Retrospective Cohort Study

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Nomogram development and validation for predicting minimally invasive step-up approach failure in infected necrotizing pancreatitis patients: a retrospective cohort study

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Background: Previous studies have shown that minimally invasive treatment for infected necrotizing pancreatitis (INP) may be safer and more effective than open necrosectomy (ON), but ON is still irreplaceable in a portion of INP patients. Furthermore, there is a lack of tools to identify INP patients at risk of minimally invasive step-up approach failure (eventually received ON or died), which may enable appropriate treatment for them. Our study aims to identify risk factors that can predict minimally invasive step-up approach failure in INP patients and to develop a nomogram for early prediction.

Methods: Multivariate logistic regression was performed to evaluate the association between minimally invasive step-up approach failure and factors regarding demographics, disease severity, laboratory index, and the location of extrapancreatic necrotic collections. A novel nomogram was developed, and its performance was validated both internally and externally by its discrimination, calibration, and clinical usefulness.

Results: There were 267, 89, and 107 patients in the training, internal, and external validation cohorts, respectively. Multivariate logistic regression demonstrated that the computed tomography severity index (CTSI) greater than 8 points, Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 16 points or more, early spontaneous bleeding, fungi infection, granulocyte and platelet decrease within 30 days of acute pancreatitis onset, and extrapancreatic necrosis collection located in small bowel mesentery were independent risk factors for minimally invasive step-up approach failure. The area under the curve and coefficient of determination (R^2) of the nomogram constructed from the above factors were 0.920 and 0.644, respectively. The Hosmer–Lemeshow test showed that the model had good fitness ($P = 0.206$). In addition, the nomogram performed well in both the internal and external validation cohorts.

Conclusions: The nomogram had a good performance in predicting minimally invasive step-up approach failure, which may help clinicians distinguish INP patients at risk of minimally invasive step-up approach failure early.

Keywords: failure, infected necrotizing pancreatitis, minimally invasive step-up approach, open necrosectomy, prediction model

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal disorders with an incidence of 13–45 cases per 100 000 persons every year[1]. Although AP is mild in most patients, pancreatic necrosis develops in ~20% of them and the mortality rate is ~15%, and up to 30% for cases of infected necrotizing pancreatitis (INP), which can lead to sepsis and multiple organ failure resulting in increased mortality and longer hospital stay[2–4].

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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The approach of INP management has evolved significantly over the last 20 years and continues to evolve as experience, new techniques, and research data accumulate[5]. For suspected or confirmed INP, the 'step-up' approach, an optimal interventional strategy for draining/debriding the necrosis collection including catheter drainage (CD), minimally invasive necrosectomy (MIN), and open necrosectomy (ON), has been suggested in the IAP (International Association of Pancreatology)/APA (American Pancreatic Association) evidence-based guidelines[1,6–8]. Though previous studies have shown that this minimally invasive step-up approach was safe and effective in draining/debriding necrosis collection, there are still many INP patients who inevitably received ON or died as previous studies described[9–12]. Early identification of INP patients at risk of minimally invasive step-up approach failure (eventually received ON or died) may enable appropriate treatment for them[13].

In an international study involving 1980 acute necrotizing pancreatitis (ANP) patients, ON was still considered as a reasonable treatment option in low-risk and intermediate-risk patients[14]. Furthermore, Huang *et al.*[15] proposed that INP patients who are likely to require surgical intervention should be offered a step-jump (primary ON) treatment strategy rather than the standard step-up sequence of therapeutic procedures. Therefore, clinical prediction models are needed to identify those at risk of minimally invasive step-up approach failure (eventually received ON or died). Recently, there were several studies have investigated the risk factors of catheter drainage failure (CDF) or minimally invasive necrosectomy failure (MINF) and built several clinical prediction models, but all with a limited sample size. From then on, no prediction model of minimally invasive step-up approach failure has been reported.

Therefore, the purpose of this study is to identify independent risk factors for minimally invasive step-up approach failure and construct a predictive model for further validation.

HIGHLIGHTS

- There is a lack of tools in predicting minimally invasive step-up approach failure (MIF).
- We found several independent risk factors for MIF and constructed a nomogram.
- Pancreatic necrosis in small bowel mesentery may require primary open necrosectomy.
- The nomogram performs well in predicting MIF, which may help clinical decision-making.

Materials and methods

Study design and population

This study is a retrospective cohort study. The study cohort was consecutive INP patients admitted to a tertiary referral center from January 2017 to December 2020. Data were extracted from an electronic database of acute pancreatitis (AP database) with the approval of the Acute Pancreatitis Database Management Committee (2019NZKY-003-03), and all the analyses were conducted under the committee's regulation. We divided all INP patients of the study cohort into the training cohort and internal validation cohort in a 3:1 ratio randomly. The external validation cohort was consecutive INP patients admitted to another tertiary referral center from 1st January 2019 to 31st December 2020. Data were extracted from a prospectively maintained database with the approval of the Ethics Committee (No: 2011001). Routine written informed consent was obtained for data collection, storage, and academic use of data from all patients or their next of kin at admission. The inclusion criteria were as follows: diagnosis of INP[16]; the time from AP onset to admission is less than 30 days; received surgical interventions (including CD, MIN, and ON) in our center. The exclusion criteria were as follows: patients with surgical interventions recorded incompletely;

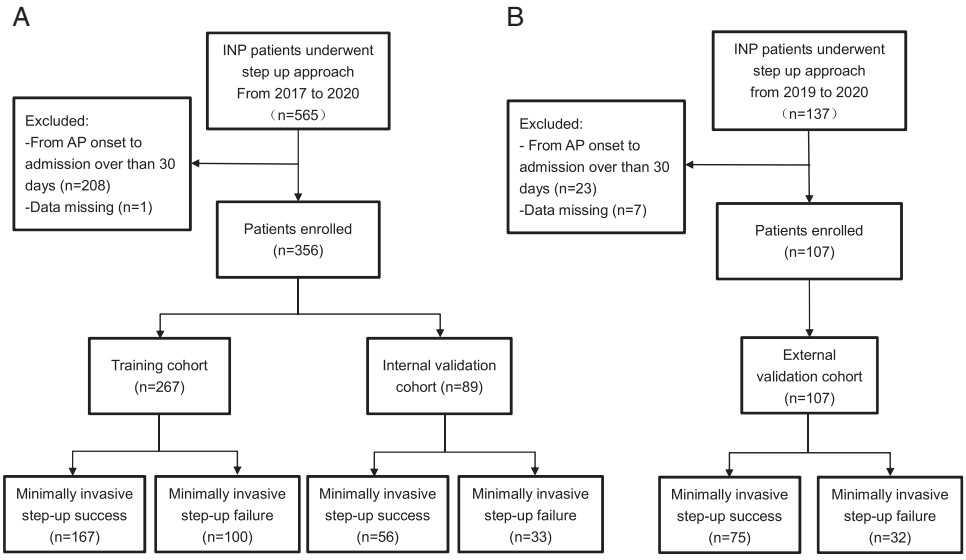

Figure 1. Flowchart for patient selection. (A) Training cohort and internal validation cohort. (B) External validation cohort. AP, acute pancreatitis; ANP, acute necrotizing pancreatitis.

Table 1

General characteristics.

Variables	The study cohort (training and internal validation, $n=356$), *N* (%)	Minimally invasive step-up, *N* (%)			Cohort, *N* (%)		
		Success ($n=223$)	Failure ($n=133$)	*P*	Training ($n=267$)	Internal validation ($n=89$)	External validation ($n=107$)
Age, year				0.414			
< 34	89 (25)	61 (27.4)	28 (21.1)		70 (26.2)	19 (21.3)	14 (13.1)
34–55	183 (51.4)	111 (49.8)	72 (54.1)		131 (49.1)	52 (58.4)	68 (63.6)
< 55	84 (23.6)	51 (22.9)	33 (24.8)		66 (24.7)	18 (20.2)	25 (23.4)
Gender				0.837			
Female	104 (29.2)	66 (29.6)	38 (28.6)		73 (27.3)	31 (34.8)	45 (42.1)
Male	252 (70.8)	157 (70.4)	95 (71.4)		194 (72.7)	58 (65.2)	62 (57.9)
BMI, kg/m^2				0.002			
< 24	133 (37.4)	99 (44.4)	34 (25.6)		99 (37.1)	32 (36)	55 (51.4)
24–27.9	156 (43.8)	86 (38.6)	70 (52.6)		119 (44.6)	37 (41.6)	36 (33.6)
≥ 28	67 (18.8)	38 (17.0)	29 (21.8)		49 (18.3)	20 (22.4)	16 (15.0)
Etiology				0.814			
Biliary	192 (53.9)	122 (54.7)	70 (52.6)		138 (51.7)	54 (60.7)	50 (46.7)
Hypertriglyceridemia	143 (40.2)	87 (39.0)	56 (42.1)		112 (41.9)	31 (34.8)	42 (39.3)
Others	21 (5.9)	14 (6.3)	7 (5.3)		17 (6.4)	4 (4.5)	15 (14.0)
CTSI				< 0.001			
≤ 8	260 (73.0)	198 (88.8)	62 (46.6)		198 (74.2)	62 (69.7)	77 (72.0)
> 8	96 (27.0)	25 (11.2)	71 (53.4)		69 (25.8)	27 (30.3)	30 (28.0)
APACHE II				< 0.001			
< 8	90 (25.3)	83 (37.2)	7 (5.3)		68 (25.5)	22 (24.7)	42 (39.3)
8–16	183 (51.4)	120 (53.8)	63 (47.4)		136 (50.9)	47 (52.8)	55 (51.4)
> 16	83 (23.3)	20 (9.0)	63 (47.4)		63 (23.6)	20 (22.5)	10 (9.3)
Bloodstream infection	44 (12.4)	13 (5.9)	31 (23.3)	< 0.001	34 (12.8)	10 (11.2)	22 (20.6)
Fungi infection				< 0.001			
None	311 (87.4)	213 (95.5)	98 (73.7)		235 (88)	76 (85.4)	81 (75.7)
≤ 14 days	10 (2.8)	6 (2.7)	4 (3.0)		7 (2.6)	3 (3.4)	11 (10.3)
≤ 30 days	35 (9.8)	4 (1.8)	31 (23.3)		25 (9.4)	10 (11.2)	15 (14.0)
ESB	75 (21.3)	19 (8.6)	57 (42.9)	< 0.001	57 (21.5)	19 (21.3)	19 (17.8)
Platelet decrease				< 0.001			
None	241 (67.7)	185 (83.0)	56 (42.1)		176 (65.9)	65 (73)	76 (71.0)
≤ 14 days	51 (14.3)	19 (8.5)	32 (24.1)		42 (15.7)	9 (10.1)	26 (24.3)
≤ 30 days	64 (18.0)	19 (8.5)	45 (33.8)		49 (18.4)	15 (16.9)	5 (4.7)
Granulocyte decrease	79 (22.2)	34 (15.4)	45 (33.8)	< 0.001	59 (22.3)	20 (22.5)	18 (16.8)
First intervention time				< 0.001			
≥ 4 weeks	149 (41.9)	113 (50.7)	36 (27.1)		152 (56.9)	54 (60.7)	64 (59.8)
< 4 weeks	207 (58.1)	110 (49.3)	97 (72.9)		115 (43.1)	35 (39.3)	43 (40.2)
Nutrition							
Total enteral nutrition	249 (70.0)	204 (91.5)	45 (33.8)	< 0.001	188 (70.4)	61 (68.5)	61 (57.0)
Combined parenteral	72 (20.2)	19 (8.5)	53 (39.8)	< 0.001	52 (19.5)	20 (22.5)	42 (39.3)
Unfit for nutrition	35 (9.8)	0	35 (26.3)	< 0.001	27 (10.1)	8 (9.0)	4 (3.7)
Location of EPN							

Table 1

(*Continued*)

Variables	The study cohort (training and internal validation, $n=356$), *N* (%)	Minimally invasive step-up, *N* (%)			Cohort, *N* (%)		
		Success ($n=223$)	Failure ($n=133$)	*P*	Training ($n=267$)	Internal validation ($n=89$)	External validation ($n=107$)
Lesser omental bursa	330 (92.7)	203 (91.0)	127 (95.5)	0.118	244 (92.4)	83 (93.3)	100 (93.5)
Anterior pararenal region				< 0.001			
None	52 (14.6)	44 (19.7)	8 (6.0)		40 (15)	12 (13.5)	23 (21.5)
Right or left	149 (41.9)	98 (43.9)	51 (38.3)		110 (41.2)	39 (43.8)	44 (41.1)
Bilateral region	155 (43.5)	81 (36.3)	74 (55.6)		117 (43.8)	38 (42.7)	40 (37.4)
Posterior pararenal region				0.003			
None	200 (56.2)	138 (61.9)	62 (46.6)		151 (56.6)	49 (55.1)	70 (65.4)
Right or left	121 (34.0)	71 (31.8)	50 (37.6)		86 (32.2)	35 (39.3)	28 (26.2)
Bilateral region	35 (9.8)	14 (6.3)	21 (15.8)		32 (11.2)	5 (5.6)	9 (8.4)
Paracolic gutter				< 0.001			
None	109 (30.6)	83 (37.2)	26 (19.5)		82 (30.7)	27 (30.3)	26 (24.3)
Right or left	132 (37.1)	85 (38.1)	47 (35.3)		98 (36.7)	34 (38.2)	49 (45.8)
Bilateral region	115 (32.3)	55 (24.7)	60 (45.1)		87 (32.6)	28 (31.5)	32 (29.6)
Pelvis	54 (15.2)	21 (9.4)	33 (24.8)	< 0.001	42 (15.9)	12 (13.5)	36 (33.6)
Small bowel mesentery	135 (37.9)	58 (26.0)	77 (57.9)	< 0.001	99 (37.5)	36 (40.4)	37 (34.6)
Transverse mesocolon	232 (65.2)	136 (61.0)	96 (72.2)	0.032	176 (66.7)	54 (60.7)	41 (38.3)
Greater omentum	69 (19.4)	29 (13.0)	40 (30.3)	< 0.001	56 (21.3)	13 (14.6)	16 (15.0)
Death or surgery							
Death	48 (13.5)	0	48 (36.1)	< 0.001	100 (37.5)	33 (37.1)	32 (29.9)
ON	48 (13.5)	0	48 (36.1)	< 0.001			
Death after ON	37 (10.4)	0	37 (27.8)	< 0.001			

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CTSI, computed tomography severity index; EPN, extrapancreatic necrosis; ESB, early spontaneous bleeding; ON, open necrosectomy.

received ON before admission. This study follows the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement[17], Supplemental Digital Content 1, http://links.lww.com/JS9/A401 and reports in line with the STROCSS (strengthening the reporting of cohort, cross-sectional and case–control studies in surgery) criteria[18], Supplemental Digital Content 2, http://links.lww.com/JS9/A402.

Data collection and definition

The primary outcome of this study is minimally invasive step-up approach failure and it is defined as in-hospital death or requirement of escalation to ON following the step-up approach.

Baseline variables and potential risk factors for minimally invasive step-up approach failure were all extracted from the AP database as follows: demographics data (age, gender, BMI), etiology of AP, days from AP onset, the computed tomography severity index (CTSI) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, fungi infection, granulocyte and platelet decrease, the timing of the first surgical intervention, nutrition pathway (total enteral and combined parenteral nutrition), and the location of extrapancreatic necrosis collections (lesser omental bursa, anterior pararenal region, posterior pararenal region, paracolic gutter, pelvis, small bowel mesentery, transverse mesocolon, and greater omentum).

The diagnosis, etiology, and complications of AP were defined according to the 2012 revision of the Atlanta Classification[16]. Early spontaneous bleeding (ESB) was defined as when the bleeding could be detected on contrast-enhanced computed tomography within 30 days of AP onset without any prior minimally invasive or surgical intervention[19]. The definition of extrapancreatic necrosis (EPN) location referred to the previous research of Gupta *et al*.[20] All the study subjects underwent routine computed tomography (CT) examinations at admission according to a standard unenhanced/double-phase enhanced protocol. The application of additional monitoring CT scans is determined by the treating physician based on the clinical deterioration of patients. The extent and location of pancreatic (or extrapancreatic) necrosis were assessed by two senior radiologists, who reported the findings independently and were blinded to the patient's clinical information. All the controversial cases were reviewed and resolved through discussions.

Statistical analysis

Continuous data are reported as medians and interquartile ranges (IQR) and analyzed by Mann–Whitney's test. Categorical data are expressed as frequencies and percentages. The comparison of categorical data between groups was performed using the χ^2 test or Fisher's exact test.

Univariate and multivariate binary logistic regression analyses were performed. All risk factors reaching a univariate analysis P less than 0.2 were included in the multivariable logistic regression model using the backward elimination method. In this study, continuous variables were converted to dichotomous or trichotomous ones according to their median or IQR for age, CTSI, and APACHE II, and established obesity/overweight definitions for BMI[21]. We incorporated all the categorical variables as ordinal variables in the logistic model. A nomogram was formulated based on the results of multivariate logistic regression analysis. The nomogram is based on proportionally converting each regression coefficient in multivariate logistic regression from a 0-point to a 100-point scale. The effect of the variable with the highest β coefficient (absolute value) is assigned 100 points. The points are added across independent variables to derive total points, which are converted to predicted probabilities. No imputation was performed for missing data.

Afterward, the prediction model was validated internally and externally by the Hosmer–Lemeshow test and coefficient of determination (R^2) to assess the fitness of the model. The receiver operating characteristic (ROC) curve, area under the ROC curve (AUC), concordance index (C-index), and calibration curve were used to evaluate the accuracy and consistency of the models. The decision curve analysis (DCA) showed the net benefit of the models for clinical decisions. Discrimination and calibration were assessed by bootstrap methods with 1000 repetitions.

Statistical tests were two-sided, and P values less than 0.05 were considered significant. All data processing was done in SPSS 25 software and R 4.1.3 software (R Foundation for Statistical Computing).

Results

General characteristics

There were 267, 89, and 107 eligible patients in the training, internal validation, and external validation cohorts, respectively. The flowchart of the study is shown in Figure 1. The demographic and clinical characteristics of these three cohorts are summarized in Table 1 and Supplementary Table S1, Supplemental Digital Content 3, http://links.lww.com/JS9/A403. The baseline characteristics were roughly similar between the training and validation cohorts. Minimally invasive step-up approach failure occurred in 100 (37.5%), 33 (37.1%), and 32 (29.9%) patients in the two cohorts, respectively.

Risk factors prediction

All variables were enrolled into univariate and multivariate logistics regression analysis and the results are shown in Table 2. Nineteen variables in univariate logistics regression analysis that included BMI, CTSI score, APACHE II score, bloodstream infection, ESB, fungi infection, platelet decrease and granulocyte decrease within 30 days of AP onset, the timing of the first surgical intervention, nutrition pathway, and location of EPN showed a P value of less than 0.2.

Afterward, potential predictors were included in the multivariate logistics regression model, and seven factors were proved to be the independent predictors for minimally invasive step-up approach failure. The independent predictors included CTSI score greater than 8 points [odds ratio (OR): 5.097, 95% CI: 2.508–10.360], APACHE II score of 16 points or more (OR: 8.138, 95% CI: 2.761–23.990), ESB (OR: 5.632, 95% CI: 2.457–12.909), fungi infection (OR: 10.635, 95% CI: 2.773–40.792), platelet decrease (OR: 5.749, 95% CI: 2.505–13.194), granulocyte decrease (OR: 2.891, 95% CI: 1.357–6.161), and EPN located in small bowel mesentery (OR: 2.673, 95% CI: 1.382–5.169). The model incorporating CTSI and APACHE II as continuous variables yields similar results (Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/JS9/A403).

Table 2

Univariable and multivariable logistic regression: risk factors for outcome.

	Univariable ($P < 0.2$)		Multivariable ($P < 0.05$)	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, year				
< 34	1			
34–55	1.413 (0.826–2.417)	0.207		
> 55	1.410 (0.754–2.636)	0.282		
Gender, Male	1.051 (0.655–1.687)	0.837		
BMI, kg/m^2				
< 24	1			
24–27.9	2.370 (1.436–3.913)	< 0.001		
≥ 28	2.222 (1.194–4.134)	0.012		
Etiology				
Biliary	1			
Hypertriglyceridemia	1.122 (0.718–1.753)	0.614		
Others	0.871 (0.336–2.262)	0.777		
CTSI				
≤ 8	1		1	
> 8	9.070 (5.297–15.528)	< 0.001	5.097 (2.508–10.360)	< 0.001
APACHE II				
< 8	1		1	
8–16	6.225 (2.716–14.269)	< 0.001	2.133 (0.829–5.487)	0.116
> 16	37.350 (14.871–93.809)	< 0.001	8.138 (2.761–23.990)	< 0.001
Bloodstream infection	4.863 (2.440–9.691)	< 0.001		
Fungi infection				
None	1		1	
≤ 14 days	1.449 (0.400–5.251)	0.572	1.003 (0.189–5.320)	0.997
≤ 30 days	16.844 (5.787–49.030)	< 0.001	10.635 (2.773–40.792)	< 0.001
ESB	7.974 (4.454–14.275)	< 0.001	5.632 (2.457–12.909)	< 0.001
Platelet decrease				
None	1			
≤ 14 days	5.564 (2.929–10.568)	< 0.001	1.923 (0.752–4.915)	0.172
≤ 30 days	7.824 (4.235–14.457)	< 0.001	5.749 (2.505–13.194)	< 0.001
Granulocyte decrease	2.812 (1.685–4.695)	< 0.001	2.891 (1.357–6.161)	0.006
First intervention time ≤ 4 weeks	2.768 (1.741–4.402)	< 0.001		
Nutrition				
Total enteral	0.048 (0.026–0.086)	< 0.001		
Combined parenteral	7.113 (3.965–12.760)	< 0.001		
Location of EPN				
Lesser omental bursa	2.085 (0.816–5.333)	0.125		
Anterior pararenal region				
None	1			
Right or left	2.862 (1.253–6.537)	0.013		
Bilateral region	5.025 (2.221–11.370)	< 0.001		
Posterior pararenal region				
None	1			
Right or left	1.567 (0.980–2.507)	0.061		
Bilateral region	3.339 (1.593–6.995)	< 0.001		
Paracolic gutter				
None	1			
Right or left	1.765 (1.002–3.110)	0.049		
Bilateral region	3.483 (1.964–6.174)	< 0.001		
Pelvis	3.174 (1.747–5.768)	< 0.001		
Small bowel mesentery	3.912 (2.479–6.172)	< 0.001	2.673 (1.382–5.169)	0.003
Transverse mesocolon	1.660 (1.043–2.642)	0.033		
Greater omentum	2.909 (1.697–4.984)	< 0.001		

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CTSI, computed tomography severity index; EPN, extrapancreatic necrosis; ESB, early spontaneous bleeding; OR, odds ratio.

Development and validation of a minimally invasive step-up approach failure-predicting nomogram

Seven independent risk factors were used to form the nomogram in predicting minimally invasive step-up approach failure (Fig. 2). The regression model was internally validated using the bootstrap validation method ($B = 1000$ repetitions) and the Hosmer–Lemeshow test demonstrated that the model had a good fitness ($P = 0.206$). The nomogram demonstrated good accuracy in

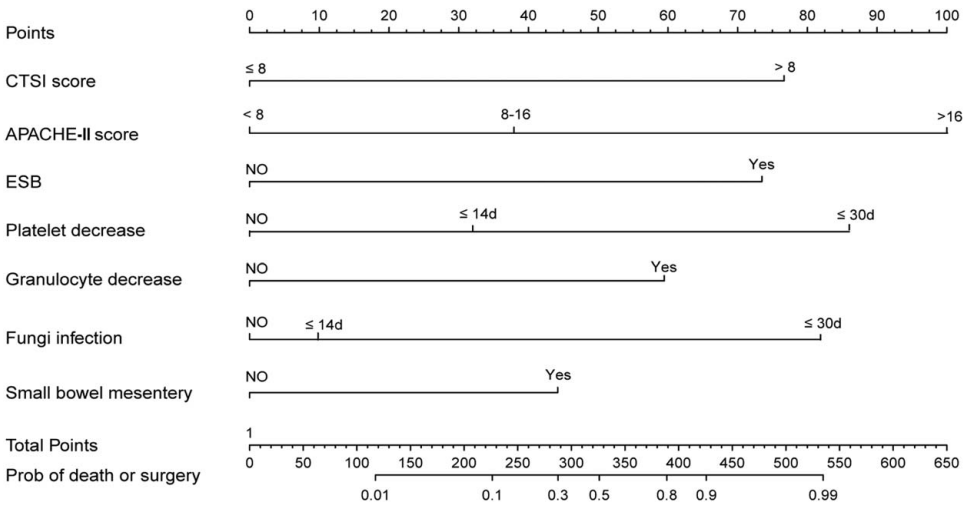

Figure 2. Nomogram for predicting minimally invasive step-up approach failure. APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CTSI, the computed tomography severity index; ESB, early spontaneous bleeding.

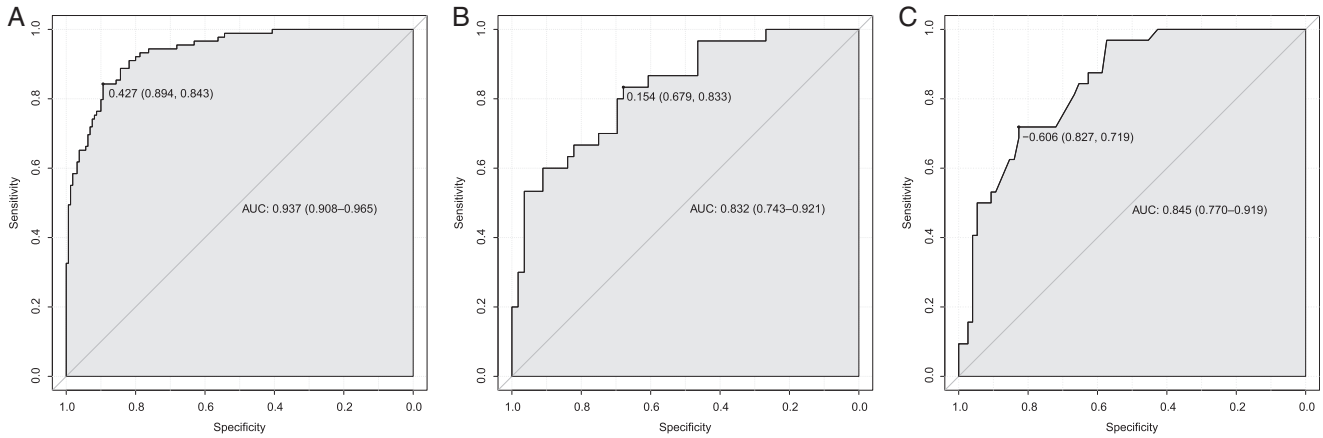

Figure 3. Receiver operating curves. (A) Training cohort. (B) Internal validation cohort. (C) External validation cohort. AUC, area under the ROC (receiver operating characteristic) curve.

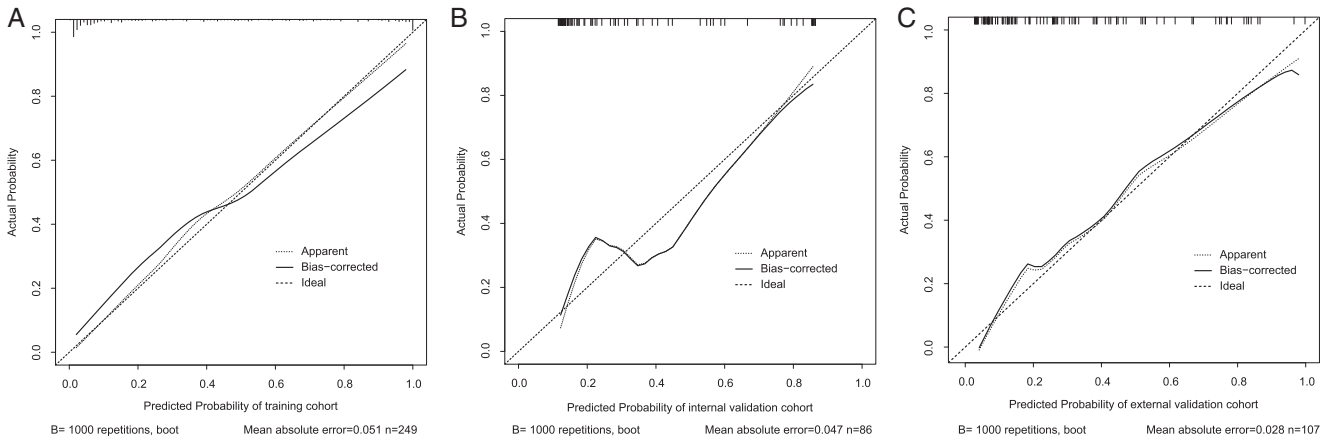

Figure 4. Calibration curves for predicting the probability of minimally invasive step-up approach failure. (A) Training cohort. (B) Internal validation cohort. (C) External validation cohort.

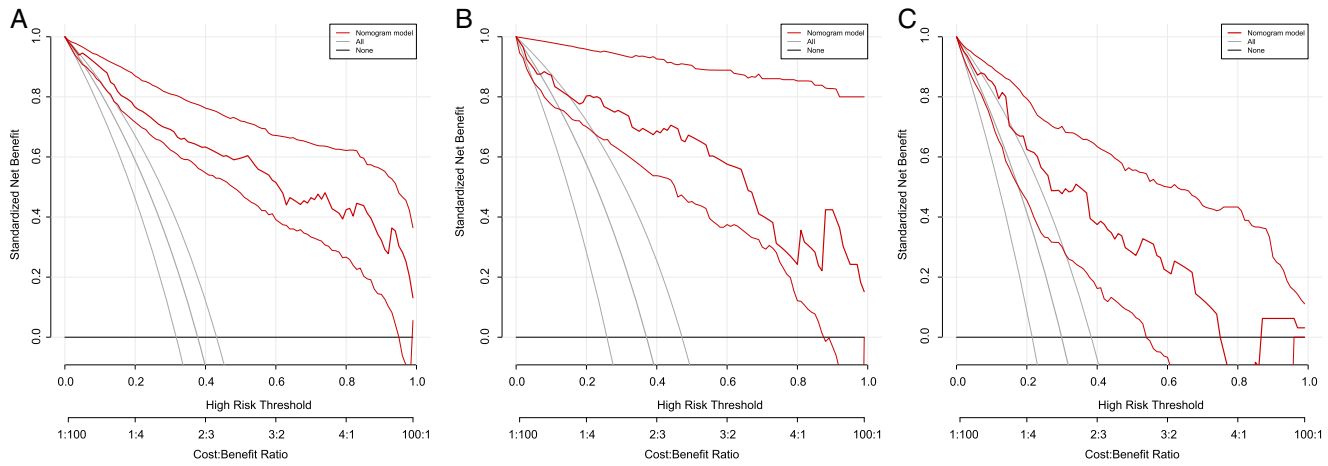

Figure 5. Decision curve analysis in the prediction of minimally invasive step-up approach failure. (A) Training cohort. (B) Internal validation cohort. (C) External validation cohort.

estimating the risk of minimally invasive step-up approach failure, with an AUC of 0.920 (95% CI, 0.893-0.948) and $R^2 = 0.644$. For each patient, higher total points indicated a higher risk of minimally invasive step-up approach failure. The nomogram developed by the model incorporating CTSI and APACHE II as continuous variables yields similar results, with a similar AUC of 0.928 (Supplementary Figures S1, S2, Supplemental Digital Content 3, http://links.lww.com/JS9/A403).

In the training cohort, the AUC and R^2 were 0.937 and 0.691, respectively (Fig. 3A), and the calibration curve was close to the ideal diagonal line (Fig. 4A). Furthermore, the DCA showed a significant net benefit in the prediction model (Fig. 5A). In the internal validation cohort, 89 patients were used for testing the nomogram. The AUC was 0.832 (Fig. 3B), showing a good accuracy of the nomogram. Meanwhile, the calibration curve of the validation cohort was also close to the ideal diagonal line (Fig. 4B). Moreover, the DCA in the internal validation cohort also showed a significant net benefit of the prediction model (Fig. 5B). In the external validation cohort, 107 patients were used for testing the nomogram; the AUC and R^2 were 0.845 and 0.411, respectively (Fig. 3C), suggesting good accuracy of the nomogram. Meanwhile, the calibration curve of the validation cohort was also close to the ideal diagonal line (Fig. 4C). Moreover, the DCA in the external validation cohort also showed a significant net benefit of the prediction model (Fig. 5C).

Discussion

The step-up approach was gradually accepted since Besselink *et al.* conducted the PANTER (PAncreatitis, Necrosectomy versus sTEp up appRoach) trial to compare the efficacy of primary ON with the step-up approach in patients with INP[6,22]. However, when to initiate the primary ON instead of following the step-up approach is still unknown. Our study revealed that CTSI scores greater than 8 points, APACHE II scores of 16 points or more, ESB, fungi infection, platelet and granulocyte decrease within 30 days of AP onset, and EPN located in small bowel mesentery were independent risk factors of minimally invasive step-up approach failure (eventually received ON or died). INP patients who meet these factors may be at high risk of minimally invasive step-up approach failure and may benefit from an alternative approach, while the classic minimally invasive step-up approach should remain the choice of treatment for those at low risk.

Several studies have strived to identify patients requiring primary ON or suffering minimally invasive interventions failure. Babu *et al.* found that renal failure, APACHE II score at the first intervention, and the number of bacteria isolated per patient are independent predictors of ON[23]. Besides, the Dutch Pancreatitis Study Group found male sex, multiple organ failure, increased percentage of pancreatic necrosis, and heterogeneity of the collection on CT are predictors for CDF in INP patients[24]. Furthermore, Garret *et al.* conducted a retrospective study investigating the external validity of the Dutch nomogram and found several additional predictors of CDF, including BMI, heterogeneous collection, and respiratory failure onset within 24 h before the first CD[25]. Our study differs from these studies in several aspects: First, we included a greater number of patients (356 INP patients, with 133 suffering minimally invasive step-up approach failure), which allowed us to investigate more potential predictors. Second, Garret *et al.*'s study indicated a significant association between BMI and CDF, but it had not been validated by other studies[25]. On the contrary, our study did not show a significant association between BMI and minimally invasive step-up approach failure, nor did other studies[26,27]. However, there are also some similarities in our results. First, APACHE II score and single or multiple organ failure were the two strongest predictors in their study[23–25], which is consistent with our findings. This could be explained by the fact that multiple organ failure is significantly associated with mortality in AP, increasing the rate of minimally invasive step-up approach failure[28,29]. Second, the Dutch Pancreatitis Study Group found that the increased percentage of pancreatic necrosis was a predictor for CDF in INP patients[24], which was consistent with our results in the CTSI score[30].

In the multivariate analysis, fungi infection within 30 days after the onset of ANP was found to be an independent predictor for minimally invasive step-up approach failure, which is similar to the studies of Moka *et al*.[31] and Guru *et al*.[32] They found that fungal infection was associated with increased mortality rate, prolonged hospital stay, and ICU stay[32]; moreover, patients with fungal infection can present with fulminant septic shock[31], suggesting that fungal infection may contribute to the further requirement of ON by worsening the clinical condition of patients. In addition, low platelet and neutrophil count within 30 days of AP onset were also found to be the independent risk factors for minimally invasive step-up approach failure. Previous studies demonstrated that both the decreased platelet count and granulocyte count were indicators of AP severity and associated with worse prognosis, including persistent OF and increased risk of infected pancreatic necrosis[33–37], which could partly explain their relationship with minimally invasive step-up approach failure. However, the role of decreased platelet and granulocyte count in predicting minimally invasive step-up approach failure still needs further validation.

The ESB was also an independent predictor for minimally invasive step-up approach failure in this study. Our previous study has demonstrated that ESB developed in 3.2% of severe acute pancreatitis patients, and ESB patients were more likely to suffer much more severe conditions compared with non-bleeding as well as post-intervention massive bleeding patients, with a mortality of up to 54%[19]. Furthermore, Flati *et al*. considered that massive hemorrhage was more frequently associated with massive pancreatic necrosis, with a mortality rate of 37.9%, intraperitoneal arterial bleeding should be controlled by early angiographic embolization, and primary ON should be considered as a complementary method[38]. Overall, ESB is significantly associated with the deterioration of AP, which may affect the success of a minimally invasive step-up approach.

Nowadays, more complex collections may require transluminal instrumentation with lavage, debridement, and necrosectomy[39], and the location of pancreatic necrosis may affect the success of a minimally invasive step-up approach. In our study, necrotic collection located in small bowel mesentery was also an independent predictor for minimally invasive step-up approach failure and was included in our predictive model. However, our results are contrary to Gupta *et al*.'s[20] study, which found that the site and size of EPN were associated with the severity and clinical outcomes of AP patients, while no association between the location of pancreatic collection and ON requirement was found. Several reasons may explain this discrepancy: First, Gupta *et al*.[20] included relatively fewer patients with EPN in certain locations compared with us, which may introduce some bias. Second, collections in small bowel mesentery, transverse mesocolon, sigmoid mesocolon, and omentum were seen as a whole group in their study[20], but in our research, each of them was a separate group, which may improve the accuracy of the findings. Overall, more research is needed to confirm these findings in the future.

In this study, our nomogram performed well in predicting minimally invasive step-up approach failure in both the training and validation cohorts, with good accuracies, consistencies, calibrations, and net benefits. Furthermore, to our knowledge, this is the first study to predict minimally invasive step-up approach failure and detected some rarely used variables, such as fungi infection, platelet decrease, and locations of EPN collections. Using this tool, we are better poised to identify those at risk of failure with conventional minimally invasive procedures, and a step-jump strategy (primary ON) or other techniques may suit them better. Specifically, techniques that are more efficient for debridement or can reach the necrotic collection located in the small bowel mesentery should be considered.

Moreover, there are several limitations to our investigation: First, the chief limitation might be that it was a single-center retrospective study, and internal bias cannot be avoided. Secondly, our center is one of the largest tertiary referral pancreatitis centers in China, and almost all patients were tertiary referrals, inevitably leading to the loss of pre-hospital clinical data. Finally, although we conducted both internal and external validations, it is still desirable to perform more prospective studies to validate our findings.

Conclusions

In this study, we found that higher CTSI score, APACHE II score, ESB, fungi infection, decreased platelet and granulocyte count within 30 days of AP onset, and extrapancreatic necrotic collection located in small bowel mesentery were independent risk factors for minimally invasive step-up approach failure in INP patients. Using these independent predictors, we built a nomogram and it may help clinicians early distinguish INP patients at risk of minimally invasive step-up approach failure so that they can be treated more appropriately.

Ethical approval

This retrospective study meeting the ethical standards of the Helsinki Declarations was approved by the Acute Pancreatitis Database Management Committee of Jinling Hospital (2019NZKY-003-03) and the Ethics Committee of the First Affiliated Hospital of Nanchang University (No: 2011001).

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Author contribution

G.L.: conceptualization, data curation, funding acquisition, validation, and writing – review and editing; S.L.: data curation, formal analysis, software, visualization, writing – original draft, and writing – review and editing; L.C.: data curation, formal analysis, methodology, software, writing – original draft, and writing – review and editing; W.M.: data curation, formal analysis, methodology, funding acquisition, writing – original draft, and writing – review and editing; J.Z.: data curation and writing – review and editing; B.Y.: data curation and writing – review and editing; J.Z. and L.D.: data curation and writing – review and editing; Y.Z.: resources, data curation, and writing – review and editing; L.K.: conceptualization, funding acquisition, supervision, resources, and writing –

review and editing; Y.L.: methodology, supervision, validation, and writing – review and editing; Z.T.: conceptualization, supervision, resources, and writing – review and editing; W.L.: conceptualization, supervision, resources, writing – review and editing, and project administration. All authors approved the final version of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique identifying number or registration ID: researchregistry8628.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/63c771ba5fe58b0012f3a158/

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Data availability statement

The datasets used and/or analyzed for the present study are available from the corresponding author on reasonable request.

Provenance and peer review

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