

Original Article

Development of a nomogram to predict prolonged drainage time after cardiac surgery

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Received February 5, 2017; Accepted April 21, 2017; Epub June 1, 2017; Published June 15, 2017

Abstract: Background: Drainage tube indwelling after cardiac surgery is very important, and an accurate prediction of prolonged postoperative drainage risk can help surgeons choose a better treatment strategy. We aimed to develop a nomogram to predict the risk of prolonged drainage time after cardiac surgery. Materials and methods: We retrospectively collected data of 246 consecutive patients who underwent open cardiac surgery in Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University between 1 January 2014 and 1 January 2016. Patients who underwent surgery at an earlier period comprised the training cohort (n=152) for nomogram development; those who underwent surgery thereafter comprised the validation cohort (n=94) to confirm the model's performance. Multivariate logistic regression was used to identify independent risk factors associated with postoperative drainage time, which were later incorporated into the nomogram. Results: Univariate analysis found that sex, cardiopulmonary bypass time (CPB time), history of smoking, white blood cell count (WBC), preoperative creatinine (Cr), left atrial diameter (LAD), ejection fraction (EF) and prothrombin time-international normalized ratio (PT-INR) were significant predictors of postoperative drainage time. The nomogram's C-index was 0.78 in the training cohort and 0.66 in the validation cohort. The sensitivity of the nomogram was 80.0% (95% CI, 69.2-95) and 80.65% (95% CI, 62.5-92.5) in the training and validation cohorts, respectively. The area under the ROC analysis was 0.78 (95% CI, 0.71-0.86) and 0.66 (95% CI, 0.54-0.77) in the training and validation cohorts, respectively. Positive odds ratios were 2.43 (95% CI, 1.7-3.4) and 0.52 (95% CI, 1.1-2.0), and negative odds ratio were 0.30 (95% CI, 0.2-0.5) and 0.41 (95% CI, 0.2-0.9) in the training and validation cohorts, respectively. Conclusion: The nomogram achieved an optimal prediction of the risk of prolonged drainage time after cardiac surgery, which may be useful to make appropriate therapeutic choices.

Keywords: Cardiac surgery, postoperative drainage time, nomogram

Introduction

Although cardiothoracic surgery has been performed for decades and the techniques have improved, it is still among the most difficult and complicated types of surgeries. Additionally, the postoperative management and treatment of patients remain a serious problem [1].

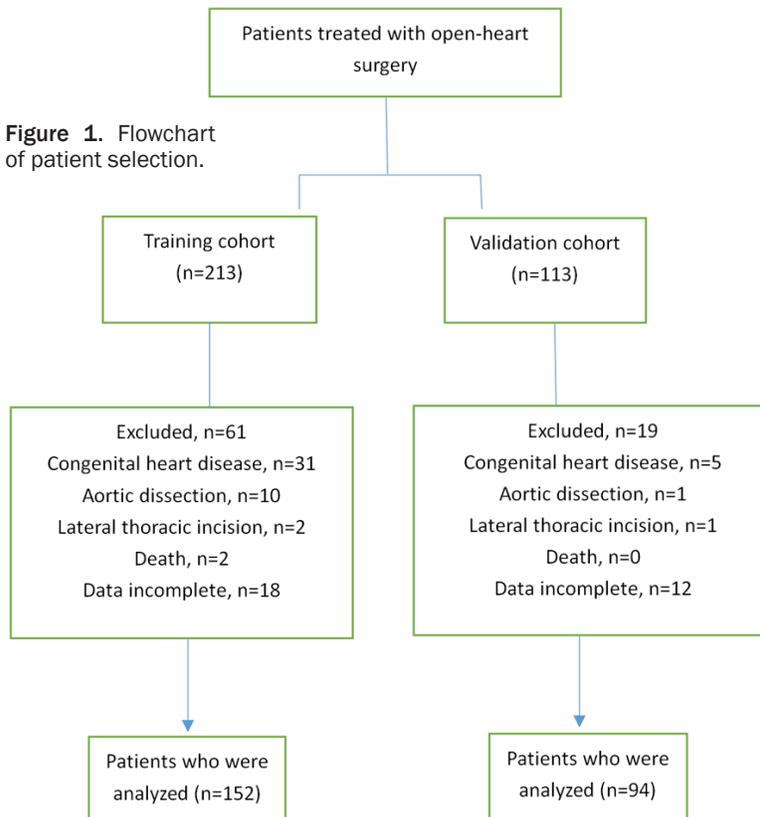
Placing drainage tubes is an intraoperative measure that plays an important role in managing cardiac surgery patients as it is useful to remove postoperative effusion, accelerate wound healing, and prevent postoperative infection. However, this measure also affects the

patients' early postoperative activities and it increases the risk of postoperative infection if the indwelling catheter time is prolonged. Moreover, it can also result in prolonged hospital stay, and thus may lead to the use of more medical resources that can be used for other patients.

Currently, the duration of the drainage time after cardiac surgery may be determined far too late as this is difficult to estimate. Therefore, the influence of diagnosis on early decision making is limited for this particular measure. Although many prediction models have been developed for cardiac surgery [2, 3], there is a

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Figure 1. Flowchart of patient selection.



lack of specific and practical methods to predict the risk of prolonged drainage time. Undoubtedly, developing a model for predicting the risk of prolonged postoperative drainage time is really a necessity. Such a model would be very useful for cardiac surgery patients as it may lead to identifying patients at high risk of requiring prolonged postoperative drainage time, and we can therefore take early intervention measures.

Of all the available models, a nomogram can provide individualized, evidence-based, highly accurate risk estimation. Moreover, nomograms are easy to use and can facilitate management-related decision making [4-6]. To our knowledge, we have established the first nomogram for risk estimation of prolonged postoperative drainage time in patients undergoing cardiac surgery.

Methods

Patients

Figure 1 shows the patient selection process in detail. Consecutive patients diagnosed with coronary heart diseases (CHD) or valvular heart

diseases (VHD) by cardiac ultrasonography and coronary arteriography (CAG), who underwent open-heart surgery by routine median sternotomy within four weeks at the affiliated Sun Yat-sen Memorial Hospital of Sun Yat-sen University were included in this study. These patients comprised the initial analysis set. Patients were excluded if they did not undergo open-heart surgery by routine median sternotomy [7], or undergo routine extracorporeal circulation before surgery. Additionally, patients diagnosed with congenital heart disease and aortic dissection were excluded. Finally, patients with incomplete data were also excluded. Patients treated between January 2014 and January 2016 (n=152) were screened for eligibility as the training cohort. Another cohort of 94

patients treated in the same Cardiac Center with the same selection criteria between January and April 2016 were enrolled into as an independent external validation set. The study protocol was approved by the Ethical Review Board of the Sun Yat-sen Memorial Hospital (No. 024, 2012). All the patients had the capacity to consent and written informed consent was obtained from all patients before the study.

Surgical procedure and drainage time

Cardiopulmonary bypass and surgery were performed by the standard procedure [8]. Open-heart surgery was performed using a routine median sternotomy approach; all procedures were performed using conventional ascending aorta and bicaval cannulation under moderate hypothermia. After cardiologic arrest, the surgery was performed as usual. Routine indwelling pericardial or pleural drainage tube was inserted after cardiac surgery, and the sternotomy incision was closed with a steel wire. As drainage amount is an important prognostic indicator, close monitoring of drainage was performed following surgery. However, there are no standard criteria for the timing of drain removal. In the existing literature, it is suggested that

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Table 1. Baseline demographics of patients undergoing cardiac surgery

Variables	Training (n=152)	Validation (n=94)	P-value
	Mean (25%-75%)	Mean (25%-75%)	
Age, year	58.1 (50-66)	50.99 (40-65)	0.048
Male, n (%)	80 (52.98%)	45 (47.87%)	0.304
BMI	23.79 (20.77-25.95)	21.17 (18.74-23.22)	<0.001
CPB time, min	134.19 (102-166)	117.3 (87-149)	0.001
Aortic-clamping time, min	89.4 (68-107)	80.27 (51.25-110)	0.02
Smoking, n (%)	53 (35.10%)	24 (25.53%)	0.113
Drinking, n (%)	20 (13.25%)	11 (11.70%)	0.761
Operation history, n (%)	40 (26.49%)	13 (13.83%)	0.017
Hypertension, n (%)	59 (39.07%)	23 (24.47%)	0.023
Diabetes, n (%)	25 (16.56%)	11 (11.770%)	0.322
CHD, n (%)	49 (32.45%)	29 (30.85%)	0.668
PT-INR	1.13 (1-1.14)	1.13 (1.01-1.11)	0.356
WBC, 10 ⁹ /L	7.7 (5.7-8.74)	7.66 (5.85-8.31)	0.919
Hb, mg/L	129.7 (121-140.75)	125.8 (110-141)	0.224
PLT, 10 ⁶ /ml	210.5 (162.25-250)	232.5 (180-281)	0.042
Neutrophil, %	62.96 (56.1-69.05)	59.92 (51-70.68)	0.255
AST, U/L	30.48 (19-30)	25.81 (13-33.5)	<0.001
ALT, U/L	33.81 (15.25-32.75)	29.88 (18-30.5)	0.526
Cr, umol/L	102.34 (78-110)	91.84 (75-100)	0.098
UA, umol/L	457.46 (355-530.5)	426.3 (279.5-492.75)	0.001
hs-CRP	11.03 (0.843-9.21)	6.5 (3.8-5.3)	<0.001
FBG, mmol/L	5.16 (4.32-5.5)	27.48 (2.03-19.34)	0.48
N-proBNP, pg/ml	1961.43 (261-2220)	2827. (299.95-3228)	0.25
ECG (AF, n (%))	45 (29.80%)	24 (25.53%)	0.423
LAD, mm	42.72 (36-48)	40.45 (34-47.75)	0.03
LVD, mm	52.99 (47-58.75)	21.25 (45-56.75)	0.183
RVD, mm	21.79 (19-23)	21.52 (18-23)	0.143
EF (%), mean ± SD	60.04 (53.25-68)	60.01 (54-67.75)	0.823
Drainage time, day	5.13 (3-6)	4.6 (3-5)	0.011

BMI: Body Mass Index; CPB time: cardiopulmonary bypass time; CHD: coronary heart disease; PT-INR: prothrombin time-international normalized ratio; WBC: white blood cell count; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine; UA: uric acid; hs-CRP: hypersensitive c-reactive protein; FBG: fasting blood-glucose; N-proBNP: N-terminal brain natriuretic peptide precursor; ECG: Electrocardiograph LAD: left atrial diameter; LVD: left ventricular dimension; RVD: right ventricular diameter; EF: ejection fraction.

drainage tube removal should be performed soon as possible, and always within 1 to 2 days after surgery. Smulders, Y. M [9] recommended drainage tube removal when amount of drainage was less than 100 ml within 8 hours. Gercekoglu, H [10] suggested that the drainage tube should be removed when the amount of drainage is less than 50 ml within 5 hours.

Data collection

Routine pre-surgical imaging (chest radiograph, cardiac ultrasonography, CAG, and 12-lead

electrocardiogram) was performed 3 to 5 days before the cardiac surgery. All laboratory examinations, including white blood cell (WBC) as well as liver and renal function parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine (Cr), were determined several days before the surgery. Endocrine and metabolic indices, including fasting blood-glucose and uric acid (UA), were performed. Moreover, for patients with AF under continuous oral anticoagulation, such as warfarin, the dynamic changes in prothrombin time-international normalized ratio (PT-INR) were recorded. Additionally, details of patients' past medical history and lifestyle history, including hypertension, diabetes and smoking and drinking habits, were recorded. Baseline demographic characteristics, such as age, body mass index (BMI) and sex, were also recorded. Intraoperative parameters of all patients, such as regular evaluations, including aortic clamp-

ing time and cardiopulmonary bypass (CPB) time were recorded by researchers. The amount of postoperative drainage was quantified and timing of tube removal was recorded.

Statistical analysis

All enrolled patients (n=246) were classified in the training (n=152) and validation cohorts (n=94). Continuous variables were tested by normality. The non-normally distributed continuous variables are expressed as means with the 25th and 75th percentile. The non-paramet-

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Table 2. Independent risk factors of prolonged postoperative drainage time after cardiac surgery

Variable	Time ≤4, n=76%	Time >4, n=76%	Univariate		Multivariate			
			OR (95% CI)	P-value	β	OR (95% CI)	P-value	
Sex, Male (%)	31 (40.8)	27 (35.5)	2.634 (1.367-5.075)	0.004				
Age, per	55.96 ± 14.5	60.4 ± 11.9	1.026 (1.001-1.052)	0.045				
CPB≥130 min	26 (34.2)	47 (61.8)	3.117 (1.607-6.045)	0.001	0.87	2.39 (1.11-5.13)	0.025	
Aortic clamping time ≥95 min	17 (22.4)	36 (47.4)	3.125 (1.547-6.307)	0.001				
Smoking, Yes	18 (23.7)	35 (46.1)	2.9 (1.448-5.908)	0.004	0.82	2.26 (1.07-5.07)	0.048	
Diseasestyle, CHD	23 (30.3)	36 (47.4)	0.482 (0.248-0.938)	0.032				
PT-INR≥1.15	11 (14.5)	22 (28.9)	4.425 (1.109-17.649)	0.035	1.26	3.51 (1.33-9.33)	0.012	
WBC≥6.6×10 ⁹ /L	34 (44.7)	50 (65.8)	2.376 (1.234-4.573)	0.01	0.86	2.35 (1.08-5.07)	0.032	
AST≥40 U/L	4 (5.3)	13 (17.1)	3.714 (1.152-11.974)	0.028				
ALT≥30 U/L	16 (21.1)	28 (36.8)	2.187 (1.063-4.503)	0.034				
Cr≥105 umol/L	11 (14.5)	33 (43.4)	4.535 (2.071-9.929)	<0.001	1.33	3.76 (1.56-9.03)	0.003	
Trioxypurin ≥470 mol/L	26 (34.2)	38 (50)	1.935 (1.004-3.732)	0.049				
N-proBNP≥125 pg/ml	64 (84.2)	74 (97.4)	6.937 (1.496-32.163)	0.013				
LAD≥41 mm	30 (39.5)	46 (60.5)	2.351 (1.227-4.506)	0.01				
EF<55%	12 (15.8)	27 (35.5)	2.939 (1.354-6.380)	0.006				

BMI: Body Mass Index; CPB time: cardiopulmonary bypass time; PT-INR: prothrombin time-international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase, CHD: coronary heart disease; N-proBNP: N-terminal brain natriuretic peptide precursor; LAD: left atrial diameter; EF: ejection fraction; Cr: creatinine; WBC: white blood cell count.

ric Mann-Whitney U test was used to compare between the training and validation cohorts. Categorical variables were tested by chi square test and were expressed as ratios. The training cohort patients were categorized into two groups by the postoperative drainage time: the prolonged group (n=76), the shortened group (n=76). Univariate analysis was used to detect the related risk factors which could affect the postoperative drainage time. Then, independent risk factors of prolonged postoperative drainage time were included in the multivariate analyses. The “RMS” package for R (R3.3.0, USA.) was used to make the nomogram model. At the same time, the model was validated by a random method of bootstrap sampling (1000 times) for the training and validation cohorts, as shown in the calibration curve. The risk score values of each patient were calculated with this nomogram model. Finally, the optimum cut-off value for the diagnosis was investigated by maximizing the Youden index. The detailed performance of the nomogram model to predict the risk of prolonged drainage time of patients undergoing cardiac surgery was assessed by the sensitivity, specificity, and respective areas under the curves (AUCs) of the receiver operating characteristic (ROC) curves with 95% confidence intervals (CI). All reported *P* values were two-tailed, and *P*<0.05 was considered statistically significant.

Results

Baseline demographics of patients receiving cardiac surgery

Table 1 summarizes the baseline characteristics of all 246 patients undergoing cardiac surgery. Of these, patients were divided into the derivation cohort (n=152) and validation cohort (n=94). Although we tried to randomly allocate patients, there were no significant differences in baseline characteristics between the training and validation sets. There were some differences between groups in CPB time (*P*=0.001), BMI (*P*<0.001), aortic clamping time (*P*=0.02), AST (*P*<0.001), hypersensitive C-reactive protein (*P*<0.001), uric acid (*P*=0.001), left atrial diameter (LAD) (*P*=0.03) and drainage time (*P*=0.011).

Independent factors of the risk for prolonged postoperative drainage time after cardiac surgery

We used data from the training cohort to identify independent factors associated with the risk for prolonged postoperative drainage time after cardiac surgery. In the training cohort, the results from the univariate analysis showed that sex, age, CPB time, ascending aorta blocking time, smoking, disease type, WBC count, PT-INR, preoperative Cr, ALT, AST, N-terminal

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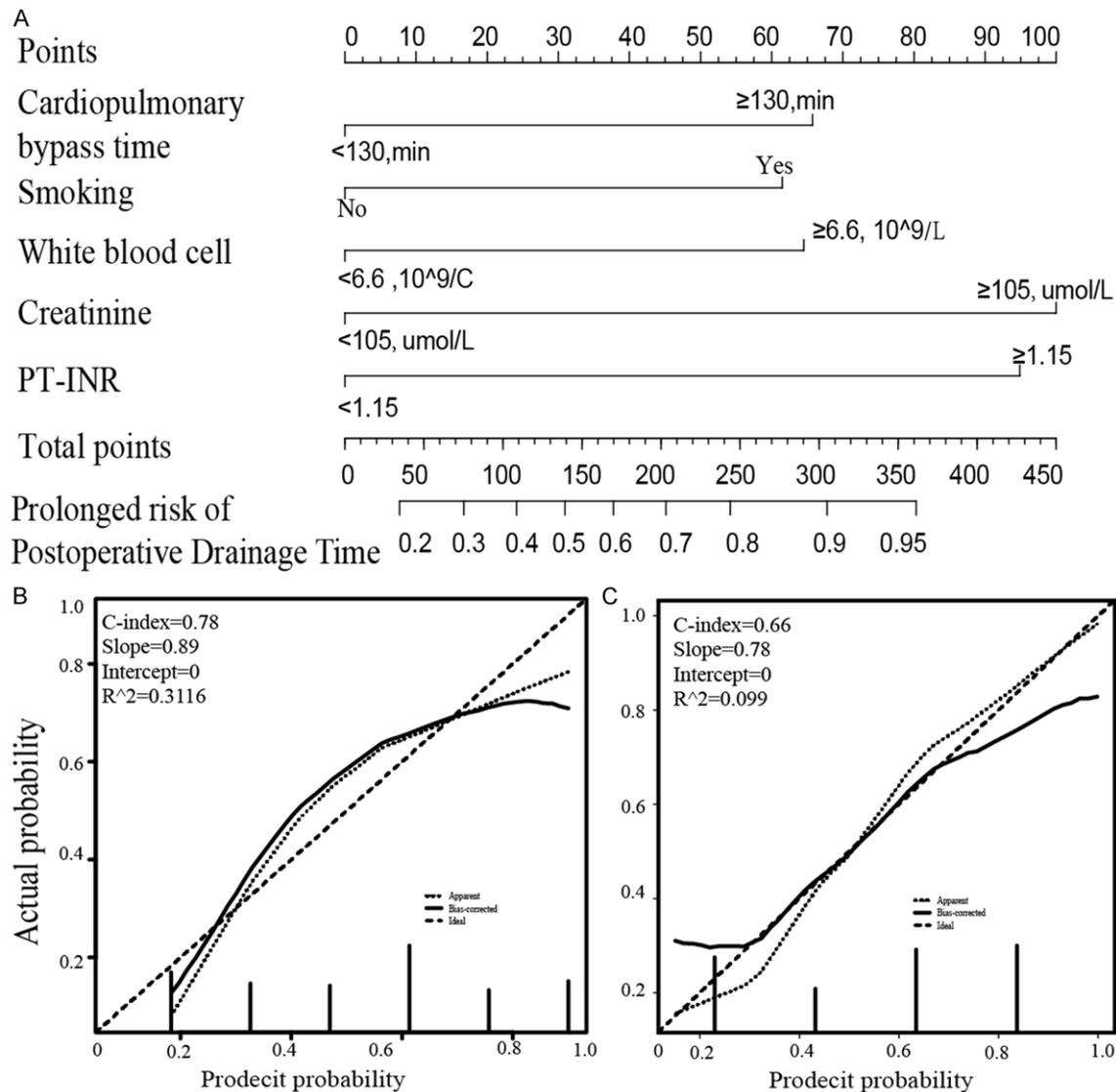


Figure 2. Development and validation of the nomogram model to determine the risk of prolonged postoperative drainage time. A. Nomogram model for determining the risk of prolonged postoperative drainage time. B. The calibration curve of the nomogram model effect for the training cohort. C. The calibration curve of the model in the validation cohort.

brain natriuretic peptide precursor, LAD and ejection fraction were significantly correlated with postoperative drainage time ($P < 0.05$), while other indicators, such as BMI and right ventricular diameter, had no obvious correlation with drainage time. The results from multivariable analysis suggested that smoking (odds ratios [OR], 2.26, 95% CI: 1.07-5.07, $P = 0.048$), preoperative Cr (OR, 3.76, 95% CI: 1.56-9.03, $P = 0.003$), WBC count (OR, 2.35, 95% CI: 1.08-5.07, $P = 0.032$), CPB time (OR, 2.39, 95% CI: 1.11-5.13, $P = 0.025$), PT-INR (OR, 3.51, 95% CI: 1.33-9.33, $P = 0.012$) were significant indepen-

dent risk factors for prolonged drainage time after cardiac surgery in the training cohort. The significant results of univariate and multivariate logistic analysis are presented in **Table 2**.

Development of a nomogram model for determining the risk of prolonged postoperative drainage time

A nomogram was constructed for predicting prolonged postoperative drainage time after cardiac surgery according to the results of the multivariate analysis (**Figure 2A**) of data from

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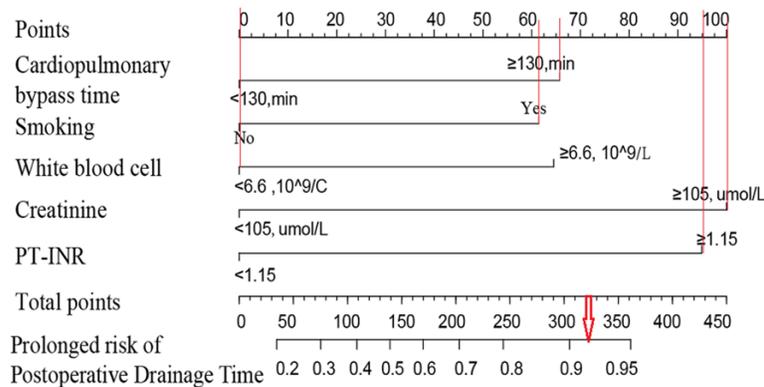


Figure 3. How to use the nomogram.

the training cohort. This nomogram's C-index was 0.78 in the training cohort, and it was 0.66 in the validation cohort (**Figure 2B**) which suggested that this nomogram model had good consistency in the calibration curve and could be used to predict prolonged postoperative drainage time after cardiac surgery.

How to use the nomogram model

Each variable has a corresponding score in this nomogram. We used the score value of each presented variable to calculate the comprehensive score and then find the corresponding risk ratio. For example, if a patient who smokes (62 points) will undergo open-heart surgery, has a WBC count less than $6.6 \times 10^9/L$ (0 points), CPB time greater than 130 minutes (66 points), preoperative PT-INR greater than 1.15 (95 points) and preoperative Cr greater than $105 \mu\text{mol/L}$ (100 points), then the corresponding total score is 323 ($62+0+66+95+100$), and the related risk of prolonged postoperative drainage time is greater than 92% (**Figure 3**).

Validation and performance of the nomogram

After the nomogram had been created, we put it into practice for external validation. Each of the patients in the validation cohort was analyzed to obtain a total score using the nomogram model. The cut-off point was set at 171 points. This nomogram's C-index was 0.66 in the validation cohort (**Figure 2C**). And the sensitivity of the nomogram was 80.0% (95% CI: 69.2-95) and 80.65% (95% CI: 62.5-92.5) in training and validation cohorts, respectively. The AUC of the ROC analysis was 0.78 (95% CI: 0.71-0.86) and 0.66 (95% CI: 0.54-0.77) in training and validation cohorts, respectively (**Figure 4**).

The positive ORs were 2.43 (95% CI, 1.7-3.4) and 1.52 (95% CI, 1.1-2.0); the negative ORs were 0.30 (95% CI, 0.2-0.5) and 0.41 (95% CI, 0.2-0.9) for the training and validation cohorts, respectively (**Table 3**). These results suggest that this nomogram model has a good predictive value for identifying patients at risk of prolonged postoperative drainage time.

Discussion

Prolonged drainage after open-heart surgery has been associated with a higher risk of complications [11], which can lead to a greater consumption of medical resources. Thus, early intervention is very important for high-risk patients. Unfortunately, there is no prediction model to estimate the risk of prolonged postoperative drainage time after cardiac surgery. In this study, we developed a nomogram model for this purpose which seems to have a great prediction value. Compared with the traditional forecast model, the nomogram is easier to use for cardiothoracic surgeons, it also has a greater value in clinical practice to achieve individualized predictions [6].

If postoperative pericardial effusion is considerable, prolonged drainage time is attributed mostly to post-pericardiotomy syndrome (PPS) [12, 13]. The PPS is associated with specific clinical symptoms, such as fever, pericarditis, or pleurisy after cardiac surgery. One of the main factors that may affect the postoperative prognosis significantly is the prolonged time of postoperative pericardial or pleural drainage. The pathogenesis of the cardiac effusion is not yet clear. Most of the previous studies suggested that an immune-mediated inflammatory response may be triggered [14], while other researchers considered that surgical trauma [15], inflammatory activity [16], or perioperative infection are associated with the amount of postoperative cardiac drainage [12]. The end results of this study are in line with those of previous studies [13, 14, 16, 17]. However, our study has also led to some new insights.

The univariate logistic analysis indicated that age, hypertension, and diabetes among other factors were not significantly related with the

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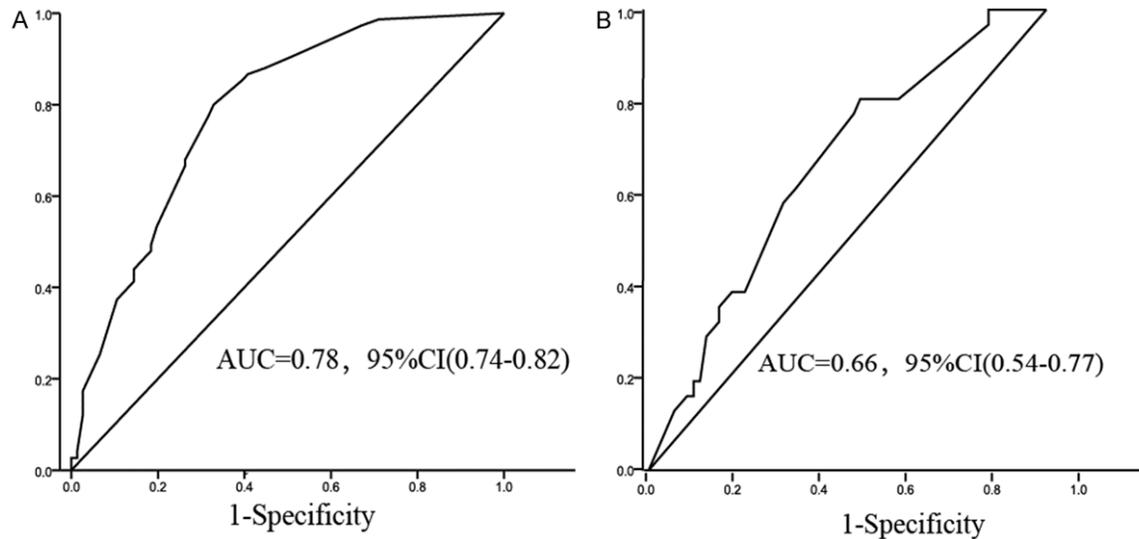


Figure 4. The receiver operator curve of the nomogram for patients (A) in the training cohort and (B) in the validation cohort.

Table 3. The performance of nomogram with ROC analysis in the training cohort and validation cohort

Variables	Training cohort (n=152)	Validation cohort (n=94)
AUC (95% CI)	0.784 (0.711-0.857)	0.660 (0.540-0.77)
Cut-off points (95% CI)	171	171
Sensitivity (95% CI)	80 (69.2-88.4)	80.65 (62.5-92.5)
Specificity (95% CI)	67.11 (55.4-77.5)	46.77 (34.0-59.9)
Youden index	0.4711	0.2742
PLR (95% CI)	2.43 (1.7-3.4)	1.52 (1.1-2.0)
NLR (95% CI)	0.3 (0.2-0.5)	0.41 (0.2-0.9)

and INR within the normal range, and a shorter CPB time were associated with a shorter postoperative drainage time among those undergoing open-heart surgery by routine median sternotomy. Ashikhmina et al. [13] also found that CPB time, renal function, disease types and immune function were correlated with postoperative drainage time; those with longer transit time, poorer renal function and poorer immune function experienced longer drainage time.

risk of prolonged drainage time. However, Lehto J [18] found that postoperative drainage time after cardiac surgery was correlated with diabetes, as patients with hyperglycemia were prone to require longer postoperative drainage time. Our study was conducted in a single center, and our sample size was not large, which may have led to weak statistical correlations between factors.

Although sex, age, aortic clamping time, disease types, white blood cell count, ALT, AST, N-proBNP, LAD, and left ventricular systolic function were associated with postoperative drainage time in the univariate logistic analysis, none of these factors were significantly correlated with drainage time in the multivariate analysis, and were therefore excluded from our model. The nomogram model showed that lack of smoking history, preoperative Cr, WBC count

The correlation between immune function and postoperative drainage time after cardiac surgery has been previously discussed. Jaworska-Wilczynska et al. [17] and Ashikhmina et al. [13] proposed that the immune function has a negative correlation with postoperative drainage time; thus, a worse immune function was associated with a longer drainage time. Conversely, Imazio et al. [12] reported a positive correlation between the immune function and postoperative drainage time after cardiac surgery. Our study results are similar to those by Nakatseva EV et al. [19], which suggest that a stronger inflammatory response will lead to a higher risk of prolonged postoperative drainage time that may be affected by the perioperative infection.

The nomogram also indicated that PT-INR has a significant influence on the postoperative drain-

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age time: with a higher the PT-INR, the probability of prolonged postoperative drainage time is greater. The pathophysiology studies suggest that PT-INR changes are dynamic and influenced by many factors [20], including treatment with drugs like warfarin which are used by AF patients [21]. However, we found in the present study that the preoperative INR value is closely related to the postoperative drainage tube indwelling time [8].

There is no safe and effective intervention measure for prolonged postoperative cardiac drainage time [22]. Previous studies reported that nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids may decrease the drainage, but NSAIDs and hormones are associated with many side effects, and thus these are not used in clinical practice [23, 24]. Recently, Mack et al. R [25], Finkelstein et al. [26] and Imazio et al. [27] found that colchicine is an effective drug for the early prevention of prolonged postoperative cardiac drainage time. Large randomized trials performed by Imazio in 2012 [28, 29], also validated this treatment, but colchicine has not been widely adopted in routine clinical practice.

The present study has some limitations. First, this retrospective study was susceptible to certain biases that could not be completely avoided. Second, a large sample size of patients undergoing cardiac surgery should be analyzed to improve the nomogram prediction effect. Finally, this study was dependent on the data of a single institutional cohort of patients from the Asia-Pacific region, and the main underlying diseases were VHD and CHD. Thus, prospective studies are required to validate the prognostic accuracy determined herein.

Conclusions

We found that smoking history, preoperative Cr values, WBC count, CPB time and PT-INR were independent risk factors for prolonged postoperative drainage time after cardiac surgery. Additionally, the nomogram model was developed based on the five independent risk factors with great accuracy and conduciveness.

Acknowledgements

This work was supported by the grants from the Natural Science Foundation Project in Guang-

dong province, China (Grant No. 2016A030-313295) and the Major Project Development and Emerging, Interdisciplinary Funding Projects of Sun Yat-sen University (Grant No. 15ykjc17b).

Disclosure of conflict of interest

None.

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