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Original Article

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Comparative analysis of surgical outcomes: post-ERCP laparoscopic cholecystectomy versus elective laparoscopic cholecystectomy

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ABSTRACT

Aims: Gallstones are widespread in the adult population. In some patients, the stones are not confined to the gallbladder but are also found in the biliary tract. Although the treatment approach for this group of patients is controversial, the most widely accepted treatment is laparoscopic cholecystectomy (LC) after removal of the stones by endoscopic retrograde cholangiopancreaticography (ERCP). Opinions differ as to whether LC should be performed early or late. With this study, we wanted to shed light on this question based on our own clinical experience.

Methods: A total of 100 patients who underwent LC in our clinic were included in the study. These patients were divided into two groups; 50 patients who underwent ERCP and early cholecystectomy (group 1) and 50 patients who underwent elective LC for gallstones (group 2). Patients who underwent ERCP for malignant or benign stricture, patients with porcelain sac, patients with previous abdominal surgery, patients who underwent emergency LC, patients younger than 18 years old, and patients with incomplete data, incomplete records, or patients whose necessary information could not be accessed were excluded.

Results: There was no statistically significant difference between age and preoperative amylase levels. The mean length of hospital stay was 3.9±1.6 days in patients who underwent elective LC and 5.5±3.2 days in patients who underwent LC after ERCP. There was a statistically significant difference between postoperative amylase level, hemoglobin level and length of hospital stay ($p<0.05$). Postoperative amylase levels and length of hospital stay were higher in group 1. There was a significant difference between the groups in terms of surgical procedure ($p<0.05$). In group 1, laparoscopic cholecystectomy (LC) was performed in 78% of patients, while in group 2, LC was performed in 94% of patients. It was found that the rate of conversion to patency was higher in group 1. There was no statistically significant difference between the groups in terms of postoperative and preoperative complications

Conclusion: Our study highlights early cholecystectomy after ERCP to reduce potential complications in the treatment of gallstones, while emphasising the need for close patient follow-up and further research validation.

Keywords: Post-ERCP laparoscopic cholecystectomy, elective laparoscopic cholecystectomy, ERCP, cholecystectomy, gallbladder stone, bile duct stone

INTRODUCTION

Gallstones occur in 10% of the adult population. Choledochal stones are also found in 4-15% of patients.[1] Endoscopic retrograde cholangiopancreatography (ERCP) is an important examination and treatment procedure for diseases of the biliary tract and pancreas. However, ERCP-related procedures have a high risk of adverse events (AEs) such as post-ERCP pancreatitis (PEP), bleeding, perforation and cholangitis. PEP is the most important complication because it can be fatal in severe cases. Although the incidence of PEP has been reported as 1.6-15% in some studies, recent systematic reviews have reported an incidence of 3.47% [95% confidence interval (CI): 3.19-3.75%] and a mortality rate of 0.11%.[1-5] In patients with cholelithiasis associated with choledochal calculi, the most accepted treatment approach by most clinicians today is to first remove the stone obstructing the duct with endoscopic retrograde cholangiopancreaticography

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(ERCP) and then perform laparoscopic cholecystectomy (LC).[1,2] There is no consensus on the timing of LC after ERCP, with some surgeons advocating early surgery and others advocating late surgery.[3] There is also a view that the more time that passes after ERCP until surgery, the more biliary complications occur.[4,5] ERCP is the standard of care for the treatment of choledocholithiasis; however, it carries the risk of complications that can result in significant morbidity and mortality. While current guidelines support the use of ERCP for the treatment of symptomatic bile duct stones, the need for ERCP in incidentally found asymptomatic choledocholithiasis is more controversial.[6-9]

In our clinic, we perform early LC because complications such as acute cholecystitis, choledocholithiasis, biliary pancreatitis, and cholangitis may occur while waiting for surgery after ERCP. In this study, we compared LC cases in which surgery was decided after ERCP with elective LC cases in our clinic.

METHODS

Ethics

The thesis study was initiated with the approval of the Afyonkarahisar Health Sciences University Medical Faculty Clinical Researches Ethics Committee (Date: 18.12.2014, Decision No: 277). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Patient Selection

A total of 100 patients admitted to Department of General Surgery, Afyonkarahisar Health Sciences University University Faculty of Medicine Hospital between 01.01.2013 and 31.12.2013 were included in this retrospective study.

Inclusion criteria: Patients with biliary tract pathology with gallstones who underwent early LC after ERCP and patients who underwent elective LC for gallstones who underwent ERCP were included in the study. Patients with at least one abdominal imaging report (USG, MRI and MRCP, CT) and recent laboratory results performed before ERCP and adult patients over 18 years of age were included in the study.

Exclusion criteria: Patients without at least one abdominal imaging report performed before ERCP, patients undergoing ERCP for malignant or benign stricture, patients with porcelain sac, patients with previous abdominal surgery, patients undergoing emergency LC, patients younger than 18 years of age, and patients with incomplete data, incomplete files, or patients whose necessary information could not be accessed were excluded.

Grouping of Cases

Patients with biliary tract pathology with gallstones who underwent early LC (24-72 hours) after ERCP were included in group 1. Patients who underwent elective LC due to gallbladder stones with indication in outpatient clinics and wards were included in group 2. All ERCP procedures were performed in the same department and by a single endoscopist. Age, gender, body mass index (BMI), postoperative hemoglobin levels, amylase levels, complications, peroperative complications, surgical interventions after conversion to open surgery, and length of hospital stay were retrospectively evaluated in these two groups.

Statistical Analysis

SPSS 19.0 statistical package program was used for data analysis. Descriptive statistical methods (frequency, percentage, mean, standard deviation) and Pearson Chi-square, Fisher Chi-square or Yates Chi-square tests were used to compare quantitative data. The conformity of the data to normal distribution was performed with the Kolmogorov-Smirnow test. In the study, independent samples-t test was used in the evaluation of quantitative data showing normal distribution; values less than p=0.05 were considered significant and significant difference between groups.

RESULTS

Demographic data and laboratory results of group 1 are given in Tables 1, 2.

Table 1. Mean data of post-ERCP cholecystectomy patients

	Post-ERCP cholecystectomy (n=50)
	Mean±SD
Age (year)	57.8±18.5
BMI (kg/m^2)	30.1±5.8
Amylase (U/L)	100.6±214.4
Icterus (mg/dl)	3.3±3.0
Choledochal diamater (mm)	11.2±4.5
Post-ERCP icterus	2.9±3.0
Post-ERCP amylase (U/L)	331.9±518.5
Post-ERCP leucocytosis leucocytosis (x10^3/mm^3)	10.5±4.2
Postoperative amylase (U/L)	160.4±197.9
Postoperative hemoglobin (g/dl)	11.4±1.6
Postoperative leucocytosis (x10^3/mm^3)	10.2±4.2
Length of hospital stay (day)	5.5±3.2

ERCP: Endoscopic retrograde cholangiopancreatography, BMI: Body-mass index, SD: Standart deviation

Demographic data and laboratory results of group 2 are given in Tables 3, 4.

There was no statistically significant difference between the groups in terms of gender, BMI and American Society of Anesthesiologists (ASA) score. Although there was no statistical difference between the age groups, the number of patients aged ≥70 years was higher in the elective cholecystectomy group (82% and 64%, respectively). LC was performed in 76% of patients in group 1, while 94% of patients in group 2 (p<0.05). The rate of conversion to open surgery was higher in group 1 than in group 2 (12 and 3 patients, respectively) (Tables 2, 4).

There was no statistically significant difference between age and preoperative amylase levels. The mean length of hospital stay was 3.9±1.6 days in group 2 and 5.5±3.2 days in group 2. There was a statistically significant difference between postoperative amylase level, postoperative hemoglobin level and length of hospital stay (p<0.05). Postoperative amylase level and length of hospitalization were higher in group 1 (Table 5).

Table 2. Demographic and clinical/laboratory data of post-ERCP cholecystectomy patients		
Gender		**%**
Female		52.0
Male		48.0
Age group		
Year <70		64.0
Year >70		36.0
BMI		
Normal		20.0
Overweight		30.0
Obese		50.0
ERCP endication		
Cholangitis		16.0
Choledochal stone		72.0
Pancreatitis		12.0
Icterus		
<2		44.0
2-5		32.0
>5		24.0
Elevated liver function test		
No		6.0
Yes		94.0
Lococytosis		
No	31	62.0
Yes	19	38.0
ASA score		
ASA 1	18	36.0
ASA 2	13	26.0
ASA 3	15	30.0
ASA 4	4	8.0
Presence of stones on pre-ERCP imaging		
No	20	40.0
Yes	30	60.0
Choledochal diameter (mm)	**n**	**%**
<10	17	34.0
10-15	28	56.0
>15	5	10.0
Stent application		
No	29	58.0
Yes	21	42.0
Standard sphincterotomy		
No	20	40.0
Yes	30	60.0
Balloon application		
No	6	12.0
Yes	44	88.0
Precut sphincterotomy		
No	30	60.0
Yes	20	40.0
ERCP procedure complication		
No	46	92.0
Bleeding	2	4.0
Perforation	1	2.0
Respiratory failure	1	2.0
Papilla		
Normal	22	44.0
Atrophic	15	30.0
Edematous	10	20.0
Atrophic-edematous	3	6.0

Table 2. Demographic and clinical/laboratory data of post-ERCP cholecystectomy patients (continues)		
Diverticulum		
No	44	88.0
Yes	6	12.0
Stone extraction		
No	20	40.0
Yes	30	60.0
Pancreas canulaton		
No	41	82.0
Yes	9	18.0
	Post-ERCP cholecystectomy (n=50)	
Failed cannulation	**n**	**%**
No	48	96.0
Patients' intolerance	1	2.0
Premedication	1	2.0
Post-ERCP complication		
No	26	52.0
Cholangitis	8	16.0
Pancreatitis	16	32.0
Surgery performed		
Open cholecystectomy, choledochal exploration, primary repair	2	4.0
Open cholecystectomy, choledochal exploration and tube application	3	6.0
Laparoscopic-onset open cholecystectomy	7	14.0
Laparoscopic cholecystectomy	38	76.0
Postoperative complication		
No	40	80.0
Postoperative bleeding	2	4.0
Gastroparasia	2	4.0
Bile leakage	3	6.0
Wound site infection	3	6.0
Peroperative complication		
No	33	66.0
Gallbladder perforation	8	16.0
Bed hemorrhage	5	10.0
Biliary tract injury	1	2.0
Vascular bleeding	3	6.0
Oddi disfunctions		
No	45	90.0
Yes	5	10.0
Difficult cannulation		
No	46	92.0
Yes	4	8.0
Reason for switching to open surgery		
No	39	78.0
Gallbladder injury	1	2.0
Vascular bleeding	3	6.0
Adhesion	7	14.0

ERCP: Endoscopic retrograde cholangiopancreatography, BMI: Body-mass index, ASA: American Society of Anesthesiologist

Table 3. Data of patients undergoing elective cholecystectomy	
	Cholecystectomy (n=50)
	Mean±SD
Age **(year)**	56.3±14.7
BMI (kg/m^2)	27.8±3.9
Amylase (U/L)	84.6±202.7
Postoperative amylase (U/L)	73.8±66.8
Postoperative hemoglobin gr/dl	13.1±1.4
Length of hospitalization (day)	3.9±1.6

SD: Standart deviation, BMI: Body mass index

Table 4. Data of patients undergoing elective cholecystectomy

	Cholecystectomy (n=50)	
Gender	**n**	**%**
Female	28	56.0
Male	22	44.0
Age group	**n**	**%**
Age <70	41	82.0
Age ≥70	9	18.0
BMI		
Normal	12	24.0
Overweight	19	38.0
Obese	19	38.0
Operation in the past		
No	50	100.0
Preoperative diagnosis		
Cholelytiasis	50	100.0
Elevation of liver function tests		
No	24	48.0
Yes	26	52.0
Leukocytosis		
No	21	42.0
Yes	29	58.0
ASA score		
ASA 1	17	34.0
ASA 2	21	42.0
ASA 3	10	20.0
ASA 4	2	4.0
Surgery performed		
Open cholecystectomy with laparoscopic onset	3	6.0
Laparoscopic cholecystectomy	47	94.0
Postoperative complications	**n**	**%**
No	40	80.0
Bleeding at the drain site	2	4.0
Gastroparesis	1	2.0
Bile leakage	2	4.0
Wound site infection	3	6.0
Abscess in the sac lodge	1	2.0
Biliary tract injury	1	2.0
Peroperative complication		
No	36	72.0
Gallbladder perforation	7	14.0
Site hemorrhage	5	10.0
Reason for switching to open surgery		
No	47	94.0
Vascular bleeding	1	2.0
Adhesion	2	4.0

BMI: Body-mass index, ASA: American Society of Anesthesiologist

Table 5. Comparison of amylase levels and length of hospital stay between groups

	Post-ERCP cholecystectomy (n=50)	Cholecystectomy (n=50)	
	Mean±SD	**Mean±SD**	**p**
Age (year)	57.8±18.5	56.3±14.7	0.664
Amylase (U/L)	100.6±214.4	84.6±202.7	0.703
Postoperative amylase (U/L)	160.4±197.9	73.8±66.8	0.005
Length of hospital stay (day)	5.5±3.2	3.9±1.6	0.002

ERCP: Endoscopic retrograde cholangiopancreatography, SD: Standart deviation

There was no statistically significant difference between the groups in terms of postoperative ERCP complications and postoperative complications related to age, gender, BMI, choledochal diameter, stenting, ASA scores, leukocyte level, KCFT level and type of surgery performed (p>0.05).

There was no statistically significant difference between group 1 and the group 2 in terms of postoperative complications (p>0.05) (Table 6).

Table 6. Comparison between groups in terms of postoperative complications

	Post-ERCP cholecystectomy (n=50)		Cholecystectomy (n=50)		
Postoperative complication	**n**	**%**	**n**	**%**	**p**
No	40	80.0	40	80.0	0.865
Bleeding at the drain site	2	4.0	2	4.0	
Gastroparasia	2	4.0	1	2.0	
Bile leakage	3	6.0	2	4.0	
Wound site infection	3	6.0	3	6.0	
Abscess in the sac lodge	--	--	1	2.0	
Biliary tract injury	--	--	1	2.0	

ERCP: Endoscopic retrograde cholangiopancreatography

There is also a statistically significant difference in terms of bile duct injury, vascular bleeding, adhesions (p >0.05). There was no statistically significant difference between the groups in terms of age, gender, BMI, choledochal diameter, stenting, ASA scores, leukocyte level, KCFT level, type of surgery performed in terms of postoperative ERCP complications and postoperative complications (p>0.05).

In the Precut Sphincterotomy-complications comparison, it was found that there was no statistically significant difference between ERCP procedure complications and postoperative complications and precut sphincterotomy (p >0.05), while there was a statistically significant difference between post-ERCP complications and precut sphincterotomy (p <0.05). While 33.3% of patients without precut sphincterotomy developed post-ERCP complications, 70.0% of patients with precut sphincterotomy developed post-ERCP complications. In other words, the rate of post-ERCP complications was found to be higher in patients who underwent precut sphincterotomy.

In the stone extraction-complication comparison, it was found that there was no statistically significant difference between ERCP procedure complication, post-ERCP complication and postoperative complications and stone extraction (p>0.05).

In the liver function tests elevation-complication comparison; it was found that there was no statistically significant difference between ERCP procedure complication, post-ERCP complication and postoperative complications and Liver function tests elevation (p>0.05).

In the pancreatic cannulation-complication comparison, it was found that there was no statistically significant difference between ERCP procedure complication and postoperative complications and pancreatic cannulation (p>0.05), while there was a statistically significant difference between post-ERCP complication and pancreatic cannulation (p<0.05). While 41.5% of patients without pancreatic cannulation developed Post-ERCP Complications, 77.8% of patients with pancreatic cannulation had a higher rate of Post-ERCP complications.

In the comparison of oddi dysfunction-complication; it was found that there was no statistically significant difference between ERCP procedure complication and postoperative complications and oddi dysfunction (p >0.05), while there was a statistically significant difference between post-ERCP complication and oddi dysfunction (p <0.05). Post-ERCP complications did not develop in 53.3% of patients with oddi dysfunction no, while 20% of patients with oddi dysfunction yes did not develop post-ERCP complications. In other words, it was found that the rate of post-ERCP complications was higher in patients with oddi dysfunction.

In terms of perioperative complications, none of the patients who underwent open cholecystectomy, choledochal exploration, and primary repair developed complications, while peroperative complications developed in all patients who underwent open cholecystectomy, choledochal exploration, and t-tube application, 57.1% of patients who underwent laparoscopic-onset open cholecystectomy, and 23.7% of patients who underwent LC.

In terms of perioperative complications, postoperative complications developed in 100% of patients who underwent open cholecystectomy, choledochal exploration and primary repair, 100% of patients who underwent open cholecystectomy, choledochal exploration and t-tube application, 14.3% of patients who underwent open cholecystectomy with laparoscopic onset and 10.5% of patients who underwent LC.

In the age group-complication comparison, it was found that there was no statistically significant difference between the age groups in terms of postoperative complications (p>0.05), while in terms of preoperative complications, 22% of patients younger than 70 years of age had preoperative complications, while patients aged 70 years and older had more preoperative complications (55.6%) (p<0.05).

DISCUSSION

In our study, the rate of conversion to open surgery in elective LC patients was 6%. This result was in accordance with the data of similar studies in the literature.[10,12-15] In our study, the rate of conversion to open surgery in LC's performed after ERCP was 22%. Laparoscopic operations may require conversion to open surgery for many reasons.[6] Different rates of conversion to open surgery are given in series (2%-14%).[7-15] Open surgery is performed early to avoid biliary tract injury due to forced cholecystectomy secondary to adhesions. This was thought to be the reason why our rate of conversion to open surgery was higher than the literature.

In the study by Stefanova et al.[11] 216 patients were included. The median age was 76 years (interquartile range 70-83). Most patients (80%, n=172) had mild pancreatitis and 12% (n=26) had severe disease. 24% (n=55) were treated with ERCP-sphincterotomy (ERCP-s); 40% (n=87) underwent LC alone; 11% (n=23) underwent ERCP-s followed by LC; and 25% (n=55) had no intervention. Patients without intervention were older (p<0.001) and more frail (p<0.001). Post-procedural readmission rates were lowest in the LC-only group with 6% (n=5) compared with 27% (n=14) for ERCP-s, 33% (n=7) for ERCP+LC and 31% (n=17) for the no intervention group (p=0.0001). Biliary-related mortality was highest in the non-intervention group (n=11, 20%). In our study, the lowest rates (in terms of conversion to open surgery and development of complications) were seen in those who underwent elective LC.

We found a statistically significant difference between the groups of patients who underwent elective LC and LC after ERCP in terms of postoperative amylase (100.6±214.4 U/L; 84.6±202.7 U/L, respectively) and length of hospital stay (5.5±3.2; 3.9±1.6 days, respectively). It was thought that this may be due to the reduction in the severity of cholecystitis after ERCP with relief of obstruction and decrease in inflammation.

In our study, the preoperative minor complication rate in group 1 patients was 26% and no major complications were observed. In group 2 patients, the per-operative minor complication rate was 28% and the major complication rate was 8%. The most common per-operative complication in both groups was gallbladder perforation and spillage of bile and gallstones into the peritoneal cavity. Another complication was leaking hemorrhages from the liver bed. There was no statistically significant difference between group 1 and group 2 patients in terms of per-operative complications.

In the literature, peroperative complications that can be corrected with simple surgical intervention, such as lung flushing after gallbladder perforation, cleaning stones that fall into the abdominal cavity, and using coagulation systems for bleeding from the liver bed, are called minor complications.[7,8,16-18] Unstoppable bleeding from the liver bed, major vessel injuries, luminal organ injuries, and biliary tract injuries are defined as major complications.[19-23] The preoperative minor and major complication rates are quite variable in the literature.[18-25] In our study, bile leakage and wound infection were the most common postoperative complications. When we evaluated group 1 and group 2 patients, there was no statistically significant difference in postoperative complications.

Difficult cannulation has been seen as a risk for complications after ERCP in many studies.[1,14,18] Repetitive trauma to the papilla and pancreatic sphincter is thought to play a role in the development of pancreatitis by disruption of pancreatic drainage by developing edema in the early period and stricture in the late period. The numbers of pancreatitis development according to the number of attempts of papilla cannulation are variable. Freeman et al.[16] determined this value as 6 in their study. One should not insist on attempting difficult cannulation because complications increase after

repeated cannulation due to mechanical damage caused by pancreatic and biliary tract instrumentation, hydrostatic damage after excessive injection, chemical and allergic damage caused by contrast material, enzymatic damage caused by intestinal contents, infection, and thermal damage. In our study, more than 3 repeated cannulation attempts in ERCP were termed as difficult cannulation and it was seen in 4 patients (8%).[16,18-20] The presence of diverticulum was detected in 2 patients and atrophic papilla was detected in the other patients as the cause of difficult cannulation. One patient developed pancreatitis and one patient developed cholangitis after difficult cannulation. In our study groups, the complication rate was 50% in both groups with and without difficult cannulation and the results were not statistically significant.[18-20]

Guidewire advancement into the pancreatic duct plays a role in the development of pancreatitis with mechanical damage. Lee et al.[17] reported in their prospective study that unintentional pancreatic cannulation played a role in the development of pancreatitis. In the study, complications developed in 6 (5.5%) of 106 patients without pancreatic cannulation, while complications developed in 20 (25.3%) of 79 patients with pancreatic cannulation. In our study, while the complication rate after ERCP was 41.5% in patients without pancreatic cannulation, this rate increased to 77.8% after unintentional pancreatic cannulation. These results are statistically significant ($p<0.048$).

Precut papillatomy refers to several endoscopic techniques used to access the bile duct (or pancreatic duct). Precut techniques are often used after failure of conventional methods of biliary cannulation. The reported complication rate due to endoscopic precut sphincterotomy is 6.9-9.8%.[16-20] In our study, it was shown that precut with needle-tipped sphincterotomy increased the development of complications ($p<0.05$).

The complication (cholangitis, cholecystitis, duodenal perforation, bleeding, pancreatitis, proximal and distal bile duct migration and recurrent biliary obstructions) rate after biliary stenting in ERCP varies between 8-10%. Due to long-term use of stents, duodenal wall necrosis and perforation may develop after pressure of the intradouodenal part of the stent on the duodenal wall. In patients without biliary stenting, 37.9% of patients had complications after ERCP; this rate increased to 61.9% in patients with stenting. In our study, stenting was performed 42% of the time, 32% for therapeutic and 10% for prophylactic purposes. Prophylactic plastic stent placement may increase the risk of complications in cases where stone removal from the bile duct is inadequate or unsuccessful. Consistent with the literature, stent placement increased the complication rate after ERCP in our patients.[1,7-11,15-20]

In our study, OSD was detected in 10% of the patients who underwent ERCP; while the post-ERCP complication rate was 46.7% in patients without OSD, this rate increased to 80% in patients with OSD. It was observed that the increase in post-ERCP complication rates in patients with OSD was consistent with the literature ($p<0.05$).

In our study, 32% of patients developed acute pancreatitis after ERCP, which is higher than the reported rates. We think that this rate is high due to the limited number of patients, the selection of a non-homogeneous patient group, and the presence of gallbladder stones along with biliary tract stones in the patients. Transient pancreatic enzyme elevation after ERCP is a common condition. In the literatüre, the frequency of hyperamylasemia after ERCP is reported to be between 25-75%.[1,7,10,15-21] In our study, the post-procedural amylase values of patients who underwent laparoscopic cholecystectomy after ERCP were 160.4±197.9U/L and hyperamylasemia was found in 44% of patients who underwent ERCP.

Cholangitis occurs in 0.4-1.8% of patients undergoing ERCP.[7,10,18,20,21] The most common infectious complication of ERCP is ascending cholangitis. It is defined as a clinical syndrome characterized by fever, jaundice and abdominal pain as a result of bile duct stasis and infection. It frequently occurs after ERCP as a result of inadequate drainage of the infected and obstructed biliary system. In our study, 8 (16%) patients developed acute cholangitis and this rate is above the limits given in the literature. All of the patients were diagnosed with obstructive icterus with different levels of elevated bilirubin levels before ERCP. These patients were considered to have cholangitis after the ERCP procedure because of procedure-related abdominal pain, elevated bilirubin levels and leukocytosis. Patients with elevated bilirubin levels before the procedure have an increased risk of concomitant ascending infection and increased complications after ERCP. In our study, abdominal tenderness with the smallest increase in the initially high bilirubin level after ERCP was accepted as a complication of cholangitis. Therefore, we think that the complication of acute cholangitis after ERCP is higher than the literature.

Although there is no consensus in the literature on when to perform ERCP, preoperative ERCP followed by laparoscopic cholecystectomy is the widely accepted method.[10,17,20-23] The effects of ERCP on the severity of cholecystitis and the technical difficulty of subsequent laparoscopic cholecystectomy are still debated. However, the opposing view is that ERCP may have a palliative effect on cholecystitis and indirectly on laparoscopic cholecystectomy because it provides source control by removing the bile duct stone and evacuates the gallbladder when the cystic duct is open.[24-30]

If stones in the common bile duct have not been reduced by ERCP and residual stones are suspected, the bile duct should be explored laparoscopically or openly. Although laparoscopic bile duct exploration is more popular these days, it is not practiced by many surgeons. Long operative time, special techniques, high morbidity and the risk of incomplete removal of stones detract from laparoscopic surgery. Therefore, open choledochal exploration is still widely used. It should be kept in mind that primary choledochal closure has been found to be safe in most of the studies in which choledochal exploration has been performed, but its prevalence is lower than that of t-tube. However, although the t-tube is widely used, its follow-up may pose some problems for surgeons and patients.[31-36]

Laparoscopic operations may require conversion to open surgery for various reasons. Different rates for conversion to open surgery are given in various series. Akın et al.[37] reported that 8.1% of 192 patients, Alabaz et al.[38] reported that 11% of 192 patients, and Ağalar et al.[39] reported that 6% of 500 patients started laparoscopic operation and switched to open surgery for various reasons. In our study, the rate of conversion to open surgery in elective laparoscopic cholecystectomy

patients was 6%. This result was in accordance with the literature. In our study, the rate of conversion to open surgery was 22% in laparoscopic cholecystectomies performed after ERCP. Open surgery was performed early to avoid bile duct injury due to forced cholecystectomy secondary to adhesions. Therefore, our rate of conversion to open surgery is higher than the literature.

The most common postoperative complications in our study were bile leakage and wound infection. Other postoperative complications were bleeding from the incision site, hiccups, gastroparesis, and hematoma in the pouch lumen. There was no statistically significant difference in postoperative complications between group 1 and group 2 patients ($p<0.865$). In general, there was no difference between the groups when the presence of complications was compared, but abscess development in the gallbladder lumen and biliary tract injury were found more frequently in group 1 patients.

Limitations

The retrospective design of the study is our most important limitation. In addition, although 100 patients were not few, the number of patients remained small in subgroups due to the fact that the patients were divided into many subgroups due to the distribution of post-procedures and complications; therefore, a larger number of patients for such frequent operations would provide more valuable data.

CONCLUSION

It is important to correctly determine the indication for an ERCP, to be aware of possible complications and to avoid unnecessary procedures that can lead to complications. We believe that appropriate treatment should be initiated for any complication that occurs during or after ERCP and that close follow-up of the patient after ERCP is necessary. Each patient should be evaluated individually and physicians should determine the appropriate method according to demographic, clinical and laboratory findings. The experience of the team performing the procedure is also very important in choosing the method. We believe that early cholecystectomy is more appropriate before complications occur after ERCP.

ETHICAL DECLARATIONS

Ethics Committee Approval

This thesis study was initiated with the approval of Afyonkarahisar Health Sciences University Medical Faculty Clinical Researches Ethics Committee (Date: 18.12.2014, Decision No: 277).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Effect of glucose lymphocyte ratio on prognosis in patients operated with the diagnosis of pancreatic adenocarcinoma

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ABSTRACT

Aims: Pancreatic adenocarcinoma is one of the most aggressive cancers, and predicting prognosis and survival clinically is challenging. Prognostic markers, easily accessible and routinely evaluated in diagnostic tests, are frequently seen in the literature for survival prediction. So far, the glucose lymphocyte ratio (GLR) has emerged as an indicator that can assess both metabolic dysregulation and immune response. In this study, the aim was to assess the impact of GLR on prognosis and survival by following patients diagnosed with pancreatic adenocarcinoma who underwent surgery.

Methods: Between January 1, 2016, and April 31, 2021, a totalof 58 patients who underwent Whipple procedure due to pancreatic adenocarcinoma at the Department of General Surgery, Hitit University, were included in the study. Demographic characteristics, tumor features, laboratory results, and survival durations of the patients were collected. GLR was determined as a mortality predictor, and estimated survival times associated with GLR were determined using Kaplan-Meier Survival analysis. The optimal GLR value was determined through ROC analysis.

Results: During the postoperative period, the average follow-up time for patients was 11.39 months, with the longest follow-up time being 48 months. During this period, 43 patients (74.14%) were deceased, while 15 patients (25.86%) survived. The mean age and ASA scores of deceased patients were significantly higher compared to survivors ($p < 0.001$ and $p < 0.001$, respectively). Glucose levels were significantly higher in the mortality group compared to the survival group ($p=0.008$). GLR was notably higher in the mortality group ($p=0.170$; $p=0.703$; $p=0.429$; and $p=0.031$). The GLR value that best distinguished the two groups was found to be 94.6387 with 93.3% specificity and 95.8% positive predictive value. Crossing this threshold increased the mortality risk approximately 4.27 times within one year and increased the overall mortality risk by approximately 15 times ($p=0.014$ and $p=0.002$). The estimated life expectancy for patients below the threshold value was calculated to be an average of 20.996 months, whereas for patients above the threshold value, this expectation was calculated to be an average of 4.427 months ($p < 0.001$).

Conclusion: We believe that GLR may be helpful in predicting one-year survival and determining overall survival duration in patients undergoing surgery for pancreatic adenocarcinoma.

Keywords: Pancreatic adenocarsinoma, glucose lymphocyte ratio, prognosis, survival

INTRODUCTION

Pancreatic cancer ranks 12th in incidence according to 2022 WHO data, yet it ranks 6th in mortality.[1] This signifies its highly aggressive nature. The 5-year survival rate is reported at 9%, with a 20-year survival rate of only 5%.[2,3] It is projected that the incidence of pancreatic cancer will rapidly increase.[4] While surgical resection is the most effective treatment, in this disease, which typically progresses silently and is often diagnosed in advanced stages, efforts are made to maximize benefits through neoadjuvant or adjuvant chemotherapy, radiotherapy, and immunotherapy. Knowing the prognosis is crucial for treatment planning, as it's necessary to understand how much benefit a patient will derive from treatment. Therefore, numerous studies have been conducted on the prognosis of pancreatic adenocarcinoma, identifying various prognostic factors and formulas.[3,5-9] Glucose lymphocyte ratio (GLR) has been identified as a prognostic marker in many cancers such as gastric cancer, hematoma, colorectal cancer, breast cancer, and esophageal cancer. However, there is limited research on the use of GLR as a prognostic marker in pancreatic cancer.[10-13] This study aimed to investigate

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the impact of GLR on prognosis and survival in patients undergoing surgery for pancreatic adenocarcinoma.

METHODS

The study was carried out with the permission of Hitit University Non-interventional Studies Ethics Committee (Date: 03.06.2021, Decision No: 2021-69). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Between January 1, 2016, and April 31, 2021, a retrospective analysis was conducted on 103 patients aged 18 to 90 who underwent Whipple procedure at the Department of General Surgery, Hitit University. Exclusion criteria included pathologies other than pancreatic adenocarcinoma, hematologic diseases, medication use affecting hematologic and biochemical parameters, inflammatory or infectious diseases. A total of 58 patients were included in the study. Demographic characteristics, tumor features, laboratory results, and survival durations were collected. Statistically significant prognostic markers, including GLR, were identified.

Statistical Analysis

This study was prospectively designed. IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA) was utilized for all statistical analyses. Descriptive statistics were employed to present categorical variables as counts and percentages, and numerical variables were expressed as mean±standard deviation for normally distributed variables or median (minimum-maximum value) for non-normally distributed variables. The normality of the distribution of data was evaluated using the Shapiro-Wilks test. Pearson and Spearman correlation coefficients were employed to assess correlations between variables, depending on the data distribution. To compare numerical measurements between independent groups, such as WBC, neutrophil count, platelet count, clucose, CRP, GLR, NLR, PLR, and overall survival duration the Mann-Whitney U test was utilized for comparisons among two groups, considering the distribution of the data. Student t-test analysis was conducted to assess age and lymphocyte count, in accordance with the distribution of the data. Categorical variables such as gender, ASA scores, localization, differentiation and 1 year survival rate were evaluated for ratio comparisons between research groups using the Chi-square test. Receiver operating characteristic (ROC) curves were utilized to demonstrate the discriminative ability of statistically significant variables. Cut-off values for these markers were determined using the area under the curve and the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy values were calculated based on these cut-off values. Odds ratio values were computed for these cut-off points. Kaplan-Meier survival analyses for disease-free survival were performed, and statistical significance between the two groups was assessed through the Log-Rank test. A linearity diagram illustrating GLR and overall total survival duration was generated. A significance level of $p<0.05$ was deemed statistically significant.

RESULTS

During the postoperative period, the average follow-up time for patients was 11.39 months, with the longest follow-up time being 48 months. During this period, 43 patients (74.14%) passed away, while 15 patients (25.86%) survived. A total of 27 patients (62.7%) died within 0-3 months postoperatively due to early complications. The causes of death were as follows: 4 (9.3%) due to COVID-19, 7 (16.2%) due to cardiac disease, 6 (13.9%) due to pulmonary disease, and 10 (23.2%) due to anastomotic leakage-sepsis. Additionally, 16 patients (37.3%) were lost during follow-up after discharge due to underlying diseases.

The mean age of deceased patients was 72±8 years, whereas the mean age of surviving patients was 62±11 years, showing a statistically significant difference ($p <0.001$). The 58 patients were divided into two groups: 15 survivors and 43 deceased. When comparing groups based on gender, tumor localization, tumor differentiation, neutrophil, lymphocyte, and platelet count, CRP level, NLR, and PLR, no statistically significant differences were observed.

Of the 58 patients, 23 (39.66%) were classified as ASA3, and 35 (60.34%) were classified as ASA4. Among the surviving patients, 12 (80%) were ASA3, and 3 (20%) were ASA4; among the deceased patients, 11 (25.58%) were ASA3, and 32 (74.42%) were ASA4, showing a significant statistical difference ($p<0.001$). The median glucose level for all patients was 116 (70-360) mg/dl, while among survivors it was 97 (70-193) mg/dl, and among deceased patients it was 118 (79-360) mg/dl, with a statistically significant higher level observed among deceased patients ($p=0.008$). The median glucose lymphocyte ratio for all patients was 83.85 (23.74-280.95), among survivors it was 76.52 (30.3-177.06), and among deceased patients it was 98.29 (23.74-280.95), with a statistically significant higher level observed among deceased patients ($p=0.031$). The median survival time for all patients was 3 (0-48) months, 27 (3-48) months for survivors, and 1 (0-40) month for deceased patients, with a statistically significant difference observed ($p <0.001$). When examining one-year survival durations, it was observed that 23 out of 58 patients (39.66%) survived beyond one year, while all patients in the surviving group (15 patients, 100%) lived longer than one year. In contrast, only 8 out of 43 deceased patients (18.6%) survived one year, showing a statistically significant difference between the two groups ($p <0.001$) (Table 1).

The significant difference in GLR values between the alive and mortality groups prompted an assessment of the optimal cut-off value for distinguishing between the two using ROC analysis, resulting in an AUC of 0.668 (95% CI=0.544-0.833, $p=0.031$) (Figure 1). The optimal GLR value identified for mortality prediction was 94.6387, with 93.3% specificity, 53.5% sensitivity, 95.8% positive predictive value, 41.2% negative predictive value, and 63.79% test accuracy (OR 16.1, 95% CI 1.941-133.516, $p=0.002$) (Table 2). GLR above 94.6387 was associated with approximately a 4.27-fold increase in the risk of mortality within one year and an approximately 15-fold increase in the overall mortality risk ($p=0.014$ and $p=0.002$). Additionally, a negative correlation was observed between GLR and overall total survival duration ($r=-0.282$, $p=0.032$) (Figure 2).

Furthermore, comparing the overall survival times of patients stratified by their GLR values revealed a significant difference in median survival time between those with GLR values below and above 94.6387. The median survival time for patients with GLR values below this threshold was 8.8 months, while for those above the threshold, it was 1 month. Kaplan-Meier Survival Analysis also showed a significant difference in estimated overall survival time between the two groups, with patients having GLR <94.6387 showing a longer estimated survival time (20.996 months) compared to those with GLR ≥94.6387 (4.427 months, $p <0.001$) (Table 3 and Figure 3).

Table 1. Assessment of all patients and statistical comparison results between alive and deceased patients

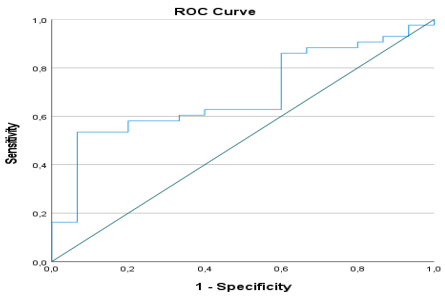
Variables		All patients (n=58)	Alive (n=15; 25.86%)	Deceased (n=43; 74.14%)	Statistical significance
Age		70±10	62±11	72±8	<0.001
Gender	Male	35 (60.34%)	9 (60%)	26 (60.47%)	0.975
	Female	23 (39.66%)	6 (40%)	17 (39.53%)	
ASA	ASA 3	23 (39.66%)	12 (80%)	11 (25.58%)	<0.001
	ASA 4	35 (60.34%)	3 (20%)	32 (74.42%)	
Localization	Ampulla	14 (24.14%)	5 (33.33%)	9 (20.93%)	0.484
	Head	44 (75.86%)	10 (66.67%)	34 (79.07%)	
Differentiation	Well-differentiated	9 (15.52%)	1 (6.67%)	8 (18.6%)	0.354
	Moderately-differentiated	42 (72.41%)	11 (73.33%)	31 (72.09%)	
	Poorly-differentiated	7 (12.07%)	3 (20%)	4 (9.3%)	
WBC		6.88 (3.61-16.13)	6.49 (4.68-12.51)	7.04 (3.61-16.13)	0.908
Neutrophil count		4.57 (1.28-15)	4.19 (2.57-9.2)	4.7 (1.28-15)	0.894
Lymphocyte count		1.58±0.63	1.59±0.47	1.57±0.68	0.907
Platelet count		252 (108-737)	256 (108-345)	250 (117-737)	0.993
Glucose		116 (70-360)	97 (70-193)	118 (79-360)	0.008
CRP		11.5 (3-150)	7 (3-90)	14 (3-150)	0.170
GLR		83.85 (23.74-280.95)	76.52 (30.3-177.06)	98.29 (23.74-280.95)	0.031
NLR		3.08 (0.64-35.71)	2.76 (1.34-7.28)	3.39 (0.64-35.71)	0.703
PLR		172.52 (38.58-619.51)	173.45 (56.25-289.92)	171.58 (38.58-619.51)	0.429
1-year Survival	Deceased	35 (60.34%)	0 (0%)	35 (81.4%)	<0.001
	Survived (1 year)	23 (39.66%)	15 (100%)	8 (18.6%)	
Overall total survival duration		3 (0-48)	27 (3-48)	1 (0-40)	<0.001

ASA: American Society of Anesthesiologists, WBC: White blood count, CRP: C-reactive protein, GLR: Glucose lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet/lymphocyte ratio

Table 2. Diagnostic value of GLR in the prediction of mortality

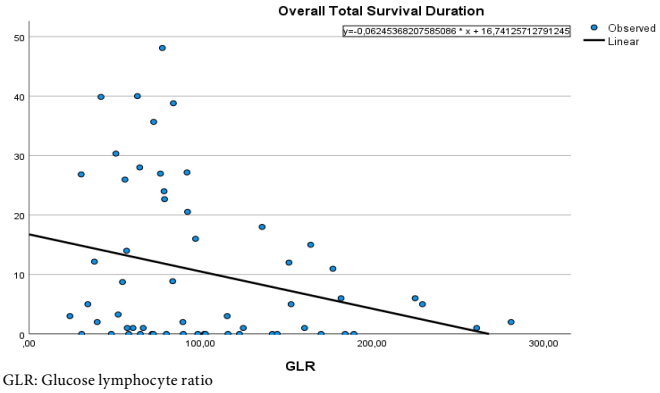
Variables	Cut-off value	Diagnostic parameters					ROC analysis			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (SE)	95% CI	p	Odds Ratio	95% CI	p
GLR	94.6387	53.50%	93.30%	95.80%	41.20%	63.79%	0.668 (0.074)	0.544-0.833	0.031	16.100	1.941-133.516	0.002

GLR: Glucose lymphocyte ratio, ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval



GLR: Glucose lymphocyte ratio

Figure 1. Receiver operating curve of GLR in the distinction of alive and mortality patient groups



GLR: Glucose lymphocyte ratio

Figure 2. Linear graph of overall total survival duration and GLR

Table 3. Kaplan-Meier survival analysis-estimated overall total survival duration according to patient groups

Group	Estimated Mean	95% CI	Log-Rankp
Negative (<94.6387)	20.996 (3.69)	13.763-28.229	<0.001
Positive (>94.6387)	4.427 (1.249)	1.979-6.875	
Overall	14.182 (2.5)	9.281-19.083	

CI: Confidence interval

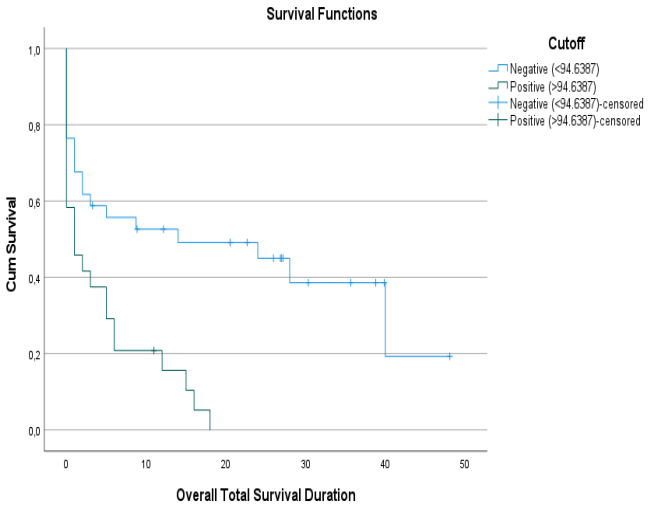


Figure 3. Kaplan-Meier survival analysis-cumulative survival to overall total survival duration graph according to patient groups

When evaluating only the one-year period, patients with GLR <94.6387 had a longer estimated life expectancy (7.043 months) compared to those with GLR ≥94.6387 (3.75 months, p=0.016). Additionally, approximately 80% of patients with GLR ≥94.6387 died within the first year, while this rate was approximately 45% in patients with GLR <94.6387 (Table 4 and Figure 4).

Table 4. Kaplan-Meier survival analysis-estimated 1-year period survival duration table according to patient groups

Group	Estimated mean	95% CI	Log-Rank p
Negative (<94.6387)	7.043 (0.941)	5.198 (8.889)	0.016
Positive (>94.6387)	3.75 (0.951)	1.887 (5.613)	
Overall	5.667 (0.71)	4.275 (7.06)	

CI: Confidence interval

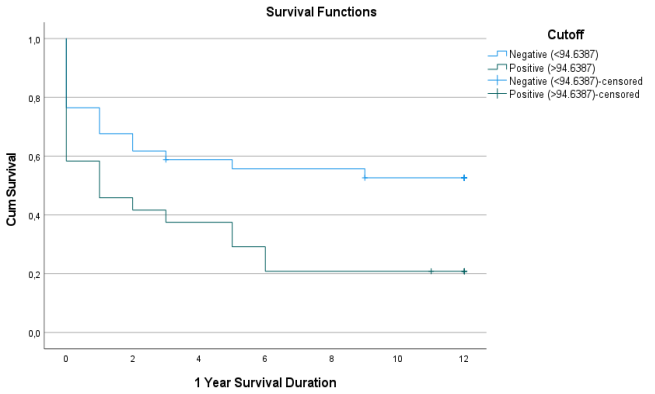


Figure 4. Kaplan-Meier survival analysis-cumulative survival to 1-year survival period graph according to patient groups

DISCUSSION

Periampullary tumors are characterized by their insidious clinical presentation, often resulting in delayed diagnosis, and typically being diagnosed in advanced stages, which contribute to their aggressive course and poor prognosis. According to the WHO's 2022 data, the incidence of these tumors is 510,992, with a mortality rate of 467,409 patients.[1] Despite ranking 12th in incidence, they rank 6th in mortality. Given their relatively common occurrence and poor prognosis, research efforts have been and continue to be focused on finding the most effective treatments for these tumors.

Knowing the prognosis of the disease is crucial for determining the appropriate treatment. Studies have focused on various factors including demographic information such as age, comorbidities, ASA score, and gender; easily detectable inflammatory markers such as neutrophil count, lymphocyte count, platelet count, hemoglobin level, CEA level, Ca 19-9 level, CRP level, glucose, and HbA1c levels, AST/ALT level; tumor-related information such as tumor location, differentiation, perineural or lymphovascular invasion status, lymph node metastasis, stage, proliferation index; as well as biomarkers such as IL-15, GM-CSF, and genetic analyses related to various genes such as FZD, GSTM4, ICOSLG.

Zhang et al.[2] categorized the pathogenesis of pancreatic cancer into inflammation, desmoplastic stroma, immunosuppressive tumor microenvironment, epithelial-mesenchymal transition, angiogenesis, cancer stem cells, and gut microbiota. Inflammation has been proposed to play a significant role in the initiation and progression of pancreatic cancer.[14] It has been understood that inflammatory cells such as monocytes, lymphocytes, neutrophils, and cytokines released by these cells interact with cancer cells and are effective in the tumor microenvironment.[14]

Lymphocytes are an essential component of the immune system working to eliminate tumor cells. A decrease in lymphocyte count can result in both a reduction in lymphocyte cytotoxic effects and a weakening of immunity due to decreased cytokine levels. Glucose also plays a crucial role in metabolism, and its regulation is vital. Impaired glucose regulation in diabetic patients is associated with chronic inflammation. Studies have reported that high glucose levels are associated with poor prognosis in both pancreatic cancer and other cancer patients[15,16]. Additionally, diabetes mellitus (DM) has been shown to have an impact on the development, perioperative complications, and prognosis of pancreatic cancer.[17]

While some of the prognostic factors mentioned and unspecified can be evaluated in secondary and tertiary care hospitals, certain markers such as genetic analyses are complex, expensive, and time-consuming tests primarily available in specialized centers. Therefore, as evident from the literature review, research has predominantly focused on developing formulas and scoring systems based on easily accessible and cost-effective inflammatory markers and simple laboratory results, which provide objective outcomes.

The Gustave Roussy Immun Score (GRIm-Score), initially defined by Bgot and al.[18] in 2017, is calculated based on serum lactate dehydrogenase (LDH), serum albumin, and neutrophil-lymphocyte ratio (NLR). Önder et al.[19] and Başoğlu et al.[7] have demonstrated that GRIm-Score is a readily applicable prognostic marker in colorectal cancers and pancreatic adenocarcinomas, respectively.

The modified Glasgow Prognostic Score (mGPS) is a prognostic indicator easily accessible, determined by C-reactive protein (CRP) and albumin levels. There are numerous studies and differing opinions regarding mGPS. Petrelli et al.[20] have shown it to be a weak prognostic marker for colorectal cancers. Conversely, Imakoa et al.[21] have argued it to be a robust prognostic marker for pancreatic cancer.

The Memorial Sloan Kettering Prognostic Score (MPS), an alternative scoring system to the Glasgow Prognostic Score, is based on albumin and neutrophil-lymphocyte ratios. In a study by Lebenthal et al.[22] MPS was found to be an independent tool predicting survival in metastatic pancreatic cancers.

The Globulin-lymphocyte ratio (GLR) has been associated with poor prognosis in various cancer types including lung, breast, stomach, liver, esophageal, kidney, colorectal cancers, and melanoma, as evidenced by a study encompassing 2172 patients.[10] Similarly, Hannarici et al.[13] for metastatic stomach cancer and Yang et al.[12] for colorectal cancers have shown GLR to be an independent prognostic marker.

In this study, age, ASA score, glucose, and GLR were identified as prognostic factors. ROC analysis was employed to determine the optimal cut-off value for GLR, resulting in 94.6387. While the specificity and positive predictive value were high, sensitivity and negative predictive value were found to be low. It was demonstrated that having a GLR value above the cut-off posed a 15-fold risk for overall survival and a 4.27-fold risk for 1-year survival. Survival analysis conducted by dividing patients into two groups based on GLR

cut-off revealed an estimated survival time of 20.996 months for those with low GLR and 4.427 months for those with high GLR. When examining the 1-year survival, it was estimated that 80% of those with high GLR and 45% of those with low GLR would die within a year. Furthermore, although NLR and TLR ratios, which have shown significance in other studies, did not demonstrate statistical significance in our study.

Zhong et al.[23] conducted a study with 360 pancreatic adenocarcinoma patients, investigating the role of NLR, TLR, GLR, and LMR in predicting the prognosis of pancreatic cancer based on pre-treatment laboratory parameters. They found GLR to be significant with 66.4% sensitivity and 77.6% specificity in ROC analysis. Similarly, PLR, LMR, and NLR were also found to be significant. However, when subjected to multivariate analysis, only GLR and CA19-9 were identified as independent factors for survival, with GLR being superior to CA19-9.

Zhang et al.[24] examined 259 patients with pancreatic adenocarcinoma. In their study, they applied ROC analysis to inflammatory markers including NLR, PLR, CLR, LMR, and CA19-9, comparing them with each other. Only PLR had a higher AUC value than GLR. In univariate analyses, T and N stage, tumor differentiation, neural invasion, and GLR were identified as prognostic factors for survival. In multivariate analysis, N stage and GLR were independent prognostic factors, although GLR was not found to be prognostic for OS. Subsequently, they divided these patients into a subgroup and reanalyzed, revealing prognostic significance in young male patients with pancreatic body-tail, N1 lymph node involvement, and CA19-9>200 U/ml.

Limitations

Some limitations of our study can be identified as follows. Firstly, due to being conducted in a single center and within a limited period, our sample size remained at 58. Conducting the study in a larger patient cohort could provide more reliable results. While our study addressed some prognostic factors mentioned in the literature, expanding the number of factors and conducting the study with more detailed data could be beneficial. Independent factors can be identified through multivariate analyses. There have been numerous studies on inflammatory markers, and different results have been obtained among them. While markers such as NLR, TLR, GLR, and LMR have been found to be prognostic in some studies, they have not been found to be so in others. We believe this may be related to other events triggering inflammation. Although conditions triggering inflammation have been excluded from the studies, the retrospective nature of the conducted studies reduces their reliability.

CONCLUSION

We believe that GLR may be helpful in predicting one-year survival and determining overall survival duration in patients undergoing surgery for pancreatic adenocarcinoma. We believe that prospective studies with pre-defined exclusion criteria would be more meaningful and reliable.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Hitit University Non-interventional Studies Ethics Committee (Date: 03.06.2021, Decision No: 2021-69).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data availability statement

Data and materials in this study can be requested upon reasonable request directly from the corresponding author.

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Review

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The impact of psychological factors on in vitro fertilization (IVF) outcomes: a comprehensive review

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ABSTRACT

This comprehensive review explores the significant impact of psychological factors on the outcomes of in vitro fertilization (IVF) treatments. Despite the advancements in medical technology enhancing the physical success rates of IVF procedures, the psychological well-being of individuals undergoing these treatments plays a crucial role in their overall effectiveness. This paper delves into the various psychological stressors faced by couples, including anxiety, depression, and stress, and their direct correlation with IVF treatment outcomes. By examining a wide range of studies, this review highlights the importance of psychological interventions and support systems in improving the success rates of IVF treatments. Furthermore, it discusses the current gaps in the literature and suggests directions for future research. The findings of this review underscore the necessity of integrating psychological care into fertility treatments to address the mental health needs of individuals undergoing IVF, thereby enhancing their quality of life and increasing the likelihood of successful outcomes. Through a detailed analysis of existing research and methodologies, this paper aims to contribute to the understanding of the psychosocial aspects of IVF and encourage the development of more holistic treatment approaches.

Keywords: IVF, psychological factors, fertility treatment, anxiety, depression, treatment outcomes

INTRODUCTION

In vitro fertilization (IVF) stands as a pivotal solution for countless individuals and couples grappling with infertility. This advanced reproductive technology involves extracting eggs, retrieving a sperm sample, and then manually combining an egg and sperm in a laboratory dish. The embryo(s) is subsequently transferred to the uterus, aiming to initiate a successful pregnancy. Since the inception of the first IVF baby in 1978, the procedure has undergone extensive advancements, integrating cutting-edge technologies and methodologies to augment success rates.[1]

While the focus predominantly lies on the physical and medical facets of IVF, the psychological ramifications for individuals embarking on this intricate journey warrant considerable attention. The emotional and psychological stressors, including financial burdens, societal pressures, and the oscillation between hope and disappointment, significantly influence the treatment experience and outcomes.[2] Evidence suggests that psychological distress can profoundly affect IVF success rates, impacting physiological responses to treatment and influencing decisions regarding the continuation or termination of treatment efforts.[3]

The aim of this comprehensive review is to elucidate the complex interplay between psychological factors and IVF outcomes. This exploration into how stress, anxiety, depression, and coping strategies affect IVF success rates endeavors to underscore the critical need for psychological support and interventions within the IVF treatment protocol. Moreover, this paper seeks to highlight the lacunae in existing literature and chart future research directions, advocating for a holistic approach to fertility treatment that prioritizes both physical and psychological health.

This research extends its purview to assess the efficacy of psychological interventions, such as counseling and stress management techniques, in enhancing IVF outcomes. By amalgamating data from diverse studies, including quantitative and qualitative research as well as meta-analyses, this review aims to furnish a thorough perspective on the prevailing knowledge landscape in this domain.

Comprehending the psychological aspects of IVF is paramount in devising effective support mechanisms and interventions that can ameliorate the well-being of individuals undergoing

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treatment, thereby potentially elevating IVF success rates. As infertility remains a formidable challenge for many, the amalgamation of psychological care into fertility treatments emerges as a crucial element of a comprehensive care paradigm. This review aspires to contribute to the ongoing discourse on the imperative of addressing the psychological needs of individuals and couples navigating the complexities of IVF, calling for a treatment paradigm that holistically addresses both the physical and emotional facets of fertility challenges.

Common Psychological Problems Observed in Couples Applying for In Vitro Fertilization Treatment

Couples undergoing IVF treatments frequently experience psychological distress, including anxiety, depression, and stress. The prevalence of anxiety and depression among individuals facing infertility is significantly higher compared to the general population, with reported rates of anxiety and depression among women undergoing fertility treatments ranging up to 40% and 30% in men.[2] The psychological impact of infertility and the stressors associated with the IVF process-such as the uncertainty of outcomes, financial burden, and societal pressures-contribute to these high levels of distress.[4]

The Effects of Psychological Factors on Treatment Outcomes

The interaction between psychological distress and IVF outcomes is a critical area of research. Studies have indicated that stress and anxiety may adversely affect the outcomes of fertility treatments, including reducing the chances of successful implantation and pregnancy.[5,6] The mechanisms proposed include alterations in physiological processes such as hormonal imbalances and changes in immune function, which could impact embryo quality and implantation success.[3]

Gaps in the Existing Literature

While the link between psychological distress and IVF outcomes is recognized, there remains a paucity of research in several areas. Notably, longitudinal studies examining the psychological impact over multiple IVF cycles are scarce.[7] The effectiveness of specific psychological interventions aimed at improving IVF outcomes needs further exploration through randomized controlled trials.[8] Additionally, the psychological experiences of men undergoing IVF treatments are underrepresented in the literature, highlighting a significant gap in understanding the couple's experience as a whole.[9]

METHODS

The methodology employed in this comprehensive literature review was meticulously designed to encompass a broad spectrum of empirical and theoretical studies addressing the psychological factors influencing IVF treatment outcomes. The overarching goal was to synthesize a diverse array of scholarly works to discern patterns, identify gaps, and illuminate the multifaceted relationship between psychological distress and IVF success rates. This section delineates the systematic approach adopted in compiling relevant literature, including the databases searched, keywords utilized, and the criteria for study selection. Additionally, it outlines the types of studies examined, ranging from experimental and observational studies to meta analyses, to provide a holistic understanding of the subject matter.

Database Search and Keywords

A systematic search was conducted across multiple electronic databases recognized for their extensive repository of academic and clinical research in the fields of psychology, medicine, and social sciences. The primary databases included PubMed, PsycINFO, Scopus, and Web of Science, due to their comprehensive coverage of peer-reviewed journal articles, conference proceedings, and other scholarly works pertinent to the topic. The search strategy employed a combination of keywords and MeSH terms tailored to capture the breadth of research on psychological factors and IVF outcomes. Key search terms included "in vitro fertilization," "IVF," "psychological stress," "anxiety," "depression," "mental health," "IVF outcomes," "fertility treatment success," and "psychosocial interventions." Boolean operators (AND, OR) were utilized to refine the search and ensure a comprehensive retrieval of relevant literature.

Selection Criteria

The inclusion criteria for studies in this review were defined to ensure the selection of high-quality and relevant research. Studies were considered eligible if they: (1) were published in peer-reviewed journals, (2) focused on the psychological aspects of IVF treatments, including psychological distress, interventions, and their impact on treatment outcomes, and (3) were conducted on human subjects undergoing IVF treatments. Both qualitative and quantitative studies were included to encompass a wide range of perspectives and methodologies.

Exclusion criteria were applied to maintain the review's focus and quality. Studies were excluded if they: (1) were not published in English, (2) focused solely on medical or biological aspects of IVF without addressing psychological factors, or (3) were case reports, editorials, or commentaries, given their limited empirical data.

Types of Studies Examined

To ensure a comprehensive understanding of the psychological factors affecting IVF outcomes, this review included a variety of study designs.

Experimental studies: Randomized controlled trials examining the efficacy of psychological interventions (e.g., counseling, cognitive-behavioral therapy, mindfulness-based stress reduction) on IVF success rates were included. These studies offer robust evidence on the causal relationships between interventions and outcomes.

Observational studies: Cohort, case-control, and cross-sectional studies providing insights into the prevalence of psychological distress among IVF candidates and its correlation with treatment outcomes were reviewed. These studies contribute to understanding the association between psychological factors and IVF success rates in real-world settings.

Meta-analyses and systematic reviews: Meta-analyses and systematic reviews synthesizing the results of multiple studies were particularly valued for their ability to provide a high-level overview of existing research, assess the overall effectiveness of psychological interventions, and identify patterns and gaps in the literature.

RESULTS

The systematic review of the literature reveals significant insights into the impact of psychological factors on IVF success rates, elucidating the role of psychological support and interventions, and the potential effects of psychological stress on sperm/ova quality, embryo development, and implantation.

The analysis underscores the profound influence of psychological interventions on enhancing IVF outcomes. Studies within this review demonstrate that couples undergoing IVF who participated in psychological support programs, including counseling, stress management workshops, and cognitive-behavioral therapy, exhibited markedly lower levels of stress and anxiety.[10,11] Furthermore, these psychological interventions were correlated with improved IVF success rates, evidenced by higher pregnancy rates and lower miscarriage rates among participants receiving such support compared to control groups.[12,13]

The review highlights a range of strategies and methods employed to support the psychological health of couples undergoing IVF treatments. These include individual and couples counseling, group therapy sessions focused on stress reduction and emotional coping, and mindfulness-based stress reduction programs designed to enhance emotional well-being and resilience.[14,15] Additionally, online support forums and telehealth psychological services have emerged as vital resources, offering accessibility and anonymity for those seeking support.[16]

Emerging research within the scope of this review suggests that psychological stress may have direct physiological effects on gamete quality, embryo development, and the implantation process. Studies have found correlations between high stress and anxiety levels with decreased sperm motility and concentration, as well as alterations in ova quality.[17,18] Furthermore, elevated stress levels have been associated with reduced embryo quality and lower implantation rates, positing stress as a potential mediator in the physiological processes underlying successful IVF outcomes.[19,20]

CONCLUSION

The intricate journey of IVF is a beacon of hope for many aspiring parents grappling with infertility, a path laden with not only medical but also significant psychological challenges. The synthesis of literature presented in this review underscores the profound impact of psychological factors on IVF outcomes and elucidates the critical role of psychological support and interventions in enhancing the success rates of these treatments. Furthermore, it brings to light the various strategies employed to bolster the psychological health of couples embarking on this arduous journey, as well as the potential physiological effects of psychological states on sperm/ova quality, embryo development, and implantation.

A cardinal finding of this review is the demonstrable benefit of psychological interventions, such as counseling, cognitive-behavioral therapy, and stress management techniques, in mitigating the emotional and psychological distress experienced by IVF candidates. These interventions not only foster a more positive psychological state but are also associated with improved IVF outcomes, indicating a bidirectional relationship between psychological well-being and treatment success. This revelation highlights the indispensability of integrating psychological care into fertility treatments, advocating for a holistic approach that addresses both the mental and physical aspects of fertility challenges.

Moreover, the exploration of strategies to support the psychological health of couples has revealed a multifaceted approach encompassing individualized counseling, support groups, and mindfulness practices. These methods provide a scaffold for couples, offering them the resilience and emotional fortitude needed to navigate the uncertainties of IVF treatments. The potential physiological effects of psychological factors on reproductive outcomes further accentuate the complexity of the fertility journey, suggesting that emotional states may influence biological processes critical to the success of IVF.

The findings of this review accentuate the paramount importance of understanding and managing psychological factors in the context of IVF treatments. The emotional and psychological dimensions of infertility and fertility treatments are inextricably linked to their medical counterparts, each influencing the other in a complex interplay that shapes the treatment experience and outcomes. Recognizing and addressing these psychological factors is not merely an adjunct to fertility treatments but a cornerstone of comprehensive care that can significantly enhance the likelihood of successful outcomes.

Future research should endeavor to fill the identified gaps in the literature, particularly concerning the long-term psychological impact of IVF, the effectiveness of specific psychological interventions, and the role of male psychological health in treatment outcomes. Longitudinal studies examining the cumulative effect of repeated IVF cycles on psychological well-being, randomized controlled trials assessing the efficacy of novel psychological interventions, and research exploring the psychological experiences of men in the context of IVF are urgently needed. Additionally, the influence of cultural and societal factors on psychological distress and IVF outcomes warrants further exploration, emphasizing the need for culturally sensitive approaches to care.

In conclusion, the integration of psychological support and interventions into IVF treatments offers a beacon of hope for enhancing treatment success and improving the overall well-being of individuals facing the challenges of infertility. As we move forward, a more nuanced understanding of the psychological aspects of IVF, coupled with a commitment to addressing these factors, will undoubtedly pave the way for more effective and compassionate fertility care.

ETHICAL DECLARATIONS

Referee Evaluation Process
Externally peer-reviewed.

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Journal of Comprehensive Surgery

Case Report

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A rare indication for appendectomy: acute appendicitis following ingestion of a foreign body

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ABSTRACT

Foreign body ingestion is mostly seen in the pediatric age group but can also occur accidentally or intentionally in adults. However, only about 20% of cases require endoscopic intervention, and less than 1% necessitate surgical intervention. Rarely, ingested foreign bodies can lead to acute appendicitis, requiring appendectomy. In the presented case, a patient who swallowed a screw seven days prior was closely monitored, and when the foreign body did not change position, colonoscopy was performed up to 20 cm proximal to the ileocecal valve without finding the object. As the patient developed tenderness upon abdominal examination, treatment was completed with appendectomy. It should be kept in mind that, although rare, acute appendicitis can develop in patients who have ingested foreign bodies and may require appendectomy.

Keywords: Foreign body , acute appendicitis, foreign body, a rare indication

INTRODUCTION

Ingestion of foreign bodies commonly occurs in the pediatric age group but can also happen accidentally or intentionally in adults. In the United States, over 100,000 cases of foreign body ingestion are encountered annually.[1] About 80% of ingested foreign bodies pass spontaneously through the gastrointestinal tract without causing complications, while endoscopic intervention is required in about 20% of cases. Less than 1% of cases necessitate surgical intervention.[2] Sharp and pointed foreign bodies can lead to perforation, bleeding, ulceration, and erosion in the gastrointestinal tract. In such cases, endoscopic intervention within 24 hours is recommended.[3]

Appendectomy is a commonly performed emergency surgery in general surgical clinics. The pathology underlying appendicitis usually involves obstruction of the appendiceal lumen, primarily due to lymphoid tissue, fecaliths, tumors, or parasitic infections. A very rare cause is the lodgment of an ingested foreign body within the appendiceal lumen. The estimated incidence of this condition is approximately 0.0005%, and about 75% of foreign bodies are radiopaque.[4,5]

Sharp and pointed objects are more likely to cause inflammation if they penetrate the appendix.[6] The aim of this study is to demonstrate that, albeit very rarely, ingestion of foreign bodies can lead to acute appendicitis in patients, thereby emphasizing the importance of patient monitoring.

The aim of this case presentation is to describe a patient who presented with right lower abdominal pain following the ingestion of a screw, which was unsuccessfully managed with endoscopy and subsequently required appendectomy, in light of the literature.

CASE

A 26 year old female patient accidentally ingested a screw while repairing something at home five days ago. When she presented four days later, an outpatient abdominal X-ray showed the foreign body at the level of the small bowel, and due to the absence of abdominal tenderness, outpatient follow-up was recommended (Figure 1).

Upon reevaluation, the patient complained of tenderness in the right lower quadrant, and both abdominal X-ray and computed tomography (CT) revealed the metallic object in the right lower quadrant peri-cecal area (Figure 2, Figure 3).

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Figure 1. 1. day antero-posterior erect view

Figure 3. Foreign body on CT on the 4th day

The patient was admitted for observation. Over the course of three days, the foreign body did not change its position on abdominal X-ray (Figure 4), prompting colonoscopy.

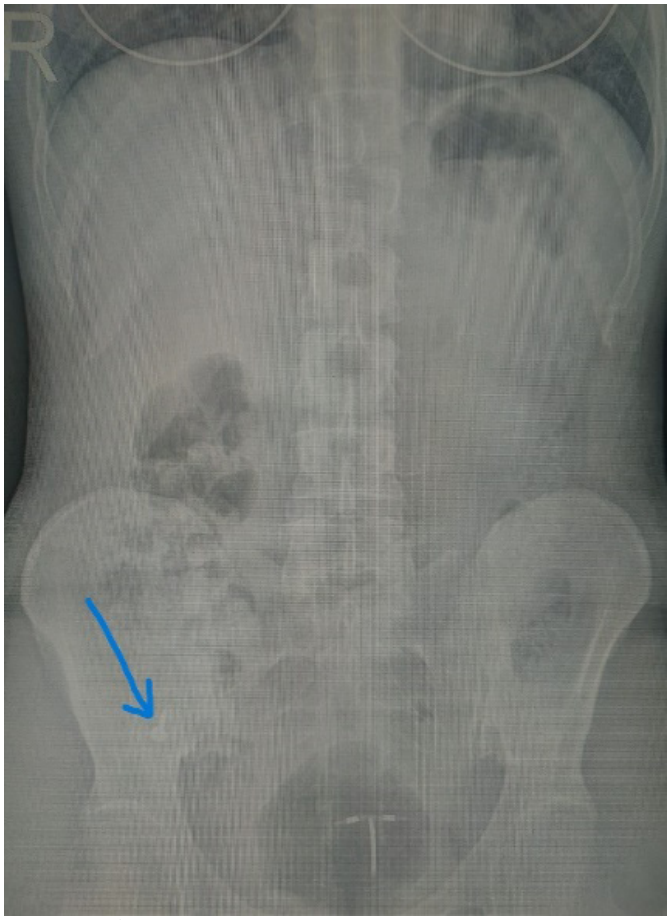

Figure 2. 4. day antero-posterior erect view

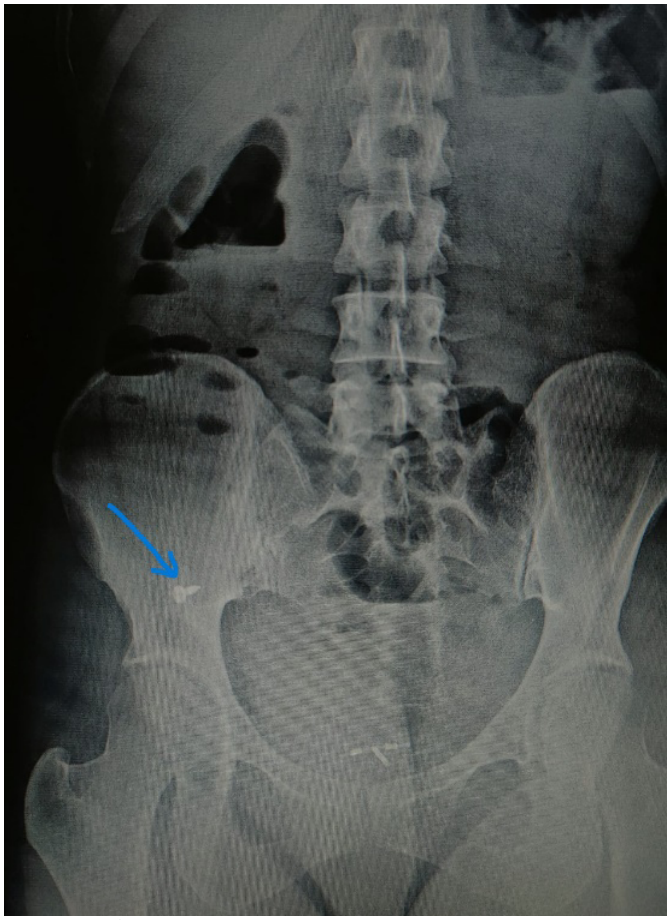

Figure 4. 1. day antero-posterior erect view

Despite advancing up to 20 cm proximal to the ileocecal valve, the object was not found. The colon was partially dirty. A follow-up abdominal X-ray taken one day after the procedure showed the foreign body still in the same location. As the patient exhibited tenderness in the right lower quadrant upon examination, a decision was made to proceed with surgery. Median incision below the umbilicus was made, and exploration of the abdomen revealed no perforation but an inflamed appendix. A hard object was palpated at the base of the appendix. The appendix was incised 1 cm from the base, and the screw was removed. Subsequently, the mesoappendix and base were ligated and excised, and the appendectomy was completed (Figure 5). A drain was placed in the rectovesical area. The patient resumed oral intake on the first postoperative day and was discharged without complications on the third postoperative day.

Figure 5. Foreign body in the intraoperative radix appendix

DISCUSSION

The management of foreign body ingestion varies depending on the type, shape, timing of ingestion, and clinical symptoms of the patient. While sharp and pointed objects carry a higher risk of complications, blunt objects, batteries, objects longer than 6 cm, and objects larger than 2 cm in diameter also pose a significant risk. Batteries can cause chemical reactions leading to erosion and perforation of the gastrointestinal mucosa. Objects longer than 6 cm are likely to get lodged in the duodenum, while those larger than 2 cm in diameter are more likely to remain in the stomach. Most foreign bodies remaining in the upper gastrointestinal tract can be removed endoscopically.[7]

The harmful mechanical effects of ingested foreign bodies typically occur at sudden openings of the gastrointestinal tract or at sites of narrowing such as adhesions and strictures.[8]

When a foreign body is heavier than the intestinal fluid, it may stop advancing upon reaching the cecum and may tend to move downward due to gravity. Once a foreign body enters the appendix orifice and settles, peristalsis may not be sufficient to expel it. The lodgment of a foreign body in the appendix is a rare occurrence with an estimated incidence of 0.0005%, and about 75% of these objects are radiopaque.[4,5] Various objects such as screws, drill bits, piercings, needles, bone fragments, seeds, and toothpicks have been reported to lodge in the appendix.[6,9-15] Sharp and penetrating objects lodged in the appendix can cause perforation, while blunt objects may obstruct the lumen and lead to acute appendicitis with an inflammatory response. Occasionally, a foreign body may remain silent in the appendix without causing an inflammatory response. As a result, patient presentations can vary from days to years after ingestion.[6]

In patients who present with abdominal pain and have a foreign body detected in the appendix on X-ray, the diagnosis of appendicitis should be confirmed by CT scan. Patients with a foreign body detected in the appendix should be closely monitored. If the foreign body does not change position on daily X-rays, endoscopic intervention should be planned. In cases where endoscopy fails, surgical intervention with appendectomy should be considered to prevent potential complications.

CONCLUSION

In our presented case, a patient who ingested a screw seven days prior was closely monitored, and after the foreign body did not change position, colonoscopy was performed up to 20 cm proximal to the ileocecal valve without finding the object. As the patient developed tenderness upon abdominal examination, appendectomy was performed for treatment. It should be kept in mind that acute appendicitis can rarely develop in patients who have ingested foreign bodies and may require appendectomy.

ETHICAL DECLARATIONS

Informed Consent

The patient signed the free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

A conflict of interest has not been declared by the author.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Letter to the Editor

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Intraoperative detection of bile leakage using hydrogen peroxide during laparoscopic cholecystectomy

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Dear Editor,

Bile leakage remains a significant concern for patients undergoing laparoscopic cholecystectomy (LC). Unrecognized segmental/sectoral duct injury (SDI) leads to a complex postoperative course after LC, often complicated by biliary peritonitis, sepsis, or secondary vascular complications. There are two types of SDI, based on the size and drainage territory of the injured duct: (type 1) injury to the right anterior/posterior sectoral duct or any other segmental bile duct draining at least one Couinaud segment and (type 2) injury to a minor biliary radical in the gallbladder fossa, i.e., injury to the subvesical biliary duct or the duct of Luschka, which is usually less than 1 mm in diameter.[1] Intraoperative cholangiography through the injured duct was performed to delineate the corresponding liver segments in patients with type 1 SDI. When recognized intraoperatively, a biliary-enteric anastomosis in a Roux-en-Y hepaticojejunostomy or hepatojejunostomy is required for a transected major sectoral duct or segmental bile duct owing to large amounts of bile production. In patients with type 2 SDI, oversewing with 5-0 polypropylene or polydioxanone sutures is usually sufficient to control leaks.[2,3]

However, type 2 SDI is usually difficult to detect by intraoperative cholangiography or postoperative CT, MRCP, or endoscopic retrograde cholangio pancreatography (ERCP) because the injured duct drains only a small portion of the liver parenchyma.[1,4] Therefore, when a suspicious bile leak occurs in the gallbladder fossa intraoperatively, additional diagnostic procedures are required to identify the leak site precisely.

Although none have gained widespread acceptance, several tests for bile leakage have recently been proposed to detect minor bile leak sites from the cut surface of the liver after hepatic resection. The conventional intraoperative bile leakage test, which involves injecting normal saline through the cystic duct, is a low-cost and easily reproducible method; however, this technique is ineffective for detecting minor bile leakage from the transected liver surface due to the transparent nature of the solution.[5] Additionally, injection of various dye solutions, including methylene blue, is advised; however, this method entails dyeing the field of interest and masking additional bile leak sites.[6] The white test, which involves injecting a fat emulsion solution through the cystic duct, has also been recommended.[5] However, fat emboli, immunosuppressive effects, and fungal infections are among the drawbacks of the white test.[7] Furthermore, because they are performed on the cystic duct, these techniques are both time-consuming and challenging to adapt to laparoscopic cholecystectomy. A recent study showed that intraoperative fluorescent cholangiography using indocyanine green could detect bile leakage from subvesical aberrant bile duct injuries during laparoscopic cholecystectomy.[8] However, only some hospitals have special equipment and expertise to perform bile leakage tests using fluorescent cholangiography.

The topical application of 1.5% diluted hydrogen peroxide (H_2O_2) during surgery has recently raised awareness about potential bile injuries that could be overlooked intraoperatively.[7] Bile leakage is easily detected using 1.5% diluted hydrogen peroxide, which produces thick white foam (Figure). Moreover, it is non-invasive, easy to apply, harmless to tissues, and easily removed without leaving behind false tissue coloration. It also has the advantage of applying to laparoscopic surgeries. Currently, we effectively use H_2O_2 for the detection of bile leakage not only during laparoscopic cholecystectomy but also during major liver resections and liver hydatid surgery.

In conclusion, we recommend the topical application of 1.5% diluted hydrogen peroxide to investigate bile leakage. This is a simple, non-invasive, less time-consuming, repeatable, and readily available technique with no adverse effects.

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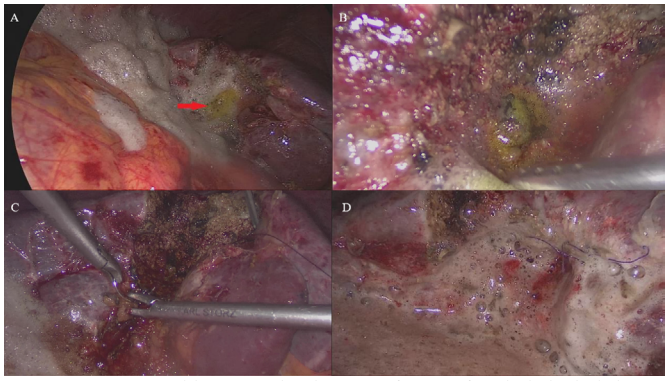

Figure. A 53-year-old man with a history of ERCP for choledocholithiasis underwent LC. Because severe inflammation stiffened the gallbladder wall, the dissection direction was slightly shifted towards the liver parenchyma adjacent to the body of the gallbladder

After the gallbladder was removed, saline-diluted hydrogen peroxide was applied to the transected surface of the liver to detect any leakage. (A) Following this application, yellow bile became visible on the cut surface of the gallbladder fossa. (B) After the site of bile leakage was detected, it was primarily closed with polydioxanone sutures. (C) No bile leakage was observed in the repeated test using diluted hydrogen peroxide (D); **ERCP:** Endoscopic retrograde cholangio pancreatography, **LC:** Laparoscopic cholecystectomy

Keywords: Bile leakage, hydrogen peroxide, laparoscopic cholecystectomy

ETHICAL DECLARATIONS

Informed Consent
The patient signed the free and informed consent form.

Referee Evaluation Process
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The authors have no conflicts of interest to declare.

Financial Disclosure
A conflict of interest has not been declared by the author.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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