The therapeutic value of "bile transfer" for complications of acute pancreatitis: A real-world study

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Informed Consent Statement: All study participants or their legal guardians provided informed written consent for personal and medical data collection before study enrollment.

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Abstract

Background Acute pancreatitis (AP) has a severe disease course and is challenging to treat, with global incidence rising annually. Despite a drop in fatality rates, AP-related complications remain high, impacting prognosis. This real-world study introduces the concept of “bile transfer” (BT) and explores its potential in reducing AP-related complications.

Methods This single-center, retrospective cohort study evaluated 344 AP patients with gallbladder enlargement at our hospital from January 2019 to December 2023. Patients were classified into three groups: percutaneous transhepatic gallbladder drainage (PTGD) + bile reinfusion (BT group), PTGD-alone, and conventional treatment to assess complication rates. Logistic regression identified independent risk factors for treatment outcomes, which were used to create a nomogram for individualized predictions. Restricted cubic splines (RCS) were employed to identify optimal indications for BT.

Findings Among the 344 patients, the incidence of new complications in the BT group was 21.50%, significantly lower than in the PTGD-alone (46.59%) and conventional treatment groups (61.07%) (p<0.001). Logistic regression identified total bilirubin (TBIL), Ca^{2+}, WBC, and AST/ALT as independent predictors of poor BT outcomes. RCS analysis showed TBIL <23.6μmol/L, WBC<10.6×10^9/L, and Ca^{2+}>2.12 mmol/L as optimal indicators for BT use.

Interpretation This study confirmed that BT can effectively reduce the incidence of complications in AP patients. We identified optimal indications and predictors for BT and developed a nomogram for individualized predictions. These findings are clinically important for improving AP patient prognosis.

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Keywords: Acute pancreatitis; Complications; Bile transfer; Percutaneous transhepatic gallbladder drainage; Bile reinfusion

Research in context

Evidence before this study

Acute pancreatitis (AP) has a severe disease course and is challenging to treat, with global incidence rising annually. Despite a drop in fatality rates, AP-related complications remain high, impacting prognosis.

Added value of this study

This study introduces bile transfer (BT) and shows that PTGD combined with bile reinfusion significantly reduces complications in AP patients. We identified optimal indications and predictors for BT and developed a nomogram for individualized predictions.

Implications of all the available evidence

BT can effectively reduce the incidence of complications in patients with AP, accelerate the recovery of patients and improve the prognosis of patients.

1. Introduction

Acute pancreatitis (AP) is a common inflammatory disease of the digestive system, with an annual incidence of approximately 34 per 100,000 in high-income countries[1]. Most patients present with mild acute pancreatitis (MAP), while about 20% progress to moderately severe acute pancreatitis (MSAP) or severe acute pancreatitis (SAP). MAP is often self-limited and resolves within a week, whereas SAP involves necrosis of the pancreas or peripancreatic tissue and persistent organ failure, resulting in a mortality

rate of 20%-40%[2-6]. Local complications of AP include peripancreatic fluid collections, pancreatic pseudocysts, and walled-off necrosis, while systemic complications encompass organ failure, systemic inflammatory response syndrome (SIRS), and sepsis[7]. Studies indicate that local complications occur in approximately 33.3% of AP patients[8], and organ failure affects about 20%[9]. SAP with persistent organ failure significantly contributes to mortality[10]. Therefore, effectively reducing the incidence of AP complications is crucial for improving overall prognosis.

The course of AP is often linked to gallbladder enlargement, poor bile drainage, cholestasis, and biliary hypertension[11]. In biliary AP, 27%-35% of patients show abnormal gallbladder sizes, while around 40% have gallbladder wall thicknesses over 3 mm[12]. Biliary hypertension results from cholelithiasis[13,14]and inflammation in the pancreatic head, leading to tissue edema that compresses the distal common bile duct, causing impaired bile outflow[15]. This condition can result in bile reflux, potentially inflaming the pancreas[16]. Therefore, addressing cholestasis and biliary hypertension is crucial for improving patient outcomes. Percutaneous transhepatic gallbladder drainage (PTGD) is a minimally invasive procedure that alleviates biliary obstruction and reduces pressure in the gallbladder and pancreas, thereby decreasing AP complications[17,18]. However, it disrupts enterohepatic circulation, which may lead to fat malabsorption[19]. Bile acids (BAs) regulate fat, glucose, and energy metabolism, playing a key role in nutrient absorption[20]. Bile reinfusion during external biliary drainage can restore intestinal barrier function and prevent nutritional deficiencies[21]. Thus, bile reinfusion may preserve enterohepatic circulation and BAs integrity. However, the effectiveness of PTGD combined with bile reinfusion (bile transfer, BT) in AP patients remains uncertain.

In this real-world study (RWS), we retrospectively analyzed data from AP patients at the First Affiliated Hospital of Harbin Medical University (January 2019 - December 2023) to assess the value of BT (PTGD + bile reinfusion) in reducing AP complications. We also used restricted cubic splines (RCS) to evaluate BT indications, offering insights for improving AP prognosis.

2. Patients and methods

2.1 Study design and population

This investigation was a real-world, single-center retrospective cohort study involving 1,103 AP patients admitted to the hospital from January 2019 to December 2023. Inclusion criteria were: (1) aged 18–80 years; (2) met the 2012 revised Atlanta Classification criteria for AP[7]; (3) exhibited "gallbladder enlargement" (defined as long diameter ≥8 cm and/or transverse diameter ≥4 cm per Perez et al.[22]); (4) first hospital admission for AP; and (5) no history of other pancreatic diseases. Exclusion criteria included: (1) failure to meet gallbladder enlargement criteria; (2) treatment via biliary tract drainage methods other than PTGD; (3) critically missing clinical data; (4) age <18 or >80 years; (5) repeated AP admissions; and (6) prior pancreatic disease. Ultimately, 759 patients were excluded: 700 for non-compliance with gallbladder size criteria, 53 for receiving non-PTGD drainage, and 6 for missing data. A total of 344 AP patients with gallbladder enlargement were included and divided into three groups based on treatment: PTGD + bile reinfusion (107 patients), PTGD alone (88 patients), and conventional treatment (149 patients) (Figure 1). The PTGD + bile reinfusion group received PTGD within 48 hours of admission, followed by reinfusion of drained bile. This study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (IRB-AF/SC-08/06.0).

2.2 Treatment measures

2.2.1 Conventional treatment

Patients underwent pancreatic CT, abdominal ultrasound, and relevant laboratory tests within 24 hours of admission to confirm AP. Each patient's Charlson comorbidity index (CCI), Marshall organ failure score, and BISAP score were calculated, categorizing them into MAP, MSAP and SAP groups based on the 2012 revised Atlanta Classification[7]. Treatment adhered to the "step-up" principle[23]. All patients fasted, received nasal oxygen via catheter, continuous gastrointestinal decompression,

nutritional support, pain relief, and antispasmodic therapy. Water, electrolyte, and acid-base imbalances were closely monitored and corrected, and gastric acid and pancreatic enzyme secretion were inhibited. Surgical intervention was performed when indicated[24].

2.2.2 PTGD

PTGD was performed by an experienced imaging physician. Prior to the procedure, Doppler ultrasound was used to assess the size, location, and surrounding organs of the gallbladder. The patient was positioned supine, with puncture sites chosen in the 8th and 9th intercostal spaces along the right anterior axillary or midaxillary line under ultrasound guidance. After routine disinfection and draping, local anesthesia was administered with 2% lidocaine. Color Doppler flow imaging (CDFI) guided the puncture to avoid intrahepatic vessels. The puncture needle was inserted from the gallbladder bed through the skin and liver into the gallbladder. After aspirating bile, a guidewire was placed through the needle, followed by the removal of the needle. An 8F external drainage tube was then advanced along the guidewire, which was subsequently withdrawn. The position of the drainage tube within the gallbladder was confirmed, ensuring patency. The skin was sutured to secure the drainage tube, and a sterile drainage bag was attached. An appropriate volume of bile was collected for bacteriological examination, and the drainage tube was flushed with normal saline daily to maintain patency.

The indications for drainage tube removal included[17]: 1) drainage duration exceeding one week; 2) alleviation of AP symptoms; 3) clear bile that was yellow or greenish without pus; and 4) a negative bile culture. Once these criteria were met, the drainage tube was clamped. If the patient remained asymptomatic for 3–5 days and follow-up color ultrasound confirmed normalization of gallbladder size, the drainage tube was removed.

2.2.3 Bile reinfusion

A Japanese study indicated that bile reinfusion should begin orally within 2–3 days after biliary tract external drainage[25]. If the bile is turbid, purulent, or green, indicating

infection, reinfusion should be suspended[25]. A 2013 study also demonstrated the use of an endoscopic method to place a feeding tube through the nostril into the duodenum for importing gauze-filtered bile[26]. Based on these methods and considering clinical costs and patient compliance, we adopted the following protocol: starting on the second day post-PTGD, bile was collected every 4–6 hours, filtered through four layers of sterile gauze, and stored in sterile containers before being administered via a nasogastric tube. If the bile appeared turbid, purulent, or green, indicating infection, reinfusion was halted.

2.3 Outcome measures

The main outcome measures included the incidence of new-onset complications, defined as local/systemic complications that developed during hospitalization[23]. Following the 2012 revised Atlanta Classification[7], local complications were categorized as peripancreatic fluid collection, pancreatic pseudocysts, walled-off necrosis (sterile or infected), pancreatic abscess, pancreatic fistula, digestive tract fistula, hemorrhage, pneumonia, and pleural effusion. Systemic complications included SIRS, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), hypoproteinemia, and sepsis.

Secondary outcome measures accounted for surgical impact on clinical results, dividing patients into surgical and nonsurgical groups. In the surgical group, we observed changes in various blood parameters (routine blood, coagulation function, liver and kidney function, ions, blood glucose, procalcitonin (PCT), and C-reactive protein (CRP)) at admission and one week after operation. Similarly, the nonsurgical group underwent the same blood analysis at admission and one week after admission. Additionally, surgery rates, ICU occupancy, and total length of stay were recorded for each group.

2.4 Statistical analysis

A t-test was used for normally distributed continuous numerical data, expressed as mean ± standard deviation (SD). A Mann–Whitney test was applied for non-normally

distributed data, presented as median and interquartile range (IQR). Categorical comparisons utilized the χ^2 test or Fisher's exact test. Logistic regression analyzed univariate and multivariate factors, including those with P<0.2 in univariate analysis. RCS examined relationships between numerical and outcome variables, determining the optimal node number based on the minimum AIC value. A nomogram was created from multivariate analysis results and validated with the Hosmer–Lemeshow test. The receiver operating characteristic (ROC) curve, concordance index (C-index), and calibration curve assessed model accuracy. Decision curve analysis (DCA) evaluated the model's net clinical benefit. All tests were two-sided, with P<0.05 indicating significance. Data processing was performed using SPSS 26.0 and R 4.1.3.

Role of the funding source

The funders have no role in the study design, data collection, data analysis, interpretation or report writing.

3. Results

3.1 General characteristics

In this study, the incidence of gallbladder enlargement in AP patients was 36.54% (Figure 1). The baseline characteristics of the patients are summarized in Table 1. Significant differences were observed in age (p=0.008), BMI (p=0.003), and etiology (p=0.004) among the three patient groups. No significant differences were found in the male-to-female ratio, gallbladder dimensions, severity classification, CCI, Marshall organ failure score, or BISAP score. Furthermore, the operation and ICU admission rates in the PTGD+bile reinfusion group were lower than in the other groups, although this difference was not statistically significant. However, the PTGD+bile reinfusion group had a significantly shorter median hospitalization time (14 days) compared to the conventional treatment group (16 days, p=0.01).

3.2 Imaging Comparison of the Gallbladder and Pancreas Before and After PTGD Treatment

We compared imaging findings in three AP patients with enlarged gallbladders before and one week after PTGD. A pre-PTGD CT scan showed significant gallbladder enlargement and substantial peripancreatic fluid accumulation (Figure 2A, C, and E). One week post-PTGD, the gallbladder had shrunk markedly, peripancreatic effusion had decreased, and AP symptoms had improved significantly (Figure 2B, D, and F). Additionally, on the day after PTGD, the drained bile was dark brown and thick, indicating cholestasis (Figure 3).

3.3 Main Outcome Measures

We first analyzed the incidence of new-onset complications among the three patient groups. The overall complication rate in the PTGD+bile reinfusion group was 21.50%, significantly lower than the PTGD-alone (46.59%) and conventional treatment groups (61.07%) (p<0.001). The PTGD+bile reinfusion group also had a significantly lower incidence of local complications (p<0.001). Although the systemic complication rate was lower in the PTGD+bile reinfusion group, this difference was not statistically significant. Individual complications showed that the incidence of pancreatic abscess, pneumonia, and pleural effusion was significantly lower in the PTGD+bile reinfusion group (Table 2). For peripancreatic fluid collection and walled-off necrosis, the PTGD+bile reinfusion group's incidence was significantly lower than that of the conventional treatment group, with no significant difference from the PTGD-alone group.

We then conducted a subgroup analysis dividing patients into MAP and non-MAP groups. In the MAP group (Table S1), the overall complication rate in the PTGD+bile reinfusion group was significantly lower than in the other two groups (11.43% vs. 25.45% vs. 47.56%, p<0.001). The incidence of peripancreatic fluid collection in the PTGD+bile reinfusion group (11.43%) was significantly lower than in the conventional treatment group (32.93%). In the non-MAP group (Table S2), we found a similar trend: the overall complication rate in the PTGD+bile reinfusion group was significantly lower (40.54% vs. 81.82% vs. 77.61%, p<0.001). Individual complication analysis

showed that walled-off necrosis incidence was significantly lower in the PTGD+bile reinfusion group compared to the conventional treatment group, while pancreatic abscess and pleural effusion rates were significantly lower than in both the PTGD-alone and conventional treatment groups.

3.4 Secondary Outcome Measures

To assess the influence of surgery on laboratory test results, we divided the patients into surgical and nonsurgical groups based on whether surgical intervention was performed. For the surgical group, we collected various test results one week post-surgery and compared them to admission values (Table 3). At admission, no statistically significant differences were observed in blood test results among the three groups. One week after surgery, the total bilirubin (TBIL) level in the PTGD+bile reinfusion group was significantly lower than in the PTGD-alone group, and the white blood cell (WBC) count was significantly lower than in the conventional treatment group. Notably, the reductions in neutrophil proportion, PCT, and CRP levels in the PTGD+bile reinfusion group were significantly greater than in the other groups.

For the nonsurgical group, we collected test results one week after admission and compared them to admission values (Table 4). At admission, no significant differences in blood results were noted among the groups. One week post-admission, the TBIL level, WBC count, neutrophil proportion, and CRP level in the PTGD+bile reinfusion group were significantly lower than in the other two groups, while the PCT level was significantly lower only compared to the conventional treatment group. Overall, the declines in TBIL, WBC, and PCT values in the PTGD+bile reinfusion group were significantly greater than those in the conventional treatment group, with greater reductions in neutrophil and CRP proportions compared to the other groups.

3.5 Risk Factor Prediction

In this study, we defined the combined process of external bile drainage and bile reinfusion as BT. The results indicate that BT effectively reduces complications in patients with AP and accelerates the recovery of various laboratory indicators.

To analyze independent risk factors affecting BT efficacy and construct a predictive model, we categorized patients in the PTGD+bile reinfusion group into good treatment effect (no new-onset complications) and poor treatment effect (new-onset complications) groups based on their discharge outcomes. Clinical data at admission were included in logistic regression for univariate and multivariate analyses (Table 5). Univariate analysis showed that the P values for aetiology, serum AST/ALT ratio, TBIL, Ca^{2+}, glucose (GLU), and WBC levels were all less than 0.2. These six factors were included in the multivariate logistic regression, revealing that TBIL (p=0.001), Ca^{2+} (p=0.035), WBC (p=0.004), and the AST/ALT ratio (p=0.013) were independent predictors of poor BT treatment effectiveness.

These independent risk factors were utilized to construct a nomogram predicting poor BT outcomes (Figure 4). A higher total score indicated a greater risk of poor response to BT (i.e., new-onset complications). The Hosmer–Lemeshow test confirmed the model's good fit (p=0.247). We evaluated the nomogram's predictive power using ROC curves, DCA and calibration curves. The area under the curve (AUC) was 0.859 (95% CI: 0.778–0.941) (Figure S1), with the calibration curve close to the ideal diagonal line (Figure S2). DCA also demonstrated significant net benefits from the prediction model (Figure S3). Overall, these results indicate that the nomogram model effectively predicts the risk of poor BT treatment outcomes in patients.

3.6 The indications of BT

Using multivariate logistic regression results, we applied RCS to analyze indications for BT. Figure 5 shows that TBIL, WBC count, and Ca^{2+} levels were linearly related to BT outcomes. Higher TBIL and WBC levels were linked to an increased risk of poor BT effectiveness, while higher Ca^{2+} levels were associated with decreased risk. The optimal cut-off values were determined at OR=1: TBIL < 23.6 μmol/L, WBC < 10.6×10^9/L, and Ca^{2+} > 2.12 mmol/L.

4. Discussion

RWS involves analyzing real-world data in clinical settings[27]. Our analysis revealed a 36.54% incidence of AP associated with gallbladder enlargement. This condition often leads to poor bile outflow and elevated biliary pressure, resulting in bile reflux into the pancreas, worsening pancreatitis severity[13,28]. We propose a novel treatment concept of BT — combining external bile drainage and bile reinfusion — to reduce complication rates in AP patients. We also developed a patient-specific nomogram model based on logistic regression results and evaluated its predictive accuracy, refining BT treatment indications for AP patients.

PTGD is a minimally invasive technique that drains bile externally, effectively reducing pressure in the pancreas and bile ducts[17]. Yu et al.[18]found that PTGD lowers mortality and complication rates in early SAP patients. Research on SAP model rats shows that biliary drainage mitigates organ damage and decreases levels of tumor necrosis factor-α (TNF-α) and interleukin-6 in tissues[29]. Continuous biliary drainage reduces serum amylase, TNF-α, and nuclear transcription factor (NF)-κB-p65, while upregulating haem oxygenase-1, thus delaying SAP progression and protecting organs[30]. Our study revealed that the complication rate in the PTGD-alone group was significantly lower than in the conventional treatment group (Table 2). Among nonsurgical patients, the decrease in PCT levels after one week was significantly greater in the PTGD-alone group (Table 4), confirming PTGD's efficacy in reducing inflammation in AP patients. However, while PTGD drains bile effectively, it disrupts normal enterohepatic circulation and internal environment[31,32]. Therefore, we pioneered bile reinfusion in AP patients to evaluate its therapeutic effects.

Bile reinfusion involves reintroducing bile secretions into the intestine to restore natural BAs. In this study, we combined PTGD with bile reinfusion (the BT process) to reestablish normal enterohepatic circulation and minimize fluid and electrolyte loss. The overall complication rate in the PTGD+bile reinfusion group was significantly lower than in the PTGD-alone group (Table 2). Among surgical patients, the decrease in TBIL one week post-operation was significantly greater in the PTGD+bile reinfusion group, and the changes in neutrophil ratio, PCT, and CRP indicated faster recovery of

inflammatory markers compared to the PTGD-alone group (Table 3). For nonsurgical patients, TBIL levels at one week were significantly lower in the PTGD+bile reinfusion group, with similar improvements in neutrophil and CRP values (Table 4). In summary, bile reinfusion after PTGD effectively reduces complication rates in AP patients and accelerates the recovery of laboratory indicators.

We believe the observed results are influenced by several factors. First, bile reinfusion replenishes BAs, water, and electrolytes lost after PTGD. BAs, the main component of bile, regulate fat, glucose, and energy metabolism while maintaining the dynamic balance of liver and intestinal metabolism[20,33]. After secretion into the duodenum, BAs are converted into secondary forms by intestinal bacteria and reabsorbed into the liver, a process known as "enterohepatic circulation," crucial for nutrient absorption, metabolic regulation, and balance[20,34-36]. Additionally, BAs possess antibacterial properties[37], which may help reduce complications in patients with AP. Second, bile reinfusion supports intestinal microecological stability. Disruptions in intestinal microecology are closely linked to inflammatory responses and intestinal barrier dysfunction in AP patients[38,39]. Approximately 59% of AP patients experience intestinal barrier damage, leading to increased mucosal permeability and potential bacterial translocation, which can result in infections, pancreatic necrosis, and MODS[40,41]. Therefore, maintaining intestinal microecological stability is vital for reducing complications in AP. BAs enhance immune function by modulating the intestinal flora and inflammatory responses[42]. They also regulate intestinal fluid secretion, electrolyte transport, and epithelial barrier function[43], while their antibacterial activity and effects on host signaling pathways help stabilize the intestinal environment[37]. Thus, bile reinfusion can decrease AP complications by replenishing lost BAs and maintaining intestinal microecological stability.

We employed RCS to investigate specific indications for PTGD combined with bile reinfusion. RCS offers a flexible modeling approach to evaluate the influence of continuous variables on treatment outcomes, allowing visualization of relationships without prior assumptions about function forms[44]. Our findings revealed that optimal

indicators for BT application were TBIL levels<23.6 μmol/L, WBC counts <10.6×10^9/L, and Ca^{2+} levels >2.12 mmol/L (Figure 5). Oxidative stress significantly contributes to the pathogenesis of AP[45-47]. Bilirubin, as an endogenous antioxidant, plays a crucial role in mitigating oxidative stress[48,49]. Elevated serum TBIL levels serve as a diagnostic factor for SAP and are associated with increased in-hospital mortality[50]. Our study supports these findings, demonstrating that a TBIL level <23.6 μmol/L is the best threshold for determining BT candidacy. The WBC count is a primary marker for assessing inflammation in AP patients. Neutrophils exacerbate pancreatic injury and necrosis through oxidative damage and increased trypsinogen activation[51]. Huang et al.[52] noted a significant correlation between WBC counts and AP severity. Our analysis confirmed that a WBC count <10.6×10^9/L is a strong predictor of BT treatment outcomes. Patients with AP often exhibit decreased blood Ca^{2+} levels due to saponification of free fatty acids and hypoalbuminemia, affecting calcium binding[53,54]. Research by Mehmet et al.[55] indicates that initial calcium levels correlate with AP severity, with a higher incidence of SAP in low-calcium patients. These observations suggest that hypocalcemia is linked to severe disease and increased risk of poor BT outcomes, while elevated Ca^{2+} levels may enhance treatment effectiveness. In summary, our study underscores the importance of serum TBIL, WBC, and Ca^{2+} levels as independent predictors of BT treatment outcomes. We constructed a nomogram based on multivariate logistic regression to predict the risk of adverse outcomes in individual patients, demonstrating robust predictive performance. These findings may assist clinicians in identifying patients who would benefit most from BT in managing AP.

However, this study has several limitations. First, being a single-center retrospective analysis, it is susceptible to internal selection bias. Second, our subjects were first-time admitted patients with AP, leaving the efficacy of BT for recurrent or chronic pancreatitis patients uncertain. We aim to validate these findings in a future multicenter, prospective study.

5. Conclusion

In this study, for the first time, we proposed the treatment concept of BT on the basis

of a real clinical background and proved that BT can effectively reduce the incidence of complications in AP patients through PTGD combined with bile reinfusion. In addition, the best application indication for BT was determined through multivariate logistic regression analysis and RCS analysis, and a nomogram model was constructed to predict the treatment effect in individualized patients to provide a reference for the clinical treatment of AP patients.

Contributors: Liang Zhang, Menglu Yang and Yusen Feng worked together to design and conceive the project and to write the paper, and they contributed equally to the work. Zijian Huang, Hongtao Li, Jinbo Huang, Baiqiang Lin interpreted and analyzed the data. Professor Gang Wang and Zhengtian Li revised the manuscript for important key contents. All the authors have read and approved the manuscript for publication.

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Table 1. Patient baseline characteristics

Characteristics	PTGD+bile reinfusion group	PTGD-alone group	Conventional treatment group	P value
n	107	88	149	
Gender				0.475
Female	39 (36.45%)	26 (29.55%)	55 (36.91%)	
Male	68 (63.55%)	62 (70.45%)	94 (63.09%)	
Age (years)	44 (36, 56)[a]	50 (45, 63)[b]	46 (37, 55)[a]	0.008
BMI (kg/m^2)	23.60 (21.40, 25.58)[a]	24.50 (22.30, 25.60)[a]	24.97 (22.86, 27.34)[b]	0.003
Long diameter of gallbladder (cm)	7.68 (7.29, 8.25)	7.60 (7.20, 8.40)	7.52 (6.89, 8.33)	0.110
Transverse diameter of gallbladder (cm)	3.83 (3.41, 4.21)	3.90 (3.50, 4.25)	3.90 (3.33, 4.32)	0.546
Aetiology				0.004
Biliary	30 (28.04%)[a]	46 (52.27%)[b]	46 (30.87%)[a]	
Hyperlipidaemic	15 (14.02%)[a]	9 (10.23%)[a]	25 (16.78%)[a]	
Others	62 (57.94%)[a]	33 (37.50%)[b]	78 (52.35%)[a]	
Severity classification				0.451
MAP	70 (65.42%)	55 (62.50%)	82 (55.03%)	
MSAP	28 (26.17%)	26 (29.55%)	55 (36.91%)	
SAP	9 (8.41%)	7 (7.95%)	12 (8.06%)	
CCI	1.11 ± 1.06	1.14 ± 1.06	1.11 ± 1.01	0.978
Marshall organ failure score	1.31 ± 1.28	1.49 ± 1.45	1.18 ± 1.20	0.211
BISAP score	0.78 ± 1.01	1.06 ± 1.13	0.87 ± 1.02	0.169
Operation				0.325
NO	77 (71.96%)	62 (70.45%)	95 (63.76%)	
YES	30 (28.04%)	26 (29.55%)	54 (36.24%)	
Admission to the ICU				0.583
NO	90 (84.11%)	69 (78.41%)	120 (80.54%)	
YES	17 (15.89%)	19 (21.59%)	29 (19.46%)	
Length of hospital stay (days)	14 (10, 24)[a]	15 (12, 24)[ab]	16 (13, 24)[b]	0.035

a, b, c: The same letters indicate that at the 0.05 level, there was no statistically significant difference between the two groups. CCI: Charlson comorbidity index; BMI: Body mass index.

Table 2. Overall incidence of complications in the three groups of patients

Characteristics	PTGD+bile reinfusion group	PTGD-alone group	Conventional treatment group	P value
n	107	88	149	
Overall new-onset complications				< 0.001
NO	84 (78.50%)[a]	47 (53.41%)[b]	58 (38.93%)[c]	
YES	23 (21.50%)[a]	41 (46.59%)[b]	91 (61.07%)[c]	
Local complications				< 0.001
NO	89 (83.18%)[a]	49 (55.68%)[b]	66 (44.30%)[b]	
YES	18 (16.82%)[a]	39 (44.32%)[b]	83 (55.70%)[b]	
Peripancreatic fluid collection				0.036
NO	99 (92.52%)[a]	76 (86.36%)[ab]	121 (81.21%)[b]	
YES	8 (7.48%)[a]	12 (13.64%)[ab]	28 (18.79%)[b]	
Pancreatic pseudocyst				0.113
NO	106 (99.07%)	85 (96.59%)	140 (93.96%)	
YES	1 (0.93%)	3 (3.41%)	9 (6.04%)	
Walled-off necrosis				0.016
NO	107 (100.00%)[a]	85 (96.59%)[ab]	140 (93.96%)[b]	
YES	0 (0.00%)[a]	3 (3.41%)[ab]	9 (6.04%)[b]	
Pancreatic abscess				0.001
NO	106 (99.07%)[a]	82 (93.18%)[b]	128 (85.91%)[b]	
YES	1 (0.93%)[a]	6 (6.82%)[b]	21 (14.09%)[b]	
Pancreatic fistula				0.384
NO	104 (97.20%)	88 (100.00%)	147 (98.66%)	
YES	3 (2.80%)	0 (0.00%)	2 (1.34%)	
Digestive tract fistula				0.769
NO	106 (99.07%)	86 (97.73%)	146 (97.99%)	
YES	1 (0.93%)	2 (2.27%)	3 (2.01%)	
Haemorrhage				0.489
NO	106 (99.07%)	85 (96.59%)	146 (97.99%)	
YES	1 (0.93%)	3 (3.41%)	3 (2.01%)	
Pneumonia				0.017

Characteristics	PTGD+bile reinfusion group	PTGD-alone group	Conventional treatment group	P value
NO	99 (92.52%)[a]	72 (81.82%)[b]	119 (79.87%)[b]	
YES	8 (7.48%)[a]	16 (18.18%)[b]	30 (20.13%)[b]	
Pleural effusion				< 0.001
NO	100 (93.46%)[a]	66 (75.00%)[b]	109 (73.15%)[b]	
YES	7 (6.54%)[a]	22 (25.00%)[b]	40 (26.85%)[b]	
Systemic complications				0.153
NO	94 (87.85%)	71 (80.68%)	117 (78.52%)	
YES	13 (12.15%)	17 (19.32%)	32 (21.48%)	
SIRS				0.461
NO	99 (92.52%)	77 (87.50%)	132 (88.59%)	
YES	8 (7.48%)	11 (12.50%)	17 (11.41%)	
ARDS				0.903
NO	105 (98.13%)	87 (98.86%)	147 (98.66%)	
YES	2 (1.87%)	1 (1.14%)	2 (1.34%)	
MODS				0.956
NO	106 (99.07%)	87 (98.86%)	147 (98.66%)	
YES	1 (0.93%)	1 (1.14%)	2 (1.34%)	
Hypoproteinaemia				0.157
NO	103 (96.26%)	80 (90.91%)	134 (89.93%)	
YES	4 (3.74%)	8 (9.09%)	15 (10.07%)	
Sepsis				0.956
NO	106 (99.07%)	87 (98.86%)	147 (98.66%)	
YES	1 (0.93%)	1 (1.14%)	2 (1.34%)	

a, b, c: The same letters indicate that at the 0.05 level, there was no statistically significant difference between the two groups. SIRS: systemic inflammatory response syndrome; ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome.

Table 3. Changes in the laboratory indicators of patients in the surgical group

Characteristics	PTGD+bile reinfusion group	PTGD-alone group	Conventional treatment group	P value
n	30	26	54	
Severity				0.064
MAP	10 (33.33%)	11 (42.31%)	10 (18.52%)	
MSAP	13 (43.33%)	13 (50.00%)	37 (68.52%)	
SAP	7 (23.34%)	2 (7.69%)	7 (12.96%)	
TBIL				
At the time of admission (μmol/L)	26.75 (20.76, 33.08)	28.68 (17.45, 47.32)	22.52 (16.77, 37.13)	0.400
One week after surgery (μmol/L)	12.00 (9.65, 17.78)[a]	19.40 (13.45, 32.24)[b]	12.43 (9.38, 17.05)[a]	0.002
Proportional change value (%)	-51.32 (-64.75, -26.85)[a]	-29.08 (-38.95, -6.52)[b]	-47.61 (-61.10, -16.16)[a]	0.019
WBC				
At the time of admission (10^9/L)	10.67 (7.85, 14.58)	12.01 (6.28, 15.91)	13.82 (9.12, 16.82)	0.126
One week after surgery (10^9/L)	7.71 (5.27, 8.81)[a]	8.68 (6.95, 10.35)[ab]	9.21 (6.98, 11.84)[b]	0.008
Proportional change value (%)	-35.85 (-52.18, -18.01)	-26.56 (-35.81, -5.83)	-21.54 (-43.60, -4.50)	0.231
Proportion of neutrophils				
At the time of admission（%）	81.49 (73.36, 86.06)	82.10 (70.01, 87.45)	80.15 (71.75, 85.43)	0.581
One week after surgery（%）	65.77 ± 6.63[a]	69.80 ± 9.02[ab]	70.59 ± 4.61[b]	0.004
Proportional change value (%)	-18.52 (-27.41, -11.17)[a]	-8.92 (-16.96, -4.37)[b]	-11.03 (-17.28, -2.30)[b]	0.014
PCT				
At the time of admission (ng/mL)	1.20 (1.01, 2.58)	1.27 (0.44, 2.73)	0.96 (0.24, 2.62)	0.620
One week after surgery (ng/mL)	0.23 (0.11, 0.45)	0.86 (0.26, 1.67)	0.64 (0.20, 2.09)	0.081
Proportional change value (%)	-86.70 (-92.72, -57.69)[a]	-19.49 (-42.17, -6.74)[b]	-23.68 (-34.97, -9.01)[b]	< 0.001
CRP				
At the time of admission (mg/L)	159.00 (121.50, 182.00)	142.60 (102.97, 221.75)	149.00 (118.50, 217.00)	0.905
One week after surgery (mg/L)	109.70 (65.93, 119.80)	100.05 (72.03, 178.35)	111.00 (82.80, 169.00)	0.509
Proportional change value (%)	-38.73 (-44.43, -33.45)[a]	-25.69 (-31.72, -19.10)[b]	-22.66 (-29.78, -20.30)[b]	0.006

a, b, c: The same letters indicate that at the 0.05 level, there was no statistically significant difference between the two groups. TBIL: total bilirubin; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein

Table 4. Changes in the laboratory indicators of patients in the nonsurgical group

Characteristics	PTGD+bile reinfusion group	PTGD-alone group	Conventional treatment group	P value
n	77	62	95	
Severity				0.678
MAP	2 (2.60%)	5 (8.06%)	5 (5.26%)	
MSAP	60 (77.92%)	44 (70.97%)	72 (75.79%)	
SAP	15 (19.48%)	13 (20.97%)	18 (18.95%)	
TBIL				
At the time of admission (μmol/L)	21.86 (15.17, 36.09)	28.32 (16.95, 51.54)	23.28 (18.20, 34.20)	0.148
One week after surgery (μmol/L)	12.50 (9.60, 13.65)^{a}	16.30 (11.10, 26.05)^{b}	15.00 (11.50 19.30)^{b}	＜0.001
Proportional change value (%)	-47.50 (-64.53, -26.36)^{a}	-39.83 (-56.82, -5.72)^{ab}	-32.12 (-50.83, -4.32)^{b}	0.006
WBC				
At the time of admission (10^{9}/L)	11.24 (5.73, 13.81)	10.65 (8.31, 16.52)	10.94 (9.16, 12.87)	0.206
One week after surgery (10^{9}/L)	6.73 (4.61, 7.92)^{a}	7.92 (5.47, 12.10)^{b}	8.95 (6.54, 11.23)^{b}	＜0.001
Proportional change value (%)	-31.31 (-46.51, -4.88)^{a}	-25.55 (-40.30, -2.98)^{ab}	-16.25 (-27.58, -0.13)^{b}	0.012
Proportion of neutrophils				
At the time of admission（%）	83.70 (76.55, 87.90)	85.00 (77.58, 86.99)	83.20 (79.00, 88.60)	0.929
One week after surgery（%）	66.73 (62.70, 72.85)^{a}	70.67 (61.90, 80.74)^{b}	72.60 (64.90, 78.20)^{b}	0.011
Proportional change value (%)	-17.10 ± 10.19^{a}	-12.97 ± 9.15^{b}	-12.91 ± 9.81^{b}	0.010
PCT				
At the time of admission (ng/mL)	2.05 (1.82, 2.27)	1.74 (1.00, 4.71)	1.88 (1.11, 4.42)	0.752
One week after surgery (ng/mL)	0.36 (0.13, 1.00)^{a}	0.38 (0.12, 0.68)^{a}	1.07 (0.39, 2.07)^{b}	0.011
Proportional change value (%)	-78.84 (-93.78, -60.80)^{a}	-77.32 (-86.62, -63.19)^{a}	-56.14 (-70.56, -26.59)^{b}	0.015
CRP				
At the time of admission (mg/L)	197.91 ± 62.57	169.38 ± 53.78	192.20 ± 58.09	0.393
One week after surgery (mg/L)	12.20 (9.37, 37.73)^{a}	59.90 (17.98, 105.43)^{b}	75.30 (22.80, 110.00)^{b}	0.012
Proportional change value (%)	-92.07 (-94.94, -91.03)^{a}	-63.71 (-83.66, -42.43)^{b}	-57.97 (-79.30, -52.31)^{b}	0.011

a, b, c: The same letters indicate that at the 0.05 level, there was no statistically significant difference between the two groups. TBIL: total bilirubin; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein

Table 5. Results of univariate and multivariate logistic regression

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Sex	107				
Male	68	Reference			
Female	39	1.833 (0.719-4.672)	0.204		
Age (years)	107	1.010 (0.975-1.045)	0.593		
BMI (kg/m^2)	107	1.036 (0.900-1.193)	0.619		
Long diameter of the gallbladder (cm)	107	0.831 (0.514-1.345)	0.452		
Transverse diameter of the gallbladder (cm)	107	1.214 (0.598-2.461)	0.592		
Aetiology	107				
Biliary	30	Reference		Reference	
Hyperlipidaemic	15	3.273 (0.627-17.091)	**0.160**	3.364 (0.357-31.706)	0.289
Others	62	3.130 (0.835-11.735)	**0.091**	3.795 (0.617-23.338)	0.150
ALT (U/L)	107	0.991 (0.976-1.006)	0.228		
AST (U/L)	107	0.993 (0.981-1.005)	0.201		
TBIL (μmol/L)	107	1.048 (1.014-1.083)	**0.005**	1.088 (1.036-1.143)	**0.001**
K^+ (mmol/L)	107	1.539 (0.777-3.052)	0.217		
Ca^{2+} (mmol/L)	107	0.177 (0.034-0.923)	**0.040**	0.098 (0.011-0.854)	**0.035**
Glu (mmol/L)	107	1.076 (0.965-1.200)	**0.187**	1.023 (0.853-1.228)	0.804
WBC ($10^9/L$)	107	1.173 (1.064-1.294)	**0.001**	1.186 (1.057-1.332)	**0.004**

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Neutrophil ratio (%)	107	0.997 (0.955-1.041)	0.887		
AST/ALT	107				
<1	69	Reference		Reference	
≥1	38	1.935 (0.758-4.942)	**0.168**	5.628 (1.438-22.021)	**0.013**
PCT (ng/mL)	107	1.057 (0.936-1.194)	0.373		
CRP (mg/L)	107	1.002 (0.997-1.006)	0.451		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; Glu: glucose; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein.

Figure 1. Research flow chart

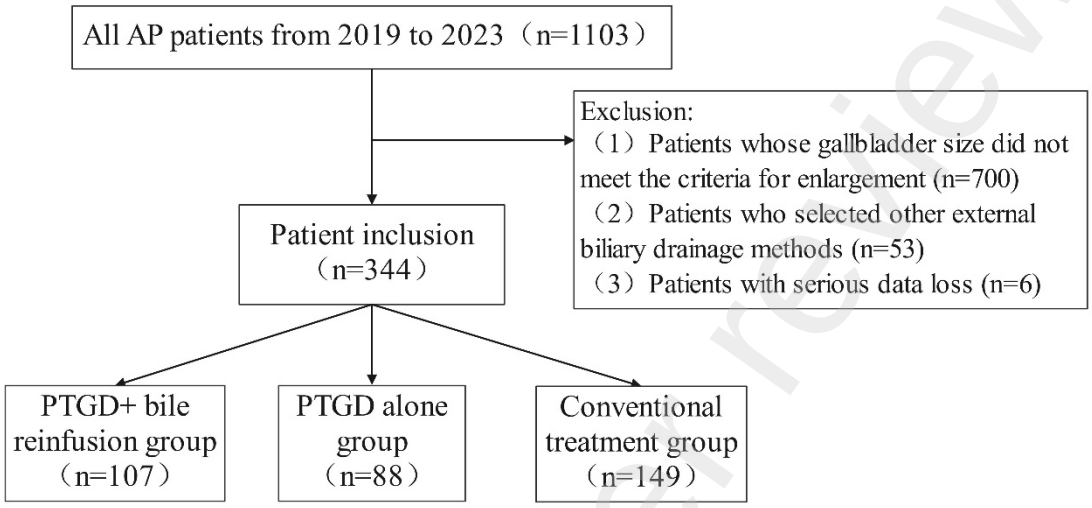

Figure 2. Plain-scan CT of the pancreas before and after PTGD treatment.(A, C, E) Before PTGD; (B, D, F) One week after PTGD: the black arrow indicates the drainage tube.

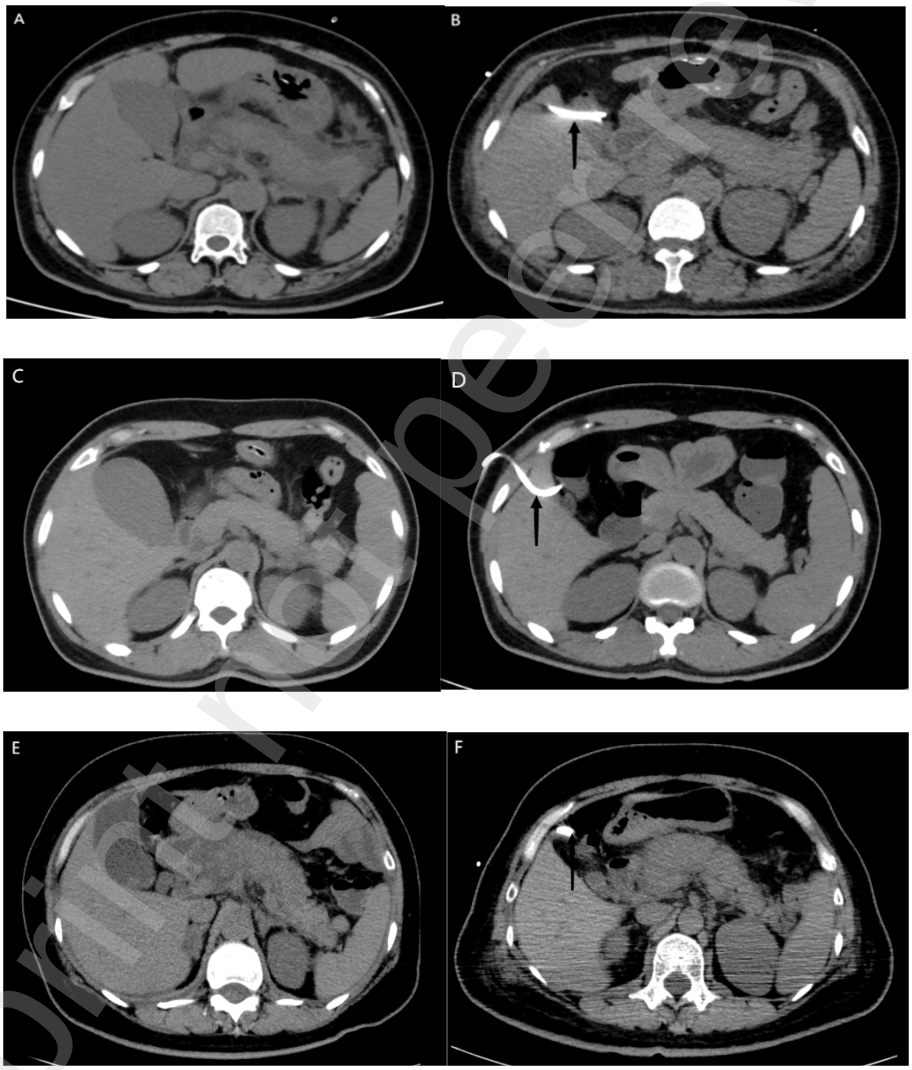

Figure 3. Characteristics of the bile drainage on the second day after PTGD treatment

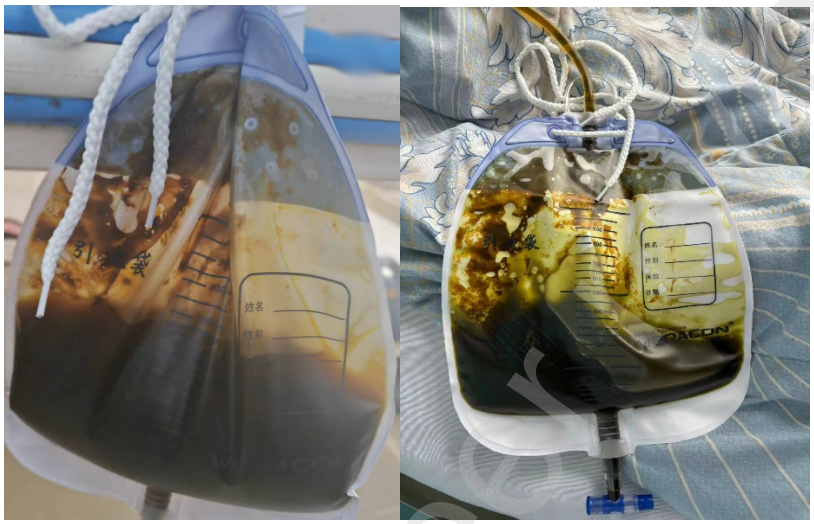

Figure 4. Nomogram for predicting the therapeutic effect of bile transfer

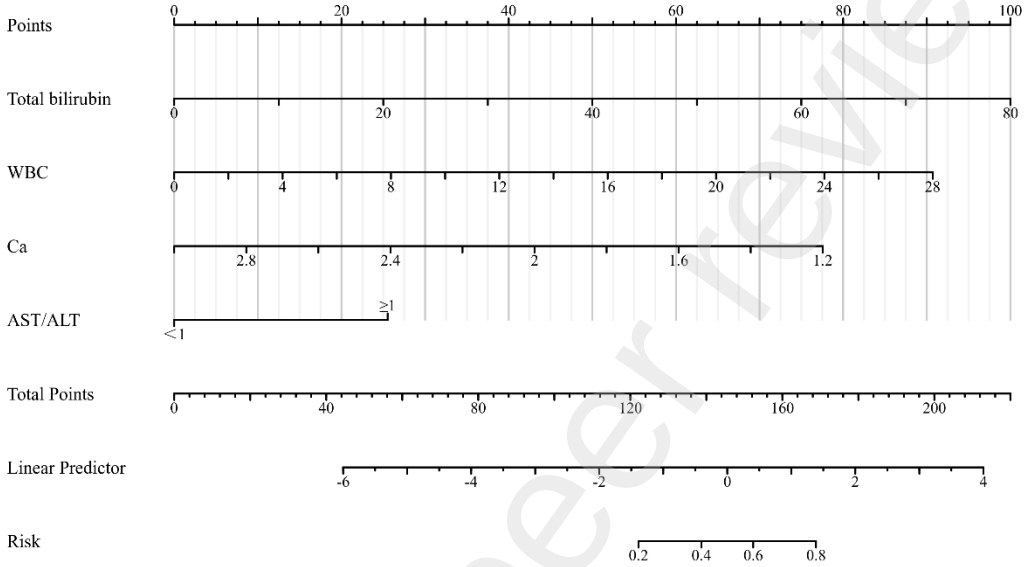

Figure 5. RCS diagrams of the TBIL, WBC and Ca^{2+} levels.(A) The relationship between the OR and the TBIL level. (B) The relationship between the OR and the WBC count. (C) The relationship between the OR and the Ca^{2+} levels. The blue curve indicates the OR, and the shaded area represents the 95% CI.