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Early prediction of in-hospital mortality in acute pancreatitis: A retrospective study based on a large multicentre critical care database

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041893
Article Type:	Original research
Date Submitted by the Author:	19-Jun-2020
Complete List of Authors:	li, caifeng; Tianjin Medical University General Hospital, Department of critical medicine Ren, Qian; Tianjin Daily, Advertising center Wang, Zhiqiang; Tianjin Medical University General Hospital, Department of critical medicine wang, guolin; Tianjin Medical University General Hospital, Department of critical medicine
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Gastroenterology < INTERNAL MEDICINE

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4 **1 Early prediction of in-hospital**
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7 **2 mortality in acute pancreatitis: A**
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9 **3 retrospective study based on a large multicentre critical care**
10
11 **4 database**

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1 Abstract

2 **Objective:** To develop and validate a prediction model for predicting in-hospital mortality in patients
3 with acute pancreatitis (AP).

4 **Design:** A retrospective study based on a large multicentre critical care database.

5 **Setting:** All subject data were collected from the eICU Collaborative Research Database (eICU-CRD),
6 which covers 200,859 ICU admissions of 139,367 patients in 208 US hospitals between 2014 and 2015.

7 **Participants:** A total of 746 patients with AP were drawn from eICU-CRD. Due to loss to follow-up
8 (4 patients) or incomplete data (364 patients), 378 patients were enrolled in the primary cohort to
9 establish a nomogram model and conduct internal validation.

10 **Primary and secondary outcome measures:** The outcome of the prediction model was in-
11 hospital mortality. All risk factors found significant in the univariate analysis were considered for
12 multivariate analysis to adjust for confounding factors. Then a nomogram model was established. The
13 performance of the nomogram model was evaluated by the concordance index (C-index) and the
14 calibration plot. The nomogram model was internally validated using the bootstrap resampling method.
15 The predictive accuracy of the nomogram model was compared with that of Acute Physiology, Age, and
16 Chronic Health Evaluation (APACHE) IV. Decision curve analysis (DCA) was performed to evaluate
17 and compare the potential net benefit using of different predictive models.

18 **Results:** The overall in-hospital mortality rate is 4.447%. Age, BUN, and lactate (ABL) were the
19 independent risk factors determined by multivariate analysis. The C-index of nomogram model ABL was
20 similar to that of APACHE IV [0.896 (95% confidence interval [CI]: 0.861 to 0.925), $P=0.499$], showing
21 a comparable discriminating power. Calibration plot demonstrated good agreement between the

1 predicted and actual in-hospital mortality. DCA showed that the nomogram model ABL was clinically
2 useful.

3 **Conclusions:** Nomogram model ABL, which used readily available data, exhibited high predictive
4 value for predicting in-hospital mortality in AP.

5 **Strengths and limitations of this study**

6 This is an original research to develop and internally validate a user-friendly prediction model using
7 easily obtainable clinical and laboratory parameters.

8 The nomogram model ABL presents an excellent prognostic ability for predicting in-hospital mortality
9 in AP patients.

10 The retrospective study design could lead to certain types of bias (e.g., confounding bias, selection bias).

11 The suitability of the model in larger population needs further external validation.

12 **Background**

13 AP is a relatively common, but poorly understood, inflammatory disease of the exocrine pancreas. So
14 far, the detailed pathogenesis of AP still remains unclear and no specific and effective treatment has been
15 proposed yet [1]. The clinical manifestation and disease course of AP also vary dramatically from self-
16 limiting simple edema pancreatitis to severe acute necrotizing pancreatitis characterized by systemic
17 inflammatory response syndrome and multiple organ failure [2]. With a mortality rate of less than 5%,
18 the mild edematous AP runs a benign course and recovers spontaneously without any sequelae in about
19 70% - 80% of patients, while nearly 20% - 30% of patients will develop severe necrotic pancreatitis with
20 a high mortality rate up to 20% - 30% [3-9].

1 Two peaks of mortality have been noted in patients with severe AP. Early death usually occurs in the
2 first two weeks owing to multiple organ dysfunction syndromes (MODS) caused by the production and
3 release of diverse cytokines [9-11]. Late death generally happens two weeks later as a result of
4 peripancreatic necrosis, infection, and secondary MODS [9, 10]. Studies found that patients in the high-
5 risk group may benefit from closer monitoring, early aggressive fluid resuscitation, rational use of
6 antibiotics, and timely invasive strategies, such as endoscopic sphincterotomy and radiologic
7 intervention [12, 13]. Once diagnosed as AP, early identification of high-risk patients is therefore
8 essential to improve survival.

9 Since the first scoring system for AP severity was proposed in 1974, about 20 different predictive models
10 have been developed [14]. However, there are some practical problems that restrict wide clinical
11 application of these predictive models. For instance, based on more than 10 parameters, APACHE II is
12 cumbersome and complex for rapid assessment within 24 hours after admission [15, 16]. Moreover,
13 APACHE II is a generic scoring system for all critical patients, so some parameters may be irrelevant to
14 the prognosis of AP [17]. Developed as an easy-to-use risk stratification tool, the BISAP score
15 outperforms other predictive models in specificity, but showing a suboptimal sensitivity in evaluating
16 the severity of AP [18, 19]. Despite its high sensitivity, RANSON score is less operative because it takes
17 at least 48 hours to be completed, resulting in a delay of triage and management [16, 20]. The computed
18 tomography severity index (CTSI) requires high-cost and radioactive CT scans, which might be
19 unavailable for most patients at their first visit [16, 21]. In addition, pancreatic necrosis might be
20 undetectable by an early CT scan within 24 hours [22]. Even in the first 3-4 days, contrast-enhanced CT
21 scan seems unreliable in estimating the extent of pancreatic necrosis [22, 23].

22 In view of the shortcomings of these currently available predictive models, there is consequently an

1 urgent need for an easy-to-use and accurate prognostic tool for predicting in-hospital mortality in AP
2 patients. Therefore, we collected demographics, clinical factors, laboratory data from a freely available,
3 multi-center database eICU-CRD and explored the risk factor for in-hospital mortality. Furthermore, we
4 incorporated these independent prognostic factors and developed a nomogram model in patients with AP
5 for better clinical guidance.

6 **Patients and methods**

7 **Study design**

8 We extracted subject data from eICU-CRD, a large multicentre critical care database. The database is
9 publicly and freely accessible to researchers, according to data usage agreement by the review board of
10 PhysioNet (Our record ID: 33047414). The eICU-CRD covers 200,859 ICU admissions of 139,367
11 patients in 208 US hospitals between 2014 and 2015. All data were stored automatically and retrieved
12 electronically through the Philips Healthcare eICU program. It includes records of demographics,
13 physiological indexes from bedside monitors, diagnosis via International Classification of Diseases, 9th
14 Edition, Clinical Modification (ICD-9-CM) codes, and other laboratory data obtained during routine
15 medical care. All data were de-identified by the eICU program and anonymous to researchers before
16 analysis [24]. As this research was an observational, retrospective study based on data from eICU-CRD,
17 no ethical approval was required from our local ethics committee. This study was reported following the
18 recommendations of the Transparent Reporting of a multivariable prediction model for Individual
19 Prognosis Or Diagnosis (TRIPOD) statement [25].

1 **Participants**

2 The study population was drawn from eICU-CRD. According to the 2012 Atlanta Criteria, the diagnosis
3 of AP can be made if two or more of the following criteria are present: (1) abdominal pain (acute and
4 persistent epigastric pain usually radiating to the back); (2) serum amylase or lipase level being at least
5 3 times greater than the normal upper limit; (3) characteristic abdominal imaging findings of AP [26].
6 The ICD-9-CM diagnostic code used for selecting patients with AP is 577.0.

7 **Data retrieval**

8 All subject data within the first 24 hours after admission were collected from eICU-CRD using the
9 Structure Query Language. The physiological variables, including body temperature (BT), heart rate
10 (HR), mean blood pressure (MBP), and respiratory rate (RR) were obtained from the table *apacheApsVar*.
11 The baseline characteristics such as age, gender, weight, height, APACHE IV, Glasgow Coma Scale
12 (GCS) score, and the history of past illnesses were collected from the tables of *patient*,
13 *apachePatientResult* and *pastHistory*. The laboratory indexes, for instance, serum albumin, lactate, base
14 excess (BE), total bilirubin, glucose, blood urea nitrogen (BUN), white blood cell (WBC), hematocrit,
15 platelet (PLT), calcium, lactic dehydrogenase (LDH), aspartate aminotransferase (AST), cholesterol,
16 triglycerides, amylase, lipase, and arterial oxygen pressure (PaO₂) were extracted from the table *lab*.
17 Potential risk factors associated with in-hospital mortality were identified from previous predictive
18 models [16, 27], from literature or guidelines [7, 14, 28, 29], and from consulting clinic medical experts.
19 The decisions of their inclusion in the univariate logistic regression analysis were based on the following
20 criteria that the potential risk factors: (1) were objective parameters, (2) were routinely measured in

1 medical practice, and (3) were completely recorded or missing randomly in the dataset. The worst value
2 of each variable recorded during the first 24 hours after admission was used to analyze and establish the
3 nomogram model.

4 **Statistical analysis**

5 Continuous variables, expressed as mean with standard deviation (SD) or median with interquartile range
6 (IQR), were analyzed using the Student t-test (for data with normal distribution) or Mann–Whitney U
7 test (for data without normal distribution). Categorical variables, expressed as absolute numbers (n) and
8 proportions (%), were compared using the Chi-square test or Fisher's exact test. Univariate logistic
9 regression analysis was performed to determine the possible correlation between in-hospital mortality
10 and potential risk factors. All significant risk factors ($P < 0.1$) in the univariate logistic regression analysis
11 were eligible for inclusion in the multivariate logistic regression analysis to adjust for confounding
12 factors. Based on the results of the multivariate logistic regression analysis, a nomogram was constructed.
13 The performance of the nomogram model was assessed using its calibration and discrimination.
14 Calibration describes the level of agreement between predicted and actual risks, and is usually evaluated
15 by calibration plot and Hosmer-Lemeshow Chi-square test [30]. Discrimination refers to the ability of a
16 model to distinguish high-risk and low-risk patients, and is generally evaluated by C-index or area under
17 the receiver operator characteristic curve (AUROC) [31]. In order to address overfitting and quantify
18 optimism, the predictive model was internally validated using bootstrap resampling. Optimism represents
19 the difference between the apparent (unadjusted) model performance and bootstrap (bias) corrected
20 estimated model performance. Internal validation involved refitting the model to a series of 1000 random
21 samples drawn from the original dataset with replacement, and produced an overall C-index from all

1 samples. This process adjusted the C-index for overoptimism which may arise when a model was
2 validated with the same dataset used to build the model [32]. DCA was performed to evaluate the clinical
3 usefulness of the nomogram model by quantifying the net benefits under different threshold probabilities.
4 For all analyses, *P* value less than 0.05 was considered to be statistically significant. All statistical
5 analyses were carried out on GraphPad Prism 7 (GraphPad Prism, GraphPad Software, La Jolla, CA) and
6 R 3.6.1 (R Development Core Team). The packages of *rms*, *Hmisc*, *pROC*, *stats*, *PredictABEL*, and *rmda*
7 were involved in this process.

8 **Results**

9 **Baseline characteristics and outcomes**

10 A total of 746 patients with AP were extracted from the database, of whom 4 patients were excluded due
11 to loss to follow-up, thus resulting in 742 evaluable patients included in our study. The demographic and
12 clinical characteristics of all patients are listed in [Table 1](#). The total cohort consisted of 291 women
13 (39.218%) and 451 men (60.782%), with a female-to-male ratio of 0.645:1. The age ranged from 18 to
14 89 years old and the average age was 52 years old. The median body mass index (BMI) was 28.430
15 kg/m² (IQR: 24.750-32.870). The participants were of diverse racial and ethnic backgrounds, with 567
16 Caucasians (76.415%), 54 African Americans (7.278%), 35 Hispanics (4.717%), 9 Native Americans
17 (1.213%), 9 Asians (1.213%), and 61 Others (8.221%). About 505 patients were admitted to medical-
18 surgical intensive care unit (Med-Surg ICU) (68.059%), 76 to medical intensive care unit (MICU)
19 (10.243%), 65 to surgical intensive care unit (SICU) (8.760%), 96 to other ICUs (12.938%). Many
20 patients have similar commodities, 340 of whom were complicated with hypertension (45.822%), 109

1 with diabetes mellitus (DM) (14.690%), 74 with chronic obstructive pulmonary diseases (COPD)
2 (9.973%), 43 with chronic heart failure (CHF) (5.795%), 29 with stroke (3.908%), 28 with myocardial
3 infarction (MI) (3.774%), 42 with renal insufficiency (RI) (5.660%), and others did not have prominent
4 comorbidities (12.803%). Eventually, 39 patients underwent surgical treatment for AP (5.256%). We
5 also analyzed the incidence of severe complications and found that respiratory failure requiring
6 ventilation and renal failure requiring dialysis were 62 (8.356%) and 11 (1.482%) respectively. Finally,
7 33 patients died in hospital and the mortality rate was 4.447%.

8 **Prognostic factors for in-hospital mortality**

9 Univariate logistic regression analysis was performed for each potential risk factor. Age, GCS score,
10 MBP, albumin, lactate, bilirubin, BUN, WBC, calcium, AST, and comorbidities of CHF, COPD,
11 hypertension were risk factors for in-hospital mortality determined by univariate logistic regression
12 analysis ($P < 0.1$). Thereafter, all these risk factors were entered simultaneously into the multivariable
13 logistic regression analysis to control possible confounding factors. Finally, age, BUN, and lactate (ABL)
14 were proved to be independent risk factors for predicting in-hospital mortality (Table 2). Due to
15 incomplete data, 364 patients were excluded, leaving 378 evaluable patients included in the nomogram
16 model ABL. The flow chart of the inclusion of eligible patients is shown in Fig. 1. The diagnostic
17 equation built on multivariate logistic regression analysis is as follows:

$$18 \text{ Logit } P = -10.3074 + 0.0831 * \text{Age} + 0.4032 * \text{Lactate} + 0.0201 * \text{BUN}$$

19 **Fig. 1** Flow chart of patient selection.

1 **Development of a nomogram predicting in-hospital mortality**

2 Based on the multivariate logistic regression analysis, a nomogram was constructed by assigning a
3 weighted point to each independent risk factor on the point scale (Fig. 2). A higher total point of all risk
4 factors refers to a higher in-hospital mortality rate. For example, a patient who is 70 years old (71 points),
5 with BUN of 20 mg/dL (6 points), lactate of 10 mmol/L (63 points) would score 140 points, which
6 corresponds to an estimated 50% risk of in-hospital death.

7 **Fig. 2** Nomogram for predicting in-hospital mortality in AP. To obtain nomogram predicted in-hospital
8 mortality, locate the value of each independent risk factor at each axis, draw a vertical line to the “Point”
9 axis to get the point for each risk factor, then sum all the points, locate the sum on the “Total Points”
10 axis to get the predicted probability on “Predicted in-hospital mortality” axis. AP, acute pancreatitis

11 **Performance of the nomogram model ABL**

12 The discrimination and calibration, two basic characteristics of model validation, were tested to evaluate
13 the performance of the nomogram model ABL [33]. Model discrimination was assessed using the C-
14 index that measures the ability to predict the outcomes. A higher C-index refers to a greater ability to
15 discriminate the outcomes. The C-index of our nomogram model ABL was 0.896 (95%CI: 0.861 to
16 0.925), showing a great discrimination ability. The receiver operating characteristic (ROC) curves of age,
17 lactate, BUN, and the nomogram model ABL for predicting in-hospital mortality were shown in Fig. 3A.
18 By visual inspection of AUROC, nomogram model ABL showed better performance than any other
19 individual risk factor. Model calibration was evaluated using the Hosmer-Lemeshow Chi-square test and
20 a calibration plot. The Hosmer-Lemeshow Chi-square which measured the calibration was 7.201 ($P =$

1 0.515), demonstrating that there was no significant difference from a perfect fit. The calibration plot was
2 shown in **Fig. 3B**. Visual inspection of the calibration plot further indicated good agreement between the
3 predicted and actual in-hospital mortality.

4 **Fig. 3** (A) ROC curves for the nomogram model ABL and individual risk factors for predicting in-
5 hospital mortality. AUROC represents the discrimination ability of a predictive model. (B) Calibration
6 plot comparing the actual and predicted in-hospital mortality. The x-axis indicates the deciles of predicted
7 in-hospital mortality. Each bar in the graph stands for the actual and predicted in-hospital mortality.
8 ROC, receiver operating characteristic; AUROC, area under the receiver operator characteristic curve

9 **Validation of the nomogram model ABL**

10 The bootstrapping technique was employed to internally validate model performance [32]. During
11 internal validation, nomogram model ABL retained its excellent discrimination in the bootstrap samples,
12 showing an optimism corrected C-index of 0.892 (set seed 123). The calibration curve was used to assess
13 the ability of a predictive model to obtain unbiased estimates of the outcome, and a perfectly calibrated
14 predictive model would produce a curve on which the predicted and actual probabilities fall along a 45-
15 degree diagonal line [34]. The calibration curve of nomogram model ABL was very close to the 45-
16 degree ideal line, showing good agreement between the predicted and actual in-hospital mortality (**Fig.**
17 **4**).

18 **Fig. 4** Calibration curve of nomogram model ABL. The x-axis represents the predicted in-hospital
19 mortality calculated according to the model, while the y-axis exhibits the actual in-hospital mortality.
20 The vertical lines show the frequency distribution of the predicted in-hospital mortality. The apparent
21 calibration curve (dotted line) indicates the model performance in the original data, while the bias-

1 corrected curve (solid line) represents the model performance after correction for optimism using 1000
2 bootstrapped resamples. Perfect prediction would fall on the 45-degree (dashed) reference line.

3 **Comparison of predictive accuracy for in-hospital mortality between** 4 **the nomogram model ABL and APACHE IV**

5 Complete APACHE IV data were available for 606 patients (81.167%), of whom 27 patients (4.455%)
6 died in the hospital. The median APACHE IV was 46 in the survival group and 90 in the death group.
7 The C-index was calculated to estimate the discrimination ability of APACHE IV [0.857 (95% CI: 0.826
8 to 0.884)]. There was no statistically significant difference between the C-index of the nomogram model
9 ABL and that of APACHE IV ($P = 0.499$), indicating the nomogram model ABL had a similar predictive
10 accuracy with APACHE IV. The ROC curves for the nomogram model ABL and APACHE IV also
11 demonstrated comparable discriminating power (Fig. 5A).

12 The integrated discrimination improvement index (IDI) is a method to quantify the incremental
13 predictive value of new methods to existing predictive models [35]. In this study, IDI was calculated to
14 assess the improvement in risk stratification using different models. The IDI was 0.105 (95%CI: -0.016
15 to 0.226), indicating no significant difference ($P = 0.088$) in performance between the nomogram model
16 ABL and APACHE IV.

17 The DCA can depict the overall net benefit of using predictive models compared with the treat-all-
18 patients and treat-none scheme. Fig. 5B showed the net benefit of using the nomogram model ABL and
19 APACHE IV, with several overlaps, the net benefit of the nomogram model ABL was comparable to
20 that of APACHE IV.

21 **Fig. 5 (A)** ROC curves for the nomogram model ABL and APACHE IV. Visual comparison of ROC

1 curves indicates the discrimination performance of the nomogram model ABL was comparable to that
2 of APACHE IV. (B) Decision curve analysis for the nomogram model ABL and the APACHE IV. The
3 y-axis measures the net benefit, and the x-axis shows the threshold probability. The horizontal black
4 line along the x-axis represents the assumption that no patient will die in the hospital (i.e., no patient
5 should undergo close monitoring and aggressive treatment), whereas the solid gray line represents the
6 assumption that all patients will die in the hospital (i.e., all patients should undergo close monitoring
7 and aggressive treatment). The red line indicates the nomogram model ABL and the blue line
8 represents the APACHE IV. ROC, receiver operating characteristic; APACHE, Acute Physiology,
9 Age, and Chronic Health Evaluation

10 Discussion

11 AP is a heterogeneous digestive system disease. Most patients with AP will relieve spontaneously
12 without any organ failure, while about 20% of cases will evolve into severe form, which is associated
13 with MODS, sepsis, and high mortality [6]. Thus, it is imperative to identify patients who might develop
14 severe AP and initiate more aggressive intervention [26]. Through early identification and reasonable
15 treatment, patients at high risk of mortality might be converted to low risk, which is the main goal of our
16 model development.

17 Using demographic, clinical and conventional laboratory data from a large-scale publicly available ICU
18 database, the following independent risk factors for predicting in-hospital mortality of AP were identified:
19 age, BUN, and lactate (ABL). These factors are consistent with the risk factors traditionally associated
20 with in-hospital mortality. Except for age, other risk factors are modifiable by timely and aggressive
21 treatment, which is particularly important for improving outcomes. Nomograms could provide predictive

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4 1 information tailored to the individual, by establishing a simple graphical representation of a complex
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6 2 statistical prediction model [34]. Currently, nomograms are increasingly being used to improve clinical
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9 3 decision making. In this study, we incorporated age, BUN and lactate into an easy-to-use and reliable
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11 4 nomogram model ABL. Our predictive model also generates an equation on a continuous scale rather
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14 5 than an arbitrary “cutoff” for each parameter. The outstanding advantage of the nomogram model ABL
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17 6 is its simplicity and accuracy. There are only three parameters in the current model, which requires no
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20 7 extra calculations and is convenient for clinicians. In addition, all these parameters are objective and can
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23 8 be easily obtained following a general hospital admission. We calculated the C-index to quantify the
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26 9 discriminatory power of our model. A C-index of 1 represents perfect prediction accuracy, whereas a C-
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29 10 index of 0.5 indicates no better than random guesses. With a C-index of 0.896, the nomogram model
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32 11 ABL exhibited perfect model discrimination performance. The ROC curve also showed that the
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35 12 nomogram model ABL provide great model prediction accuracy. Internal validation via bootstrap
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38 13 resamples demonstrated an adjusted C-index of 0.892, which was in excellent agreement with the original
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41 14 data. Moreover, the calibration curve indicated a sufficient fit of predicted and actual in-hospital mortality.
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44 15 This user-friendly nomogram model ABL might be a valuable tool for clinical practice because it could
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47 16 provide a simple and accurate way to predict in-hospital mortality in patients with AP.
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50 17 As is well known to all, age is an important and useful indicator of poor prognosis in various entities.
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53 18 Furthermore, many acknowledged predictive models have incorporated age for predicting the severity or
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56 19 mortality of AP in the field of clinical medicine [7, 14]. Our study also demonstrates that age is an
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59 20 independent risk factor for in-hospital mortality in patients with AP. With age incremented by 10 years,
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21 the risk for in-hospital mortality was increased by 6.776% in our study.
22 In this study, we found that hyperlactatemia (≥ 2 mmol/L) were very common in AP (50.131%). Lactate,

1 a byproduct of glycolysis under anaerobic conditions, is generally considered as a powerful indicator of
2 ischemia and hypoxia in body tissues. However, diseases with elevated plasma catecholamine, such as
3 huge trauma or shock, can also lead to exaggerated glycolysis and increased lactate level [36-38].
4 Hyperlactatemia in AP might be related to the above factors. Single plasma lactate level, especially that
5 measured immediately after admission to the ICU or arrival at the emergency room, is regarded as a
6 powerful predictor of subsequent multiorgan failure and mortality. In 1965, Peretz et al. [39] first
7 described the relationship between plasma lactate level and mortality and revealed a death rate of 100%
8 when the plasma lactate level is higher than 13.3 mmol/L. More recently, Nichol et al. [40] and Haas et
9 al. [41] also found that the mortality rate of patients with a plasma lactate level greater than 10 mmol/L
10 was up to 80%. Recent studies demonstrated that early lactate clearance and continuous dynamic
11 monitoring of the plasma lactate level could serve as a useful prognostic factor and guide timely
12 intervention of critically ill patients [41-46]. In 2017, Valverde-López et al. [47] reported that elevated
13 plasma lactate level was closely related to persistent multiorgan failure of patients with AP, lactate might
14 become a useful biomarker for predicting poor clinical outcomes of AP on admission, especially for the
15 prediction of mortality, lactate exhibited an excellent AUROC of 0.870. Moreover, lactate performed
16 much better than CRP in predicting ICU requirements and mortality [47]. Our research demonstrated
17 that the lactate level was strongly associated with in-hospital mortality of AP, with a great AUROC of
18 0.776. By multivariate logistic regression analysis, lactate has been proven to be an independent risk
19 factor for predicting in-hospital mortality, which is consistent with previous studies [47].
20 BUN as a useful predictor of in-hospital mortality is consistent with the current existing literature.
21 Previous studies have shown that BUN on admission and BUN rise in the first 24 hours following
22 admission can predict mortality of patients with AP [29, 48-51]. Many studies believe that increased

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4 1 BUN in AP is owing to the loss of body fluid, the decrease of intravascular blood volume, and the
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6 2 development of prerenal azotemia [48, 50]. If the hypovolemic state cannot be corrected completely at
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9 3 early stage, the patients will suffer from further depletion of effective circulatory blood volume, from
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11 4 severe decrease in glomerular filtration fraction and eventually leading to prerenal insufficiency. If the
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14 5 disease progresses further, it may lead to multiple organ and system failure, which is the main cause of
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17 6 death [10, 28]. Therefore, many scoring systems used in clinical practice are based on the urea level
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20 7 (Ranson, Glasgow, POP, BISAP) [7, 52-54]. The Hong Kong criterion is based on only two parameters,
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22 8 the urea, and glycemia [55].

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25 9 In order to further evaluate the value of nomogram model ABL in clinical use, we compared its
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27 10 performance with the APACHE scoring system. APACHE II is one of the most powerful and widely
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30 11 used prognostic tool for all ICU patients to predict severity and mortality. Later this scoring system was
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33 12 extrapolated to AP, the study results showing perfect prognostic value [15, 56]. The APACHE II had
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36 13 been modified many times since its launch in 1985, and the latest version was the APACHE IV published
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38 14 in 2006 [57, 58]. Involving about 52 different physiologic indexes, APACHE IV accounts for
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41 15 hepatobiliary parameters, sedation status, and multiple comorbidities simultaneously. Due to such wide
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43 16 range of physiologic variables, APACHE IV has a much better performance compared with APACHE II
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46 17 [59, 60]. In 2015, a study reported that an APACHE IV of 44 or higher would predict mortality in 100%
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49 18 of cases, and the AUROC for APACHE IV was 0.93 [61]. However, the main drawback of APACHE IV
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52 19 is that it relies on many variables that are not routinely collected during general hospital admission [7].
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54 20 Nevertheless, our nomogram model ABL could attain a comparable predictive accuracy of the more
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56 21 complex APACHE IV with fewer parameters in patients with AP.

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58 22 An ideal predictive model should be reliable and easy-to-use at the early stage of the disease, using
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1 readily available data [62]. The nomogram model ABL achieves many of these characteristics: it is
2 generated from data within 24 hours after admission, using age and some easily obtainable, reliable, and
3 inexpensive clinical and laboratory parameters in a model, and is feasible in a user-friendly manner.
4 Moreover, the nomogram model ABL presents an excellent prognostic ability for in-hospital mortality,
5 which is comparable to that of APACHE IV.
6 Our study still has some limitations. First, this study included patients with AP from one database, which
7 may caution us from generalizing this nomogram model ABL to a larger population. Second, although
8 we tried to adjust confounding factors as much as possible by performing multivariate logistic regression
9 analysis, residual confounding factors through unknown or unmeasured covariates might not be
10 completely ruled out. Finally, the database that we used did not cover information on etiology, initial or
11 recurrent episodes of pancreatitis, which might affect in-hospital mortality.

12 **Conclusion**

13 We propose a refined nomogram model ABL with age, easily obtainable clinical and biochemical
14 parameters, the BUN and lactate. This nomogram model ABL shows excellent performance and allows
15 clinical practitioners to perform early and quick risk-stratification and guide early management strategies
16 for AP patients.

17 **Abbreviations**

18 AP: acute pancreatitis; eICU-CRD: eICU Collaborative Research Database; C-index: concordance index;
19 ICU: intensive care unit; CI: confidence interval; MODS: multiple organ dysfunction syndromes; CTSI:
20 computed tomography severity index; TRIPOD: Transparent Reporting of a multivariable prediction

1 model for Individual Prognosis Or Diagnosis; BT: body temperature; HR: heart rate; MBP: mean blood
2 pressure; RR: respiratory rate; GCS: Glasgow Coma Scale; BE: base excess; BUN: blood urea nitrogen;
3 WBC: white blood cell; PLT: platelet; LDH: lactic dehydrogenase; AST: aspartate aminotransferase;
4 PaO₂: arterial oxygen pressure; SD: standard deviation; OR: odds ratio; AUROC: area under the receiver
5 operator characteristic curve; BMI: body mass index; IQR: interquartile range; Med-Surg ICU: medical-
6 surgical intensive care unit; MICU: medical intensive care unit; SICU: surgical intensive care unit; DM:
7 diabetes mellitus; COPD: chronic obstructive pulmonary diseases; CHF: chronic heart failure; MI:
8 myocardial infarction; RI: renal insufficiency; ROC: receiver operating characteristic; IDI: integrated
9 discrimination improvement index; APACHE: Acute Physiology, Age and Chronic Health Evaluation.

10 **Declarations**

11 **Conflicts of interest:** The authors declare that they have no conflict of interest.

12 **Acknowledgments:** Not applicable.

13 **Funding:** There is no funding.

14 **Availability of data and material:** The data were available on the eICU-CRD website at

15 <https://eicu-crd.mit.edu/>.

16 **Authors' contributions:** Caifeng Li conceived the idea, extracted the data, performed the analysis, and
17 drafted the manuscript. Guolin Wang helped to frame the idea of the study, interpret the results and revise
18 the manuscript. Qian Ren helped to edit pictures and revised the manuscript. All authors read and
19 approved the final manuscript.

20 **Ethics approval and consent to participate:** The study was an analysis of a third-party anonymized
21 publicly available database with pre-existing institutional review board approval.

1 **Consent for publication:** Not applicable.

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2 Table 1 Characteristics and outcomes of participants

Characteristics	Survived to Discharge (N=709)	Died in the Hospital (N = 33)	P Value
Demographics			
Age (median [IQR])	51.00 [40.00, 63.00]	65.00 [60.00, 78.00]	<0.001
Gender male, n (%)	427 (60.2)	24 (72.7)	0.209
Ethnicity, n (%)			0.348
African American	49 (7.0)	5 (15.2)	
Asian	9 (1.3)	0 (0.0)	
Caucasian	542 (77.2)	25 (75.8)	
Hispanic	34 (4.8)	1 (3.0)	
Native American	8 (1.1)	1 (3.0)	
Other/Unknown	60 (8.5)	1 (3.0)	
Height (cm, median [IQR])	172.00 [163.00, 178.00]	172.70 [165.10, 178.43]	0.685
Weight (kg, median [IQR])	83.90 [70.90, 98.10]	93.30 [78.97, 103.50]	0.037
Clinical Factors			
ICU type, n (%)			0.002
Med-Surg ICU	485 (68.4)	20 (60.6)	
MICU	76 (10.7)	0 (0.0)	
SICU	55 (7.8)	10 (30.3)	
Other ICUs	93(13.1)	3(9.1)	
Comorbidities, n (%)			
CHF	37 (5.3)	6 (18.2)	0.007
COPD	67 (9.6)	7 (21.2)	0.062
Hypertension	317 (45.4)	23 (69.7)	0.01
DM	105 (15.0)	4 (12.1)	0.836
MI	26 (3.7)	2 (6.1)	0.825
RI	38 (5.4)	4 (12.1)	0.218
Vital signs			
BT (°C, median [IQR])	36.70 [36.40, 36.90]	36.60 [36.40, 36.82]	0.509
RR (/min, median [IQR])	30.00 [12.00, 37.00]	33.00 [27.00, 39.00]	0.113
HR (/min, median [IQR])	118.00 [102.00, 134.00]	120.00 [100.00, 135.00]	0.908
MBP (mm Hg, median [IQR])	98.00 [60.00, 125.50]	51.00 [43.00, 70.00]	<0.001
APACHE IV (median [IQR])	46.00 [34.00, 62.00]	90.00 [71.00, 105.00]	<0.001
GCS (median [IQR])	15.00 [14.00, 15.00]	13.00 [10.00, 15.00]	<0.001
Invasive intervention, n (%)			
Operation	36 (5.1)	3 (9.1)	0.541
Intubation	34 (5.2)	7 (24.1)	<0.001
Ventilation	53 (8.1)	9 (31.0)	<0.001
Dialysis	9 (1.4)	2 (6.9)	0.12
Laboratory Data			

Albumin (g/dL, median [IQR])	2.90 [2.40, 3.40]	2.40 [1.95, 2.80]	<0.001
Lactate (mmol/L, median [IQR])	1.90 [1.20, 3.10]	5.20 [2.20, 8.57]	<0.001
BE (mEq/L, median [IQR])	-3.20 [-7.00, 0.50]	-5.10 [-9.20, -3.00]	0.245
Total bilirubin (mg/dL, median [IQR])	1.00 [0.60, 2.30]	2.10 [0.80, 3.90]	0.105
Glucose (mg/dL, median [IQR])	167.00 [128.00, 237.75]	194.00 [162.00, 247.00]	0.065
BUN (mg/dL, median [IQR])	18.00 [12.00, 31.00]	37.00 [23.00, 54.00]	<0.001
WBC ($\times 10^9/L$, median [IQR])	10.80 [7.37, 15.70]	14.00 [7.85, 23.70]	0.106
Hematocrit (% , median [IQR])	34.90 [30.50, 39.88]	33.00 [29.08, 37.18]	0.272
PLT (% , median [IQR])	178.50 [126.00, 241.00]	172.00 [118.00, 236.00]	0.634
Calcium (mg/dL, median [IQR])	7.80 [7.20, 8.30]	7.45 [6.50, 8.20]	0.129
LDH (Units/L, median [IQR])	350.00 [236.00, 557.50]	469.50 [317.25, 634.50]	0.439
AST (Units/L, median [IQR])	67.00 [32.00, 160.25]	110.00 [39.00, 301.50]	0.052
Cholesterol (mg/dL, median [IQR])	191.00 [127.50, 296.00]	137.00 [137.00, 137.00]	0.466
Triglycerides (mg/dL, median [IQR])	188.00 [105.75, 1083.75]	189.00 [151.00, 374.00]	0.946
Amylase (Units/L, median [IQR])	362.00 [112.00, 949.00]	581.60 [102.75, 1091.25]	0.8
Lipase (Units/L, median [IQR])	952.00 [364.00, 2995.00]	1538.00 [75.50, 4323.50]	0.887
PaO ₂ (mmHg, median [IQR])	75.75 [67.00, 93.50]	98.50 [74.75, 101.75]	0.24

1 *Abbreviations:* IQR interquartile range, ICU intensive care unit, Med-Surg ICU medical-surgical intensive care unit, MICU medical
2 intensive care unit, SICU surgical intensive care unit, CHF chronic heart failure, COPD chronic obstructive pulmonary diseases,
3 DM diabetes mellitus, MI myocardial infarction, RI renal insufficiency, BT body temperature, RR respiratory rate, HR heart rate,
4 MBP mean blood pressure, APACHE Acute Physiology, Age and Chronic Health Evaluation, GCS Glasgow Coma Scale, BE base
5 excess, BUN blood urea nitrogen, WBC white blood cell, PLT platelet, LDH lactic dehydrogenase, AST aspartate aminotransferase,
6 PaO₂ arterial oxygen pressure.

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Table 2. Univariate and multivariate logistic regression analysis with stepwise variable selection

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P Value	OR	95%CI	P Value
Demographics						
Age	1.0538	1.0305-1.0792	0	1.0798	1.0174-1.16	0.0201
Gender	1.7611	0.8345-4.0548	0.1554			
BMI	1.0321	0.986-1.0756	0.1526			
Clinical Factors						
Comorbidities						
CHF	3.976	1.415-9.66	0.0042	5.2176	0.6046-45.9861	0.1257
COPD	2.5396	0.9855-5.7822	0.0361	0.8789	0.1098-6.4035	0.8993
Hypertension	2.7716	1.335-6.1756	0.0083	2.2653	0.5367-11.4279	0.2842
DM	0.7803	0.228-2.0334	0.6482			
MI	1.67	0.2617-5.9465	0.4978			
RI	2.3993	0.686-6.4923	0.1173			
Vital signs						
BT	0.9811	0.7461-1.4972	0.9175			
RR	1.0227	0.9959-1.0512	0.1018			
HR	0.9988	0.9867-1.0118	0.8491			
MBP	0.9797	0.9661-0.9914	0.0017	0.9909	0.9715-1.0072	0.3028
GCS	0.9178	0.8682-0.9755	0.0035	0.991	0.8342-1.2101	0.9228
Laboratory Data						
Albumin	0.3357	0.1911-0.5761	0.0001	0.4189	0.108-1.5017	0.1882
Lactate	1.3811	1.2217-1.5719	0	1.6353	1.2683-2.2129	0.0004
BE	0.9559	0.8919-1.0274	0.2069			
Total bilirubin	1.08	0.9749-1.174	0.0915	0.8698	0.629-1.0969	0.3193
Glucose	1.0009	0.9983-1.003	0.4174			
BUN	1.0245	1.0138-1.035	0	1.0278	1.0037-1.0523	0.0186
WBC	1.0501	1.0067-1.0913	0.0164	0.9748	0.9054-1.0448	0.4721
Hematocrit	0.9724	0.9198-1.0259	0.3144			
PLT	0.9983	0.9942-1.0018	0.3698			
Calcium	0.7605	0.5565-1.0501	0.0916	0.9943	0.4857-2.1647	0.9878
LDH	0.9998	0.9971-1.0014	0.8382			
AST	1.0002	0.9999-1.0005	0.0946	0.9997	0.9987-1.0005	0.5251
Cholesterol	0.9889	0.9421-1.0035	0.5197			
Triglycerides	0.9996	0.9984-1.0001	0.2623			
Amylase	1	0.9994-1.0004	0.8752			
Lipase	1	0.9998-1.0002	0.796			
PaO2	1.0003	0.9824-1.0125	0.9619			

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Abbreviations: AP acute pancreatitis, OR odds ratio, CI confidence interval, CHF chronic heart failure, COPD chronic obstructive pulmonary diseases, DM diabetes mellitus, MI myocardial infarction, RI renal insufficiency, BT body temperature, RR respiratory

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1 rate, HR heart rate, MBP mean blood pressure, GCS Glasgow Coma Scale, BE base excess, BUN blood urea nitrogen, WBC white
2 blood cell, PLT platelet, LDH lactic dehydrogenase, AST aspartate aminotransferase, PaO2 arterial oxygen pressure.

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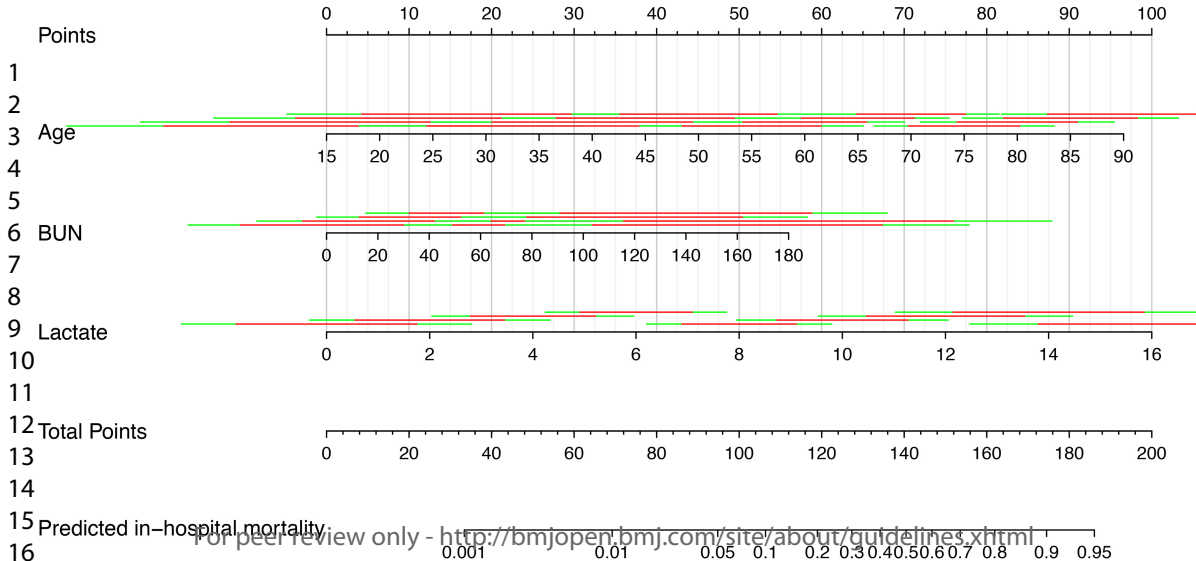
1 746 patients with acute pancreatitis admitted
2 to ICU from eICU database

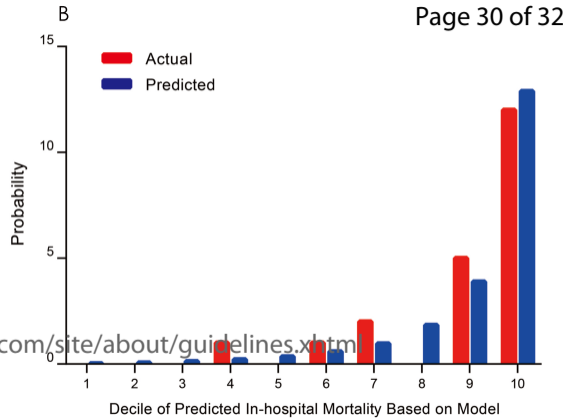
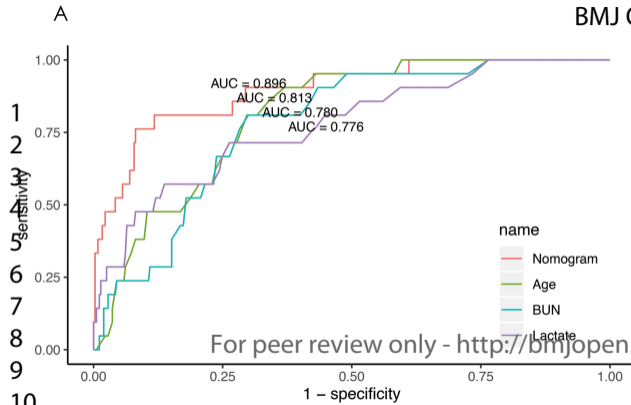
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6 4 patients excluded due
7 to loss of follow-up
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12 742 patients were included for clinical
13 characteristics analysis and risk factor selection
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21 364 patients with
22 incomplete data excluded
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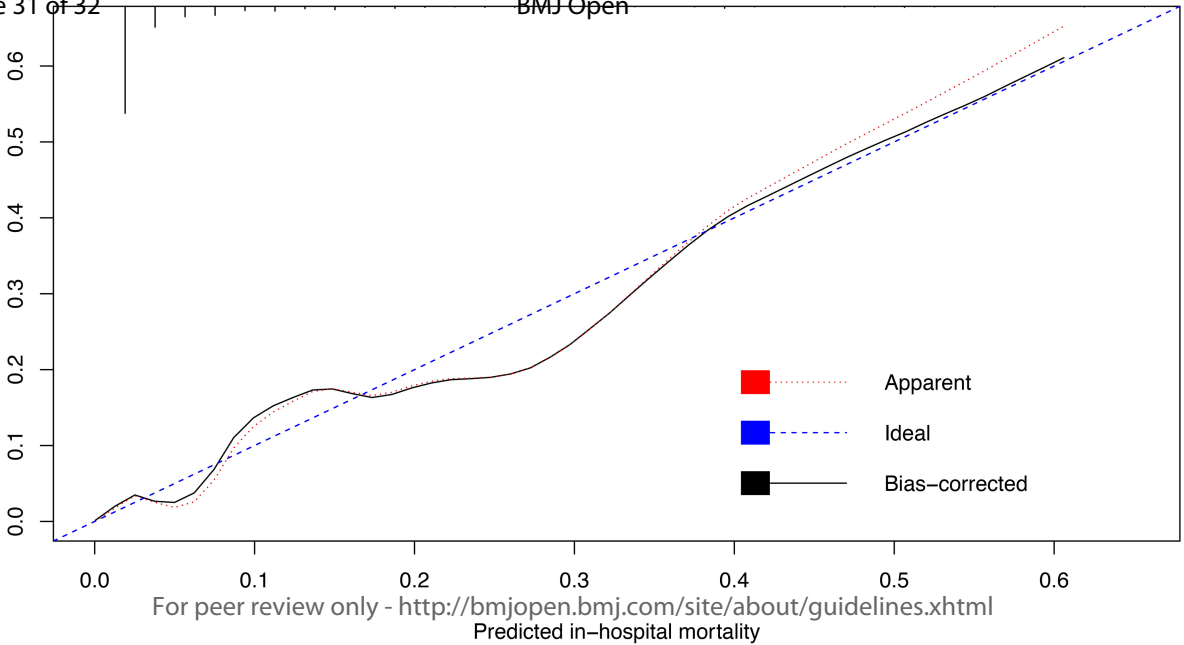
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28 378 eligible patients for nomogram
29 development and useful evaluation
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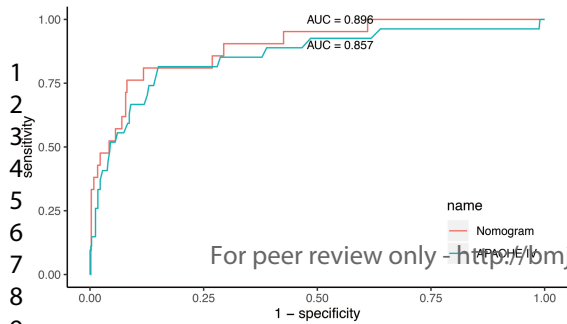


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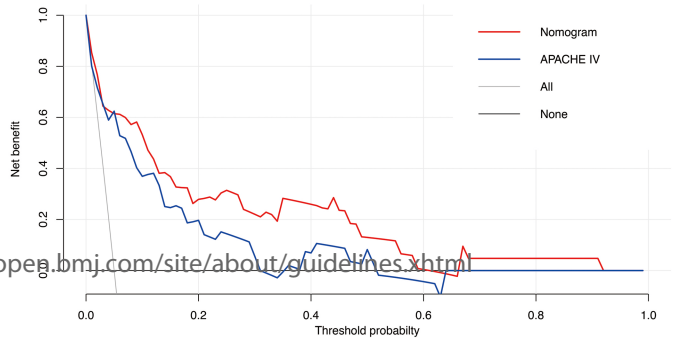
B= 1000 repetitions, boot

Mean absolute error=0.01 n=378

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3-4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5-6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5-6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5-6
	5b	D;V	Describe eligibility criteria for participants.	5-6
	5c	D;V	Give details of treatments received, if relevant.	Not Applicable
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	Not Applicable
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Not applicable
Sample size	8	D;V	Explain how the study size was arrived at.	8
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	9
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6-7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Not applicable
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Not applicable
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Not applicable
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8-9
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8-9
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Not applicable
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	9
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	9
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	D	Explain how to use the prediction model.	9-10
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	10-13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Not applicable
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16-17
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	13-14
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13-16
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Not applicable
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Not applicable

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Early prediction of in-hospital mortality in acute pancreatitis: A retrospective observational cohort study based on a large multicentre critical care database

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041893.R1
Article Type:	Original research
Date Submitted by the Author:	13-Sep-2020
Complete List of Authors:	li, caifeng; Tianjin Medical University General Hospital, Department of critical medicine Ren, Qian; Tianjin Daily, Advertising center Wang, Zhiqiang; Tianjin Medical University General Hospital, Department of critical medicine wang, guolin; Tianjin Medical University General Hospital, Department of critical medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Gastroenterology < INTERNAL MEDICINE

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1 **Early prediction of in-hospital** 2 **mortality in acute pancreatitis: A** 3 **retrospective observational cohort study based on a large** 4 **multicentre critical care database**

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1 Abstract

2 **Objective:** To develop and validate a prediction model for predicting in-hospital mortality in patients
3 with acute pancreatitis (AP).

4 **Design:** A retrospective observational cohort study based on a large multicentre critical care database.

5 **Setting:** All subject data were collected from the eICU Collaborative Research Database (eICU-CRD),
6 which covers 200,859 ICU admissions of 139,367 patients in 208 US hospitals between 2014 and 2015.

7 **Participants:** A total of 746 patients with AP were drawn from eICU-CRD. Due to loss to follow-up
8 (4 patients) or incomplete data (364 patients), 378 patients were enrolled in the primary cohort to
9 establish a nomogram model and conduct internal validation.

10 **Primary and secondary outcome measures:** The outcome of the prediction model was in-
11 hospital mortality. All risk factors found significant in the univariate analysis were considered for
12 multivariate analysis to adjust for confounding factors. Then a nomogram model was established. The
13 performance of the nomogram model was evaluated by the concordance index (C-index) and the
14 calibration plot. The nomogram model was internally validated using the bootstrap resampling method.
15 The predictive accuracy of the nomogram model was compared with that of Acute Physiology, Age, and
16 Chronic Health Evaluation (APACHE) IV. Decision curve analysis (DCA) was performed to evaluate
17 and compare the potential net benefit using of different predictive models.

18 **Results:** The overall in-hospital mortality rate is 4.447%. Age, BUN, and lactate (ABL) were the
19 independent risk factors determined by multivariate analysis. The C-index of nomogram model ABL
20 [0.896 (95% confidence interval [CI]: 0.825 to 0.967)] was similar to that of APACHE IV ($P = 0.086$),
21 showing a comparable discriminating power. Calibration plot demonstrated good agreement between the

1 predicted and actual in-hospital mortality. DCA showed that the nomogram model ABL was clinically
2 useful.

3 **Conclusions:** Nomogram model ABL, which used readily available data, exhibited high predictive
4 value for predicting in-hospital mortality in AP.

5 **Strengths and limitations of this study**

6 This is an original research to develop and internally validate a user-friendly prediction model using
7 easily obtainable clinical and laboratory parameters.

8 The nomogram model ABL presents an excellent prognostic ability for predicting in-hospital mortality
9 in AP patients.

10 The retrospective observational cohort study design could lead to certain types of bias (e.g., confounding
11 bias, selection bias).

12 The suitability of the model in larger population needs further external validation, due to the small sample
13 size and small number of events.

14 **Background**

15 AP is a relatively common, but poorly understood, inflammatory disease of the exocrine pancreas. So
16 far, the detailed pathogenesis of AP still remains unclear and no specific and effective treatment has been
17 proposed yet [1]. The clinical manifestation and disease course of AP also vary dramatically from self-
18 limiting simple edema pancreatitis to severe acute necrotizing pancreatitis characterized by systemic
19 inflammatory response syndrome and multiple organ failure [2]. With a mortality rate of less than 5%,
20 the mild edematous AP runs a benign course and recovers spontaneously without any sequelae in about

1 70% - 80% of patients, while nearly 20% - 30% of patients will develop severe necrotic pancreatitis with
2 a high mortality rate up to 20% - 30% [3-9].

3 Two peaks of mortality have been noted in patients with severe AP. Early death usually occurs in the
4 first two weeks owing to multiple organ dysfunction syndromes (MODS) caused by the production and
5 release of diverse cytokines [9-11]. Late death generally happens two weeks later as a result of
6 peripancreatic necrosis, infection, and secondary MODS [9, 10]. Studies found that patients in the high-
7 risk group may benefit from closer monitoring, early aggressive fluid resuscitation, rational use of
8 antibiotics, and timely invasive strategies, such as endoscopic sphincterotomy and radiologic
9 intervention [12, 13]. Once diagnosed as AP, early identification of high-risk patients is therefore
10 essential to improve survival.

11 Since the first scoring system for AP severity was proposed in 1974, about 20 different predictive models
12 have been developed [14]. However, there are some practical problems that restrict wide clinical
13 application of these predictive models. For instance, based on more than 10 parameters, APACHE II is
14 cumbersome and complex for rapid assessment within 24 hours after admission [15, 16]. Moreover,
15 APACHE II is a generic scoring system for all critical patients, so some parameters may be irrelevant to
16 the prognosis of AP [17]. Developed as an easy-to-use risk stratification tool, the BISAP score
17 outperforms other predictive models in specificity, but showing a suboptimal sensitivity in evaluating
18 the severity of AP [18, 19]. Despite its high sensitivity, RANSON score is less operative because it takes
19 at least 48 hours to be completed, resulting in a delay of triage and management [16, 20]. The computed
20 tomography severity index (CTSI) requires high-cost and radioactive CT scans, which might be
21 unavailable for most patients at their first visit [16, 21]. In addition, pancreatic necrosis might be
22 undetectable by an early CT scan within 24 hours [22]. Even in the first 3-4 days, contrast-enhanced CT

1 scan seems unreliable in estimating the extent of pancreatic necrosis [22, 23].

2 In view of the shortcomings of these currently available predictive models, there is consequently an
3 urgent need for an easy-to-use and accurate prognostic tool for predicting in-hospital mortality in AP
4 patients. Therefore, we collected demographics, clinical factors, laboratory data from a freely available,
5 multi-center database eICU-CRD and explored the risk factor for in-hospital mortality. Furthermore, we
6 incorporated these independent prognostic factors and developed a nomogram model in patients with AP
7 for better clinical guidance.

8 **Patients and methods**

9 **Study design**

10 We extracted subject data from eICU-CRD, a large multicentre critical care database. The database is
11 publicly and freely accessible to researchers, according to data usage agreement by the review board of
12 PhysioNet (Our record ID: 33047414). The eICU-CRD covers 200,859 ICU admissions of 139,367
13 patients in 208 US hospitals between 2014 and 2015. All data were stored automatically and retrieved
14 electronically through the Philips Healthcare eICU program. It includes records of demographics,
15 physiological indexes from bedside monitors, diagnosis via International Classification of Diseases, 9th
16 Edition, Clinical Modification (ICD-9-CM) codes, and other laboratory data obtained during routine
17 medical care. All data were de-identified by the eICU program and anonymous to researchers before
18 analysis [24]. As this research was a retrospective observational cohort study based on data from eICU-
19 CRD, no ethical approval was required from our local ethics committee. This study was reported
20 following the recommendations of the Transparent Reporting of a multivariable prediction model for

1 Individual Prognosis Or Diagnosis (TRIPOD) statement [25].

2 **Participants**

3 The study population was drawn from eICU-CRD. According to the 2012 Atlanta Criteria, the diagnosis
4 of AP can be made if two or more of the following criteria are present: (1) abdominal pain (acute and
5 persistent epigastric pain usually radiating to the back); (2) serum amylase or lipase level being at least
6 3 times greater than the normal upper limit; (3) characteristic abdominal imaging findings of AP [26].

7 The ICD-9-CM diagnostic code used for selecting patients with AP is 577.0.

8 **Data retrieval**

9 All subject data within the first 24 hours after admission were collected from eICU-CRD using the
10 Structure Query Language. The physiological variables, including body temperature (BT), heart rate
11 (HR), mean blood pressure (MBP), and respiratory rate (RR) were obtained from the table *apacheApsVar*.
12 The baseline characteristics such as age, gender, weight, height, APACHE IV, Glasgow Coma Scale
13 (GCS) score, and the history of past illnesses were collected from the tables of *patient*,
14 *apachePatientResult* and *pastHistory*. The laboratory indexes, for instance, serum albumin, lactate, base
15 excess (BE), total bilirubin, glucose, blood urea nitrogen (BUN), white blood cell (WBC), hematocrit,
16 platelet (PLT), calcium, lactic dehydrogenase (LDH), aspartate aminotransferase (AST), cholesterol,
17 triglycerides, amylase, lipase, and arterial oxygen pressure (PaO₂) were extracted from the table *lab*.
18 Potential risk factors associated with in-hospital mortality were identified from previous predictive
19 models [16, 27], from literature or guidelines [7, 14, 28, 29], and from consulting clinic medical experts.
20 The decisions of their inclusion in the univariate logistic regression analysis were based on the following

1 criteria that the potential risk factors: (1) were objective parameters, (2) were routinely measured in
2 medical practice, and (3) were completely recorded or missing randomly in the dataset. The worst value
3 of each variable recorded during the first 24 hours after admission was used to analyze and establish the
4 nomogram model.

5 **Statistical analysis**

6 Continuous variables, expressed as mean with standard deviation (SD) or median with interquartile range
7 (IQR), were analyzed using the Student t-test (for data with normal distribution) or Mann–Whitney U
8 test (for data without normal distribution). Categorical variables, expressed as absolute numbers (n) and
9 proportions (%), were compared using the Chi-square test or Fisher's exact test. Univariate logistic
10 regression analysis was performed to determine the possible correlation between in-hospital mortality
11 and potential risk factors. All significant risk factors ($P < 0.1$) in the univariate logistic regression analysis
12 were eligible for inclusion in the multivariate logistic regression analysis to adjust for confounding
13 factors. Based on the results of the multivariate logistic regression analysis, a nomogram was constructed.
14 The performance of the nomogram model was assessed using its calibration and discrimination.
15 Calibration describes the level of agreement between predicted and actual risks, and is usually evaluated
16 by calibration plot and Hosmer-Lemeshow Chi-square test [30]. Discrimination refers to the ability of a
17 model to distinguish high-risk and low-risk patients, and is generally evaluated by C-index or area under
18 the receiver operator characteristic curve (AUROC) [31]. In order to address overfitting and quantify
19 optimism, the predictive model was internally validated using bootstrap resampling. Optimism represents
20 the difference between the apparent (unadjusted) model performance and bootstrap (bias) corrected
21 estimated model performance. Internal validation involved refitting the model to a series of 1000 random

1 samples drawn from the original dataset with replacement, and produced an overall C-index from all
2 samples. This process adjusted the C-index for overoptimism which may arise when a model was
3 validated with the same dataset used to build the model [32]. DCA was performed to evaluate the clinical
4 usefulness of the nomogram model by quantifying the net benefits under different threshold probabilities.
5 For all analyses, *P* value less than 0.05 was considered to be statistically significant. All statistical
6 analyses were carried out on GraphPad Prism 7 (GraphPad Prism, GraphPad Software, La Jolla, CA) and
7 R 3.6.1 (R Development Core Team). The packages of *rms*, *Hmisc*, *pROC*, *stats*, *PredictABEL*, and *rmda*
8 were involved in this process.

9 **Results**

10 **Baseline characteristics and outcomes**

11 A total of 746 patients with AP were extracted from the database, of whom 4 patients were excluded due
12 to loss to follow-up, thus resulting in 742 evaluable patients included in our study. Thirty-three patients
13 died during hospitalization with in-hospital mortality rate of 4.447%. The demographic and clinical
14 characteristics of all patients are listed in Table 1.

15 **Prognostic factors for in-hospital mortality**

16 Univariate logistic regression analysis was performed for each potential risk factor. Age, GCS score,
17 MBP, albumin, lactate, bilirubin, BUN, WBC, calcium, AST, and comorbidities of CHF, COPD,
18 hypertension were risk factors for in-hospital mortality determined by univariate logistic regression
19 analysis ($P < 0.1$). Thereafter, all these risk factors were entered simultaneously into the multivariable

1 logistic regression analysis to control possible confounding factors. Finally, age, BUN, and lactate (ABL)
2 were proved to be independent risk factors for predicting in-hospital mortality (Table 2). Due to
3 incomplete data, 364 patients were excluded, leaving 378 evaluable patients included in the nomogram
4 model ABL. The flow chart of the inclusion of eligible patients is shown in Fig. 1. The characteristic
5 features of patients included and excluded from the development of the nomogram is demonstrated in
6 Table S. The diagnostic equation built on multivariate logistic regression analysis is as follows:

$$\text{Logit P} = -10.3074 + 0.0831 * \text{Age} + 0.4032 * \text{Lactate} + 0.0201 * \text{BUN}$$

8 **Development of a nomogram predicting in-hospital mortality**

9 Based on the multivariate logistic regression analysis, a nomogram was constructed by assigning a
10 weighted point to each independent risk factor on the point scale (Fig. 2). A higher total point of all risk
11 factors refers to a higher in-hospital mortality rate.

12 **Performance of the nomogram model ABL**

13 The discrimination and calibration, two basic characteristics of model validation, were tested to evaluate
14 the performance of the nomogram model ABL [33]. Model discrimination was assessed using the C-
15 index that measures the ability to predict the outcomes. A higher C-index refers to a greater ability to
16 discriminate the outcomes. The C-index of our nomogram model ABL was 0.896 (95%CI: 0.825 to
17 0.967), showing a great discrimination ability. The receiver operating characteristic (ROC) curves of age,
18 lactate, BUN, and the nomogram model ABL for predicting in-hospital mortality were shown in Fig. 3A.
19 By visual inspection of AUROC, nomogram model ABL showed better performance than any other
20 individual risk factor. Model calibration was evaluated using the Hosmer-Lemeshow Chi-square test and

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2
3
4 1 a calibration plot. The Hosmer-Lemeshow Chi-square which measured the calibration was 7.201 ($P =$
5
6 2 0.515), demonstrating that there was no significant difference from a perfect fit. The calibration plot was
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8
9 3 shown in Fig. 3B. Visual inspection of the calibration plot further indicated good agreement between the
10
11
12 4 predicted and actual in-hospital mortality.

5 **Validation of the nomogram model ABL**

6 The bootstrapping technique was employed to internally validate model performance [32]. During
7
8 7 internal validation (set seed 123), nomogram model ABL retained its excellent discrimination in the
9
10 8 bootstrap samples, showing an optimism corrected C-index of 0.892 (95%CI: 0.822 to 0.962). The
11
12 9 calibration curve was used to assess the ability of a predictive model to obtain unbiased estimates of the
13
14 10 outcome, and a perfectly calibrated predictive model would produce a curve on which the predicted and
15
16 11 actual probabilities fall along a 45-degree diagonal line [34]. The calibration curve of nomogram model
17
18 12 ABL was very close to the 45-degree ideal line, showing good agreement between the predicted and
19
20 13 actual in-hospital mortality (Fig. 4).

14 **Comparison of predictive accuracy for in-hospital mortality between** 15 **the nomogram model ABL and APACHE IV**

16 Complete age, BUN, lactate and APACHE IV data were available for 334 patients , of whom 21 patients
17
18 17 died in the hospital. The median APACHE IV was 50 in the survival group and 91 in the death group.
19
20 18 The C-index was calculated to estimate the discrimination ability of APACHE IV [0.837 (95% CI: 0.730
21
22 19 to 0.944)]. There was no statistically significant difference between the C-index of the nomogram model
23
24 20 ABL and that of APACHE IV ($P = 0.086$), indicating the nomogram model ABL had a similar predictive

1 accuracy with APACHE IV. The ROC curves for the nomogram model ABL and APACHE IV also
2 demonstrated comparable discriminating power (Fig. 5A).

3 The integrated discrimination improvement index (IDI) is a method to quantify the incremental
4 predictive value of new methods to existing predictive models [35]. In this study, IDI was calculated to
5 assess the improvement in risk stratification using different models. The IDI was 0.105 (95%CI: -0.016
6 to 0.226), indicating no significant difference ($P = 0.088$) in performance between the nomogram model
7 ABL and APACHE IV.

8 The DCA can depict the overall net benefit of using predictive models compared with the treat-all-
9 patients and treat-none scheme. Fig. 5B showed the net benefit of using the nomogram model ABL and
10 APACHE IV, with several overlaps, the net benefit of the nomogram model ABL was comparable to
11 that of APACHE IV.

12 Discussion

13 AP is a heterogeneous digestive system disease. Most patients with AP will relieve spontaneously
14 without any organ failure, while about 20% of cases will evolve into severe form, which is associated
15 with MODS, sepsis, and high mortality [6]. Thus, it is imperative to identify patients who might develop
16 severe AP and initiate more aggressive intervention [26]. Through early identification and reasonable
17 treatment, patients at high risk of mortality might be converted to low risk, which is the main goal of our
18 model development.

19 Using demographic, clinical and conventional laboratory data from a large-scale publicly available ICU
20 database, the following independent risk factors for predicting in-hospital mortality of AP were identified:
21 age, BUN, and lactate (ABL). These factors are consistent with the risk factors traditionally associated

1 with in-hospital mortality. Except for age, other risk factors are modifiable by timely and aggressive
2 treatment, which is particularly important for improving outcomes. Nomograms could provide predictive
3 information tailored to the individual, by establishing a simple graphical representation of a complex
4 statistical prediction model [34]. Currently, nomograms are increasingly being used to improve clinical
5 decision making. In this study, we incorporated age, BUN and lactate into an easy-to-use and reliable
6 nomogram model ABL. Our predictive model also generates an equation on a continuous scale rather
7 than an arbitrary “cutoff” for each parameter. The outstanding advantage of the nomogram model ABL
8 is its simplicity and accuracy. There are only three parameters in the current model, which requires no
9 extra calculations and is convenient for clinicians. In addition, all these parameters are objective and can
10 be easily obtained following a general hospital admission. We calculated the C-index to quantify the
11 discriminatory power of our model. A C-index of 1 represents perfect prediction accuracy, whereas a C-
12 index of 0.5 indicates no better than random guesses. With a C-index of 0.896, the nomogram model
13 ABL exhibited perfect model discrimination performance. The ROC curve also showed that the
14 nomogram model ABL provide great model prediction accuracy. Internal validation via bootstrap
15 resamples demonstrated an adjusted C-index of 0.892, which was in excellent agreement with the original
16 data. Moreover, the calibration curve indicated a sufficient fit of predicted and actual in-hospital mortality.
17 This user-friendly nomogram model ABL might be a valuable tool for clinical practice because it could
18 provide a simple and accurate way to predict in-hospital mortality in patients with AP.

19 As is well known to all, age is an important and useful indicator of poor prognosis in various entities.
20 Furthermore, many acknowledged predictive models have incorporated age for predicting the severity or
21 mortality of AP in the field of clinical medicine [7, 14]. Our study also demonstrates that age is an
22 independent risk factor for in-hospital mortality in patients with AP. With age incremented by 10 years,

1 the risk for in-hospital mortality was increased by 6.776% in our study.

2 In this study, we found that hyperlactatemia (≥ 2 mmol/L) were very common in AP (50.131%). Lactate,
3 a byproduct of glycolysis under anaerobic conditions, is generally considered as a powerful indicator of
4 ischemia and hypoxia in body tissues. However, diseases with elevated plasma catecholamine, such as
5 huge trauma or shock, can also lead to exaggerated glycolysis and increased lactate level [36-38].
6 Hyperlactatemia in AP might be related to the above factors. Single plasma lactate level, especially that
7 measured immediately after admission to the ICU or arrival at the emergency room, is regarded as a
8 powerful predictor of subsequent multiorgan failure and mortality. In 1965, Peretz et al. [39] first
9 described the relationship between plasma lactate level and mortality and revealed a death rate of 100%
10 when the plasma lactate level is higher than 13.3 mmol/L. More recently, Nichol et al. [40] and Haas et
11 al. [41] also found that the mortality rate of patients with a plasma lactate level greater than 10 mmol/L
12 was up to 80%. Recent studies demonstrated that early lactate clearance and continuous dynamic
13 monitoring of the plasma lactate level could serve as a useful prognostic factor and guide timely
14 intervention of critically ill patients [41-46]. In 2017, Valverde-López et al. [47] reported that elevated
15 plasma lactate level was closely related to persistent multiorgan failure of patients with AP, lactate might
16 become a useful biomarker for predicting poor clinical outcomes of AP on admission, especially for the
17 prediction of mortality, lactate exhibited an excellent AUROC of 0.870. Moreover, lactate performed
18 much better than CRP in predicting ICU requirements and mortality [47]. Our research demonstrated
19 that the lactate level was strongly associated with in-hospital mortality of AP, with a great AUROC of
20 0.776. By multivariate logistic regression analysis, lactate has been proven to be an independent risk
21 factor for predicting in-hospital mortality, which is consistent with previous studies [47].
22 BUN as a useful predictor of in-hospital mortality is consistent with the current existing literature.

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4 1 Previous studies have shown that BUN on admission and BUN rise in the first 24 hours following
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6 2 admission can predict mortality of patients with AP [29, 48-51]. Many studies believe that increased
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9 3 BUN in AP is owing to the loss of body fluid, the decrease of intravascular blood volume, and the
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11 4 development of prerenal azotemia [48, 50]. If the hypovolemic state cannot be corrected completely at
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14 5 early stage, the patients will suffer from further depletion of effective circulatory blood volume, from
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17 6 severe decrease in glomerular filtration fraction and eventually leading to prerenal insufficiency. If the
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20 7 disease progresses further, it may lead to multiple organ and system failure, which is the main cause of
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22 8 death [10, 28]. Therefore, many scoring systems used in clinical practice are based on the urea level
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25 9 (Ranson, Glasgow, POP, BISAP) [7, 52-54]. The Hong Kong criterion is based on only two parameters,
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28 10 the urea, and glycemia [55].

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30 11 In order to further evaluate the value of nomogram model ABL in clinical use, we compared its
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32 12 performance with the APACHE scoring system. APACHE II is one of the most powerful and widely
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35 13 used prognostic tool for all ICU patients to predict severity and mortality. Later this scoring system was
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38 14 extrapolated to AP, the study results showing perfect prognostic value [15, 56]. The APACHE II had
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41 15 been modified many times since its launch in 1985, and the latest version was the APACHE IV published
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44 16 in 2006 [57, 58]. Involving about 52 different physiologic indexes, APACHE IV accounts for
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47 17 hepatobiliary parameters, sedation status, and multiple comorbidities simultaneously. Due to such wide
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50 18 range of physiologic variables, APACHE IV has a much better performance compared with APACHE II
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53 19 [59, 60]. In 2015, a study reported that an APACHE IV of 44 or higher would predict mortality in 100%
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56 20 of cases, and the AUROC for APACHE IV was 0.93 [61]. However, the main drawback of APACHE IV
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59 21 is that it relies on many variables that are not routinely collected during general hospital admission [7].
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22 22 Nevertheless, our nomogram model ABL could attain a comparable predictive accuracy of the more

1 complex APACHE IV with fewer parameters in patients with AP.

2 An ideal predictive model should be reliable and easy-to-use at the early stage of the disease, using

3 readily available data [62]. The nomogram model ABL achieves many of these characteristics: it is

4 generated from data within 24 hours after admission, using age and some easily obtainable, reliable, and

5 inexpensive clinical and laboratory parameters in a model, and is feasible in a user-friendly manner.

6 Moreover, the nomogram model ABL presents an excellent prognostic ability for in-hospital mortality,

7 which is comparable to that of APACHE IV.

8 Our study still has some limitations. First, this study included patients with AP from one database, due

9 to the small sample size and small number of events, the statistical power of this study was limited, which

10 may caution us from generalizing this nomogram model ABL to a larger population. And thus, further

11 large-scale prospective trials are needed to verify the prognostic model. Second, although we tried to

12 adjust confounding factors as much as possible by performing multivariate logistic regression analysis,

13 residual confounding factors through unknown or unmeasured covariates might not be completely ruled

14 out. Finally, the database that we used did not cover information on etiology, initial or recurrent episodes

15 of pancreatitis, duration of the disease, which might affect in-hospital mortality.

16 **Conclusion**

17 We propose a refined nomogram model ABL with age, easily obtainable clinical and biochemical

18 parameters, the BUN and lactate. This nomogram model ABL shows excellent performance and allows

19 clinical practitioners to perform early and quick risk-stratification and guide early management strategies

20 for AP patients.

1 Abbreviations

2 AP: acute pancreatitis; eICU-CRD: eICU Collaborative Research Database; C-index: concordance index;
3 ICU: intensive care unit; CI: confidence interval; MODS: multiple organ dysfunction syndromes; CTSI:
4 computed tomography severity index; TRIPOD: Transparent Reporting of a multivariable prediction
5 model for Individual Prognosis Or Diagnosis; BT: body temperature; HR: heart rate; MBP: mean blood
6 pressure; RR: respiratory rate; GCS: Glasgow Coma Scale; BE: base excess; BUN: blood urea nitrogen;
7 WBC: white blood cell; PLT: platelet; LDH: lactic dehydrogenase; AST: aspartate aminotransferase;
8 PaO₂: arterial oxygen pressure; SD: standard deviation; OR: odds ratio; AUROC: area under the receiver
9 operator characteristic curve; BMI: body mass index; IQR: interquartile range; Med-Surg ICU: medical-
10 surgical intensive care unit; MICU: medical intensive care unit; SICU: surgical intensive care unit; DM:
11 diabetes mellitus; COPD: chronic obstructive pulmonary diseases; CHF: chronic heart failure; MI:
12 myocardial infarction; RI: renal insufficiency; ROC: receiver operating characteristic; IDI: integrated
13 discrimination improvement index; APACHE: Acute Physiology, Age and Chronic Health Evaluation.

14 Declarations

15 **Conflicts of interest:** The authors declare that they have no conflict of interest.

16 **Acknowledgments:** Not applicable.

17 **Funding:** There is no funding.

18 **Availability of data and material:** The data were available on the eICU-CRD website at

19 <https://eicu-crd.mit.edu/>.

20 **Authors' contributions:** Caifeng Li conceived the idea, extracted the data, performed the analysis, and

1 drafted the manuscript. Guolin Wang and Zhiqiang Wang helped to frame the idea of the study, interpret
2 the results and revise the manuscript. Qian Ren helped to edit pictures and revised the manuscript. All
3 authors read and approved the final manuscript.

4 **Ethics approval and consent to participate:** The study was an analysis of a third-party anonymized
5 publicly available database with pre-existing institutional review board approval. Informed consent was
6 not required in this database study because of the non-identifying and anonymous nature of the database.

7 **Consent for publication:** All authors consent to publication.

8 **Patient and public involvement:** No patient involved.

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1 Table 1. Characteristics and outcomes of participants

Characteristics	Survived to Discharge (Overall number = 709)	n	Died in the Hospital (Overall number = 33)	n	<i>P</i> Value
Demographics					
Age (median [IQR])	51.00 [40.00, 63.00]		65.00 [60.00, 78.00]		<0.001
Gender male, n (%)	427 (60.2)		24 (72.7)		0.209
Ethnicity, n (%)					0.348
African American	49 (7.0)		5 (15.2)		
Asian	9 (1.3)		0 (0.0)		
Caucasian	542 (77.2)		25 (75.8)		
Hispanic	34 (4.8)		1 (3.0)		
Native American	8 (1.1)		1 (3.0)		
Other/Unknown	60 (8.5)		1 (3.0)		
Height (cm, median [IQR])	172.00 [163.00, 178.00]	702	172.70 [165.10, 178.43]	32	0.685
Weight (kg, median [IQR])	83.90 [70.90, 98.10]	692	93.30 [78.97, 103.50]	32	0.037
Clinical Factors					
ICU type, n (%)					0.002
Med-Surg ICU	485 (68.4)		20 (60.6)		
MICU	76 (10.7)		0 (0.0)		
SICU	55 (7.8)		10 (30.3)		
Other ICUs	93(13.1)		3(9.1)		
Comorbidities, n (%)					
CHF	37 (5.3)		6 (18.2)		0.007
COPD	67 (9.6)		7 (21.2)		0.062
Hypertension	317 (45.4)		23 (69.7)		0.01
DM	105 (15.0)		4 (12.1)		0.836
MI	26 (3.7)		2 (6.1)		0.825
RI	38 (5.4)		4 (12.1)		0.218
Vital signs					
BT (°C, median [IQR])	36.70 [36.40, 36.90]	611	36.60 [36.40, 36.82]	28	0.509
RR (/min, median [IQR])	30.00 [12.00, 37.00]	648	33.00 [27.00, 39.00]	29	0.113
HR (/min, median [IQR])	118.00 [102.00, 134.00]	647	120.00 [100.00, 135.00]	29	0.908
MBP (mm Hg, median [IQR])	98.00 [60.00, 125.50]	647	51.00 [43.00, 70.00]	29	<0.001
APACHE IV (median [IQR])	46.00 [34.00, 62.00]	579	90.00 [71.00, 105.00]	27	<0.001
GCS (median [IQR])	15.00 [14.00, 15.00]	709	13.00 [10.00, 15.00]	33	<0.001
Invasive intervention, n (%)					
Operation	36 (5.1)		3 (9.1)		0.541
Intubation	34 (5.2)		7 (24.1)		<0.001
Ventilation	53 (8.1)		9 (31.0)		<0.001
Dialysis	9 (1.4)		2 (6.9)		0.12
Laboratory Data					
Albumin (g/dL, median [IQR])	2.90 [2.40, 3.40]	660	2.40 [1.95, 2.80]	31	<0.001
Lactate (mmol/L, median [IQR])	1.90 [1.20, 3.10],	359	5.20 [2.20, 8.57]	21	<0.001

BE (mEq/L, median [IQR])	-3.20 [-7.00, 0.50]	170	-5.10 [-9.20, -3.00]	13	0.245
Total bilirubin (mg/dL, median [IQR])	1.00 [0.60, 2.30]	449	2.10 [0.80, 3.90]	25	0.105
Glucose (mg/dL, median [IQR])	167.00 [128.00, 237.75]	694	194.00 [162.00, 247.00]	33	0.065
BUN (mg/dL, median [IQR])	18.00 [12.00, 31.00]	697	37.00 [23.00, 54.00]	33	<0.001
WBC ($\times 10^9/L$, median [IQR])	10.80 [7.37, 15.70]	533	14.00 [7.85, 23.70]	28	0.106
Hematocrit (% , median [IQR])	34.90 [30.50, 39.88]	538	33.00 [29.08, 37.18]	28	0.272
PLT (% , median [IQR])	178.50 [126.00, 241.00]	676	172.00 [118.00, 236.00]	33	0.634
Calcium (mg/dL, median [IQR])	7.80 [7.20, 8.30]	669	7.45 [6.50, 8.20]	32	0.129
LDH (Units/L, median [IQR])	350.00 [236.00, 557.50]	99	469.50 [317.25, 634.50]	6	0.439
AST (Units/L, median [IQR])	67.00 [32.00, 160.25]	664	110.00 [39.00, 301.50]	31	0.052
Cholesterol (mg/dL, median [IQR])	191.00 [127.50, 296.00]	215	137.00 [137.00, 137.00]	1	0.466
Triglycerides (mg/dL, median [IQR])	188.00 [105.75, 1083.75]	320	189.00 [151.00, 374.00]	11	0.946
Amylase (Units/L, median [IQR])	362.00 [112.00, 949.00]	277	581.60 [102.75, 1091.25]	14	0.8
Lipase (Units/L, median [IQR])	952.00 [364.00, 2995.00]	581	1538.00 [75.50, 4323.50]	22	0.887
PaO2 (mmHg, median [IQR])	75.75 [67.00, 93.50]	92	98.50 [74.75, 101.75]	10	0.24

Abbreviations: IQR interquartile range, ICU intensive care unit, Med-Surg ICU medical-surgical intensive care unit, MICU medical intensive care unit, SICU surgical intensive care unit, CHF chronic heart failure, COPD chronic obstructive pulmonary diseases, DM diabetes mellitus, MI myocardial infarction, RI renal insufficiency, BT body temperature, RR respiratory rate, HR heart rate, MBP mean blood pressure, APACHE Acute Physiology, Age and Chronic Health Evaluation, GCS Glasgow Coma Scale, BE base excess, BUN blood urea nitrogen, WBC white blood cell, PLT platelet, LDH lactic dehydrogenase, AST aspartate aminotransferase, PaO2 arterial oxygen pressure.

1 Table 2. Univariate and multivariate logistic regression analysis with stepwise variable selection

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P Value	OR	95%CI	P Value
Demographics						
Age	1.0538	1.0305-1.0792	0	1.0798	1.0174-1.16	0.0201
Gender	1.7611	0.8345-4.0548	0.1554			
BMI	1.0321	0.986-1.0756	0.1526			
Clinical Factors						
Comorbidities						
CHF	3.976	1.415-9.66	0.0042	5.2176	0.6046-45.9861	0.1257
COPD	2.5396	0.9855-5.7822	0.0361	0.8789	0.1098-6.4035	0.8993
Hypertension	2.7716	1.335-6.1756	0.0083	2.2653	0.5367-11.4279	0.2842
DM	0.7803	0.228-2.0334	0.6482			
MI	1.67	0.2617-5.9465	0.4978			
RI	2.3993	0.686-6.4923	0.1173			
Vital signs						
BT	0.9811	0.7461-1.4972	0.9175			
RR	1.0227	0.9959-1.0512	0.1018			
HR	0.9988	0.9867-1.0118	0.8491			
MBP	0.9797	0.9661-0.9914	0.0017	0.9909	0.9715-1.0072	0.3028
GCS	0.9178	0.8682-0.9755	0.0035	0.991	0.8342-1.2101	0.9228
Laboratory Data						
Albumin	0.3357	0.1911-0.5761	0.0001	0.4189	0.108-1.5017	0.1882
Lactate	1.3811	1.2217-1.5719	0	1.6353	1.2683-2.2129	0.0004
BE	0.9559	0.8919-1.0274	0.2069			
Total bilirubin	1.08	0.9749-1.174	0.0915	0.8698	0.629-1.0969	0.3193
Glucose	1.0009	0.9983-1.003	0.4174			
BUN	1.0245	1.0138-1.035	0	1.0278	1.0037-1.0523	0.0186
WBC	1.0501	1.0067-1.0913	0.0164	0.9748	0.9054-1.0448	0.4721
Hematocrit	0.9724	0.9198-1.0259	0.3144			
PLT	0.9983	0.9942-1.0018	0.3698			
Calcium	0.7605	0.5565-1.0501	0.0916	0.9943	0.4857-2.1647	0.9878
LDH	0.9998	0.9971-1.0014	0.8382			
AST	1.0002	0.9999-1.0005	0.0946	0.9997	0.9987-1.0005	0.5251
Cholesterol	0.9889	0.9421-1.0035	0.5197			
Triglycerides	0.9996	0.9984-1.0001	0.2623			
Amylase	1	0.9994-1.0004	0.8752			
Lipase	1	0.9998-1.0002	0.796			
PaO2	1.0003	0.9824-1.0125	0.9619			

2 *Abbreviations:* AP acute pancreatitis, OR odds ratio, CI confidence interval, CHF chronic heart failure, COPD chronic obstructive
3 pulmonary diseases, DM diabetes mellitus, MI myocardial infarction, RI renal insufficiency, BT body temperature, RR respiratory
4 rate, HR heart rate, MBP mean blood pressure, GCS Glasgow Coma Scale, BE base excess, BUN blood urea nitrogen, WBC white
5 blood cell, PLT platelet, LDH lactic dehydrogenase, AST aspartate aminotransferase, PaO2 arterial oxygen pressure.

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4 **Fig. 1** Flow chart of patient selection.
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6 **Fig. 2** Nomogram for predicting in-hospital mortality in AP. To obtain nomogram predicted in-hospital
7 mortality, locate the value of each independent risk factor at each axis, draw a vertical line to the “Point”
8
9 mortality, locate the value of each independent risk factor at each axis, draw a vertical line to the “Point”
10
11 axis to get the point for each risk factor, then sum all the points, locate the sum on the “Total Points”
12
13 axis to get the predicted probability on “Predicted in-hospital mortality” axis. AP, acute pancreatitis
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17 **Fig. 3** (A) ROC curves for the nomogram model ABL and individual risk factors for predicting in-
18 hospital mortality. AUROC represents the discrimination ability of a predictive model. (B) Calibration
19
20 plot comparing the actual and predicted in-hospital mortality. The x-axis indicates the deciles of predicted
21
22 in-hospital mortality. Each bar in the graph stands for the actual and predicted in-hospital mortality.
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27 ROC, receiver operating characteristic; AUROC, area under the receiver operator characteristic curve
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30 **Fig. 4** Calibration curve of nomogram model ABL. The x-axis represents the predicted in-hospital
31 mortality calculated according to the model, while the y-axis exhibits the actual in-hospital mortality.
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33 The vertical lines show the frequency distribution of the predicted in-hospital mortality. The apparent
34
35 calibration curve (dotted line) indicates the model performance in the original data, while the bias-
36
37 corrected curve (solid line) represents the model performance after correction for optimism using 1000
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39 bootstrapped resamples. Perfect prediction would fall on the 45-degree (dashed) reference line.
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45 **Fig. 5** (A) ROC curves for the nomogram model ABL and APACHE IV. Visual comparison of ROC
46
47 curves indicates the discrimination performance of the nomogram model ABL was comparable to that
48
49 of APACHE IV. (B) Decision curve analysis for the nomogram model ABL and the APACHE IV. The
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51 y-axis measures the net benefit, and the x-axis shows the threshold probability. The horizontal black
52
53 line along the x-axis represents the assumption that no patient will die in the hospital (i.e., no patient
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55 should undergo close monitoring and aggressive treatment), whereas the solid gray line represents the
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1 assumption that all patients will die in the hospital (i.e., all patients should undergo close monitoring
2 and aggressive treatment). The red line indicates the nomogram model ABL and the blue line
3 represents the APACHE IV. ROC, receiver operating characteristic; APACHE, Acute Physiology,
4 Age, and Chronic Health Evaluation
5

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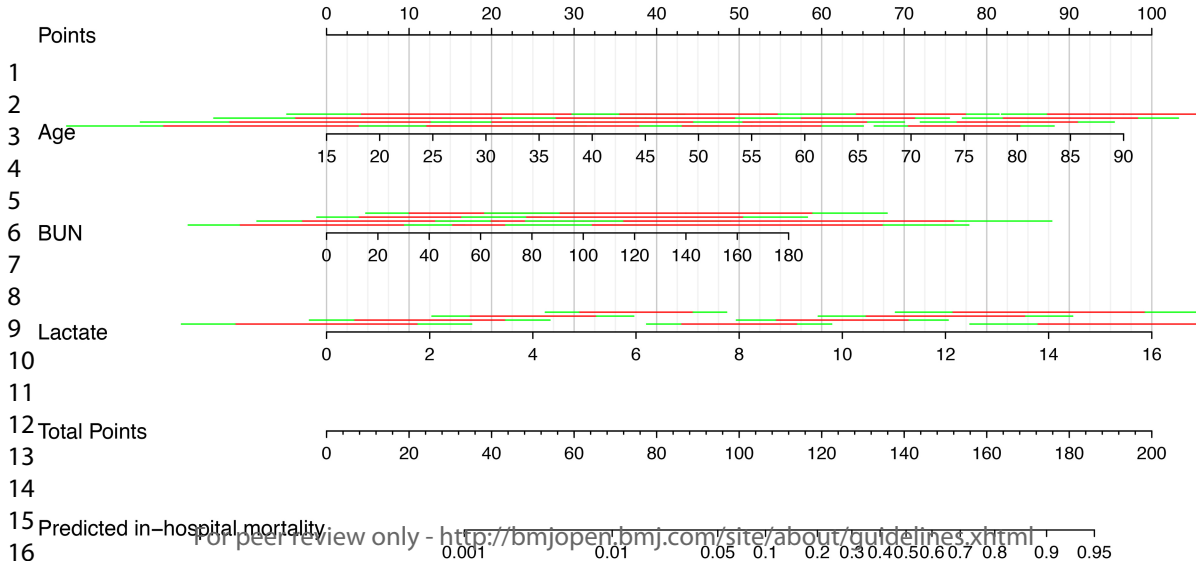
1 746 patients with acute pancreatitis admitted
2 to ICU from eICU database

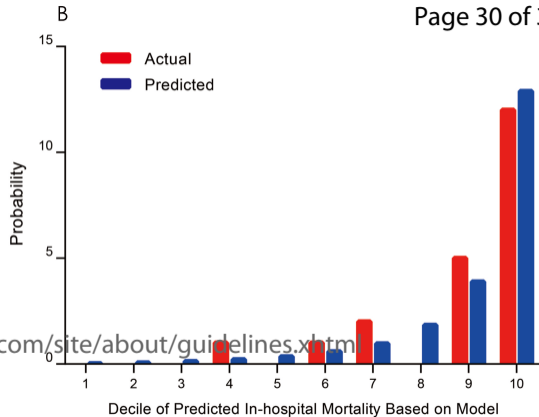
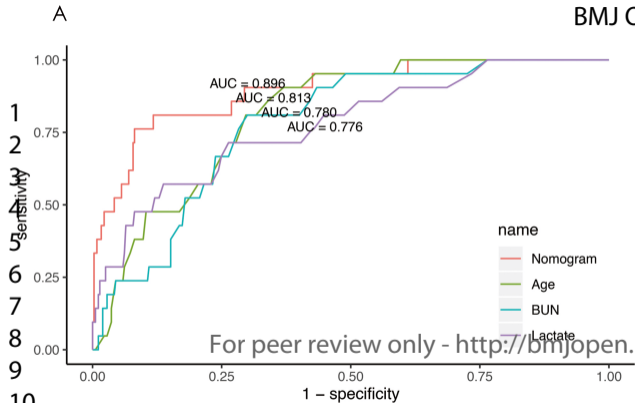
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6 4 patients excluded due
7 to loss of follow-up
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12 742 patients were included for clinical
13 characteristics analysis and risk factor selection
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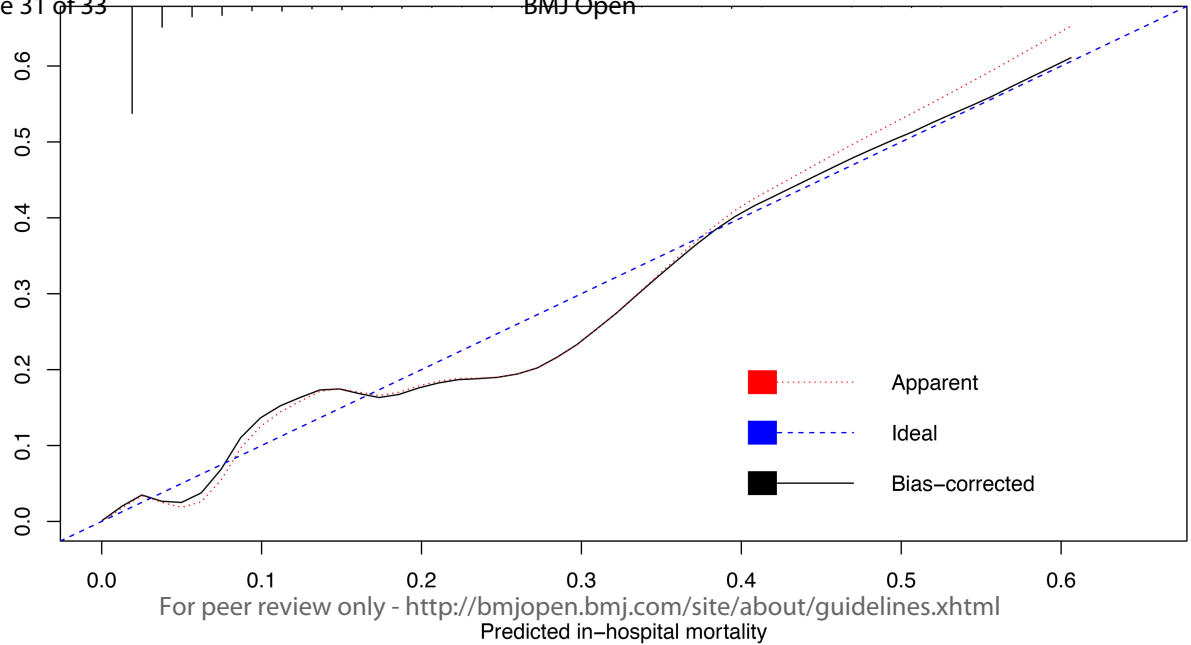
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21 364 patients with
22 incomplete data excluded
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27 378 eligible patients for nomogram
28 development and useful evaluation
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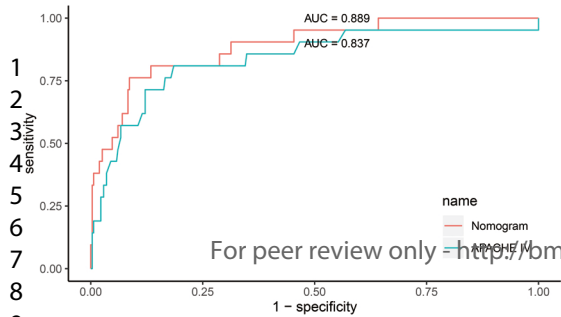


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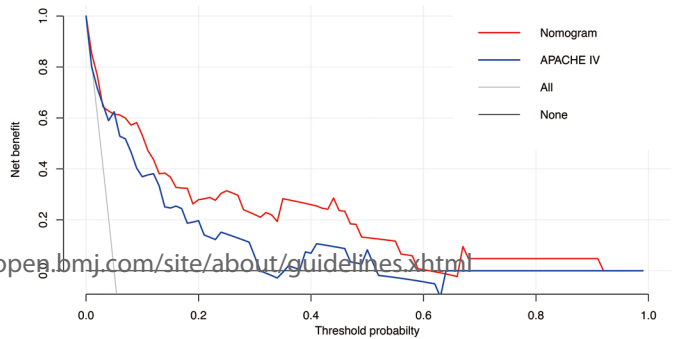
B= 1000 repetitions, boot

Mean absolute error=0.01 n=378

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1 Table S. Characteristic of patients included and excluded from the development of the nomogram ABL

Characteristics	Patients included (N=364)	Patients excluded (N = 378)	P Value
Demographics			
Age (median [IQR])	52.00 [41.00, 65.00]	52.00 [40.00, 64.00]	0.523
Gender male, n (%)	218 (59.9)	233 (61.6)	0.68
Ethnicity, n (%)			0.91
African American	28 (7.8)	26 (6.9)	
Asian	4 (1.1)	5 (1.3)	
Caucasian	274 (76.3)	293 (77.9)	
Hispanic	18 (5.0)	17 (4.5)	
Native American	3 (0.8)	6 (1.6)	
Other/Unknown	32 (8.9)	29 (7.7)	
Height (cm, median [IQR])	172.70 [163.00, 178.00]	172.00 [163.80, 178.00]	0.946
Weight (kg, median [IQR])	81.65 [69.00, 95.70]	86.19 [72.65, 100.15]	0.005
Clinical Factors			
ICU type, n (%)			0.267
Med-Surg ICU	252 (69.2)	253 (66.9)	
MICU	43 (11.8)	33 (8.7)	
SICU	28 (7.7)	37 (9.8)	
Other ICUs	41(11.3)	55(14.6)	
Comorbidities, n (%)			
CHF	22 (6.1)	21 (5.6)	0.912
COPD	39 (10.8)	35 (9.4)	0.605
Hypertension	163 (45.3)	177 (47.6)	0.582
DM	55 (15.3)	54 (14.5)	0.853
MI	12 (3.3)	16 (4.3)	0.624
RI	21 (5.8)	21 (5.6)	1
GCS (median [IQR])	15.00 [14.00, 15.00]	15.00 [14.00, 15.00]	0.513
In-hospital mortality	12 (3.3)	21 (5.6)	0.189

2 *Abbreviations:* IQR interquartile range, ICU intensive care unit, Med-Surg ICU medical-surgical intensive care unit, MICU medical
3 intensive care unit, SICU surgical intensive care unit, CHF chronic heart failure, COPD chronic obstructive pulmonary diseases,
4 DM diabetes mellitus, MI myocardial infarction, RI renal insufficiency, GCS Glasgow Coma Scale.



TRIPOD Checklist: Prediction Model Development and Validation

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Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3-4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5-6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5-6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5-6
	5b	D;V	Describe eligibility criteria for participants.	5-6
	5c	D;V	Give details of treatments received, if relevant.	Not Applicable
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	Not Applicable
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Not applicable
Sample size	8	D;V	Explain how the study size was arrived at.	8
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	9
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6-7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Not applicable
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Not applicable
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Not applicable
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8-9
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8-9
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Not applicable
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	9
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	9
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	D	Explain how to use the prediction model.	9-10
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	10-13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Not applicable
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16-17
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	13-14
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13-16
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Not applicable
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Not applicable

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.