6)
	Intentional self harm	6 (1.2)
	Railway associated injury	27 (5.3)
	Unknown	9 (1.8)
Injury presentation interval (Median, IQR) (hr)		6 (3-8)
ED Intubation, n (%)		67 (13.3)
Initial Heart rate >100, n (%)		167 (33.1)
Acidosis on initial ABG (Median, IQR)		267 (52.9)
Hypotensive on arrival, n (%)		159 (31.5)
Head injury, n (%)		53 (10.5)
System involved, n (%)	Abdomen	65 (12.9)
	Thorax	73 (14.5)
	Extremity and Pelvis	123 (24.4)
	Head and Neck	24 (4.8)
	Maxillofacial	15 (3)
	Soft Tissue Injury	5 (1)
	Polytrauma	200 (39.6)
Outcomes	Hospital stay (Median, IQR)	8 (5-13)
	Hospital free days (Median, IQR)	21 (11-25)
	ICU stay (Median, IQR)	0 (0-2)
	ICU free days (Median, IQR)	30 (26-30)
	Mortality (n, %)	42 (8.3%)

ED: Emergency department, SD: Standard deviation, ISS: Injury Severity Score, NISS: New Injury Severity Score, RTS: Revised Trauma Score, GCS: Glasgow Coma Scale, IQR: Interquartile range, ICU: Intensive care unit.

The development of hospital course complications was more common among patients admitted to the ICU than among patients hospitalized without ICU admission, similar to another study on ICU complications after trauma (18). Our ICU patients' overall complication rate was 79.87%, which was much higher than the 52.03% complication rate reported in the index study. It might be because we can admit only very sick patients to our ICU, owing to ICU bed limitations.

Our study population's overall mortality rate correlates with our trauma registry data (8.47% for the year 2018), which is more than HICs. According to a study from NHS hospitals over ten years, overall mortality was 8.3% among 248,234 patients with an ISS≥ 9 (19). Our study had 381 of 505 patients with an ISS≥ 9, and mortality among them was 10.5%. HICs like the United States, with robust trauma systems, have a significantly lower overall mortality rate (4.39% as per the ACS National Trauma Data Bank Annual Report 2016) (20).

Table 4. Comparison of patient characteristics and final outcomes among patients with or without complications

Patient characteristics		Patients without complications (n= 257)	Patients with complications (n= 248)	p
Age (Mean, SD)		29.39 (15.16)	32.85 (14.2)	0.002
Male, n (%)		228 (88.7)	219 (88.3)	0.88
Trauma Scores	ISS (Median, IQR)	9 (5-16)	17 (11-25)	<0.001
	NISS (Median, IQR)	9 (5-16)	19 (13-29)	<0.001
	RTS (Mean, SD)	7.81 (0.23)	7.22 (1.24)	<0.001
	GCS (Median, IQR)	15 (15-15)	15 (15-15)	-
Injury presentation interval (Median, IQR) (hr)		6 (3.5-8)	6 (3-9)	0.73
ED Intubation, n (%)		2 (0.7)	65 (26.2)	<0.001
Initial heart rate >100, n (%)		39 (15.18)	128 (51.61)	<0.001
Acidosis on initial ABG (Median, IQR)		117 (45.52)	150 (60.48)	0.001
Hypotensive on arrival, n (%)		35 (13.62)	124 (50)	<0.001
Mechanism of injury, (n)	Road traffic injury	154	164	0.15
	Blunt assault	23	17	0.38
	Accidental/Unintentional	52	25	0.002
	Penetrating assault low velocity	11	4	0.08
	Penetrating assault high velocity	4	9	0.14
	Intentional self-harm	6	0	0.015
	Railway associated injury	5	22	0.001
	Unknown	2	7	0.08
System involved, (n)	Abdomen	34	31	0.81
	Thorax	45	28	0.04
	Extremity and pelvis	69	54	0.18
	Head and neck	9	15	0.18
	Maxillofacial	12	3	0.02
	Soft tissue injury	2	3	0.62
	Polytrauma	86	114	0.004
Outcomes	Hospital stay (Median, IQR)	5 (4-8)	12 (8-20)	<0.001
	Hospital free days (Median, IQR)	25 (23-26)	13.5 (0-20)	<0.001
	ICU stay (Median, IQR)	0	0.5 (0-9.5)	<0.001
	ICU free days (Median, IQR)	30 (30-30)	29 (9-30)	<0.001
	Mortality, n(%)	0	42 (16.9%)	-

ED: Emergency department, SD: Standard deviation, ISS: Injury Severity Score, NISS: New Injury Severity Score, RTS: Revised Trauma Score, GCS: Glasgow Coma Scale, IQR: Interquartile range, ICU: Intensive care unit.

Before the advent of the ACDiT scale, mortality was the only outcome variable used to access the treatment care quality and compare among different centers. However, there is a considerable burden of morbidity or non-mortality complications, which gets hidden and is never quantified. Although it does not explicitly list the individual complications, this scale is the best available tool to initially screen a trauma center's performance and highlight it at audit meetings. Along with quality control, this scale would help us determine whether a new intervention effectively improves the system, measured by the grades of complications occurring before and after such an intervention. It can also be used across different trauma centers (both in LMICs and HICs) to compare the quality of care, thereby motivating, and aiding in trauma research.

Table 5. Patient characteristics and length of stay according to the plan of management (Non operative management vs operative)

Patient characteristics		Non operative management (n= 230)	Surgery (n= 275)	p
Age (Mean, SD)		33.06 (17.53)	29.45 (11.81)	0.06
Male, n (%)		198 (86.1)	249 (90.5)	0.89
Trauma scores	ISS (Median, IQR)	14 (9-22)	13 (5-21)	0.02
	NISS (Median, IQR)	16 (9-25)	13 (6-24)	0.03
	RTS (Mean, SD)	7.64 (0.69)	7.42 (1.08)	<0.001
	GCS (Median, IQR)	15 (15-15)	15 (15-15)	-
Complications present, n (%)		104 (45.2)	144 (52.4%)	0.11
Outcomes	Hospital stay (Median, IQR)	7 (5-12)	8 (5-14)	0.45
	Hospital free days (Median, IQR)	23 (15-25)	20 (7-24)	0.007
	ICU stay (Median, IQR)	0 (0-0)	0 (0-3)	0.003
	ICU free days (Median, IQR)	30 (30-30)	30 (24-30)	0.002
	Mortality, n (%)	13 (5.6%)	29 (10.5%)	0.04

SD: Standard deviation, ISS: Injury Severity Score, NISS: New Injury Severity Score, RTS: Revised Trauma Score, GCS: Glasgow Coma Scale, IQR: Interquartile range, ICU: Intensive care unit.

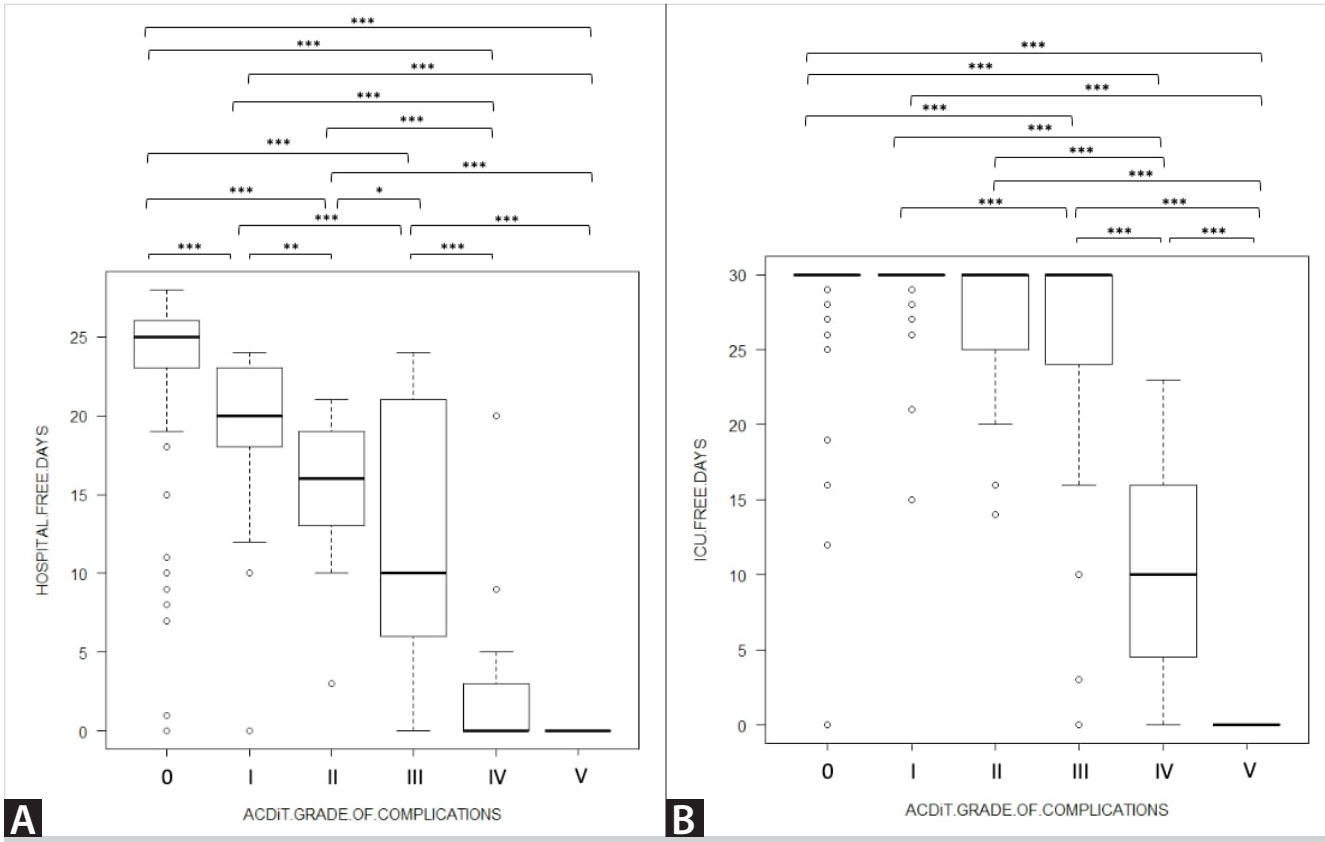

Figure 1. Comparison of Hospital free days **(A)** and ICU free days **(B)** across ACDiT grades (Horizontal bars represent median values; upper and lower boundaries of boxes represent the 25th to 75th percentiles (i.e., IQR); whiskers represent 10th to 90th percentiles; circles represent outliers). Statistical significance using Tukey's multiple comparison of means is illustrated using *p< 0.05, **p< 0.01, ***p< 0.001.

There are, however, certain limitations in our study. First, the ACDiT considers only the highest grade of complication, leading to underestimation of overall postoperative/post-trauma morbidity. Besides, the comparison of patients with more than one complication is difficult. The authors propose incorporating total hospital stay and ICU stay into the ACDiT grading criteria to overcome these limitations. Second, grade V complication in ACDiT means death, which ideally should not be a part of a grading system designed for non-mortality complications. Another limitation of our study is that missed injuries, which were diagnosed 24 hours after admission and needed to be separately treated, were considered as complications. Finally, undetected co-morbidities may have acted as confounding factors. The authors propose the use of co-morbidity indices to overcome this.

CONCLUSION

We propose that the ACDiT scale is valid in LMICs and can be included as part of the in-hospital trauma database/registry in HICs as well as LMICs. In this way, morbidity can be analyzed and compared across different trauma care systems. Alternative methods for grading complications do not accommodate non-operative management as a treatment option, which is nowadays a mainstay in trauma.

Ethics Committee Approval: This study was approved by All India Institute of Medical Sciences Ethics Committee for Post Graduate Research (Ref. no: IECPG-458/29.11.2017, Date: 05.12.2017).

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Travmada Uyarlanmış Clavien Dindo (ACDiT) sınıflamasının 1. seviye bir travma merkezinde tedavi komplikasyonlarının derecelendirmesindeki geçerliliği

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ÖZET

Giriş ve Amaç: Travma yönetimi sırasındaki komplikasyonlar, tedavi maliyetindeki genel artıştan sorumlu ana faktördür. Travma hastalarında komplikasyon yükünü ölçmek için çok az derecelendirme sistemi vardır. Uyarlanmış Clavien Dindo in Trauma (ACDiT) sınıflaması kullanılarak ve bunun geçerliliğini merkezimizde araştırma amacıyla ileriye dönük bir çalışma yürütüldü. İkinci amaç ise yatışı yapılan hastalarımızfa mortalite yükünü ölçmekti.

Gereç ve Yöntem: Çalışma özel bir travma merkezinde yapıldı. Akut yaralanma ile başvuran tüm hastalar çalışmaya dahil edildi. Yatışı müteakip 24 saat içinde bir "ilk tedavi planı" yapıldı. Bundan her türlü sapma kaydedildi ve ACDiT'e göre derecelendirildi. Derecelendirme, 30 gün içinde hastanesiz ve yoğun bakım ünitesiz günlerle ilişkilendirildi.

Bulgular: Bu çalışmaya ortalama yaşı 31 olan toplam 505 hasta dahil edildi. En yaygın yaralanma mekanizması, medyan ISS ve NISS sırasıyla 13 ve 14 olan karayolu trafik kazasıydı. Beş yüz beş hastanın 248'inde ACDiT skalası tarafından belirlenen komplikasyonlar vardı. Hastanesiz günler (13,5'e karşı 25; p< 0,001), aynı YBÜ'süz günler gibi (29'a karşı 30; p< 0,001) komplikasyonları olan hastalarda komplikasyonu olmayanlara göre anlamlı olarak daha düşüktü. Çeşitli ACDiT dereceleri arasında ortalama hastanesiz ve yoğun bakımsız günleri karşılaştırırken de anlamlı farklılıklar gözlendi. Genel mortalite %8,3 idi; bunların çoğunluğu varışta hipotansifti ve yoğun bakım ünitesine ihtiyaç duymuştu.

Sonuç: ACDiT sınıflamasını merkezimizde başarıyla doğruladık. Hastane içi komplikasyonları objektif olarak ölçmek ve travma yönetimi kalitesini iyileştirmek için bu sınıflamayı kullanmanızı öneririz. ACDiT sınıflaması, herhangi bir travma veritabanı/kaydında veri noktalarından biri olmalıdır.

Anahtar Kelimeler: Morbidite, travma, kalite iyileştirme, sonuç değerlendirmesi

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ORIGINAL ARTICLE
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Incidence of chylothorax over nineteen years of transhiatal esophagectomy: A case series and review study

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ABSTRACT

Objective: Chylothorax (CTx) is the leak and accumulation of lymphatic fluid within the pleural cavity. The incidence of CTx has the highest rate after esophagectomy. This study aimed to present three cases of post-esophagectomy chylothorax among 612 esophagectomies that were performed over 19 years, in which post-esophagectomy chylothorax was reviewed in terms of risk factors, diagnosis, and management.

Material and Methods: Six hundred and twelve patients were included in the study. Transhiatal esophagectomy was used for all patients. In three cases, chylothorax was detected. In all of the three cases, secondary surgery was performed for the management of chylothorax. Mass ligation was performed for the first and third cases having leak from the right side. In the second case, the leak was from the left side without prominent duct; and despite mass ligation that was done several times, no significant reduction in chyle was observed.

Results: In the first case, in spite of reduced output, the patient gradually progressed to respiratory distress. His condition deteriorated over time and he died after three days. In the second case that needed third surgery, the patient's condition deteriorated and she died after two days due to respiratory failure. The third patient had postoperative recovery. The patient was discharged on fifth day after the second operation.

Conclusion: In post-esophagectomy chylothorax, the key to preventing high mortality rates can be the identification of risk factors as well as timely detection of symptoms and proper management. Besides, early surgical intervention should be considered to prevent early complications of chylothorax.

Keywords: Chylothorax, transhiatal esophagectomy, post-esophagectomy chylothorax

INTRODUCTION

Chylothorax (CTx) is the leak and accumulation of lymphatic fluid, enzymes, and immunoglobulins within the pleural cavity following obstruction or leakage of the main thoracic duct (TD) or one of its branches (1,2). The etiology of chylothorax can be divided into spontaneous and traumatic categories. Non-traumatic or spontaneous type may have congenital, infectious, or neoplastic causes. Among the various etiologies, the most common factor of traumatic CTx is a surgical complication occurring following thoracic surgeries (2).

Among thoracic procedures, the incidence of CTx has the highest rate after esophagectomy and has been reported between 0% and 21% in various studies (1-5).

Diagnosis of chylothorax should be considered in conditions in which the chest tube drainage is milky or when the quantity of secretions is high. Confirmatory test may include sending a sample of the chest tube secretions for laboratory examination, which will be diagnosed by the presence of chylomicrons in lipoprotein analysis of pleural fluid (1,5). Beginning enteral feeding with olive oil and measuring serum triglyceride levels for diagnosis of chylothorax will also be helpful. Chylothorax is confirmed when triglyceride levels are >110 mg/dL (1).

Although chylothorax is a relatively uncommon complication after esophagectomy, it is lethal and is associated with high morbidity and mortality rates (3-5). Chylothorax is a serious pathology that can prevent lung expansion and lead to complications such as mediastinal shift (pulmonary malfunction), immunocom-

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promise, metabolic disarrangement, malnutrition, as well as intake and output imbalances (3,5). Patients with CTx typically have complaints of respiratory distress, dyspnea, chest pain and cough, which are similar to a pleural effusion exerting mechanical pressure on the heart and lungs (2). Long-term complications of CTx can include lymphocytopenia (peripheral lymphocytes in a circulation <1.500), which will be directly associated with a longer period of chyle leak (2,6).

The underlying cause of postoperative chylothorax may be inadequate identification and poor thoracic duct exposure during esophagectomy (4). When the surgeon releases esophagus and removes the mediastinal lymph nodes in adipose tissue surrounding the thoracic duct, poor visualization may damage the thoracic duct (1,7).

Currently, identifying the risk factors for chylothorax remains a controversial issue (3). In various studies, factors such as high BMI, neoadjuvant treatment, transhiatal esophagectomy, tumor type, serum albumin levels, and underlying diseases have been identified as predictors for chylothorax after esophagectomy (8,9).

At present, there is no standard consensus regarding the therapeutic strategy and optimal management of chylothorax given the lack of clinical trials meant to introduce therapeutic interventions (3,10). Furthermore, given the low incidence of chylothorax, few studies with a low sample size have addressed it (1). Conservative treatments include low-fat diets, TPNs, octreotide and supportive care (3,6). In addition, invasive procedures such as pleurodesis, lymphangiography followed by coiling and embolization and even radiotherapy are among the accepted alternative treatment modes (3). If conservative treatment is not successful, surgical intervention for thoracic duct ligation is considered by thoracotomy or thoracoscopic procedure although it may be associated with increased recovery time, longer hospital stay as well as morbidity and mortality rate (3,6). However, there are no studies suggesting the exact timing of revision surgery (1).

Most studies have reported CTx as a fatal complication; therefore, what emerges from the studies is that the inconsistency in the identification of risk factors as well as the lack of a standard treatment algorithm emphasizes the importance of this issue and that further studies are needed to detect risk factors, methods of management and treatment of chylothorax.

In this regard, we conducted this study with the aim of presenting three cases of chylothorax that occurred out of 612 cases of esophagectomy performed over nineteen years, and we also reviewed post-esophagectomy chylothorax in previous studies in a more comprehensive manner in terms of risk factors, diagnosis and management.

MATERIAL and METHODS

This is a retrospective case series and review study involving a total of 612 patients suffering from esophageal adenocarcinoma or squamous cell carcinoma who underwent transhiatal esophagectomy at Imam Khomeini University Hospital of Urmia University of Medical Sciences from December 2002 until January 2022.

To include data in the study, informed consent was obtained from the patient/guardian or legally authorized representative. Mean age of the patients was 61.06 ± 11.89 years. The youngest and oldest patients were 17 and 91 years old, respectively. Three hundred and forty-seven patients (56.6%) were males and 265 (43.2%) were females. All patients with remote metastasis and invasion to the trachea or great vessels were excluded from the operation.

Patients who had undergone surgery before 2011 did not receive neoadjuvant therapy but all esophagectomies after that period were subject to surgery after neoadjuvant therapy (except for three cases that were in T2). All patients underwent metastasis workup using chest, abdomen and pelvic CT-SCAN with oral and intravenous contrast. Fiber-optic bronchoscopy was done for all patients with mid esophageal cancer.

Surgical Technique

The operation started under general anesthesia in the rose position with a roll between shoulders, after insertion of Foley catheter and nasogastric tube. Aside from noninvasive monitoring, arterial monitoring was done during the operation.

After upper midline laparotomy and exploring the abdomen, gastrolysis was done on the base of right gastroepiploic artery and extensive kocherization was performed. However, no pyloroplasty or pyloromyotomy was done in any case.

The diaphragm was radially incised and hiatus dilated after releasing the cardia and ligating of veins in the inferior surface of the diaphragm.

In the cervical phase of surgery, an incision was made in the anterior border of the left sternocleidomastoid, and after incising the strap muscles, exploring recurrent nerve and ligations of inferior thyroid artery, the esophagus was encircled by Penrose drain. In this stage, right aberrant subclavian artery must be born in mind.

In the mediastinal step of the surgical procedure, the posterior aspect of the esophagus was freed from the vertebral column, bluntly. Subsequently, a Deaver retractor was inserted from the dilated hiatus, and the anterior of the esophagus was dissected sharply under direct vision as far as possible. Then, using the right hand that was inserted into the thorax from the dilated hiatus, with the aid of the index and mid fingers of the left hand

from above, the trachea was elevated and thoracic dissection completed. Cervical esophagus was incised from 3-4 cm below the upper esophageal sphincter and delivered to the abdomen surgical wound.

Once again, the diaphragm was elevated with Deaver retractor and under direct vision, lower mediastinal lymphadenectomy was done sharply as high as possible.

In the next step, a gastric conduit was created using linear stapler and the staple line was reinforced with 000 silk stitches. Gastric conduit was guided from below to the neck, through the posterior mediastinal route, and esophagogastrostomy was done with 000 silk Gambee sutures.

Diaphragmatic hiatus was repaired with 0 silk U stitches, feeding jejunostomy was created with 16 French Foley catheter, and bilateral chest tube was inserted routinely in all patients.

Postoperative Management

After the surgery, all patients were transferred to intensive care unit and extubated there 36-48 hours after operation, starting feeding from the jejunostomy tube. On the first postoperative day, a chest x-ray was taken for monitoring the location of chest tubes, and the drainage tube was removed when the drainage of the chest tube decreased to >100-150 mL per 24 hours.

Chest tubes were removed in all 612 patients except for three cases. Unlike other patients, in these three cases, the chest tubes output was increased to an average of >500 mL until the fifth postoperative day.

Postoperative Case Presentation

The first case was a 72-year-old male with adenocarcinoma at the distal third of the esophagus who was operated on in September 2010. For this case, no neoadjuvant therapy was performed.

The second case was a 62-year-old female with adenocarcinoma in the distal third of the esophagus who was operated on in March 2018. In this case, there was a six-month interval between neoadjuvant therapy and surgery.

The third case was a 71-year-old male suffering from poorly differentiated squamous cell carcinoma at the middle third of the esophagus who was operated in January 2019. Also in this case, there was an interval of 42 days between neoadjuvant therapy and surgery.

In the first and third cases, chylothorax was identified on the right side, and in the second one, it was on the left side. Color of the secretions was serosanguinous in all cases in the early phases. In all cases, the triglyceride level of the secretions was <110 mg during the early phases. In all cases, after initiation of enteral feeding via Jejunostomy tube, the color of the chest tube secretions changed to milky, which confirmed post-esophagectomy chylothorax. Therefore, conservative route was chosen as the initial treatment. Our conservative treatment plan was keeping NPO and total parenteral nutrition (TPN) as well as medication therapy with octreotide. As a result, feeding on jejunostomy tube was discontinued and TPN started via central venous catheter. Unfortunately, it was not successful at either of the cases and we had to operate all three cases.

A second surgery was performed in all three cases via right posterolateral thoracotomy. Olive oil was given via jejunostomy tube during operation to facilitate perfect visualization of the thoracic duct and identify chyle leakage.

In the first and third cases, where leakage was from the right side, the chyle leak was seen obviously as soon as the gastric conduit was set aside from the vertebral column. The leakage location was approximately 4-5 cm below the azygos arch. After identifying the exact location, mass ligation was performed with 00 silk suture 2-3 cm below the leakage site, which immediately resulted in elimination of chyle leak. Before closing the chest cavity, another dose of olive oil was given through the jejunostomy tube, and the chest cavity was closed after reassuring that the leak was discontinued.

In the second case, the leak was from the left side and obvious chyle leak was seen from the hiatus without prominent duct. Despite mass ligation by suture several times with 00 silk, no significant reduction occurred. After mechanical abrasion with gauze and chest tube insertion, the thoracic incision was closed.

Postoperative Period of the Second Operation

First Case

Chest tube drainage reduced significantly in the first patient who had right side leakage. Although the patient had a semi-liquid diet, maximum chest drainage was 200 mL of serosanguinous fluid after five days. Therefore, the chest tube was removed on the fifth day after the second surgery.

The patient became dyspneic two days after chest tube removal. Chest X-Ray showed pleural effusion with right lower lobe collapse. Therefore, once again a chest tube was inserted and 400 mL serosanguinous fluid evacuated from the pleural space. Although the patient had a semi liquid diet, the color of the secretions was serosanguinous. The triglyceride level of fluid and albumin level of serum were 12 mg/dL and 2 gr/dL, respectively. Despite continuing feeding from jejunostomy tube, chest tube output decreased to <150-200 cc/24 h compared to the first day. In spite of reduced output, we did not remove the chest tube for reassurance. The patient gradually progressed to respiratory distress. Due to deterioration of his respiration, chest CT-SCAN was performed that showed air bronchogram in the

right lower lobe without any significant pleural effusion. Despite the administration of continued intravenous antibiotics, the patient's condition deteriorated, and atrial fibrillation was added to his problems. Therefore, we had to intubate the patient and return him to the intensive care unit. Unfortunately, his condition deteriorated gradually, and he was deceased after three days.

Second Case

After the operation, the output of the left side chest tube reduced in this patient, but her right chest tube output increased nearly 1000 mL daily and became milky. In other words, the side of chylothorax was changed. We managed conservatively two days without any reduction in chest tube output; therefore, the patient was scheduled for another operation.

Due to the failure of the second surgery from the right side, the third operation was done from the left side. Left posterolateral thoracotomy was done from seven intercostal space. Unfortunately, we were faced with a scenario like the previous operation. The chyle was boiling from hiatus without obvious duct. It seemed that the chyle originated from the abdomen. Therefore, we did mass ligation that was not successful and the chest was closed after chest tube insertion. After the operation, the patient was transformed to intensive care unit. Unfortunately, not only did her chest tube output remain unchanged but also her condition deteriorated and she died after two days as a result of respiratory failure.

Third Case

The third patient had eventless post-op, and chest tube drainage reduced dramatically in him. Semiliquid diet was started on the third day after operation. Chest tube drainage was not significant, and chest-X-ray showed full lung expansion. Therefore, we removed the chest tube and the patient was discharged on fifth day after the second operation. During the nine month follow up, the patient showed no problems.

DISCUSSION

Chylothorax is among the deadly complications of esophagectomy, especially in those who are subject to it for the treatment of esophageal cancer. Although it may have a low incidence, chylothorax is associated with high mortality and morbidity rates (4,8). The chance of death in patients with chylothorax is increased fivefold during hospitalization and remains high until the 30th day after surgery. The mortality rate is also significantly high over 90 days after esophagectomy (9,11-13). In our study, we lost two out of three patients (mortality rate of 66%).

Risk Factors

Although chylothorax can occur following any type of cardiothoracic surgery, the close association of the thoracic duct with the esophagus can cause accidental damage to the thoracic duct and increase the incidence of chylothorax in esophagectomy (8,11,14). In other words, lack of visualization of the thoracic duct and its proximity to thoracic esophagus is the major cause of iatrogenic injury during surgery that can lead to chylothorax (9).

Another controversial issue is that the incidence of this complication has not been determined accurately and that there are major differences between various reports in this regard (8,12,13,15,16). There is considerable difference between studies regarding the reports of post- esophagectomy chylothorax, with low incidence in our patients but higher prevalence reported in other studies (2,17). In addition, there are no documented risk factors for post-esophagectomy chylothorax, although several issues have been addressed in this respect (3).

Many studies have identified squamous cell carcinoma (SCC) as one of the risk factors of chylothorax (9,12,16,18,19). SCC often causes lesions in the middle part of the esophagus that is close to the thoracic duct (12,20). A possible explanation is that in the thoracic cavity, the thoracic duct is completely in contact with aorto-oesophageal groove, where in the midline position at the level of thoracic vertebrae T4 to T6, it crosses from the right side to the left hemithorax (9,21). Surgical manipulation in these areas can increase the possibility of damage to the thoracic duct. However, in the present study, most cases were SCC patients, and out of three cases of chylothorax, only one was afflicted with SCC. It can be concluded that the low incidence of chylothorax in our study does not support the results of previous investigations.

Du et al. (4). and Shah et al. (9) in separate studies have reported that in addition to SCC, tumor location, tumor staging, and nodal status will increase the likelihood of chylothorax since they are associated with difficulty in surgery. The reason for the association between the stage of tumor and increasing risk of chylothorax is that the thoracic duct is more likely to be subjected to mechanical damage in more advanced tumors where the lymph node involvement is wider, requiring further dissection and lymphadenectomy (3,4). However, C. Bolger et al. (11), Batol et al. (1) and Hou et al. (22) have stated that they found no significant effect of tumor location, tumor pathology category, TNM stage and histology type on post-esophagectomy chylothorax. In the present study, all three chylothorax cases had operable tumors. In the last two cases, we performed endoscopic ultrasound, which indicated a locally advanced stage; therefore, we scheduled them to preoperative chemo-radiotherapy. It should be noted that we did not perform neoadjuvant therapy in the first case because we did not have access to endoscopic ultrasound, and due to the absence of screening tools in our country before 2011, diagnosis of esophageal cancer in T1 N0M0 was unusual. In general, from the viewpoint of tumor stage, some cases were locally advanced, but all 612 patients were operable.

Another controversial issue about predisposing factors is the type of surgical procedure, namely transthoracic versus transhiatal (7). Rationally, in transthoracic approaches such as Ivor Lewis and Mckeown surgical procedures, if prophylactic thoracic duct mass ligation is done, it is expected that the occurrence of chylothorax should be lower than transhiatal operation that is nearly blind (23). However, reported documents show controversial issues (7,18,23-26). In this regard, Tsoon et al. (5) have reported 14 cases (9%) of chylothorax out of 155 transthoracic esophagectomies. In a study by Stefano et al. (23), it has been reported that the incidence of chylothorax in patients operated through a transthoracic approach was 1%, while in transhiatal esophagectomy, there was 1.3% prevalence of chylothorax. Kranzfelder et al. (8), Gupta et al. (12) and Varshney et al. (19) have also suggested that the type of surgery has no effect on chylothorax.

Body mass index (BMI) is another issue addressed as a risk factor for this complication. In various studies, BMI< 25-30 is considered as a predisposing factor (1,4,9,18). The reason for this may be that during surgical manipulation, the adipose tissues around the thoracic duct prevents it from damage (18).

Since in patients with BMI> 25, the passage of fingers from two hands in the hiatus and neck surgical site is difficult, in the present study, only the patients who had BMI< 25 were selected for transhiatal surgery.

Diagnosis of Post-esophagectomy Chylothorax

Accurate diagnosis of the cause of chylothorax is the key to determining the ideal course of treatment for each individual. Since chyle is rich in lymph and free of fatty acids, chylothorax can rapidly lead to severe nutritional and immune disorders, necessitating immediate closure of the leak site (2).

One of the distinctive signs of post-surgical chylothorax is chest tube output. The increase of which must arouse suspicion of chylothorax (1,27,28). In a study by Batol et al. (1), a significant increase has been found in secretions in the group that had chylothorax. They have also suggested that an increase in chylothorax secretion from day four to >100 mL could be associated with a high rate of chylothorax occurrence. Shah et al. (9) have also claimed that a high suspicion of chylothorax in patients with chest drainage exceeding 4 mL/kg (400 mL) may be useful for early diagnosis of chylothorax, despite the appearance of drainage. In the present study, in all three cases, chest tube output was significantly higher than other cases and reached an average of >500 mL until the fifth postoperative day, which increases the suspicion of chylothorax and denotes the importance of the chest tube borderline laboratory tests.

Another golden clinical clue in the diagnosis of chylothorax is the changing color of the chest tube secretions to milky after starting enteral feeding orally or via jejunostomy tube that leaves no doubt about the diagnosis (2,18,29). On the other hand, it must be remembered that although massive milky pleural effusion in a post-esophagectomy patient confirms the diagnosis of chylothorax, the absence of it does not rule out the diagnosis of chylothorax (2,28), especially in NPO patients (30). Similar to the report of Stefano et al. (23), in our study, the drainage of chest tube in all cases during the primary phase had serosanguinous appearance and showed ambiguous laboratory results that were common; however, it changed to milky color after the start of enteral feeding. In other words, it should be noted that liquid color is merely a subjective assessment that must not be invoked for an accurate diagnosis (28) because it can be deceptive. Although the milky appearance of secretions can confirm the diagnosis, only half of the cases show a classic milky appearance of the chest drainage (8,18,30).

In laboratory reports, triglyceride (TG) levels are used as a simple screening test to detect chylothorax. In assessing triglyceride levels, if TG level is >110 mg/dL, the chances of not having chylothorax in the patient is <1%; if TG level is <50 mg/dL, the probability of chylothorax is <5%; and in the borderline values, measurement of chylomicron level is recommended (5,18,26,29,30). In the present study, TG level in the primary phase among all three cases was <110 mg/dL, which may be due to fasting of our patients during examination or low laboratory sensitivity. However, after the appearance of profuse milky outputs of chest tubes, there was no doubt about the diagnosis.

Clinical suspicion is an important factor in the diagnosis of chylothorax, especially in the early phase of the disease when the patient is fasting. Therefore, patients with prolonged and profuse postoperative pleural effusion should be carefully monitored. If pleural effusion due to chylothorax is suspected, fluid analysis should be performed and repeated if still suspected (8,26).

In addition to chest CT-scan, lymphangiography is another way to determine the exact location of the chyle leak, which could also be used as a conservative therapeutic technique (13,19,31,32). However, lymphangiography is not widely used as a clinical routine, particularly in postoperative cases (8,30).

Treatment for Post-esophagectomy Chylothorax

Rapid loss of chyle can lead to systemic hypovolemia, respiratory disorders, and malnutrition. In addition, significant loss of immunoglobulins, T lymphocytes and proteins can cause immune compromise and ultimately will develop the risk of infectious disorders, including pneumonia. All of the above mentioned facts denote the importance of effective treatment (5,9).

Management of chylothorax may be conservative or surgical. Conservative treatment consists of administration of octreotide

and etilefrine (33), nutritional support (13,34,35), drainage of pleural space and lung expansion (13), and reduction of chyle production with the hope of spontaneous closure (2,13).

Drainage of the pleural cavity plays a key role in measuring the output of chyle as well as resolving and preventing respiratory complications by assisting in lung expansion and in closure of leakage (21,30,36). Meanwhile, in post-surgical patients who have already had a chest tube, loculated collections should be drainages (37). After resuscitation, drainage of the pleural space and full expansion of the lungs are the next priorities for the reduction of chyle (30). We did chest CT-SCAN in all three cases for exploring the collection in a hidden area of the chest.

Keeping NPO and TPN is a time-honored early treatment for post-surgical chylothorax with variable success rates (21,30,34,35,38), and it was our primary treatment plan. As an adjunctive to TPN and fasting, somatostatin and its analogs such as octreotide have been suggested by some authors (13,14,21,30,31), and we administrated it in two patients without a successful outcome. In a study, P. Guillem et al. (33) have claimed that etilefrine infusion could cease chyle flow in a few days.

The most important issue in conservative treatment is how long it must be continued before reoperation. In other words, should all post-surgical chylothorax patients be prescribed with a single treatment plan?

Traditionally, TPN and conservative management of chylothorax must continue for two weeks (39), but it has been questioned by some authors (13,18,21,23), particularly when the output of the chest heralds that spontaneous closure is uncertain (18) as in our patients who all had more than 500 mL daily output and none of them responded to conservative treatment.

Surgery is the mainstay of treatment if conservative treatment goes wrong, and it should be done as the primary treatment when data such as volume of chylothorax fades spontaneous closure with a high percentage of success (2,21,23).

Surgery can be done through a thoracoscopic or thoracotomy (10,13,21), although the studies have not stated variation in success results for thoracoscopic vs. thoracotomy (10). In the present study, in all three cases, we performed open thoracotomy following failure of conservative treatment.

A questionable matter about surgical approach is the side of the operation, especially when the culprit side is in the left hemithorax (36). Because of the proximity of the thoracic duct to the right side of vertebral column, its ligation from the right hemithorax is easier than left hemithorax (21). This may lead the surgeon to operate on the right hemithorax for ligation of the thoracic duct despite the fact that chylothorax is in the left side as practiced by us for one of the patients.

For better visualization of leakage and injured thoracic duct, it is recommended that just before starting the operation, fatty liquid diet be given enterally, and we gave olive oil for all our patients (4,30).

During surgery and after exploring the chest cavity, the best scene for the surgeon is obvious leaking in the path of the thoracic duct. In these conditions, the best approach is the direct ligation of the thoracic duct with surrounding tissue (2,26), as practiced in two of our patients. If the location of the leak is not directly identifiable during the operation, the recommended approach in this situation is supradiaphragmatic mass ligation of the thoracic duct where it enters the thoracic cavity (26). If the intervention is successful, the leakage will stop instantly and does not increase despite giving oils such as olive via jejunostomy tube or nasogastric tube as was done in two cases of the present study in whom leakage was obvious 3-4 cm below the azygous arch. Mechanical pleurodesis is usually done at the end of the operation (2). Failure of ligation is the worst event for the surgeon as it may be apparent during surgery or in postoperative period with increasing chest tube output. The pleuroperitoneal shunt has been suggested by some authors with questionable results pertaining to the manipulation of the peritoneum during the first operation (2).

CONCLUSION

Chylothorax remains a challenging and potentially life-threatening postoperative complication after esophagectomy. However, the key to preventing high mortality rates can be the identification of risk factors as well as timely detection of symptoms and proper management. According to the results of the present study, consistent with previous studies, it can be concluded that if the drainage discharge is more than 500 mL on the fourth or fifth days post-surgery, there is a suspicion of chylothorax, and fluid analysis must be immediately performed to avoid delay in diagnosis. Besides, early surgical intervention and thoracic duct ligation should be considered to prevent early complications of chylothorax and avoid the increase of mortality rates, especially when data such as volume of chylothorax fades spontaneous closure with a high percentage of success.

Ethics Committee Approval: This study was approved by Urmia University Medical Sciences Research Ethics Committee (Decision no: IR.UMSU.REC.1401.324, Date: 02.11.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – RM; Design – RM, AY; Supervision – RM; Data Collection and/ or Processing – RM, AY; Analysis and/or Interpretation – RM, AY; Literature Search – RM, AY; Writing Manuscript – RM, AY; Critical Reviews – RM.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2022; 38 (4): 401-408

Ondokuz yıllık transhiatal özofajektomide şilotoraks ensidansı: Olgu serisi ve inceleme çalışması

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ÖZET

Giriş ve Amaç: Şilotoraks (CTx), lenfatik sıvının plevral boşlukta sızması ve birikmesidir. CTx ensidansı özofajektomi sonrası en yüksek orana sahiptir. Bu çalışmanın amacı, özofajektomi sonrası şilotoraksın risk faktörleri, tanı ve yönetimi açısından gözden geçirildiği 19 yılda yapılan 612 özofajektomiden üç tanesini sunmayı amaçladık.

Gereç ve Yöntem: Çalışmaya 612 hasta dahil edildi. Tüm hastalara transhiatal özofajektomi uygulandı. Üç olguda şilotoraks saptandı. Her üç olguda da şilotoraksın yönetimi için sekonder cerrahi uygulandı. Sağ taraftan kaçak olan birinci ve üçüncü olgulara kütle ligasyonu uygulandı. İkinci olguda, sızıntı belirgin bir kanal olmadan sol taraftandı ve birkaç kez yapılan kütle ligasyonuna rağmen şilde önemli bir azalma gözlenmedi.

Bulgular: İlk olguda, sızıntı azalmasına rağmen, hasta yavaş yavaş solunum sıkıntısına ilerledi. Hastanın durumu zamanla kötüleşti ve üç gün sonra hasta kaybedildi. Üçüncü ameliyat gerektiren ikinci olguda ise hastanın durumu kötüleşti ve iki gün sonra solunum yetersizliği nedeniyle hayatını kaybetti. Üçüncü hastada ameliyat sonrası iyileşme görüldü. Hasta ikinci ameliyatının ardından beşinci günde taburcu edildi.

Sonuç: Özofajektomi sonrası şilotoraksta, yüksek mortalite oranlarını önlemenin anahtarı, risk faktörlerinin yanı sıra semptomların zamanında saptanması ve uygun yönetimi olabilir. Ayrıca şilotoraksın erken komplikasyonlarını önlemek için erken cerrahi müdahale düşünülmelidir.

Anahtar Kelimeler: Şilotoraks, transhiatal özofajektomi, post-özofajektomi şilotoraks

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CASE REPORT
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Treatment conundrums in osteosarcoma of the breast: Case report of two cases from a tertiary care cancer center in India

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ABSTRACT

Extraosseous sarcoma of the breast is an infrequent entity and a harbinger of poor prognosis. Histogenesis of this tumor is uncertain, and it can arise both in denovo and metastatic settings. Morphologically, it is indistinguishable from its skeletal counterpart and clinically, it presents like any other subtype of breast cancer. Tumor recurrence with a propensity for hematogenous rather than lymphatic spread plagues with this malicious disease. Treatment guidelines are mainly extrapolations from those of treatment of other extra-skeletal sarcomas as literature is limited in this context. In this study, it was aimed to present two clinical cases with similar clinical profiles and different treatment outcomes. The intent of this case report is to contribute to the limited database available for management of this rare disease.

Keywords: Extraosseous, breast carcinoma, osteosarcoma, chemotherapy, sarcomas, mesenchymal

INTRODUCTION

Mammary osteosarcoma represents less than 0.1% of all breast tumors and 12% of all breast sarcomas (1). They are subcategorized in the group of mesenchymal tumors as per the World Health Organization classification of tumors of the breast (1). Osteosarcomas of the breast arise primarily in the breast or rarely as metastasis from a primary bone sarcoma. They occur almost exclusively in women with a reported median age of 64.5 years unlike bone sarcomas which occur at a much younger age. Literature search revealed that these cases are infrequently reported as case reports except a detailed retrospective clinicopathologic analysis of 50 cases (2). Diagnostic dilemmas and lack of treatment guidelines surround this rare entity and justify the reporting of these cases.

CASE REPORT

Clinical Case 1

A 55-year-old female presented to our hospital in her postoperative period in November 2012. She gave a history of lumpectomy of the left breast. She had first noticed the mass two months previously. Her medical and family history was unremarkable. She had been evaluated at an outside oncology facility and had undergone lumpectomy for the breast lump. The histopathological report had given differentials of metaplastic carcinoma versus osteogenic sarcoma. She came to our center for further management. A mammographic re-review revealed a BIRADS IV lesion (Figure 1). Confirmation of the histopathological diagnosis was done performing immunohistochemistry (IHC) with pan-cytokeratin (CK) and epithelial membrane antigen (EMA) on the submitted blocks. Definitive diagnosis of osteosarcoma was made as both these markers failed to be highlighted. The hormone profile and human epidermal growth factor receptor-2 (HER2) testing revealed the disease to be triple negative breast cancer (TNBC). After due discussions with the family and in the multidisciplinary tumor board, it was decided to do a simple mastectomy keeping in view the unclear margin status and also keeping her in close

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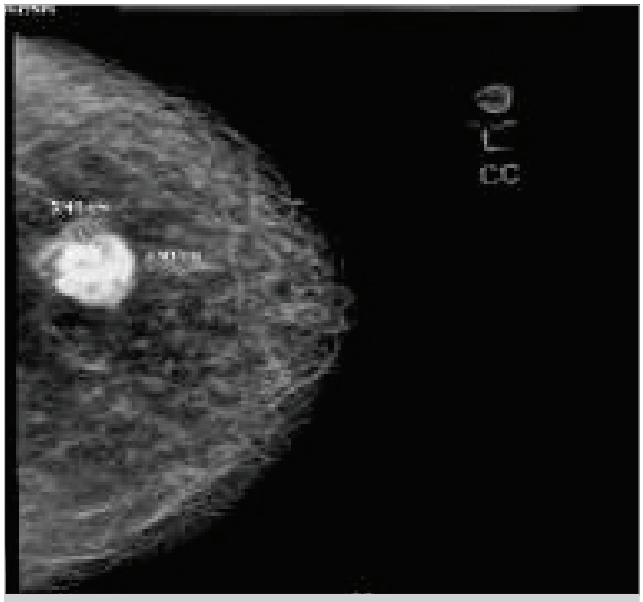

Figure 1. (Case 1) Mammogram of left breast showing a well circumscribed mass with prominent calcifications.

follow up (for six months). Adjuvant therapy was not considered necessary in the presence of adequate local control and the absence of metastatic disease. Interim metastatic evaluations using positron emission tomography and computed tomography (PET-CT) showed her to be well without any tumor recurrence at 52 months.

Clinical Case 2

Another 54-year-old diabetic and hypertensive female presented in August 2015 with complaints of lump in the left breast for 1.5 months duration. She had unremarkable family history and gynecologic history. There was no history of radiation exposure, birth control or hormone replacement therapy. On clinical examination, the patient had a hard palpable, 3x2 cm lump in the upper quadrant of left breast with no palpable axillary nodes. Mammography revealed the mass to be a BIRADS IV disease (Figure 2). Fine needle aspiration cytology from the lesion was inconclusive. Ultrasound guided biopsy from the left breast confirmed the lesion to be malignant with suggested differentials of metaplastic carcinoma and osteosarcoma. The patient underwent breast conservative surgery with left axillary nodal dissection. Histopathological examination showed marked proliferation of neoplastic spindle cells with extensive osteoid deposition (Figure 3). Other notable features included

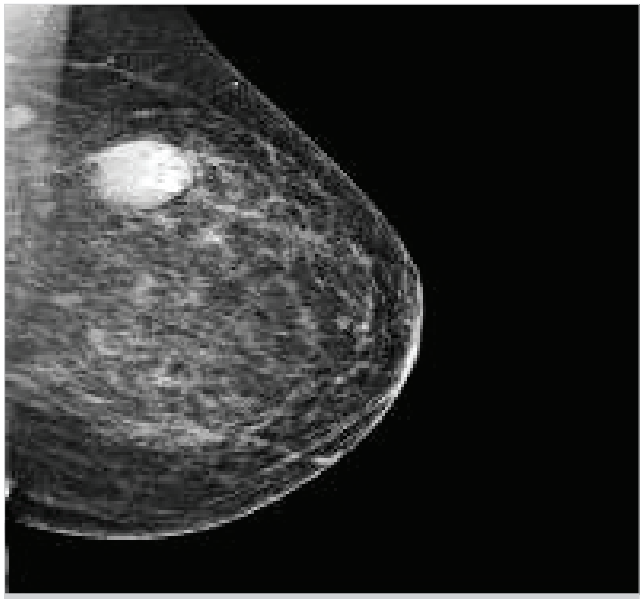

Figure 2. (Case 2) Mammogram of left breast showing a well-defined oval mass in the upper outer quadrant with indistinct margins and foci of calcification.

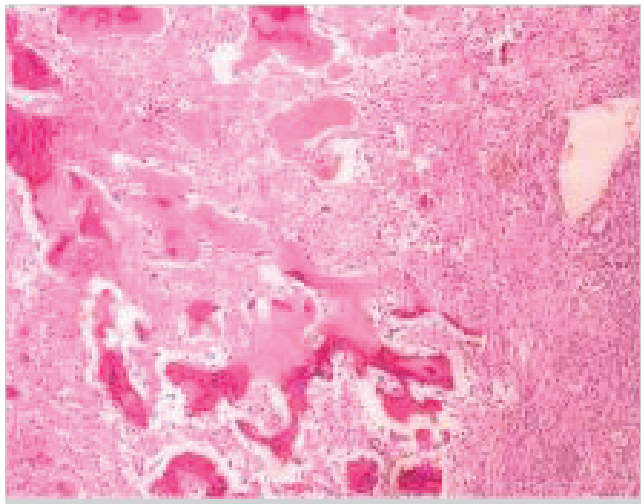

Figure 3. Proliferation of neoplastic spindle cells with extensive osteoid (arrow) deposition (H&E; X10 magnification).

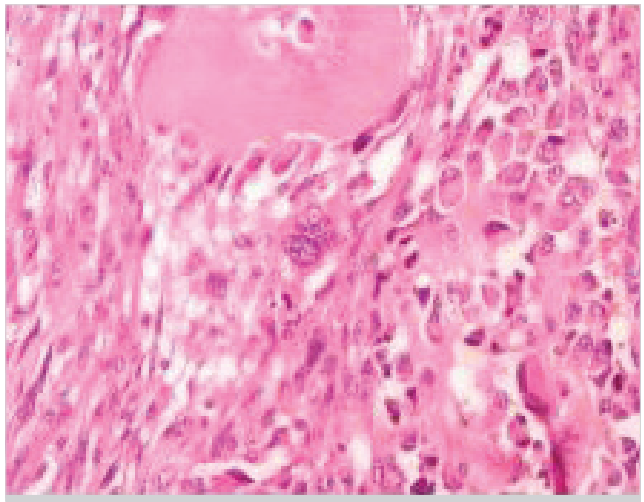

Figure 4. Plump spindle to epithelioid neoplastic cells with high grade nuclear atypia, mitosis (thin arrow) and tumor giant cell (thick arrow) (H&E; X40 magnification).

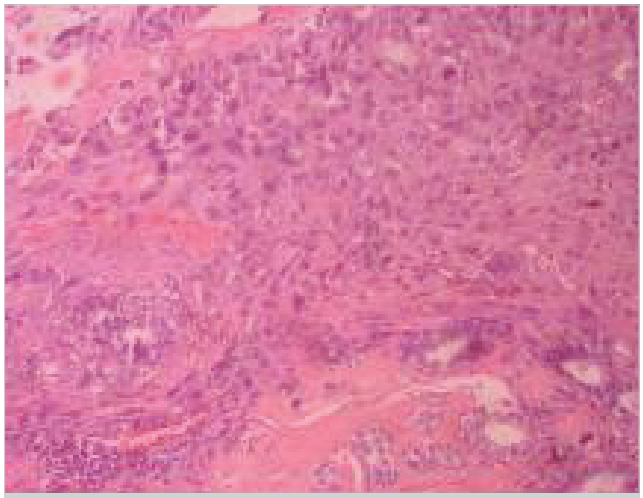

Figure 5. Cytokeratin (CK) highlights the entrapped normal duct while the tumor cells are negative (IHC stain; x20 magnification).

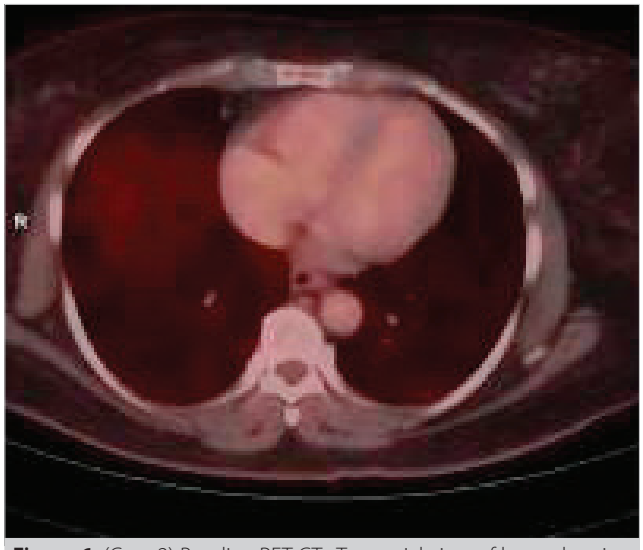

Figure 6. (Case 2) Baseline PET CT : Transaxial view of lung showing no metabolically active lesions.

high grade nuclear atypia, mitosis and tumor giant cells (Figure 4). Extensive sampling was done for evidence of ductal carcinoma in-situ which was absent and confirmed by ancillary testing with CK and EMA (Figure 5). Hormone receptor and HER2 testing showed the disease to be TNBC. After having explained the nature of the disease and intent of the treatment, she was started on ifosphamide, adriamycin and paclitaxel based chemotherapy (CT). The chemotherapy plan was changed post 2 cycles to ifosphamide and adriamycin due to gastrointestinal intolerance. She completed six cycles of CT in January 2016. Both interim and post treatment PET-CT showed her to be disease free (Figure 6). A follow-up evaluation in February 2017 showed progressive disease in the right lower lobe of the lung (Figure 7). She was further offered metastasectomy and palliative CT with six cycles of ifosphamide and paclitaxel. The patient completed treatment and achieved a complete response in July 2017, following which she is now on a six-monthly follow-up. A telephonic update in March 2018 revealed the patient to be alive with no evidence of disease at eight months.

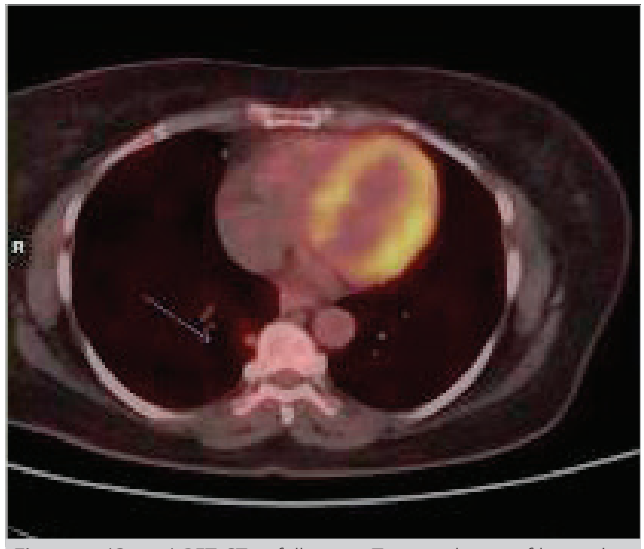

Figure 7. (Case 2) PET CT at follow up: Transaxial view of lung showing metabolically active lesion(0.7cm x 0.7cm) in right lower lobe lung.

DISCUSSION

Mammary osteosarcomas are highly aggressive lesions, and uncertainty exists regarding their histogenesis and optimal therapy. Clinical presentation, though not specific for this subtype, presents as a hard palpable mass without axillary lymphadenopathy (3). Though most cases arise denovo, radiation has been elucidated as a possible predisposing factor.

Mammography at diagnosis may or may not show microcalcifications, and a radiological presentation as a well circumscribed lesion can mimic a fibroadenoma (4). Preoperative diagnosis is difficult, and complete histomorphological confirmation after surgical resection remains the mainstay. The most common differential diagnosis includes metaplastic carcinoma, phyllodes tumor with osteosarcomatous differentiation. IHC using CK will help establish epithelial differentiation in the spindle cells, and it would rule out the possibility of primary osteosarcoma (5). Other noteworthy histological findings include spindle to epithelioid neoplastic cells with high grade nuclear atypia, mitosis (Figure 2), tumor giant cells, and extensive osteoid.

Long term prognosis is difficult to ascertain as there is limited literature. The literature shows an overall five-year survival of 38%, with 28% of the patients developing local recurrence and 41% metastasis (2). There is higher propensity for hematogenous dissemination to the lungs, bones and liver (6). Till date, there are no validated treatment guidelines but the best approach documented for localized disease is wide local excision or mastecto-

my with negative resection margins as margin involvement is a major factor in local recurrence (6). Axillary lymph node removal is optional as these tumors do not spread through lymphatics. It has been observed that specific data on the role of adjuvant chemotherapy and radiotherapy is absent, so extrapolation of treatment data from skeletal osteosarcomas and other extraosseous sarcomas can be done. Polychemotherapy using methotrexate, cisplatin, ifosphamide, adriamycin and paclitaxel have been shown to improve survival in osteosarcoma bone and similar observations have been documented in short reports of osteosarcoma breast. Postoperative radiotherapy is advisable in cases where tumor free margins are not obtained (7,8).

CONCLUSION

We reported two cases of osteosarcoma breast which, though being matched for age, stage and hormone receptor status, responded very differently to therapy. The patient who received a single modality of treatment i.e. surgery is alive without any evidence of disease at 52 months in contrast to the patient who received a multimodality treatment including surgery, adjuvant therapy and presented with distant metastasis at 12 months. Our cases highlight the treatment conundrums surrounding the treatment of osteosarcoma breast. More research is needed to understand the biology of this disease and explain the arising controversies. Due to its rarity, we have started pooling tissues in our tissue bank to conduct further molecular research.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – DCD; Design – DCD; Supervision – DCD; Materials – PG; Data Collection and/ or Processing – JT, GG; Analysis and/ or Interpretation – JT, SP; Literature Search – KDC; Writing Manuscript – JT; Critical Reviews – DCD.

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OLGU SUNUMU-ÖZET
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Meme osteosarkomunda tedavi açmazı: Hindistan'daki üçüncü basamak kanser merkezinden iki olgu sunumu

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ÖZET

Memenin ekstraosseöz sarkomu nadir görülen bir durumdur ve kötü prognozun habercisidir. Bu tümörün histogenezi belirsizdir ve hem denovo hem de metastatik ortamlarda ortaya çıkabilir. Morfolojik olarak iskelet benzerinden ayırt edilemez ve klinik olarak meme kanserinin diğer herhangi bir alt tipi gibi ortaya çıkar. Lenfatik yayılımdan ziyade hematojen yayılım eğilimi olan tümör nüksü, bu kötücül hastalıkta sorun yaratır. Literatür bu bağlamda sınırlı olduğundan, tedavi kılavuzları esas olarak diğer iskelet dışı sarkomların tedavisinden ekstrapolasyonlardır. Bu çalışmada benzer klinik profillere ve farklı tedavi sonuçlarına sahip iki klinik vaka sunulması amaçlandı. Bu olgu sunumunun amacı, bu nadir hastalığın tedavisi için mevcut sınırlı veri tabanına katkıda bulunmaktır.

Anahtar Kelimeler: Ekstradosseöz, meme karsinomu, osteosarkoma, kemoterapi, sarkomalar, mezenkimal

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CASE REPORT
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Gardner's syndrome: Simultaneous diagnosis and treatment in monozygotic twins

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ABSTRACT

Gardner's syndrome (GS) is a very rare autosomal dominant multisystem disease. Osteomas, skin and soft tissue tumors are present with gastrointestinal polyposis. The polyps have very high malignancy potentials. If prophylactic resection is not performed, colorectal cancer development is inevitable in all patients with GS. Polyposis is usually asymptomatic. Therefore, careful evaluation of extraintestinal findings of the disease is very important for early diagnosis. In this article, diagnosis and treatment of GS are presented in monozygotic twins, which have not been previously described in the literature. The diagnostic process, which started with dental complaints of one case, was carried out in an effective manner and then, prophylactic surgery was performed in twins. This article aimed to make clinicians and dentists attentive for early diagnosis of disease and to review treatment options.

Keywords: Gardner syndrome, twins, intestinal polyposis, osteoma, colorectal neoplasms

INTRODUCTION

Gardner's Syndrome (GS) is an autosomal dominant disorder considered to be a subtype of familial adenomatous polyposis (FAP). Typically, polyposis coli is accompanied by bone and mesenchymal tissue neoplasms, such as osteomas, lipomas, fibromas and desmoid tumors (1). Colon polyps are frequently asymptomatic and have high potential for malignant transformation. Therefore, early diagnosis and treatment of the disease are very important (2). In clinical practice, skeptical approach to the disease is valued in terms of the prevention of polyposis leading to colorectal cancer by prophylactic surgical procedures and the detection of other gastrointestinal malignancies, bone, soft tissue and thyroid tumors that may accompany this syndrome. In the literature, GS is usually presented as a single case or as few unrelated cases. In this article, it was aimed to draw attention to this rare disease by presenting simultaneous diagnosis and treatment in monozygotic twins. Written consent was obtained from the patients and their families for the use of medical data.

CASE REPORT

Case 1

A 16-year-old male patient born as a monozygotic twin. In the panoramic X-ray image of the patient who applied to the dentist with various dental problems, a lesion was seen in the jawbone. He was referred by the dentist to the head and neck surgery department. Maxillofacial computed tomography (CT) examination revealed a sclerotic lesion compatible with osteoma with exophytic, partially lobulated contour, measuring approximately 17 mm in diameter (Figures 1,2). Facial magnetic resonance (MR) examination showed a 17x12 mm sized low-weighted signal with no contrast enhancement in the lateral part of the left mandibular ramus (Figure 3). It was thought that the lesion originated from the left mandibular ramus and had cortex continuity with the left mandibular ramus cortex, and was considered to be compatible with the osteoma. It was learned that the patient had intermittent diarrhea and abdominal pain for about a year. Colonoscopic examination was

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performed by gastroenterology. A few mucosal polyps with diameter less than 5 mm were detected in the rectum, while approximately 30-35 polyps were found in all of the other colon segments. All segments were pathologically sampled via biopsy and snare polypectomy. Colonic polyps were adenomatous polyps with mild and severe dysplasia, rectal polyps were adenomatous polyps with mild dysplasia. Adenomatous polyposis coli (APC) gene mutation test revealed heterozygous mutant. In systematic examination, a rigid and immobile mass, approximately 2x2 cm in diameter in the left mandible was revealed. A subcutaneous lipomatous mass approximately 2x2 cm in diameter was found in the left lumbar region. There was no disease in family history. The patient's laboratory parameters, eye examination and thyroid ultrasound (US) were normal. We performed rectosigmoidoscopy and did not see any other polyp in the rectum. Upper gastrointestinal system endoscopy, small bowel passage examination and abdominal MR showed no pathological findings. Total colectomy and ileorectal anastomosis were performed after giving information about treatment options to the patient and his family. The patient was discharged without any problems on the 7th day after the operation.

Case 2

The patient, who is the monozygotic twin brother of first case, did not have any complaints. A panoramic X-ray was taken because of the detection of an osteoma-like lesion in his twin. The findings were similar. Therefore, the twins were examined simultaneously. In maxillofacial CT examination, minimal expansive sclerotic patch lesions were observed in the anterior of both mandibular corpora. In addition, a sclerotic lesion compatible with 15 mm diameter osteoma was observed in the left mandibular ramus (Figures 1,2). Facial MR examination revealed multiple, bilateral sclerotic lesions in the mandible hemispheres. This image was mostly interpreted as osteomas leading to the enlargement of the left mandibulae (Figure 3). Unlike his twin, he had no intestinal or abdominal complaints. Colonoscopy revealed several polyps in the rectum, and about 20-25 polyps in the other colon segments. All segments were pathologically sampled. Rectal polyps were diagnosed as mild dysplastic adenomatous polyps, whereas polyps in other colon segments were adenomatous polyps containing high dysplasia. Adenomatous polyposis coli (APC) gene mutation test revealed heterozygous mutant. On systemic physical examination, a rigid, fixed lesion was found in the left mandibular region about 1.5x2 cm in diameter. Like this, two smaller diameter lesions with the same features were also found in the right mandible. In addition, fibro-lipomatous lesions of approximately 1x1 cm in diameter were detected in the posterior region of the neck and inferior region of the left scapula. The patient's laboratory parameters, eye examination and thyroid US were normal. We performed rectosigmoidoscopy and did not see any other polyp in the rectum. Upper gastrointestinal system endoscopy, small bowel passage examination and abdominal MR showed no pathological findings. The patient was treated with the same surgical procedure on the same day as his twin. When the lumen of the colon was opened, millimeter-diameter polyps were observed. Both were discharged on the 7th day of surgery. Close follow-up was planned with the attendance of periodic physical examination, rectoscopy, gastroduodenoscopy and radiological imaging.

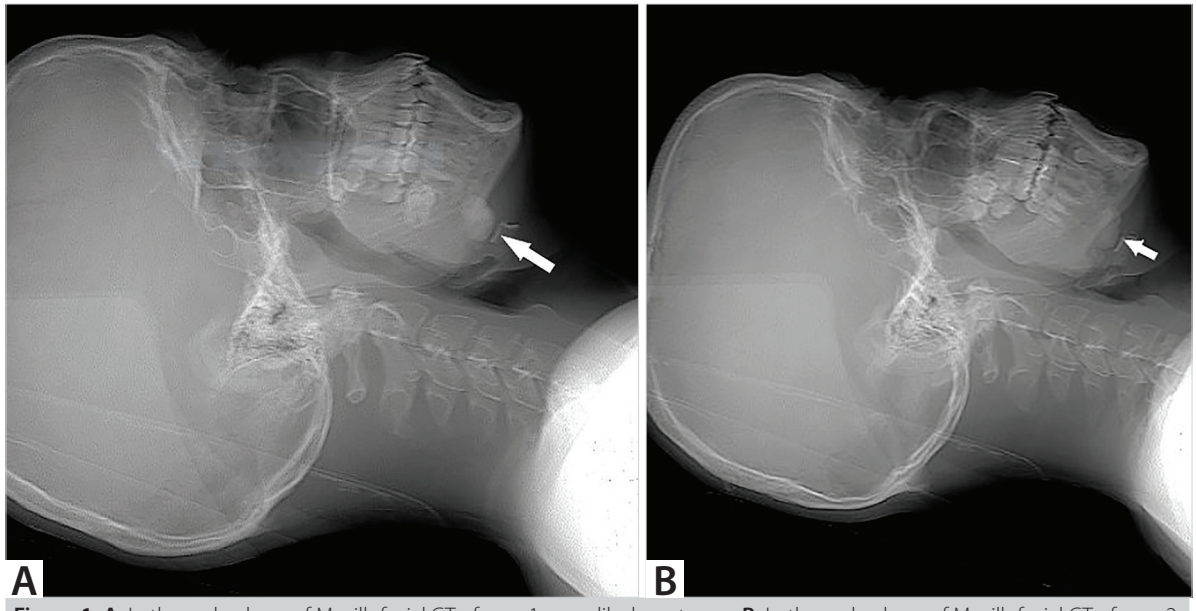

Figure 1. A. In the early phase of Maxillofacial CT of case 1, mandibular osteoma **B.** In the early phase of Maxillofacial CT of case 2, mandibular osteoma.

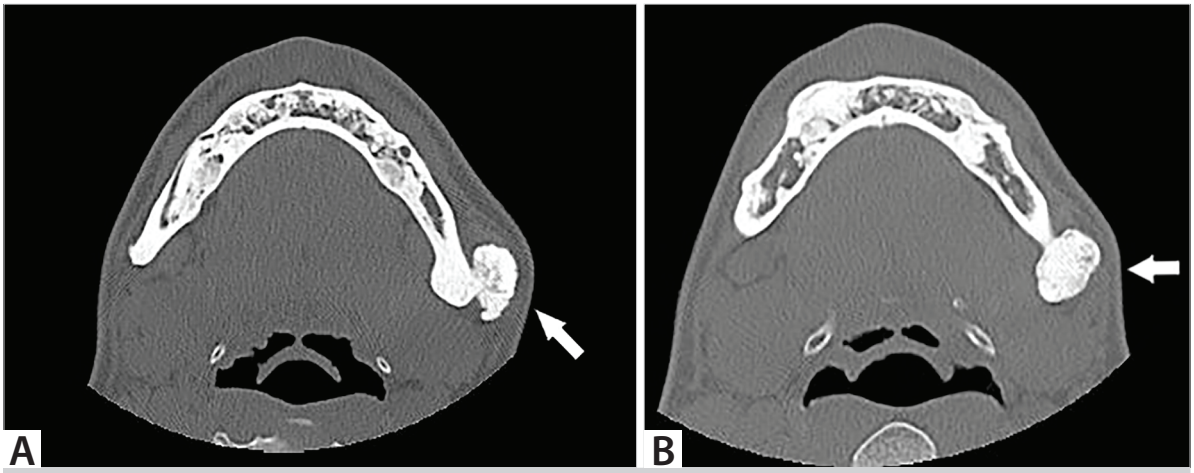

Figure 2. A. Left mandibular osteoma in Maxillofacial CT of case 1, **B.** Left mandibular osteoma in Maxillofacial CT of case 2.

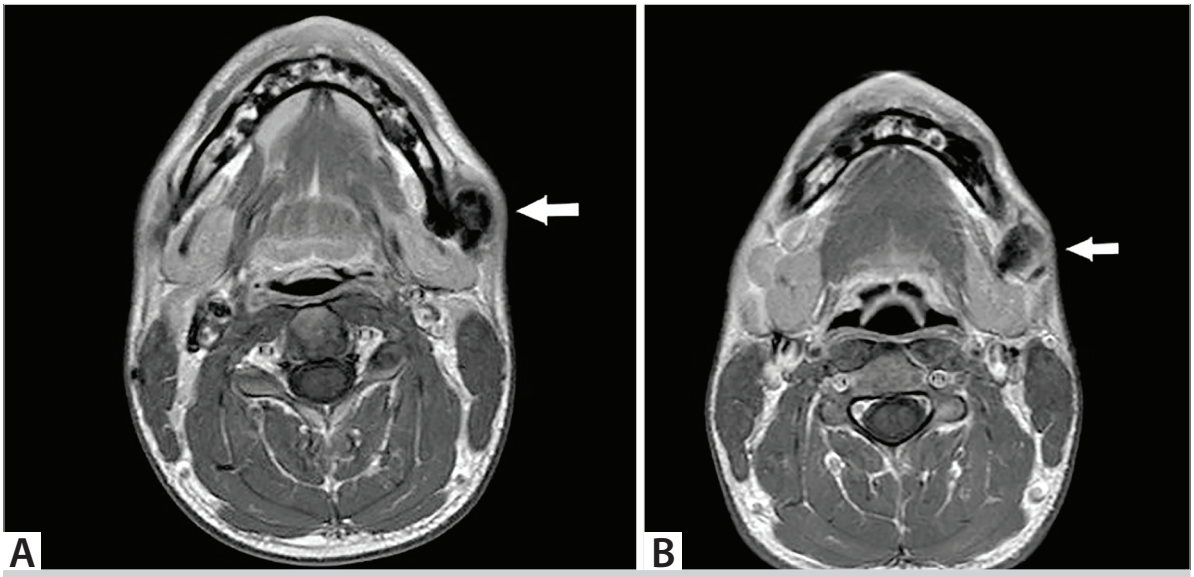

Figure 3. A. Left mandibular osteoma in Facial MR of case 1, **B.** Left mandibular osteoma in Facial MR of case 2.

DISCUSSION

Gardner et al. first identified a link between colonic polyposis characterizing malignant transformation and soft tissue tumors in 1951 and subsequently revealed the autosomal dominant inheritance pattern of the disease (1,3). All patients with GS have colorectal polyposis, while other gastrointestinal system pathologies are less common. Stomach and small bowel polyps can be seen in 12% of the patients and periampullary tumors in 2% (4). Therefore, preoperative upper gastrointestinal system endoscopy and small bowel passage examination were performed. GS affects more than one tissue and organ system. Polyposis usually does not have a specific symptom. Although the disease is usually symptomatic in the second decade, it can be seen anywhere from two months to 70 years (5). It is often the diagnosis of extraintestinal involvement that initiates the diagnostic process of the patients. Common findings are soft tissue and bone tumors and epidermoid cysts. The most common skin finding is epidermoid cysts, which are observed in about 70% of the patients. They are most commonly seen during adolescence and mostly in the head and neck region (6,7). Fibroma, lipoma, leiomyoma and hyperpigmented skin lesions are less common skin and subcutaneous tissue-related lesions (7). In our patients, subcutaneous masses compatible with fibromas and lipomas were also observed. It should also be kept in mind that periampullary carcinoma, thyroid papillary carcinoma, hepatoma, hepatoblastoma, biliary and adrenal neoplasms may also be seen in patients with GS (2). Therefore, we examined our patients by abdominal MR, thyroid USG and endoscopy.

Presence of multiple and bilateral congenital hypertrophy in the retinal pigment epithelium is considered as a marker for the disease (8). These eye findings in GS patients are significantly higher than the normal population although the absence of

eye pathology does not prove that the patient is not GS or FAP (8). Eye examinations of our patients were normal.

The rates of dental pathologies vary between 30-75% (5,9). Most teeth and chin pathology can be easily seen on panoramic X-rays. As a matter of fact, in our patient, the diagnosis process was started with dental complaints. CT and MR examinations revealed osteomas in the mandible. Osteomas are seen in almost half of the patients. It is mostly located in the head region and is often affected by mandibles and maxillary bones. It is mostly asymptomatic and pain is not often seen. They usually become symptomatic when they cause asymmetry (5,7,10).

Desmoid tumors are not as common as bone and cutaneous lesions. However, they are the most important cause of morbidity and mortality in patients with GS. These tumors most commonly occur in surgical incisions, abdominal cavity, and retroperitoneum. Although they may be seen at any stage, they often occur within the first three years after colon surgery (11).

Although a 75-year-old woman survives without treatment in the literature, almost all authors report that all untreated patients will develop colorectal cancer before the age of 40 (2,5-7,11,12). Therefore, early diagnosis and prophylactic surgery are very important. Prophylactic resection should be performed before the age of 25, ideally between the ages of 16 and 20 (7). Surgical treatment options include proctocolectomy and permanent terminal ileostomy, restorative proctocolectomy and ileal pachanal anastomosis, total colectomy and ileo-rectal anastomosis. There is no consensus on the surgical procedure to be chosen, but rectal involvement and patient factors must be considered. The first option seems to be the safest approach with no colorectal epithelium remaining, but it is not usually preferred due to the morbidity and low patient comfort caused by permanent ileostomy. Some authors describe restorative proctocolectomy and ileal pouch-anal anastomosis procedure as the best operative choice for GS (2). It provides functional intestinal continuity by protecting the patient from ileostomy but has higher morbidity and mortality. It may also be necessary to add a temporary ileostomy to this procedure. The preference of the patient should be taken into account in this option, especially since urinary complications, sexual complications and infertility rates are higher (13,14). It should also be remembered that after this surgery, life-long proctoscopic follow-up will be necessary due to the possibility of residual mucosa. The third approach, total colectomy and ileorectal anastomosis, is controversial because of the malignancy potential of the remained rectum (2,7). However, some studies have also shown that the incidence of locoregional recurrence is low in selected cases (15). This procedure may be a good option for patients with partially preserved rectum in the adolescent age group, who are aware of the fact that residual rectum will must be kept under follow-up during the life (7,11,14). Patients and families did not accept permanent ileostomy and restorative proctocolectomy because of their mortality and morbidity. The family had a sociocultural level to understand the importance of periodic controls. In our patients, rectal involvement was also limited. For all of these reasons, we performed total colectomy and iliorectal anastomosis.

CONCLUSION

Due to the correct management of the diagnosis process, which begins with dental complaints in one of the monozygotic twins, two adolescent patients were diagnosed with GS, and prophylactic treatments were performed. This suggests that clinicians and dentists should be cautious and skeptical about the diagnosis of this rare disease, especially in early-stage patients who present with extraintestinal findings.

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Gardner sendromu: Monozigotik ikizlerde eş zamanlı tanı ve tedavi

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ÖZET

Gardner sendromu (GS) oldukça nadir görülen, otozomal dominant geçişli, multisistemik bir hastalıktır. Tipik olarak gastrointestinal polipozise osteomalar ile deri ve yumuşak doku tümörleri eşlik ederler. Poliplerin malignite potansiyelleri çok yüksek olup erken profilaktik rezeksiyon yapılmaması halinde kolorektal kanser gelişimi kaçınılmazdır. Bu hastalarda polipozisin genellikle asemptomatik olması erken tanı için hastalığın ekstraintestinal bulgularına karşı daha dikkatli olunmasını gerektirmektirir. Bu yazıda daha önce literatürde tariflenmemiş olan monozigotik ikizlerde GS'nin eş zamanlı tanı ve tedavisi sunulmuştur. Bir olguya ait dental şikayetler ile başlayan tanı sürecinin doğru bir şekilde yönetilmesi sonucunda iki hasta eş zamanlı tedavi edilmiştir. Bu makale, klinisyen ve diş hekimlerinin hastalığın erken tanısı açısından farkındalıklarını arttırmayı ve tedavi seçeneklerini gözden geçirmeyi hedeflemektedir.

Anahtar Kelimeler: Gardner sendromu, ikizler, intestinal polipozis, osteoma, kolorektal neoplazmlar

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