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Biliary Stricture after Necrotizing Pancreatitis: An Underappreciated Challenge

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Abstract

Objective

Biliary stricture in necrotizing pancreatitis (NP) has not been systematically categorized; therefore, we sought to define the incidence and natural history of biliary stricture caused by NP.

Summary/Background Data

Benign biliary stricture occurs secondary to bile duct injury, anastomotic narrowing, or chronic inflammation and fibrosis. The profound loco-regional inflammatory response of NP creates challenging biliary strictures.

Methods:

NP patients treated between 2005-2019 were reviewed. Biliary stricture was identified on cholangiography as narrowing of the extrahepatic biliary tree to <75% of the diameter of the unaffected duct. Biliary stricture risk factors and outcomes were evaluated.

Results:

Among 743 NP patients, 64 died, 13 were lost to follow up; therefore, a total of 666 patients were included in the final cohort. Biliary stricture developed in 108 (16%) patients. Mean follow up was 3.5±3.3 years. Median time from NP onset to biliary stricture diagnosis was 4.2 months (IQR, 1.8-10.9). Presentation was commonly clinical or biochemical jaundice, n = 30 (28%) each. Risk factors for stricture development were splanchnic vein thrombosis and pancreatic head parenchymal necrosis. Median time to stricture resolution was 6.0 months after onset (2.8-9.8). A mean of 3.3±2.3 procedures were performed. Surgical intervention was required in 22 (20%) patients. Endoscopic treatment failed in 17% (17/99) of patients and was not associated with stricture length. Operative treatment of biliary stricture was more likely in patients with infected necrosis or NP disease duration ≥6 months.

Conclusion:

Biliary stricture occurs frequently after necrotizing pancreatitis and is associated with splanchnic vein thrombosis and pancreatic head necrosis. Surgical correction was performed in 20%.

Keywords: pancreatitis, acute necrotizing; benign bile duct stricture; splanchnic vein thrombosis; choledochostomy; inflammatory stricture

Mini-Abstract:

Biliary strictures in necrotizing pancreatitis are challenging to treat and have not been systematically categorized. This complication developed in 16% of patients and was associated with pancreatic head necrosis and splanchnic vein thrombosis. Endoscopic treatment is effective in most; however, 20% of patients underwent operative correction.

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Abstract

Author contribution: Dr. Maatman was involved in the conception of the project, acquisition, analysis, and interpretation of data, and drafting and revising the work. Dr. Zyromski serves as the mentor and corresponding author for the work. He was involved in the conception, interpretation, revision, and final approval of the work; Dr. Zyromski agrees to be accountable for the work. Drs. Ceppa, Easler, Fogel, Gromski, House, Nakeeb, Schmidt, and Sherman were involved in the conception of the project, revision of the work, and final approval.

Introduction:

The morbidity of acute necrotizing pancreatitis (NP) is exceedingly high and mortality rates can range from 15-30%[1, 2]. Common complications in patients with NP include infection, organ failure, and pancreatic endocrine and exocrine insufficiency[1-5]. Long-term sequelae of NP are becoming better known and include complications such as disconnected pancreatic duct syndrome (DPDS) and splanchnic vein thrombosis (SVT)[4, 6-9]. Rarely reported are the foregut complications from NP, which can involve the stomach and duodenum, bile duct, and pancreatic duct.

Biliary stricture is a well-described complication in 3-21% of chronic pancreatitis (CP) patients and can result in life-threatening cholangitis, progressive liver impairment and secondary biliary cirrhosis[10-13]. On the other hand, the true incidence of biliary stricture in acute pancreatitis (AP) and its impact on patient outcomes is not known. Case reports and case series of NP patients undergoing necrosectomy have described biliary stricture as a complication, but this complication has not been systematically characterized in a large cohort of NP patients[14-16]. As such, the ideal treatment strategy and impact on patient outcomes remain unknown.

Therefore, the aim of this study was to evaluate the incidence of biliary stricture in a large cohort of necrotizing pancreatitis patients including risk factors for its development, and outcomes. Based on our clinical experience, we hypothesized that biliary stricture in necrotizing pancreatitis is more common than previously appreciated and may be difficult to treat definitively by endoscopic technique.

Methods:

Patient Population

All patients treated for NP at Indiana University Health University Hospital (IU-UH) between January 2005 and June 2019 were included in this study regardless of age, pancreatitis

etiology, or treatment strategy. All NP patients are routinely followed long-term by their designated pancreatic specialist. Retrospective review of a prospectively maintained institutional NP database was performed to identify patients developing biliary stricture after NP. In all patients, informed consent was obtained prior to inclusion in the NP database. The Indiana University Institutional Review Board approved this study and all data were compiled and stored in compliance with the Health Insurance Portability and Accountability Act.

Parameters Assessed

In all patients, demographic and clinical information prior to disease onset were recorded including age, sex, and medical comorbidities. Clinical information during the course of NP included pancreatitis etiology, computed tomography severity index (CTSI), organ failure lasting > 48 hours, infected pancreatic necrosis, necrosis intervention (medical, percutaneous, endoscopic, and surgical), SVT, DPDS, and disease duration. In patients developing biliary stricture, the treatment strategy, number of interventions, and time to stricture resolution were recorded.

Definitions

Diagnostic criteria were defined according to the 2012 revision of the Atlanta classification[3]. Acute pancreatitis (AP) was defined as the presence of at least two of the following three criteria: abdominal pain characteristic of AP, serum amylase or lipase concentration at least three times greater than the upper limit of normal, or characteristic findings of AP on contrast-enhanced cross-sectional imaging. Necrotizing pancreatitis was defined as a lack of enhancement of the pancreatic parenchyma on contrast-enhanced cross-sectional imaging or the presence of an acute necrotic collection (ANC) or walled-off necrosis (WON)[3]. Infected pancreatic necrosis was diagnosed in the setting of extraluminal gas in the pancreatic and/or

peripancreatic tissues on cross-sectional imaging and confirmed with positive bacteria and/or fungi on Gram stain and culture of aseptically obtained pancreatic necrosis specimens[3]. Minimally invasive necrosis intervention included percutaneous drainage, endoscopic drainage/debridement, videoscopic assisted retroperitoneal debridement (VARD), or laparoscopic debridement.

Per the revised Atlanta classification recommendations, organ failure was defined according to the modified Marshall scoring system for organ dysfunction as a score of two or greater[3]. Splanchnic vein thrombosis included thrombosis of the portal vein, superior mesenteric vein, and/or splenic vein and was diagnosed by contrast-enhanced cross-sectional imaging as a filling defect within the lumen of the vessel or non-visualization of the vein with demonstration of multiple collateral veins[8]. Disconnected pancreatic duct syndrome (DPDS) was diagnosed when necrosis involved at least two centimeters of the pancreas with viable upstream (left-sided) pancreatic parenchyma and extravasation of contrast or total cutoff of the main pancreatic duct on pancreatography[17, 18].

Biliary stricture was diagnosed by magnetic resonance (MRC) or endoscopic retrograde (ERC) cholangiography as any narrowing of the biliary tree to less than 75% of the diameter of the unaffected duct in the setting of abnormal liver function tests[19]. This definition was utilized during the entire time period of the study by our interventional gastroenterologists and is consistent with previous institutional randomized controlled trials evaluating biliary stricture[19]. Cases of clear external compression of the bile duct by pancreatic necrosis were not considered as biliary stricture. Stricture resolution was achieved when the affected bile duct diameter was confirmed to be 75% or more of the duct above and below the site of the stricture on cholangiogram and without subsequent reintervention over a six month period[19].

Acute NP disease resolution was defined as the absence of clinical symptoms attributable to pancreatic necrosis in the setting of radiographic resolution of pancreatic necrosis without recurrence of necrotic collections during long-term follow up.

Statistical Analysis

Categorical data are described as number with percentage and were compared using the chi-squared test. Normally distributed continuous data are reported as mean with standard deviation (SD) and were compared using independent samples t-test. Non-normally distributed continuous data are reported as median with interquartile range (IQR) and were compared using the Mann-Whitney U test. Odds ratios are reported with 95% confidence intervals (95% CI). *P*-values < 0.05 were accepted as statistically significant. Univariate analysis was used to identify significant risk factors for biliary stricture development. Multivariable binary regression analysis was used to confirm these risk factors and included evaluation of any variables with $P < 0.1$ on univariate analysis. Statistical analysis was performed using IBMM SPSS version 26.0 (IBM, Inc., Armonk, NY, USA).

Results:

Study Population

A total of 743 NP patients were treated at IU-UH during the study period. Biliary etiology (n = 354, 48%) was the most common cause of pancreatitis followed by alcohol (n = 165, 22%), post-ERCP (n = 44, 6%) and hypertriglyceridemia (n = 43, 6%); pancreatitis was idiopathic in 113 (15%) patients. Twenty-three patients developed pancreatitis from less common etiologies including medication (n = 16), pancreas divisum (n = 5), pancreatic ductal adenocarcinoma (n = 1), hypercalcemia (n = 1), and mucinous cystadenoma (n = 1). The mean

age at pancreatitis onset was 52±16 years and 484 (65%) patients were male. The median NP disease duration was 5.1 (3.3-8.1) months. Sixty-four (9%) patients died from NP and 13 (2%) patients were lost to long-term follow-up; the remaining 666 (89%) patients were followed long-term for a median of 38 (11-77) months.

Incidence, Presentation, and Morphology

Of these 666 NP patients, biliary stricture developed in 108 (16%) patients a median of 4.2 (1.8-10.9) months after NP onset. Twenty-seven (25%) of these patients developed biliary stricture greater than one year after NP onset. The presentation of biliary stricture in NP was most often clinical jaundice (n = 30, 28%) or biochemical jaundice (n = 30, 28%); other clinical presentations included biliary ductal dilation on routine follow-up imaging (n = 29, 27%), abdominal pain (n = 15, 14%), and cholangitis (n = 4, 4%). In patients with biliary stricture identified incidentally on imaging, subsequent serum testing revealed abnormal liver chemistry in 11 (38%) patients including elevated alkaline phosphatase in seven patients, both elevated alkaline phosphatase and total bilirubin in three patients, and elevated total bilirubin in one patient. All patients developed stricture in the distal common bile duct. The median stricture length was 1.0 (0.5-1.5) centimeters. The median total bilirubin and alkaline phosphatase at diagnosis was 1.8 (0.7-6.6) mg/dL and 411 (139-661) U/L, respectively.

Risk Factors

Baseline risk factors for biliary stricture development on univariate analysis included male sex and history of atrial fibrillation, Table 1. Risk factors during the clinical course of NP included infected pancreatic necrosis, SVT, pancreatic head necrosis, and longer disease

duration. On multivariable analysis atrial fibrillation (OR, 2.55), SVT (OR, 2.25), and pancreatic head necrosis (OR, 1.54) remained significant risk factors. Odds ratios and 95% confidence intervals for these risk factors are shown in Figure 1. All patterns of SVT were associated with biliary stricture development, even isolated splenic vein thrombosis (Table 2).

In the 123 patients who did not require pancreatic necrosis intervention, biliary stricture developed in eight (7%) patients. Among the 543 patients who underwent necrosis intervention, biliary stricture developed in 100 (18%) patients. The increased incidence of biliary stricture among patients who underwent intervention was statistically significant ($P = 0.004$). Biliary stricture rates were highest among those patients who underwent a combination of minimally invasive and surgical necrosis intervention, Figure 2. When comparing patients whose necrosis was treated successfully with minimally invasive intervention only (N = 241) to patients resolving with surgical intervention only (N = 120) no difference in the rate of biliary stricture was observed (18% vs. 15%, $p = 0.4$).

Treatment

Among the 108 NP patients developing biliary stricture, 106 (98%) patients had intervention. The median time to stricture resolution was 6.0 (2.8-9.8) months. Biliary stricture resolved after a mean of 3.4±2.3 procedures. A summary of the treatment to achieve definitive biliary stricture resolution is shown in Figure 3. Surgical intervention was performed in 22 (20%) patients. Three patients underwent surgical intervention as the first step in therapy. In the remaining patients, surgery was performed after initial endoscopic (n = 17) or percutaneous (n = 2) management of biliary stricture; surgery was performed after a median of 7.0 (2.0-10.5) months of biliary stenting. Endoscopic therapy was successful in 83% of patients; the median

duration of endobiliary stenting was 5.8 (2.9-8.6) months. Unsuccessful endoscopic therapy was not associated with stricture length (Success, 1.3±0.9 cm; Failure, 1.0±0.6 cm; $P = 0.2$). Surgical intervention was performed with similar rates in patients with biliary stricture that developed within one year of NP onset (18 of 81, 22%) when compared to patients with biliary stricture that developed greater than one year after NP onset (4 of 27, 15%), $p = 0.4$. A greater likelihood of unsuccessful endoscopic therapy requiring surgery was observed in patients with a history of infected necrosis (OR, 3.2; 95% CI, 1.1-9.0; $P = 0.02$) or NP disease duration ≥6 months (OR, 5.7; 95% CI, 1.8-18.2; $P = 0.002$). Treatment for biliary stricture resulted in inpatient hospital admission in 43 (40%) patients for a mean of 13±11 total days. Prior to stricture resolution, twenty-eight patients were admitted one time, 13 patients were admitted twice, and 2 patients were admitted three times. One patient died prior to any biliary stricture intervention and one patient deferred treatment altogether; in these two patients biliary stricture was diagnosed incidentally on surveillance imaging. The median follow-up time after biliary stricture resolution was 16 (5-51) months.

Postoperative Outcomes

A total of 22 patients underwent surgical intervention for biliary stricture. Nine (41%) patients underwent choledochoduodenostomy, seven (32%) patients underwent hepaticojejunostomy, four (18%) patients underwent pancreatoduodenectomy, and two (9%) patients underwent choledochojejunostomy. The median postoperative length of stay was 9 days (7-16 days). Five (23%) patients developed a postoperative complication including surgical site infection (N = 3), acute cholangitis (N = 1), and bile leak requiring reoperation and redo choledochojejunostomy (N = 1). Four (18%) patients required hospital readmission

postoperatively. No patients died in the immediate postoperative period and no patient who underwent surgical intervention of biliary stricture developed recurrent stricture.

Discussion:

In this series of 743 NP patients treated at a single, academic institution, biliary stricture developed in 16% of patients surviving acute NP and was diagnosed a median of 4 months after NP onset. Risk factors for biliary stricture in NP included male sex, atrial fibrillation, infected pancreatic necrosis, splanchnic vein thrombosis, pancreatic head necrosis, and NP duration of six months or longer. Independent risk factors were atrial fibrillation, SVT, and pancreatic head necrosis. Most patients (74%) were treated successfully and durably by endoscopic technique and these patients underwent a mean of 3.4 procedures to achieve stricture resolution over a period of six months. Surgical correction was required in 20% of patients with biliary stricture. Predictors of unsuccessful endoscopic therapy included patients with a history of infected necrosis or NP disease duration of six months or longer.

Biliary stricture is a known complication of chronic pancreatitis and occurs in 3-21% of CP patients in large series[10, 11]; however, the incidence of biliary stricture in NP patients to date has not been systematically described. Only one moderate sized study has reported the incidence of biliary stricture to be 6% of 141 AP patients with a fluid collection[16]. In this series, biliary stricture was diagnosed a median of 150 days after AP onset[16], similar to our experience. In this study by Sugimoto et al. the incidence of biliary stricture was highest in patients with disconnected pancreatic duct syndrome (19%)[16]. We report an incidence of biliary stricture in NP patients of 16%, higher than previously appreciated and more similar to the incidence observed in CP. As a similar parallel to CP patients[10, 20], the presentation of biliary stricture in NP was

most often jaundice (biochemical or clinical) and the morphology not surprisingly involved the distal common bile duct. It is noteworthy that 27% of NP patients in the current series were identified to have "incidental" biliary ductal dilation on imaging during the follow-up period of NP, a phenomenon seen in up to 17% of patients with CP[20]. In this setting, Kalvaria et al reported that elevated alkaline phosphatase is more common than elevated bilirubin[20], a finding also observed in the current series of NP patients with incidental biliary stricture diagnosed on follow-up imaging.

The timing of biliary stricture diagnosis was a median of 4 months after NP onset, a time during which most NP patients have active imaging surveillance. The timing of biliary stricture in NP in this series corroborates the timeline reported previously by Sugimoto et al[16]. The majority of patients developed biliary stricture within the first year after NP onset, yet, one in four patients developed biliary stricture greater than one year after NP onset. The latter point highlights the importance of long-term follow-up to which not only biliary stricture, but other, often initially subtle long-term problems may arise in this complex group of patients.

In their descriptive report of biliary stricture in AP, Sugimoto et al reported the incidence of biliary stricture was highest among patients with DPDS (19%) with 27% of a subset of patients with DPDS involving the head/neck of the pancreas developing biliary stricture[16]. Associated risk factors help provide insight as to potential pathophysiologic mechanisms of biliary stricture development in NP. While our study did not find an association with DPDS and biliary stricture, pancreatic necrosis located in the head of the pancreas was identified as an independent risk factor. In the current study, infected necrosis and longer NP disease duration were also associated with biliary stricture. These findings suggest that the location (head of

pancreas), severity (infected necrosis), and duration of inflammation (prolonged disease course) all play a role in biliary stricture development in NP patients.

Furthermore, an interesting observation is that patients that underwent both minimally invasive intervention and surgical intervention developed biliary stricture with the highest frequency. One may speculate that more rapid necrosis evacuation and removal of the inflammatory focus may decrease locoregional inflammation, thereby attenuating biliary stricture development. Supporting this thesis is the increased incidence of biliary stricture observed in NP patients with acute disease lasting longer than six months. On the other hand, patients undergoing both minimally invasive and surgical intervention of necrosis suggests that more severe disease contributes to a higher incidence of biliary stricture. The hypothesis that prolonged locoregional inflammation predisposes to biliary stricture requires more robust study to determine its impact but may have important clinical implications that would promote more aggressive necrosis evacuation once intervention has been initiated.

Splanchnic vein thrombosis was independently associated with biliary stricture development in this study. It is possible the development of SVT may simply be a surrogate for the degree of locoregional inflammation, as regional pancreatic necrosis has been previously associated with SVT[21]. However, impaired venous outflow may impact the blood supply to the common bile duct and contribute to biliary stricture development by an ischemic mechanism. It may also be possible that common bile duct ischemia develops at a microvascular level in NP patients. Endothelial dysfunction and hypercoagulability are known to be associated with severe acute pancreatitis and microcirculatory dysfunction plays an important role in the development of NP[22-27]. The locoregional and systemic inflammation in NP may result in a hypercoagulable state, microvascular thrombosis, relative bile duct ischemia, and eventual biliary stricture.

Favoring this theory over venous outflow obstruction is the observation that all patterns of SVT, including *isolated* splenic vein thrombosis, were associated with biliary stricture development. Isolated splenic vein thrombosis does not impact biliary venous outflow and instead may reflect the impact of NP on local and systemic inflammation and coagulation.

The ideal treatment strategy for biliary stricture in NP is unknown; however, principles in treating benign biliary strictures can be applied to this clinical scenario. In this series, endoscopic stenting of biliary strictures in NP was the first line treatment in 92% of patients and achieved definitive resolution in 83%. This success rate is comparable to endoscopic treatment of postoperative biliary strictures (80-90%)[28, 29] and substantially greater than that achieved in the setting of chronic pancreatitis (50-70%)[29]. The number of procedures (3.4 per patient) and the duration of endobiliary stenting (6 months) were similar to that observed in the treatment of benign biliary stricture. Predictors of unsuccessful endoscopic treatment requiring operative correction included NP disease duration greater than 6 months or a history of infected necrosis. Therefore, patients with these clinical factors may be considered for earlier operative intervention.

The retrospective nature of this study limits its ability to identify the pathophysiologic mechanisms that result in biliary stricture in NP patients and the proposed mechanisms hypothesized in this study clearly warrant further investigation. The independent association between atrial fibrillation and biliary stricture may be phenomenological or could represent a surrogate for coexisting vascular pathology predisposing patients to ischemic biliary stricture; however, the number of patients with atrial fibrillation in this study precluded an in-depth subgroup analysis. Clear cases of external bile duct compression by necrosis were not considered as biliary stricture; however, it is possible that external compression of the bile duct by necrosis

could result in misdiagnosis as biliary stricture, falsely increasing the incidence of biliary stricture reported in this study. On the other hand, serial liver function tests during follow up to detect biliary stricture development were not routinely evaluated in this study and may underestimate the true incidence of biliary stricture after NP. Additionally, patients who died or were lost to long-term follow up were not evaluated for biliary stricture. A significant strength of this study is its size, which provides benchmark data that have not been previously systematically described for biliary stricture in NP, its natural history, treatment, and patient outcomes.

The findings in this study have resulted in a number of changes to the long-term follow up of NP survivors at our institution. Given a number of potential sequelae of NP that may develop years after acute disease resolution, all NP patients are followed long-term by the responsible pancreatologist (pancreatic surgeon and/or gastroenterologist)[30]. In the first few years after NP disease resolution, patients now undergo serial serum evaluation of liver function tests at intervals of 3-6 months to screen for biliary stricture development. This practice is important to continue at 6-12 month intervals during long-term follow-up, as 25% of patients developed biliary stricture beyond one year after NP diagnosis. Early detection and treatment of biliary stricture after NP may prevent life-threatening complications such as acute cholangitis or secondary biliary cirrhosis.

Endoscopic biliary stenting is the first line treatment in all NP patients with biliary stricture. Patients with a history of infected necrosis or NP lasting greater than six months are counseled regarding the decreased likelihood of success with endoscopic treatment alone. Operative correction becomes a consideration after six months of attempted endoscopic treatment and is determined on a case-by-case basis with multidisciplinary input. In patients with

a history of infected necrosis or prolonged disease, operative intervention is considered earlier. The ideal treatment strategy for NP patients with normal serum liver function tests and biliary stricture diagnosed incidentally on surveillance imaging remains an unanswered question. In this setting with chronic pancreatitis patients, the decision to intervene or observe with serial liver function tests remains an area of debate[10].

Conclusion:

Biliary stricture occurs frequently after necrotizing pancreatitis and is associated with splanchnic vein thrombosis and pancreatic head necrosis. Surgical correction was performed in 20% and is more likely to be necessary in patients with a history of infected necrosis or necrotizing pancreatitis lasting greater than six months. Endoscopic treatment of biliary strictures from necrotizing pancreatitis is successful in the majority of patients.

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Figure Legend:

Figure 1. Independent risk factors for biliary stricture identified on multivariable analysis and associated odds ratios with 95% confidence intervals.

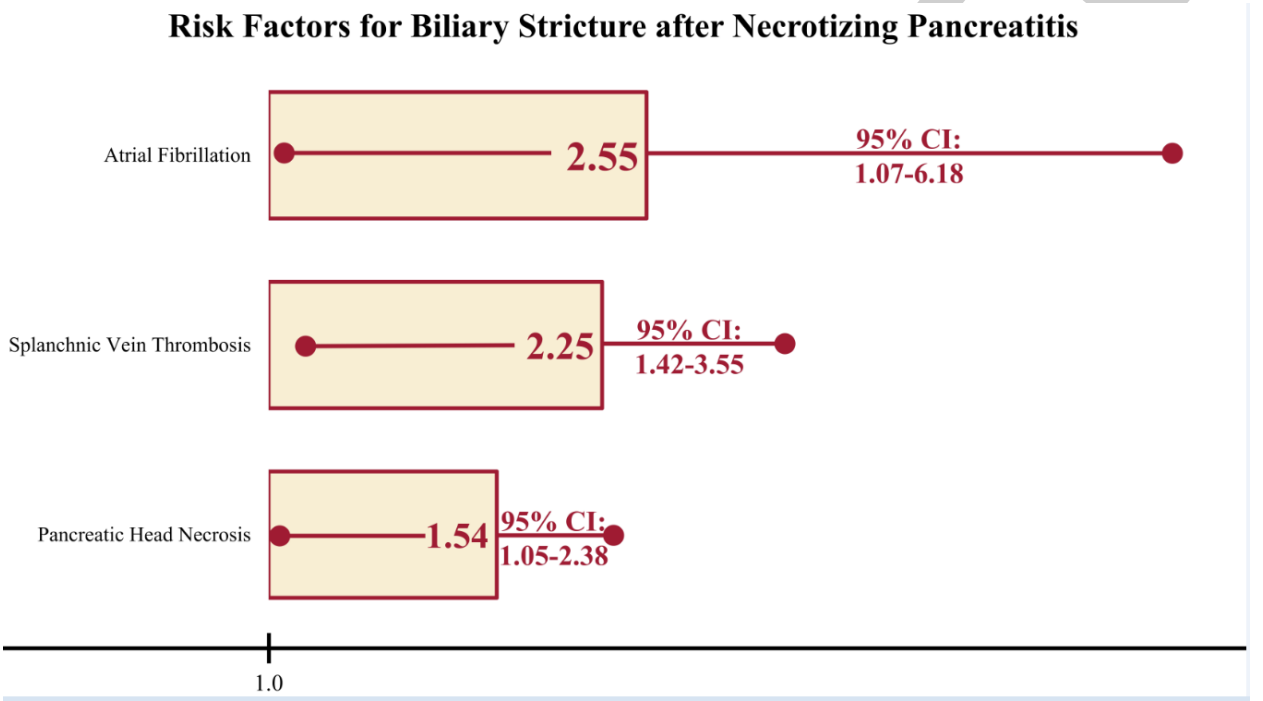

Figure 2. The incidence of biliary stricture was lowest among patients that did not require necrosis intervention and highest among those requiring a combination of minimally invasive and surgical necrosis intervention, $P = 0.001$.

Footnote: Minimally invasive necrosis intervention includes percutaneous drainage, endoscopic drainage/debridement, videoscopic assisted retroperitoneal debridement, or laparoscopic debridement. Abbreviations: NP – necrotizing pancreatitis

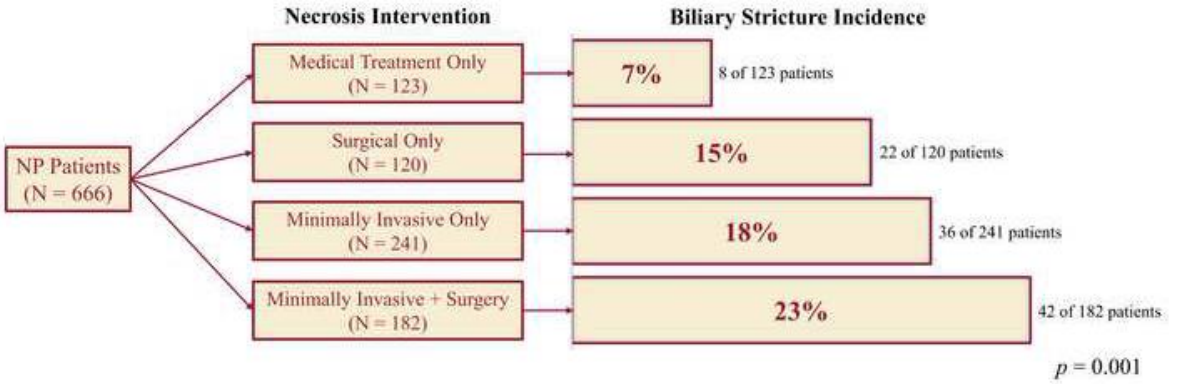

Figure 3. Summary of Intervention to Achieve Biliary Stricture Resolution

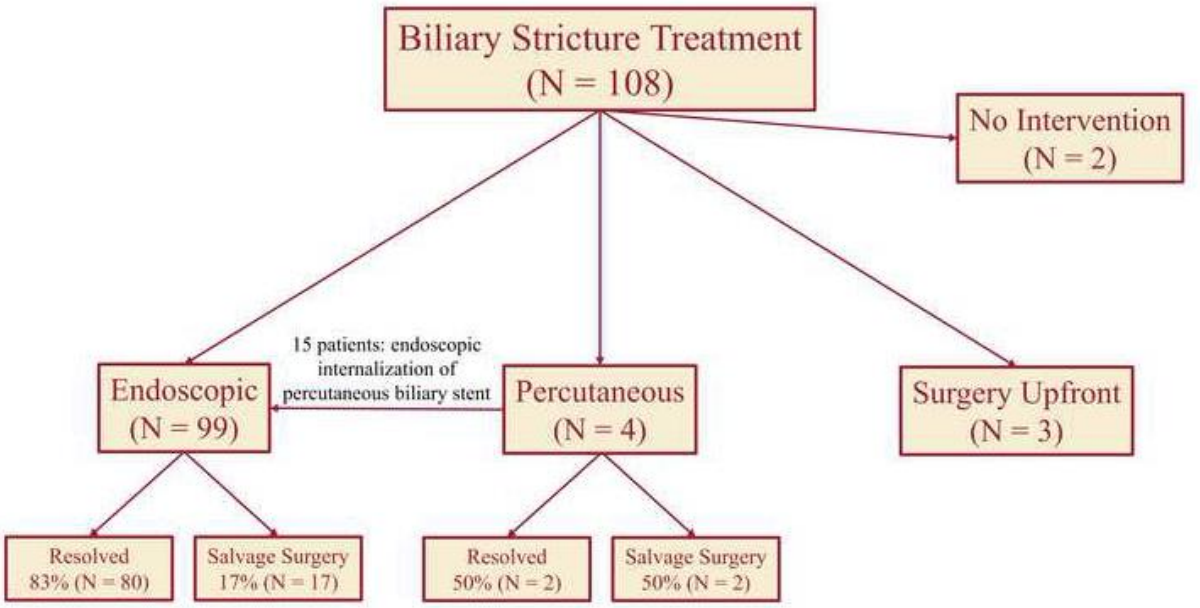

Table 1. Univariate and multivariable analysis comparing demographic and clinical variables between patients without biliary stricture (Control) and patients with biliary stricture after necrotizing pancreatitis.

Risk Factor	Control (n = 558) n, (%)	Biliary Stricture (n = 108) n, (%)	*P* Univariate	*P* Multivariable
Pancreatitis Etiology			0.6	-----
Biliary	265 (47)	60 (56)		
Alcohol	129 (23)	19 (18)		
Triglyceride	32 (2)	7 (6)		
Post-ERCP	32 (6)	6 (6)		
Idiopathic/Other	100 (18)	16 (15)		
Age, Years*	50.6±15.6	52.8±15.3	0.2	-----
Male Sex	353 (63)	79 (73)	**0.049**	0.2
Alcohol Abuse	91 (16)	17 (16)	0.9	-----
Asthma	28 (5)	4 (4)	0.6	-----
Atrial Fibrillation	17 (3)	9 (8)	**0.01**	**0.03**
Coronary Artery Disease	59 (11)	12 (11)	0.9	-----
Chronic Kidney Disease	17 (3)	1 (1)	0.2	-----
COPD	43 (8)	7 (6)	0.7	-----
CVA/TIA	17 (3)	7 (6)	0.08	0.2
Diabetes Mellitus	141 (25)	34 (31)	0.2	-----
Hyperlipidemia	184 (33)	40 (37)	0.4	-----
Hypertension	321 (58)	65 (60)	0.6	-----
Obesity	266 (48)	53 (49)	0.8	-----
Tobacco Use	232 (42)	43 (40)	0.8	-----
Infected Necrosis	224 (40)	55 (51)	**0.04**	0.1
Any organ failure	195 (35)	37 (34)	0.9	-----
Respiratory	156 (28)	34 (31)	0.5	-----
Renal	99 (18)	24 (22)	0.3	-----
Cardiovascular	53 (9)	12 (11)	0.6	-----
DPDS	263 (47)	52 (48)	0.9	-----
Splanchnic Vein Thrombosis	222 (40)	69 (64)	**0.00001**	**0.001**
Pancreatic Head Necrosis	221 (40)	58 (54)	**0.007**	**0.045**
CT Severity Index*	6.6±2.0	7.0±2.0	0.05	0.9
NP Duration, Days**	150 (93-233)	186 (112-278)	**0.005**	0.1
NP Duration >6 Months	218 (39)	58 (54)	**0.005**	0.5

Abbreviations: ERCP- endoscopic retrograde cholangiopancreatography; COPD – chronic obstructive pulmonary disease; CVA – cerebrovascular accident; TIA – transient ischemic attack; DPDS – disconnected pancreatic duct syndrome; CT – computed tomography; NP – necrotizing pancreatitis

*Mean values (± standard deviation) compared using independent groups t-test.

**Median values (with interquartile range) compared using the Mann-Whitney U test.

Table 2. Incidence of biliary stricture among different patterns of splanchnic vein thrombosis.

Splanchnic Vein Thrombosis	**Control (n = 558) n, (%)**	**Biliary Stricture (n = 108) n, (%)**	***P***
Portal Vein†	61 (11)	24 (22)	0.001
Superior Mesenteric Vein†	68 (12)	25 (23)	0.003
Portal and/or Superior Mesenteric Veins	107 (19)	37 (34)	0.0005
Isolated Splenic Vein	115 (21)	32 (30)	0.04

†Either alone or in combination with another splanchnic vein