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Original Article

Surgical resection for non-Asian intrahepatic lithiasis: The Brazilian experience

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ABSTRACT

Background: Intrahepatic lithiasis (IHL) is a rare disease in the western world. Complications associated with IHL include acute cholangitis, liver atrophy, secondary biliary cirrhosis, and risk for intrahepatic cholangiocarcinoma. Liver resection is considered the treatment of choice for IHL. The objective of this study was to analyze patients who underwent liver resection for non-Asian hepatolithiasis.

Methods: 127 patients with symptomatic non-Asian hepatolithiasis underwent resection in six institutions. Demographic data, clinical presentation, diagnosis, classification according to stone location, presence of atrophy, bile duct stricture, biliary cirrhosis, incidence of cholangiocarcinoma, treatment and postoperative course were evaluated.

Results: 52 patients (40.9%) were male and the mean age was 46.1 years. Sixty-six patients (51.9%) presented with history of cholangitis. Stones were located in the left lobe in 63 (49.6%), and right lobe in 28 patients (22.0%). Atrophy was observed in 31 patients (24.4%) and biliary stenosis in 18 patients (14.1%). The most common procedure performed was left lateral sectionectomy in 63 (49.6%) patients, followed by left hepatectomy in 36 (28.3%), right hepatectomy in 19 (15.0%), and associated hepaticojejunostomy in 28 (22.0%). Forty-two patients (33.0%) presented postoperative complications and the most common were biliary fistula (13.3%) and surgical site infection (7.0%). Postoperative mortality was 0.7%. Intrahepatic cholangiocarcinoma was observed in 2 patients (1.5%). Recurrence was identified in 10 patients (7.8%), mostly with bilateral stones and/or hepaticojejunostomy.

Conclusion: Liver resection is the standard treatment for symptomatic unilateral or complicated IHL with good operative results. Risk of cholangiocarcinoma was low in non-Asian patients.

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1. Introduction

Intrahepatic lithiasis or hepatolithiasis is defined when stones are identified within the bile ducts, proximal to the bifurcation of the right and left ducts, with or without gallstones in the gallbladder and/or main bile duct. Intrahepatic lithiasis is common in Southeast Asia including China, South Korea, Taiwan, and Japan, and is more commonly observed in the 5th and 6th decades but no gender preference has been observed.^{1–3}

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Some complications have been associated with the disease including liver atrophy, acute cholangitis, biliary strictures, secondary biliary cirrhosis, hepatic abscess and portal hypertension. Intrahepatic cholangiocarcinoma has also been associated with long-term intrahepatic lithiasis.^{2,4,5}

When the stones are originated into the liver, the so called primary hepatolithiasis, anatomic variation of the bile duct, parasites such as *Clonorchis sinensis* and ascariasis, bile duct infection, cholestasis, nutritional status and genetic and environmental factors, are considered to be associated with the etiology of the disease. Local dilation and biliary strictures are common findings in primary intrahepatic lithiasis. The left lobe is the most common location of intrahepatic stones and can be related to an acute angle between the left hepatic duct and the common hepatic duct leading to bile stasis.^{2,5–8}

Although some patients can be diagnosed with intrahepatic lithiasis on abdominal imaging for vague symptoms, the majority of patients are symptomatic including epigastric pain or discomfort, fever, nausea, vomiting and jaundice. A typical triad of symptoms with fever, chills, and jaundice featuring cholangitis can be observed in half of the patients. Acute pancreatitis is an uncommon condition related to migration of intrahepatic stones.^{2,5,9}

The treatment of intrahepatic lithiasis must include the control of the infection, removal of stones, avoid recurrence, and minimize the risk of cholangiocarcinoma. These can be achieved by endoscopic procedures and surgery.^{2,5,9}

Hepatic resection associated or not with biliary drainage is a common procedure and considered the classical indication for symptomatic patients with intrahepatic lithiasis. It removes the stones, bile duct strictures, the atrophic liver parenchyma, and promotes a satisfactory biliary drainage when necessary. The potential risk for cholangiocarcinoma can be minimized. Due to the increase of the expertise in hepatobiliary surgery and intensive care, morbidity and mortality rates for hepatic resection have decreased significantly.^{2–5,10–12}

Primary intrahepatic lithiasis despite being a common disease in Southeast Asia, is rare in the western world. The large number of cases of this rare disease in Brazil motivated us to perform this study.

The objective of this retrospective multi-institutional study was to analyze immediate and long term results for patients that underwent liver resection as the treatment of non-Asian hepatolithiasis.

2. Methods

From March 2002 to December 2018, a total of 127 patients with symptomatic benign non-Asian hepatolithiasis who underwent surgical resection were analyzed (23.2% of 548 patients with intrahepatic lithiasis). A retrospective study with prospective data was performed in six institutions in Brazil. The study project on liver surgery has been approved and has received an identification number (N.275.500 Brazil Platform). Demographic data regarding gender, age, clinical manifestations, anatomic location of the stones, history of previous biliary surgery, intraoperative findings, and postoperative course were evaluated.

A complete evaluation of all patients with intrahepatic lithiasis was performed including liver functions tests, abdominal computed tomography or magnetic resonance imaging, and magnetic resonance cholangiography.

Patients with intrahepatic lithiasis were classified according to (1) stone location: right lobe, left lobe and bilobar, (2) presence of atrophy of the hepatic parenchyma, (3) presence of stricture of intrahepatic bile ducts, (4) presence of fibrosis/cirrhosis, (5) presence of portal hypertension, and (6) presence of extra-hepatic

stones. The patients were evaluated in order to identify an associated cholangiocarcinoma.

All cases were presented in multidisciplinary meetings to define the best therapeutic option. Liver resection was indicated in symptomatic patients with intrahepatic lithiasis associated with irreversible lesions as cholangitic abscess, parenchyma atrophy or fibrosis, and biliary stenosis. Isolated intrahepatic lithiasis and critical clinical conditions of the patient were contraindications to liver resection. Five (3.9%) symptomatic patients with intrahepatic biliary stenosis were referred to our department after unsuccessful interventional radiology or endoscopic treatment. Roux-en-Y hepaticojejunostomy was associated to liver resection in selected cases with common bile duct stones, bile duct dilation of more than 2 cm in diameter or according to the surgeon discretion. All the resected specimens were sent to histopathological evaluation to identify the presence of cholangiocarcinoma and the stage of the disease. Per operative complications were evaluated and classified according to the Dindo-Clavien score.¹³

The patients' follow up depicted symptoms, laboratory analysis, and images as magnetic resonance, and magnetic resonance cholangiography. The definition of residual stones was the presence of calculi within three months after resection and recurrent stones if the calculi were identified after three months of follow-up.

3. Results

A total of 127 symptomatic patients with intrahepatic lithiasis underwent liver resection. There were 52 (40.9%) male and 75 (59.1%) female, with a mean age of 46.1 years (range 18–78 years). No Asian-Brazilian patient was included in this study. Previous history of cholangitis was the most common clinical presentation in 66 patients (51.9% - Table 1).

No history of previous of liver resection was recorded however, previous history of surgery in the biliary tract before liver resection was observed in 72 patients (56.7%), which include cholecystectomy associated bile duct exploration in 26 (20.4%), hepaticojejunostomy in 13 (10.2%) and isolated endoscopic retrograde cholangiopancreatography (ERCP) in 10 patients (7.8%). Previous history of common bile duct stones was identified in 12 patients (9.4%). As co-morbidities, arterial hypertension was identified in 39 patients (30.7%) and Diabetes mellitus in 12 patients (9.4%).

Liver function evaluation was recorded and aminotransferases were abnormal in 10 patients (7.8%), serum bilirubin was increased in 25 patients (19.7%), alkaline phosphatase and gamma-glutamyl transpeptidase were elevated in 19 (15.0%) and 29 (22.8%), respectively. Leukocytosis was observed in eight (6.3%) patients. Tumor marker CA 19.9 was raised in 2 patients (1.5%). No signs of chronic liver disease or liver failure were identified on clinical evaluation.

Ultrasonography, magnetic resonance imaging with magnetic resonance cholangiography (MRCP), and computed tomography scan were used for preoperative diagnostic evaluation and surgical planning (Fig. 1). Endoscopic retrograde cholangiopancreatography (ERCP) had been performed for diagnostic evaluation and treatment (papillotomy and biliary stenting to relieve biliary stasis) of

Table 1
Clinical presentation of patients with hepatolithiasis.

Clinical presentation	n	%
Previous cholangitis	66	51.9
Abdominal pain	39	30.7
Jaundice	15	11.8
Liver abscess	5	3.9
Weight loss	5	3.9

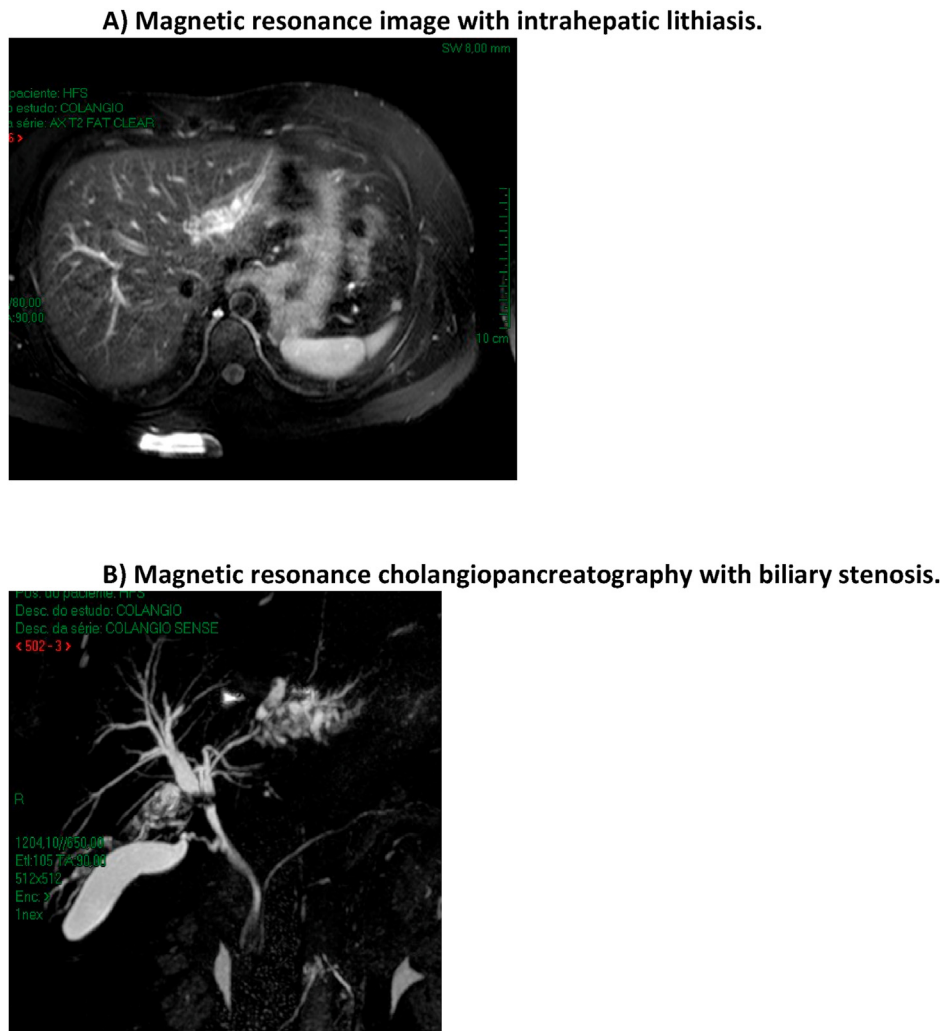


Figure 1. (a) Magnetic resonance image with intrahepatic lithiasis (arrow); (b) Magnetic resonance cholangiopancreatography with biliary stenosis (arrow).

acute cholangitis in 4 patients (3.1%), mainly after MRCP. The location of intrahepatic stones and the associated complications of hepatolithiasis are presented in [Table 2](#).

Intraoperative cholangiography was performed as a routine complementary evaluation of the biliary tree in all patients. All patients underwent liver resection and the most common procedures performed were left lateral sectionectomy in 63 (49.6% - [Table 3](#) – [Fig. 2](#)). Major liver resection (three or more Couinaud segments) was performed in 55 patients (43.3%). 14 patients (11.0%) underwent laparoscopic liver resection (left lateral sectionectomy) according to expertise and surgeon discretion. In 8 resected patients (6.3%), an associated liver abscess was observed. When indicated, additional hepaticojejunostomy was associated in 28

Table 3
Surgical treatment of intrahepatic lithiasis.

Surgical procedure	n	%
Left lateral sectionectomy	63	49.6
Left hepatectomy	36	28.3
Right hepatectomy	19	15.0
Right posterior sectionectomy	3	2.3
Bisegmentectomy 5/6	1	0.7
Bisegmentectomy 5/8	1	0.7
Bisegmentectomy 5/8 + 2/3	1	0.7
Segmentectomy 5	1	0.7
Segmentectomy 4	1	0.7
Non-anatomic hepatectomy	1	0.7
Additional hepaticojejunostomy	28	22.0

Table 2
Location of the intrahepatic lithiasis and associated complications.

Intrahepatic lithiasis and complications	n	%
Right lobe stones	28	22.0
Left lobe stones	63	49.6
Bilateral stones	36	28.3
Atrophy	31	24.4
Stenosis	18	14.1
Parenchyma fibrosis/cirrhosis	5	3.9
Extra-hepatic biliary stones	19	14.9

patients (22.0%) to improve the biliary drainage in grossly dilated bile duct. Sixteen patients received intraoperative blood transfusion (12.6%), mainly patients who underwent major liver resections (15 patients – 93.7%). The mean operative time was 235 min (135–560 min).

Clearance of biliary stones from the remnant or contralateral liver after resection was performed through the intrahepatic bile duct stump in 43 patients (33.8%). Cholangiographic study

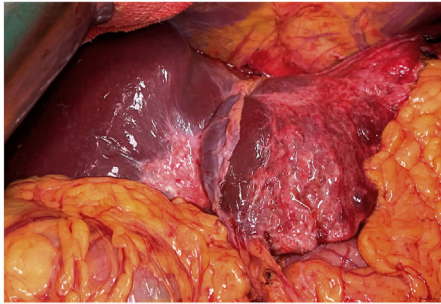
A) Atrophy of the left lobe.**B) Left lateral sectionectomy with atrophy and stones.****C) Left lobe with cholangitis, micro abscess and stones.**

Figure 2. (a) Atrophic left lobe; (b) Left lateral sectionectomy with atrophy and stones; (c) Left lobe with cholangitis, microabscess and stones.

confirmed the absence of residual stones. The intrahepatic bile duct stump was sutured after cholangiography confirms absence of residual intrahepatic stones.

Thirty-one patients (24.4%) presented postoperative complications and the most common were biliary fistula and surgical site infection (Table 4). Perioperative complications Clavien-Dindo $\geq 3b$ were observed in 5 patients (3.9%). The treatment of the complications included exploratory laparotomy associated with control of bleeding, abdominal and pleural drainage, dialysis, and antibiotics. The mean hospital stay was 11.7 days (range 1–71 days), and the postoperative 30-days mortality occurred in 1 patient (0.7%) who underwent left hepatectomy complicated with biliary fistula, and intraabdominal abscess.

The median follow-up period was 39 months (range 1–142 months) and the postoperative complications are presented in Table 4. During follow-up, infectious complications as cholangitis were observed in patients who underwent hepaticojejunostomy; From 28 patients with hepaticojejunostomy, 9 presented infections complications during follow-up (32.4%). Two asymptomatic patients (1.5%) presented with residual stones during routine image evaluation (before three months of liver resection) and were followed-up without endoscopic or surgical intervention. Recurrence of intrahepatic lithiasis was identified in 10 patients (7.8%), being in 8 patients (80%) with previous bilobar stones and/or hepaticojejunostomy. Six of these patients (60.0%) presented post hepatectomy cholangitis.

Good long-term results (when there were no complications $\geq 3b$ related to the procedure or due to recurrence of stones as cholangitis during the follow-up period) were observed in 88.2% of patients.

The histopathologic analysis of the specimens identified intrahepatic lithiasis associated to chronic cholangitis in 67 patients (52.7%), portal fibrosis in 40 (31.5%), steatosis in 16 (12.6%), liver abscess in 8 (6.3%), and intrahepatic cholangiocarcinoma in 2 patients (1.5%). Intrahepatic cholangiocarcinoma occurred in atrophic left lobe in both patients, associated with episodes of recurrent cholangitis in one patient. The resection margins of patients with intrahepatic cholangiocarcinoma were free, and after recovery from surgery, the patients were sent for clinical oncologist evaluation.

4. Discussion

Intrahepatic lithiasis is characterized by its frequent rate of complications and intractable nature. In Southeast Asia, this disease is epidemic, and the prevalence is up to 50% of patients undergoing cholecystectomy for cholelithiasis in some regions as China, Taiwan, Japan, and South Korea. Intrahepatic lithiasis is very uncommon in the Western world.^{4,8,9} In Brazil, intrahepatic lithiasis presents different dietary, environmental and genetic factors when compared with Asian patients. In the present study, no Asian-

Table 4
– Postoperative complications.

Complication	n	%
Biliary fistula	17	13.3
Surgical site infection	9	7.0
Intra-abdominal abscess	5	3.9
Pneumonia	4	3.1
Subphrenic abscess	2	1.5
Pleural effusion	2	1.5
Abdominal bleeding	2	1.5
Ileus	2	1.5
Acute renal failure	2	1.5
Liver ischemia	1	0.7
Ascites	1	0.7
Haemothorax	1	0.7

Brazilian or Asian descendant was included. Moreover, low socioeconomic conditions and malnutrition, common in some regions in Brazil, are not associated with a high incidence of hepatolithiasis. However, many cases have been reported with some similarities to those with Asian hepatolithiasis.¹ In the western world, small series from Brazil, Italy and Chile have been reported.^{11,14,15} To our knowledge, this is the largest experience of surgical treatment for non-Asian intrahepatic lithiasis.

Previous history of cholangitis is the most common clinical presentation observed in these patients; however some patients have abdominal pain or discomfort, nausea or vomiting as the main symptoms. The left hepatic duct is more commonly affected and more susceptible to strictures probably due to the fact that the duct meets in a nearly right angle with the common hepatic duct, leading to a greater possibility of more biliary stasis and a point of greater risk for stone impaction. The biliary epithelium damage due to the impacted stone or the strictures caused by recurrent cholangitis are the most common cause of recurrence of intrahepatic stones and its consequences.^{2,3,16,17}

Surgical treatment is advised in symptomatic intrahepatic lithiasis and the presence of a myriad of clinical symptoms has been observed. Careful evaluation with magnetic resonance image or computed tomography is necessary including the location of the stones, if the disease is unilobar or bilobar, presence of extrahepatic disease, cholangitis, liver abscess or fibrosis, and atrophy. The ideal treatment include the removal all stones, the intrahepatic bile ducts with strictures, clearance of the infected segments of the liver, promote adequate drainage of the bile from compromised bile duct to the small bowel, and minimize the risk of complications.^{2,17,18,19,48} In the present study isolated intrahepatic lithiasis was not an indication for liver resection. These patients were sent to the department of endoscopy or interventional radiology, according to the location of the stones. Similarly, patients with parenchyma atrophy and fibrosis or stenosis were not referred to endoscopic or interventional radiology treatment.

According to Tazuma et al.³ the treatment of intrahepatic lithiasis includes peroral cholangioscopy (POCS), percutaneous transhepatic cholangioscopy (PTCS) and surgical resection. PTCS or POCS are indicated in symptomatic patients with intrahepatic lithiasis associated to past history of bile duct reconstructive surgery and the presence of bile duct stenosis. Surgical resection is suggested in patients with suspected intrahepatic cholangiocarcinoma or liver atrophy and unsuccessful POCS and/or PTCS. However, liver resection for intrahepatic lithiasis results in significantly lower residual stone rate when compared with choledocholithotomy or hepaticojunostomy alone or other nonsurgical treatments. The procedure is also associated with lower risk of related complications such as recurrent cholangitis, liver abscess, secondary biliary cirrhosis, portal hypertension and liver failure.^{3,20,21} In the present study the indications for surgical treatment were different when compared with patients referred to endoscopic or interventional radiology treatment.

In symptomatic patients, without extrahepatic disease, left lateral sectionectomy is an easy and safe procedure with low morbidity and has been performed by laparoscopy with excellent results and short hospital stay. In this case, all the diseased liver parenchyma can be resected and the rate of clearance of intrahepatic stones in the left lobe is high with low incidence of residual stones. In this study 49.6% of the patients underwent left lateral sectionectomy and, in the last years, by laparoscopic approach, all with good outcomes.^{21–24}

In patients with bilobar intrahepatic lithiasis, the treatment is more complicated and difficult. The decision to resect and how many segments to resect is difficult mainly due to the extent of the resection, the risk of residual stones and associated complications

such as recurrent cholangitis, biliary fistula and liver failure. Extensive hepatectomy is frequently not recommended for patients with hepatolithiasis. In the present study blood transfusion was more frequently observed in patients submitted to major resections. In general, for patients with bilateral stones, resection is indicated when an irreversible lesion (stenosis, severe fibrosis, atrophy) is found in one of the sides of the liver; Resection is then complemented by intraoperative stone clearance of the remnant liver, and eventually an associated hepaticojunostomy.^{25–28}

In the present study we observed that liver resection is an effective procedure for patients with symptomatic intrahepatic lithiasis associated to parenchymal fibrosis, biliary stenosis or atrophy. In patients with unilateral disease, hepatectomy has low morbidity and mortality, and the rate of success is better when compared with other interventional procedures.

Biliary dilation and stricture have been observed in the majority of patients submitted to liver resection and the presence of complications is associated with recurrence, therefore resections of these structures must be included in the procedure. Bilioenteric anastomosis has been indicated for patients with dilated bile duct of 2 cm or more and hepaticojunostomy is the most common procedure in the majority of the studies. Hepaticojunostomy has been associated with high rate of recurrence and postoperative complications such as biliary fistula, recurrent cholangitis, liver abscess and cholangiocarcinoma.²⁹ Other techniques as choledochoduodenostomy and choledochojunostomy are associated with gastrointestinal dysfunction and biliary reflux. When biliary drainage is required and patients presented with stones and bile duct dilation, the success rate is lower. In the present study, hepaticojunostomy was associated with more infectious complications, possibly due to the presence of extrahepatic biliary disease, inadequate drainage and stone formation. A better understanding of the therapeutic impact of hepatectomy associated with bile duct exploration and biliary drainage for intrahepatic lithiasis is necessary. Recurrence of symptoms revealed that bilioenteric anastomosis is not the ideal solution for intrahepatic lithiasis.^{23,30–32}

Biliary fistula was the most common complication in the present study (13.3%) and infectious complications were observed in 13 patients (10.2%), related mainly to biliary fistula and previous cholangitis. The higher incidence of biliary fistula in patients with liver resection for hepatolithiasis when compared with other causes for hepatectomy brings into discussion the necessity of routine drainage of the raw surface. Four between the six groups in this study, perform routine drainage after liver resection for hepatolithiasis. No operative mortality was associated to these complications even in patients with liver abscess or cholangitis.

Residual stones are a common finding.^{31–36} However, in the present study residual stones were observed in two asymptomatic patients (1.5%), a lower rate when compared with studies where liver resection was not performed. Recurrence was observed in 10 patients (7.8%) and post hepatectomy cholangitis was the main complication in 6 patients. To minimize the risk of complications, the affected bile duct and atrophied liver should be removed routinely. In some cases with bilateral stones and when a hepaticojunostomy is performed, a subcutaneous hepaticojunol loop has been used for the treatment of recurrent stones; however the majority of groups prefer the percutaneous approach for these cases.³⁷ Moreover, for patients with bilobar disease and associated biliary cirrhosis or portal hypertension, liver transplantation is indicated.^{38,39}

Intrahepatic lithiasis is a well-known risk factor for cholangiocarcinoma due to recurrent cholangitis. Furthermore, intrahepatic cholangiocarcinoma is the most important prognosis predictor of survival. The incidence has been reported to be as high as 15% of the patients with intrahepatic lithiasis. In Japan, a

nationwide survey observed that in 88% of patients with bile duct cancer, the tumor was located at the atrophic hepatic lobe.⁴⁰ In patients with biliary strictures and/or liver atrophy, the complete resection of this area should be recommended.^{41–44}

Some predictive factors are associated with progression to cholangiocarcinoma in patients with intrahepatic lithiasis including smoking, duration of intrahepatic stones, stone location, serum carcinoembryonic antigen (CEA), serum alkaline phosphatase, serum albumin, hepatitis virus B (HBV) and hepatitis virus C (HCV) infection. However, these risk factors have been observed in Asian intrahepatic lithiasis, and there is no data regarding risk factors for Non-Asian patients.^{2,3,40–43} In the present study cholangiocarcinoma was identified in two patients (1.5%) with hepatolithiasis.

Laparoscopic liver resection for intrahepatic lithiasis has been associated with significantly shorter hospital stay and no difference in morbidity and mortality. However in some patients the deformed biliary anatomy and perihepatic adhesions associated to cholangitis may increase the risk of complications.^{44–48} In this study only selected patients (11%) underwent laparoscopic liver resection (left lateral sectionectomy) and the mean operative time was shorter and no complications were observed.

We identified a large number of patients with intrahepatic lithiasis and this caught our attention about a rare disease. Our data reflected that the non-Asian hepatolithiasis presents the same clinical and pathological characteristics observed in Asian patients and that the treatment should be individualized according to the clinical presentation of the disease.

5. Conclusion

Liver resection is considered the standard treatment for patients with symptomatic intrahepatic lithiasis, especially in unilateral disease and when an irreversible damage to biliary duct or liver parenchyma has occurred. Resection removes the stones, the atrophy of the parenchyma, strictures, and promotes an adequate biliary drainage if necessary. Recurrence was more frequently observed in patients with bilobar stones and/or with a hepaticojunostomy. The risk of malignant transformation is low in non-Asian patients.

Declaration of competing interest

“The authors declare that they have no conflict of interest for this article.”

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