Novel multiparametric nomogram for overall survival prediction in complicated intra-abdominal infection: A multicenter study in China

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Research

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Abstract

Background: Complicated Intra-abdominal infections (cIAIs) in the abdominal cavity or within an abdominal organ are numerous and frequent dangerous entities in the treatment of critically ill patients. Early clinical evaluation is necessary.

Methods: This retrospective multi-center study included patients from ten intensive care units (ICUs). Risk factors for the overall survival (OS) of patients with cIAI were selected using least absolute shrinkage and selection operator regression, a nomogram was constructed subsequently. Calibration curve and receiver operating characteristic (ROC) curve were used to evaluate the calibration and discriminative ability.

Results: In total, 544 patients diagnosed with cIAI were enrolled and divided into the study (n = 276) and validation (n = 268) sets. Sex, acute gastrointestinal injury, acute kidney injury, rare bacterium infection, Charlson score, and APACHE II score were identified as independent risk factors and were constructed for the nomogram. The nomogram showed marked calibration capability with a concordance index (C-index) of 0.909 and 0.831 in the study and validation set. Comparing with common clinical prognostic scoring system, the nomogram achieved the highest discrimination ability with an area under the curve (AUC) value of 0.91 and 0.83 in the study set and validation set, respectively.

Conclusions: Our newly constructed nomogram provides a useful tool for risk stratification and prognosis evaluation of cIAI.

Introduction

Intra-abdominal infections (IAIs) are responsible for nearly 20% of sepsis cases and are the second most common cause of infectious morbidity and mortality after pneumonia in intensive care units (ICUs) [1]. IAIs are further classified as uncomplicated and complicated. Uncomplicated IAI rarely presents as the only cause for the admission of patients to ICU.

Complicated intra-abdominal infections (cIAI) are more likely to cause drug-resistant bacterium infections, surrounding organ damage, and even systemic inflammatory reactions, subsequently contributing to the accumulation of hospitalization costs, length of stay, and morbidity [2, 3]. Mortality associated with cIAI is generally high at 23–38% [4, 5]. Achieving prompt control over infection of an anatomic source is the cornerstone of cIAI management but is not always successful [4]. Several risk factors including delayed interventions, antibiotic-resistant pathogens, high severity of illness, advanced age, poor nutritional status, and pre-existing chronic medical conditions have been reported to cause treatment failure [6-9]. Early clinical evaluation is essential for the illness stratification and the subsequent decision-making process, and even for auditing and research. However, specific scoring system is unavailable. Oddeke [10] also reported that “none of the widely-used scoring systems to predict overall outcome in critically ill patients are of clinical value”. Nevertheless, few studies have comprehensively explored the risk factors for cIAI prognosis.
Therefore, this study aimed to identify factors that significantly influence the mortality of patients with cIAI in the ICU. Three different general organ function scores including the Charlson, Acute Physiologic and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment (SOFA) scores as well as several organ specific evaluation systems like the Glasgow Coma Scale (GCS), Chinese DIC scoring system (CDSS), acute kidney injury (AKI), and acute gastrointestinal injury (AGI) were investigated. We also incorporated patient characteristics, comorbidities, and infection source for a comprehensive assessment. The first nomograph for cIAI prognosis was constructed and confirmed in this study.

**Methods**

**Study population**

This was a retrospective, multicenter study conducted in 10 hospitals including Ruijin Hospital North, the First Affiliated Hospital of Wenzhou Medical School, The Second Affiliated Hospital of Zhejiang University School of Medicine, the First Hospital of Lanzhou University, the First People's Hospital of Kunshan, Huashan Hospital, Changhai Hospital, Minhang Hospital, Qingpu Branch of Zhongshan Hospital, and the Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine from January 2017 to October 2018. In total, 544 patients (age, 18–80 years) who were diagnosed with cIAI were enrolled in this study. Patients with primary peritonitis, with missing clinical data, or whose hospitals stay shorter than 48 h were excluded. This retrospective study was reviewed and approved by the Ruijin Hospital North. The included patients were randomly divided into a study set (n = 276) and validation set (n = 268) at a ratio of 1:1.

**Date Collection**

The patient characteristics and clinical data of each patient were carefully collected and scrutinized. Clinical data such as the Charlson score, APACHE II score, SOFA score, GCS score, DIC score, AGI Grade, AKI Grade, and liver function were acquired on the first day in the ICU. Variables related to intra-abdominal infection included infection sites such as the biliary system, pancreas, and intestine, abdominal trauma, spontaneous peritonitis, and others. Pathogens having the highest drug resistance during hospitalization were recorded. Comorbidities occurring before admission included stroke, chronic obstructive pulmonary disease (COPD), chronic liver disease (CLD), diabetes, chronic kidney disease (CKD), malignancy, and hemopathy. The day of discharge or death was considered as the end point of the study.

**Definitions**

Complicated intra-abdominal infection (cIAI) was defined as a generalized inflammatory process extending beyond the hollow viscus of origin into the peritoneal cavity that affects multiple organs and causes abscesses or peritonitis [11]. Rare bacterium infection was defined as seldom-seen bacterium infection of cIAI such as *Proteus spp*, *Serratia spp*, *Staphylococcus spp*, *Stenotrophomonas maltophilia* in China.
Construction and validation of the nomogram

We incorporated all the clinical data as prognostic features to select the most useful predictive variables in the study group. The least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation was used to shrink all the regression coefficients towards zero. The penalty parameter lambda controls the amount of shrinkage, so lambda.min (the Lambda at which the minimal MSE [Mean Square Error] is achieved) was identified at first, and lambda.1sd (One standard deviation of lambda.min) was used to select features for the nomogram construction of cIAI overall survival (OS).

A calibration curve was used to assess consistency between the nomogram-predicted survival probability and the actual fraction survival probability. According to the median risk probability of death predicted by the nomogram, patients with cIAI were classified into high and low risk groups. The potential association of the nomogram score with OS was first assessed in the study cohort and was then validated in the validation cohorts using Kaplan-Meier survival analysis. The clinical utility of the nomogram model was assessed by a decision curve analysis (DCA) in the testing and independent validation cohorts by quantifying the net benefits at different threshold probabilities. The receiver operating characteristic (ROC) curve and area under the curve (AUC), which is useful to estimate the predictive accuracy of prognostic predictors, were also used to assess and compare the performance of the nomogram and conventional evaluation systems such as APACHE II score, and SOFA score. A larger AUC indicated more accurate prognostic stratification.

Statistical analysis

Continuous variables not following normal distribution were expressed as median (interquartile range [IQR]) and analyzed using the rank-sum test. Categorical variables were expressed as frequency or ratio and were analyzed using the χ² test. All statistical analyses were performed using R (version 3.6.2). The “glmnet” package was used to perform the LASSO Cox regression model analysis. All statistical tests were two-sided, and P values < 0.05 were considered statistically significant.

Results

Clinical characteristics

The clinical characteristics of the study and validation cohorts are shown in Table 1. The study and validation groups included 268 and 276 patients, respectively. There were 137 (51%) patients in the study set and 149 (54%) patients in the validation set that also had sepsis. The hospital duration of the study set was 18 (IQR, 11–30) days and the ICU duration was 9 (IQR, 4–17) days. The hospital duration of validation set was 18 (IQR, 12–34) days and the ICU duration was 8 (IQR, 4–16) days. The mortality in the study and validation set was 20% and 18%, respectively. All characteristics were well balanced in both the study and validation cohorts (p > 0.05).
Table 1
Demographic and Clinical Characteristics of Study Patients

| Variables                        | All         | Study (n = 268) | Validation (n = 276) | p      |
|----------------------------------|-------------|----------------|----------------------|--------|
| *Age, Median (IQR)-yr*           | 65 (53, 76) | 65 (51, 75)    | 64.5 (55, 76)        | 0.467  |
| *Sex, Male, n (%)*               | 355 (65.7)  | 180 (67.2)     | 175 (63.4)           | 0.406  |
| **Comorbidities**                |             |                |                      |        |
| Cardiovascular disease, n (%)    | 153 (28.1)  | 65 (24.3)      | 88 (31.9)            | 0.060  |
| Dementia, n (%)                  | 38 (7.0)    | 17 (6.3)       | 21 (7.6)             | 0.681  |
| COPD, n (%)                      | 28 (5.1)    | 15 (5.6)       | 13 (4.7)             | 0.784  |
| CLD, n (%)                       | 58 (10.7)   | 30 (11.2)      | 28 (10.1)            | 0.797  |
| Diabetes mellitus, n (%)         | 86 (15.8)   | 46 (17.2)      | 40 (14.5)            | 0.462  |
| CKD, n (%)                       | 34 (6.3)    | 18 (6.7)       | 16 (5.8)             | 0.790  |
| Solid tumor, n (%)               | 150 (27.6)  | 64 (23.9)      | 86 (31.2)            | 0.071  |
| Hematological malignancies, n (%)| 6 (1.1)     | 1 (0.4)        | 5 (1.8)              | 0.216  |
| **Etiology**                     |             |                |                      |        |
| Biliary tract disease, n (%)     | 59 (10.85)  | 35 (13.1)      | 24 (8.7)             | 0.203  |
| Acute pancreatitis, n (%)        | 69 (12.7)   | 30 (11.2)      | 39 (14.1)            | 0.203  |
| Intestinal perforation or obstruction, n (%) | 286 (52.6) | 131 (48.9) | 155 (56.2) | 0.203 |
| Abdominal trauma, n (%)          | 46 (8.5)    | 24 (9.0)       | 22 (8.0)             | 0.203  |
| Complicated appendicitis, n (%)  | 39 (7.2)    | 21 (7.8)       | 18 (6.5)             | 0.203  |
| Others, n (%)                    | 45 (8.3)    | 27 (10.1)      | 18 (6.5)             | 0.203  |
| **Microbioorganisms**            |             |                |                      |        |
| Gram-Positive Bacteria           |             |                |                      |        |
| Enterococcus spp, n (%)          | 80 (14.7)   | 38 (14.2)      | 42 (15.2)            | 0.825  |
| Streptococcus spp, n (%)         | 10 (1.8)    | 3 (1.1)        | 7 (2.5)              | 0.34   |

Abbreviation: APACHE II, Acute Physiologic and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; CDSS, Chinese DIC scoring system; AGI, Acute Gastrointestinal Injury; AKI, Acute Kidney Injury; CRRT, Continuous Renal Replacement Therapy; COPD, Chronic Obstructive Pulmonary Disease; CLD, Chronic Liver Disease; CKD, Chronic Kidney Disease; MDR, multidrug-resistance; ICU, Intensive Care Units.
| Variables                                    | All          | Study (n = 268) | Validation (n = 276) | p       |
|----------------------------------------------|--------------|----------------|----------------------|---------|
| Gram-Negative Bacteria                       |              |                |                      |         |
| Klebsiella spp, n (%)                        | 37 (6.8)     | 17 (6.3)       | 20 (7.2)             | 0.804   |
| Escherichia coli, n (%)                      | 290 (53.3)   | 139 (51.9)     | 151 (54.7)           | 0.563   |
| Pseudomonas aeruginosa, n (%)                | 22 (4.0)     | 10 (3.7)       | 12 (4.3)             | 0.883   |
| Acinetobacter baumanii, n (%)                | 33 (6.1)     | 15 (5.6)       | 18 (6.5)             | 0.786   |
| Enterobacter spp, n (%)                      | 4 (0.7)      | 1 (0.4)        | 3 (1.1)              | 0.624   |
| Rare bacterium infection, n (%)              | 65 (11.2)    | 26 (9.7)       | 35 (12.7)            | 0.334   |
| Fungi, n (%)                                 | 35 (6.4)     | 19 (7.1)       | 16 (5.8)             | 0.660   |
| MDR, n (%)                                   | 278 (51.1)   | 132 (49.3)     | 146 (52.9)           | 0.445   |
| Clinical Status at the Time of ICU Admission |              |                |                      |         |
| Charlson score, Median (IQR)                 | 1 (0, 3)     | 1 (0, 3)       | 2 (0, 3)             | 0.573   |
| APACHE II score, Median (IQR)                | 11.5 (7, 18) | 12 (7, 18)     | 11 (7, 18)           | 0.467   |
| SOFA score, Median (IQR)                     | 4 (1, 8)     | 4 (1, 8)       | 4.5 (1, 9)           | 0.676   |
| GCS score, Median (IQR)                      | 15 (14, 15)  | 14.5 (14, 15)  | 15 (14, 15)          | 0.324   |
| CDSS score, Median (IQR)                     | 3 (2, 5)     | 3 (2, 5)       | 3 (2, 5)             | 0.735   |
| AGI                                          |              |                |                      |         |
| No AGI, n (%)                                | 89 (16.4)    | 51 (19.0)      | 38 (13.8)            | 0.316   |
| AGI Grade1, n (%)                            | 240 (44.1)   | 121 (45.1)     | 119 (43.1)           | 0.316   |
| AGI Grade2, n (%)                            | 101 (18.6)   | 45 (16.8)      | 56 (20.3)            | 0.316   |
| AGI Grade3, n (%)                            | 63 (11.6)    | 30 (11.2)      | 33 (12.0)            | 0.316   |
| AGI Grade4, n (%)                            | 51 (9.4)     | 21 (7.8)       | 30 (10.9)            | 0.316   |
| AKI                                          |              |                |                      |         |
| No AKI, n (%)                                | 363 (66.7)   | 179 (66.8)     | 184 (66.7)           | 0.866   |

Abbreviation: APACHE II, Acute Physiologic and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; CDSS, Chinese DIC scoring system; AGI, Acute Gastrointestinal Injury; AKI, Acute Kidney Injury; CRRT, Continuous Renal Replacement Therapy; COPD, Chronic Obstructive Pulmonary Disease; CLD, Chronic Liver Disease; CKD, Chronic Kidney Disease; MDR, multidrug-resistance; ICU, Intensive Care Units.
### Variables

|                  | All       | Study (n = 268) | Validation (n = 276) | p      |
|------------------|-----------|----------------|----------------------|--------|
| AKI Grade1, n (%)| 62 (11.4) | 30 (11.2)      | 32 (11.6)            | 0.866  |
| AKI Grade2, n (%)| 53 (9.7)  | 24 (9.0)       | 29 (10.5)            | 0.866  |
| AKI Grade3, n (%)| 66 (12.1) | 35 (13.1)      | 31 (11.2)            | 0.866  |
| Liver injury, n (%)| 222 (40.8) | 114 (42.5) | 108 (39.1)          | 0.471  |
| Sepsis, n (%)    | 286 (52.6) | 137 (51.1)    | 149 (54.0)           | 0.560  |

#### Treatment Variables

|                  | All       | Study (n = 268) | Validation (n = 276) | p      |
|------------------|-----------|----------------|----------------------|--------|
| Glucocorticoid, n (%)| 94 (17.3) | 42 (15.7)      | 52 (18.8)            | 0.388  |
| CRRT, n (%)       | 67 (12.3) | 33 (12.3)      | 34 (12.3)            | 1      |
| Inappropriate antibiotic exposure, n (%)| 27 (5.0) | 10 (3.7)       | 17 (6.2)             | 0.269  |

#### Outcomes

|                                | All       | Study (n = 268) | Validation (n = 276) | p      |
|--------------------------------|-----------|----------------|----------------------|--------|
| Length of hospitalization, Median (IQR)-d | 18 (11, 32) | 18 (11, 30) | 18 (12, 34)          | 0.272  |
| ICU duration, Median (IQR)-d        | 9 (4,16)  | 9 (4, 17)      | 8 (4, 16)            | 0.929  |
| In-hospital mortality, n (%)        | 103 (18.9)| 53 (19.8)      | 50 (18.1)            | 0.700  |

Abbreviation: APACHE II, Acute Physiologic and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; CDSS, Chinese DIC scoring system; AGI, Acute Gastrointestinal Injury; AKI, Acute Kidney Injury; CRRT, Continuous Renal Replacement Therapy; COPD, Chronic Obstructive Pulmonary Disease; CLD, Chronic Liver Disease; CKD, Chronic Kidney Disease; MDR, multidrug-resistance; ICU, Intensive Care Units.

### Nomogram Development

A LASSO Cox regression model was used as a prognostic classifier, which successfully identified 6 potential predictors from the 37 features with nonzero coefficients in the study cohort (Fig. 1). Sex, AGI, AKI, rare bacterium infection, Charlson score, and APACHE II score were independent risk factors (Fig. 1, 2). A nomogram was constructed subsequently (Fig. 2).

### Validation Of Nomogram

The nomogram was well calibrated as revealed by the calibration curves and its prediction of death showed a good correlation between the actual observed outcome and the nomogram prediction (Fig. 3A, B) in the study group (p > 0.05). This was further verified in the validation cohort (p > 0.05). The C-index of the nomogram for the prediction was 0.909 and 0.831 in the study and validation set, respectively. Accordingly, patients were classified into low-risk and high-risk groups based on the nomogram.
Meier survival analysis showed that the actual survival rate of cIAI differed significantly from patients with low risk to those with high risk both in the study and validation sets (p < 0.001) (Fig. 3C, D).

**Comparison Of The Nomogram With Conventional Evaluation Systems**

The DCA in the study cohort showed that our multi-parametric nomogram had a better overall net benefit compared to the SOFA Score, APACHE II Score, and the treat-all patients strategy or the treat-none strategy at different threshold probabilities across the majority of the range between 4% and 100% (Fig. 4A). DCA in the validation cohort showed an equal net benefit with the nomogram and the SOFA Score or APACHE II Score (Fig. 4B).

The ROC curves (Fig. 4C, D) were used to assess the discrimination ability of nomogram, SOFA, and APACHE II for the mortality of IAI. AUC values were the highest for the nomogram in the study group (AUC = 0.91) (Fig. 4C), and the validation group (AUC = 0.83) (Fig. 4D). The performances of SOFA and APACHE II are summarized in Table 2.

| Predictors     | Study cohort | validation cohort |
|----------------|--------------|------------------|
|                | AUC  | 95% CI     | Sensitivity (%) | Specificity (%) |
| Nomogram       | 0.91 | 0.22–5.13  | 81.13           | 84.19           |
| APACHE II      | 0.85 | 0.21–2.90  | 84.91           | 70.70           |
| SOFA           | 0.83 | 0.30–3.33  | 77.36           | 76.74           |
| Nomogram       | 0.83 | 0.25–3.09  | 82.00           | 73.45           |
| APACHE II      | 0.82 | 0.38–3.37  | 70.00           | 79.20           |
| SOFA           | 0.83 | 0.30–2.99  | 78.00           | 73.89           |

Table 2: AUC for Nomogram, APACHE II and SOFA in Study cohort and Validation cohort

Abbreviation: AUC, Area under Curve; CI, Confidence Interval; APACHE II, Acute Physiologic and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

**Discussion**

We conducted a multicenter retrospective study in which we successfully enrolled 544 patients with cIAI to construct a nomograph for the evaluation of mortality risk. Sex, AGI, AKI, rare bacterium infection, Charlson score, and APACHE II score were identified as the risk factors, and were used to constitute the nomograph for prognosis prediction of cIAI in the testing cohort. Internal validations further confirmed the nomograph as a successful prognostic evaluation system. Compared with commonly used scoring
system in ICU, SOFA and APACHE II, the nomograph presented better overall net benefits in DCA and higher AUC value in ROC, which demonstrated the incremental value for evaluation of cIAI prognosis.

A precise definition of cIAI and guidelines for management of intra-abdominal infections are available, but an accurate prognosis prediction of cIAI is not feasible. SOFA and APACHE II score were commonly used in ICU even for the severity definition of cIAI [12–14]. Koray et al. [15] recruited 34 patients with intra-abdominal sepsis and treated them with planned relaparotomy. They also found that APACHE II is more reliable for prediction of mortality. Another study identified APACHE II $\geq 13$ as the independent risk factors for failure of initial antibiotic therapy of cIAI [16]. But the prognosis prediction ability of APACHE II or SOFA score was controversial. Pascal reported that APACHE II score was associated with the presence of *Pseudomonas aeruginosa* in peritoneal fluid culture but not with the prognosis [17]. Our study identified APACHE II score but not SOFA score as the risk factor for patients with cIAI. As far as we know, there was no study evaluate the risk stratification function of APACHE II, SOFA for cIAI. Therefore, we firstly compared the prognosis prediction ability of our newly constructed nomograph with APACHE II, SOFA score. Both DCA and ROC curves identified a better overall net benefit and better discrimination ability of the nomograph compared with APACHE II, SOFA score in the study group, even though the comparation of the three in the validation cohort showed an equal benefit.

Risk factors such as old age, malignant disease, and pre-existing medical comorbidities may also attribute to the patient's underlying condition. Ana et al. [6] reported that elderly patients with intra-abdominal infection tend have a narrow therapeutic window, and old age is associated with significantly increased morbidity and mortality compared with younger patients. However, age was not identified in this study, which may be owing to the minimal differences between ages for all the patients had an advanced age (62.9 [61.5–64.3]) (Table 1). It is also indicated that cIAI mainly occurred in elderly patients. Interestingly, our study first identified sex as the risk factor, male patients tended to have higher mortality and prolonged hospital stay. Similar observations were made by others in infectious diseases or septic shock, wherein males of any age showed worse prognosis [18]. Females have better prognosis, there is a hypotheses that it is probably ascribed to a higher neutrophilic inflammation and lower extracellular milieu's pH [19]. Considering the comorbidities and malignant diseases, we used Charlson score instead. Previous studies showed that Charlson score was significantly associated with all-cause mortality in patients with bacteraemia [20] or sepsis [21], and our results corroborate these findings.

Effects on function of specific organs, especially gastrointestinal system which was first and foremost influenced, should be considered. The Working Group on Abdominal Problems of the European Society of Intensive Care Medicine firstly developed the definitions of AGI with four grades of severity making it possible to estimate the gastrointestinal function of critically ill patients [22]. AGI is widely used in ICU in recent years [23, 24]. Multi-prospective study in China which recruited patients admitted in ICU diagnosed with AGI showed that AGI grading was positively correlated with all-cause mortality [25, 26]. This study is the first one identify that cIAI patients with AGI can have a higher risk of death. AKI is a common disease in the critically ill individuals, and is associated with high mortality [27]. Alejandro's study showed the incidence of AKI in surgical septic patients with secondary peritonitis was 58.8% [28]. This study also had
181 (33.3%) patients with cIAI developed into AKI (Table 1) and identified AKI as an independent risk factor using LASSO Cox regression model.

Achieving a prompt source control over the infection is crucial for abdominal infection management [4]. Multi-pathogen infections often cause the failure of source control but are easily overlooked [29]. This study identified infection with other gram-negative bacteria as the risk factor for cIAI prognosis. We investigated several common pathogens including Enterococcus spp, Streptococcus spp, Escherichia coli, Klebsiella, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterobacter spp. Based on this, we can come to the conclusion that patients infected with seldom seen bacteria for abdominal infection may tend to have poor prognosis. The underlying mechanism may be a lack of prompt and efficient antibacterial treatment when uncommon bacterium infection occurred. A emergent source control is necessary for cIAC with sepsis that the most recent Surviving Sepsis Campaign Guidelines focus on early antibiotic treatment to be initiated within one hours [30, 31]. Antibiotic treatment mainly depends on experience, and cephalosporins and imipenem are commonly used to treat cIAI in China [32]. It may lead to a treatment delay when a rare bacterium infection lack of effective antibiotic treatment promptly. Furthermore, the infection rate of multidrug-resistant (MDR) pathogens was as high as 51.1% in this study, which is alarming.

Based on the results of LASSO Cox regression analysis, a simple and practical multiparametric nomogram was designed that collectively considered sex, AGI, AKI, rare bacterium infection, Charlson score, and APACHE II score. Even though the World Society of Emergency Surgery cIAIs Score Study (WISS) specifically constructed a WISS score which includes severe sepsis or septic shock, healthcare associated infections, delay in source control, origin of the IAIs, age, and immunosuppression to evaluate the severity of illness for patients with cIAI [33], it lacks verification and was principally used in surgical research since it was constructed in 2015 [34]. Our newly constructed nomogram not only evaluated the whole condition (Charlson score and APACHE II score), but also included specific organs fuction (AGI, AKI) of patients with cIAI. Moreover, it emphasized the important role of timely specific pathogens identification for improving prognosis. The nomogram is more suitable for the evaluation of prognosis of cIAI in ICU. We even certificated the nomogram with a high calibration (Fig. 3A, B) and discriminative ability (Fig. 4C, D).

This study has a few limitations mainly related to its retrospective design. Firstly, the evaluation of infection control effect was not generally conducted in this study, which is different from the WISS score. However, as far as we know, infection control was more like a result after we evaluated the illness and took measures. Further studies will evaluate the factors influencing infection control effect. Secondly, owing to the limitation of data collection, we have not identified drug resistance of each pathogen but simply designated pathogens as MDR. It will affect the result of our evaluation; further study may identify more risk factors. Thirdly, the prognosis prediction ability comparation of the nomograph, APACHE II and SOFA score in the validation cohort showed an equal benefit. A large sample prospective study is necessary to evaluate the feasibility of our newly constructed nomogram.
Conclusions

Our newly constructed nomogram which included sex, AGI, AKI, rare bacterium infection, Charlson score, and APACHE II score could take a full consideration of the illness of cIAI, and can predict its overall survival time accurately, provided as a useful tool for risk stratification in cIAI.

List Of Abbreviations

cIAls  Complicated Intra-abdominal infections
ICUs  Intensive care units
OS  Overall survival
ROC  Receiver operating characteristic
C- index  Concordance index
AUC  Area under the curve
IAIs  Intra-abdominal infections
APACHE II  Acute Physiologic and Chronic Health Evaluation II
SOFA  Sequential Organ Failure Assessment
GCS  Glasgow Coma Scale
CDSS  Chinese DIC scoring system
AKI  Acute kidney injury
AGI  Acute gastrointestinal injury
COPD  Chronic obstructive pulmonary disease
CLD  Chronic liver disease
CKD  Chronic kidney disease
LASSO  Least absolute shrinkage and selection operator
MSE  Mean Square Error
DCA  Decision curve analysis
IQR  Interquartile range
MDR Multidrug-resistant
WISS World Society of Emergency Surgery cIAIs Score Study

Declarations

Ethics approval and consent to participate
This retrospective study was reviewed and approved by the Ruijin Hospital North. No consent to participate was needed.

Consent for publication
Not applicable.

Availability of data and materials
The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare no conflict of interest.

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Authors' contributions
All the authors have participated in clinical practice, literature retrieval and viewpoint discussion in this article. Sisi Huang and Limin Chen contributed in writing this article. Sheng Zhang processing and analyzing the data. Dechang Chen and Jiao Liu revised this article. All authors read and approved the final manuscript.

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References
1 Vincent, J L, J Rello, J Marshall, E Silva, A Anzueto, C D Martin, et al., International study of the prevalence and outcomes of infection in intensive care units. JAMA, 2009. 302(21): 2323-9. DOI: 10.1001/jama.2009.1754.
2 Pelletier, S J, D P Raymond, T D Crabtree, T G Gleason, T L Pruett, and R G Sawyer, Outcome analysis of intraabdominal infection with resistant gram-positive organisms. Surg Infect (Larchmt), 2002. 3(1): 11-9. DOI: 10.1089/109629602753681113.

3 Schneider, C P, C Seyboth, M Vilsmaier, H Kuchenhoff, B Hofner, K W Jauch, et al., Prognostic factors in critically ill patients suffering from secondary peritonitis: a retrospective, observational, survival time analysis. World J Surg, 2009. 33(1): 34-43. DOI: 10.1007/s00268-008-9805-4.

4 van de Groep, K, T L Verhoeff, D M Verboom, L D Bos, M J Schultz, M J M Bonten, et al., Epidemiology and outcomes of source control procedures in critically ill patients with intra-abdominal infection. J Crit Care, 2019. 52: 258-264. DOI: 10.1016/j.jcrc.2019.02.029.

5 De Waele, J, J Lipman, Y Sakr, J C Marshall, P Vanhems, C Barrera Groba, et al., Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. BMC Infect Dis, 2014. 14: 420. DOI: 10.1186/1471-2334-14-420.

6 Berlin, A and J M Johanning, Intraabdominal Infections in Older Adults. Clin Geriatr Med, 2016. 32(3): 493-507. DOI: 10.1016/j.cger.2016.02.002.

7 Labricciosa, F M, M Sartelli, L M Abbo, P Barbadoro, L Ansaloni, F Coccolini, et al., Epidemiology and Risk Factors for Isolation of Multi-Drug-Resistant Organisms in Patients with Complicated Intra-Abdominal Infections. Surg Infect (Larchmt), 2018. 19(3): 264-272. DOI: 10.1089/sur.2017.217.

8 Friedrich, A K and M Cahan, Intraabdominal infections in the intensive care unit. J Intensive Care Med, 2014. 29(5): 247-54. DOI: 10.1177/0885066613476465.

9 Sartelli, M, F Catena, F M Abu-Zidan, L Ansaloni, W L Biffl, M A Boermeester, et al., Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. World J Emerg Surg, 2017. 12: 22. DOI: 10.1186/s13017-017-0132-7.

10 van Ruler, O, J J Kiewiet, K R Boer, B Lamme, D J Gouma, M A Boermeester, et al., Failure of available scoring systems to predict ongoing infection in patients with abdominal sepsis after their initial emergency laparotomy. BMC Surg, 2011. 11: 38. DOI: 10.1186/1471-2482-11-38.

11 Hecker, A, M Reichert, C J Reuss, T Schmoch, J G Riedel, E Schneck, et al., Intra-abdominal sepsis: new definitions and current clinical standards. Langenbecks Arch Surg, 2019. 404(3): 257-271. DOI: 10.1007/s00423-019-01752-7.

12 Plaudis H, Rudzats A, Melberga L, Kazaka I, Suba O, Pupelis G. Abdominal negative-pressure therapy: a new method in countering abdominal compartment and peritonitis - prospective study and critical review of literature. Ann Intensive Care. 2012;2 Suppl 1(Suppl 1):S23. DOI:10.1186/2110-5820-2-S1-S23.

13 Suarez-de-la-Rica A, Maseda E, Anillo V, et al. Biomarkers (Procalcitonin, C Reactive Protein, and Lactate) as Predictors of Mortality in Surgical Patients with Complicated Intra-Abdominal Infection. Surg
Suarez-de-la-Rica A, Anillo V, Montero A, et al. Risk factors for acute kidney injury in critically ill patients with complicated intra-abdominal infection. J Crit Care. 2017;38:104-108. DOI:10.1016/j.jcrc.2016.10.031

Das, K, M Ozdogan, F Karateke, A S Uzun, S Sozen, and S Ozdas, Comparison of APACHE II, P-POSSUM and SAPS II scoring systems in patients underwent planned laparotomies due to secondary peritonitis. Ann Ital Chir, 2014. 85(1): 16-21.

Chong YP, Bae IG, Lee SR, et al. Clinical and economic consequences of failure of initial antibiotic therapy for patients with community-onset complicated intra-abdominal infections. PLoS One. 2015;10(4):e0119956. Published 2015 Apr 24. DOI:10.1371/journal.pone.0119956.

Augustin, P, A Tran-Dinh, N Valin, M Desmard, M A Crevecoeur, C Muller-Serieys, et al., Pseudomonas aeruginosa post-operative peritonitis: clinical features, risk factors, and prognosis. Surg Infect (Larchmt), 2013. 14(3): 297-303. DOI: 10.1089/sur.2012.084.

Papathanassoglou, E, N Middleton, J Benbenishty, G Williams, M D Christofi, and K Hegadoren, Systematic review of gender- dependent outcomes in sepsis. Nurs Crit Care, 2017. 22(5): 284-292. DOI: 10.1111/nicc.12280.

Casimir, G J, N Lefevre, F Corazza, J Duchateau and M Chamekh, The Acid-Base Balance and Gender in Inflammation: A Mini-Review. Front Immunol, 2018. 9: 475. DOI: 10.3389/fimmu.2018.00475.

Eskesen, A N, M A Belle and A Blomfeldt, Predictors of one-year all-cause mortality and infection-related mortality in patients with Staphylococcus aureus bacteraemia. Infect Dis (Lond), 2018. 50(10): 743-748. DOI: 10.1080/23744235.2018.1470666.

Oh, T K, Y T Jeon, S H Do and J W Hwang, Pre-operative assessment of 30-day mortality risk after major surgery: the role of the quick sequential organ failure assessment: A retrospective observational study. Eur J Anaesthesiol, 2019. 36(9): 688-694. DOI: 10.1097/EJA.0000000000000957.

Reintam Blaser, A, M L Malbrain, J Starkopf, S Fruhwald, S M Jakob, J De Waele, et al., Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med, 2012. 38(3): 384-94. DOI: 10.1007/s00134-011-2459-y.

Zhang, D, H Li, Y Li and L Qu, Gut rest strategy and trophic feeding in the acute phase of critical illness with acute gastrointestinal injury. Nutr Res Rev, 2019. 32(2): 176-182. DOI: 10.1017/S0954422419000027.
24 Xing, J, Z Zhang, L Ke, J Zhou, B Qin, H Liang, et al., Enteral nutrition feeding in Chinese intensive care units: a cross-sectional study involving 116 hospitals. Crit Care, 2018. 22(1): 229. DOI: 10.1186/s13054-018-2159-x.

25 Li, H, D Zhang, Y Wang and S Zhao, Association between acute gastrointestinal injury grading system and disease severity and prognosis in critically ill patients: A multicenter, prospective, observational study in China. J Crit Care, 2016. 36: 24-28. DOI: 10.1016/j.jcrc.2016.05.001.

26 Hu, B, R Sun, A Wu, Y Ni, J Liu, F Guo, et al., Severity of acute gastrointestinal injury grade is a predictor of all-cause mortality in critically ill patients: a multicenter, prospective, observational study. Crit Care, 2017. 21(1): 188. DOI: 10.1186/s13054-017-1780-4.

27 Uchino, S, J A Kellum, R Bellomo, G S Doig, H Morimatsu, S Morgera, et al., Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA, 2005. 294(7): 813-8. DOI: 10.1001/jama.294.7.813.

28 Suarez-de-la-Rica, A, V Anillo, A Montero, C Hernandez-Gancedo, A Lopez-Tofino, F Gilsanz, et al., Risk factors for acute kidney injury in critically ill patients with complicated intra-abdominal infection. J Crit Care, 2017. 38: 104-108. DOI: 10.1016/j.jcrc.2016.10.031.

29 Tellor, B, L P Skrupky, W Symons, E High, S T Micek, and J E Mazuski, Inadequate Source Control and Inappropriate Antibiotics are Key Determinants of Mortality in Patients with Intra-Abdominal Sepsis and Associated Bacteremia. Surg Infect (Larchmt), 2015. 16(6): 785-93. DOI: 10.1089/sur.2014.166.

30 Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018;44(6):925-928. doi:10.1007/s00134-018-5085-0

31 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

32 Liu L, Ni Y. Antimicrobial susceptibilities of specific syndromes created with organ-specific weighted incidence antibiograms (OSWIA) in patients with intra-abdominal infections. BMC Infect Dis. 2018;18(1):584. Published 2018 Nov 19. doi:10.1186/s12879-018-3494-x

33 Sartelli, M, F M Abu-Zidan, F Catena, E A Griffiths, S Di Saverio, R Coimbra, et al., Global validation of the WSES Sepsis Severity Score for patients with complicated intra-abdominal infections: a prospective multicentre study (WISS Study). World J Emerg Surg, 2015. 10: 61.

34 Abdel-Kader, S, M Sartelli and F M Abu-Zidan, Complicated intra-abdominal infections: a prospective validation study of the WSES Sepsis Severity Score. Singapore Med J, 2019. 60(6): 317-321.

**Figures**
Figure 1

Risk factor selection using the least absolute shrinkage and selection operator (LASSO) cox regression model. (A) LASSO coefficient profiles of the 35 factors for OS. (B) Tuning parameter (lamda) selection in the LASSO model used 10-fold cross-validation via minimum criteria for OS.
Figure 2

Nomogram of OS in complicated intra-abdominal infection
Figure 3

Calibration curves and Kaplan-Meier survival curves for the nomogram in study cohort and validation cohort of cIAI. (A) Calibration curve of the nomogram in study cohort. (B) Calibration curve of the nomogram in validation cohort. (C) Kaplan-Meier survival curve of the nomogram in study cohort. (D) Kaplan-Meier survival curve of the nomogram in validation cohort.
Figure 4

Decision curve and ROC curve for the nomogram in study cohort and validation cohort of cIAI. (A) Decision curve of the nomogram in study cohort. (B) Decision curve of the nomogram in validation cohort. (C) ROC curve of the nomogram in study cohort. (D) ROC curve of the nomogram in validation cohort.