Predrainage and Postdrainage Prognostic Nomograms to Predict Outcome of Percutaneous Drainage for Infected Pancreatic and Peripancreatic Necrotic Collections

Rajesh Gupta, MCh, Aditya A. Kulkarni, MCh,* Raghavendra Babu, MCh,* Sunil Shenvi, MCh,* Rahul Gupta, MCh,* Gopal Sharma, MS,* Mandeep Kang, MD,† Vishal Sharma, DM,‡ Harjeet Singh, MCh,* Praveen Kumar-M, MD,§ and Surinder Rana, DM‡*

Objectives: This study aimed to identify factors affecting outcome of percutaneous catheter drainage (PCD) in management of infected pancreatic necrosis treated with step-up approach.

Methods: This was a single-center retrospective cohort study that included patients with infected necrosis undergoing PCD as initial intervention. Patients who did not respond underwent necrosectomy. Predictors of PCD failure (ie, mortality or need for necrosectomy) were analyzed. Models were constructed for predrainage and postdrainage use and were internally validated.

Results: Of 304 patients included, catheter drainage was successful in 59.8%, with overall mortality of 22%. Predrainage model consisted of Acute Physiologic and Chronic Health Evaluation II score at admission, early organ failure, and pancreatic necrosis of greater than 50%. Postdrainage model consisted of Acute Physiologic and Chronic Health Evaluation II at first PCD, early organ failure, pancreatic necrosis of greater than 50%, sepsis reversal within 1 week of PCD and *Escherichia coli* in PCD culture. Both models were internally validated with area under receiver operating characteristics curve of 71.2% for pre-PCD and 81.2% for post-PCD model. Prognostic nomograms were constructed using the models.

Conclusions: Percutaneous catheter drainage alone was successful in 59.8% with mortality of 22%. The nomograms can help in guiding treatment strategy and referral of high-risk cases.

Key Words: necrotizing pancreatitis, percutaneous catheter drainage, step-up approach, predictors, necrotic fluid collection, open pancreatic necrosectomy

(*Pancreas* 2019;48: 1212–1219)

Necrosis of pancreatic/peripancreatic tissues develops in around 20% of all patients with acute pancreatitis. Infection of necrosis and peripancreatic fluid collections occurs in 14% to 62% of these patients.[1,2] Open surgical necrosectomy has traditionally been regarded as the standard treatment for infected pancreatic necrosis (IPN). However, it is associated with high morbidity and mortality rates.[3] Hence, the step-up approach, as popularized by the PANTER trial,[4] has become the preferred treatment strategy.[5]

From the *Division of Surgical Gastroenterology, Department of General Surgery, †Department of Radiodiagnosis, ‡Department of Gastroenterology, and §Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Received for publication May 4, 2019; accepted August 12, 2019.

Address correspondence to: Rajesh Gupta, MCh, Division of Surgical Gastroenterology, Department of General Surgery, Postgraduate Institute of Medical Education and Research, 5th Floor, Nehru Hospital, Sector-12, Madhya Marg, Chandigarh, India (e-mail: rajsarakshi@gmail.com).

The authors declare no conflict of interest.

R.G. is the guarantor of the article.

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

DOI: 10.1097/MPA.0000000000001395

Image-guided percutaneous catheter drainage (PCD) of necrotic collections is currently the first step in the step-up approach for IPN. Initially, PCD was intended to act as a bridge to surgery by stabilizing the patient and potentially reversing organ failure. It was soon realized that, with persistence, PCD alone can lead to disease resolution in a subgroup of patients. In a recent review of PCD as primary treatment for necrotizing pancreatitis, the success rate of PCD was 55.7%.[6] Thus, more than half of patients with IPN can be treated definitively with PCD as a definitive modality.

The efficacy of PCD can be improved by using drains proactively, with measures such as use of multiple drains, high-volume saline irrigation, upsizing, repositioning, and use of necrolytics.[7–12] Proactive PCD use significantly reduces the need for necrosectomy in IPN, without affecting hospital stay and mortality.[11] Successful nonsurgical management of IPN was possible in 68.5% of patients using step-up approach with intention to avoid surgery with proactive PCD drainage.[9]

Despite widespread adoption of the step-up approach, the exact indication and timing for step-up to necrosectomy are not standardized. Currently, the decision for surgery largely depends on clinical judgment. It is important to predict which patients are more likely to fail PCD drainage and require necrosectomy. A model to predict this subgroup of patients would allow timely *step-up*. Unfortunately, there are few studies that have thrown light on this question.

Hence, the aim of this study was to determine clinical and radiological factors predictive of outcome of PCD in necrotizing pancreatitis with necrotic pancreatic/peripancreatic collections. The present study was designed to use these factors to develop and validate models to predict the outcome of PCD.

MATERIALS AND METHODS

Design and Setting

This was an observational cohort study with retrospective analysis of a prospectively maintained database of patients with acute pancreatitis who were diagnosed and treated in the Division of Surgical Gastroenterology and Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, a tertiary care referral center in North India. The period of the study was from April 2008 to December 2017. The study population also included a subset of patients whose outcomes have already been reported previously by us.[9,13] Informed consent was provided by all subjects for data to be included in the prospective database. The study was approved by the institutional ethics committee.

Inclusion and Exclusion Criteria

We included patients diagnosed with severe and moderately severe necrotizing pancreatitis (as per the revised Atlanta Classification 2012) who had undergone PCD as initial intervention as part of step-up approach. Patients younger than 18 years old, patients

with mild acute pancreatitis or acute-on-chronic pancreatitis, patients who underwent initial intervention at other hospitals, and patients managed without PCD as the primary invasive intervention were excluded. Patients in whom endoscopic transmural drainage and necrosectomy were performed were excluded.

Treatment Protocol

Step 1

After diagnosis of acute pancreatitis was made (by presence of clinical, biochemical, or imaging criteria), initial management was supportive with fluid resuscitation, analgesics, and nutritional support. Contrast-enhanced computed tomography (CT) scan was performed at least 4 days after pain onset to assess severity and local complications.

Step 2

In case of failure to improve with conservative management, insertion of PCD was performed under radiologic guidance. The indications for PCD insertion were as follows: suspected IPN on radiologic and clinical criteria, sterile pancreatic necrosis with clinical deterioration or pressure symptoms, and acute fluid collection with persistent unwellness on conservative management. The number of catheters placed in a cavity depended on the clinical symptoms and imaging findings. Saline irrigation was used using a Y-connector attached to the pigtail catheter, and volume of irrigation was increased as tolerated. The response to initial drainage was monitored clinically. Reduction in the size of the cavity and/or appearance of new collections was assessed by performing repeat ultrasound or CT scan. In case of persistent collection, inadequate drainage, or collection at a different location on reimaging, patients were taken up for upsizing, repositioning, replacement, or placing additional catheters in the cavity. More than 1 catheter in the cavity allowed for ingress of saline and the others for egress of drainage fluid.

Step 3

Indications of step-up to necrosectomy were persistent sepsis (persistently elevated white blood cell count, fever spikes), worsening of organ failure or new-onset organ failure, failure to thrive, and complications of acute pancreatitis or PCD (eg, gut necrosis, uncontrolled enterocutaneous fistula, bowel obstruction). Failure to improve within 1 week was taken as an indication to step-up. A CT scan was repeated before the procedure to act as a roadmap. Video-assisted retroperitoneal debridement or conventional open necrosectomy with closed lesser sac drainage and lavage was performed in patients with persistent residual necrosis and failure to improve clinically. Large bore drains (commonly 24 Fr [French] Foley catheter with multiple side holes) were placed in the cavity for postoperative lavage.

Data Collection

The definitions used in the study are detailed in Table 1. We collected data on baseline characteristics like sex, age, etiology, and time from onset to hospital transfer. Severity assessment was done at admission and at the time of initial PCD insertion. For this, we used clinical parameters, organ failure scores and Acute Physiologic and Chronic Health Evaluation II (APACHE II) scores. All contrast-enhanced CT scans were reviewed by the consultant radiologist (M.K.) with interest in abdominal radiology. Details noted were as follows: modified CT severity index (mCTSI) score, location (total/subtotal, right sided or left sided) and extent (<30%, 30%–50%, and >50%) of pancreatic necrosis, and location and size of extrapancreatic collections.

In addition, we also recorded timing of first PCD procedure (days from admission), sizes of drain, total number of drains placed, total number of interventions, and positive microbiological cultures from the first PCD. In patients undergoing surgical intervention, details on timing, route of intervention, operative details, and outcome were recorded.

Statistical Analysis

Normally distributed data were expressed as mean (standard deviation [SD]) and were compared using the Student *t* test for 2 groups. Skewed data were expressed as median with interquartile range (IQR) and compared using the Mann-Whitney test for 2 groups. Proportions were compared using the χ^2 test or Fisher exact test. Initial analysis for potential predictors of failure was done using univariate analysis based on the type of data. All statistical tests were 2-sided and performed at a significance level of $P < 0.05$.

Factors significantly associated with failure of PCD were included in multivariate regression analysis using backward stepwise selection. Multiple predictive models were developed by including selected variables, based on their statistical significance

TABLE 1. Definitions Used in the Study[13]

Term	Definition
Organ failure	Organ failure persisting for more than 48 h at any time after disease onset and after appropriate medical management
Renal failure	Creatinine level >170 μmol/L (1.9 mg/dL) after rehydration
Circulatory failure	Systolic blood pressure <90 mm Hg despite adequate fluid resuscitation
Respiratory failure	PaO_2/FiO_2 ratio <300 or need for mechanical ventilation
Multiorgan failure	Failure of 2 or more organ systems (as defined above)
Early organ failure	Organ failure occurring within the first week of illness
IPN	Positive culture obtained either from needle aspiration or the first specimen obtained after PCD insertion *or* patients showing air foci (emphysematous changes) within necrotic collection in CT scan done before radiologic intervention
Sepsis	Systemic inflammatory response syndrome with a documented source of infection
Sepsis reversal with PCD	Defined as defervescence, reversal of leucocytosis, and sepsis-related organ failure after PCD insertion
PCD success	Resolution of disease with PCD as the sole intervention
PCD failure	Need for further step-up, i.e., surgical intervention in patient on PCD, or disease-specific mortality in a patient with PCD in place

($P < 0.05$) in the univariate analysis. The calibration of the models was initially assessed using the Hosmer-Lemeshow goodness-of-fit test. Area under curve was estimated using receiver operating characteristics curve. Akaike and Bayesian information criteria were used to further compare between the competing models. Final model selection was performed, giving priority to variables with clinical relevance. The final models were selected on the basis of a good fit, maximum area under curve, and least loss of predictive ability while maintaining parsimonity.

Nomograms were constructed based on the developed models for pre-PCD and post-PCD separately, as described by Zhang and Kattan.[14] For internal validation of the nomogram, simple bootstrap resampling was done on the original cohort to obtain 3000 samples. The optimism-corrected area under the receiver operating characteristics curve (AUROC) of the model validated by bootstrap multivariate logistic regression analysis was calculated to assess the discriminative ability of the model. In addition, a calibration curve was plotted to determine concordance between the predicted and empirically observed probabilities over the range of probabilities.

All statistical analysis was carried out using the SPSS version 20 statistics software package (IBM Corp, Armonk, NY) and R version 3.4.4 (R foundation for Statistical Computing, Vienna, Austria) along with additional packages, rms and rmda.[15,16]

RESULTS

Demographic Parameters

During the 10-year period of study, a total of 304 patients diagnosed with acute necrotizing pancreatitis underwent PCD of peri/pancreatic collections in our center. Of these, PCD was successful in 182 (59.8%) and failed in 122 (40.1%). The mean age for the whole cohort was 39.6 (SD, 12.8) years. The cohort consisted of 228 males and 76 females. Alcohol was the commonest etiological factor in both in the groups. Median interval between symptom onset and presentation/referral to our center was 7 days (IQR, 1–15.75 days). There was no significant difference in the demographic characteristics of the 2 groups (Table 2).

Disease Severity

Patients were classified as having moderate or severe pancreatitis as per the revised Atlanta classification. The cohort had 221 patients (72.6%) with severe pancreatitis and 83 (27.3%) with moderate disease (Table 2). The commonest organ to fail was respiratory in 208 (68.4%), followed by renal in 90 (29.6%) and circulatory failure in 54 patients (17.8%). Early-onset organ failure (within the first week of illness) was seen in 101 patients (33.2%). Single-organ failure was present in 99 patients (32.6%), whereas multiorgan failure was present in 122 (40.1%). The median APACHE score at presentation was 9 (IQR, 6–12). The mCTSI at first CT scan was 10 (IQR, 8–10) (Table 3).

PCD Characteristics

The details of PCD interventions are given in Table 4. Percutaneous catheter drainage was performed at a median of 19 days (range, 8–200 days; IQR, 13–29 days) after onset of disease. A median of 2 catheters per patient was used (range, 1–8; IQR, 1–3). A single catheter was used in 93 (30.6%), 2 catheters in 104 (34.2%), and 3 in 58 (19.1%). In 49 patients (16.1%), 4 or more catheters were used. Total number of interventions (drain insertion, repositioning, and upsizing) was 1189, with a median of 3 interventions per patient (range, 1–12; IQR, 2–5), and was higher in PCD failure arm. In 123 patients (40.5%), catheter drains were upsized to larger catheter drains. The size of the catheter drain used varied from 8 to 32 F, and the median drain size was 12 F (IQR, 12–14 F), which was similar between the 2 groups. The median duration of PCD drainage was 35 days (range, 2–235 days; IQR, 20–60 days).

TABLE 2. Comparison of Demographic and Disease Severity Data in the 2 Arms

	PCD Success (n = 182)	PCD Failure (n = 122)	*P*
Age, median (IQR), y	40 (30–47)	37 (28–48)	0.43
Sex, male, n (%)	140 (76.9)	88 (72.1)	0.348
Etiology of pancreatitis, n (%)			0.694
Alcohol	106 (58.2)	65 (53.3)	
Gallstones	44 (24.2)	33 (27.0)	
Other (drug-induced, ERCP, idiopathic, etc)	32 (17.6)	24 (19.7)	
Prereferral (initial) treatment received, n (%)	121 (66.5)	75 (61.5)	0.394
Days to referral after pancreatitis onset, median (IQR)	6 (0–15)	7 (2–18)	0.274
Total hospital stay, median (IQR), d	44 (30–66)	30 (20–48)	<0.001
Total ICU stay, median (IQR), d	14 (6–20)	18 (10–30)	0.002
Need for ventilation, n (%)	34 (18.7)	75 (61.5)	<0.001
Days on ventilator, median (IQR)	10 (7–16.25)	6 (3–11.25)	0.019
Severity of pancreatitis by revised Atlanta classification, n (%)			0.001
Severe	120 (65.9)	101 (82.78)	
Moderately severe	62 (34)	21 (17.21)	
APACHE II score at presentation, median (IQR)	8 (5–11)	10.5 (8–13)	<0.001
Organ failure, n (%)			
Early organ failure	43 (32.3)	58 (55.2)	<0.001
Single-organ failure	64 (35.2)	35 (28.7)	0.238
Multiorgan failure	56 (30.8)	66 (54.1)	<0.001

ERCP indicates endoscopic retrograde cholangiopancreatography.

TABLE 3. Comparison of CT Characteristics on First Contrast-Enhanced CT Scan Between the 2 Arms

	PCD Success (n = 182)	PCD Failure (n = 122)	*P*
mCTSI, median (IQR)	10 (8–10)	10 (8–10)	
Extent of pancreatic necrosis, n (%)			
<30%	56 (31.8)	29 (24.4)	0.191
30–50%	16 (13.4)	49 (27.8)	0.03
>50%	71 (40.3)	74 (62.2)	<0.001
Location of necrotic collections, n (%)			
Peripancreatic	165 (90.7)	114 (93.4)	0.387
Right pararenal	16 (8.8)	7 (5.7)	0.324
Left pararenal	98 (53.8)	96 (78.7)	<0.001
Right paracolic	14 (7.7)	5 (4.1)	0.204
Left paracolic	64 (35.2)	54 (44.3)	0.111
Perihepatic	31 (17)	20 (16.4)	0.884
Perisplenic	37 (20.3)	23 (18.9)	0.751
Root of mesentery	18 (9.9)	20 (16.4)	0.093
Pelvis	44 (24.2)	27 (22.1)	0.680

Sepsis reversal with PCD was seen within 1 week of PCD insertion in 154 patients (50.6%). In addition, 32 patients (10.5%) who had PCD success showed sepsis reversal more than 1 week after insertion of PCD. We noted that patients in whom sepsis reversal did not occur within 1 week of PCD insertion had significantly higher chance of PCD failure (Table 4).

Bacteriological Data

In the present study, 269 patients (88.5%) had infected necrosis. Unimicrobial infection was present in 101 (33.2%) and polymicrobial in 168 (55.3%). Spectrum of organisms isolated from initial PCD culture did not vary between the 2 groups, with the exception of *Escherichia coli*. Growth of *E. coli* in initial culture was significantly higher in patients with PCD failure (Table 4).

Operative Data

In all, 87 patients (28.6%) underwent surgical necrosectomy. The median interval from onset of illness to surgery was 48.5 days (IQR, 36.5–64.25 days). Of the 87 patients, open necrosectomy was performed in 67 (77%) and minimally invasive necrosectomy in 20 patients (22.9%). The majority of open procedures were performed in the initial years of our experience. Reoperation

TABLE 4. Comparison of PCD and Bacteriologic Characteristics Between the 2 Arms

	PCD Success (n = 182)	PCD Failure (n = 122)	*P*
APACHE II score at first PCD, median (IQR)	8.5 (6–12)	13 (9.75–15)	<0.001
Interval between onset of pancreatitis to first PCD,* median (IQR), d	20 (13–30)	19 (13–26.5)	0.687
No. drains, median (IQR), n	2 (1–3)	2 (2–3)	0.005
No. interventional procedures,† median (IQR), n	3 (2–5)	4 (3–5.25)	0.003
Upsizing of drain, n (%)	66 (36.3)	57 (46.7)	0.069
Maximum diameter of drain, median (IQR), F	10 (10–14)	12 (10–14)	0.112
Drainage duration, median (IQR), d	40 (24–64.5)	30.5 (15.75–54.25)	0.408
Sepsis reversal within 1 week of PCD, n (%)	117 (64.3)	37 (30.3)	<0.0001
Infected necrosis, n (%)	160 (87.9)	109 (89.3)	0.701
Unimicrobial/polymicrobial infection, n/n	65/95	36/73	0.206
Causative organism in initial PCD culture, n (%)			
Escherichia coli	81 (44.5)	70 (57.4)	0.028
Proteus mirabilis	21 (17.2)	31 (17)	0.967
Pseudomonas aeruginosa	15 (12.3)	20 (11)	0.727
Klebsiella pneumoniae	46 (37.7)	60 (33)	0.396
Acinetobacter baumannii	32 (26.2)	35 (19.2)	0.149
Enterococcus spp.	3 (2.5)	10 (5.5)	0.200
Positive bacterial blood culture, n (%)	54 (29.7)	56 (45.9)	0.004
Positive fungal blood culture/serology, n (%)	39 (21.4)	36 (29.5)	0.123

*Data missing for 14 patients.

†Interventional procedures include drain insertion, repositioning, and upsizing, under radiologic guidance. Simple flushing or irrigation was not included as a separate intervention.

was performed in 15 patients, the reasons being postoperative enterocutaneous fistula (n = 6), residual necrosis with ongoing sepsis (n = 3), suspected colonic gangrene (n = 2), and bleeding through operatively placed drain (n = 3). Two patients underwent repeated surgeries (5 and 6 times, respectively) for recurrent bleeding. Both of these patients survived.

Mortality

Overall mortality in the study was 22% (68/304 patients). The commonest cause of mortality was sepsis with multiorgan failure. In patients who underwent surgical necrosectomy, the mortality was 37.9% (33/87 patients). In patients who underwent PCD alone, mortality was 16% (35/217).

Factors Predictive of PCD Failure

We performed univariate analysis to look for factors predicting PCD failure. The significant factors were as follows: multiorgan failure ($P < 0.0001$), APACHE II score at presentation ($P < 0.0001$), organ failure in the first week of illness ($P < 0.0001$), greater than 50% pancreatic necrosis ($P < 0.0001$), total/subtotal pancreatic involvement (head, body, and tail) ($P = 0.006$), left pararenal collection ($P < 0.0001$), APACHE score at first intervention ($P < 0.001$), sepsis reversal within 1 week of initial PCD ($P < 0.0001$), positive bacterial blood culture ($P = 0.004$), and *E. coli* in initial PCD culture ($P = 0.028$).

Binomial Logistic Regression Analysis

Our aim was to construct 2 prediction nomograms, one designed for use before PCD insertion, ideally at admission, and another for use after initial PCD. Stepwise logistic regression analysis was performed separately for both models. Multiple models were analyzed (Supplemental Table 1, http://links.lww.com/MPA/A743, which demonstrates all the models). The pre-PCD models included early organ failure, APACHE II score at admission, organ failure as per Marshall score, percentage of pancreatic necrosis of greater than 50%, and left pararenal collection. The post-PCD models included information available both before and after PCD insertion. Variables included in the post-PCD model were early organ failure (in first week of illness), pancreatic necrosis of greater than 50%, left pararenal collection, APACHE II score at first PCD insertion, sepsis reversal within 1 week of first PCD insertion, and growth of *E. coli* in initial PCD culture.

The final models chosen are presented in Table 5. Left pararenal collection was not included in the final model. This was because left pararenal collections are often extension of the lesser sac collection and including this variable would confound the variable pancreatic necrosis of greater than 50%. In fact, eliminating this variable from the models did not result in any significant loss of information and led to improved model fit.

The models were internally validated with bootstrap resampling with 3000 patients. The optimism-corrected AUROC for pre-PCD model was 0.711, and that for post-PCD model was 0.812. Pre-PCD and post-PCD prognostic nomograms predicting probability of failure were designed using the variables obtained from the corresponding logistic regression model (Figs. 1, 2). Calibration plots were plotted for concordance between the predicted and empirically observed probabilities of failure (Fig. 3). Both pre-PCD and post-PCD nomogram calibration plots demonstrated high reliability in predicting probability of PCD failure.

DISCUSSION

In this retrospective study, we evaluated factors predicting outcome of PCD in management of necrotizing pancreatitis. The aim was to develop a prognostic nomogram to guide decision making, both before and after percutaneous drainage. Previously, we have reported our experience with 70 patients of necrotizing pancreatitis of which 56 patients underwent PCD drainage as part of step-up approach.[13] Percutaneous catheter drainage successfully avoided surgery in 48%. We found that the use of PCD as the first intervention in the step-up approach alters the natural course of the disease by achieving reversal of sepsis and organ failure. In the past 10 years, we have built upon this experience, and the current study represents the expansion of this data set to over 300 patients with necrotizing pancreatitis.

It is important to highlight the wide variability in the use of PCD. In the PANTER trial,[4] a maximum of 2 drainage procedures were allowed before step-up to minimally invasive necrosectomy. In most of the studies, 50 mL of saline was instilled 8 hourly mainly to keep catheters patent, whereas continuous saline irrigation was not used. In a retrospective study by the Dutch Pancreatitis Study group,[11] a proactive PCD strategy consisting of frequent and early drain revision and upsizing led to improvement in PCD success rate to 71.4% compared with standard PCD protocol. They observed that new-onset organ failure was lower in proactive PCD arm; however, hospital stay and mortality remained the same. At our center, we routinely use continuous saline irrigation, either using a Y-connector for a single drain or using cross irrigation using 2 or more catheters. The purpose has been to use these drains akin to those in open necrosectomy with closed lesser-sac lavage. Main advantage of continuous irrigation is that it removes infected fluid containing inflammatory mediators and flushes out loose necrotic debris.

TABLE 5. Bootstrap Validated Final Models Obtained by Binary Logistic Regression Analysis

Parameter	Odds Ratio (95% CI)	*P*
Pre-PCD model		
Early organ failure (in first week of illness)	2.48 (1.47–4.16)	0.001
Percentage of pancreatic necrosis >50%	2.16 (1.31–3.55)	0.002
APACHE II score at admission	1.12 (1.05–1.19)	<0.001
Post-PCD model		
Early organ failure (in first week of illness)	2.83 (1.55–5.18)	0.001
Percentage of pancreatic necrosis >50%	1.82 (1.05–3.15)	0.033
APACHE II score at first PCD insertion	1.19 (1.11–1.27)	<0.001
Sepsis reversal within 1 week of first PCD insertion	0.184 (0.103–0.328)	<0.001
E. coli in initial PCD culture	2.27 (1.28–4.02)	0.005

CI indicates confidence interval.

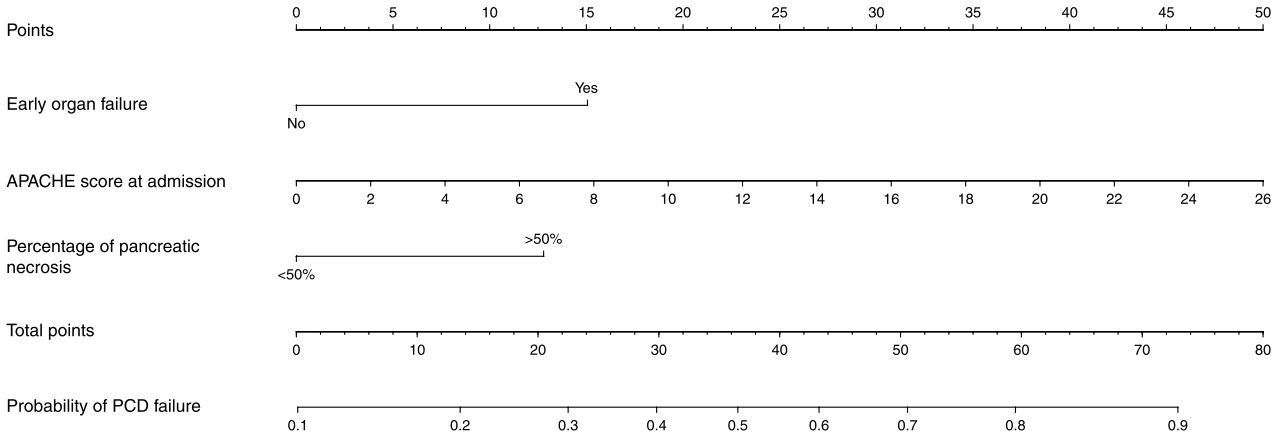

FIGURE 1. Pre-PCD nomogram for predicting the probability of PCD failure.

In our study, in the pre-PCD model, we identified 3 factors that were significantly associated with PCD failure: APACHE II score at presentation, pancreatic parenchymal necrosis of greater than 50%, and organ failure in first week of illness. Extensive pancreatic necrosis has been shown to correlate with organ failure and increased risk of mortality.[17,18] Similarly, persistent organ failure has been shown to increase risk of mortality. Early organ failure in acute pancreatitis also impacts the course of illness adversely.[19,20] Previously, Hollemans et al[21] investigated factors responsible for success of PCD in infected necrotic collections. In a relatively small sample size of 130 patients from 22 centers, they identified male sex, multiple organ failure, percentage of necrosis, and heterogeneous density of the collection on CT as predrainage predictors of PCD failure. There are certain drawbacks in this model. First, preponderance of male sex in PCD failure is difficult to explain and has not been reported elsewhere. Second, density of the collections in the setting of necrotizing pancreatitis (categorized as homogeneous or heterogeneous) has limited utility because all the collections are likely to be heterogenous. We also believe that the low success rate of PCD (35%) reported in this study may be related to lesser number of radiologic interventions like drain upsizing (15%) and additional drain placement (only 10% of patients had more than 2 drains). Also, while formulating this model, the authors did not consider any post-PCD parameter, which has been found to be vital for PCD success in our study.

Previously, the studies on necrotizing pancreatitis have defined organ failure using modified Marshall scoring system. However, APACHE II score has been shown to be better for predicting severe disease than the Marshall scoring system.[22] Also, when compared with the Marshall scoring system, APACHE II score offers a comprehensive reflection on the physiological status of the patient and also takes into account chronic health variables, which may have a bearing on the ability of the patient to launch immune attack against pancreatic necrosis. Hence, our model includes APACHE II score rather than modified Marshall score.

Post-PCD model in our study included organ failure in the first week of illness, pancreatic necrosis of greater than 50%, APACHE II score at first PCD insertion, sepsis reversal within a week of first PCD insertion, and growth of *E. coli* in initial PCD culture. Severe acute pancreatitis is a dynamic disease, and the clinicoradiological response to initial PCD insertion plays an important role in determining eventual PCD outcome. In the present study, we found that patients in whom sepsis reversal did not occur within 1 week of initial PCD insertion had a significantly higher chance of eventual PCD failure. This finding was a significant marker of failure in the previous study as well.[13] However, over the last 10 years, we have come to realize that improvement in clinical condition secondary to PCD can often occur beyond 72 hours or even beyond 1 week. In our current study, there were 32 patients (10.5%) who did not have reversal of sepsis within 1 week after initial PCD insertion but had successful outcome ultimately with PCD alone. This demonstrates that there is merit in waiting for a longer time in a patient who shows partial clinical

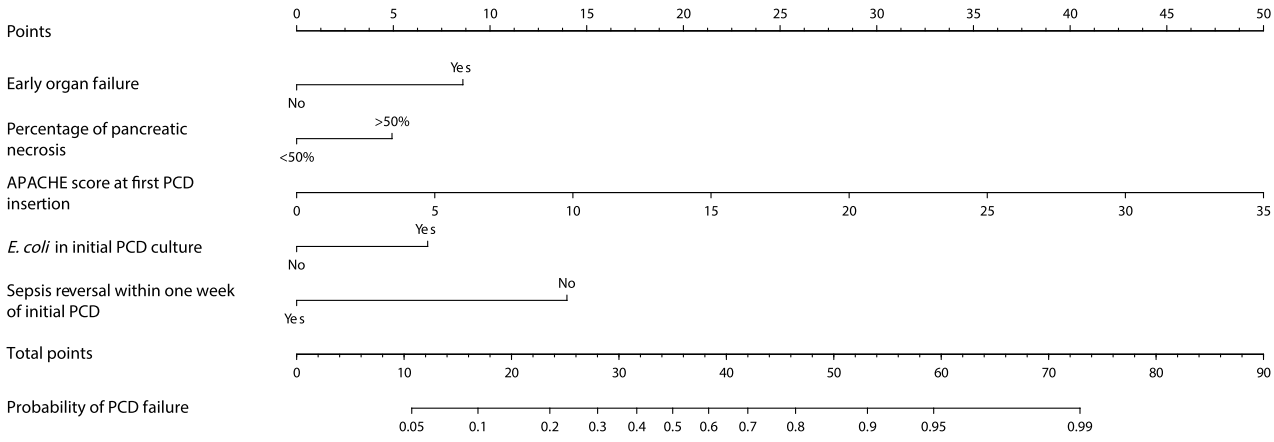

FIGURE 2. Post-PCD nomogram for predicting the probability of PCD failure.

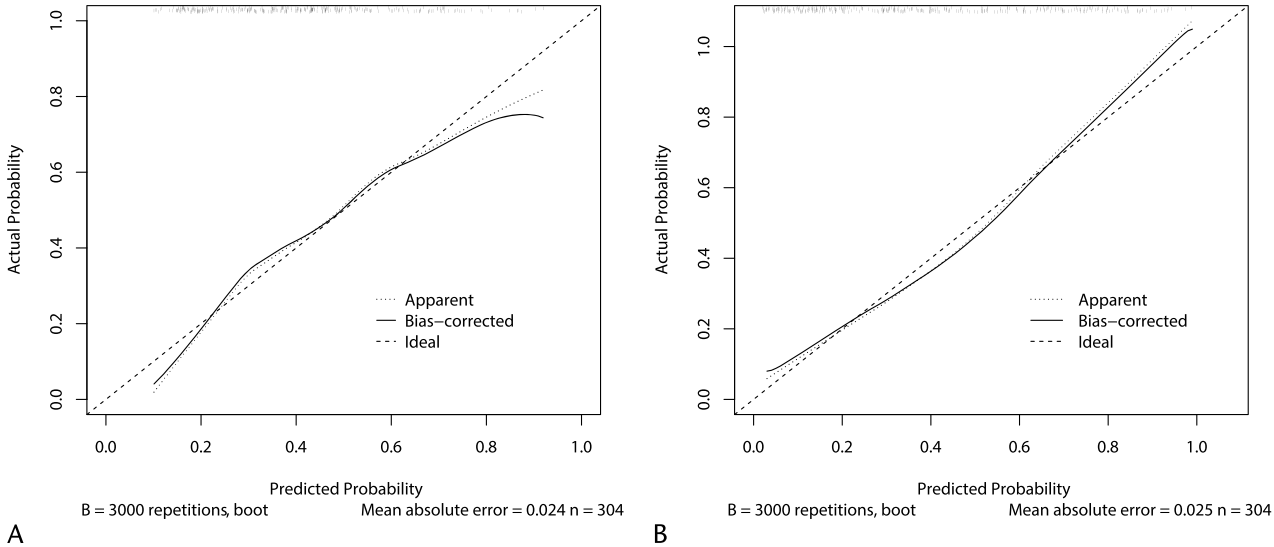

FIGURE 3. Calibration curve for (A) pre-PCD nomogram and (B) post-PCD nomogram. The bias corrected curve and the ideal curve nearly approximate each other, indicating a well-calibrated nomogram.

response. Such patients can be reimaged, and any residual/persistent collections can be managed by upsizing or putting additional PCDs, and increasing the volume of irrigation.

Previously, 2 studies have evaluated impact of post-PCD factors on eventual outcome of PCD. Cao et al[23] in a study of 74 patients identified extent of pancreatic necrosis, multiorgan failure, and reduction of fluid collection to less than 50% within 3 days of PCD insertion as factors associated with PCD failure. The model-predicted AUROC was 0.827, which is comparable with the present study. However, our study has larger sample size and more robust internal validation with a bootstrap of 3000 resamples compared with 200 in their study. Our post-PCD model also included sepsis reversal, which is a clinical parameter, as opposed to a purely radiological marker, that is, reduction in the size of the cavity.

In another post-PCD model reported by Ji et al,[24] which looked at factors 3 days after PCD insertion, the authors observed that mean CT density, multiorgan failure, and serum procalcitonin levels predicted the necessity of surgical necrosectomy with a sensitivity of 63.5% and specificity of 69.0%. The authors used cutoff value of serum procalcitonin greater than 1.9 μg/mL with a sensitivity of 61% and specificity of 59.5% to predict PCD failure. However, procalcitonin is not a specific marker of infection of pancreatic origin, and elevated values may be caused by extrapancreatic infections as well. In such a scenario, a delta value comparing pre-PCD and post-PCD levels may be more useful than a single value. It is generally believed that collections that are well-encapsulated and have homogenous or predominantly liquid contents are more amenable to PCD.[21] Ji et al[24] reported that mean CT density (in Hounsfield units [HU]) of necrotic fluid collection was predictive of PCD failure and need for surgery. Mean HU value of greater than 20 HU was 68.2% sensitive and 68.1% specific for predicting need for necrosectomy. However, calculating mean CT density of collections is a time-consuming and labor-intensive exercise and is not routinely performed in most centers unless done as part of protocol. We feel that a trial of PCD and saline irrigation for 5 to 6 days is worthwhile, even in collections with significant amount of solid debris. Using this protocol, we have been able to manage 49 patients with complete or near-complete pancreatic necrosis and 71 patients with more than 50% pancreatic necrosis successfully with PCD. We generally institute high-volume irrigation after PCD insertion and wait for 5 to 6 days before decision of surgery is made. In the study by Ji et al,[24] the authors have reported PCD success rate of 35.3%, which is considerably below 55.7% reported in a systematic review[6] and the present study.

In the current study, the majority (269 patients, 88.4%) of patients had infected necrosis. We found that bacterial infection of necrosis per se was not a factor influencing the outcome of PCD. However, the growth of *E. coli* in initial PCD culture was significantly associated with PCD failure. This is a finding that has not been reported previously. Although we do not have any evidence for a causal association of *E. coli* for PCD failure, we believe that the problem is one of multidrug resistance (MDR). *Escherichia coli* is one of the commonest organisms isolated from cultures of infected necrosis.[2,25,26] In the present study, the prevalence of *E. coli* was 49.7%. In our last hospital antibiogram, nearly 60% of *E. coli* isolates were found to be resistant to β-lactam/β-lactam inhibitors, and more than 20% were resistant to carbapenems (unpublished data, Antimicrobial Susceptibility Data 2017, PGIMER, Chandigarh, India). Most of the patients had received antimicrobials before referral, which were often broad spectrum agents. It is known that infections caused by MDR pathogens carry a higher burden of morbidity and mortality. In a study from the Mayo Clinic, up to 20% of *E. coli* isolates were found to be multidrug resistant.[27] In a study from another tertiary center in North India,[26] infection with MDR organisms was termed as *complicated IPN* and was associated with significantly higher mortality (25% vs 85%). In their study, *E. coli* was the commonest isolated organism and also most common MDR organism isolated. We did not find a significant association with *Klebsiella pneumoniae* and *Acinetobacter baumannii* in our study, although majority of these are MDR. This could perhaps be because of relatively smaller numbers of these isolates and the fact that their isolation was not uniformly distributed temporally through the period of the study with majority of them being reported in the last 4 years. It is likely that, in the coming years, they may also contribute significantly to worse prognosis. Further studies on the step-up approach should focus on the bacteriological aspect of infected necrosis as well.

Recognizing the dynamic nature of necrotizing pancreatitis, we have designed pre-PCD and post-PCD models. We believe that pre-PCD nomogram will be useful at time of admission and post-PCD nomogram will be useful to predict course of disease after initial PCD insertion, ideally at anytime within the first week after

PCD insertion. Points are awarded for a factor if the patient has that risk factor. The sum of all points awarded constitutes the total score. The higher the score a patient has, the higher the probability the patient has of failing the PCD. We expect the pre-PCD nomogram to have greatest application in primary and secondary centers. This model is likely to help primary care providers to tailor the management strategy at time of admission and allow timely referral of high-risk patients to tertiary care centers. Likewise, the post-PCD nomogram would serve as a useful guide to internists and gastroenterologists to involve surgical colleagues early in the course of illness.

We acknowledge that the major limitation of the present study is its retrospective nature. The other drawback is that it is a study from a single center with a dedicated multidisciplinary team having special interest in management of SAP. This may also be one of the reasons for higher success rate of PCD in the present study, which is very labor intensive and requires unique expertise. Finally, our models were internally validated with bootstrap resampling and need external validation. In conclusion, the present retrospective study with prospective database of last 10 years had a PCD success rate of nearly 60% using saline irrigation, with a mortality of 22%. The study provides 2 robust and comprehensive nomograms (71.1% AUROC for pre-PCD and 81.2% AUROC for post-PCD) for prediction of PCD outcome. The pre-PCD model includes APACHE II score at admission, early organ failure, and percentage of necrosis of greater than 50%. The post-PCD model includes APACHE II score at first PCD, early organ failure, percentage of necrosis of greater than 50%, sepsis reversal within 1 week of first PCD, and growth of *E. coli* in initial PCD culture. Both nomograms can be easily applied in clinical practice.

REFERENCES

1. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101:2379–2400.
2. Büchler MW, Gloor B, Müller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Ann Surg*. 2000;232:619–626.
3. Rau B, Bothe A, Beger HG. Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in a 19-year, single-center series. *Surgery*. 2005;138:28–39.
4. van Santvoort HC, Besselink MG, Bakker O, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *New Eng J Med*. 2010;362:1491–1502.
5. van Grinsven J, van Brunschot S, Bakker OJ, et al. Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study. *HPB (Oxford)*. 2016;18:49–56.
6. van Baal MC, van Santvoort HC, Bollen TL, et al. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Br J Surg*. 2011;98:18–27.
7. Brown L, Hong J, Petrov M, et al. The use of gastric juice to aid in liquefaction and drainage of pancreatic necrosis. *HPB (Oxford)*. 2016;18(suppl 1):e327–e328.abstract EP02A-027.
8. Gupta R, Gupta R, Kang M, et al. Mo1342 use of streptokinase for enhancement of percutaneous drainage of pancreatic necrosis: a double blinded randomized controlled trial. *Gastroenterology*. 2015;148(suppl 1):S-677.abstract.
9. Shenvi S, Gupta R, Kang M, et al. Timing of surgical intervention in patients of infected necrotizing pancreatitis not responding to percutaneous catheter drainage. *Pancreatology*. 2016;16:778–787.
10. Sugimoto M, Sonntag DP, Flint GS, et al. Better outcomes if percutaneous drainage is used early and proactively in the course of necrotizing pancreatitis. *J Vasc Interv Radiol*. 2016;27:418–425.
11. van Grinsven J, Timmerman P, van Lienden KP, et al. Proactive versus standard percutaneous catheter drainage for infected necrotizing pancreatitis. *Pancreas*. 2017;46:518–523.
12. Becker V, Huber W, Meining A, et al. Infected necrosis in severe pancreatitis—combined nonsurgical multi-drainage with directed transabdominal high-volume lavage in critically ill patients. *Pancreatology*. 2009;9:280–286.
13. Babu RY, Gupta R, Kang M, et al. Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. *Ann Surg*. 2013;257:737–750.
14. Zhang Z, Kattan MW. Drawing Nomograms with R: applications to categorical outcome and survival data. *Ann Transl Med*. 2017;5:211.
15. Harrell FE Jr. rms: Regression Modeling Strategies. R package version 5.1-2. January 7, 2018. Available at https://CRAN.R-project.org/package=rms. Accessed December 18, 2018.
16. Brown M. rmda: Risk Model Decision Analysis. R package version 1.6. July 17, 2018. Available at https://CRAN.R-project.org/package=rmda. Accessed December 18, 2018.
17. Garg PK, Madan K, Pande GK, et al. Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. *Clin Gastroenterol Hepatol*. 2005;3:159–166.
18. Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. *Br J Surg*. 1999;86:1020–1024.
19. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut*. 2004;53:1340–1344.
20. Thandassery RB, Yadav TD, Dutta U, et al. Dynamic nature of organ failure in severe acute pancreatitis: the impact of persistent and deteriorating organ failure. *HPB (Oxford)*. 2013;15:523–528.
21. Hollemans RA, Bollen TL, van Brunschot S, et al. Predicting success of catheter drainage in infected necrotizing pancreatitis. *Ann Surg*. 2016;263:787–792.
22. Rao SN, Kumar Gupta A, Karigoudar A, et al. A comparative study of Marshall score versus APACHE-II score in assessing severity of acute pancreatitis. *Hellenic J Surg*. 2016;88:5–12.
23. Cao X, Cao F, Li A, et al. Predictive factors of pancreatic necrosectomy following percutaneous catheter drainage as a primary treatment of patients with infected necrotizing pancreatitis. *Exp Ther Med*. 2017;14:4397–4404.
24. Ji L, Wang G, Li L, et al. Risk factors for the need of surgical necrosectomy after percutaneous catheter drainage in the management of infection secondary to necrotizing pancreatitis. *Pancreas*. 2018;47:436–443.
25. Beger HG, Bittner R, Block S, et al. Bacterial contamination of pancreatic necrosis. A prospective clinical study. *Gastroenterology*. 1986;91:433–438.
26. Jain S, Mahapatra SJ, Gupta S, et al. Infected pancreatic necrosis due to multidrug-resistant organisms and persistent organ failure predict mortality in acute pancreatitis. *Clin Transl Gastroenterol*. 2018;9:190.
27. Sannapaneni S, Sharma A, Vege SS. Sa1419 — multi-drug resistant *E. coli* is the commonest organism in infected pancreatic necrosis. *Gastroenterology*. 2018;154(suppl 1):S-299.abstract.