

Epigastric port site complications and affecting factors used for gallbladder specimen extraction in laparoscopic cholecystectomy

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ABSTRACT

Introduction: Complications occur at the port site where the specimen is excised after laparoscopic cholecystectomy (LC). In this study, it was aimed to investigate port-site complications.

Materials and Methods: The results of patients who underwent LC surgery in our center between January 01, 2018, and December 31, 2020, were retrospectively analyzed. Patients who were decided to have open surgery and reside abroad were excluded from the study. Pre-operative, intraoperative, and post-operative factors of all patients, which were considered to impact the development of complications, were noted down.

Results: A total of 357 patients were included in the study. A total of 24 (6.7%) patients had epigastric trocar site infection (EPSI). It was found out that trocar site hematoma was a risk factor causing a 39.37-fold increase in the development of EPSI ($p < 0.001$) (95% confidence interval = 10.69–144.97), while dilatation at the trocar site was a risk factor causing a 3.1-fold increase ($p = 0.027$) (95% confidence interval = 1.14–8.48). Ten patients had epigastric trocar insertion site hernia (EPSH). As a result of the multivariate analysis, it was determined that the development of EPSI caused the development of EPSH 27.59 times more (95% confidence interval = 5.92–128.7) ($p < 0.001$), while the accompanying additional laparoscopic procedure caused the development of EPSH 6.2 times more (95% confidence interval = 6.2–1.17) ($p = 0.032$).

Conclusion: Preventing the occurrence of hematoma in the epigastric trocar insertion site, where the specimen is excised after LC surgery, reduces the risk of EPSI, and indirectly reduces the incidence of EPSH. Moreover, we recommend careful follow-up for EPSH in patients who underwent additional laparoscopic surgery during LC.

Keywords: Laparoscopic cholecystectomy, Port site complications, Port site hernia, Port site infection

Introduction

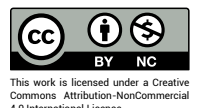
Laparoscopic cholecystectomy (LC) continues to be one of the most frequently performed surgeries. Albeit there is a slight decrease in the number of all elective sur-

geries performed under current pandemic conditions, it is reported that an average of half a million LC surgeries is performed each year.^[1] Hence, although it has a low incidence, many patients develop complications after



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LC surgery. Bile duct, portal vein, and hepatic artery injury are serious complications that develop during LC.^[1,2] On the other hand, less risky complications such as port site infection (PSI) and hernia (PSH) may develop as well.^[2,3] It has been reported that these complications are more common at the umbilical region port site, specifically at the time of specimen excision.^[4,5] Although PSI often occurs in the early period (first 30 days), PSH is common as a late complication.^[2,6,7] Some risk factors, such as longer duration of operation, obesity, and bile contamination, have been reported to cause the development of these complications.^[2,3,5,8-10] There is no detailed study on the complications and risk factors in the port site where the specimen is excised in the epigastric region. In this study, we aimed to investigate the factors that may lead to infection epigastric trocar site infection (EPSI) and epigastric trocar insertion site hernia (EPSH) at the epigastric port site where the specimen was excised in patients who underwent LC surgery in our center.

Materials and Methods

Following the approval of the ethics committee of Istanbul Yeni Yuzyil Universty, dated October 14, 2021, and numbered 2021/10-713, the results of all patients who underwent LC surgery in Istanbul Yeni Yuzyil Universty Gazismanpaşa Hospital General Surgery Clinic between January 01, 2018, and December 31, 2020, were retrospectively analyzed. After obtaining written consent from all patients, three or four port LC surgery was performed. The skin incision was made using a scalpel or a monopolar cutter. The peritoneal cavity was inflated using a Veress needle. An 11 mm port was used in the umbilicus and epigastric region and a 5 mm port was used in the subcostal region. The same kind of plastic torches was used (11 mm in diameter), both new and resterilized. In some patients, the puncture was performed due to gallbladder hydrops, and in some patients, bile contamination occurred due to perforation of the gallbladder during surgery. The gallbladder specimen was always excised from the epigastric port site. During this procedure, an endobag was used in some patients (to prevent contamination of purulent bile). In case of difficulty in removing the sample, dilatation of the port hole was performed and this operation was recorded in the video recordings (Figs. 1a and b). Although a fascial suture was always placed at the umbilical port site, no fascial suture was placed

at the site of the epigastric port. The skin was closed subcuticularly with absorbable sutures. Patients who converted to open surgery (four patients) and who were followed up abroad (15 patients) were excluded from the study. In addition to the demographic data of the patients, post-operative follow-up physical examination findings, surgical video recordings, and information recorded in the national E-NabızR personal health information systems were obtained by phone call and noted down. The films of those who had thorax tomography, which was commonly taken from these patients during the COVID-19 pandemic period, were also examined (Fig. 2). For EPSI, superficial and deep surgical site infection findings were determined based on Centers for Disease Control and Prevention criteria.^[11] For EPSH, detection of a fascial defect at the suprapubic port site as a result of physical examination, superficial ultrasonography, and computed tomography was considered as a criterion.

All parameters were recorded in three categories as pre-operative, intraoperative, and post-operative (Table 1). Patients who developed EPSI and EPSH after LC was identified and the factors that could impact the development of these complications were assessed.

Statistical Method

Shapiro–Wilk test was used for assessing whether the variables follow normal distribution or not. Continuous variables were presented as median (minimum: maximum) values. Categorical variables were reported as n (%). According to the normality test results, Mann–Whitney U test was used in comparison between two groups. Pearson Chi-squared test or Fisher’s exact test was used for comparing categorical variables. Multiple logistic regression analysis was performed to determine the risk factors affecting the incidence of herni and PSI. Variables are included in multiple logistic

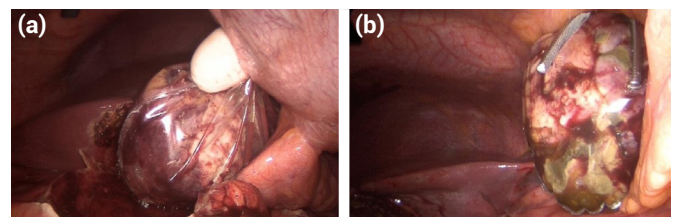


Figure 1. (a) Manual dilatation at the epigastric trocar site for the resection of specimen (b) Dilatation with Kocher clamp at the epigastric trocar site for the resection of specimen.

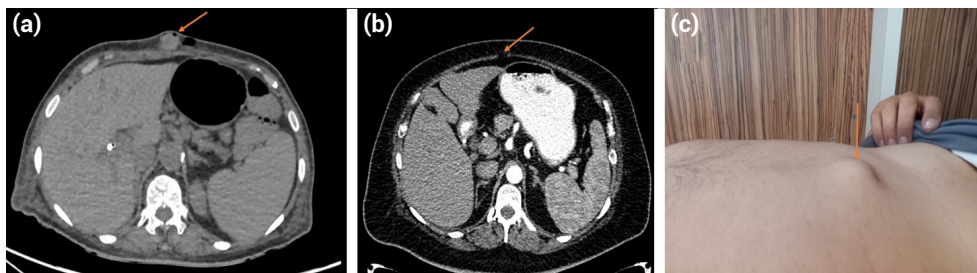


Figure 2. (a) EPSI with air bubbles in it (red arrow), (b) EPSH detected in the patient who underwent thoracic CT during the pandemic (red arrow), (c) EPSH detected during physical examination (red arrow).

regression model using Enter method. The variables found to be significant in the model were determined as independent variables. Multiple logistic regression models were found to be significant ($p < 0.001$). SPSS

(IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and $p < 0.05$ was considered statistically significant.

Table 1. Factors assessed to determine EPSI and EPSH risk factors

Impact factors and findings		
Pre-operative	Intraoperative	Post-operative
Gender	Type of skin incision in epigastric port incision (scalpel/cauter cutter)	Post-operative antibiotic prophylaxis
Patient age	Intraoperative appearance of the gallbladder. Hydrops in the gallbladder	Hematoma at the site of the epigastric trocar
BMI	Intraoperative gallbladder puncture	Infection at the epigastric trocar site
Alcohol intake	Perforation of the intraoperative gallbladder. Endoback use	
Smoking	Drain use	
Coronary artery disease	Duration of operation	
HT	Concurrent additional laparoscopic surgery. Type of Trocar	
DM	Bleeding from the trocar site	
COPD	Dilatation of the epigastric trocar site	
KCS		
Comorbidity		
Anticoagulant medication use		
ASA		
WBC		
Hb		
Type of surgery		
Preoperative pancreatitis (1 week)		
Reason for LC		
Number of stones in the gallbladder		
Stone size in the gallbladder		
Preoperative antibiotic prophylaxis		
Previous laparotomy		

LC: Laparoscopic cholecystectomy; BMI: Body mass index; HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; KCS: Liver cirrhosis; ASA: The American Society of Anesthesiologists; WBC: White blood cells.

Results

A total of 357 LC patients, 214 (59.94%) female, and 143 (40.06%) male were included in the study. The mean age of the patients was 52.04 years. In 25 (7%) patients, LC was performed within 1–2 days of the ERCP procedure performed following a pancreatitis episode. Endobag was used for specimen extraction in 62 (17.37%) patients. Dilatation was performed at the epigastric port inlet during specimen removal in 165 (46.22%) patients. In a total of 25 (7%) patients, additional laparoscopic procedures were performed concurrently (Table 2).

In 13 (3.64%) patients, hematoma developed at the epigastric port site during follow-up. EPSI in the form of superficial infection occurred in a total of 24 (6.7%) patients. EPSH was developed in 10 (2.8%) patients during different follow-up periods. In the univariant analysis, it was determined that the rate of dilatation to remove the specimen at the epigastric port site ($p=0.037$) and port site hematoma rates ($p>0.001$) was higher in the patient group who developed EPSI (Table 3).

As a result of the multivariant analysis, it was found out that the port site dilatation procedure was performed for specimen removal ($p=0.027$) and the hematoma developed at the epigastric port site ($p<0.001$) caused a significant increase in the risk of developing EPSI (Table 4).

On the other hand, the rates of concurrent surgery ($p=0.026$), hematoma developing at the epigastric port site ($p=0.047$), and EPSI ($p<0.001$) were associated with an increased risk of developed EPSH (Table 3).

As a result of multivariate analysis, it was determined that simultaneous surgery and EPSI development was associated with an increased risk of EPSH development (Table 5). Other factors other than these did not cause any risk increase in the development of EPSI and EPSH.

Table 2. Concurrent procedures performed with LC

Additional surgeries performed	n (24)
Laparoscopic umbilical hernia repair	8
Laparoscopic appendectomy	5
Laparoscopic incisional hernia repair	5
Laparoscopic TAH+BSO	4
Laparoscopic nissen fundoplication	2
TAH+BSO-Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy.	

Discussion

LC is one of the most commonly performed surgical procedures worldwide. Numerous studies have reported low complication rates after LC. Particularly, large vascular and biliary tract injuries cause remarkable morbidity and mortality.^[2,12,13] Apart from these, there are complications such as hematoma at the port site, PSI, and PSH with a relatively higher rate. PSI after LC is the most common complication in the first 30 days and has been reported at an incidence of 2.34–9.6% in the literature.^[14-16] In our study, this rate was 6.7% and was found to be in line with the literature. In the literature, male gender, obesity, iatrogenic gallbladder injury, specimen resection from the umbilical region, smoking, long duration of operation, emergency surgery, and infected gallbladder have been reported as risk factors for the occurrence of PSI.^[8,17-19] In our study, it was found that these factors did not cause a significant increase in the risk of developing EPSI in combination with other systemic diseases (Diabetes mellitus, hypertension, coronary artery disease, and chronic obstructive pulmonary disease). Pre-operative antibiotic prophylaxis and post-operative oral antibiotic use, endobag use, intraoperative gallbladder perforation, use of drains, use of resterilized buckle, and high ASA score (The American Association of Anaesthetists) were not found to be significant risk factors for the development of EPSI and were found to be consistent with similar studies in the literature.^[4,15,20-23] In our study, it was observed that the dilatation procedure performed when removing the specimen from the epigastric port region and post-operative port site hematoma caused a rise in the incidence of EPSI. On literature review, we could not find literature information to compare the rates of dilatation at the port site and the associated EPSI rates. We consider that this increase is because of the trauma developed in the tissues due to the use of the blunt dissection technique. In 13 (3.61%) patients, hematoma developed at the epigastric port site, which was consistent with the rates of 0.7–6.6% reported in the literature.^[24-26] Although Memon et al. reported this rate as 5.33% in their study, they did not reveal the incidence of EPSI occurred due to hematoma.^[27] It is well-documented that hematoma developed at the wound site after surgery is a risk factor for surgical infection.^[28] In our study, it was determined that hematoma formed at the port site increased the incidence of EPSI 38.08 times. We could not find literature information to compare our rate of EPSI developed after hematoma at the epigastric port site.

Table 3. Univariate analysis results for EPSI and EPSH

Factor	EPSI			EPSH		
	Absent (333)	Present (24)	p	Absent (347)	Present (10)	p
Age	55 (29.79)	52 (20.89)	0.678a	49 (23.79)	52 (20.89)	0.211a
BMI	27.76 (22.60:34.77)	28.25 (15.05:49.73)	0.286a	27.18 (20.65:36.33)	28.25 (15.05:49.73)	0.247a
Gender						
Female	201 (60.36%)	13 (54.17%)	0.550b	209 (60.23%)	5 (50%)	0.530c
Male	132 (39.64%)	11 (45.83%)		138 (39.77%)	5 (50%)	
Smoking						
No	232 (69.67%)	15 (62.50%)	0.463b	242 (69.74%)	5 (50%)	0.295c
Yes	101 (30.33%)	9 (37.50%)		105 (30.26%)	5 (50%)	
Alcohol use						
No	303 (90.99%)	24 (100%)	0.244b	317 (91.35%)	100 (100%)	>0.99c
Yes	30 (9.01%)	0		30 (8.65%)	0	
Coronary artery disease						
No	288 (86.49%)	21 (87.50%)	>0.99c	301 (86.74%)	8 (80%)	0.630c
Yes	45 (13.51%)	3 (12.50%)		46 (13.26%)	2 (20%)	
Hypertension						
No	228 (68.47%)	17 (70.83%)	0.809b	237 (68.30%)	8 (80%)	0.731c
Yes	105 (31.53%)	7 (29.17%)		110 (31.70%)	2 (20%)	
DM						
No	279 (83.78%)	20 (83.33%)	>0.99c	291 (83.86%)	8 (80%)	0.669c
Yes	54 (16.22%)	4 (16.67%)		56 (16.14%)	2 (20%)	
COPD						
No	319 (95.80%)	24 (100%)	0.611c	333 (95.97%)	10 (100%)	>0.99c
Yes	14 (4.20%)	0		14 (4.03%)	0	
Comorbidity						
No	230 (69.07%)	20 (83.33%)	0.141b	242 (69.74%)	8 (80%)	0.729c
Yes	103 (30.93%)	4 (16.67%)		105 (30.26%)	2 (20%)	
Anticoagulant Therapy						
No	280 (84.08%)	22 (91.67%)	0.556c	293 (84.44%)	9 (90%)	>0.99c
Yes	53 (15.92%)	2 (8.33%)				
ASA score						
I	136 (40.84%)	12 (50%)	0.625c	143 (41.21%)	5 (50%)	0.900c
II	165 (49.55%)	11 (45.83%)		171 (49.28%)	5 (50%)	
III	31 (9.31%)	1 (4.17%)		32 (9.22%)	0	
IV	1 (0.30%)	0		1 (0.29%)	0	

Table 3. CONT.

Factor	EPSI			EPSH		
	Absent (333)	Present (24)	p	Absent (347)	Present (10)	p
Presence of the previous laparotomy						
No	314 (94.29%)	24 (100%)	0.628c	328 (94.52%)	10 (100%)	>0.99c
Yes	19 (5.71%)	0		19 (5.48%)	0	
WBC	7.02 (4.89:74.34)	8.04 (2.60:27)	0.447a	8.18 (4.89:74.34)	7.99 (2.60:27)	0.115a
Hb	12.80 (9.30:17.50)	13.30 (1.10:24.40)	0.780a	13.70 (9.30:91)	13.30 (1.10:91)	0.380a
CRP	32.40 (6.70:35.70)	9.60 (0.552:70)	-	25.90 (0.46:35.70)	9.61 (0.552:70)	-
Type of LC						
Urgent	88 (26.43%)	8 (33.33%)	0.461b	93 (26.80%)	3 (30%)	0.732c
Elective	245 (73.57%)	16 (66.67%)		254 (73.20%)	7 (70%)	
Presence of pancreatitis in the last 1 week						
No	307 (92.19%)	23 (95.83%)	>0.99c	320 (92.22%)	10 (100%)	>0.99c
Yes	26 (7.81%)	1 (4.17%)		27 (7.78%)	0	
Reason for LC						
Acalculous	6 (1.80%)	1 (4.17%)	0.732c	7 (2.02%)	0 (0%)	0.390c
Polyp	9 (2.70%)	1 (4.17%)				
Stone	318 (95.50%)	22 (91.67%)				
Number of Stones	7 (1:7)	7 (0:7)	0.142a	3.50 (0:7)	7 (0:7)	0.806a
Stone Size (mm)	7 (5:19)	9 (0:34)	0.153a	11.75 (0:29)	9 (0:34)	0.091a
Preoperative antibiotic prophylaxis (Cefazole)						
No	46 (13.81%)	0	0.056c	46 (13.26%)	0 (0%)	0.372c
Yes	287 (86.19%)	24 (100%)		301 (86.74%)	10 (100%)	
Use of antibiotics after LC						
No	159 (47.75%)	8 (33.33%)	0.172b	164 (47.26%)	3 (30%)	0.347c
Yes	174 (52.25%)	16 (66.67%)		183 (52.74%)	7 (70%)	
Intraoperative gallbladder appearance						
Chronic	231 (69.37%)	16 (66.67%)	0.845b	240 (69.16%)	7 (70%)	0.711c
Acute	82 (24.62%)	7 (29.17%)		87 (25.07%)	2 (20%)	
Ulcerophle-gmanous	20 (6.01%)	1 (4.17%)		20 (5.76%)	1 (10%)	
Hydrops in the gallbladder						
No	226 (68.07%)	16 (66.67%)	>0.99c	235 (67.92%)	7 (70%)	>0.99c
Yes	106 (31.93%)	8 (33.33%)		111 (32.08%)	3 (30%)	
Intraoperative gallbladder puncture						
No	314 (94.29%)	23 (95.83%)	>0.99c	327 (94.24%)	10 (100%)	>0.99c
Yes	19 (5.71%)	1 (4.17%)				

Table 3. CONT.

Factor	EPSI			EPSH		
	Absent (333)	Present (24)	p	Absent (347)	Present (10)	p
Intraoperative gallbladder perforation (iatrogenic)						
No	228 (68.47%)	19 (79.17%)	0.273b	238 (68.59%)	9 (90%)	0.185c
Yes	105 (31.53%)	5 (20.83%)		109 (31.41%)	1 (10%)	
Endobag Usage						
No	276 (82.88%)	19 (79.17%)	0.584c	287 (82.71%)	8 (80%)	0.687c
Yes	57 (17.12%)	5 (20.83%)		60 (17.29%)	2 (20%)	
Drain use						
No	224 (67.27%)	17 (70.83%)	0.719b	234 (67.44%)	7 (70%)	>0.99c
Yes	109 (32.73%)	7 (29.17%)		113 (32.56%)	3 (30%)	
Presence of liver cirrhosis						
No	316 (94.89%)	24 (100%)	0.617c	331 (95.39%)	9 (90%)	0.390c
Yes	17 (5.11%)	0		16 (4.61%)	1 (10%)	
Duration of operation	16 (10:50)	20 (8:80)	0.555a	19.50 (10:44)	20 (8:80)	
Additional laparoscopic procedure						
No	311 (93.39%)	21 (87.50%)	0.231c	325 (93.66%)	7 (70%)	0.026c
Yes	22 (6.61%)	3 (12.50%)		22 (6.34%)	3 (30%)	
Type of skin incision						
Lancet	253 (75.98%)	19 (79.17%)	0.723b	265 (76.37%)	7 (70%)	0.707c
Cautery-cutter	80 (24.02%)	5 (20.83%)		82 (23.63%)	3 (30%)	
Trocar Use						
New	70 (21.02%)	5 (20.83%)	0.983b	73 (21.04%)	2 (20%)	>0.99c
Resterilized	263 (78.98%)	19 (79.17%)		274 (78.96%)	8 (80%)	
Performing dilatation instead of the trocar						
No	184 (55.26%)	8 (33.33%)	0.037b	189 (54.47%)	3 (30%)	0.197c
Yes	149 (44.74%)	16 (66.67%)		158 (45.53%)	7 (70%)	
Development of hematoma at the trocar site						
No	328 (98.50%)	16 (66.67%)	<0.001c	336 (96.83%)	8 (80%)	0.047c
Yes	5 (1.50%)	8 (33.33%)		11 (3.17%)	2 (20%)	
EPSI						
No	-	-	-	329 (94.81%)	4 (40%)	<0.001c
Yes				18 (5.19%)	6 (60%)	

Data are expressed as n (%) and median (minimum: maximum). a: Mann-Whitney U test, b: Pearson Chi-squared test, c: Fisher's Exact test, LC: Laparoscopic cholecystectomy, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, KCS: Liver cirrhosis, ASA: The American Society of Anesthesiologists, WBC: White blood cells.

Table 4. Risk factors impacting the occurrence of EPSI

Factor	Wald	p	OR	95%CI	
				Lower	Upper
Performing dilatation instead of the trocar					
None (ref. cat.)	-	-	1	-	-
Yes (x1)	4.88	0.027	3.10	1.14	8.48
Development of hematoma at the trocar site					
None (ref. cat.)	-	-	1	-	-
Yes (x2)	30.50	<0.001	39.37	10.69	144.97

Pattern $\chi^2=4.59$; $P<0.001$, $R^2=0.237$, $n=356$. OR: Odds ratio, Ref.cat.: Reference category, CI: Confidence Interval.

Table 5. Risk factors impacting the occurrence of EPSH

Factor	Wald	p	OR	95%CI	
				Lower	Upper
Concurrent laparoscopic procedure					
None (ref. cat.)	-	-	1	-	-
Yes (x1)	4.62	0.032	6.20	6.20	1.17
Development of hematoma at the trocar site					
None (ref. cat.)	-	-	1	-	-
Yes (x2)	0.002	0.963	0.653	0.13	7.21
ETSI					
None (ref. cat.)	-	-	1	-	-
Yes(x3)	17.83	<0.001	27.59	5.92	128.70

Pattern $\chi^2=24.90$; $P<0.001$, $R^2=30\%$, $n=356$. OR: Odds ratio, Ref.cat.: Reference category, CI: Confidence Interval.

EPSH is a late complication of LC surgery and has been reported in the literature at a rate of 0.3–4.4%.^[5,10] In our study, EPSH was seen at a rate of 2.8% (ten patients) and was in line with the literature. It has been revealed in studies that obesity, port diameter, specimen resection, long operation duration, and advanced age lead to an increase in the risk of PSH development after LC, and hernia develops in the umbilical region at a rate of 88.9%.^[5,7,10,29,30] As a result of our statistical analysis, it was found that similar risk factors did not increase the development of EPSH in our study. In their study, Erdas et al. reported that 15.4% of PSHs developed after LC occurred at the epigastric port site; however, they did not state any risk factors.^[31] In our study, the rates of hematoma at the protruding site, the additional laparoscopic procedure performed concurrently, and EPSI was found to be higher among the EPSH group. As a result of the multivariate analysis, simple additional laparoscopic procedure (6.2-fold) and EPSI

(27.59-fold) significantly increased the risk of developing EPSH. Although we could not find any literature data demonstrating that the additional laparoscopic procedure caused the development of epigastric EPSH, it is remarkable that all of the additional procedures performed in this patient group were hernia repair surgery (two incisional and umbilical hernia in one patient). Thus, we are of the opinion that other risk factors that increase the development of hernia in these cases are also effective in the occurrence of EPSH.

Surgical wound infection is a considerable risk factor for the development of incisional hernia.^[28,32] In their study, which included 340 patients, Kündeş et al. reported that PSH developed with an incidence of 5.9% without specifying its localization, and they revealed that PSI was a risk factor.^[33] Bunting reported PSI as a risk factor for PSH as a result of his meta-analysis.^[29] In our study, EPSI was present in 6 (60%) of ten patients who developed EPSH,

and it was found to be a significant risk factor ($p < 0.001$).

There are some shortcomings of our study. Considering the R2 value and home-show value in binary log regression, it is noticed that the explanatory power of the model used is around 30% and the model fit is not good. Hence, it would be beneficial to conduct further studies by examining more patients and the addition of other risk factors. Besides, the inability to include the results of all our patients who underwent LC is considered to be another shortcoming of our study.

Conclusion

The number of LC surgeries performed every year is increasing and as a matter of course the number of PSI and PSH patients seen after LC surgery is also increasing. Various risk factors have been suggested to prevent these problems. It should be kept in mind that the dilatation procedure performed at the port insertion site and the formation of post-operative hematoma increase the development of EPSI. On the other hand, patients who underwent additional laparoscopic procedures with LC should be followed carefully for the development of EPSH.

Disclosures

Ethics Committee Approval: Approval dated 14 October 2021 and numbered 2021/10-713 was obtained from the ethics committee of Istanbul Yeni Yüzyıl University.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.Z., S.Ç.; Design – E.Z., S.Ç.; Supervision – E.Z., S.Ç., M.Ç.; Materials – E.Z., M.Ç., M.S.; Data collection and/or processing – E.Z., M.S., A.Ö.; Analysis and/ or interpretation – E.Z., S.Ç., A.Ö.; Literature search – E.Z., M.S., A.Ö.; Writing – E.Z., S.Ç.; Critical review – E.Z., S.Ç., M.Ç.

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