Prospective Cohort Study

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Prediction of survival in patients with infected pancreatic necrosis: a prospective cohort study

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Background: Infected pancreatic necrosis (IPN) is a severe complication of acute pancreatitis, with mortality rates ranging from 15 to 35%. However, limited studies exist to predict the survival of IPN patients and nomogram has never been built. This study aimed to identify predictors of mortality, estimate conditional survival (CS), and develop a CS nomogram and logistic regression nomogram for real-time prediction of survival in IPN patients.

Methods: A prospective cohort study was performed in 335 IPN patients consecutively enrolled at a large Chinese tertiary hospital from January 2011 to December 2022. The random survival forest method was first employed to identify the most significant predictors and capture clinically relevant nonlinear threshold effects. Instantaneous death risk and CS was first utilized to reveal the dynamic changes in the survival of IPN patients. A Cox model-based nomogram incorporating CS and a logistic regression-based nomogram were first developed and internally validated with a bootstrap method.

Results: The random survival forest model identified seven foremost predictors of mortality, including the number of organ failures, duration of organ failure, age, time from onset to first intervention, hemorrhage, bloodstream infection, and severity classification. Duration of organ failure and time from onset to first intervention showed distinct thresholds and nonlinear relationships with mortality. Instantaneous death risk reduced progressively within the first 30 days, and CS analysis indicated gradual improvement in real-time survival since diagnosis, with 90-day survival rates gradually increasing from 0.778 to 0.838, 0.881, 0.974, and 0.992 after surviving 15, 30, 45, 60, and 75 days, respectively. After further variables selection using step regression, five predictors (age, number of organ failures, hemorrhage, time from onset to first intervention, and bloodstream infection) were utilized to construct both the CS nomogram and logistic regression nomogram, both of which demonstrated excellent performance with 1000 bootstrap.

Conclusion: Number of organ failures, duration of organ failure, age, time from onset to first intervention, hemorrhage, bloodstream infection, and severity classification were the most crucial predictors of mortality of IPN patients. The CS nomogram and logistic regression nomogram constructed by these predictors could help clinicians to predict real-time survival and optimize clinical decisions.

Keywords: conditional survival, infected pancreatic necrosis, nomogram, predictors, random survival forest

Introduction

Acute pancreatitis (AP) is one of the leading causes of hospital admission for gastrointestinal disorders, with a reported global incidence of 34 cases per 100 000 person-years[1]. Although a majority of AP patients undergo an uneventful course of disease, ~20% of patients progress to moderate severe AP (MSAP) or severe AP (SAP) with pancreatic necrosis and/or organ failure, consisting of 67% sterile pancreatic necrosis and 33% infected pancreatic necrosis (IPN)[2]. Notably, IPN emerges as a crucial determinant for mortality in MSAP and SAP, with mortality rates up to 15–35%[2,3]. Therefore, early identification of mortality predictors in IPN patients is important.

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Given the significant mortality rate in severe cases, multiple prognostication models have been developed to predict the severity and mortality of AP early in the disease course, such as the Acute Physiology and Chronic Health Evaluation II, Bedside Index for the Severity in Acute Pancreatitis, and Ranson scores[4,5]. However, these models possess certain limitations, such as requiring an extensive set of mandatory variables or having low sensitivity and specificity for mortality prediction, thereby limiting their clinical application. Additionally, the current clinical scoring systems primarily focus on predicting the severity of AP rather than accurately forecasting mortality rates. Thus, it is crucial and imperative to develop a prediction model that can effectively and accurately estimate individualized patient mortality rates in IPN cases.

Recently, the random survival forest (RSF) method, a machine learning technique, has shown promising results in terms of variable selection and mortality prediction[6–10]. Specifically, it was useful for important variable selection in cases of collinearity and high dimensionality of the variables, and limitations imposed by the number of events. Moreover, RSF allowed for delineating nonlinear associations between the continuous predictors and survival outcomes, and provided valuable insights into the direction and magnitude of the effect of important predictors in dependency plots and partial dependency plots (PDP). Meanwhile, the conditional survival (CS) analysis, a methodology usually used in cancer research, could reflect the dynamic changes of survival rates over time instead of the cumulative survival rate from the onset of the disease[11,12]. Until now, identification of important variables using the RSF method, CS analysis, and predictive nomogram model for survival have not been reported in IPN patients.

Therefore, in the present study, the RSF method was employed to identify the most significant predictors and capture clinically relevant nonlinear threshold effects; the CS was utilized to reveal the dynamic changes in survival of IPN patients over time; and a Cox model-based nomogram incorporating CS was developed to provide clinicians and patients with individualized and real-time prognostic information. Additionally, a logistic regression-based nomogram was constructed to enhance practical applicability in clinical settings.

HIGHLIGHTS

- Little is known about the survival predictors in patients with infected pancreatic necrosis (IPN).
- Seven most important predictors of mortality are identified in IPN.
- Mortality reaches high plateau when organ failure lasts over 3 weeks.
- Mortality reaches low plateau when first intervention is delayed over 1 months.
- Two nomograms are built to predict real-time survival of IPN patients.

Methods

Study cohort

A prospective cohort study was performed in 355 IPN patients consecutively enrolled at a large Chinese tertiary hospital from January 2011 to December 2022. The exclusion criteria included patients with a history of chronic pancreatitis, patients with chronic organ dysfunction, patients during pregnancy and patients with incomplete data. Finally, 335 patients with IPN were included. The study was approved by the Ethics Committee of authors' hospital on 5 December 2010 (No. 201012067) and registered on www.researchregistry.com (unique identifying number: researchregistry9293, https://www.researchregistry.com/register-now#home/registrationdetails/64b8b18bc0679a0027c1e25b/). The work has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[13] (Supplemental Digital Content 1, http://links.lww.com/JS9/B219). Written informed consent was obtained from all participants or their legal representatives for the publication of the data.

Data collection and definition

The primary endpoint was all-cause mortality. Overall survival (OS) was defined as the interval, measured in days, from the initial diagnosis to the recorded date of death. Data prospectively collected included baseline characteristics and potential risk factors for mortality: demographics (age and sex), etiology, severity classification, ICU admission, organ failure (onset, duration, number, and type of failing organ systems), pancreatic and bloodstream infection (organisms, polymicrobial infection, multidrug-resistant organisms infection, carbapenem-resistant enterobacteriaceae infection, and fungal infection), surgical interventions (step-up approach/step-down approach and time from onset to first surgical intervention), complications and outcomes (gastrointestinal fistula, hemorrhage, pancreatic fistula, hospital stay, and OS).

The definition and severity classification of AP was based on the determinant-based classification[3]. SAP was defined as IPN or persistent (≥48h) organ failure, and critical acute pancreatitis (CAP) was defined as IPN and persistent (≥48 h) organ failure. The criteria for organ failure was defined as a score of 2 or more for 1 of these three organ systems (respiratory, cardiovascular, and renal) using the modified Marshall Score[14]. Multiple organ failure was defined as the failure of at least two organ systems[15]. IPN was defined as the positive culture of pancreatic necrosis or fluid obtained during the first drainage or necrosectomy[15]. Multidrug-resistant organisms infection was defined as microorganisms not susceptible to at least one agent in at least three microbial categories[16]. Carbapenem-resistant enterobacteriaceae infection was defined as the enterobacter not susceptible to carbapenem[17]. Pancreatic fungal infection was defined as at least one species of fungi cultured from the pancreatic necrosis or fluid during the first drainage or necrosectomy[18]. Candidemia was defined as at least one fungi species cultured from a blood sample collected under sterile conditions[18]. Hemorrhage was defined as intra-abdominal or retroperitoneal massive bleeding requiring radiologic, endoscopic, or surgical intervention[19]. A gastrointestinal fistula was defined as the secretion of digestive juice or fecal material from drains or necrotic tissue cavities confirmed by imaging or during surgery[19]. Pancreatic fistula was defined as the amylase content of fluid obtained from the drains greater than 3 times the serum amylase level[19].

Identification of important predictors and nonlinear effects in continuous predictors

Due to the limited number of outcome events and the presence of severe multicollinearity among covariates (25 candidate

Table 1

Baseline characteristics of patients with infected pancreatic necrosis.

Characteristics	*N* (%)
Demographic data	
Total number of patients	335 (100)
Age, years (mean ± SD)	44.7 ± 12.4
Sex, male	243 (72.5)
Etiology	
Biliary	125 (37.3)
Hypertriglyceridemia	145 (43.3)
Alcoholic	18 (5.4)
Others	47 (14.0)
Severity classification	
Severe acute pancreatitis	162 (48.5)
Critical acute pancreatitis	173 (51.6)
Intensive care unit admission	245 (73.1)
Number of organ failures	
No organ failure	152 (45.4)
Single organ failure	68 (20.3)
Multiple organ failure	115 (34.3)
Duration of organ failure, days, median (IQR)	2 (0–18)
Surgical approach	
Step-up approach	260 (77.6)
Step-down approach	75 (22.4)
Time from onset to first intervention, days, median (IQR)	22 (14–32)
Pancreatic infection	
Polymicrobial infection	217 (64.8)
Carbapenem-resistant enterobacter infection	104 (31.0)
Multidrug-resistant organisms infection	184 (54.9)
Fungal infection	88 (26.3)
Klebsiella pneumoniae infection	127 (37.9)
Acinetobacter baumanii infection	93 (27.8)
Enteroccoccus faecium infection	98 (29.3)
Escherichia coli infection	88 (26.3)
Bloodstream infection	110 (32.8)
Bloodstream multidrug-resistant organisms infection	68 (20.3)
Bloodstream carbapenem-resistant enterobacter infection	35 (10.5)
Candidemia	15 (4.5)
Complications and outcomes	
Gastrointestinal fistula	52 (15.5)
Hemorrhage	73 (21.8)
Gastrointestinal fistula or hemorrhage	105 (31.3)
Pancreatic fistula	146 (43.6)
Death	80 (23.9)

IQR, Interquartile range.

predictor variables in Table 1), we employed RSF for important variable selection (details of developing the RSF model were available in the Supplemental Methods, Supplemental Digital Content 2, http://links.lww.com/JS9/B220)[8–10]. Each variable's strength of association with mortality was assessed using two RSF outputs: variable importance (VIMP) and minimal depth (MD). As a result, seven variables in the first 10 ranks for both VIMP and MD were determined, including number of organ failures, duration of organ failure, age, time from onset to first intervention, hemorrhage, bloodstream infection, and severity classification (Fig. 1 and Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B221).

Next, the association of continuous variables (age, duration of organ failure, and time from onset to first intervention) with mortality were visualized using the dependence plots and PDP derived from the RSF model[9,20]. Dependency plots showed the overall trend of the unadjusted predicted mortality against a variable, while PDP suggested the association adjusted for all other variables included in the RSF model, thus displaying the corrected effect of the variable on the outcome. Due to the nonlinear relationship of duration of organ failure and time from onset to first intervention with mortality in PDP, these two variables were transformed into categorical variables based on thresholds (structural breakpoints) determined by the 'strucchange' package to facilitate the development of a nomogram model and clinical applicability[21]. The clinical significance of the categorized variables was verified by the Kaplan–Meier curve.

CS analysis

The instantaneous death risk refers to the risk or hazard of experiencing an event (such as death) at a particular point in time. It was calculated using the slope at different time points on the Kaplan–Meier curve. CS was calculated by $CS(y|x) = OS(y+x)/OS(x)$. $CS(y|x)$ was the probability that a patient would survive an additional y days after having survived x days from the initial diagnosis[11,12]. Furthermore, $OS(x)$ and $OS(y+x)$ were the survival rates estimated by Kaplan–Meier at x and $(x+y)$ days, respectively. Meanwhile, the CS concept was applied to the Cox regression nomogram to construct a CS nomogram for individualized prediction of real-time prognosis updated over time. It quantified patient risk and used risk scores to obtain individualized survival and CS rates.

Development and validation of nomogram models

Considering the high correlation among severity classification, number of organ failures, and duration of organ failure (Supplemental Figure 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B221), a backward stepwise regression method based on the AIC criterion was further employed to refine the variable selection. As a result, five variables were ultimately selected to develop a CS nomogram model-based on Cox regression for individualized prediction of real-time survival over time. To facilitate usability and interpretation in clinical settings, we also developed a logistic regression-based nomogram model with the same five important predictors. The performance of the nomogram models was assessed in two aspects: discrimination and calibration. Discrimination was evaluated using the concordance index (C-index) and time-dependent area under the curve for the CS nomogram, while using C-index for logistic regression nomogram. Calibration was assessed using calibration curves and the Brier score (integrated Brier score in the CS nomogram). All performance metrics above were validated internally by the 0.632 estimator in 1000 replications of the bootstrap with replacement. The decision curve analysis (DCA) was performed to validate the clinical utility of nomogram models.

Statistical analysis

Categorical variables were presented as frequency and percentage. Continuous variables were reported as means and SD that followed a normal distribution, otherwise, reported as median and interquartile range. A 2-sided P value <0.05 was considered statistically significant. R version 4.2.3 was used to perform all statistical analyses and create all figures (Supplemental Table 2,

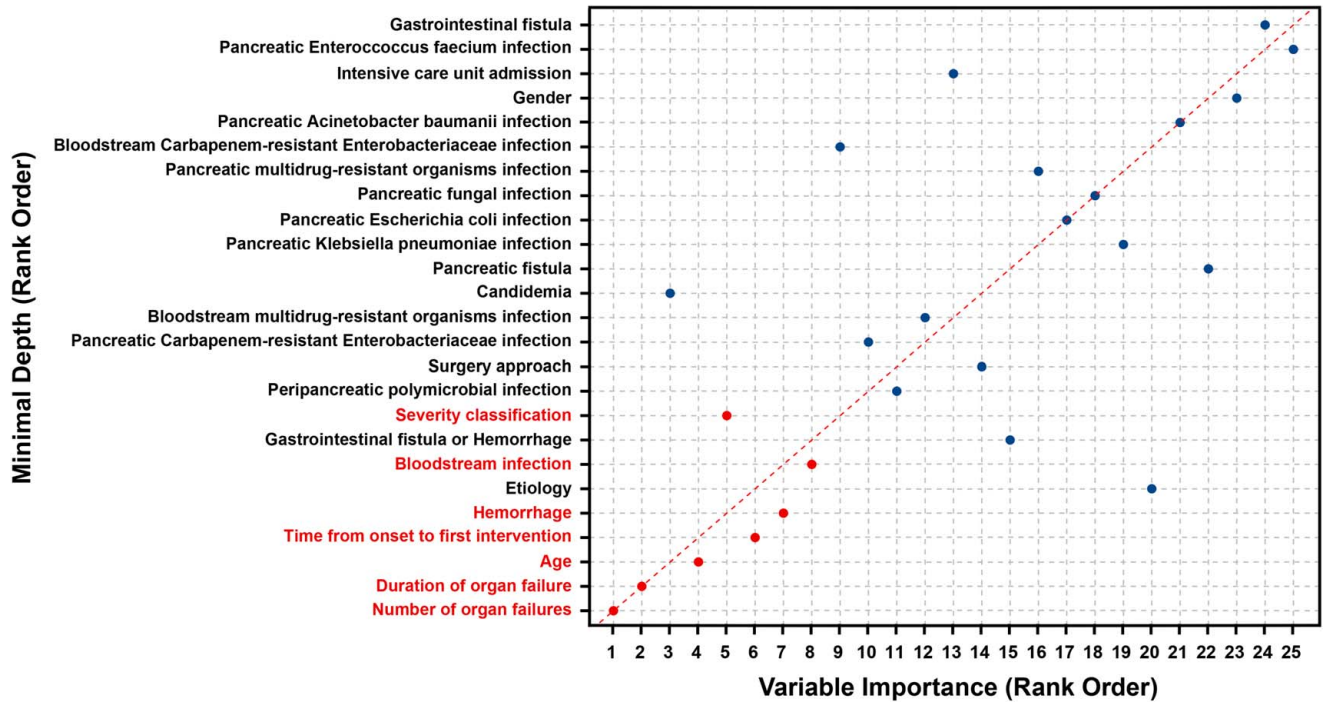

Figure 1. Relative variable importance of 25 variables ranks by variable importance and minimal depth in the random survival forest model. Seven variables in red text were identified as the most important predictors in the first 10 ranks for both variable importance and minimal depth.

Supplemental Digital Content 3, http://links.lww.com/JS9/B221). More extensive methodology and instructions were provided in the supplementary materials (Supplemental Digital Content 3, http://links.lww.com/JS9/B221).

Results

Baseline characteristics

Baseline characteristics were shown in Table 1. Of the 335 IPN patients, 72.5% were males and 27.5% were females. The average age of the cohort was 44.7 ± 12.4 years. The distribution of etiology was 43.3% of hypertriglyceridemia, 37.3% of biliary, 5.4% of alcoholic, and 14.0% of other causes. According to the determinant-based classification, CAP and SAP were seen in 51.6 and 48.4% of patients, respectively. A total of 73.1% of patients were administrated to the ICU. Multiple organ failure was present in 33.3% of patients, while 20.3% had single organ failure, and 45.4% had no organ failure. The median (range) duration of organ failure was 2 (0–18) days. Regarding the surgical approach, 77.6% of patients underwent a step-up approach, while 22.4% underwent a step-down approach, with a median of 22 (14–32) days from onset to the first intervention. The types of pancreatic infections included 64.8% of polymicrobial infection, 54.9% of multidrug-resistant organisms infection, 31.0% of carbapenem-resistant enterobacteriaceae infection, 26.3% of fungal infection, 37.9% of klebsiella pneumoniae infection, 29.3% of enterococcus faecium infection, 27.8% of acinetobacter baumanii infection, and 26.3% of *Escherichia coli* infection. Furthermore, 32.8% of patients developed bloodstream infections, comprising 20.3% multidrug-resistant organisms infections, 10.5% carbapenem-resistant enterobacteriaceae infections, and 4.5% candidemia. Complications included gastrointestinal fistulas in 15.5% of cases, hemorrhage in 21.8% of cases, a combined occurrence of gastrointestinal fistula or hemorrhage in 31.3% of cases, and pancreatic fistulas in 43.6% of cases. The overall mortality rate in the study cohort was 23.9%.

VIMP in the RSF model

In the RSF model built with all 25 variables, VIMP was evaluated by considering both MD and VIMP (Fig. 1, Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B221). Seven most important predictors, determined from the top 10 ranks in both MD and VIMP assessments, included number of organ failures (MD 2.30, VIMP 0.2372), duration of organ failure (MD 3.21, VIMP 0.0542), age (MD 3.21, VIMP 0.0370), time from onset to first intervention (MD 3.23, VIMP 0.0301), hemorrhage (MD3.89, VIMP 0.0260), bloodstream infection (MD 4.46, VIMP 0.0161) and severity classification (MD 5.03, VIMP 0.0357). However, the remaining variables indicated relatively little predictive value.

Dependence plots and PDP of seven important variables in the RSF model

Variable dependency plots for seven important variables were constructed using unadjusted predicted 90-day mortality while PDP for these seven variables were generated to demonstrate the adjusted mortality after integrating out the effects of all other variables (Fig. 2 and Supplemental Figure 2, Supplemental Digital Content 3, http://links.lww.com/JS9/B221). Regarding three continuous variables, the unadjusted predicted 90-day mortality became higher as age increased, the duration of organ failure

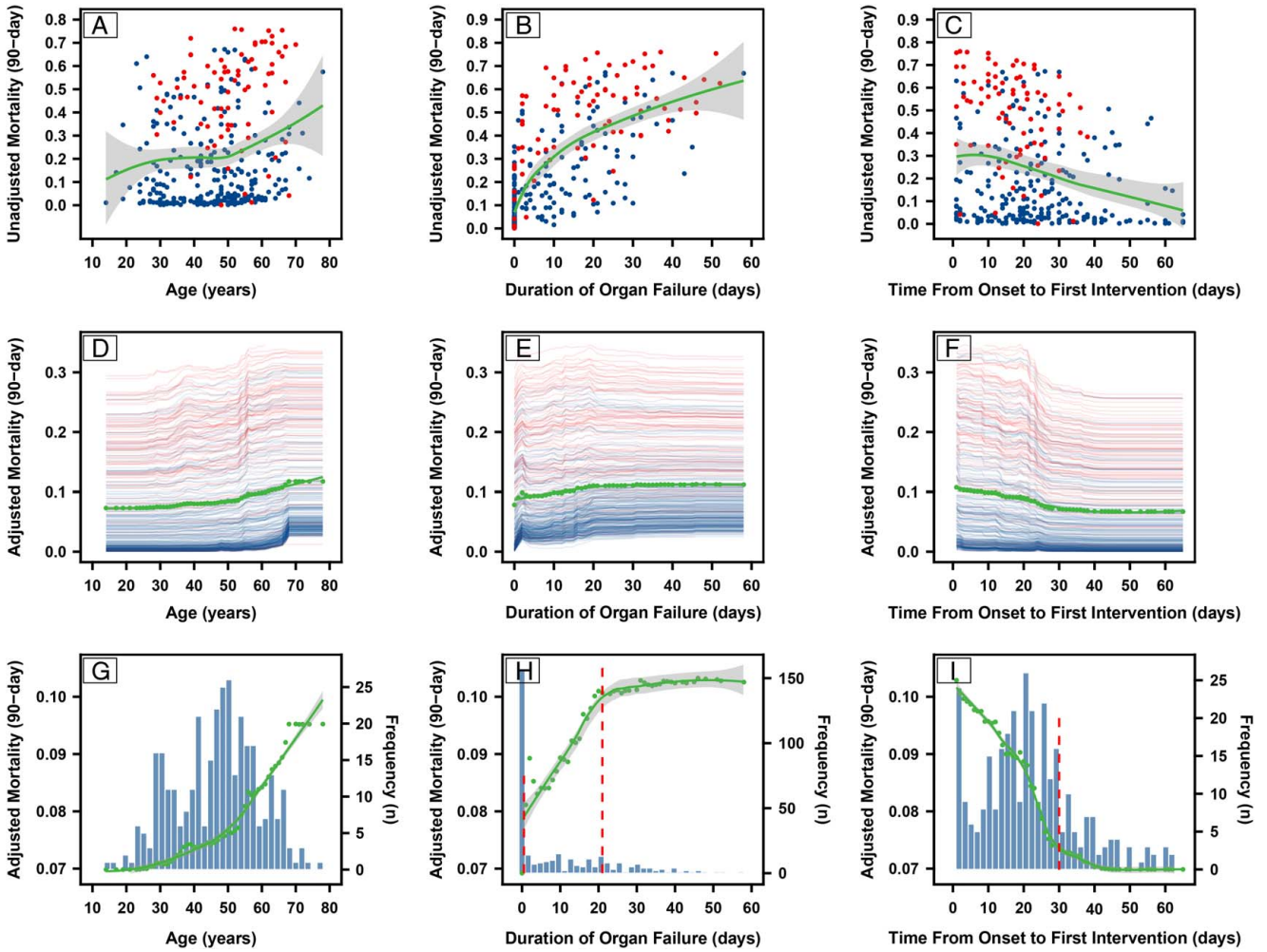

Figure 2. Variable dependency plots and partial dependency plots for three important continuous variables in the random survival forest model. Variable dependency plots and partial dependency plots for (A, D, and G) age, (B, E, and H) duration of organ failure, and (C, F, and I) time from onset to first intervention, respectively. The LOESS curve (green line) shows the overall trend as the value increases, with a 95% CI (shaded area); Each dot in variable dependency plots indicates an individual patient's data (blue represents alive and red represents death); Each semi-transparent line indicates individual conditional expectations (D, E, and F blue represents alive and red represents death). Red vertical lines represent the cutoff value determined by the structure point (H and I). Histograms represent the frequency distribution of variables (G, H, and I).

increased, and the time interval from onset to the first intervention decreased (Figs 2A, B, and C). As shown in Figures 2 D–F, the trend of these variables observed in individual conditional expectation plots was consistent with that of PDP. In the enlarged PDP, a positive linear correlation was observed between age and adjusted predicted mortality, while nonlinear effects of duration of organ failure and time interval from onset to the first intervention on 90-day adjusted mortality risk were detected (Figs 2 G, H, and I). In detail, the duration of organ failure was zero, the adjusted mortality was the lowest, then adjusted mortality increased with the duration of organ failure below 21 days, with a plateau of elevated risk thereafter (Fig. 2H). In addition, the mortality decreased with an increased time interval from onset to the first intervention when it was less than 30 days, reaching a stable risk plateau thereafter (Fig. 2I). The Kaplan–Meier survival curves for IPN patients, stratified by the thresholds observed in the PDP [duration of organ failure (0, ≤21 days, >21 days) and time from onset to first intervention (≤30 days, >30 days)], exhibited significant differences (Supplemental Figure 3, Supplemental Digital Content 3, http://links.lww.com/JS9/B221). Regarding the other four crucial categorical variables, both dependency plots and PDP indicated significant differences among the various groups, except for the insignificant difference between the no organ failure group and the single organ failure group in the PDP (Supplemental Figure 2, Supplemental Digital Content 3, http://links.lww.com/JS9/B221).

Cox regression analysis of important variables

We evaluated the prognostic value of seven most important variables derived from the RFS model using Cox regression analysis (Table 2). In the univariate Cox regression analysis, age ($P<0.001$, HR = 1.03), number of organ failures (multiple organ failure, $P<0.001$, HR = 17.85), hemorrhage ($P<0.001$, HR = 4.80), time from onset to first intervention (>30 days, $P<0.001$, HR = 0.22), bloodstream infection ($P<0.001$, HR = 4.7), severity classification (CAP, $P=0.006$, HR = 8.12) and duration of organ failure (≤21 days, $P<0.001$, HR = 9.47; >21 days, $P<0.001$,

Table 2

Univariate and stepwise Cox regression results of the seven most important variables.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, years	1.03 (1.01–1.05)	< 0.001	1.03 (1.01–1.05)	0.002
Number of organ failures				
No	1.00		1.00	
Single organ failure	2.30 (0.81–6.55)	0.120	2.11 (0.74–6.08)	0.165
Multiple organ failure	17.85 (8.18–38.98)	< 0.001	10.57 (4.55–24.54)	< 0.001
Hemorrhage				
No	1.00		1.00	
Yes	4.80 (3.09–7.46)	< 0.001	1.63 (1.01–2.62)	0.044
Time from onset to first intervention, days				
≤ 30	1.00		1.00	
> 30	0.22 (0.10–0.48)	< 0.001	0.39 (0.17–0.85)	0.018
Bloodstream infection				
No	1.00		1.00	
Yes	4.70 (2.97–7.46)	< 0.001	1.54 (0.93–2.55)	0.090
Severity classification				
Severe acute pancreatitis	1.00			
Critical acute pancreatitis	8.12 (4.18–15.75)	< 0.001		
Duration of organ failure, days				
0	1.00			
≤ 21	9.47 (4.24–21.16)	< 0.001		
> 21	14.93 (6.60–33.80)	< 0.001		

HR, hazard ratio.

HR = 14.93) were all significantly correlated with mortality of IPN patients. Next, the correlation analysis among the seven selected variables revealed strong correlations among the number of organ failures, duration of organ failure and severity classification, whereas few correlations were observed among the other variables (Supplemental Figure 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B221). Thus, we performed a stepwise backward Cox regression analysis to further control for collinearity, with age ($P = 0.002$, HR = 1.03), number of organ failures (multiple organ failure, $P < 0.001$, HR = 10.57), hemorrhage ($P = 0.044$, HR = 1.63), time from onset to first intervention (> 30 days, $P = 0.018$, HR = 0.39), bloodstream infection ($P = 0.09$, HR = 1.54) identified as the final variables set to develop a multivariate model.

Evaluation and validation of the Cox model

The discrimination of the Cox model was assessed through time-dependent area under the curve curves, which consistently remained high, demonstrating that the model maintained good discriminative ability over time, and the C-index with 1000 bootstrap resampling was 0.851 (95% CI: 0.814–0.883) (Fig. 3A), reflecting strong predictive reliability. Meanwhile, calibration plot was used to evaluate the predicted accuracy of 30-day, 60-day, and 90-day OS, which presented a remarkable correspondence with the ideal curve (Fig. 3B), and the integrated Brier score was 0.076 (95% CI: 0.062–0.091), both suggesting a high degree of model reliability. Furthermore, DCA curves indicated the good clinical applicability of using the Cox regression model as a tool for triggering medical intervention (Fig. 3C).

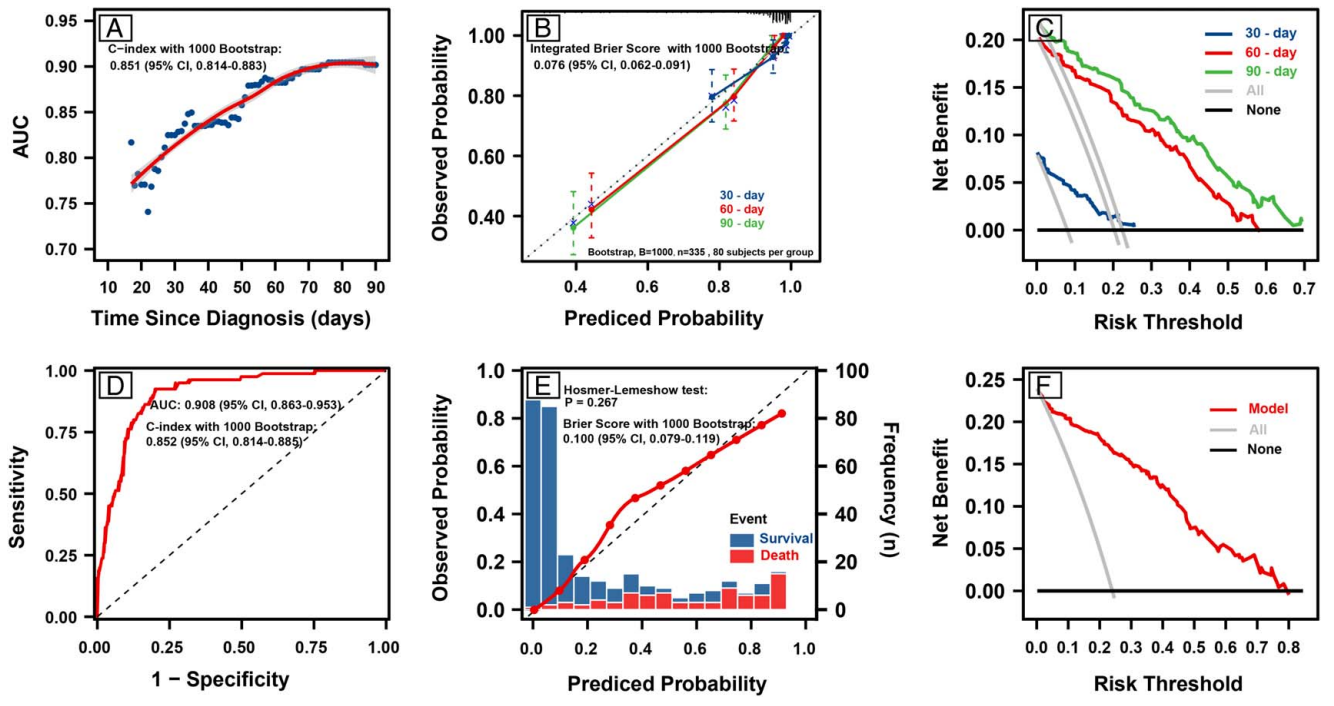

Figure 3. Evaluation and validation of nomogram models. (A) time-dependent area under curve for the Cox model; (B) calibration plots for the Cox model; (C) decision curve analysis for the Cox model; (D) time-dependent area under curve for the logistic model; (E) calibration plots for the logistic model; (F) decision curve analysis for the logistic model. Concordance index and integrated brier score for the Cox model with 1000 bootstrap resampling are 0.851 (95% CI: 0.814–0.883) and 0.076 (95% CI: 0.062–0.091), respectively. Concordance index and integrated brier score for the logistic model with 1000 bootstrap resampling are 0.852 (95% CI: 0.814–0.885) and 0.100 (95% CI, 0.079–0.119), respectively. C-index, concordance index; AUC, area under curve.

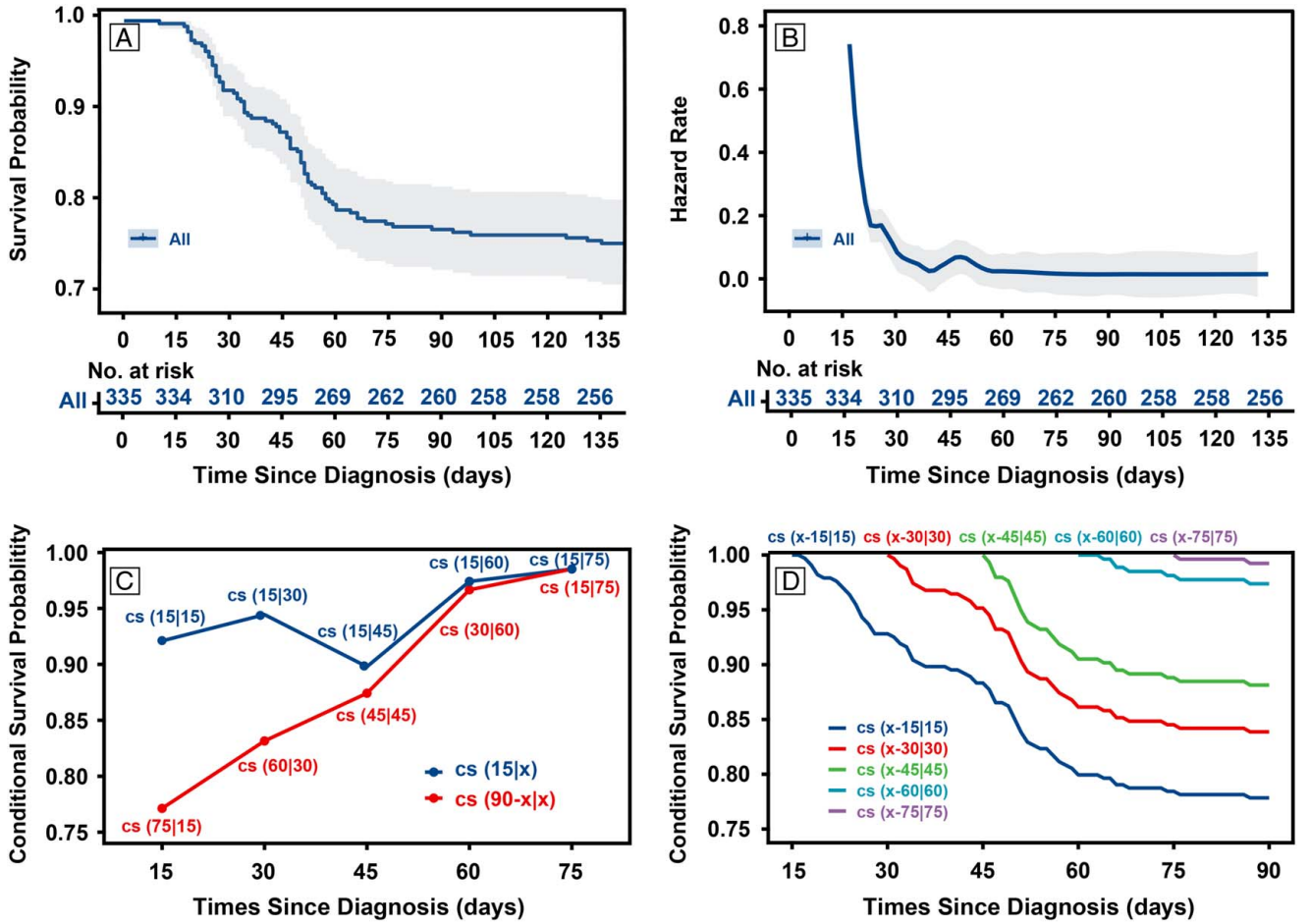

Figure 4. Survival analysis of patients with infected pancreatic necrosis. (A) Kaplan–Meier curve for all patients; (B) instantaneous death risk for all patients; (C) conditional survival (CS) curves: CS(15|*x*) curve showing another 15-day survival probability after surviving for *x* days (blue line), and CS(90-*x*|*x*) curve showing the 90-*x* days survival probability after surviving for *x* days since diagnosis; (D) conditional survival (CS) curves estimating real-time survival probability after having already survived for 15, 30, 45, 60, and 75 days.

CS analysis and CS nomogram development

The instantaneous death hazard in all IPN patients decreased over time and gradually reached a plateau up to 30 days thereafter, except for a slight rise at ~45–60 days from the onset of the disease, which was in line with the trend of the Kaplan–Meier curve (Figs 4A, B). CS analysis revealed a progressive improvement over time in real-time OS for IPN patients (Figs 4C, D). The CS (90-*x*|*x*) curve showed the 90-*x* days survival rates after the patients survived *x* days, which were gradually updated from 0.778 to 0.838, 0.881, 0.974, and 0.992 after the patients survived 15, 30, 45, 60, and 75 days, respectively. The CS (15|*x*) curve showed the survival rate for the next 15 days after patients survived *x* days. Notably, a low survival rate was observed for patients who have survived 45 days after diagnosis in terms of their probability of surviving the next 15 days [CS (15|45) =0.905 (95% CI: 0.857–0.955)]. The main reason for the decreased survival rate might be attributed to the fact that ~73% of patients who died during this period experienced severe complications, notably hemorrhage, and/or gastrointestinal fistula. The prevalence of complications was significantly greater compared to other time intervals. To provide a real-time survival prediction in IPN patients, the CS nomogram was developed using a Cox regression model that included the above five important predictors, which could quantify predictors into risk scores and calculate a total risk score corresponding to the individualized 30-day, 60-day, 90-day OS, and 90-day CS including CS (30|60), CS (45|45), and CS (60|30) (Fig. 5).

Development and validation of a logistic regression nomogram

We also evaluated the prognostic value of the most important variables derived from the RFS model in IPN patients through logistic regression. Both univariate and multivariate logistic regression analysis showed similar results compared with the Cox regression analysis (Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/JS9/B221). The ROC curves, calibration plots, and DCA curves to evaluate the logistic regression model were presented in Figures 4D–F, with a 1000 bootstrapping C-index for 0.852 (95% CI: 0.814–0.885), and a 1000 bootstrapping Brier score for 0.100 (95% CI: 0.079–0.119). Meanwhile, the logistic regression nomogram was also constructed to predict the mortality of IPN patients (Fig. 6).

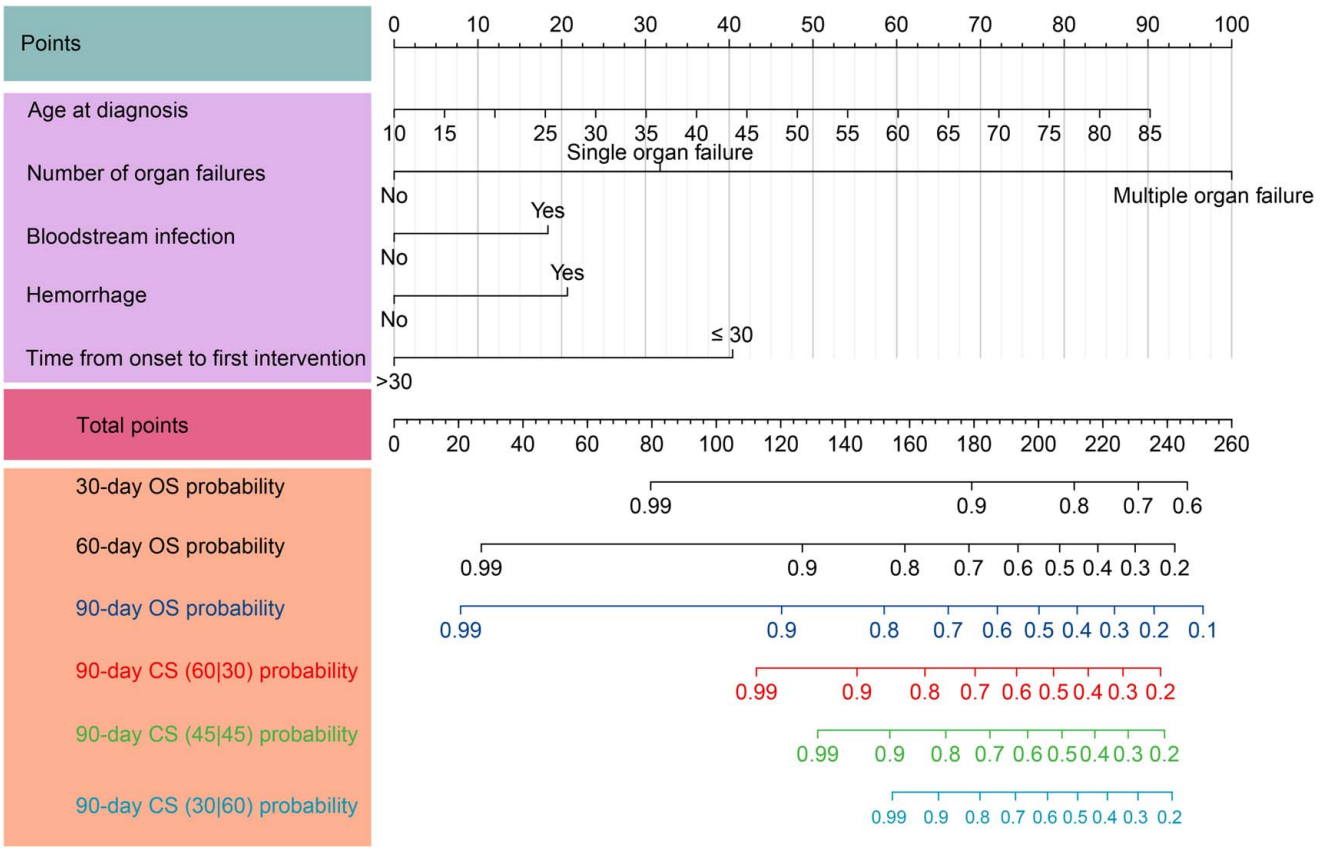

Figure 5. Conditional survival nomogram predicting 30-day, 60-day, and 90-day overall survival, and 90-day conditional survival after surviving for 30, 45, and 60 days for patients with infected pancreatic necrosis. OS, overall survival; CS, conditional survival.

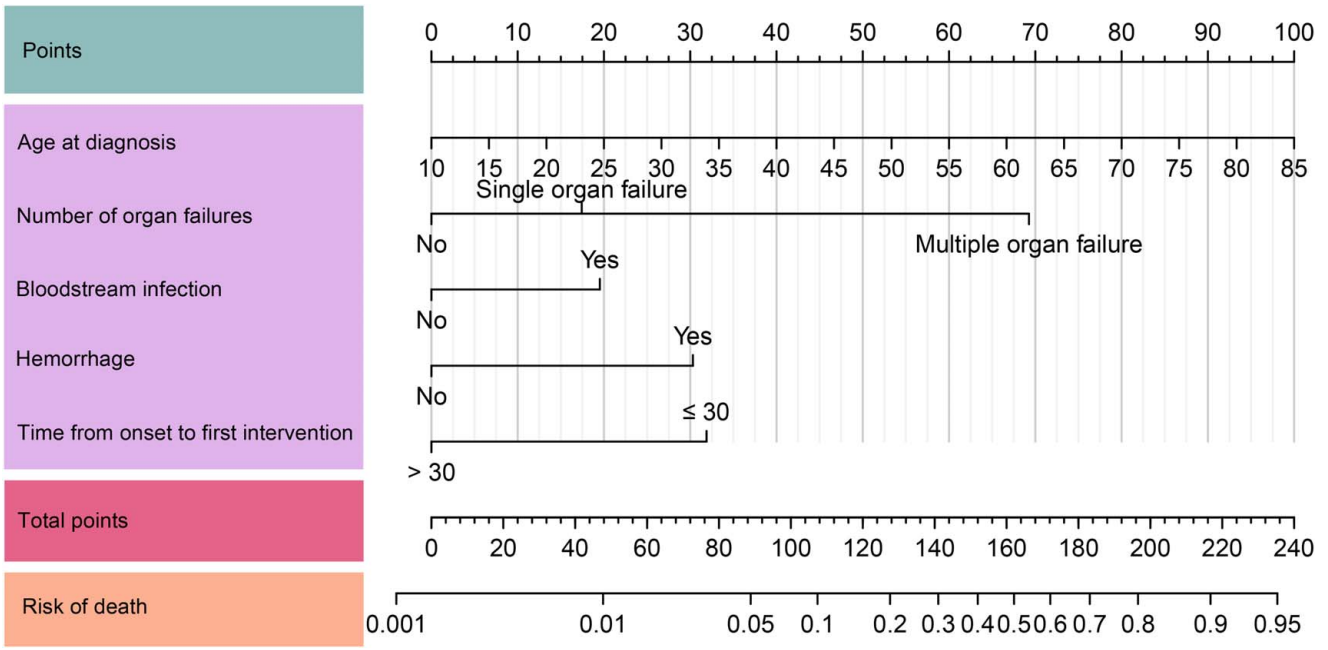

Figure 6. Logistic regression-based nomogram predicting risk of death for patients with infected pancreatic necrosis.

Discussion

In this prognostic study, we employed a machine learning RSF model to identify the predictors of mortality and clinically relevant nonlinear threshold effects in IPN patients. Furthermore, we constructed a CS nomogram and a logistic regression nomogram for individualized and real-time prediction of survival, both of which exhibited excellent discrimination, calibration, and clinical utility. To the best of our knowledge, this prospective study was conducted in one of the largest pancreatitis centers in China, which represented the first utilization of machine learning for survival prediction in IPN patients.

In the past, mortality in SAP patients exhibited two distinct peaks, including the first peak (<2 weeks) characterized by multiple organ failure and the second peak (>2 weeks) caused by IPN with substantial morbidity and mortality[22]. In recent years, advancements in intensive medical care have enabled considerable SAP patients to survive through the early phase, allowing them to be alive into the infection phase. Furthermore, the application of various endoscopic and minimally invasive surgical approaches has significantly reduced the morbidity and mortality rates among IPN patients[19,23,24]. However, despite these advancements, the mortality rate of IPN remained around 15–20% or higher even in specialized pancreatitis centers due to the complexity of the disease course[24–26]. As a result, there was a critical need for improved understanding of death predictors in IPN to facilitate enhanced surveillance and tailored treatment strategies. Using the RSF method, we identified 7 most important predictors of mortality from 25 variables in IPN patients, which included the number of organ failures, duration of organ failure, age, time from onset to first intervention, hemorrhage, bloodstream infection, and severity classification (ranking by MD from low to high). Meanwhile, we found the nonlinear effect of duration of organ failure and time interval from onset to first intervention on adjusted mortality, and these two variables demonstrated clear prognostic thresholds.

Although many of the mortality predictors identified in this study have been previously reported, the findings from these studies remained contradictory. As we know, organ failure, caused by early persistent systemic inflammatory response syndrome or late pancreatic infection accompanied by sepsis, was the most important determinant for outcome in AP[3,15,27,28]. However, the relationship between the type, number and the time of onset or duration of organ failure on mortality remained controversial, primarily due to the dynamic process of organ failure and the challenge to account for all different episodes of organ failure[29–31]. Schepers *et al.*[29] conducted a multicenter study involving a prospective database of 240 patients with necrotizing pancreatitis and organ failure from 21 hospitals, revealing no significant association between the onset and duration of organ failure and mortality. On the contrary, Shi *et al.*[30] observed that mortality was notably higher in necrotizing pancreatitis patients with organ failure lasting longer than 2 weeks compared to those with a duration of 2 weeks or less. Furthermore, mortality exhibited a significant increase with an escalating number of organ failures (5.5, 44.9, and 88.6% for 1, 2, and 3 organ failures, respectively). Huang *et al.* evaluated the influence of onset and duration of organ failure on mortality in 359 necrotizing pancreatitis patients with persistent organ failure, confirming no association with onset time but highlighting higher mortality rates with prolonged organ failure (24.7, 23.4, 42.1, and 46.7% for organ failure lasting 48 h to 1 week, 1–2 weeks, 2–3 weeks, and >3 weeks, respectively)[31]. In the present study, we identified multiple organ failure as an independent predictor of mortality in IPN. Meanwhile, we found the adjusted predicted mortality increased with prolonged duration of organ failure when it persisted for less than 21 days and gradually reached a steady risk plateau. Though the duration of organ failure was not included in the Cox and logistic regression model due to its strong correlations with the number of organ failures, we recommended that organ failure should be reversed as soon as possible within 21 days, especially when multiple organ failure was present.

The optimal timing of surgical intervention for patients with IPN has also been a subject of controversy. Although most guidelines recommended postponed intervention for at least 4 weeks until the pancreatic necrosis became walled-off, recent randomized trials and meta-analyses seemingly have questioned this opinion, suggesting early intervention was not associated with the increased complications and hospital mortality[32–36]. The possible explanation for the debate surrounding the optimal timing of the first surgical intervention was that early intervention in IPN patients, accompanied with poorly demarcated necrosis and/or organ failure, might lead to severe complications including hemorrhage or organ function deterioration, whereas delayed intervention might result in uncontrolled sepsis[37]. However, the present study identified that time from onset to the first intervention (>30 days) was still an important protective factor for mortality in IPN patients. We observed that the adjusted mortality decreased as the time from onset to the first intervention increased and gradually reached a steady risk when the time exceeded 30 days, which was generally consistent with the trend of instantaneous death hazard of IPN patients. Therefore, we proposed that early surgical or endoscopic intervention should only be considered for IPN patients with uncontrolled sepsis even in the presence of broad antibiotics.

Hemorrhage, encompassing gastrointestinal, intra-abdominal, and retroperitoneal bleeding, represented a potentially life-threatening complication that can occur at any stage of the disease[38,39]. The reported mortality of hemorrhage in AP varied from 35 to 50%[39–41]. Previous studies have demonstrated that SAP complicated with hemorrhage carried a significantly higher mortality risk than SAP alone[39]. In the present study, we observed 21% of IPN patients developed hemorrhage, which emerged as an independent predictor of mortality. Furthermore, age, bloodstream infection, and severity classification were also identified as important predictors of mortality in the present study, in line with the previous studies[3,18,26]. Notably, a positive linear correlation was observed between age and predicted mortality, indicating that adjusted mortality risk increased with advancing age, which was different from the previous study[18]. Therefore, the implementation of effective measures to prevent bloodstream infection in IPN patients was necessary, especially in elderly patients.

Additionally, our study first revealed the survival patterns of IPN patients. Most patients died within 30 days with a gradual reduction in the instantaneous death hazard and progressive improvement in real-time survival over time. The high mortality risk among IPN patients was primarily concentrated within the 15–30 days period, followed by the interval of 45–60 days. In our experience, the peak of early death risk may be consistent with the peak time of multiple organ failure, while the peak of mortality in

the 45–60-day period may be associated with the occurrence of complications after surgical intervention in IPN patients. Therefore, further research is needed to explore strategies for reducing mortality during these two critical periods. These valuable findings may help to alleviate patient anxiety and enhance the management of IPN patients.

Currently, there have been no studies concerning prognostic nomogram models in IPN patients. Thus, we constructed nomogram models based on Cox and logistic regression models for personalized prediction. Although the nomogram model was constructed using only five predictors, it was worth noting that both models showed excellent discrimination, calibration, and clinical utility. Previous research has identified one limitation of nomograms, namely their assumption that outcomes remain constant over the survival time[42]. Given that there were changes in mortality risk throughout the duration of survival, we developed CS nomograms to fit different survival periods, enabling more accurate predictions of the survival rate for specific individuals, even those who have survived for a certain time. Meanwhile, the logistic regression nomogram could provide the prediction of the final mortality. We believe these nomogram models could help clinicians to optimize clinical decisions and anticipatory management.

There are several limitations in the present study. Firstly, since the majority of IPN patients were tertiary referrals, laboratory variables and scoring systems during the early phase of the disease were unclear. Secondly, given that the results were derived from a single-center setting without external validations, potential internal biases may be present. Thirdly, while the nomogram provided valuable insights, it was important to recognize that clinical judgement cannot be wholly replaced. Consequently, future research efforts should focus on larger-scale, multicenter randomized controlled trials to validate our findings and address these limitations in a more comprehensive manner.

Conclusion

In this study, we have employed the RSF method to determine seven most important predictors of mortality, which included the number of organ failures, duration of organ failure, age, time from onset to first intervention, hemorrhage, bloodstream infection, and severity classification. Duration of organ failure and time from onset to first intervention exhibited obvious thresholds and nonlinear relationships with mortality in IPN patients. Meanwhile, we also presented the survival pattern of IPN patients with the dynamic improvement in survival over time. Furthermore, a CS nomogram and a logistic regression nomogram using these independent predictors were constructed. To the best of our knowledge, this study represented one of the largest prospective cohort to utilize machine learning to predict the real-time survival of IPN patients in the existing literature, which could help clinicians to optimize clinical decisions and anticipatory management.

Ethical approval

The study was approved by the Ethics Committee of Xiangya Hospital, Central South University, China (No. 201012067).

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Author contribution

C.N.: conceptualization, data curation, project administration, validation, writing – original draft, writing – review and editing; H.O.: conceptualization, methodology, formal analysis, software, visualization, writing – review and editing; D.S.: data curation, funding acquisition, writing – review and editing; Z.S.: data curation, resources, writing – review and editing; B.L.: data curation, writing – review and editing; X.H.: data curation, writing – review and editing; C.L.: data curation, writing – review and editing; J.L.: data curation, writing – review and editing; L.C.: supervision, writing – review and editing; X.L.: conceptualization, supervision, resources, writing – review and editing, project administration; G.H.: conceptualization, supervision, resources, funding acquisition, writing – review and editing, project administration. All authors approved the final version of the manuscript.

Conflicts of interest disclosure

The authors declared that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
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3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/register-now#home/registrationdetails/64b8b18bc0679a0027c1e25b/.

Guarantor

Gengwen Huang and Xinying Li.

Data availability statement

The datasets used and/or analyzed for the present study are available from the corresponding author (Gengwen Huang, huanggengwen@csu.edu.cn) on reasonable request.

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