Development and validation of a nomogram for predicting post-operative in-hospital poor outcome in abdominal related emergency general surgery diseases complicated with sepsis

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To the Editor: Patients who undergo emergency general surgery (EGS) procedures are up to eight times more likely to die than those undergoing the same procedure electively.\(^2\) The development of an appropriate EGS risk stratification tool could facilitate accurate triage of high-risk patients, thereby supporting surgical decision-making, informed consent, and identification of EGS patients for transfer to a higher level of care.\(^3\) However, the ideal EGS risk stratification tool does not exist yet. In 2016, a uniform system [American Association for the Surgery of Trauma (AAST) grade] for measuring anatomic severity of 16 common EGS diseases has been reported by the AAST Patient Assessment Committee. Simultaneously, the committee pointed out that this system is not intended to serve alone as a predictor of outcome. Other important factors of the outcome, such as physiological status, comorbidities, age, and complexity of operation procedures, should be integrated into the system for risk stratification.\(^4\) In our EGS center, the spectrum of diseases is mainly abdominal related diseases among the 16 diseases including acute appendicitis, acute cholecystitis, acute diverticulitis of the colon, hernias, infectious colitis, intestinal obstruction, acute pancreatitis, pelvic inflammatory disease, perirectal abscess, and perforated peptic ulcer. We have identified abdominal related EGS diseases complicated with sepsis to be a major cause of morbidity and mortality in our EGS center. We assumed that the integration of anatomic severity of EGS diseases plus physiological severity and other parameters (eg, intra-operative variables, age, and comorbidities) together could work better. Thus, this study aimed to develop and validate a nomogram for predicting post-operative in-hospital outcome in abdominal related EGS diseases complicated with sepsis.

This study was approved by the Medical Ethics and Human Research Committee of Tongji Medical College (No. 2019 S1243) and the informed consent was waived. We registered the program in the China Clinical Trials Registry (http://www.chictr.org.cn, No. ChiCTR2000039772). A total of 623 patients diagnosed with abdominal related EGS diseases complicated with sepsis (aged ≥18 years) treated with the surgical procedure were enrolled [Supplementary Table 1, http://links.lww.com/CM9/A461].

From January 2016 to October 2019, a total of 493 consecutive patients with abdominal related EGS diseases complicated with sepsis were included in our study to construct the nomogram model. Then it was applied to the database from November 2019 to October 2020 for validation. The exclusion criteria were as follows: known pregnancy, missing operation, or discharge records. All clinical data were recorded from the Electronic Medical Record System, including the pre-operative laboratory test results, pre-operative imaging findings, and intra-operative findings.

In our design, the candidate predictor variables were composed of five dimensions as committee pointed: age, anatomical related, physiological related, comorbidities related, and surgical related. For anatomical related variables, we selected AAST grade reflecting the anatomical severity. The description and grade were specifically defined using findings derived from four distinct categories: (1) clinical manifestation, (2) imaging (computed tomography [CT] findings), (3) intra-operative findings, and (4) pathology. Each EGS condition was described using a progressive scale of worsening severity. Grade I disease was limited to local disease only, confined to the organ with a limited abnormality. Grade II continued to be localized to the organ but with a severe abnormality. Grades III–V represented progression beyond the organ with local, regional, and widespread extension, respectively.\(^3\) Since not all patients underwent the same imaging examination before surgery, we utilized the intra-operative criteria based on surgery stored video or operation record. We chose the Modified Early Warning Score,
Sepsis-related Organ Failure Assessment (SOFA) score,[6] and Acute Physiology and Chronic Health Evaluation II score to establish physiological related variables. The comorbidities related variables included chronic obstructive pulmonary disease, hypertension, diabetes, chronic kidney disease, and cardiovascular disease. The surgical related variables included surgical approach, type of surgery, operation time, and past abdominal surgery history. Based on the properties of our EGS department procedures and the regional characteristics of medical insurance policy and the doctor-patient relationship, the in-hospital poor outcome was defined as the post-operative length of stay >15 days or post-operative death.

All analyses were performed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The “rms” package (cran.r-project.org/web/packages/rms) was used to construct nomogram models. Data were presented as number and percentages for categorical variables, and continuous data were expressed as mean ± standard deviation unless otherwise specified. Patient characteristics were compared using t-tests for continuous variables and \( \chi^2 \) or Fisher exact tests for categorical variables. All statistical tests were two-sided, with statistical significance set at 0.05.

A total of 493 patients were enrolled in the development cohort, with a mean age of 51.82 years [Supplemental Table 1, http://links.lww.com/CM9/A461]. One hundred and one patients had an in-hospital poor outcome event, including 58 patients who died during hospitalization, 43 patients had a post-operative hospital stay longer than 15 days. The sources of infection mainly included the appendix (33.47%), gallbladder (24.34%), small bowel (16.43%), colon (11.36%), duodenum (8.69%), and stomach (5.68%). One hundred and thirty patients were enrolled in the validation cohort, with a mean age of 53.98 years. Thirty patients had an in-hospital poor outcome event, including 12 patients who died during hospitalization, 18 patients had a post-operative hospital stay longer than 15 days.

Baseline variables which were considered clinically relevant and showed a univariate relationship with outcome were entered into the multivariable logistic regression model [Supplemental Table 2, http://links.lww.com/CM9/A461]. The stepwise selection was applied to filter variables in the multivariable logistic regression model. The selection criteria: significant level for entry is 0.15 and the significant level for stay is 0.1. The final variables that maintained their independence to predict poor outcome were age (odds ratio [OR] 1.018, 95% confidence interval [CI] 1.002–1.034, \( P = 0.0270 \)); SOFA score (OR 1.322, 95% CI 1.147–1.522, \( P = 0.0001 \)), the type of surgical approach (compared with endoscopy, the open belly [OR 5.576, 95% CI 2.493–10.565, \( P < 0.0001 \)], operation time (OR 1.321, 95% CI 1.044–1.672, \( P = 0.0202 \)), and the AAST grade (compared with Grade I, Grade II [OR 1.645, 95% CI 0.668–4.052, \( P = 0.2790 \)], Grade III [OR 2.012, 95% CI 0.880–4.597, \( P = 0.0973 \)], Grade IV [OR 3.959, 95% CI 1.443–10.865, \( P = 0.0076 \)], and Grade V [OR 10.591, 95% CI 2.659–42.185, \( P = 0.0008 \)]. Taking into account the actual uncertainty of the operation time, and its overall improvement of the model’s efficiency was not significant, we did not incorporate it into the final model. In the final, the nomogram combined four variables (including two pre-operative variables and two intra-operative variables) [Figure 1A]. The accuracy of this prediction model was relatively high, with a C-index of 0.869 in the development cohort [Figure 1B] and 0.867 in the validation cohort [Figure 1C]. The calibration curve of the nomogram showed agreement between the prediction and observation in both the development cohort [Figure 1D] and validation cohort [Figure 1E]. In decision curve analyses, it was shown that the net benefit was high, in the range from 0.1 to 0.8 in both the development cohort [Figure 1F] and validation cohort [Figure 1G], suggesting benefits in our model within a wide probability range.

Our study is a rare research to construct an EGS risk stratification tool based on the characteristics of the population and clinical medical care in a developing country. Compared with the existing scoring system that is convenient for clinical utilize in our center, the area of our model under the receiver operating characteristic curve reached 0.869. A nomogram is a user-friendly tool with a graphic interface, which is widely used for clinical decisions.[5] If in cases the risk of poor outcome is assessed to be high which is shown as a number, this may facilitate the counseling of patients and families leading to establish a better doctor-patient relationship. It also helps doctors to ascertain risk, and choose alternative and less invasive procedures, or even transfer the client to specialized or higher-level hospitals as soon as possible, which is nationally beneficial for medical healthcare fund operation.

In real clinical practice, this nomogram model could be used before surgery to indicate the risk of the operation procedure by only choose those related parameters as clinical and CT findings. Even though the anatomical severity graded by other parameters may be different from the intra-operative findings, the agreement among these parameters was moderate-strong with a kappa in the study of some EGS single diseases.[6] The risks of surgery shown as nomogram number are clearly easier to be understood by both patients and surgeons since they shared the same decision-making process. Besides the sufficient predictive and personalized significance shown in our nomogram, it also carried clinical preventive significance, which fully expresses the advanced medical concept of predictive, preventive, and personalized medicine.

Our study has a few limitations. First, our tool is constructed based on a single-center small sample size data that is not validated against other centers. Second, the stepwise regression model may not capture variables that may be significant but get discounted as other variables are selected. Third, the tool does not, at this time, assess for morbidity. Increasing the sample size (especially multicenter data), incorporating more pre-operative and intra-operative variables, and updating our model to major morbidity (post-operative complications) is an interesting and important next step in our research work.

In conclusion, we developed and validated a nomogram for predicting the in-hospital poor outcome in those abdominal
related EGS diseases complicated with sepsis. We hope that the nomogram could provide some ideas for the better construction of the risk stratification tool for EGS.

**Conflicts of interest**
None.

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**Figure 1:** (A) Nomogram to predict post-operative in-hospital poor outcome in abdominal related EGS diseases complicated with sepsis from the development cohort. (B, C) ROC curves of the nomogram in the development cohort (B) and validation cohort (C). Calibration curve of the nomogram using 1000 bootstrap re-samples in the development cohort (D) and validation cohort (E), the ideal reference line represents that the predicted likelihood perfectly matches the actual incidence. The decision curve of the nomogram in the development cohort (F) and validation cohort (G), the nomogram showed net benefits in the range from 0.1 to 0.8. AAST: American Association for the Surgery of Trauma; APACHE II: Acute Physiology and Chronic Health Evaluation II; EGS: Emergency general surgery; SOFA: Sequential organ failure assessment ROC.