

A Retrospective Analysis: Development and Validation of a Nomogram Model for Predicating 30-day Mortality in ST-Segment Elevation Myocardial Infarction Patients

Bin Wang (✉ 13575915795@163.com)

Dongyang People's Hospital <https://orcid.org/0000-0002-4709-0600>

MaoFeng Wang

Dongyang People's Hospital

ManZhen Ying

Dongyang People's Hospital

Chengjiang Liu

Anhui Medical University

Research article

Keywords: ST-Segment Elevation Myocardial Infarction,STEMI,nomogram

Posted Date: February 21st, 2020

DOI: <https://doi.org/10.21203/rs.2.24201/v1>

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Abstract

Objective: To develop and validate a personalized nomogram model to predict 30-day mortality in patients with ST-Segment Elevation Myocardial Infarction (STEMI).

Methods: A total of 1144 STEMI patients admitted to Dongyang People's Hospital from June 2013 to October 2019 were enrolled in the study and divided into two groups: Model group (n=801) and validation group (n=343). The biomarkers (maximum) in 24 hours after admission and the basic information of the patients were taken as variables, including creatinine, pro B-type natriuretic peptide (proBNP) and troponin T, as well as age, gender, etc. Logistic stepwise regression was employed to screen out independent risk factors that may led to death in patients with acute STEMI. A nomogram predication model was established with the screened independent risk factors as variables. Area under Receiver Operating Characteristic (ROC) curve and GiViTI calibration chart were adopted to estimate the classification accuracy and calibrate the predication model, respectively, and decline curve analysis (DCA) to assess the clinical efficiency of the model.

Results: Logistic stepwise regression revealed that proBNP, creatine kinase-MB (CK-MB), age, creatinine, lactic acid and percutaneous coronary intervention (PCI) surgery or not were independent risk factors that decided whether a STEMI patient would die. After the establishment of the model, area under ROC curve was 0.897 and 0.859 in model group and validation group, respectively, suggesting that the new model was a good classifier. *P* value of GiViTI calibration test was 0.834 and 0.262, respectively. $P > 0.05$ in GiViTI calibration indicated a high goodness of fit between the predication ratio of the model and the actual ratio, showing that the calibration of predications models in model group and validation group was complete. DCA curves in model group and validation group were both above two extreme curves, which suggested a good clinical significance.

Conclusion: The personalized model for predicating 30-day mortality in patients with STEMI will help screen out those STEMI patients who may die in a short term.

Introduction

Ischemic heart disease is the leading cause of death worldwide, with an increasing incidence [1]. In Europe, ischemic heart disease results in almost 1.8 million deaths every year, accounting for 20% of all deaths [2]. ST-Segment Elevation Myocardial Infarction (STEMI) is one major disease in patients with ischemic heart disease. Sweden may be the country with the most comprehensive STEMI recording information in Europe [3,4]. The morbidity of STEMI in Sweden was 58/100,000 in 2015 while that in other European countries ranged from 43–144/100,000 every year [5]. The mortality, however, is still at a high level. According to statistics of ESC countries, the in-hospital mortality in STEMI patients is between 4–12%. For this reason, when faced with acute myocardial infarction, the first-line clinicians are usually under much pressure due to the dangerous and severe disease condition, uncertainty in prognosis, etc. Besides, the top concern for a patient' family members is whether the patient will die. The Thrombolysis

in Myocardial Infarction (TIMI) and Global Registry of Acute Cardiac Events (GRACE) risk scores are tools to measure prognosis of myocardial infarction in clinical practices, but GRACE is more suitable for cases with non-ST segment elevation acute coronary syndromes (NSTEMI/ACS). Although TIMI risk score can be used to assess the short-term prognosis of STEMI patients, it is only available for patients who underwent thrombolysis and anticoagulant therapy^[9,10]. Currently, there is no available clinical methods to predicate whether STEMI patients (including those who did not receive thrombolysis therapy) will die in a short term. Therefore, it is necessary to develop a method to predicate whether STEMI patients will progress to death in a short term. This study aims to develop a reliable and accurate risk predication model, thus providing evidence and clues for early identification and screening of those STEMI patients who have a high mortality risk in a short term.

Materials And Methods

Patient enrollment

A retrospective analysis was carried out on 1144 patients with acute STEMI 1827 patients remained after excluding those complicated with acute chronic obstructive pulmonary disease (COPD), pulmonary thromboembolism (PTE), aortic dissection, pneumothorax, noncardiac shock, chronic renal failure, or hepatic failure from a total of 1839 patients and 1144 cases were finally included in the study after further excluding those with missing data) admitted in Dongyang People's Hospital (a 3B hospital) from June 2013 to October 2019. Inclusion criteria: 1. patients who suffered from chest distress or pain and then were definitely diagnosed with STEMI based on electrocardiogram, 2. Those who were complicated with PTE, COPD, aortic dissection, pneumothorax, shock or pulmonary infection were excluded, 3. Those with missing data were excluded. Among them, there were 100 deaths. All objects were randomly divided into two groups in line with R statistical software: Model group (n=80,173 deaths) and validation group (n=34,3 27 deaths). Patients who did not undergo thrombolysis or PCI were given platelet aggregation and lipid-lowering therapy to stabilize plaques in accordance with standard treatment procedures of myocardial infarction.

Moral statement

The research was approved by the ethics committee of Dongyang People's Hospital. All patients or their family members were informed of the research contents and signed the informed consent. All the data was analyzed anonymously and personal identifying information was deleted completely. This research was performed in accordance with principles in Declaration of Helsinki and its revisions.

Selection of risk factors

General data (gender, age, diabetes, hypertension), PCI or not, thrombolysis or not, troponin T (ng/mL), creatinine ($\mu\text{mol/L}$), pro B-type natriuretic peptide (proBNP) (pg/mL), creatine kinase-MB (CK-MB) (U/L), aspartate aminotransferase (AST) (U/L) and lactic acid (mmol/L) (The maximum values of these indexes in 24 hours after admission were taken as the objective data in blood tests) were collected and analyzed.

Statistical description

The enrolled patients were randomly divided model group and validation group using R software, with death as the classification standard (Troponin T above 10 and proBNP above 35,000 were treated as equal to 10 and 35,000 in EXCEL). First, the basic materials of two cohorts were compared: The categorical variables were presented as frequency (%) and tested by chi-square test. The continuous variables, which were in abnormal distribution and had a sample size below 5000, took median (quartile) and analyzed by rank sum test. The continuous variables were verified to see whether they were available for logistic regression and were in linear relation with logit (p). They were tested using BoxTidwell functions. In addition, all variables were tested with multicollinearity and variance inflation factors (VIF) were used for interpretation. Univariate and logistic stepwise regression were adopted and $p=0.05$ was taken as the testing standard for screening variables (Two models were developed using R software with 7 variables including troponin T in the multivariate logistic regression before stepwise regression. The statistical analysis revealed that there was no statistical significance between the two models, so stepwise regression was adopted for modeling). After that, 6 variables were included in the model, with which a personalized nomogram for predicating short-term death in STEMI patients was established in model group.^[11, 12] The predication model was assessed from the discrimination, calibration and clinical effects. The discrimination of a predication model means whether it can effectively predicate the survival or death in a patient with acute STEMI. The results can be evaluated by calculating the area under the ROC curve^[10]. A model is meaningful when AUC value lies between 0.5 to 1. The closer AUC for the model comes to 1, the better it is. In general, a model with AUC of 0.5-0.75 is considered to be meaningful while $\text{AUC}>0.75$ means it has excellent measure of separability^[13]. The calibration of the predication model means the consistency between the predication probability and observation density. A calibration chart was developed for judgment and it showed that the overlapping-degree of the logistic fitting curve and standard curve was high, suggesting a good predicating effect. $P>0.05$ indicated a good goodness-of-fit^[14]. In the present study, DCA curve (Figure IV) was used for assessing and interpreting clinical efficiency of the model: Y-axis is the clinical benefit of the model, X-axis is the risk value of disease and

model curve is the curve of the model. With All curve and None (two extreme curves) as standards, it was considered that the farther model curve was from two extreme curve, the better the clinical significance would be and it would generate clinical net benefits^[15, 16]. All the above procedures were completed in R software.

Results

1. Basic information of patients: In the present study, a total of 1,144 patients were enrolled and divided into model group (n=801) and validation group (n=343). The detailed information was shown in the chart(As shown in the TableI)
2. Results about whether continuous variables were in linear relation with logit (p): Based on p values, all continuous variables were in linear relation with logit (p) ($p>0.1$ was considered as statistically significant) and could be employed to perform logistic regression. (As shown in the TableII)
3. All variables were tested with multicollinearity and variance inflation factors (VIF) were used for interpretation: A VIF above 10 indicates multicollinearity and the closer it comes to 1, the less connected the variables are. (As shown in the TableIII)
4. Analysis results of univariate and logistic regression are shown in the Figure:(As shown in the TableIV).Logistic stepwise regression revealed that age, proBNP, creatinine, CKMB, LAC and PCI had p values <0.05 , with statistical significance, so they were used for modeling.
5. Establishment of nomogram

Six independent risk factors were included in the predication model based on multivariate logistic stepwise regression. Then a personalized nomogram predication model was established (FigureI). Interpretation of the nomogram: The score of each predication index was acquired based on the nomogram and the sum of all scores was taken as the total points. For example: A 60-year old patient with acute STEMI who did not receive PCI surgery and whose proBNP was 15,000 pg/mL, CK-MB 300 U/L, LAC 4 mmol/L and CR 110 μ mol/L will get a total score of 113 points, which corresponds to a death risk of 15%.

6. Evaluation of the model:

The area under ROC curve of the model cohort was 0.897, suggesting a good discrimination and the point of tangency was 0.132, which means that the death risk was above 0.132 in this patient in this model. It was considered to be a high risk in this paper. (FigureII)

Evaluation of predication accuracy: The calibration chart showed that the overlapping-degree of the logistic fitting curve and standard curve was high and $p=0.834$ suggesting a good goodness-of-fit. (Figure III)

Evaluation of clinical efficiency: DCA curve (Figure IV) was employed to evaluate the clinical efficiency. The model cohort was in the risk range of 10-90% and the curve was above the two extreme curves, without any intersection, suggest a good clinical efficiency of the model.

7. Validation of the model:

the validation of the model was also based on discrimination, calibration and clinical significance. ROC curve, calibration chart and DCA curve were drawn for validation group. The area under ROC curve of the model cohort was 0.897(FigureII), suggesting a good discrimination and while the p value of the validation cohort in calibration chart was 0.262, indicating a good goodness-of-fit of the model in this cohort(FigureIII). DCA curve was in the the risk range of 10-80% in validation group(FigureIV). All these suggested that it was valuable in clinical practices.

Discussion

STEMI is a critical part of acute myocardial infarction, a common clinical critical disease. Some recent studies underline that the wide application of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy and secondary prevention has brought down acute and long-term mortality of STEMI [2, 6, 7], but it still accounts for about 20% of the deaths due to acute myocardial infarction [17, 18]. STEMI is very worthy of investigation in view of the adverse social and economic effects caused by it.

Many factors may lead to death of STEMI patients, such as age, delayed treatment, history of myocardial infarction. Besides the above indexes, biomarkers have been used as potential clinical tools to predicate the risk of patients with acute myocardial infarction, which have provided a large amount of information to predicate prognosis [19]. Biomarkers like proBNP and hs-CRP [20, 21] have been proven to be correlated with prognosis of patients with myocardial infarction. During the screening of patients, testing results of biomarkers may often embody relevant factors that may affect prognosis. For example, a higher CK-MB index in a certain time range may indicate a delayed treatment or more cell deaths in the cardiac myocyte. The history of myocardial infarction may suggest a poor cardiac function of the patient in normal times, which will be reflected as a high proBNP [22, 23]. Therefore, biomarkers, which can reflect patients' state objectively, are valuable in the present study and they can also avoid bias caused by subjective factors.

In the present study a personalized nomogram for predicating 30-day death in STEMI patients was developed and its discrimination, predication accuracy and clinical efficiency were evaluated via ROC

curve, calibration chart and DCA curve, which all suggested a good significance, indicating that this model could be a good reference in clinical practices.

In comparison to TIMI, which only evaluates short-term mortality of STEMI patients^[9, 10], the model is not only available for STEMI patients who undergo thrombolysis, but also quantize the age of patients. The research has revealed the influence of different age groups on STEMI and eliminate the effects of subjective factors in killip classification. More research indexes have been included in the study, which can evaluate the prognosis of patients in a more comprehensive and objective way. The total score of a STEMI patient can be calculated with this model, which will enable clinicians to have a clear understanding about the death risk of the patient, communicate with family members in a better way and perform more effective clinical intervention on the one with high risk, thus lowering mortality.

There are still some deficiencies in the present study. (1) As a retrospective analysis, selection bias may occur inevitably. This research, however, has strictly limited the inclusion criteria and collected enough samples, of which, samples with missing data were removed to avoid bias caused by data interpolation, so it embodied the results calculated with actual clinical data. (2) All the data of the predication model is from one single center. Although randomization was adopted for grouping in the present study to perform internal validation, there is no external validation with data from other centers. (3) CRP indexes were not included in the research due to limitations in missing clinical data. Therefore, a more complete plan for acquiring indexes shall be designed in the following research. A project shall be designed in which blood samples will be collected from STEMI patients at admission, in 10–14 hours and in 20–24 hours after admission in the following 3–4 years. HS-CRP will be included besides the biomarkers in the present study and more deaths shall be collected to achieve a more accurate statistical analysis. Furthermore, external validation shall be conducted by persuading other medical centers to join in this research.

Conclusion

The personalized model for predicating 30-day mortality in patients with STEMI will help screen out those STEMI patients who may die in a short term.

Abbreviations

STEMI

ST-Segment Elevation Myocardial Infarction.

proBNP

pro B-type natriuretic peptide.

ROC

Receiver Operating Characteristic.

COPD

chronic obstructive pulmonary disease.

DCA

decline curve analysis.

VIF

variance inflation factors.

TIMI

Thrombolysis in Myocardial Infarction.

ACS

acute coronary syndromes.

AST

aspartate aminotransferase.

GRACE

Acute Cardiac Events.

Declarations

Ethics approval and consent to participate
Consent for publication

The Dongyang People's Hospital ethics committee that approved the study.

- Consent for publication

- Availability of supporting data
Availability of data and materials

- Competing interests
There is No Competing interests.

- Funding
There is No Funding source.

- Authors' contributions
Bin Wang. and MaoFeng Wang. collected the data, J.W. analysed the data, Chengjiang Liu. revised the statistical analyses, Bin Wang. wrote the paper, Chengjiang Liu. and ManZhen Ying revised the paper.

- Acknowledgements
Thanks for LE JIU system support, data collection depends on LE JIU system. Thanks for data provided by Dongyang people's Hospital

Conflict of interest :The authors declare no conflict of interest.

Ethical Approval and Consent to participate

- Consent for publication

- Availability of supporting data

- Competing interests

- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (Optional)

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Tables

	DEV	VAD	w/X2	Pvalue
Sex	Male 560 70.0%	Male 233 68.0%	0.35552	0.5510
	Female 241 30.0%	Female 110 32.0%		
PCI	No 374 46.7%	No 151 44.0%	0.58535	0.4442
	Yes 427 53.3%	Yes 192 56.0%		
Hyp	No 308 38.5%	No 120 35.0%	1.0889	0.2967
	Yes 493 61.5%	Yes 233 65%		
Dia	No 610 76.2%	No 248 72.3%	1.0003	0.1923
	Yes 191 23.8%	Yes 95 27.7%		
Thy	No 776 96.9%	No 330 96.2%	0.15879	0.6903
	Yes 25 3.1%	Yes 13 3.8%		
Age	60-81	62-81	135625	0.7326
	Mean 72	Mean 72		
Tropinin	0.379-4.720	0.462-5.275	131043	0.2165
	Mean 1.818	Mean 2.110		
Pro-bnp	490.4-5853	392.5-5805	140539	0.5763
	Mean 1778	Mean 1575		
Cr	70-98	68-98	137250	0.9811
	Mean 83	Mean 83		
Ckmb	28-89	27.5-94	131088	0.2197
	Mean 56	Mean 59		
Lac	1.4-2.9	1.4-3.15	130632	0.1878
	Mean 1.9	Mean 2		
Ast	40-273	40-283	132274	0.3195
	Mean 106	Mean 112		

Basic information of patients

Table 1

Variable	P value
age	0.9925
troponin	0.7866
Pro.bnp	0.4083
cr	0.3221
ckmb	0.6014
lac	0.6583
ast	0.7159

Table 2 Results about whether continuous variables were in linear relation with logit (p)

Variable	Vif
probnp	1.570283
cr	1.429362
age	1.295453
ckmb	1.214773
pci	1.205226
lac	1.199669
sex	1.159492
ast	1.153015
hypertension	1.103883
troponin	1.090189
diabetes	1.062807
thrombolysis	1.027963

Table 3 VIF of variables

	Univariate analysis		Multivariate analysis	
	Or[97.5%CI]	Pvalue	Or[97.5%CI]	Pvalue
Age	1.047660-1.107082	2.18*10 ⁻⁷	1.029383-1.101278	0.000388
Troponin	0.979424-1.064240	0.209	NA	NA
Pro.bnp	1.000085-1.000132	2.0*10 ⁻¹⁶	1.000041-1.000102	4.81*10 ⁻⁶
Thrombolysis	0.384449-4.962829	0.432	NA	NA
Cr	1.005532-1.010685	9.49*10 ⁻¹⁰	1.001291-1.006915	0.003142
Diabetes	0.140231-1.828305	0.947	NA	NA
Ckmb	1.001379-1.003525	6.35*10 ⁻⁶	1.002229-1.005383	2.38*10 ⁻⁶
Sex(female)	1.196167-3.433292	0.00803	NA	NA
Lac	1.377817-1.731043	9.66*10 ⁻¹⁴	1.100171-1.429743	0.000715
Hypertension	0.781491-2.374385	0.298	NA	NA
Pci.yes	0.149912-0.488986	1.88*10 ⁻⁵	0.213874-0.958216	0.043158
Ast	1.000534-1.001889	0.000434	NA	NA

Table 4 Analysis results of univariate and logistic regression

Figures

Nomogram diagram:

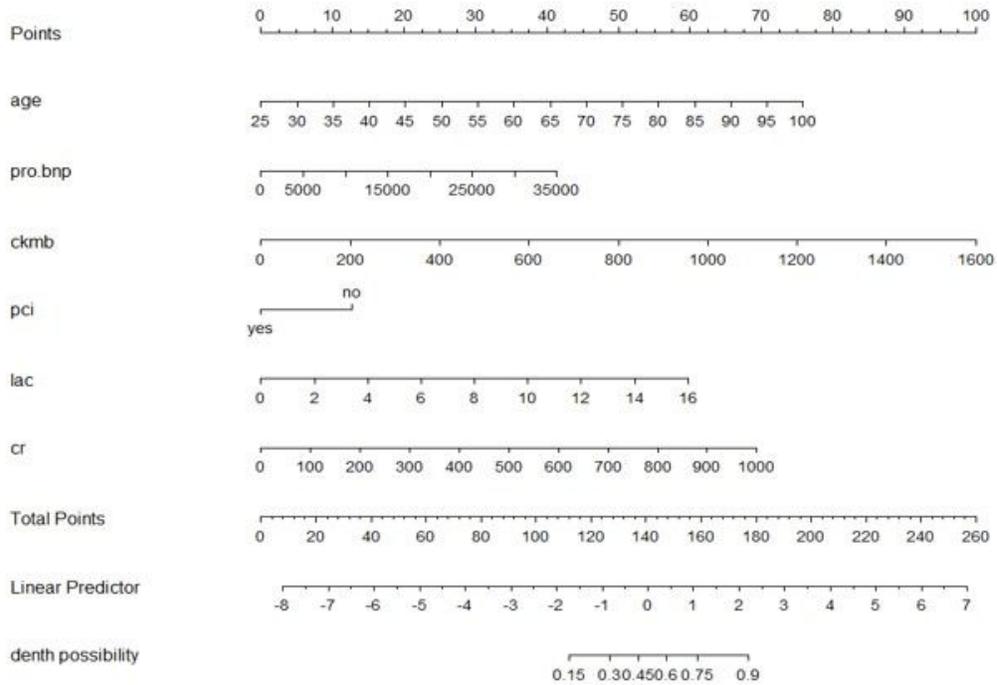


Figure 2

Six independent risk factors were included in the predication model based on multivariate logistic stepwise regression. Then a personalized nomogram predication model was established

Remarks :

The front is ROC curve of modeling crowd, and then there's ROC curve of validation population.

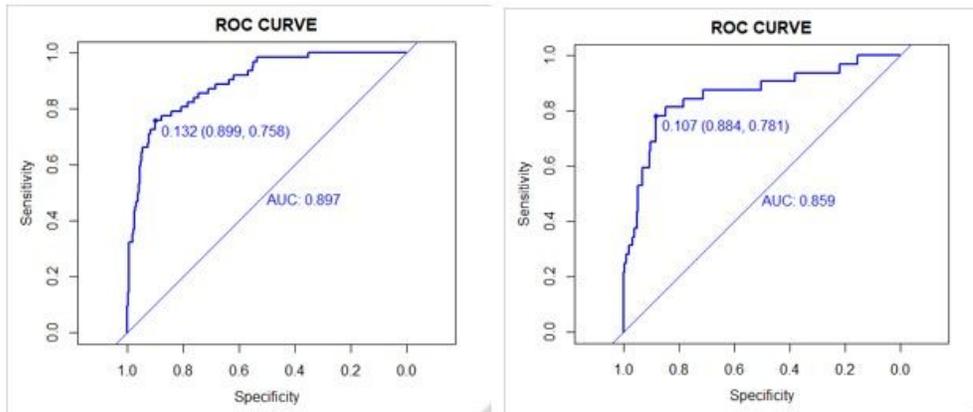


Figure 4

The area under ROC curve of the model cohort was 0.897, suggesting a good discrimination and the point of tangency was 0.132, which means that the death risk was above 0.132 in this patient in this model. It was considered to be a high risk in this paper

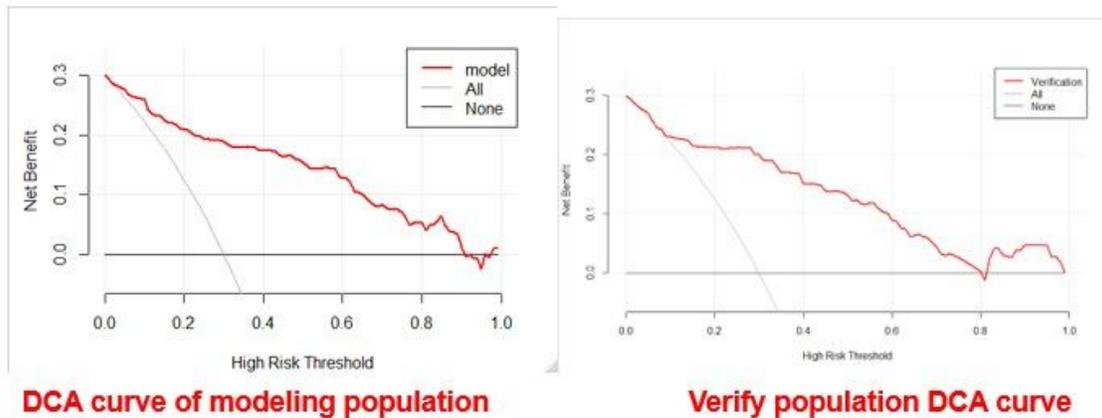


Figure 6

Evaluation of predication accuracy: The calibration chart showed that the overlapping-degree of the logistic fitting curve and standard curve was high and $p=0.834$ suggesting a good goodness-of-fit.

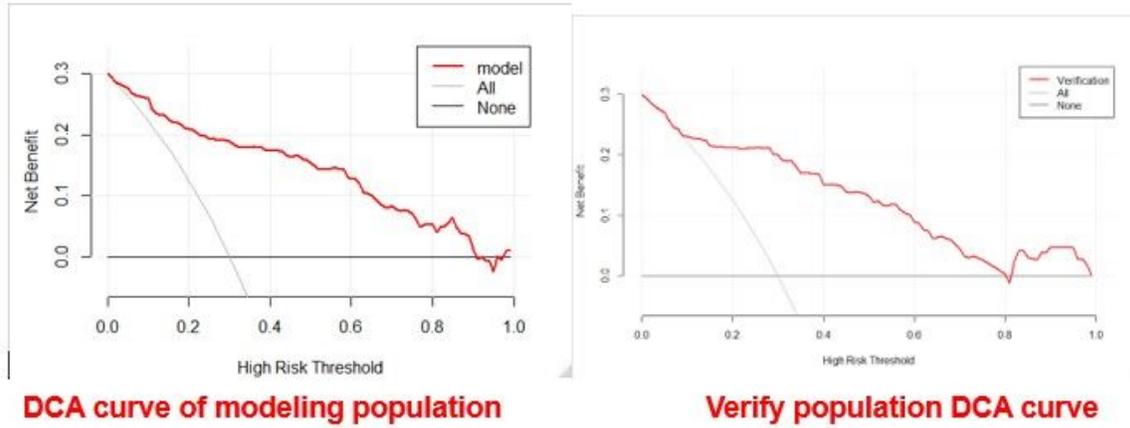


Figure 8

Evaluation of clinical efficiency: DCA curve