

Characteristics of Preoperative Acute Myocardial Infarction in Elderly Hip Fracture Patients and Construction of a Clinical Prediction Model: A Retrospective Cohort Study

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Background: The prognosis of elderly patients with acute myocardial infarction (AMI) is poor, and this study aimed to investigate the characteristics and predictors of preoperative AMI in elderly hip fracture patients and to propose a valid clinical prediction model.

Methods: We collected clinical data of older hip fracture patients from January 2019 to December 2020. The data collected include demographic and clinical characteristics, underlying diseases and laboratory results. In AMI patients, we further collected type of myocardial infarctions, clinical symptoms, electrocardiogram (ECG), Killip class and diagnosis method. The prediction model was constructed by using Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression analyses. In addition, the constructed prediction model was transformed into a nomogram. The performance of the model was evaluated using the area under receiver operating characteristic curve (AUC), calibration curve, and decision curve analysis (DCA). Bootstrapping was used for validation.

Results: There are 40 (4.2%) cases developed AMI in all 958 patients. There were 685 (71.5%) female patients and 273 (28.5%) male patients. Among 40 AMI patients, 38 (95.0%) had Type 2 myocardial infarction (T2MI) and 2 (5.0%) had Type 1 myocardial infarction (T1MI). The majority of these ECG were ST segment depression (57.5%). Most elderly AMI patients (67.5%) presented asymptomatic. Predictors for preoperative AMI were higher age (OR 2.386, 95% CI 1.126–5.057), diabetes (OR 5.863, 95% CI 2.851–12.058), Hb \leq 100 g/L (OR 3.976, 95% CI 1.478–10.695), CRP \geq 40 mg/L (OR 6.998, 95% CI 2.875–17.033), and ALB \leq 35 g/L (OR 2.166, 95% CI 1.049–4.471). Good discrimination and calibration effect of the model was showed. Interval validation could still achieve the C-index value of 0.771. DCA demonstrated this nomogram has good clinical utility.

Conclusion: This model has a good predictive effect on preoperative AMI in elderly patients with hip fracture, which can help to better plan clinical evaluation.

Keywords: hip fracture, myocardial infarction, characteristics, prediction model

Introduction

Osteoporosis-related hip fracture is common serious disease in older adults and associated with higher disability, mortality and economic costs.¹ It has been estimated the number of hip fractures in women and men will increase 3.5 times by 2025, owing to fast population growth.^{2,3} A study found that the mortality in the first year after hip fracture of elderly patients was 22–30%.⁴

Researches have suggested that the complications after fracture may carry a high burden and mortality in older patients.^{5,6} Among all the complications, AMI is one of the most devastating complications in hip fracture population.⁷ Additional studies have shown that the incidence of perioperative AMI of non-cardiac surgery ranges from 6% to 36%^{8,9}, and this has been associated with a higher mortality.¹⁰ A recent study found that hip fracture confers higher risk of subsequent AMI.¹¹ Shea et al found that the rate of early postoperative MI within the first seven days of surgery was 10.4%.¹² Several investigations demonstrated that postoperative MI significantly affects length of hospitalization, hospital mortality early and long-term mortality.^{8,13} The study mentioned that most perioperative AMI in elderly patients were asymptomatic or presented with atypical ischemic symptoms,¹⁴ which adds substantial difficulty to the diagnosing AMI. More attention should focus on these AMI patients. In addition, earlier studies on AMI related to hip fracture focus on patients with postoperative AMI after fracture surgery,^{15,16} while there are few studies on preoperative acute myocardial infarction.

In our study, we identified the characteristics of older hip fracture patients who developed AMI before fracture surgery. Furthermore, we constructed a LASSO regression and multivariate logistic regression analysis to predict individual risks and propose an effective clinical prediction model for preoperative AMI.

Materials and Methods

Patients and Groups

In this retrospective study, we collected data in the Third Hospital of Hebei Medical University from January 2019 to December 2020. The older adults (age ≥ 65) with hip fracture whose hospital admission less than 48 hours were included in our study. The study protocol was approved by the Institutional Review Board of the Third Hospital of Hebei Medical University with an informed waiver. The inclusion criteria were: (1) age ≥ 65 ; (2) Patients with hip fracture; (3) the injury time of hip fractures was ≤ 48 h before admission. The exclusion criteria were: (1) age < 65 ; (2) the time of hip fracture injury was > 48 h before admission incomplete medical information; (3) patients who had multiple fracture, periprosthetic fracture, or pathological fracture; (4) incomplete medical information. AMI was diagnosed as elevated troponin I $> 99\%$ of the upper reference limit (0.04 ng/mL) and must meet at least one of the following criteria: (1) new ischemic ECG changes (ST segment elevation or depression, evolutionary Q-wave, T waves symmetric inversion); (2) ischemic symptoms; (3) the abnormal imaging evidence of new myocardial loss or new regional wall motion.¹⁷ Patients with hip fracture were divided into two groups: AMI group and No-AMI group.

Data Collection

The information we collected contain gender, age, and fracture types, comorbidities, and laboratory data on admission. Laboratory data included white blood cell (WBC), Hb, ALb, CRP and blood glucose (Glu) levels. In AMI group, we further collected troponin I level, types of myocardial infarction, clinical symptoms, ECG, Killip class and diagnosis method. According to the pathological and clinical differences,¹⁸ AMI was classified into T1MI and T2MI. ECG could be shown as: ST segment elevation or depression, T wave inversion, and no new ST segment abnormalities. Killip class was categorized as Killip I, II, III, IV. The clinical symptoms include chest distress, chest pain, palpitations, nausea and vomiting, hypotension and no obvious symptoms.

Statistical Analysis

The statistical analyses were performed by IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY) and R software version 4.2.1 and the “glmnet” package (R Foundation for Statistical Computing, Vienna, Austria). Continuous parametric variables were presented as mean \pm standard deviation using Student's *t*-test or analysis of variance while Categorical variables were shown as numbers and percentages and compared using the chi-square test or Fisher's exact test. The prediction model was developed by LASSO and multivariable logistic regression and draw a nomogram. Area under the curve (AUC) of receiver operating characteristic curve (ROC) analysis was performed in order to assess how accurate the nomogram was at predicting risk. The calibration curve and decision curve analysis were used to assess calibration and clinical value of the nomogram separately. The level of significance was set at $p < 0.05$.

Results

The Characteristics of AMI

The characteristics of AMI are shown in Table 1. The types of AMI in older hip fracture patients were T1MI (5.0%) and T2MI (95.0%). The ECGs from these patients at first presentation showed ST segment depression (57.5%) and new T wave inversion (20.0%), and only a small proportion of them showed ST segment elevation (5%). In addition, 17.5% patients showed no new ST segment abnormalities. More than 2/3 of patients were asymptomatic (67.5%), other symptoms include chest tightness (10.0%), chest pain (7.5%), palpitations (7.5%), hypotension, nausea and vomiting (5.0%) and hypotension (2.5%). In these cases, there were 24(60.0%), 10(25.0%), 4(10.0%), and 2(5.0%) patients with killip I, killip II, killip III and killip IV, respectively. Twenty patients had a well-established coronary angiogram after AMI, 10 patients had a well-established coronary CTA, and 10 patients did not have both tests.

The Comparison of the AMI Group and No-AMI Group

As shown in Table 2, 40 (4.2%) occurred preoperative AMI. There were 958 patients were enrolled in our study, including 273 men and 685 women. The average age was 79.5 years old. Patients with AMI were older (age ≥ 80 , $p = 0.030$) than no-AMI patients. AMI patients had more comorbidities than non-AMI patients ($p = 0.001$), which include hypertension ($p = 0.041$), CHD ($p = 0.021$) and diabetes ($p = 0.000$). There were no differences in sex and fracture type between the AMI and no-AMI groups ($p = 0.198$, $p = 0.483$). In addition, among AMI patients, CRP on admission was higher ($p = 0.000$) and albumin lower ($p = 0.000$) compared with the non AMI ones. Other laboratory results showed no differences were considered significant ($p > 0.05$).

Table 1 The Characteristics of AMI

	Number	Percentage (%)
Type of myocardial infarction		
T2MI	38	95.0
T1MI	2	5.0
First episode ECG changes		
New ST segment depression	23	57.5
New T-wave inversion	8	20.0
No new ST segment abnormalities	7	17.5
ST segment elevation	2	5.0
Clinical symptoms		
No obvious symptoms	27	67.5
Chest tightness	4	10.0
Chest pain	3	7.5
Palpitations	3	7.5
Nausea and vomiting	2	5.0
Hypotension	1	2.5
Killip class		
I	24	60.0
II	10	25.0
III	4	10.0
IV	2	5.0
Diagnosis method		
Coronary angiography	20	50.0
Coronary CTA	11	27.5
None	9	22.5

Notes: Values are presented as the number (n) and percentage (%).

Table 2 The Comparison of the AMI Group and No-AMI Group

	Overall (n=958)	AMI (n=40)	No-AMI (n=918)	p value
Age	79.5±7.4	82.1±7.7	79.4±7.3	0.022
Age ≥80	510(53.2)	28(70.0)	482(52.5)	0.030
Gender n (%)				
Male	273(28.5)	15(37.5)	258(28.1)	0.198
Female	685(71.5)	25(62.5)	660(71.9)	
Fracture type n (%)				
Neck of femur	451(47.1)	21(52.5)	430(46.8)	0.483
Intertrochanteric	507 (52.9)	19(47.5)	488(53.2)	
Comorbidities n (%)				
Hypertension	424 (44.3)	24(60.0)	400(43.6)	0.041
Cerebrovascular disease (CVD)	404(42.2)	16(40.0)	388(42.3)	0.776
CHD	276 (28.8)	18(45.0)	258(28.1)	0.021
Diabetes	175(18.3)	17(42.5)	158(17.2)	0.000
Pulmonary disease	21(2.2)	2(5.0)	19(2.1)	0.492
Tumor	36(3.8)	3(7.5)	33(3.6)	0.397
Comorbidities≥3	150(15.6)	14(35.0)	136(14.8)	0.001
Hb≤100 g/L	220(23.0)	14(35.0)	206(22.4)	0.064
WBC≥10 ⁹ /L	228(23.8)	13(32.5)	215(23.4)	0.187
CRP≥40 mg/L	316(33.0)	24(60.0)	292(31.8)	0.000
ALB≤35 g/L	270(28.2)	21(52.5)	249(27.1)	0.000
GLU≥6 mmol/L	590(61.6)	26(65.0)	564(61.4)	0.650

Selection of Variables as Predictors and Derivation and Evaluation of the Prediction Model

LASSO regression initially included 15 variables, but eventually included 7 candidate variables that were significantly associated with AMI (age ≥ 80 , CHD, diabetes, comorbidities ≥ 3 , Hb ≤ 100 g/L, CRP ≥ 40 mg/L, ALb ≤ 35 g/L) were included (Figure 1a). When $\log(\lambda) = -4.4830$ and $\lambda = 0.0113$, the five risk factor weights were analyzed with the logistic regression model (Figure 1b). Table 3 summarizes the findings of the analysis among higher age (OR 2.386, 95% CI 1.126–5.057), diabetes (OR 5.863, 95% CI 2.851–12.058), Hb ≤ 100 g/L (OR 3.976, 95% CI 1.478–10.695), CRP ≥ 40 mg/L (OR 6.998, 95% CI 2.875–17.033), and ALB ≤ 35 g/L (OR 2.166, 95% CI 1.049–4.471). By combining these independent predictors, a model was built and presented as a nomogram (shown in Figure 2). Calibration curves used for estimating preoperative AMI in hip fracture patients showed good agreement across the cohort. The AUC for the predictive nomogram model was 0.771 (95% CI 0.697–0.846) (shown in Figure 3). With a p value of 0.783. The calibration curve indicated a good calibration effect of the nomogram. The internal validation C-index using bootstrapping (resampling = 1000) is 0.771. DCA demonstrated this nomogram has good clinical utility (shown in Figure 4).

Discussion

There were 40 (4.2%) older patients occurred AMI in 958 cases. The incidence of AMI after fracture was 4.2%. Among 40 AMI patients, T2MI was the most common type of myocardial infarction. The ECG of AMI in such patients mostly showed ST segment depression. 67.5% AMI patients were asymptomatic. The Killip class of the AMI was mostly Killip I. Five prediction factors constitute the prediction model, including Higher age, combined with diabetes, Hb ≤ 100 g/L,

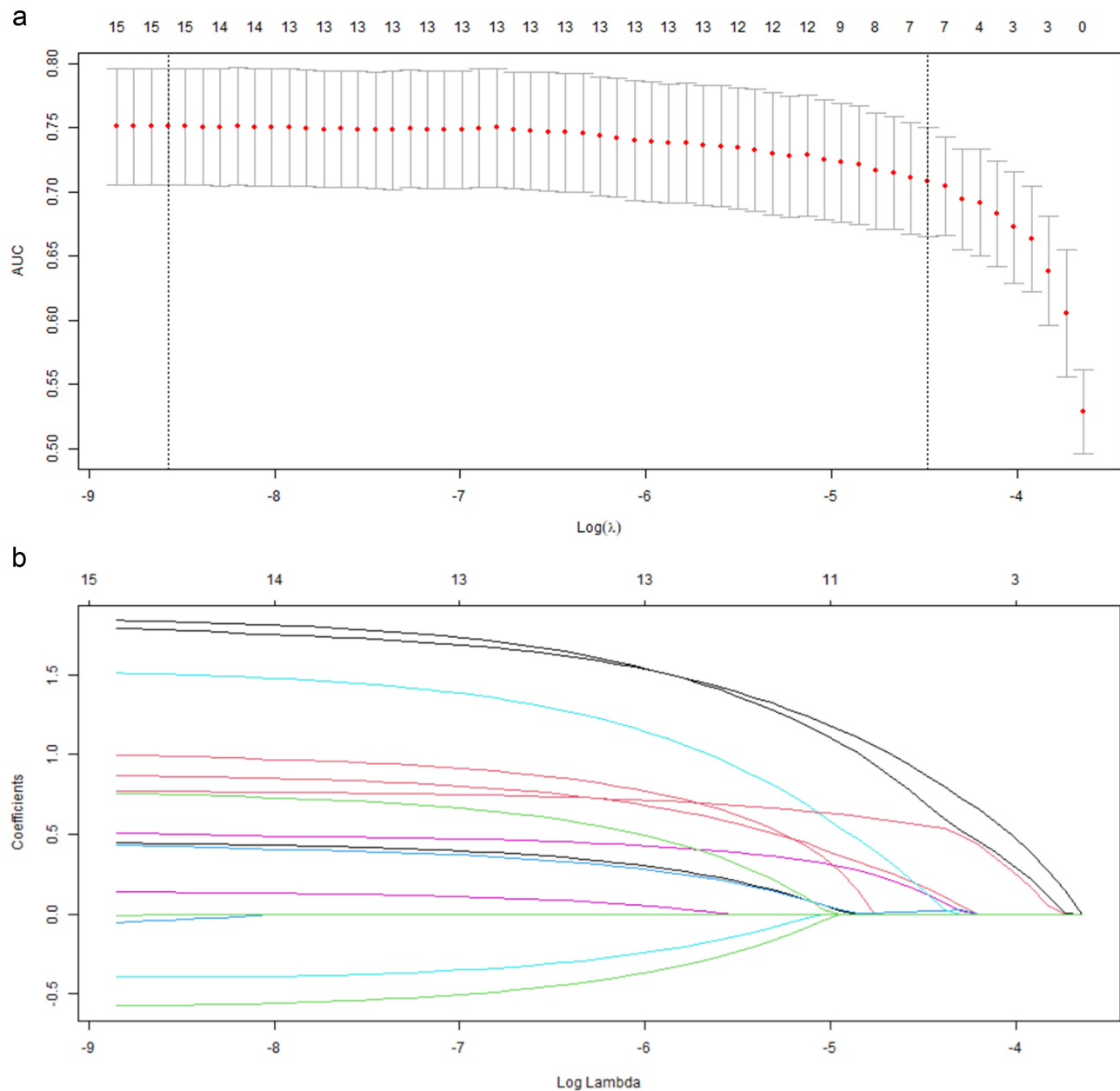


Figure 1 (a) The cross-validation results of LASSO-Logistic regression. (b) LASSO coefficient profiles of the variables.

Notes: The figure above shows the 10-fold cross-validation AUC score corresponding to different logs (λ). Under the 10-fold cross validation, $\lambda=0.000208$, and the AUC is 0.7497. In order to prevent overfitting, the rule of one standard deviation is adopted, $\lambda=0.000208, 0.012440$, and the AUC is 0.7115. The figure above shows a curve of coefficients for different λ values.

CRP ≥ 40 mg/L, and ALB ≤ 35 g/L, which are easily available in clinical practice. The nomogram could predict the preoperative AMI risk in hip fracture patients accurately.

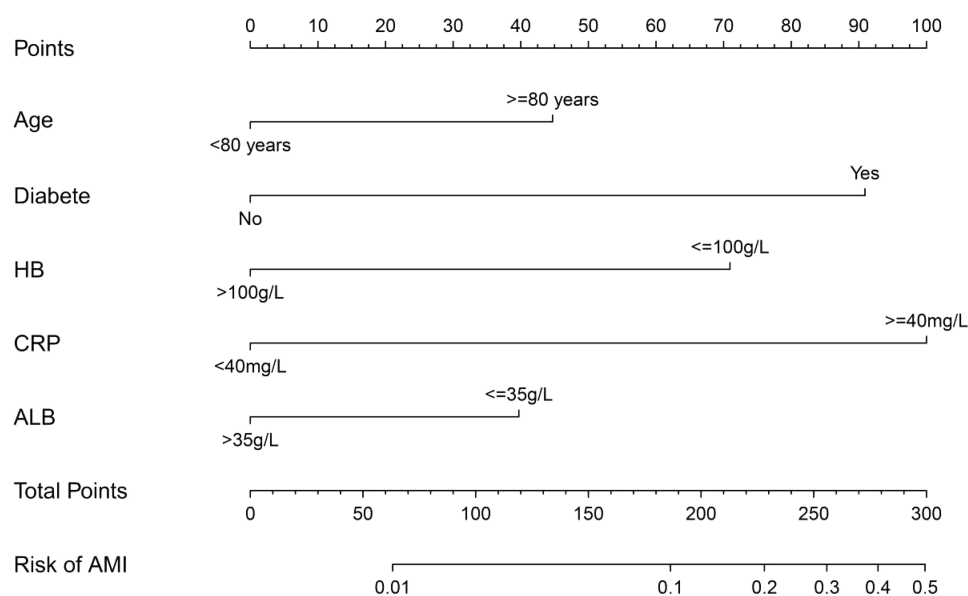
AMI is a complication associated with adverse outcomes of hip fracture patients, particularly in older adults. There is also evidence that risk factors for fracture and CVD overlap considerably.¹⁹ A recent study found that hip fracture was associated with an increased risk of AMI.¹¹ We suggest that the development of AMI after fracture in the elderly is associated with greater traumatic stress. The physical inactivity, blood loss, pain and fear after fracture increases the release of stress hormones such as thyroxine, glucagon, epinephrine, glucocorticoids and others,²⁰ which can exacerbate pre-existing cardiovascular risk. We think this contributed to the development of AMI after hip fracture. Our study differs

Table 3 Prediction Factors of Preoperative AMI in Elderly Patients After Hip Fracture

Variables	β	Odds Ratio	95% CI	p value
Age ≥ 80	0.807	2.386	1.126–5.057	0.023
Diabetes	1.769	5.863	2.851–12.058	0.000
Hb ≤ 100 g/L	1.380	3.976	1.478–10.695	0.006
CRP ≥ 40 mg/L	1.946	6.998	2.875–17.033	0.000
ALB ≤ 35 g/L	0.773	2.166	1.049–4.471	0.037

from previous studies, the AMI that occurred with hip fracture in our study was prior to hip surgery. The proportion of AMI after hip fracture was 4.2%. According to pathological and clinical differences, myocardial infarction is classified into different types. Patients with AMI were classified as T1MI and T2MI in our study, and the AMI patients mostly had T2MI. T1MI is an atherosclerotic thrombus due to plaque rupture or erosion, while T2MI results from an imbalance of myocardial oxygen supply–demand imbalance without atherothrombosis.¹⁸ On the basis of the original stenosis, stress reactions such as anemia and pain after fracture will aggravate ischemia, leading to the occurrence of T2MI. Patients with T2MI were older and had a higher proportion of women than men compared with patients with T1MI.¹⁸ This result overlapped with our results. In our study, some clinical symptoms of AMI patients were not obvious. This result is consistent with studies by others.²¹ Their ECGs were mostly in fact of ST segment depression, and about 1/3 of them was asymptomatic. A study has shown that silent AMI occurred more frequently in patients with diabetes.¹⁸ We think that this also may be related to cognitive decline in the elderly.²² The clinical symptoms of these patients were atypical and could be easily missed, which needs to draw our attention.

In our study, higher age, combined with diabetes were significant predictors of preoperative AMI. Numerous studies show that advancing age is one of the main causes for the increased incidence of fractures and perioperative complications.^{23,24} This may be due to the poorer health conditions and more underlying diseases in elderly people than younger individuals.²⁵ We obtained the same result in old AMI patients with hip fracture. The elderly hip fracture patients with AMI have a variety of underlying diseases, including hypertension, diabetes, CHD, etc. Hypertension and diabetes are the main risk factors for AMI,²⁶ which accelerate the progression of atherosclerosis. The formation and

**Figure 2** A model of risk prediction for AMI.

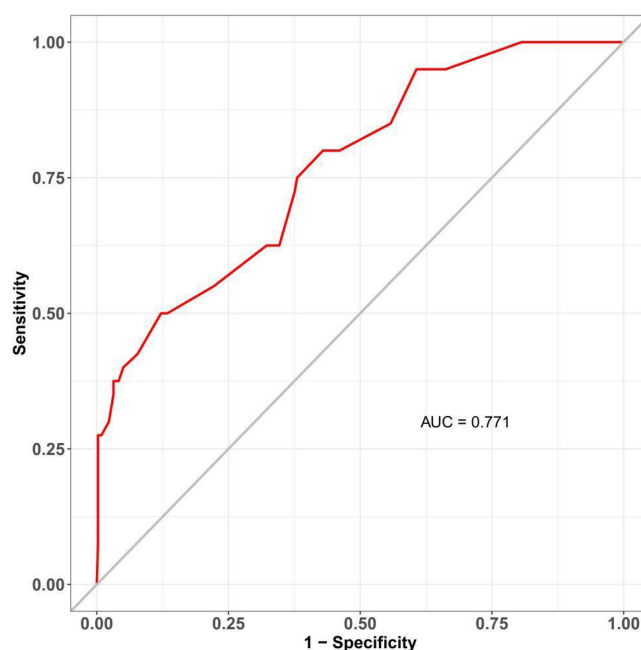


Figure 3 Analysis of ROC curve for the predictive values of preoperative AMI.

progression of atherosclerotic plaques is the major pathological basis of the cardio-cerebrovascular diseases.²⁷ Moreover, additional studies determined that patients with diabetes or stress-induced hyperglycemia were at increased risk of cardiac complications after hip fracture surgery.^{20,28} Our results suggest that diabetes also has an important predictive role for preoperative AMI.

Hb \leq 100g/L, CRP \geq 40mg/L, and ALb \leq 35 g/L also were significant predictors of preoperative AMI. CRP is a general stress-response protein, which is produced in response to inflammation.²⁹ CRP is considered to be a marker of atherosclerosis and CHD, and plays an important role in the formation of plaque in the arterial wall and the initiation of cardiovascular and cerebrovascular events.³⁰ Acute trauma after fracture leads to a systemic inflammatory response, and inflammatory factors such as CRP and IL-6 subsequently increase.³¹ This may initiate and exacerbate myocardial injury that can lead to AMI. The studies documented that anemia or low hemoglobin levels on admission increased the risk of CVD and fracture in older adults.^{32,33} Anemia is more likely to cause T2MI,³⁴ and we obtained the same results in patients with AMI after fracture. Hypoalbuminemia occurs in nearly 50% of elderly hip fracture patients and is associated with the development of perioperative complications and an increased risk of mortality.^{35,36} At present, the mechanism of perioperative acute myocardial infarction is not very clear. Some studies believe that it may be related to the strong stress suffered after fracture, sympathetic nerve excitation induces increased release of glucocorticoids, glucagon, epinephrine and other hormones, which can accelerate the production of oxygen-free radicals, damage cardiomyocytes, cause myocardial stunning and can also lead to microvascular contraction, endothelial function damage, affect cardiac function and promote microcirculation dysfunction and thrombosis, and ultimately leading to perioperative myocardial ischemia and injury.³⁷ Immuno-inflammatory promoted production of inflammatory cytokines and superoxide, leading to perioperative myocardial injury. Changes in the metabolic function may lead to anemia, low albumin and others.³⁸ Anemia and hypoproteinemia also increase the risk of perioperative AMI after hip fracture. For this reason, timely monitoring of Hb, Alb, and CRP levels on admission of fracture patients is beneficial for early assessment of the risk of AMI.

Limitations

Our study has some limitations worthy of discussion. First, this is a retrospective study and the inherent limitations of the design seem inevitable. Second, due to the small sample size, there is a possibility of selection bias. The conclusion cannot completely and reliably reflect the general clinical characteristics. Third, patients with AMI after hip fracture

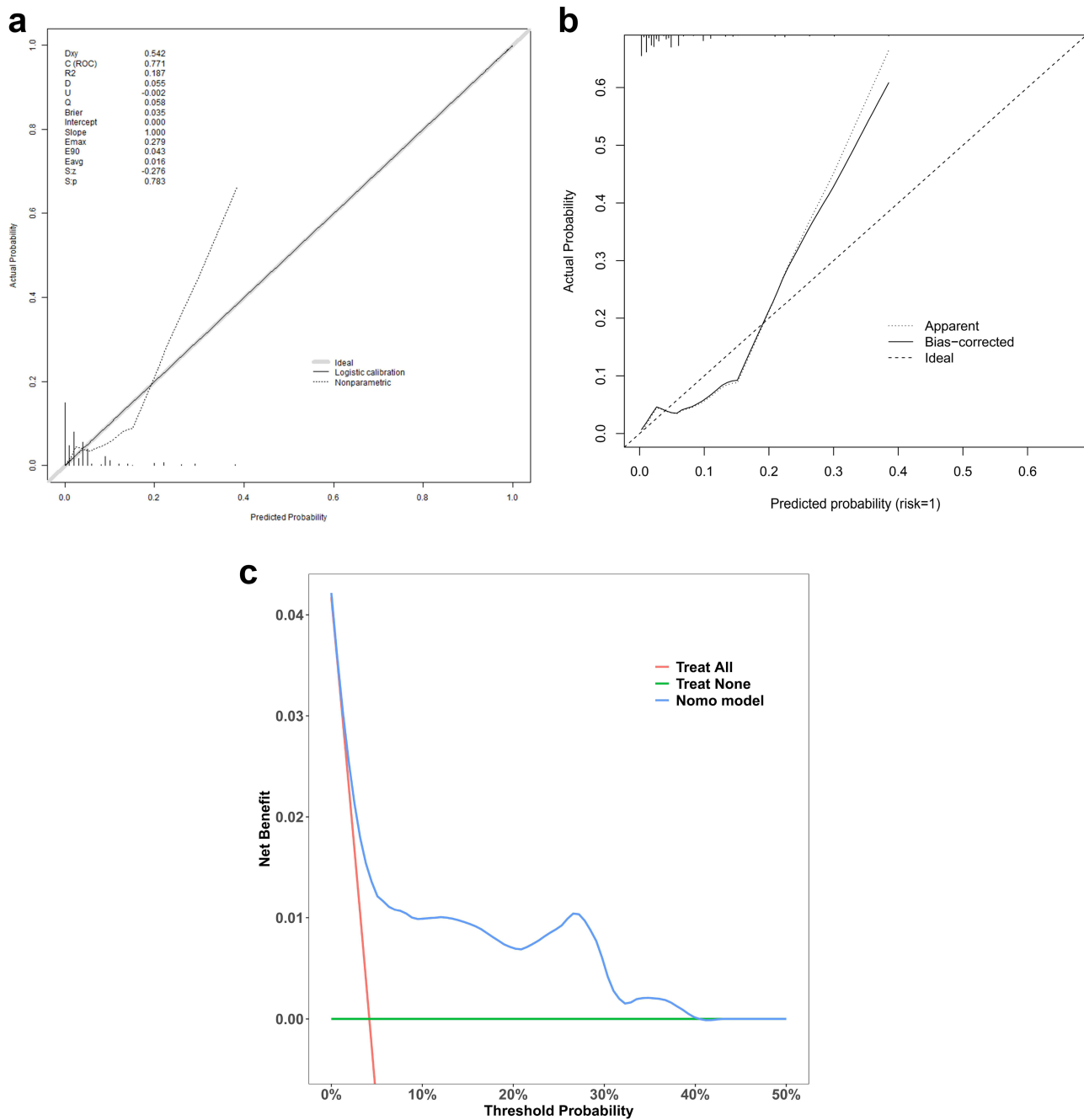


Figure 4 (a) Calibration curves of nomogram; (b) calibration curves of nomogram; (c) decision curve analysis of nomogram.

surgery were not included in this study. Further studies are needed to compare the different characteristics of AMI after hip fracture and AMI after surgery.

Conclusions

In summary, we observed that the overall incidence of perioperative AMI in older patients with hip fracture was 4.2%. Higher age, combined with diabetes, $Hb \leq 100g/L$, $CRP \geq 40mg/L$, and $ALB \leq 35 g/L$ were the independent risk factors for perioperative AMI, and a readable nomogram is further formed to facilitate its use in practice, thus reducing the potential risk of AMI. Future prospective and multicenter design studies will help validate our findings.

Abbreviations

AMI, Acute Myocardial Infarction; ECG, Electrocardiogram; LASSO, Least absolute shrinkage and selection operator; AUC, Area under receiver operating characteristic curve; DCA, Decision curve analysis; CHD, Coronary heart disease; Hb, Hemoglobin; CRP, C-reactive protein; Alb, Albumin; T1MI, Type 1 myocardial infarction; T2MI, Type 2 myocardial infarction; WBC, White blood cell; Glu, Blood glucose; CVD, Cardiovascular disease; coronary CTA, Coronary computed tomographic angiography.

Data Sharing Statement

The data used to support the findings of this study are available from Zhiqian Wang upon request.

Ethical Approval and Informed Consent

This study was approved by the institutional review board of the third Hospital of Hebei Medical University in compliance with the Helsinki and an exemption from the informed consent was obtained. All data were anonymized before the analysis to safeguard patient privacy.

Funding

This study was supported by the 2021 clinical medical talent training program funded by the Hebei provincial government.

Disclosure

The authors declared no potential conflicts of interest in this work.

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