Development and External Validation of a Diagnostic Model for in-Hospital Mortality in Patient with Acute ST Elevation Myocardial Infarction

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Abstract

Objective: To develop and externally validate a diagnostic model of in-hospital mortality in the population of unselected real-world patients with acute ST elevation myocardial infarction (STEMI).

Design: Multivariable logistic regression of a cohort of hospitalized patients with acute STEMI.

Setting: Emergency department ward of a university hospital.

Participants: Diagnostic model development: Totally 2183 hospitalized patients with acute STEMI from January 2002 to December 2011. External validation: Totally 7485 hospitalized patients with acute STEMI from January 2012 to August 2019.

Outcomes: In-hospital mortality.

Results: Totally 61 (2.8%) patient died in the development dataset and 127(1.7%) patient died in the validation dataset. The strongest predictors of in-hospital mortality were age and Killip classification. We developed a diagnostic model of in-hospital mortality. The area under the receiver operating characteristic (ROC) curve (AUC) was $0.9126 \pm 0.0166$, 95% confidence interval (CI) $= 0.88015 \sim 0.94504$ in the development set. We constructed a nomograms using the development database based on age and Killip classification. The AUC was $0.9305 \pm 0.0113$, 95% confidence interval (CI) $= 0.9083 \sim 0.9527$.
CI= 0.90827 ~ 0.95264 in the validation set. Discrimination, calibration, and decision curve analysis were satisfactory.

Conclusions: We developed and externally validated a strong diagnostic model of in-hospital mortality in patients with acute STEMI.

We registered this study with WHO International Clinical Trials Registry Platform (ICTRP) (registration number: ChiCTR1900027129; registered date: 1 November 2019).

http://www.chictr.org.cn/edit.aspx?pid=44888&htm=4.

Key Words: coronary disease  ST elevation myocardial infarction  in hospital mortality  nomograms

Background

Coronary heart disease remains the leading cause of mortality. [1] In American, the estimated annual incidences of acute myocardial infarction (AMI) events is 605,000. [1] In Europe, in-hospital mortality of patients with ST elevation myocardial infarction (STEMI) varies between 4 and 12%. [2] Prevention of in-hospital mortality is a crucial step. A tool is needed that can help identify patients with increased in-hospital mortality early. The Global Registry of Acute Coronary Events (GRACE), [3-6] and the Thrombolysis in Myocardial Infarction (TIMI) [7] risk scores are too cumbersome to be readily applied. We have developed and externally validated a diagnostic model for in-hospital mortality in the population of unselected real-world patients with acute STEMI. The aim of our study was 4-fold: (1) to identify predictive factors; (2) to develop a diagnostic model; (3) to create a nomogram and (4) to externally validate diagnostic model.

Methods

We used type 2b of prediction model studies covered by Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement. [8] The data was divided into two groups non-randomly according to time: one group was used to develop a
prediction model, and the other group was used to evaluate its prediction performance. Type 2b was called "external verification study". The derivation cohort was 2183 patient with acute STEMI from January 2002 to December 2011 in Beijing Anzhen Hospital, Capital Medical University. The validation cohort was 7485 patient with acute STEMI from January 2012 to August 2019 in Beijing Anzhen Hospital, Capital Medical University. Inclusion criteria. 1. patient hospitalized with STEMI; 2. age of more than 18 years. We established the diagnosis of AMI and STEMI base on fourth universal definition of myocardial infarction. Exclusion criteria. none. It was a retrospective analysis and informed consent was waived by Ethics Committee of Beijing Anzhen Hospital Capital Medical University. Outcome of interest was in-hospital mortality. All cause in-hospital mortality defined as cardiac or non-cardiac death during hospitalization. The presence or absence of in-hospital mortality was decided blinded to the predictor variables and based on the medical record. We selected 12 predictor according to clinical relevance and the results of baseline descriptive statistics. Since the purpose of this work was to develop a diagnostic model that could be calculated at the time of the first medical contact, we were only interested in clinical variables that could be easily get in the emergency department. The potential candidate variables were age, sex, Killip classification, atrioventricular block (AVB), atrial fibrillation (AF), and medical history such as hypertension, diabetes, myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), cerebrovascular disease (HCD), chronic kidney disease (CKD). All of them based on the medical record and blinded to the predictor variables. AF defined as all type of AF during hospitalization. AVB defined as all type of AVB during hospitalization. Some people suggested that each candidate variable had at least 10 events for model derivation and at least 100 events for validation studies. Our sample and the number of deaths in the hospital exceeded all methods of determining the sample size, so it was expected to provide a very reliable estimate. To ensure reliability of data, we excluded patient who had missing information on key predictors: in-hospital mortality, age and Killip classification.

Statistical Analysis
We kept all continuous data as continuous and retained on the original scale. We used univariable and multivariable logistic regression models to identify the correlates of in-hospital mortality. We entered all variables of Tables 1 into the univariable logistic regression. Based on the variables significantly generated by univariate logistic regression, we constructed a multivariate logistic regression model using the backward variable selection method. We use Akanke Information Criteria (AIC) and Bayes Information Criteria (BIC) to select predictors. It considers model fitting and penalizes the estimated number of parameters, which is equivalent to using $\alpha = 0.157$.

[8] Internal validity was evaluated by means of bootstrap techniques. [8] We assessed the predictive performance of the diagnostic model in the validation data sets by examining measures of discrimination, calibration and decision curve analysis (DCA). [8] Discrimination is the ability of the diagnostic model to differentiate between patient who with and without in-hospital mortality. This measure is quantified by calculating the area under the receiver operating characteristic (ROC) curve (AUC). [8] Calibration refers to how closely the predicted in-hospital mortality agrees with the observed in-hospital mortality. The Brier score is an aggregate measure of disagreement between the observed outcome and a prediction—the average squared error difference. We used DCA to describe and compare the clinical effects of diagnostic model. [8] We performed statistical analyses with STATA version 15.1 (StatCorp, College Station, TX), R version 4.0.0 (R Development Core Team; http://www.r-project.org) and the RMS package developed by Harrell (Harrell et al). All tests were two-sided and a P value <0.05 was considered statistically significant.

Results
We drew a flow diagrams (Figure 1). Totally 61 (2.8%) patient hospitalized died in the development dataset. Baseline characteristics of the patient was shown in Table 1. Six variables (age, sex, history of myocardial infarction, history of CABG, Killip classification, and AF) were significant differences in the two groups of patient (p < 0.157). After application of backward variable selection method, AIC and BIC, age remained as a significant independent predictor of in-hospital mortality; Killip classification remained as a rank variable of in-hospital mortality. Results are
shown in Table 2 and Table 3. According to the above risk factors, we can calculate the predicted probability of in-hospital mortality using the following formula: 

\[ P = \frac{1}{1 + \exp(-(-8.771 + 0.056 \times \text{AGE} + 2.11 \times \text{KIII} + 3.67 \times \text{KIV})))} \]

KIII = Killip III (0=No, 1=Yes), KIV = Killip IV(0=No, 1=Yes). The ROC curve was drawn. AUC was 0.9126±0.0166, 95% confidence interval (CI) = 0.88015 – 0.94504. We constructed the nomogram (Figure 2) using the development database based on the two prognostic markers: age and Killip classification. The results of internal validation showed that the model’s prediction discrimination rate (c index is 0.83) was not “over-optimism”, and the c index remains at 0.83 when using the bootstrap technique. Totally 1.7% (127/7485) hospitalized patients suffered in-hospital mortality in the validation data sets. Baseline characteristics of the patient was shown in Table 4. We can calculate the predicted probability of in-hospital mortality using the following formula: 

\[ P = \frac{1}{1 + \exp(-(-8.771 + 0.056 \times \text{AGE} + 2.11 \times \text{KIII} + 3.67 \times \text{KIV})))} \]

KIII = Killip III (0=No, 1=Yes), KIV = Killip IV(0=No, 1=Yes). We drew the ROC curve. AUC was 0.9305±0.0113, 95% CI= 0.90827 – 0.95264. We drew a calibration plot (Figure 3) with distribution of the predicted probabilities for individuals with and without in-hospital mortality in the validation data sets. Hosmer-Lemeshow chi2(10) = 10.82, Prob > chi2 = 0.3721 >0.05. Brier score = 0.014 < 0.25. DCA (Figure 4) in the validation data sets.

**Discussion**

We assessed the predictive performance of the diagnostic model in the validation data sets by examining measures of discrimination, calibration and DCA. AUC was 0.9383±0.01, 95% CI= 0.919-0.957 in the validation data sets. Hosmer-Lemeshow chi2(10)=10.82, Prob>chi2 = 0.3721 >0.05. Brier score < 0.25. Discrimination, calibration, and DCA were satisfactory.

The mortality in STEMI patients is affected by many factors, including advanced age and Killip class, and so on. In this study, we investigated the predisposing factors of in-hospital mortality in patients with acute STEMI. A frequency of in-hospital mortality was 2.8% (61/2183). Age is a significant independent predictor of in-hospital mortality; Killip classification is a rank variable of
in-hospital mortality.

High Killip classification is associated with an increased risk of in-hospital mortality. Killip classification involved bedside stratification. This stratification was based on the physical examination. The higher the Killip class, the greater the risk of death.\[11-19\]

Advanced age has been reported to be an independent risk factor of in-hospital mortality. As older patients may present with atypical symptoms that result in treatment delays.\[20\] Elder patients have a higher risk of mechanical complications.\[10\] Elder patients have more comorbidities and are less likely to receive reperfusion therapy.\[21-23\]

Granger CB et al. observed that age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac enzyme findings, and heart rate were independent predictors of in-hospital mortality among 11,389 patients in the GRACE.\[3\] Karen S. Pieper et al. generated the updated GRACE risk model and a nomogram.\[5\]

The GRACE risk model has since been upgraded\[6\] and simplified.\[24\] TIMI Risk Score predicting 30-day mortality at presentation of fibrinolytic-eligible patients with STEMI.\[7\] C-ACS\[25\] is simple four-variable scores that have been developed to enable risk stratification at first medical contact.

So far, clinicians and researchers usually use TIMI or GRACE scores to guide treatment decisions. Our diagnostic model of in-hospital mortality builds upon these studies in several ways. Our in-hospital mortality diagnostic model outperforms these studies in several ways. It is not a relative value but an absolute value. It includes only baseline factors, including age and Killip classification. It is easily calculated at patient presentation. No matter what treatment is used (such as invasive care or antithrombotic drugs), it can retain discriminatory, thereby improving its effectiveness in clinical decision-making. It was developed in unselected real-world populations, including those who received initial invasive strategies and catheterization, and those who were conservatively treated without revascularization. The nomogram we built for the in-hospital
mortality captures most of the diagnostic information provided by the complete logistic regression model and is easier to use at the bedside.

**Study Limitations**

This is a single center experience. Some patients were enrolled >10 years ago thus their treatment may not conform to current standards and techniques.

**Conclusions**

We developed and externally validated a strong diagnostic model of in-hospital mortality in patients with acute STEMI.

**List of abbreviations.**

AF = atrial fibrillation; AIC = Akanke information criterion; AMI = acute myocardial infarction; AUC = area under the receiver operating characteristic curve; AVB = atrioventricular block; BIC = Bayesian information criterion; CABG = coronary artery bypass grafting; CI = confidence interval; CKD = chronic kidney disease; HCD = history of cerebrovascular disease; PCI = percutaneous coronary intervention; MI = myocardial infarction; ROC = receiver operating characteristic; STEMI = ST elevation myocardial infarction.

**Declarations**

**Ethics approval and consent to participate**

Ethic committee approved the study. Approved No. of ethic committee: 2019039X.

Name of the ethic committee: Ethics committee of Beijing Anzhen Hospital Capital Medical University. It was a retrospective analysis and informed consent was waived by Ethics Committee of Beijing Anzhen Hospital Capital Medical University.

**Statement of human and animal rights**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was not conducted with animals.

Consent for publication
None.

Availability of data and material
The data used to support the findings of this study are included within the supplementary file.

Code availability
The data are demographic, clinical, and angiographic characteristics of patients with acute STEMI. AGE= age; ALLAF = atrial fibrillation; AVB = atrioventricular block; CABG = history of coronary artery bypass grafting; CKD = history of chronic kidney disease; DIE = in-hospital mortality; DM = history of diabetes; HBP = history of hypertension; HCD = history of cerebrovascular disease; HPCI = history of percutaneous coronary intervention; KI = Killip I; KII = Killip II; KIII = Killip III; KIV = Killip IV; OMI = history of myocardial infarction; PCI = underwent PCI during hospitalization; S = sex.

Competing interests
The authors declare that they have no competing interests.

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None.

Authors' contributions
Yong Li contributed to generating the study data, analysed, interpreted the study data, drafted the manuscript, and revised the manuscript. Yong Li is responsible for the overall content as guarantor.

All authors have read and approved the manuscript.

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None.

Table 1. Demographic and clinical characteristics of patients with and without in-hospital mortality in the development data sets

| Characteristic                  | Total (n=2183) | In-hospital deaths (n =61) | In hospital survivors (n=2122) | P value |
|--------------------------------|---------------|---------------------------|-------------------------------|---------|
| Age(year,x±s)[21,91]           | 60±13         | 71±12                     | 59±12                        | <0.001  |
| Mann(%)0=No,1=Yes              | 1688(77.3)    | 36(59)                    | 1652(77.9)                   | 0.001   |
| Medical history                |               |                           |                              |         |
| Hypertension                   | 1243(56.9)    | 36(59)                    | 1207(56.9)                   | 0.740   |
| Diabetes                       | 674(30.9)     | 19(31.1)                  | 655(30.9)                    | 0.963   |
| Myocardial infarction          | 231(10.6)     | 13(21.3)                  | 218(10.3)                    | 0.007   |
| PCI                            | 159(7.3)      | 3(4.9)                    | 156(7.4)                     | 0.474   |
| CABG                           | 17(0.8)       | 2 (1.6)                   | 15(0.7)                      | 0.041   |
| CKD                            | 48(2.2)       | 2(3.3)                    | 46(2.2)                      | 0.563   |
| HCD                            | 172(7.9)      | 5(8.2)                    | 167(7.9)                     | 0.926   |
| Killip classification          |               |                           |                              |         |
| Killip I                       | 163(7.5)      | 1(1.6)                    | 162(7.6)                     | 0.113   |
| Killip II  | 1607(73.6) | 8(13.1) | 1599(75.4) | <0.001 |
| Killip III | 252(11.5)  | 16(26.2) | 236(11.1)  | <0.001 |
| Killip IV  | 161(7.4)   | 36(59)   | 125(5.9)   | <0.001 |
| AF n(%) 0=No, 1=Yes | 161(18) | 11(18) | 113 (5.3) | <0.001 |
| AVB n(%) 0=No, 1=Yes | 104(6.6) | 4(6.6) | 100(4.7)  | 0.507 |

CABG = coronary artery bypass grafting; CKD = chronic kidney disease; HCD = cerebrovascular disease; AVB = atrioventricular block; AF = atrial fibrillation.

Table 2. Predictor of in-hospital mortality obtained from multivariable logistic regression models (odds ratio) in the development data set

| In-hospital mortality | Odds ratio | Std.Err | Z     | P>|Z| | 95% CI     |
|-----------------------|------------|---------|-------|------|----------|
| Age                   | 1.058      | .015    | 3.98  | <0.001 | 1.029~1.088 |
| Killip III            | 8.249      | 3.607   | 4.83  | <0.001 | 3.502~19.433 |
| Killip IV             | 39.234     | 15.4    | 9.35  | <0.001 | 18.178~84.679 |
| _cons                 | .0002      | .0002   | -8.86 | <0.001 | .00002 ~.001 |

CI = confidence interval.

Table 3. Predictor of in-hospital mortality obtained from multivariable logistic regression models (Coeff) in the development data sets

| In-hospital mortality | Coef | Std.Err | Z     | P>|Z| | 95% CI     |
|-----------------------|------|---------|-------|------|----------|
| Age                   | .056 | .014    | 3.98  | <0.001 | .029~.084  |
| Killip III            | 2.11 | .437    | 4.83  | <0.001 | 1.253~2.967 |
| Killip IV             | 3.67 | .393    | 9.35  | <0.001 | 2.9~4.439  |
| _cons                 | -8.771 | .99  | -8.86 | <0.001 | -10.711~6.831 |
Table 4. Demographic and clinical characteristics of patient with and without in-hospital mortality in the validation data sets

| Characteristic                          | Total [lower limit, upper limit] (n =7485) | In-hospital mortality [lower limit, upper limit] (n =127) | In hospital survivors [lower limit, upper limit] (n=7358) | P value |
|----------------------------------------|------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|---------|
| Age (year, x±s) [21,91]                | 59±12                                    | 70±12                                                  | 59±12                                                  | <0.001  |
| Man n (%) 0=No, 1=Yes                  | 6033(65.4)                               | 83(65.4)                                               | 5950(80.9)                                             | <0.001  |
| Medical history, n (%) 0=No, 1=Yes     |                                          |                                                        |                                                        |         |
| Hypertension                           | 4231(67.7)                               | 86(67.7)                                               | 4145(56.3)                                             | 0.011   |
| Diabetes                               | 2254(35.4)                               | 45(35.4)                                               | 2209(30)                                               | 0.189   |
| Myocardial infarction                  | 563(12.6)                                | 16(12.6)                                               | 547(7.4)                                               | 0.031   |
| PCI                                    | 627(9.4)                                 | 12(9.4)                                                | 615(8.4)                                               | 0.66    |
| CABG                                   | 61(1.6)                                  | 2(1.6)                                                 | 59(0.8)                                                | 0.346   |
| CKD                                    | 179(2.4)                                 | 9(7.1)                                                 | 170(2.3)                                               | 0.001   |
| HCD                                    | 516(6.9)                                 | 18(14.2)                                               | 498(6.8)                                               | 0.001   |
| Killip classification                  |                                          |                                                        |                                                        |         |
| n (%) 0=No, 1=Yes                      |                                          |                                                        |                                                        |         |
| Killip I                               | 4781(64.9)                               | 7(5.5)                                                 | 4774(64.9)                                             | <0.001  |
| Killip II                              | 1847(24.9)                               | 17(13.4)                                               | 1830(24.9)                                             | 0.004   |
| Killip III                             | 407(5.3)                                 | 15(11.8)                                               | 392(5.3)                                               | 0.002   |
| Killip IV                              | 453(5)                                   | 88(69.3)                                               | 365(5)                                                 | <0.001  |
| AF n (%) 0=No, 1=Yes                   | 364(4.6)                                 | 24(18.9)                                               | 340(4.6)                                               | <0.001  |
| AVB n (%) 0=No, 1=Yes                  | 187(2.1)                                 | 14(11)                                                 | 173(2.4)                                               | <0.001  |

Abbreviations as in Table 1.
Figure 1. Flow diagrams.

Figure 2. A nomograms for predicting in-hospital mortality in patient with acute STEMI

AGE = Age (year);
KIII-factor = Killip III (0 = No, 1 = Yes);
KIV-factor = Killip IV (0 = No, 1 = Yes).
Figure 3. A calibration plot with distribution of the predicted probabilities for individuals with and without in-hospital mortality in the validation data sets.

Figure 4. DCA in the validation data sets.

References
