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# Factors affecting complications and clinical outcome in patients with Mirizzi syndrome.



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Single center experience.

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# Factors affecting complications and clinical outcome in patients with Mirizzi syndrome. Single center experience.

Mirizzi syndrome (MS) is a syndrome that causes chronic destructive and fibrotic changes because of compression and inflammation in the main biliary tract. MS remains to be a serious problem due to its high morbidity. In this study, it is aimed to evaluate the diagnostic tools, risk factors and clinical output data we apply to our patients with MS in the light of the literature.

We retrospectively analyzed the data of patients treated for MS in the last decade in our hospital, where an average of 1350 cholecystectomies are performed annually. Clinical, laboratory and imaging data obtained from patients' files were evaluated.

We identified 76 patients with MS and classified them as type 1-5 according to the Csendes classification. Abdominal pain, fever and jaundice were the most common symptoms. 42 patients had type 1 and 2 MS. Mirizzi syndrome was diagnosed with preoperative radiological imaging methods in 24 of the patients. In 41 of the patients, the surgery first started laparoscopically, and then turned to laparotomy in 39 patients. Other 35 patients were operated with conventional methods. In 11 cases, subtotal cholecystectomy was performed

Early diagnosis and surgical treatment of symptomatic cholelithiasis decrease the frequency of MS. Inflammation criteria can be used as an indicative biomarker. The patient's history, USG, ERCP and MRCP findings are currently the most important diagnostic tools. Releasing the gallbladder with the "fundus first" approach can reduce the risk of trauma. In cases where MS is suspected, a stent placed with ERCP decrease bile duct trauma.

KEY WORDS: Complication, Diagnosis, Mirizzi's syndrome, Prediction, Treatment

# Introduction

Mirizzi syndrome (Ms). Has Been known since the early 1900s, but it was defined as a syndrome by the Argentine surgeon Pablo Luis Mirizzi in 1948. He described it as a large stone in the gallbladder impacted into the infundibulum and caused intense inflammation and jaundice by compressing the main bile ducts (Type I). McSherry et al described its fistulized form in 1982 (Type II). Csendes et al described three forms of Type II and defined the Csendes classification in 1989 (Fig. 1), which is frequently used today <sup>1,2</sup>. In developed countries, 10-15% of the population has cholelithiasis. Acute cholecystitis is observed in 20% of patients with cholelithiasis, and MS is observed in 1% <sup>3-5</sup>. Patients with chronic cholecystitis are more likely to develop MS. Khan et al in their series of 5136 cases of cholelithiasis, found that stones were located in Hartman's pouch in 612 cases (11.9%), and these patients developed 4-5 times more cholecystitis and 2 times more MS <sup>5</sup>.

The cause has been reported as MS in 0.7%-1.4% of patients with obstructive jaundice <sup>1-3,7,8</sup>.

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Fig. 1: Csendens classification for Mirizzi's syndrome. F-fistula diameter C-the circumference of the common bile duct. (Reproductions were made by manuscript author Prof. Osman Nuri Dilek using internet resources).

Clinical presentations may range from acute cholecystitis, compression at the main biliary tract, cholecystobiliary fistula or gallstone ileus. The diagnosis can only be made in half of the patients with MS in the preoperative period <sup>2,10,11</sup>. In cases where the diagnosis made during surgery, bile duct and vascular injuries, which are difficult to restore and sometimes fatal, may develop<sup>12</sup>. In this study, we evaluated the clinical findings, risk factors and clinical output data and revealed the most accurate approach in the light of the literature.

# Methods

In this retrospective single-center study, the files of patients diagnosed with MS in the last decade were entered the study. Our 1100-bed hospital with an average of 1350 cholecystectomies per year is also a regional HPB center.

Patients were classified as type 1-5 according to the Csendes classification. Group A included Type 1 and 2 patients, while Group B included Type 3-5 patients (Table I). Besides the clinical and demographic data of the patients, radiological diagnosis methods, laboratory tests, operations performed, complications, morbidity and mortality rates and our clinical results were evaluated. Statistical analysis of Group A and Group B was performed according to patients with and without morbidity and additional procedures.

We defined the diagnostic criteria according to the criteria specified in Tokyo guideline (TG), Tataria et al and other studies <sup>4,13</sup>. Clinically, we evaluated the age, gender, jaundice, and comorbidity. In the radiological findings, we evaluated the presence of intrahepatic biliary tract dilatation, choledocholithiasis, hepatolithiasis, presence of a mass at the junction of the cystic duct common bile duct, and signs of meniscus <sup>4,13</sup>. We also compared the inflammatory markers such as white blood count (WBC), mean platelet volume (MPV), neutrophyl and lymphocyte ratio (NLR), thrombocyte and leucocyte ratio (TLR), and C-reactive protein (CRP) in preoperative blood parameters. Besides, the values scanned as history findings, liver function tests (LFTs) disorder, increased cholestasis enzymes, previous pancreatitis and cholangitis attacks were obtained from patient data of the last 2 years. It was found that surgery was performed in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and had pancreatitis after liver function and cholestasis enzymes returned to normal.

Data were evaluated in IBM SPSS Statistics 25.0 package program (IBM Corp., Armonk, New York, USA). Comparison of variables and the two groups was made using the Mann-Whitney U test. A p<0.05 value was considered statistically significant.

The study was carried out in accordance with the principles of the Helsinki Declaration. As a routine procedure, written informed consent was obtained from each patient for all procedures and publication. Ethics committee approval was received for this study from the Clinical Trials Ethics Committee (2020 / GOKAE / 0502).

#### Results

Totally 76 patients were entered the study. Thirty-nine (51.3%) of them were male and the mean age was 58.9 (18-72)/year. According to the Csendes classification the distribution of our patients with MS was as follows: Group A; 22 patients were defined as type I, 20 patients as type II, and Group B; 9 patients as type III, 19 patients as type IV, and 6 patients as type V.

Abdominal pain was the most common symptom with 73 (96%) patients. While jaundice was observed in 28 of our patients, 23 (30.2%) patients had fever. High bilirubin was found in 40 patients as the most common laboratory finding in the history of the patients. Elevation of liver function tests were detected in 36 of the patients. In addition, 30 patients had had an attack of cholangitis and 6 patients had been treated for biliary pancreatitis. In the history of group B patients, cholangitis attacks and cholestasis enzyme levels were significantly higher (Table I).

Serum total bilirubin was higher in 26 patients and its mean was 2.9 (0.2-34.4) mg / dL. The mean NLR value was 5.06, and the mean MPV value was 9.8 fL. Preoperative biliary drainage rate was statistically significantly higher in Group B. It was found that USG was performed in all patients in accordance with the diagnostic algorithm of cholelithiasis. Depending on the radiological, clinical and laboratory data, it was found that ERCP (n=45), magnetic resonance cholongio-pancreatography (MRCP) (n=23), endoscopic ultrasound (EUS)

#### A. Atay, et al.

	Total(n=76)	Group A (n=42)	Group B (n=34)	p value
Age (years)#	58.9±14.8	56.5±16	61.7±12.7	0.171 <sup>b</sup>
Male/Female*	39/37	22/20	17/17	0.836ª
Symptoms*				
Pain (Yes)	73 (96)	39 (92.8)	34 (%100)	0.163ª
Fever (Yes)	23 (30.2)	13 (30.9)	10 (29.4%)	$0.884^{a}$
Jaundice (Yes)	28 (36.8)	15 (35.7)	13 (38.2)	0.883ª
History*				
Abnormal LFT (Yes)	36 (47.3)	16 (38)	20 (58.8)	$0.006^{a}$
Cholestatic enzyme elevation (Yes)	37 (48.6)	17 (40.4)	20 (58.8)	0.019ª
Pancreatitis (Yes)	6 (7.8)	2 (4.7)	4 (11.7)	0.172ª
Cholangitis (Yes)	30 (39.4)	13(30.9)	17 (50)	$0.014^{a}$
Bilirubin elevation (Yes)	40 (52.6)	21 (50)	19 (55.8)	0.148ª
Comorbidities*				
Hypertension (Ves)	25 (32.8)	13 (30.9)	12 (35.2)	0 689ª
DM (Ves)	17 (22.3)	13(30.5) 12(285)	5(147)	0.009
COPD (Vec)	$\frac{1}{(52.5)}$	2(47)	2(58)	0.149
	4 ().2)	2 (4./)	2 (0.0)	0.007
ASA I	12 (157)	6 (143)	6 (17.6)	0.022
ASA II	47 (61.8)	28(667)	19(55.8)	
ASA III	17(22.3)	8 (19)	9(2647)	
Pre-operative diagnosic* (Ves)	24(315)	11(261)	13(382)	0.261ª
FRCP* (Vec)	45(59.2)	21(50)	24(70.5)	0.069ª
PBD* (Ves)	$\frac{1}{28}$ (36.8)	10(23.8)	18(529)	$0.009^{a}$
Choledocholithiacis* (Ves)	20(30.0)	15 (35.7)	14(411)	0.009
Time from admission to the hospital to the operation# (months)	11.2 + 13.4	10+11.8	12 8+15 3	0.020 0.321 <sup>b</sup>
This non admission to the hospital to the operation# (months)	11.2±1.3.4	10±11.0	12.011).)	0.921

TABLE I - Comparison of the demographic characteristics, history and comorbidities of the patients between Group A and Group B.

\*n(%), #mean±standard deviation LFT; liver function test, DM; diabetes, COPD; chronic obstructive pulmonary disease, ASA; physical status classification system by the American Society of Anesthesiologists, ERCP; endoscopic retrograde cholangiopancreatography, PBD; preoperative biliary drainagea; Chi-square, b; Mann–Whitney U-test

(n=27) were examined for differential diagnosis. MS was diagnosed in 24 cases with radiological imaging. It was found that stent placement was performed in 26 patients with ERCP and 2 patients with PTC.

Surgical techniques requiring anastomosis such as hepatojejunostomy or choledocoduodenostomy were used more in Group B patients, while cholecystectomy and cholecystectomy + T tube procedures were used more in Group A patients. The mean operative time was higher in group B patients, but it was not statistically significant. The operation started laparoscopically in 41 patients who underwent cholecystectomy, and converted to laparotomy in 39 patients. Other 35 patients were operated with conventional methods. It was observed that the complication rate was lower in patients with stents. However, the difference was not statistically significant (Table II).

Interestingly, it was found that patients in group A were usually operated on for cholelithiasis or acute cholecystitis by physicians who performed routine general surgery or emergency surgery, and most of the patients in group B were operated by teams performing hepatobiliary surgery. However, Group B stayed in hospitals more than Group A, which was statistically significant (p = 0.039) (Table II). It was determined that ERCP was performed in 45 patients, stent was placed in 26 patients, and stent was placed in 2 patients with PTC. Surgery-related complications were found to be less common in patients with ERCP stent.

According to Clavien-Dindo classification, 2nd grade complications were the most common type of complication. In addition, the inflammatory markers of the patients with grade 3 and above and those with grade 3 were compared, NLR and TLR values were statistically significantly higher in patients with grade 3 and above. In addition, WBC and CRP values<sup>™</sup> were higher in patients with high-grade complications, but it was not statistically significant (Table III).

#### Discussion

Mirizzi syndrome is an entity that presents challenges in its diagnosis and treatment due to the variability of the clinical picture. It has been reported in the literature that MS can be seen in 0.06-5.7% of patients with cholelithiasis <sup>2-4,7,10,13-15</sup>. Although it does not have a specific marker, MS should be considered together with

	Total(n=76)	Group A (n=42)	Group B (n=34)	p value
Treatment# (open surgery)				0.419a
CCX+Hepaticojejunostomy	13 (17.1)	3 (7.1)	10 (29.4)	
CCX + T Tube	21 (27.6)	13 (30.9)	8 (23.5)	
CCX+ Choledocoduodenostomy	7 (9.2)	-	7 (20.5)	
Total CCX	35 (46)	26 (61.9)	9 (26.4)	
Partial CCX	11 (14.4)	5 (11.9)	6 (17.6)	
Laparoscopic CCX	2 (2.63)	2 (4.7)	-	
Laparoscopic Open# (convertion)	39 (51.3)	24 (57.1)	15 (44.1)	0.259a
Emergency surgery#	8 (10.5)	5 (11.9)	3 (8.8)	0.663a
Complications, (Clavien-Dindo) #				0.644a
Grade I	2 (2.6)	2 (4.7)	-	
Grade II	8 (10.5)	3 (7.1)	5 (14.7)	
Grade III	4 (5.2)	3 (7.1)	1 (2.9)	
Grade IV	2 (2.6)	1 (2.3)	1 (2.9)	
Grade V	6 (7.8)	3 (7.1)	3 (8.8)	
Surgery time* (minute)	158.1±61.6	149.3±50.6	168.9±72.3	0.499b
Length of hospital stay* (day)	9.6±8.4	8.5±7.3	10.9±9.6	0.039b
Morbidity# (Yes)	22 (28.9)	12 (28.5)	10 (29.4)	0.936a
Mortality# (Yes)	6 (7.8)	3 (7.1)	3 (8.8)	0.556a
Long-term complications# (Yes)	14 (18.4)	9 (21.4)	5 (14.7)	0.452a

TABLE II - Comparison of patients' intraoperative treatments, length of hospital stay, morbidity and mortality between Group A and Group B

\* n(%), # mean±standard deviationCCX; cholecystectomya; Chi-square, b; Mann-Whitney U-test

anamnesis, clinical and laboratory findings and radiological data in the differential diagnosis of patients with jaundice.

#### Diagnosis

Murphy's sign is one of the local symptoms of acute cholecystitis. Therefore, the diagnostic value of Murphy's sign in chronic cholecystitis and MS cases is low <sup>13</sup>. Sianesi et al. reported MS in 46 patients in their cholecystectomy series of 4123 cases. It was reported that 19 (41.3%) of the cases in this series had acute cholecystitis findings, recurrent biliary colic pain in 28 cases, jaundice in 29 cases, and high fever in 27 cases, but most of the cases were diagnosed with MS during surgery<sup>2</sup>. In our series, abdominal pain (96%) and jaundice (36.8%) were the most common findings. Although our preoperative follow-up period has not been determined exactly, it has been reported in the literature that the patients become more complicated and the risks increase with the prolongation of the follow-up period <sup>14-18</sup>.

NLR and TLR values were significantly higher in patients with grade 3 or higher complications according to Clavien-Dindo classification. When used with clinical and radiological parameters, it can be useful markers in MS prognosis (Table III).

High Ca-19.9 is a diagnostic marker in pancreatic and biliary system tumors. There are many case reports on type II MS and very high levels of Ca-19.9 <sup>17</sup>. In our study, Ca-19.9 elevation was detected in 7 patients in group B. However, it is well known that Ca-19.9 may increase in benign pathologies of the biliary system.

Ultrasonography (USG) is the first and most used diagnostic procedure in the diagnosis and follow-up of patients. However, the sensitivity of USG in the diagnosis of MS has been reported as 8.3%-27% <sup>4,9,14,16</sup>. It has also been stated that there may be a relationship between the size and number of stones and MS. In most patients with MS, a single and large stone with intense fibrosis is observed. In Shirah et al.'s series of 64 cases, they found dense fibrosis in all (100%) of the cases, and thickening of the gallbladder wall in 84% of the cases. They also found single and large stones (> 5 cm) in 75% of the cases <sup>19</sup>. Endoscopic USG may contribute to the differential diagnosis of bile ducts, pancreas, and cases with mass.

Mirizzi syndrome may mimic cancer. Computerized tomography (CT) may be helpful in the differential diagnosis of gallbladder tumors or hilar type cholangiocellular carcinomas <sup>5,20</sup>. ERCP and CT can also provide information about the location of the mass lesion, the location and size of the fistula <sup>5,19,20</sup>.

Half of MS cases can be diagnosed with MRCP <sup>18,21</sup>. Kumar et al in their MS series of 169 cases, found gallbladder cancer in 5% (n = 8) of the cases and Xanthogranulomatous cholecystitits in 33% (n = 55) <sup>15</sup>. Redaelli et al reported that 28% of the patients in the MS series had gallbladder cancer, but there is no other series reporting similar high malignancies in the literature <sup>22,23</sup>. The sensitivity of ERCP, which is still the gold standard in the diagnosis of MS, has been reported as 50%-100% <sup>10,15,18</sup>. With ERCP, presence of a fistula can be revealed, and stones can be extracted. In type I and II lesions, MS treatment can be performed using laparoscopic cholecystectomy after cleaning the common bile duct. However, in the differentiation of Type II and III lesions, the addition of choledochoscopy to the process may be helpful in diagnosis <sup>11</sup>. In patients who are thought to have MS, ERCP and stenting (mostly in western countries) or endoscopic nasobiliary drainage (ENBS) tube applications (mostly in Japan) are the first procedures to consider. Stenting with ERCP can contribute to normalize of liver functions. In addition, it can guide the biliary tract anatomy (landmark the location of main bile duct) during the operation and help prevent trauma. However, depending on the stent, the incidence of developing infection may increase.

Diagnostic difficulties persist despite modern diagnostic methods. In their MS series of 69 cases, Kumar et al. could make a preoperative diagnosis in 32% of the cases <sup>15</sup>. Gelbard et al., in a series of 88 cases, diagnosed MS in 69% of the cases in the preoperative period <sup>24</sup>. In our series, we made preoperative diagnosis in 24 (31.5%) of 76 patients.

MS should be considered in cases of atrophic-fibrotic gall bladder, gall bladder distorted at the Calot triangle, the presence of a large stone impacted in the infundibulum (Fig. 2). In recent years, ICG injection has been used to reveal the liver biliary tract and segmental anatomy <sup>25</sup>. In cases where a mass image is detected, the possibility of a tumor should be ruled out with fresh frozen examinations.

There are studies defining scoring systems to diagnose MS in the preoperative period <sup>3,4</sup>. The TG18 guideline used in the diagnosis and treatment of acute cholecystitis may contribute to the differential diagnosis. In their scoring studies including 10 parameters, Tataria et al. reported that they determined an average of 6.72 criteria in patients with MS and 2.08 criteria in patients with cholelithiasis or cholecystitis <sup>4</sup>. In our 76-patient series, we questioned the criteria that Tataria et al. referenced, the laboratory findings that we added (such as CRP, MPV, NLR, TLR), as well as the history of pancreatitis, ERCP and stent. We found that NLR and TLR in our series play a predictive role in MS prognosis (Table III).

# TREATMENT

Early diagnosis and classification should be one of the important goals in the management of patients with MS. Also, morbidity and mortality can be reduced by 50% in patients diagnosed in the preoperative period  $^{4,14}$ . The type of surgical treatment varies according to the type of MS.

According to TG13, surgical approach in the treatment of patients with cholecystitis is considered superior to observational medical treatment <sup>3</sup>. Recurrent and nonoperative cholecystitis leads to the development of many complications. In the series of 10,304 cases by De Mestral et al, 10-20% of patients with untreated

cholelithiasis have cholecystitis. Signs of obstruction are observed in 24% of cases and pancreatitis in 6% <sup>26</sup>. The presence of cholelithiasis has been accepted as a criterion in the histories of patients with MS for a long time <sup>4</sup>. In our series, we found that 52.6% of the patients had signs of biliary obstruction and 39% had cholangitis attacks. The frequency of cholangitis in group B patients was higher and statistically significant. In addition, 6% of the patients had pancreatitis.

Although laparoscopic approach is the gold standard for the treatment of cholelithiasis, the rate of transition to open surgery in cases with MS varies between 11-100% in the literature 7,15,18. The general opinion is to start laparoscopically in Type 1 cases. However, there are surgeons who accept the laparoscopic approach as contraindicated in patients with MS due to adhesion and inflammation in the Calot triangle 14. In the series of Kumar et al. (n = 169), the rate of transition from laparoscopy to open surgery was reported as 86%. In the same series, most of the cases completed laparoscopically were patients with type I MS 15. Many studies recommend the "fundus first" approach 27. In our series, this approach is preferred in cases with MS diagnosis or MS surgeries. Laparoscopic approach is recommended for Type-1-2 in the literature. In our series, this rate is very low (2/41). Conversion from laparoscopy to laparotomy was found to be very high in our type-1-2 cases. This may be due to the fact that most of the surgeons (n=45) in our hospital performed laparoscopic cholecystectomy and preferred to return to laparotomy in cases where dissection was difficult. Surgical complications can be further reduced, especially in patients who have previously had biliary stenting.

There are also studies on subtotal cholecystectomy, which is a preferred procedure for dense adhesions in the Calot triangle to prevent biliary tract and vascular injuries. In TG18 guidelines, it was stated that subtotal cholecystectomy can be performed in patients with poor general condition and high comorbidity, and who also has severe cholecystitis and perforated cholecystitis <sup>3,13</sup>. Subtotal cholecystectomy is a method that is preferred more (72.9%) in laparoscopic surgeries. It is less preferred (8%) in cases where the laparoscopic transition is made <sup>28,29</sup>. In our series, subtotal cholecystectomy was performed in 11 cases. Six of these patients were type 3 and above according to the Csendes classification.

In type II cases, it is recommended to perform sphincterotomy and extraction of stones with ERCP first. If the procedure is successful, laparoscopic cholecystectomy is recommended. However, there are also those who recommend laparotomy in MS Type II cases. There is no definite consensus about which method is appropriate <sup>11</sup>. We believe that laparoscopic approach will become safer in cases with ERCP stenting. In our series, we found that 28 of 45 patients who underwent ERCP had biliary stent implantation. The rate of stenting was higher and statistically significant in group B patients.



Fig. 2: Picture of our Mirizzi type 1 case with bile duct trauma. The cystic canal is very short and combined with the common bile duct.

Laparotomy is the first choice in Type III and IV cases with large fistula. Intraoperative cholangiography may be helpful to view the bile ducts. If the anatomy cannot be clearly revealed and in the presence of mass lesions, removing the fibrotic segment with MS and performing hepaticojejunostomy is a frequently preferred method. There are also teams that prefer cholecystectomy and hepaticojejunostomy with robotic instruments. Subtotal cholecystectomy, choledochoplasty, and T tube drainage are among other meticulous treatment methods applied in the clinic <sup>10,30</sup>. It may be a disadvantage to keep the tube for 4-6 months to prevent stenosis in patients who have choledocoplasty over the T tube. In cases where choledocoplasty is planned after cholecystectomy, the posterior wall of the gallbladder and the posterior wall of the main bile duct should be protected as a flap. There are some studies reporting that lateral wall defects that occur after cholecystectomy can be closed with a round ligament flap <sup>31</sup>. There are also reports on Type II - IV cases with successful results in patients with MS with high comorbidity, who underwent repeated cholangioscopy or lithotripsy and stenting with ERCP 18,32. In our series, the surgeries of MS patients were performed at different times by 2 different teams. We found that the experienced team in our hospital preferred mostly cholecystectomy combined with hepaticojejunostomy or choledocoduodenostomy. The team that faced MS less frequently preferred subtotal cholecystectomy and T tube drainage.

It has been reported that complications may develop in 0-60% of cases and mortality in 0-25% of cases during the operations of patients with MS. Also bile duct trauma may develop in 0-22% of cases in the surgery of patients with MS. Lai et al. reported that bile duct trauma developed in 17% of MS patients who were operated without a diagnosis of MS<sup>12,15</sup>. As a result of MS, the gallbladder compresses the main hepatic duct. This causes a difference in diameter between the proximal and

distal bile ducts, which image increases the incidence of trauma. Due to excessive traction from the Hartman pouch during surgery, the common bile duct becomes thinner and creates a cystic canal image and the development of common bile duct trauma becomes easier. Major bile duct traumas and vascular injuries may also develop in cases where Inflammation and fibrosis are close to the hilus.

# Conclusion

Early diagnosis and treatment will decrease the frequency of MS. Among the laboratory findings, NLR, TLR can be used as a new predictive biomarker of the severity of the complications. In cases with suspected MS, the stent to be placed with ERCP may reduce bile duct trauma and additional surgical complications. Tailored surgical planning should be targeted for patients with MS. Releasing the gallbladder with the "fundus first" approach can reduce the risk of trauma. Dissection of the common bile duct distal and proximal first and the fistula area last will reduce the risks. Referring patients diagnosed with MS to experienced centers will help reduce morbidity and mortality.

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