

Low Serum Trypsin Levels Predict Deep Pancreatic Cannulation Failure During Endoscopic Retrograde Cholangiopancreatography in Patients With Symptomatic Obstructive Chronic Pancreatitis

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Objectives: Deep pancreatic cannulation (DPC) failure during endoscopic retrograde cholangiopancreatography (ERCP) in patients with chronic pancreatitis (CP) can occur in the presence of ductal obstruction due to strictures and/or stones. There are currently no simple preprocedure clinical or laboratory tests that can predict DPC failure during ERCP.

Methods: All adult patients with definite CP by M-ANNHEIM criteria referred to the pancreatitis clinic between 2010 and 2017 were evaluated. Serum trypsin levels were obtained to assess the morphologic severity of disease and/or exocrine insufficiency. Univariable and multivariable logistic regression analyses were performed to identify factors associated with DPC failure.

Results: There were 346 patients, of whom 100 underwent trypsin measurements and ERCP for symptomatic CP. Deep pancreatic cannulation failure occurred in 32 (32%). There were no significant differences with regard to age, sex, etiology, smoking, and alcohol use. Deep pancreatic cannulation failure was more likely to occur in patients with low trypsin levels (53.1% vs 25%, $P = 0.007$) compared with those with successful DPC. Low trypsin levels were independently associated with DPC failure in adjusted analysis (odds ratio, 3.7; 95% confidence interval, 1.2–11; $P = 0.02$).

Conclusions: Low serum trypsin levels independently predict DPC failure during ERCP in patients with symptomatic obstructive CP.

Key Words: endoscopic retrograde cholangiopancreatography, pancreatitis, trypsin assay

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Studies since the late 1970s have shown that serum trypsin levels are low in patients with chronic pancreatitis (CP) defined by calcifications^{1–3} or histopathology^{2–5} and in patients with unequivocal exocrine insufficiency manifested by steatorrhea.^{6,7} Despite the high sensitivity and specificity of serum trypsin as a marker of morphological and functional severity of CP, it is not commonly obtained by clinicians, likely due to a preference for cross-sectional abdominal imaging studies to diagnose CP and select patients for intervention.

Endoscopic retrograde cholangiopancreatography (ERCP) is often employed to relieve pancreatic ductal hypertension due to obstruction that results from stones and/or strictures in patients with symptomatic CP. Risk factors for cannulation failure during ERCP in CP include strictures, stones, a loop configuration of the pancreatic duct, surgically altered anatomy, and pancreas divisum.^{8–10} While patient history and abdominal imaging reveal many of these findings, deep pancreatic cannulation (DPC) success or failure cannot be determined unless ERCP is attempted. There are no simple, easy-to-obtain, and low-cost preprocedural test(s) that predict DPC failure prior to ERCP in CP. The identification of a predictive test could help endoscopists better counsel patients on the likelihood of a technically successful procedure and select patients who may benefit from extracorporeal shock-wave lithotripsy (ESWL) prior to ERCP or emerging techniques such as per-oral pancreatoscopy-guided electrohydraulic lithotripsy (EHL)¹¹ and laser lithotripsy¹² during ERCP. Since endoscopic therapy for CP typically requires multiple ERCPS for ductal stone clearance and/or stricture dilation,¹³ the identification of a predictive test could also help reduce the number of ERCPS and therefore healthcare costs, as well as the burden on patients and their caregivers.

Because serum trypsin is a simple laboratory test that correlates with the morphologic and functional severity of CP, we hypothesized that low serum trypsin may predict DPC failure during ERCP in patients with symptomatic obstructive CP.

MATERIALS AND METHODS

Study Design and Data Collection

This retrospective study was approved by the Johns Hopkins Institutional Review Board for Human Research and complied with Health Insurance Portability and Accountability Act regulations.

The demographic and clinical data for all adult (>18 years of age) CP patients referred to the multidisciplinary pancreatitis

clinic between 2010 and 2017 were reviewed. Patients underwent serum trypsin testing to assess the morphologic severity of CP and/or for evaluation of exocrine insufficiency if diarrhea, steatorrhea, and/or weight loss were reported. Symptomatic obstructive CP was defined as abdominal pain, acute or acute recurrent pancreatitis, and/or other complications (eg, upstream fluid collection or fistula) related to suspected or confirmed ductal obstruction by strictures and/or stones. Patients who failed to undergo or submit the results of trypsin testing, did not undergo ERCP, had only outside ERCPs, had ESWL/EHL prior to ERCP, or did not obtain trypsin values within 3 years of their first ERCP at our institution were excluded from the study (Fig. 1). Patients with chronic kidney disease, autoimmune pancreatitis, prior surgical resection of the pancreas, and/or type 1 diabetes mellitus were excluded because these factors can affect trypsin levels independent of CP.¹⁴⁻¹⁶ Endoscopic retrograde cholangiopancreatography was pursued only in those

patients with symptomatic obstructive CP and was performed by a single endoscopist (V.K.S.).

Definitions

The normal concentration of trypsin was 19 to 68 ng/mL or 10 to 57 ng/mL based on 2 different radioimmunoassay. Low serum trypsin was defined as values less than 19 ng/mL or less than 10 ng/mL. Definite CP was defined according to M-ANNHEIM criteria¹⁷ where 1 or more of the following features were present: (1) pancreatic calcification(s), (2) moderate or marked ductal changes per the Cambridge classification, (3) marked or persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation, and (4) typical histology from an adequate histological specimen. The abdominal computed tomography (CT) scans of all patients were reviewed to assess for morphologic changes of CP including the presence

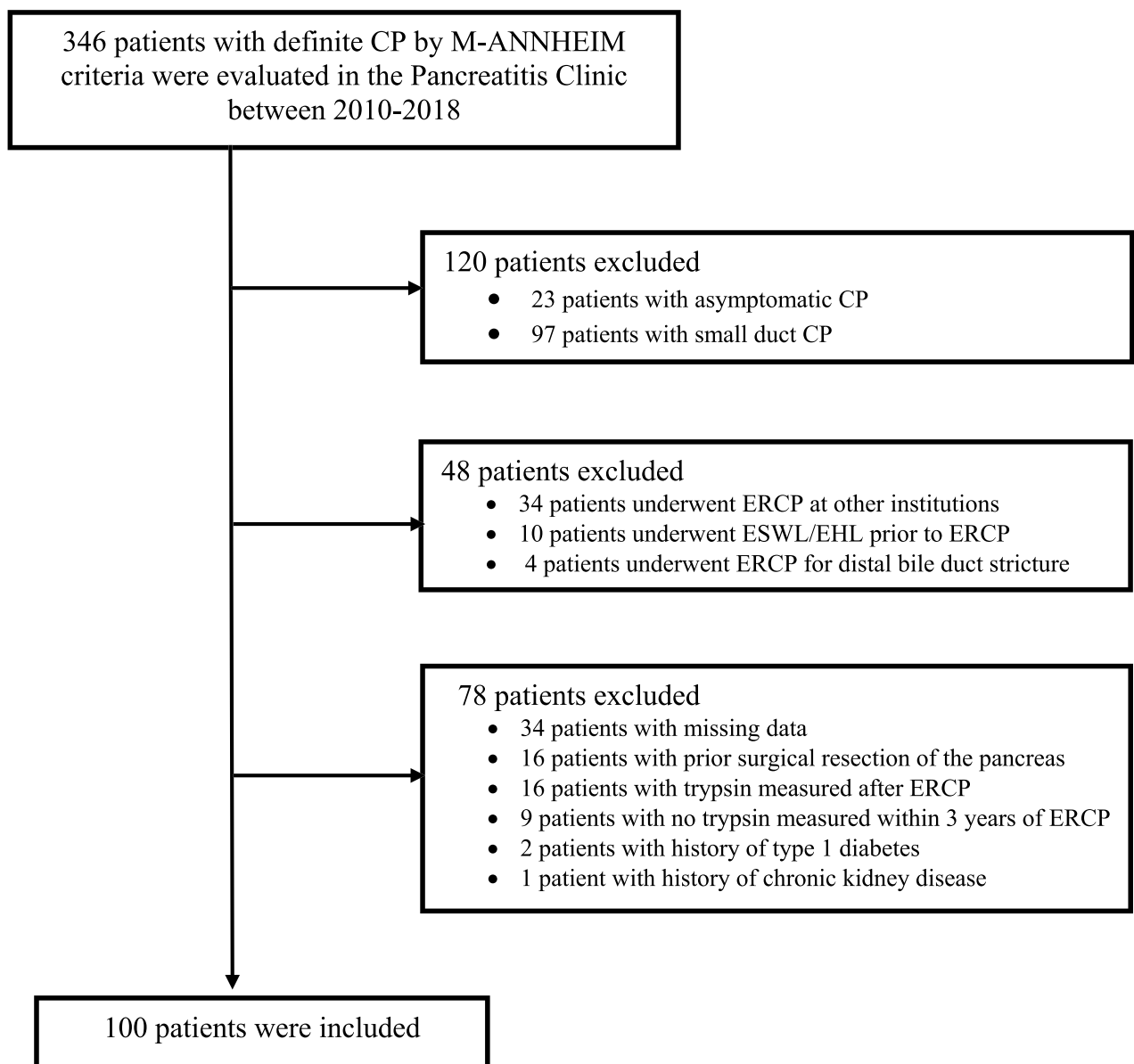


FIGURE 1. Flow diagram summarizing inclusion and exclusion criteria.

of focal/diffuse calcifications; location, number, and size of intraductal stone(s); presence and location of stricture(s); and main pancreatic duct (MPD) diameter as measured at the point of maximal dilation. Magnetic resonance cholangiopancreatography (MRCP) imaging was also reviewed, if performed, and used to evaluate for pancreas divisum. The pancreatograms obtained during ERCP for all patients were reviewed to categorize patients as normal, equivocal, mild, moderate, or marked as per the Cambridge classification.¹⁸ All of the CT and magnetic resonance imaging scans were reviewed by our radiologists (J.R.A. and A.Z.) and the pancreatograms by endoscopists (O.I.B.G., V.K.S.) who were blinded to the clinical data. Whenever possible, the findings on CT and/or MRCP were confirmed or refuted using endoscopic pancreatography as the criterion standard (eg, if a stricture was seen on CT but not on pancreatography, then the patient would be recorded as not having a stricture; or if pancreas divisum was noted on MRCP but not on pancreatography, then the patient would be recorded as not having pancreas divisum). For patients with DPC failure, MRCP was used for categorization of the pancreatogram as per Cambridge classification.

All cases were performed using a duodenoscope (TJF-160; Olympus Optical Co Ltd, Center Valley, Pa), and pancreatic duct cannulation was attempted or performed using a sphincterotome (Tri-tome; Cook Endoscopy, Winston-Salem, NC) loaded with a 0.035- and/or 0.025-inch guidewire. If superficial pancreatic cannulation was established, a small amount of contrast would be injected to visualize and attempt to advance the guidewire into the upstream duct.

Deep pancreatic cannulation failure during ERCP was defined as the inability to advance any accessory (sphincterotome, cannula, and/or guidewire) upstream of an obstructing stricture and/or stone that would be necessary for the completion of therapeutic maneuvers (stricture dilation, stone extraction, and/or stent placement).

Statistical Analysis

Baseline demographic and clinical characteristics at the time of initial clinical evaluation were reported using descriptive statistics. Logistic regression was used to identify predictors of DPC failure. The results of the logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values. The associations between low serum trypsin levels and

DPC failure were modeled separately, and the ORs were adjusted for factors that were significant on univariable analysis and a priori clinical experience. Two-tailed *P* < 0.05 was considered statistically significant. Statistical analysis was performed using STATA 15 (StataCorp, College Station, Tex).

RESULTS

A total of 346 patients with definite CP by M-ANNHEIM criteria were evaluated in the multidisciplinary pancreatitis clinic at Johns Hopkins Hospital between July 2010 and December 2017. After applying all exclusion criteria, there were 100 patients who underwent trypsin testing within 3 years of their first ERCP at our institution for the treatment of symptomatic obstructive CP (Fig. 1). The numbers of patients with individual definite M-ANNHEIM criteria are shown in Figure 2A and with 1 or more definite M-ANNHEIM criteria are shown in Figure 2B. More than three-quarters of our patient cohort met 2 or more criteria for definite CP by M-ANNHEIM. Among 18% of the patients in whom only 1 criterion was present, calcifications or moderate-marked ductal changes were found in all patients. Histology demonstrating changes of CP was based on surgery performed after ERCP, and the findings were confirmed by a review of the slides by a separate pathologist (M.N.).

The demographic, clinical, and morphologic characteristics of the 100 patients were compared between those who experienced DPC success and failure (Table 1). The mean age was 51 (standard deviation [SD], 18) years, with 59% of patients being male. The most common etiologies for pancreatitis were toxic-metabolic (58%), idiopathic (26%), and genetic (13%). Among the study population, 68 (68%) and 32 (32%) patients experienced DPC success and failure during ERCP, respectively. There were no significant differences between patients with DPC success and failure with regard to age, sex, etiology, and smoking and/or alcohol use. Low serum trypsin levels were significantly more common among those with DPC failure compared with those with DPC success (53.1% vs 25%, *P* = 0.007) and the vertical scatterplot (Fig. 3) shows the distribution of trypsin values in both groups. On univariable analysis, intraductal stone(s) in the head (44% vs 10.2%) and body (16% vs 3%) and increased MPD diameter (mean, 6.1 [SD, 2.6] vs 4.5 [SD, 2.6]) were also significantly more common among those with DPC failure (all *P* < 0.05). Number of stone(s), size of stone(s), presence of stricture(s), and location of stricture(s)

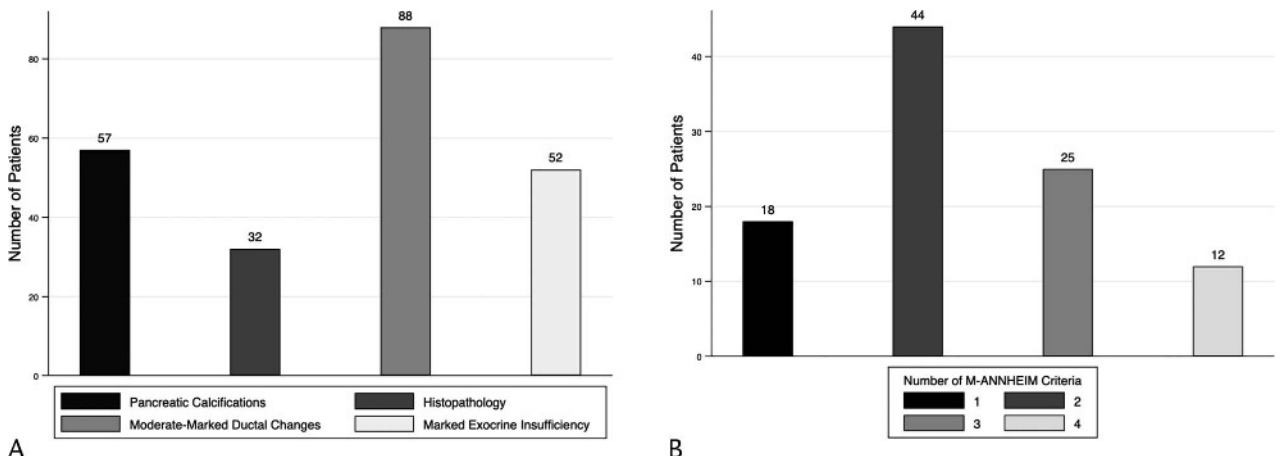


FIGURE 2. A, Number of patients with each individual M-ANNHEIM criteria for definite CP. B, Number of patients with 1 or more M-ANNHEIM criteria for definite CP.

TABLE 1. Comparison of Demographic, Clinical, and Morphologic Characteristics Between 100 Patients With Failed and Successful DPC During ERCP

| Variable | N = 100 | DPC Success (n = 68) | DPC Failure (n = 32) | OR (95% CI) | P |
|---|-----------|----------------------|----------------------|-------------------|--------|
| Age, mean (SD), y | 51 (16.6) | 50 (18) | 53.4 (14) | 1.01 (0.9–1.04) | 0.34 |
| Race, n (%) | | | | | |
| White | 76 (76) | 52 (76.5) | 24 (75) | 0.9 (0.3–2) | 0.8 |
| Black | 17 (17) | 12 (17.7) | 5 (15.6) | 0.8 (0.3–2.7) | 0.8 |
| Other | 7 (7) | 4 (6) | 3 (9.3) | 1.6 (0.3–7) | 0.5 |
| Sex, male, n (%) | 59 (59) | 41 (60) | 18 (56.2) | 0.8 (0.3–1.8) | 0.7 |
| Etiology, n (%) | | | | | |
| Toxic-metabolic | 58 (58) | 38 (56) | 20 (62.5) | 1.3 (0.6–3.4) | 0.5 |
| Idiopathic | 26 (26) | 19 (28) | 7 (21.8) | 0.5 (0.2–1.8) | 0.5 |
| Genetic | 13 (13) | 10 (15) | 3 (9.3) | 0.5 (0.1–2.3) | 0.4 |
| Other | 3 (3) | 1 (3) | 2 (6) | 0.7 (–1.2 to 2.7) | 0.4 |
| Diabetes, n (%) | 34 (34) | 19 (30) | 14 (43.7) | 1.8 (0.7–4.4) | 0.1 |
| Low serum trypsin level, n (%) | 34 (34) | 17 (25) | 17 (53.1) | 3.4 (1.4–8.2) | 0.007 |
| Intraductal stone(s), n (%) | | | | | |
| Head | 21 (21) | 7 (10.2) | 14 (44) | 6.7 (2.3–19) | <0.001 |
| Body | 7 (7) | 2 (3) | 5 (16) | 6 (1.1–33) | 0.03 |
| Tail | 7 (7) | 4 (6) | 3 (10) | 1.6 (0.4–7) | 0.5 |
| Stricture location, n (%) | | | | | |
| Head | 29 (29) | 19 (31) | 10 (33.3) | 1 (0.4–3) | 0.7 |
| Body | 3 (3) | 0 | 3 (10) | — | — |
| Tail | 1 (1) | 1 (1.6) | 0 | — | — |
| MPD diameter based on CT scan, mean (SD), mm (n = 90) | 5 (2.7) | 4.5 (2.6) | 6.1 (2.6) | 1.2 (1.05–1.4) | 0.01 |
| Pancreas divisum, n (%) | 21 (21) | 12 (17.7) | 9 (28) | 2 (0.7–5.7) | 0.2 |

Values presented as number (%) or means with SD.

were not significantly different among patients with DPC failure and those with DPC success.

On multivariable logistic regression analysis, a low serum trypsin level was independently associated with failed DPC (OR, 3.7; 95% CI, 1.2–11; *P* = 0.02) after adjusting for pancreas divisum, intraductal stone(s) in the head, stricture in the head,

and increased MPD diameter on CT scan (Table 2). No other variables were independently associated with DPC failure.

DISCUSSION

The present study is the first to demonstrate that low serum trypsin levels independently predict DPC failure during ERCP

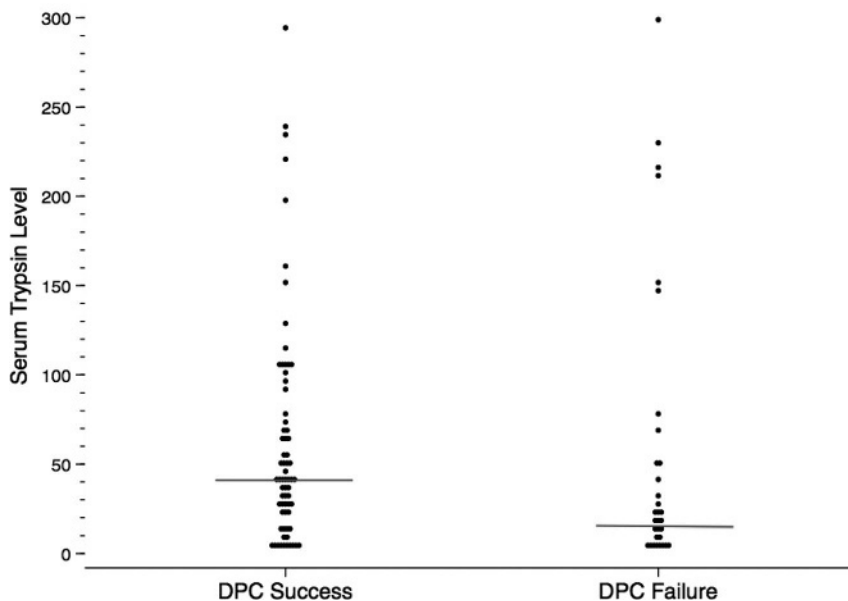


FIGURE 3. Scatterplot of serum trypsin levels in patients with DPC success and failure. Median is shown with the solid line.

TABLE 2. Multivariable Logistic Regression for Predictors of DPC Failure

| Variable | Adjusted OR (95% CI) | Adjusted P |
|------------------------------|----------------------|------------|
| Low serum trypsin level | 3.7 (1.2–11) | 0.02 |
| Pancreas divisum | 2.3 (0.6–8.5) | 0.1 |
| Intraductal stone(s) in head | 3.9 (0.9–17.3) | 0.06 |
| Stricture in the head | 0.7 (0.2–2.5) | 0.6 |
| MPD diameter on CT scan | 1.1 (0.8–1.4) | 0.3 |

for symptomatic obstructive CP after adjusting for morphologic features of advanced CP and pancreas divisum. The factors associated with the successful ductal clearance of stones in CP are well studied.^{13,19,20} Lapp et al reported that successful ductal stone clearance with ERCP was associated with fewer and smaller stones, as well as smaller duct diameter.²¹ However, there have been no studies evaluating preprocedural predictors of DPC failure in patients undergoing ERCP for symptomatic obstructive CP. Most of the previously reported factors associated with difficult cannulation were identified at the time of ERCP.²²

Low serum trypsin levels may help endoscopists counsel patients who are more likely to experience DPC failure and may benefit from alternative initial approaches including ESWL prior to ERCP, EHL, or laser lithotripsy during ERCP, or even surgery. Many studies have shown that ESWL prior to ERCP results in improved clinical outcomes in patients with CP.^{23–25} Patient selection is also important to avoid potential complications such as post-ERCP pancreatitis,²⁶ which is more likely in the setting of a difficult and failed cannulation.²⁷ Low preprocedural trypsin levels could potentially make ERCP more cost-effective by avoiding an upfront ERCP or pursuing alternative approaches that will increase the likelihood of technical success during the first ERCP, thereby resulting in a lower number of total ERCPs. A recent trial-based economic analysis from the United Kingdom showed that surgery is more cost-effective than endoscopy for the treatment of CP largely because of the greater number of therapeutic ERCPs required with a mean of 6.3 procedures among the 19 patients in the endoscopy arm.²⁸ In addition, fewer ERCPs may be associated with improved clinical success as a study showed that undergoing more than 5 ERCPs prior to surgery in 266 patients with CP was independently associated with decreased pain relief after surgery in the multivariable analysis.²⁹

The strengths of the present study include a large cohort of well-phenotyped symptomatic patients who met a validated definition for definite CP (M-ANNHEIM criteria), exclusion of patients with serum trypsin levels that may be influenced by other conditions such as chronic kidney disease, type 1 diabetes mellitus, and prior surgical resection of the pancreas, as well as review of pancreatograms and imaging by endoscopists and radiologists, respectively, who were blinded to the clinical data.

Our study does have several limitations. While nearly a third of patients undergoing ERCP experienced DPC failure in our study, it should be noted that there are few studies that specifically report DPC rates in patients with CP. Tantau et al³⁰ reported a low pancreatic cannulation failure rate of 5.4% across 129 patients with painful CP undergoing ERCP. There are several potential explanations for the difference in DPC failure rates between the study by Tantau et al and ours. The first is that the morphology of CP differs between the cohorts. In the study by Tantau et al, 69% of patients had a stricture only, 13% had intraductal stones only, and 18% had both stricture and stones; however, 33% of

the patients in our study had a stricture, 35% had intraductal stones, and 14% had both stricture and stones. Because the majority of patients in the study of Tantau et al had a stricture only, DPC failure rates would be predicted to be lower based on the results of the present study. In addition, many of our CP patients are referred to us from outside institutions with advanced morphologic changes for consideration of another ERCP after a failed initial ERCP (18%) or for surgery. Other studies have reported overall pancreatic cannulation failure rates of 13% to 16% but do not specify the proportion of failures occurring in patients with CP.^{30,31} While there was only a single endoscopist performing all procedures, this ensured overall uniformity in patient evaluation and selection for endoscopic therapy. In addition, a large study evaluating numerous patient, procedural, endoscopist, and hospital characteristics across 66 centers in the United Kingdom with 4561 patients found that neither endoscopist experience nor center volume predicted cannulation failure or an incomplete procedure in the multivariable analysis after adjusting for patient- and procedural-level factors.³² This study did find that the adjusted odds of an incomplete procedure were 3.4 times greater for pancreatic duct interventions compared with other indications. A recent systematic review and meta-analysis found that both endoscopist and center volume positively correlate with procedure success. However, procedure success was defined differently in each of the 6 studies used in this meta-analysis, with no studies specifically reporting DPC rates in CP patients.³³ Serum trypsin may also be limited as a predictor when CP patients have had a recent episode of superimposed acute pancreatitis, which should be suspected when serum trypsin is 3 times the upper limit of normal, an increase generally indicative of acute pancreatitis.³⁴ We were not able to compare the median trypsin values between the 2 groups as 2 different trypsin assays with different reference ranges were utilized and several patients had an undetectable trypsin level without a numerical value. A total of 4 patients (12%) with DPC failure had serum trypsin values in this range, but this was also seen in a similar number, 6 (9%) of patients with DPC success. The accuracy of a serum trypsin level within 3 years of ERCP may also be called into question. Serum trypsin levels in chronic calcific pancreatitis, outside of superimposed AP, have been shown to be stable over a 3-year period.³⁵ However, it should be noted that 88% of the patients in this study had their trypsin level checked within 1 year of their ERCP.

In conclusion, low serum trypsin levels independently predict DPC failure during ERCP in patients with symptomatic obstructive CP. Additional studies are needed to confirm this finding.

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