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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

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ORIGINAL ARTICLE

Retrospective Study

Development and validation of a prediction model for deep vein thrombosis in older non-mild acute pancreatitis patients

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Abstract

BACKGROUND

Deep vein thrombosis (DVT) may cause pulmonary embolus, leading to late deaths. The systemic inflammatory and hypercoagulable state of moderate and severe acute pancreatitis (non-mild acute pancreatitis, NMAP) patients may contribute to the development of venous thromboembolism. Accurate prediction of DVT is conducive to clinical decisions.

AIM

To develop and validate a potential new prediction nomogram model for the occurrence of DVT in NMAP.

METHODS

NMAP patient admission between 2013.1.1 and 2018.12.31 at the West China Hospital of Sichuan University was collected. A total of 220 patients formed the training set for nomogram development, and a validation set was constructed using bootstrapping with 100 resamplings. Univariate and multivariate logistic regression analyses were used to estimate independent risk factors associated with DVT. The independent risk factors were included in the nomogram. The accuracy and utility of the nomogram were evaluated by calibration curve and decision curve analysis, respectively.

RESULTS

A total of 220 NMAP patients over 60 years old were enrolled for this analysis. DVT was detected in 80 (36.4%) patients. The final nomogram included age, sex, surgery times, D-dimer, neutrophils, any organ failure, blood culture, and classification. This model achieved good concordance indexes of 0.827 (95%CI: 0.769-0.885) and 0.803 (95%CI: 0.743-0.860) in the training and validation sets,

respectively.

CONCLUSION
We developed and validated a prediction nomogram model for DVT in older patients with NMAP. This may help guide doctors in making sound decisions regarding the administration of DVT prophylaxis.

Key Words: Acute pancreatitis; Deep vein thrombosis; Prediction model; Bootstrap; Nomogram; Discrimination and calibration

Core Tip: Deep vein thrombosis (DVT) may cause pulmonary embolus, leading to late death. Few studies have focused on DVT in moderate and severe acute pancreatitis. We identified eight predictors and developed and established a prediction nomogram model for DVT in older patients with moderate and severe acute pancreatitis. This model achieved good concordance indexes and may help guide doctors in the administration of DVT prophylaxis.

INTRODUCTION

Acute pancreatitis (AP) is a common and potentially lethal disease with a rising incidence. The incidence of AP is 34 cases per 100,000 people in the general population per year worldwide[1]. Among gastrointestinal diseases, AP is one of the most common reasons for hospitalization in the United States, and the disease accounts for $2.6 billion health care dollars per year[2-4]. According to the 2012 Atlanta classification, most AP patients have mild acute pancreatitis. However, 20% of patients develop moderate or severe acute pancreatitis (non-mild acute pancreatitis, NMAP). Furthermore, the mortality of NMAP can reach 35%, which is significantly higher than that of mild acute pancreatitis[5]. Researchers usually focus on complications such as organ failure and infection in NMAP[6,7]. However, few of studies have paid attention to venous thromboembolism in NMAP. A previous study showed that the incidence of venous thromboembolism in hospitalized patients was approximately 0.4% to 1.3%[8]. NMAP usually requires a long hospital stay. The systemic inflammatory and hypercoagulable state of NMAP patients may contribute to the development of venous thromboembolism[9-11]. Deep vein thrombosis (DVT), a kind of venous thromboembolism, commonly develops in the lower extremities. It can cause acute pulmonary embolism (PE) when it falls and flows to the lung[12,13]. A recent study showed that the rate of DVT in AP patients could reach 38%[14]. Older patients more easily develop venous thromboembolism. This may increase the difficulty of treatment in older NMAP patients. However, there is a lack of a scoring model for predicting develop of DVT in NMAP patients. The existing scores for DVT are not suitable for critically ill patients[15-17]. In the past, nomograms were used as a graphical calculation to help solve engineering problems. As a statistical tool, nomograms have a unique advantage in visualizing the relationships of involved parameters. This approach enables users to calculate the overall probability of clinical outcome for an individual patient[18,19]. Recently, it has been widely used in clinical prediction models[20,21]. Thus, the aim of this study was to develop a prediction model for DVT in older NMAP patients.

MATERIALS AND METHODS

Study design and participants

Medical records of older NMAP patients admitted to West China Hospital from 2013.1.1 to 2018.12.31 were retrospectively collected. Included criteria were as follows: 1. AP was diagnosed in West China Hospital and classified as moderate or severe; 2. More than 60 years old. Pancreatic tumors are one of the causes of AP and are also a risk factor for DVT development[22]. Thrombosis development in other places may be a confounding factor in this study. Thus, patients who had the following diagnoses were excluded from this study: (1) Pancreatic tumor; and (2) Thromboses in other locations. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.

Data collection and definition

AP was diagnosed through a combination of clinical manifestations and signs (i.e., sudden onset of upper abdominal pain), laboratory tests (amylase or lipase levels were three times higher than normal limits), and imaging examinations (abdominal ultrasound, abdominal computed tomography (CT), and magnetic resonance imaging) [23]. AP was classified according to the revised Atlanta Classification[23]. The definition of non-mild acute pancreatitis (NMAP) is acute pancreatitis classified as moderate or severe. Acute pancreatitis patients aged over 60 years old were defined as older acute pancreatitis patients. The diagnosis of DVT was based on the results of color Doppler ultrasonography when patients presented swelling or pitting edema, redness, and leg tenderness. Organ failure (OF) was defined as a patient who had at least one failure of respiratory function, cardiovascular function, or renal function. Respiratory failure was defined as $PaO_2 < 60$ mmHg, despite FiO_2 of 0.30, or a need for mechanical ventilation. Cardiovascular failure was defined based on circulatory systolic blood pressure < 90 mmHg, despite adequate fluid resuscitation, or a need for inotropic catecholamine support. Renal failure was defined as creatinine level > 177 μmol/L after rehydration or the need for hemofiltration or hemodialysis.

The following variables were recorded for the study population: Age, sex, etiology, smoking, drinking, surgery times, any organ failure, respiratory failure, renal failure, cardiovascular failure, severity classification, onset time to diagnosis of DVT, and blood index. In DVT patients, all variables were collected until the time of DVT diagnosis. In NDVT patients, all variables were collected throughout the whole hospital stay. Repeated measurements of continuous variables are shown on average.

Statistical analysis

Continuous variables are described as the mean (SD) or median and binary variables are expressed as counts (%). Statistical analysis was performed using R software. (Version 3.6.1)

Prediction model development

Relevant predictors included age, sex, surgery times, any organ failure, respiratory failure, cardiovascular failure, renal failure, blood culture, C-reactive protein, neutrophils, serum albumin, D-dimer, severity classification of DVT in patients with AP identified from a previous study[24,25] and advice of pancreatologists. Patients with more than 30% of the preselected predictors missing were excluded from model development.

In this study, 80 patients were identified with DVT, and more than ten times patients with NDVT were identified. Due to the imbalance between the DVT and NDVT groups, undersampling was performed to adjust the number between the two groups. A total of 10% NDVT patients were randomly selected compared with DVT patients. Finally, 140 NDVT patients were selected. Thus, training data included 80 DVT and 140 NDVT patients.

Logistic regression was used to identify the variables that were significantly correlated with DVT in the training group. Variables with a *P*-value less than 0.05 and more than 0.05 but suggested by pancreatologists were fed to a multivariate logistic regression model. Stepwise selection was used to further eliminate redundant variables. The resulting multivariate logistic regression model was used to build the prediction model.

Prediction model validation

The bootstrap method was used to evaluate the performance of the prediction model. In the bootstrap method, 100 random samples were drawn with replacement from the

original data set and the coefficients were recalculated.

To validate the prediction model, two criteria were used to evaluate the prediction performance. On the one hand, the concordance index (c-index) was calculated to estimate the discrimination of the prediction model. On the other hand, calibration curves were plotted to evaluate the consistency between predicted DVT probability and actual DVT proportion. Values of 1 and 0.5 indicate perfect discrimination and no discrimination, respectively. The C-index and calibration results presented are an average of the bootstrapped samples.

RESULTS

Baseline clinical characteristics

Medical records of NMAP patients over 60 years admitted to West China Hospital from 2013.1.1 to 2018.12.31 were collected. DVT was diagnosed in 80 patients. Due to the imbalance of the data, undersampling was performed on selected NDVT patients. Finally, 140 NDVT patients were randomly selected for analysis. The baseline characteristics of the patients, including demographics, clinical indexes, and blood indexes, in the two groups are shown in Table 1. There are 81 and 49 females in the NDVT group and DVT group, respectively. The DVT group included patients aged between 60 and 88 years (mean age: 70.16 years), and the NDVT group included patients aged 69.81 years. Biliary was the most common etiology in both groups. There were 37 (26.4%) and 33 (23.6%) NDVT patients who smoked and drank, respectively. Seventeen (21.2%) and 15 (18.8%) DVT patients smoked and drank, respectively. All organ failure in the DVT group was significantly higher than that in the NDVT group. Respiratory failure accounted for the largest proportion in OF. In total, 65% of patients were classified as severe. However, 67% of patients in the NDVT group were classified as moderate. Blood culture, D-dimer, and serum albumin in the DVT group were significantly different between the two groups. Table 2 shows the thrombus location of the DVT patients. The most common location of vein thrombosis was both lower limbs, which were detected in 31 (38.8%) patients. Only 3 (3.7%) patients were found to have vein thrombosis in the left upper limb, and 12 (15%) patients had vein thrombosis detected in more than two locations.

Prediction model development

Univariate and multivariate analyses were performed to select potential predictors. A nomogram model was constructed based on the results of the multivariate logistics regression analysis and the suggestions of pancreatologists. Finally, 8 potential predictors based on 220 patients were selected. These features included sex, age, surgery times, renal failure, classification, D-dimer, blood culture, and neutrophils. Figure 1 shows the nomogram in which sex, age, surgery times, renal failure, classification, D-dimer, blood culture, and neutrophils defined the individual risk of DVT in NMAP patients. In this nomogram, D-dimer is a continuous variable and every 5 unit increase in D-dimer results in an approximately 0.8-point increase in risk points. The nomogram maps the predicted probability of DVT on a scale of 0 to 220. For each covariate, a vertical line is drawn upwards, and the corresponding points are noted. This is repeated for each covariate ending with a total score that corresponds to a predicted probability of morbidity at the bottom of the nomogram. The odds ratios of the nomogram variables are summarized in Table 3.

Validation prediction model

The C-index for the prediction nomogram was 0.827 (95%CI: 0.769-0.885). It was confirmed to be 0.803 (95%CI: 0.743-0.860) through bootstrapping validation, which suggested the model's good discrimination. The calibration curve in Figure 2 shows good concordance between the estimated risk of DVT and the actual presence of DVT.

DISCUSSION

Using data from a retrospective study including older NMAP patients with DVT, we developed and internally validated a potential new prediction model for DVT. This is the first model for predicting DVT in older NMAP patients. The performance of the prediction model was adequate. This nomogram, based on routinely available demographic and blood indexes, predicts the probability of DVT in NMAP patients.

Table 1 Demographic characteristics

Variables	NDVT	DVT	*P* value
N	140	80	
Age	69.81 (7.52)	70.16 (7.84)	0.745
Gender: Female	81 (57.9)	49 (61.3)	0.726
Etiology			
Biliary	65 (47.4)	39 (48.8)	
Alcohol	3 (0.21)	5 (0.62)	
Hyperlipidemia	23 (16.4)	10 (12.5)	
Others	49 (35.0)	26 (32.5)	
Smoking	37 (26.4)	17 (21.2)	0.507
Drink	33 (23.6)	15 (18.8)	0.487
Surgery times			< 0.001
0	114 (81.4)	47 (58.8)	
1	24 (17.1)	23 (28.7)	
2	2 (1.4)	6 (7.5)	
3	0 (0.0)	4 (5.0)	
Any organ failure	72 (51.4)	67 (83.8)	< 0.001
Respiratory failure	61 (43.6)	58 (72.5)	< 0.001
Renal failure	15 (10.7)	31 (38.8)	< 0.001
Cardiovascular failure	23 (16.4)	37 (46.2)	< 0.001
Classification			< 0.001
Moderate to severe	95 (67.9)	28 (35.0)	
Severe	45 (32.1)	52 (65.0)	
Blood index			
Blood culture positive	8 (5.7)	20 (25.0)	< 0.001
D-dimer	5.87 (5.48)	8.78 (6.47)	0.002
CRP	120.77 (84.66)	124.51 (86.79)	0.796
WBC	11.09 (4.37)	11.74 (4.63)	0.312
Neutrophils	9.05 (4.08)	9.87 (4.48)	0.177
Serum albumin	32.90 (4.13)	31.25 (4.31)	0.006

NDVT: None deep vein thrombosis; DVT: Deep vein thrombosis; CRP: C-reactive protein; WBC: White blood cell.

The recent criteria of AP classification were put forward in 2012. Non-mild acute pancreatitis patients have a poorer prognosis, and they stay in the hospital for a long time. Hospitalization has been considered a significant risk factor for VTE[26]. Furthermore, older patients usually have slow blood flow. These factors all contribute to DVT development. However, doctors usually pay attention to DVT when patients have clinical manifestations, such as calf swelling. In trauma patients, occult DVT may cause pulmonary embolus, leading to late deaths due to fatality[27]. Early detection of DVT results in decreased rates of pulmonary embolus and mortality[28]. Therefore, accurate prediction of DVT is invaluable to provide treatment for each NMAP patient.

Our findings are essentially in line with previous venous thromboembolism studies. In the present study, we found that DVT mostly develops in both lower limbs at the same time. However, isolated left upper limbs only accounted for 3.7% of patients. A previous study showed that upper limb DVT is less than 10% of all DVT[22]. In this study, more than 16.2% of patients had upper limb DVT.

Table 2 The location of deep vein thrombosis

Location of the thrombosis	Number of patients (*n* = 80)
Left upper limb isolated	3 (3.7%)
Right upper limb isolated	6 (7.5%)
Both upper limbs	4 (5.0%)
Left lower limb isolated	14 (17.5%)
Right lower limb isolated	10 (12.5%)
Both lower limbs	31 (38.8%)
More than two locations	12 (15.0%)

Table 3 Odds ratio and 95% confidence interval of nomogram parameters

Variables	OR (95%CI)	*P* value
Age	1.02 (0.983-1.066)	0.257
Gender	1.23 (0.625-2.431)	0.546
Surgery times	2.70 (1.566-4.651)	0.000
Renal failure	0.35 (0.166-0.728)	0.005
Classification	2.17 (1.133-4.164)	0.020
D-dimer	1.02 (0.971-1.081)	0.382
Blood culture	0.53 (0.218-1.267)	0.152
Neutrophils	1.01 (0.930-1.087)	0.887
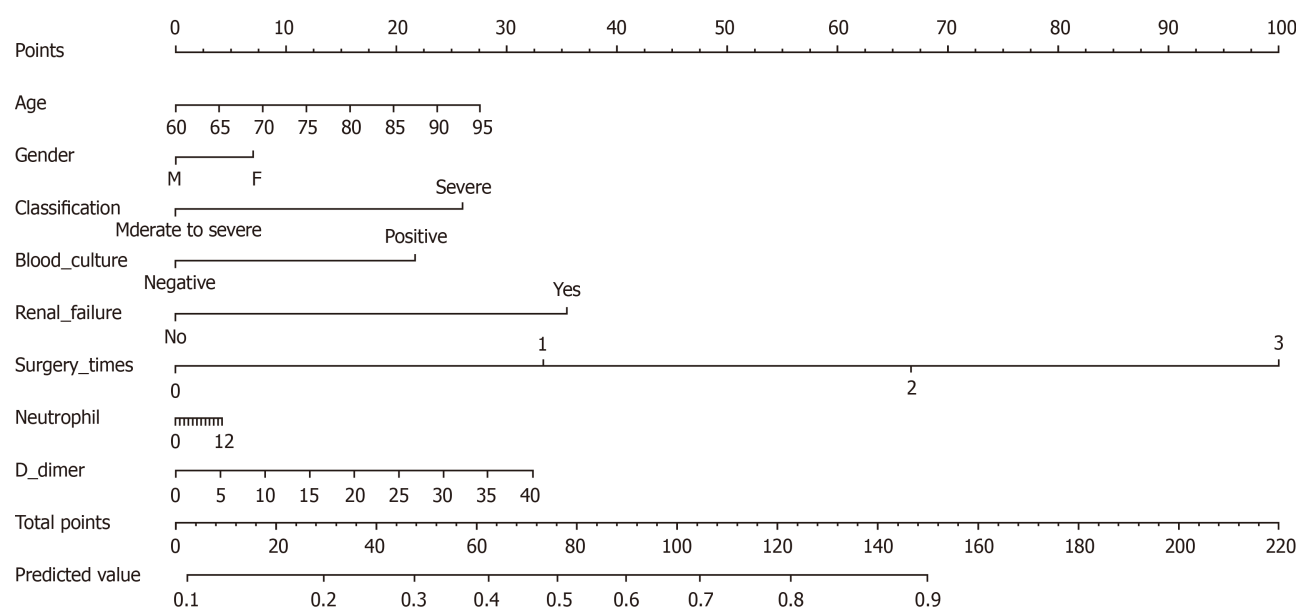
Figure 1 Nomogram for predicting deep vein thrombosis in non-mild acute pancreatitis patients. The nomogram maps the predicted probability of deep vein thrombosis (DVT) on a scale of 0 to 220. For each covariate, draw a vertical line upwards and record corresponding points. Repeated it and added the points. A total score corresponds to a predicted probability of DVT at the bottom of the nomogram.

Some predictors were already confirmed in other studies. D-dimer is the most well validated and widely used biomarker of venous thromboembolism excluded[25]. It is usually combined with the Wells score in practice. In this study, D-dimer was an important predictor of DVT. OF is regarded as one of the most important parameters of AP patients in the course of the early phase[23]. The main causes of OF are cytokine cascades resulting in systemic inflammatory response syndrome (SIRS)[29].
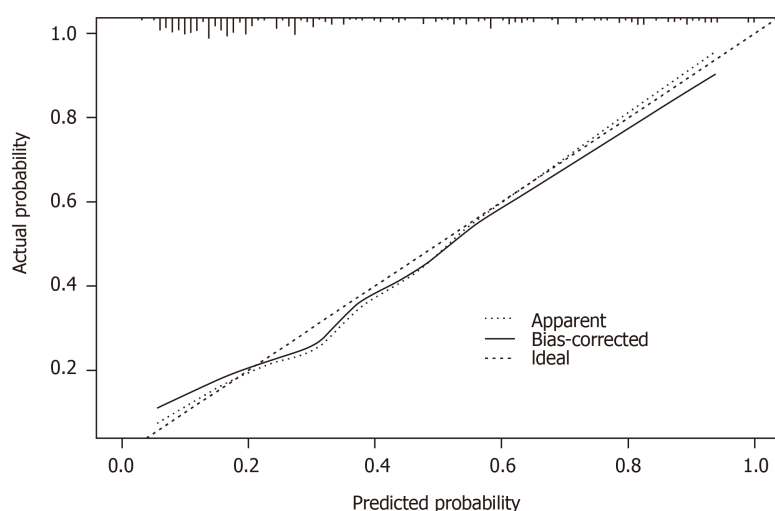
Figure 2 Calibration curve for deep vein thrombosis on the nomogram. The ideal line represents a perfect match between predicted and observed occurrence of deep vein thrombosis; Apparent line, prediction capability of the model obtained after data analysis; Bias-corrected line, prediction capability of the model obtained after bootstrap correction.

Respiratory failure, renal failure, and cardiovascular failure commonly take place in the clinical. OF can lead to long term bed rest and immobilization. Both of these contribute to DVT development[14]. However, in this study, only renal failure was in the final prediction model for DVT development. This factor was validated in a previous study[30]. Vascular endothelium is activated by proinflammatory cytokines in severe acute pancreatitis. This promotes the activation of coagulation cascades and circulating neutrophils[31]. Furthermore, neutrophils promote coagulation by inhibiting anticoagulant factors and releasing neutrophil extracellular traps[32]. These further promote thrombogenesis. Currently, mechanistic research shows that neutrophil extracellular traps hold promise for novel clinical treatment of DVT[32]. Patients with positive blood cultures have more severe inflammation than others. Additionally, infection has been thought to be a risk factor for venous thromboembolism[24]. Surgery is also a risk factor for venous thromboembolism[24]. Some NMAP patients need reoperation several times. More surgery times mean patients experience more frequent and longer bed rest.

Overall, our study first focused on the development of DVT in older NMAP patients, which has never been studied before. We analyzed the risk factors for DVT and built a nomogram model to predict the probability of developing DVT for NMAP patients. Proper use of this model can help physicians identify patients with a high risk of developing DVT.

There are several limitations in this study. First, this was a retrospective study, and the examination of DVT was not performed routinely. Thus, the diagnosis of DVT may have been missed in some patients. In addition, this was a single-center study, and validation was only performed in internal data. The results could be more convincing if external validation is performed. Moreover, due to the limitation of the sample size, potential bias may exist in the present study.

CONCLUSION

In this study, a nomogram model was built by combining eight independent risk factors for DVT. This nomogram score is a reliable and effective tool that can predict DVT in older patients with NMAP. This may help guide doctors in making sound decisions regarding the administration of DVT prophylaxis.

ARTICLE HIGHLIGHTS

Research background

Deep vein thrombosis (DVT) may cause pulmonary embolus leading to late deaths. The systemic inflammatory and hypercoagulable state of moderate and severe acute

pancreatitis (non-mild acute pancreatitis, NMAP) patients may contribute to the development of venous thromboembolism. Accurate prediction of DVT is conducive to clinical decisions.

Research motivation

There is a lack of a scoring model for predicting the development of DVT in NMAP patients.

Research objectives

We aimed to develop a prediction model for DVT in old NMAP patients.

Research methods

Univariate and multivariate logistic regression analyses were used to select independent risk factors associated with DVT. The selected risk factors were included in the nomogram. A validation set was constructed using bootstrapping with 100 resamplings. The accuracy and utility of the nomogram were evaluated by calibration curve and decision curve analysis, respectively.

Research results

Eighty DVT patients and 140 non-DVT patients were included in this study. Eight factors including age, sex, surgery times, D-dimer, neutrophils, any organ failure, blood culture, and classification constitute the prediction model. This model achieved good concordance indexes of 0.827 (95%CI: 0.769-0.885) and 0.803 (95%CI: 0.743-0.860) in the training and validation set, respectively.

Research conclusions

A reliable and effective nomogram model that can predict DVT in old patients with NMAP was constructed.

Research perspectives

The usability of the new model needs further validation by other center data.

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