Development and validation of a preoperative prediction model for all-cause mortality in patients following abdominal aortic aneurysm repair

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To the Editor: Abdominal aortic aneurysm (AAA) is a life-threatening vascular disease. Surgical intervention is typically recommended when the maximum AAA diameter reaches a threshold of 5.5 cm for men and 5.0 cm for women, or when an AAA experiences a rapid expansion of greater than 1.0 cm/year.[1] Survival after AAA repair is influenced by various factors, and the identification of independent prognostic factors and the development of accurate prediction models are crucial for optimal treatment planning, counseling, and postoperative follow-up. Although several scoring systems with varying degrees of accuracy have been developed to predict the risk of mortality after intervention for patients with ruptured AAA, conflicting results regarding their performance have been published.[2,3] Ideally, prediction models should be user-friendly and widely applicable, providing quick and reliable estimates of outcomes based on only a few readily available preoperative parameters. Unfortunately, the number of clinical models assisting clinicians in estimating the long-term mortality of general AAA patients after aneurysm repair is limited, and there is a lack of scores focusing on the Chinese population. Therefore, the objectives of the present study were to explore potential biomarkers affecting the long-term mortality risk of patients who underwent AAA repair and to establish an easy-to-use and practical preoperative risk prediction model for all-cause mortality after AAA repair in Chinese population. This model might help stratify AAA patients into different groups according to their predicted life expectancy, informing decision-making, and implementing medical intervention in clinical trials.

The study was approved by the Ethics Committee of the First Hospital of China Medical University (No. [2020]146). Written informed consent was obtained from all participants. This study included 224 patients who underwent elective AAA repair at the First Hospital of China Medical University between May 2014 and November 2017. Computed tomography angiography (CTA) was used to diagnose AAA patients and assess maximum AAA diameter. Patients were eligible if they were ≥18 years of age and their follow-up outcomes could be completely attained. The subjects were excluded if (1) they had prior aortic surgery; (2) follow-up time or survival time was unavailable. Demographic data, preoperative clinical parameters, and treatments were extracted from the hospital's medical records. Laboratory tests were conducted preoperatively. Medical comorbidities were defined based on admission diagnoses, including coronary artery disease, stroke, chronic obstructive pulmonary disease (COPD), peripheral artery disease, hypertension, diabetes, and dyslipidemia. High white blood cell (WBC) was defined as $>9.50 \times 10^9$/L. Abnormal platelet (PLT) was defined as PLT $<100 \times 10^9$/L or $>300 \times 10^9$/L. Reduced hemoglobin (Hb) was considered if <120 g/L in men and <110 g/L in women. Elevated brain natriuretic peptide (BNP), D-dimer, homocysteine (Hcy), C-reaction protein (CRP), cystatin C (Cys-C), and urea were defined when their serum levels were greater than 100 pg/mL, 0.50 μg/mL, 15 μmol/L, 5 mg/L, 1.09 mg/L, and 7.14 mmol/L, respectively. The primary endpoint was all-cause mortality within 5 years after AAA repair surgery. We obtained survival

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data by reviewing medical records and making follow-up calls with patients, their relatives, or physicians. The follow-up duration was defined as the time interval from the date of surgical treatment to the occurrence of death from any cause or the last follow-up. The last follow-up for patients enrolled in this study was conducted in November 2022.

The study dataset was randomly divided into training and validation cohorts at a ratio of 1:1. The Student's *t*-test and the chi-squared test were performed to examine the differences between the training and validation cohorts as appropriate. The nomogram model for predicting all-cause death after AAA surgery was developed using the training cohort and subsequently verified in the validation cohort. Initially, the least absolute shrinkage and selection operator (LASSO) strategy, combined with the Cox regression model, was employed to select the most useful candidate predictors for all-cause mortality after AAA surgery. The optimal λ in the LASSO Cox regression model was determined through 10-fold cross-validation using the one standard error off the minimum criteria (1-SE criteria). The triglycerides–glucose index (TyG index), a well-established risk indicator for all-cause death after AAA surgery,[4] was integrated with the variables identified by the LASSO strategy to construct the nomogram model. Additionally, an interactive dynamic nomogram was developed for a user-friendly application using shinyapps.io, an online self-service platform hosting app (https://www.shinyapps.io/). The Harrell's concordance index (C-index) and receiver operating characteristic (ROC) curves were used to estimate the model's discriminative ability, and calibration plots were applied to evaluate the model's accuracy. Generally, a C-index or area under the ROC curve (AUC) >0.70 is considered indicative of relatively good discrimination. Calibration curves were plotted to assess the concordance between predicted and actual 5-year all-cause death risk after AAA surgery, and those closer to the standard line implied a better calibration degree. Decision curve analysis (DCA) was employed to determine net benefits and clinical effectiveness under different threshold probabilities. The nomogram was utilized to calculate individuals' risk scores in both the training cohort and the validation cohort. According to the optimal cut-off value determined by X-tile software (Yale University, New Haven, CT, USA), individuals were further categorized into low- and high-risk groups. Subsequently, all-cause death curves were depicted with Kaplan–Meier analysis and compared using a log-rank test. All statistical analyses were conducted using R software (version 4.2.0; R Foundation for Statistical Computing 2022, Vienna, Austria. Available from: https://www.R-project.org/). All tests were two-tailed, and statistical significance was set at P <0.05.

As a result, a total of 224 patients participated in the study, with 112 and 112 cases randomly assigned to the training and validation cohorts, respectively. The baseline characteristics of the patients are summarized in Supplementary Table 1, http://links.lww.com/CM9/B952. At the end of the follow-up period, 29.0% (65/224) of patients in the entire cohort died. Out of the 29 candidate variables involved in the LASSO Cox regression for 112 AAA patients in the training cohort, three variables with non-zero coefficients were identified according to the lambda 1-SE criteria, including age group, ruptured type, and elevated Cys-C. The process of feature screening and cross-validation is presented in Supplementary Figure 1, http://links.lww.com/CM9/B952. These three features, along with the TyG index, were used to construct the nomogram model for predicting all-cause death after AAA surgery. The forest plot illustrated the hazard ratio (HR) and the corresponding 95% confidence interval (CI) for each predictor included in the model [Supplementary Figure 2, http://links.lww.com/CM9/B952]. A nomogram was drawn to provide a quantitative and convenient tool for predicting the risk of 5-year all-cause death after AAA surgery. As shown in Supplementary Figure 3, http://links.lww.com/CM9/B952, patients with characteristics such as age ≥75 years, ruptured AAA, elevated Cys-C, and a higher TyG index were more likely to die within 5 years of follow-up. Additionally, a user–computer interactive dynamic nomogram is available at the following link: https://guangxiao.shinyapps.io/AAA_model/. The overall performance of the prediction model was evaluated, resulting in a C-index of 0.794 (95% CI: 0.720, 0.868) in the training cohort and 0.759 (95% CI: 0.686, 0.832) in the validation cohort, respectively. The AUC for predicting 5-year all-cause death probability was 0.834 (95% CI: 0.747, 0.921) in the training cohort and 0.784 (95% CI: 0.700, 0.871) in the validation cohort [Supplementary Figure 4A,B, http://links.lww.com/CM9/B952]. Calibration curves showed a high degree of consistency between the predicted and actual probabilities of 5-year all-cause death [Supplementary Figure 4C, D, http://links.lww.com/CM9/B952]. The DCA results demonstrated that the nomogram added more net benefits than the "treat all" or "treat none" strategy when the threshold probability for 5-year all-cause death ranged from 10% to 60%, both in the training and validation sets [Supplementary Figure 5, http://links.lww.com/CM9/B952]. The probability of 5-year all-cause death for all individuals was calculated by summarizing the score of each predictor in the nomogram model. All patients were classified into the high-risk group (total score >13) and low-risk group (total score ≤13) for mortality. Kaplan–Meier survival curves showed that patients at high risk exhibited a higher all-cause death rate than those at low risk in both training and validation cohorts (all P <0.001) [Supplementary Figure 6, http://links.lww.com/CM9/B952].

The utilization of prediction models has gained widespread acceptance as a reliable tool for predicting clinical prognosis across various diseases, including AAA.[5] In the current study, four variables had significant predictive capability for long-term survival and were selected as key predictors for model construction. Importantly, these parameters are easily obtainable and readily available, enabling a prompt estimation of 5-year mortality in AAA patients after surgery. Subsequently, we carried out several measures to assess the robustness of our model. The model showed satisfactory performance, exhibiting good discrimination ability, adequate calibration degree, and potential clinical applicability for predicting the risk of 5-year all-cause death in both the training and

validation sets. As a visualized, practical, and easy-to-use clinical decision-making tool, a novel web-based dynamic nomogram was established to predict the 5-year survival probability of postoperative AAA patients. The patients at a high risk of postoperative mortality should undergo comprehensive treatment procedures and receive close long-term monitoring.

In conclusion, utilizing routine and easily accessible indices in clinical practice, we developed and internally verified a prognostic model with predictive value for the long-term mortality risk in patients who underwent AAA repair. This model displayed good discrimination, calibration, and clinical net benefits, and it was visualized as a dynamic nomogram for online use. Encouraged by these promising results, we are planning to conduct large prospective multicenter studies for additional external validation to ensure the generalization and performance of the current model.

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Conflicts of interest

None.

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