



## Removal of intrahepatic bile duct stone could reduce the risk of cholangiocarcinoma

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### Abstract

Hepatolithiasis (HL) poses a significant risk for cholangiocarcinoma (CCA) development, with reported incidences ranging from 5%-13%. Risk factors include older age, smoking, hepatitis B infection, and prolonged HL duration. Chronic inflammation and mechanical stress on the biliary epithelium contribute to CCA pathogenesis. Hepatectomy reduces CCA risk by removing stones and atrophic liver segments. However, residual stones and incomplete removal increase CCA risk. Kim *et al* identified carbohydrate antigen 19-9, carcinoembryonic antigen, and stone laterality as CCA risk factors, reaffirming the importance of complete stone removal. Nonetheless, challenges remain in preventing CCA recurrence post-surgery. Longer-term studies are needed to elucidate CCA risk factors further.

**Key Words:** Hepatolithiasis; Cholangiocarcinoma; Biliary stone; Common bile duct stone; Cholangitis

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**Core Tip:** Hepatolithiasis (HL) poses a significant risk for cholangiocarcinoma (CCA), with factors like stone location, recurrence, and incomplete removal influencing risk. While hepatectomy reduces CCA risk, residual stones and incomplete removal pose challenges. Kim *et al*'s study identifies carbohydrate antigen 19-9, carcinoembryonic antigen, and stone laterality as CCA risk factors, supporting prior findings. Nonetheless, discrepancies in bile duct stricture's impact on CCA risk highlight the need for further research. Understanding these factors aids in refining CCA risk assessment and optimizing management strategies for HL-associated CCA.

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## INTRODUCTION

The incidence of hepatolithiasis (HL) associated cholangiocarcinoma (CCA) appeared to range from 5%-13% in the literature. Risk factors for development of CCA include older age > 40 years, history of smoking, family history cancer, more extended history of HL > 10 years, history of weight loss, history of hepatitis B infection, high levels of serum alkaline phosphatase, low serum carcinoembryonic antigen (CEA) level > 4.2 ng/mL, low serum albumin, high serum carbohydrate antigen 19-9 (CA19-9) > 22 U/mL, duct stricture, focal atrophy, atrophy of liver parenchyma, and bilateral HL[1,2]. History of gastrectomy and choledochenterostomy were also the risk factors for CCA development[3]. HL associated CCA (HL-CCA) has been grouped into concomitant-CCA (C-CCA) or subsequent-CCA (S-CCA) based on its diagnosis with HL. C-CCA ranges from 5%-12%. S-CCA has been reported up to 10% of the population[4-6]. Removal of stones decreases the risk of CCA. We discuss the study's results by Kim *et al*[7] and expand on the topic.

### Mechanism of HL associated with CCA

HL-CCA occurs in areas of stone location. HL may include persistent mechanical stress and chronic inflammation of the biliary epithelium. The process of CCA appears to be a complex process involving pro-inflammatory cytokines, growth factors, cancer associated fibroblasts and biliary tract and liver microbiome changes[8-10]. This creates a tumor microenvironment with increased expression of cell surface receptors and disruption of intracellular signaling pathways, causing cell proliferation and aberrant development. Banales *et al*[8] describes common mutated genes including FGFR2 fusions, BAP1, BRAF, ARID1A, KRAS, TP53, SMAD4, PBRM1 and IDH1 and IDH2. Molecular alterations including p16 inactivation, increased expression of cyclooxygenase-2, prostaglandin E2, proto-oncogene c-met and decreased caudal-related homeobox gene 2 have been recognized in precursor lesions of CCA[10]. Wang *et al*[11] found that peripheral inflammation parameters that indicate systemic inflammation and immune response like neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and systemic immune inflammation were higher in the HL group compared to the non-HL group and without biliary stricture group. Systemic immune response was hyper-activated in HL-CCA patients. Helper and cytotoxic T cells were involved in the inflammatory process. This resulted in the bile ducts in this area becoming fibrosed, thickened, and stenosed, causing recurrent attacks of acute cholangitis. The stone-involved segments became damaged and atrophic over time. The recurrent attacks of acute cholangitis can cause CCA in stone-involved segments. Therefore, hepatectomy for the involved segments decreases the risk of CCA. Hepatectomy removes the stones, atrophied liver segments, and stricture tissue. S-CCA development is an important prognostic factor in predicting survival in these patients. Often, patients with S-CCA have advanced disease and poor prognosis at presentation.

### Can removal of intrahepatic bile duct stone reduce the risk of CCA?

Studies describe continued risk of stone formation even after initial stone removal[5]. Residual stones continue to pose an increased risk for CCA by up to 16%[12]. Inflammation of the liver tissue due to Chronic proliferative cholangitis from residual stones may lead to bile duct epithelium dysplasia and cancer[12]. The 10-year recurrence rate was doubled in the bilateral group compared to the unilateral group[12-14]. These patients continued to be at increased risk of CCA, with risk ranging up to 6.25%[12,13]. Patients with recurrent HL post hepatectomy still have a high risk of C-CCA and S-CCA. Studies often showed that S-CCA developed post-resection in the lobes closest to the resected hepatic segments. This may be due to biliary intraepithelial neoplasia from long-term inflammation in the adjacent bile ducts. Bilateral HL can also be associated with a limited ability to clear stones in diffuse distribution during hepatectomy with intraoperative lithotomy and lithotripsy. To preserve part of the liver, conservative resection can increase the risk of S-CCA.

Some studies also describe the extent of liver resection (ELR) compared to stone-affected segments. When the ELR < stone affected segments (SASs), patients are at increased risk of CCA development (20%-21.5%). When the ELR = stone - affected segments, the risk was comparably lower in unilateral and bilateral groups (3%-4.3%)[12,15]. Often, patients have incomplete stone removal on initial hepatectomy and require repeated procedures such as segmentectomy, Cholangioscopic lithotomy, or lithotripsy for stone removal[15]. There is a high chance of residual and missing stones. These can further contribute to continued atrophy, thickening, and hepatocyte fibrosis of the stone-bearing ducts, with the adjacent unaffected segments having compensatory hypertrophy. This process can also predispose to CCA[13]. Further isolated peripheral stones and varied involvement of intrahepatic duct distribution can make cholangioscopic procedures

challenging and impact complete stone removal, affecting the ELR = SAS ratio and increasing residual stones. In the absence of symptomatic HL, residual stones, biliary stricture, and hepatic atrophy after initial stone removal, careful close follow-up can be done after discussing risks and benefits with patients[16]. Ultrasound and Computed tomography imaging are primary modalities for diagnosis of HL diagnosis and for monitoring recurrence during the follow-up period. They can detect biliary dilations, strictures, and stones. Magnetic resonance imaging and magnetic retrograde cholangiopancreatography are often additional tests for abnormalities in liver enzymes or tumor markers or to define ultrasound or computed tomography abnormal findings better[6]. Monitoring liver enzymes, serological tumor markers such as CA19-9 and CEA for 6-month follow-up after stone removal and with less frequent intervals after. Endoscopic retrograde cholangiopancreatography is used to treat biliary dilation and obtain tissue for diagnosis. Endoscopic ultrasound with biopsy may be used to assess locoregional extension of CCA, evaluate biliary obstruction, and obtain tissue for diagnosis[17].

In the most recent issue of the *World Journal of Clinical Cases*, Kim *et al*[7] attempted to replicate the prior research on stone removal and the risk of CCA in a retrospective study and identify risk factors for its development.

Kim *et al*[7] found CA19-9, CEA, and bilateral stones to be risk factors for CCA, similar to prior studies. Stone removal was associated with a lower incidence of CCA. They also found complete removal without recurrence to decrease the risk of CCA, similar to prior studies. The authors found atrophy of the liver parenchyma to be a significant risk factor similar to prior studies. Some studies, like Liu *et al*[2] showed left-sided stones associated with a higher risk of CCA, and others, like Suzuki *et al*[1] showed predominant right-sided stones associated with high risk[1,2]. It is postulated that since the right intrahepatic duct is shorter and wider it is more prone to stasis, stone formation and inflammation thereby increasing risk of CCA. In the study by Kim *et al*[7] results showed left-sided stones to be at high risk. The left sided hepatic duct is anatomically at an acute angle with the common bile duct thereby more prone to stasis. The right segmental bile ducts also branch from the left hepatic thereby increasing left sided stone and CCA risk. Based on the study by Kim *et al*[7] and prior studies there may be no strong correlation between stone location and intrahepatic CCA. The varied study results may also be due to reasons specific to the study population[7].

The authors found that bile duct stricture did not increase the risk of CCA. However, these results differ from prior literature on larger patient populations. Strictured bile ducts are atrophied, fibrosed, and postulated to increase the risk of CCA. Non-surgical methods of stone removal were associated with remnant stones, recurrent stones, and increased cholangitis episodes. However, this did not reflect the decreased risk of CCA. They also found that complete removal with recurrence and incomplete removal with remnant showed a decreased risk for CCA. However, the results were not significant. Considering these groups were 6.4% and 5.6% of the study population, the small size may have yielded different results than prior literature. Further, the follow-up duration of 7 years may not have been long enough to detect further cases of CCA. Compared to patients who underwent stone removal, the risk of CCA was higher by 3 times in the patients who did not undergo removal in the study by Kim *et al*[7] (5% *vs* 15.3%). Even after complete stone removal, the risk of CCA in the study was 4.6%, similar to prior studies that showed high risk from adjacent inflamed biliary ducts. The study adds to prior literature on risk factors for CCA. A longer follow-up period of > 10 years and a larger group of patients with CCA could have yielded more information on risk factors and supported the evidence from prior studies.

## CONCLUSION

HL is a risk factor for CCA. Post hepatectomy and procedures for stone removal, patients continued to be at increased risk if there were recurrent stones or incomplete stone removal. Complete removal of stones without recurrence decreases the risk of CCA but does not eliminate the risk.

## FOOTNOTES

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