*Addiction & Health*

https://ahj.kmu.ac.ir
10.34172/ahj.1636
AHJ. 2025;17:1636

**Original Article**

# Impact of Opium Addiction on Liver Function and Biliary Tract in Patients with Bile Duct Stones: A Case-Control Study

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**Abstract**

**Background:** This study aimed to investigate the impact of opium on liver function and the biliary tract in patients with bile duct stones, comparing outcomes with non-addicted individuals.

**Methods:** This case-control study was conducted in Iran from 2016 to 2017. A total of 86 patients with bile duct stones were divided into two groups: opium-addicted ($n=40$) and non-opium-addicted ($n=46$). The patient's hepatobiliary system was evaluated using liver function tests (LFTs) and endoscopic ultrasound (EUS). Data were collected and analyzed using SPSS software.

**Findings:** LFTs showed significantly elevated levels of aspartate aminotransferase (AST) (90.67 ± 46.99 vs 55.28 ± 45.53 U/L, $P=0.036$) and aspartate aminotransferase (ALT) (120.47 ± 90.15 vs 51.83 ± 35.21 U/L, $P=0.005$) in the opium-addicted group compared to controls, and higher direct (4.05 ± 2.84 vs 2.30 ± 1.66 mg/dL, $P=0.002$) and total bilirubin levels (5.02 ± 3.94 vs 2.93 ± 2.35 mg/dL, $P=0.007$). Furthermore, the common bile duct (CBD) diameter was significantly larger in the opium-addicted group (12.21 ± 3.42 vs 7.80 ± 2.62 mm, $P=0.007$). In contrast, pancreatic duct diameters ($P=0.289$) and alanine aminotransferase (ALP) levels ($P=0.842$) showed no significant differences.

**Conclusion:** The study revealed that opium addiction is associated with significantly elevated levels of liver enzymes (AST and ALT), higher bilirubin levels, and an increased common bile duct diameter in patients with bile duct stones, while the pancreatic duct diameter and ALP levels remained unaffected. These findings highlight the potential impact of opium use on the hepatobiliary system and underscore the importance of further research to understand its long-term effects and improve clinical management.

**Keywords:** Opium, Addiction, Hepatobiliary, Biliary stone, Gallstones

**Citation:** Abedinzadeh M, Karimi M, Ahmadi Hajikolaei F, Saleh M, Diyanati M, Khosravi R, et al. Impact of opium addiction on liver function and biliary tract in patients with bile duct stones: a case-control study. *Addict Health*. 2025;17:1636. doi:10.34172/ahj.1636

**Received:** November 20,2024 **Revised:** January 17,2025, **Accepted:** June 18, 2025, **ePublished:** September 13, 2025

## Introduction

Opium addiction remains a significant public health concern, particularly in regions where its use is prevalent.[1] Opioids are widely abused worldwide due to their euphoric effects.[2] As one of the most commonly abused substances, opium has far-reaching implications on various organ systems, including the liver and biliary tract.[3,4] The liver plays a critical role in metabolizing drugs and toxins, and its dysfunction can lead to severe complications, particularly in individuals with existing biliary tract disorders, such as bile duct stones.[5,6] The detrimental effects of opium on various organ systems are well documented, but its specific impact on liver function and the biliary tract has not been thoroughly investigated.[3,7] Given the critical role of the liver and biliary system in the metabolism and excretion of substances, understanding how opium addiction influences these organs is essential for developing effective treatment strategies for affected individuals. Patients with bile duct stones represent a unique population, as the interplay between opium addiction and biliary pathology could have profound implications for both their clinical management and overall health outcomes.[8]

The liver is responsible for numerous vital functions, including detoxification, protein synthesis, and bile production. Furthermore, the biliary tract facilitates the transport of bile, which is essential for digestion

and fat metabolism.[9] Individuals with bile duct stones already face risks such as inflammation and infection, and the additional burden of opium use could further compromise liver function. Chronic opium use may lead to liver dysfunction and alterations in biliary dynamics, potentially exacerbating conditions like cholestasis and bile duct obstruction.[10,11] Opium addiction can affect the biliary and pancreatic system, leading to delayed gallbladder discharge and possible dilatation of the CBD and pancreatic duct in some patients.[12-14]

The relationship between opium addiction and liver function has attracted attention. However, existing literature often lacks a comprehensive analysis of its specific effects on patients with concurrent biliary disorders, such as bile duct stones. This knowledge gap underscores the need for targeted research that explores these connections more thoroughly. This study aimed to elucidate the impact of opium addiction on liver function and the biliary tract in patients suffering from bile duct stones, addressing a gap in the current literature regarding the interplay between substance abuse and hepatobiliary health.

## Methods

### *Study Design and Setting*

This observational case-control study was conducted at *Rouhani Hospital* in Babol, Iran, between August 2016 and October 2017. The study aimed to evaluate and compare the impact of opium addiction on the liver function and biliary tract in patients with bile duct stones in opium-addicted and non-opium-addicted patients.

### *Study Population*

The sample size was calculated using the formula for comparing means between two independent groups based on the data from the study by Zahedi-Nejad et al.[12] With a confidence level of 95% and power of 80%, the required sample size was 71 participants per group, totaling 142. Due to practical limitations, a total of 86 patients with CBD stones were included in the study and divided into two groups based on their status of opium addiction. The case group consisted of 40 opium-addicted patients, while the control group included 46 non-opium-addicted patients. They were also screened for human immunodeficiency virus (HIV) antibodies, hepatitis B antigen, and anti-hepatitis C virus antibodies.

To minimize confounding factors, patients with a history of dyslipidemia, cardiovascular disease, kidney or liver failure, fatty liver, hepatitis, diabetes, thyroid disorders, lead poisoning, gastrointestinal dysfunction, or oral contraceptive pill (OCP) use were excluded from the study. These exclusion criteria ensured that the impact of opium addiction on liver function and the biliary tract could be evaluated more precisely.

### *Data Collection*

Data collection involved obtaining a detailed case history and administering a comprehensive questionnaire. Each patient provided a thorough medical history, including information on drug sensitivities, medical conditions such as heart failure, diabetes, renal and respiratory failure, and any previous surgeries. Patients also reported the amount and method of opium consumption, as well as the history of alcohol use. Opioid dependence is defined based on the DSM-IV criteria of use for more than five years.[15] However, in this study, we considered all people who used opium three times a week for at least one year as opium addicts.[14,16]

All patients underwent liver function tests (LFTs), including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), direct bilirubin, and total bilirubin.

### *EUS Procedure*

All patients underwent an endoscopic ultrasound (EUS) under anesthesia by an expert endoscopist and an anesthesiologist who were masked to the history and opium addiction status of patients. The anesthesiologist anesthetized, supervised, and monitored patients throughout the EUS process until complete recovery, ensuring cardiovascular stability and adequate oxygenation. The endoscopist evaluated and registered the endoscopic findings, including CBD diameter, pancreatic duct diameter, cystic duct lesions, and pancreatic parenchymal characteristics. After the EUS and related procedures, the patients were transferred to the recovery department and discharged under the supervision of the anesthesiologist after complete recovery.

Endoscopic ultrasound (EUS) was performed using a Pentax 7500 series device with 30 series echoendoscopes. EUS has a sensitivity of 96% and a specificity of 86% for the diagnosis of gallstones.[17]

### *Ethics*

The study adhered to rigorous ethical standards to ensure the protection of and respect for all participants. Informed consent was obtained from all patients, guaranteeing they were fully aware of the study's nature, purpose, and potential risks before agreeing to participate. The research followed the ethical guidelines outlined in the Declaration of Helsinki, ensuring that it met internationally recognized principles for medical research involving human subjects. Additionally, the study received approval from the Ethics Committee of Babol University of Medical Sciences (MUBabol) in Babol, Iran (ethical code: MUBABOL.HRI.REC.1396.79).

### *Statistical Analysis*

Data were analyzed using SPSS version 23. The Shapiro-Wilk test was employed to assess data distribution.

Continuous variables were compared using independent *t*-tests for normally distributed data, and Mann-Whitney *U* tests were used for non-normally distributed data. When appropriate, categorical variables were analyzed using the chi-square test or Fisher's exact test. Subgroup analysis was conducted for the opium-addicted group based on oral and inhaled forms of opium use. A *P* value of less than 0.05 was considered statistically significant. A *P* value less than 0.05 was considered significant.

## Results

### *Baseline Characteristics*

In this observational study, 86 patients with a mean age of 64.08 ± 17.86 years with CBD stones were enrolled, comprising 42 males (48.8%) and 44 females (51.2%). The mean age in males and females was 66.62 ± 14.86 and 61.88 ± 20, respectively (Figure 1).

The case group included 40 patients (46.5%), while the control group had 46 patients (53.5%). This gender difference was not significant ($P = 0.266$). The mean age and height in the case group were significantly higher than in the control group ($P < 0.05$). However, BMI, weight, and gender distribution did not vary significantly between the two groups ($P > 0.05$) (Table 1).

The patients in the case group (opium addicts) were categorized into two subgroups based on their method of use: inhaled ($n = 29$) and oral ($n = 11$). The mean age for the oral and inhaled subgroups was 69.08 ± 11.67 and 62.91 ± 17.17 years, respectively; however, this difference was not statistically significant ($P = 0.065$).

### *Clinical Symptoms*

In terms of clinical presentation, the opium-addicted group exhibited significantly lower rates of jaundice (19% vs 99%; $P = 0.045$) and biliary colic (20% vs 44%; $P = 0.004$) compared to the non-addicted group (Figure 2). However, there were no significant differences between the two groups regarding the incidence of pruritus ($P = 0.916$) or NSAID use ($P = 0.557$).

### *Liver Function Tests*

The LFT revealed significant differences between the opium-addicted group and the non-addicted control group, with significantly higher levels of AST in the opium-addicted group (90.67 ± 46.99 U/L) compared to the non-addicted group (55.28 ± 45.53 U/L; $P = 0.036$) and significantly elevated ALT levels (120.47 ± 90.15 U/L vs 51.83 ± 35.21 U/L; $P = 0.005$). Although ALP levels showed no statistically significant difference (333.88 ± 174.37 U/L for the case group vs 319.87 ± 220.14 U/L for control; $P = 0.842$), direct bilirubin levels were significantly higher in the opium-addicted group (4.05 ± 2.84 mg/dL) than in the control group (2.30 ± 1.66 mg/dL; $P = 0.002$); total bilirubin levels were also significantly higher in the opium-addicted group (5.02 ± 3.94 mg/dL vs 2.93 ± 2.35 mg/dL; $P = 0.007$). These findings indicate that the opium-addicted group exhibited marked liver dysfunction compared to non-addicted controls, as evidenced by elevated liver enzymes and bilirubin levels (Table 1).

The subgroup analysis of the opium-addicted patients showed no significant differences in liver function test results between those using oral and inhaled opium, with AST ($P = 0.338$), ALT ($P = 0.256$), ALP ($P = 0.062$), direct bilirubin ($P = 0.789$), and total bilirubin ($P = 0.571$), showing no significant difference.

### *Endosonographic Findings*

Comparative evaluation of the endoscopic findings in opium-addicted patients ($n = 40$) and non-addicted controls ($n = 46$) showed that the common bile duct (CBD) diameter was significantly larger in the opium-addicted group (12.21 ± 3.42 mm) compared to the controls (7.80 ± 2.62 mm) ($P = 0.007$). However, there was no significant difference in the pancreatic duct diameter between the groups (4.00 ± 1.03 mm for the opium-addicted and 4.77 ± 1.63 mm for the controls) ($P = 0.289$) (Table 1).

## Discussion

This observational case-control study aimed to investigate the effects of opium addiction on liver function and

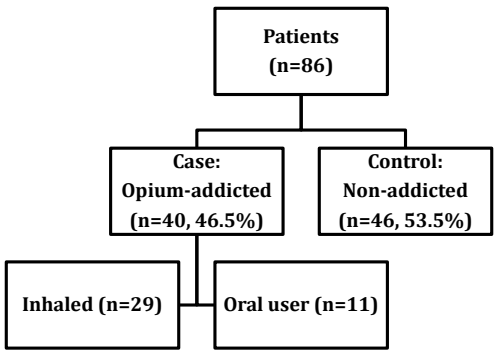


**Figure 1.** Diagram of the included patients

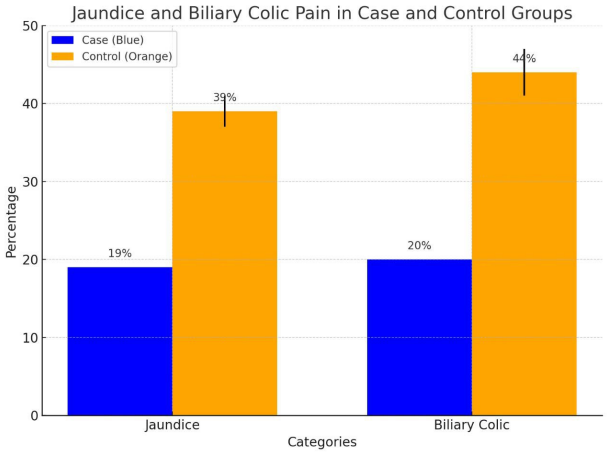


**Figure 2.** Jaundice (19% vs 39%; $P = 0.045$) and biliary colic pain (20% vs 44%; $P = 0.004$) in the case and control groups

**Table 1.** Demographic, laboratory, and endosonographic data of participants

| Variable | Opium-addicted (case = 40) | Non-addicted (control = 46) | *P* value |
|---|---|---|---|
| Demographic data | | | |
| Age (year) | 67.19 ± 13.44 | 61.40 ± 20.71 | 0.001* |
| Height (cm) | 163.06 ± 9.69 | 160.35 ± 4.77 | 0.001* |
| Weight (kg) | 67.69 ± 10.49 | 70.06 ± 11.78 | 0.870 |
| BMI (kg/m$^2$) | 25.45 ± 11.1 | 27.24 ± 5.1 | 0.240 |
| Liver function tests | | | |
| AST (U/L) | 90.67 ± 46.99 | 55.28 ± 45.53 | 0.036* |
| ALT (U/L) | 120.47 ± 90.15 | 51.83 ± 35.21 | 0.005* |
| ALP (U/L) | 333.88 ± 174.37 | 319.87 ± 220.14 | 0.842 |
| Direct bilirubin (mg/dL) | 4.05 ± 2.84 | 2.30 ± 1.66 | 0.002* |
| Total bilirubin (mg/dL) | 5.02 ± 3.94 | 2.93 ± 2.35 | 0.007* |
| Endosonographic findings | | | |
| CBD diameter (mm) | 12.21 ± 3.42 | 7.80 ± 2.62 | 0.007* |
| Pancreatic duct diameter (mm) | 4.00 ± 1.03 | 4.77 ± 1.63 | 0.289 |

*SD:* standard deviation; (Mean ± SD); BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; CBD: common bile duct.

the biliary tract using liver function tests (LFTs) and endoscopic ultrasound (EUS) in patients with bile duct stones, comparing outcomes between opium-addicted and non-addicted individuals. The findings of this study demonstrate that opium addiction is associated with significant liver dysfunction, as evidenced by elevated levels of AST, ALT, and bilirubin in the opium-addicted group compared to non-addicted controls. Additionally, the study revealed a significantly larger CBD diameter in opium-addicted individuals, suggesting that opium use may contribute to biliary tract alterations. However, no significant difference was observed in pancreatic duct diameter between the groups. These results emphasize the need for further investigation into the long-term effects of opium on liver and biliary health.

Opioids exert significant effects on the hepatobiliary system through both metabolic and receptor-mediated mechanisms. As opioids are primarily metabolized in the liver, chronic opioid use is associated with severe liver damage, as it suppresses hepatic antioxidant systems, elevates oxidative stress markers, and induces hepatocyte apoptosis, as shown in animal studies [18,19] and observations of heroin abusers.[20,21] The severity of liver injury correlates with the duration of opioid use.[21] Additionally, opioids act on mu-opioid receptors located on the sphincter of Oddi, disrupting relaxation by reducing cAMP and calcium signaling. This results in spasms that impair bile and pancreatic flow, increasing intrabiliary pressure and predisposing to conditions such as biliary colic and pancreatitis.[22]

### *Impact on Liver*

The findings from various studies underscore the profound impact of opium abuse on metabolic processes and organ function. Bijani et al[23] demonstrated that while both cigarette smoking and alcohol consumption are linked to elevated liver enzymes, inhaled opium also contributes to liver dysfunction. However, oral opium use did not show a similar effect on liver enzymes. These results suggest that the route of opium administration plays a critical role in its impact on metabolic health. Additionally, Montazerifar et al[24] highlighted that chronic opium use leads to elevated blood lead levels and decreased hemoglobin, further exacerbating the toxic effects on the body. The correlation between blood lead levels and the length of addiction points to a cumulative toxic burden from prolonged opium exposure.

Moreover, the studies reveal that opium abuse significantly contributes to an elevated risk of cardiovascular issues and cancer. Asgari et al[25] reported that prolonged opium addiction leads to worsening cardiovascular risk factors, such as increased HbA1C and C-reactive protein (CRP), alongside lower protective HDL cholesterol levels. These effects are particularly severe when opium is consumed via the "Sikh-Sang" method. In line with these findings, Marzban et al[26] found that opium use, especially in the form of teriak, is associated with an increased risk of liver cancer and disruptions in normal organ function. The increased risk of cancer and other metabolic disorders demonstrates the long-term dangers of opium abuse, with its effects worsening with higher dosages and longer addiction durations.[4,27]

This study demonstrated that individuals with CBD stones who use opium may show different biochemical results compared to non-users. Alkaline phosphatase (ALP) and bilirubin levels may not be elevated in opium users, even if they present with biliary symptoms, making further investigation necessary to detect CBD stones. Additionally, opium addiction can cause an enlarged CBD diameter without the presence of stones or obstructions.

### *CBD*

In the present study, both the opium-addicted group and the non-addicted group exhibited CBD diameters exceeding the normal range, likely due to the obstructive effects of biliary stones. Notably, the opium-addicted group had a significantly larger average CBD diameter compared to the non-addicted group. This finding aligns with the result of previous research, identifying greater CBD diameters in opium users, though our observed diameters were generally larger than those reported in other studies.[2,14,28-34] This discrepancy could be attributed to the severity of biliary obstruction in our patient cohort.

Previous studies have established that the average CBD diameter ranges between 6 and 7 mm when measured via ultrasound and EUS.[35] Conditions such as a history of cholecystectomy, choledochal duct obstruction, and patient sex can influence CBD diameter.[14,36,37] However,

no association was found between sex and CBD diameter in the present study. It is well-documented that age and cholecystectomy history can also contribute to increased duct diameter, with a typical increment of 1 mm per decade in adults.[37]

In this study, we did not find a significant difference in pancreatic duct diameters between the opium-addicted and non-opium-addicted patients. In contrast, Sharma et al[14] reported CBD dilation in all opium-addicted patients, while pancreatic duct dilation was observed only in some patients. Similarly, Sotoudehmanesh et al[32] found significantly higher diameters of both CBD and pancreatic ducts in opium-addicted patients. This inconsistency might be due to differences in study populations or measurement techniques. Moreover, Radmard et al[38] found no significant association between CBD diameter and opium dosage or consumption duration among opium users, suggesting that other factors may mediate this relationship.

Previous studies reported that opium addiction may alter biliary and pancreatic physiology, thereby affecting disease presentation and progression.[12,39] CBD dilatation is commonly observed in opium-addicted patients, while pancreatic duct dilatation is seen in only a small number of patients.[13,14] One of the effects of opium addiction on the bile system is the dysfunction of the sphincter of Oddi, which causes delayed discharge of the gallbladder.[12,39] It has been proven that opiates lead to an increase in the basal pressure and phasic contraction frequency of the sphincter of Oddi, causing an increase in internal pressure within the CBD, and following this, sphincter of Oddi spasm and internal pressure causing dilatation of the CBD and biliary stasis in addicted individuals.[14] Both asymptomatic CBD dilatation and symptomatic sphincter of Oddi dysfunction have been reported among opium users.[14,40,41]

## Strengths

This study's strengths include rigorous participant screening to exclude confounding medical conditions and lifestyle factors, comprehensive data collection, and a masked EUS procedure conducted with standardized equipment, ensuring diagnostic consistency. Additionally, the study adhered to high ethical standards and employed advanced statistical methods to enhance the reliability of the findings. However, its limitations include being a single-center study, which may limit generalizability, a small sample size that may affect the detection of clinically significant differences, potential recall bias from self-reported data, a broad definition of opium addiction, and exclusion criteria that limit applicability to a broader patient population. Furthermore, the observational case-control design can identify associations but cannot establish causality. Therefore, future research should include larger sample sizes and more detailed information on opium use, and outcomes should be reassessed after treating biliary stones.

## Conclusion

In conclusion, this study highlights the significant impact of opium addiction on liver function and the biliary tract in patients with bile duct stones. Opium use was associated with elevated liver enzymes and bilirubin levels, as well as a significantly larger common bile duct (CBD) diameter compared to non-addicted individuals, suggesting that opium may contribute to biliary tract dysfunction. However, no significant differences were observed in pancreatic duct diameters between the groups. These findings underline the importance of further research to better understand the long-term effects of opium addiction on liver and biliary health and to guide appropriate clinical management for affected individuals.

**Acknowledgments**

The authors would like to thank the patients who contributed to this study.

**Authors' Contribution**

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**Software:** Maedeh Abedinzadeh, Mehdi Karimi, Fatemeh Ahmadi Hajikolaei, Javad Shokri-Shirvani.
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**Writing–review & editing:** Mehdi Karimi.

**Consent to Participate**

Informed consent was obtained from the participants of this study. All participants participated in the survey knowingly and with consent.

**Consent for Publication**

Written informed consent was obtained from the patients for the publication of this study.

**Competing Interests**

None.

**Data Availability**
The analyzed data are reported in the published articles.

**Ethical Approval**
The Ethics Committee of Babol University of Medical Sciences approved this study (ethical code: MUBABOL.HRI.REC.1396.79). The studies were conducted following the local legislation and institutional requirements. The participants provided written informed consent to participate in this study. The study was performed according to the ethical standards in the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards.

**Funding**
None.

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