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Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients

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ABSTRACT

The crude mortality rate in critical pneumonia cases with coronavirus disease 2019 (COVID-19) reaches 49%. This study aimed to test whether levels of blood urea nitrogen (BUN) in combination with D-dimer were predictors of in-hospital mortality in COVID-19 patients. The clinical characteristics of 305 COVID-19 patients were analysed and were compared between the survivor and non-survivor groups. Of the 305 patients, 85 (27.9%) died and 220 (72.1%) were discharged from hospital. Compared with discharged cases, non-survivor cases were older and their BUN and D-dimer levels were significantly higher ($P < 0.0001$). Least absolute shrinkage and selection operator (LASSO) and multivariable Cox regression analyses identified BUN and D-dimer levels as independent risk factors for poor prognosis. Kaplan–Meier analysis showed that elevated levels of BUN and D-dimer were associated with increased mortality (log-rank, $P < 0.0001$). The area under the curve for BUN combined with D-dimer was 0.94 (95% CI 0.90–0.97), with a sensitivity of 85% and specificity of 91%. Based on BUN and D-dimer levels on admission, a nomogram model was developed that showed good discrimination, with a concordance index of 0.94. Together, initial BUN and D-dimer levels were associated with mortality in COVID-19 patients. The combination of BUN $\geq$ 4.6 mmol/L and D-dimer $\geq$ 0.845 μg/mL appears to identify patients at high risk of in-hospital mortality, therefore it may prove to be a powerful risk assessment tool for severe COVID-19 patients.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been labelled a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) [1,2]. Approximately 81% of patients with COVID-19 are mild cases. However, 5% of critically ill patients progress rapidly to acute respiratory distress syndrome and acute respiratory failure. The overall crude case fatality rate is 2.3%, whereas among critical cases the crude mortality rate reaches 49% [3]. At present, there is no established effective treatment for COVID-19. Early identification and supportive care can effectively reduce the incidence of persistent critical illness and in-hospital mortality. Hence, it is important to assess the factors related to COVID-19 to predict patient prognosis.

Blood urea nitrogen (BUN) is a nitrogenous end product of protein metabolism and has been observed to be associated with mortality in various diseases. BUN represents a surrogate marker for

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predicting persistent organ failure after 48 h of hospital admission in addition to its role in the estimation of renal function [4,5]. A multicentre study reported that BUN can independently predict mortality in critically ill patients admitted to the intensive care unit (ICU) [6]. Elevated BUN levels are a predictor of worse outcome in patients with heart failure [7]. Recent studies have shown that the BUN to serum albumin ratio is an important prognostic factor of mortality and disease severity in aspiration pneumonia, hospital-acquired pneumonia and community-acquired pneumonia (CAP) [8–10]. Moreover, serum albumin levels were also identified as prognostic factors for pneumonia diseases and demonstrated fair discriminative performance in the prediction of in-hospital mortality [11,12]. Therefore, we hypothesised that serum BUN levels could be associated with mortality in patients with COVID-19.

D-dimer levels have a central role in diagnostic algorithms to rule out venous thromboembolism. Elevated plasma D-dimer levels in adult CAP are associated with an increased inflammatory reaction and are a prognostic variable [13,14]. Recent studies have reported that D-dimer was significantly associated with the severity of COVID-19 [15,16]. D-dimer is a commonly tested laboratory marker in hospitalised patients. However, the diagnostic performance of serum D-dimer levels has not yet been reported in patients with COVID-19.

Although several studies have investigated the correlation between laboratory parameters and disease severity of COVID-19 pneumonia so far, limited data are available regarding the association between laboratory data on admission and in-hospital outcomes in such patients. The present study evaluated the association between serum BUN and D-dimer levels on admission in patients with COVID-19 with in-hospital mortality in order to improve its prognosis in the future.

2. Materials and methods

2.1. Study design and participants

This was a retrospective single-centre study that enrolled 305 patients between 8 February 2020 and 11 March 2020 at Tongji Hospital, Huazhong University of Science and Technology (Wuhan, China). The diagnosis and clinical types of COVID-19 were classified according to the clinical guidelines (version 5 trial) developed by the National Health Committee of the People's Republic of China (http://www.nhc.gov.cn/). The diagnostic criteria were as follow: clinical diagnosis criteria of (i) fever or respiratory symptoms and (ii) leukopenia or lymphopenia; and (iii) computed tomography (CT) scan showing radiographic abnormalities in the lung. Patients with at least two clinical diagnostic criteria and a positive result for high-throughput sequencing or real-time PCR assay were diagnosed as COVID-19-positive. The clinical classifications were as follows: (i) general cases, fever, respiratory tract symptoms and imaging showing pneumonia; (ii) severe cases, with any of the following: (a) respiratory distress, respiratory rate $\geq$30 beats/min; (b) in the resting state, oxygen saturation $\leq$93%; and (c) arterial blood oxygen partial pressure/oxygen concentration $\leq$ 300 mmHg (1 mmHg = 0.133 kPa); and (iii) critical cases, one of the following conditions: (a) respiratory failure requiring mechanical ventilation; (b) shock; and (c) ICU admission required for combined organ failure. The primary endpoint was in-hospital mortality. Patients with secondary vasculitis and uraemia requiring maintenance haemodialysis and those who died within 48 h of admission were excluded. The study was approved by the Tongji Hospital Ethics Committee. Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

2.2. Data collection

The demographic characteristics, clinical symptoms, laboratory data and medications were extracted from the electronic medical records. Laboratory data consisted of complete blood count, liver and renal function test, examination of haemostasis parameters, and measurement of high-sensitivity C-reactive protein (CRP), procalcitonin (PCT) and lactate dehydrogenase serum levels. Colorimetry was used to determine BUN concentration. The normal reference ranges of BUN were determined by our laboratory as 3.1–8.0 mmol/L in males and 2.6–7.5 mmol/L in females.

2.3. Statistical analysis

Categorical variables were described as frequency and percentage, and continuous variables were described as the mean $\pm$ standard deviation for normally distributed variables and as the median and interquartile range (IQR) for non-normally distributed data. The Mann–Whitney *U*-test or *t*-test were used to compare differences between survivors and non-survivors, where appropriate. Proportions for categorical variables were compared using the χ^2 test. A univariate and multivariate Cox regression model was applied to screen the risk of death from factors such as a patient's clinical characteristics. Considering the sparse data and multicollinearity problem in the regression model, least absolute shrinkage and selection operator (LASSO) analysis was used to select optimal risk factors for mortality. The discrimination capacity of the nomogram was measured by the concordance index (C-index), with the larger the C-index, the more accurate the prognostic prediction. The Kaplan–Meier method was used to assess the cumulative rate of mortality based on the median of BUN and D-dimer, compared by the log-rank test. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of BUN and D-dimer levels for predicting death. Stratified analyses were performed according to several major confounders. Age was stratified by the median value (65 years). Estimated glomerular filtration rate (eGFR) was stratified to 90 mL/min/1.73 m^2. The *P* for interaction was tested for multiplicative interactions. Tests were two-sided, and a *P*-value of $<$0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics v.23.0 (IBM Corp., Armonk, NY, USA) or R version 3.0.2 (R Project for Statistical Computing).

3. Results

3.1. Characteristics of the COVID-19 patient cohort

Of the 305 COVID-19 patients, 85 (27.9%) died and 220 (72.1%) were discharged from hospital. Among the non-survivor group, 4 patients (4.7%) were classified as general type, 5 (5.9%) as severe and 76 (89.4%) as critical cases on admission. The demographic and clinical characteristics of the patients are shown in Table 1. The median age was higher in the non-survivor group compared with the survivor group [71.0 (IQR 63.0–78.0) years vs. 63.0 (IQR 49.0–69.0) years; $P < 0.0001$]. Males accounted for 71.8% (61/85) of the enrolled death cases. The frequency of patients with at least one co-morbidity (e.g. hypertension, coronary heart disease, chronic obstructive pulmonary disease and diabetes) was significantly higher in the non-survivor group compared with the survivor group (78.8% vs. 48.6%; $P < 0.0001$). However, no significant differences in signs and symptoms (e.g. fever, cough, nausea and headache) were observed between the two groups. Regarding laboratory findings on admission, the lymphocyte count, platelet count, albumin level and eGFR in the peripheral blood of non-survivor patients were significantly lower at admission compared with survivor patients ($P < 0.0001$), whilst the white blood cell

Table 1
Demographic and clinical characteristics of COVID-19 patients[a]

Variable	Total (n = 305)	Survivors (n = 220)	Non-survivors (n = 85)	P-value [b]
Age (years)	65.0 [52.0–71.0]	63.0 [49.0–69.0]	71.0 [63.0–78.0]	<0.0001
Female	121 (39.7)	97 (44.1)	24 (28.2)	0.0112
Co-morbidities	174 (57.0)	107 (48.6)	67 (78.8)	<0.0001
Hypertension	111 (36.4)	67 (30.5)	44 (51.8)	0.0005
Diabetes	49 (16.1)	32 (14.5)	17 (20.0)	0.2448
Cardiovascular disease	36 (11.8)	16 (7.3)	20 (23.5)	<0.0001
Cerebrovascular disease	10 (3.3)	7 (3.2)	3 (3.5)	0.8370
Pulmonary disease	24 (7.9)	16 (7.3)	8 (9.4)	0.5339
Chronic kidney disease	3 (1.0)	2 (0.9)	1 (1.2)	0.6636
Signs and symptoms[c]				
Fever	269/304 (88.5)	193/220 (87.7)	76/84 (90.5)	0.5019
Cough	235/302 (77.8)	166/217 (76.5)	69/85 (81.2)	0.3788
Myalgia	78/263 (29.7)	58/179 (32.4)	20/84 (23.8)	0.1549
Headache	59/232 (25.4)	41/149 (27.5)	18/83 (21.7)	0.3283
Nausea or vomiting	65/252 (25.8)	52/180 (28.9)	13/72 (18.1)	0.0758
Diarrhoea	85/285 (29.8)	59/200 (29.5)	26/85 (30.6)	0.8542
Laboratory parameters				
WBC count ($\times 10^9$/L)	5.8 [4.7–8.0]	5.5 [4.5–6.7]	9.14 [6.1–12.7]	<0.0001
Neutrophil count ($\times 10^9$/L)	4.0 [2.8–6.1]	3.5 [2.6–4.6]	7.42 [4.7–10.9]	<0.0001
Lymphocyte count ($\times 10^9$/L)	1.1 [0.7–1.4]	1.3 [0.9–1.6]	0.64 [0.4–1.0]	<0.0001
Haemoglobin (g/L)	127.0 [115.3–139.0]	126.0 [115.0–137.0]	133.0 [117.0–145.5]	0.0575
Platelet count ($\times 10^9$/L)	232.0 [170.0–308.0]	252.0 [195.0–324.0]	162.5 [111.5–229.5]	<0.0001
Prothrombin time (s)	14.0 [13.4–14.8]	13.7 [13.2–14.2]	15.3 [14.3–18.1]	<0.0001
D-dimer (μg/mL)	0.8 [0.4–1.7]	0.6 [0.3–1.1]	5.3 [1.3–21.0]	<0.0001
Albumin (g/L)	34.5 [31.4–37.9]	35.7 [33.1–39.4]	31.1 [27.4–33.6]	<0.0001
ALT (U/L)	23.0 [15.0–39.0]	22.0 [14.0–37.0]	30.0 [18.0–47.3]	0.0019
AST (U/L)	26.0 [18.0–40.0]	23.0 [17.0–35.0]	39.0 [24.5–61.5]	<0.0001
Uric acid (μmol/L)	259.0 [196.1–310.3]	247.4 [196.0–298.0]	277.3 [196.1–351.0]	0.0753
BUN (mmol/L)	4.6 [3.5–6.5]	4.1 [3.2–5.2]	8.30 [6.1–13.8]	<0.0001
Creatinine (μmol/L)	69.0 [58.0–87.8]	65.0 [57.0–80.0]	88.0 [66.5–121.0]	<0.0001
eGFR (mL/min/1.73 m^2)	103.8 ± 38.6	111.9 ± 32.8	83.0 ± 44.3	<0.0001
Total cholesterol (mmol/L)	3.6 [3.2–4.2]	3.7 [3.3–4.3]	3.4 [2.9–3.9]	0.0003
Procalcitonin (ng/mL)	0.06 [0.05–0.27]	0.05 [0.04–0.08]	0.31 [0.14–0.90]	<0.0001
Lactic dehydrogenase (U/L)	272.0 [211.0–395.0]	248.0 [196.0–309.0]	485.5 [345.5–608.8]	<0.0001
C-reactive protein (mg/L)	22.5 [2.6–71.8]	7.9 [1.8–35.4]	77.7 [54.0–136.2]	<0.0001
Interleukin-6 (pg/mL)	16.0 [4.6–57.8]	6.3 [3.5–22.8]	59.5 [20.8–136.3]	<0.0001
Treatments[c]				
Mechanical ventilation	79/292 (27.1)	2/209 (1.0)	77/83 (92.8)	<0.0001
Antibiotic treatment	281/295 (95.3)	199/212 (93.9)	82/83 (98.8)	0.1375
Cephalosporins	92/196 (46.9)	32/117 (27.4)	60/79 (75.9)	<0.0001
Quinolones	171/196 (87.2)	112/117 (95.7)	59/79 (74.7)	<0.0001
Penicillins	30/196 (15.3)	25/117 (21.4)	5/79 (6.3)	0.0041
Antiviral treatment	268/279 (96.1)	207/208 (99.5)	61/71 (85.9)	<0.0001
Arbidol	224/268 (83.6)	173/207 (83.6)	51/61 (83.6)	0.9953
Lopinavir	28/268 (10.4)	21/207 (10.1)	7/61 (11.5)	0.7653
Oseltamivir	57/268 (21.3)	43/207 (20.8)	14/61 (23.0)	0.7149
Lianhua Qingwen granules	163/268 (60.8)	133/207 (64.3)	30/61 (49.2)	0.0341
Corticosteroids	127/292 (43.5)	62/218 (28.4)	65/74 (87.8)	<0.0001
Immunoglobins	113/292 (38.7)	54/217 (24.9)	59/75 (78.7)	<0.0001
Disease severity				<0.0001
General	106 (34.8)	102 (46.4)	4 (4.7)	
Severe	119 (39.0)	114 (51.8)	5 (5.9)	
Critical	80 (26.2)	4 (1.8)	76 (89.4)	

COVID-19, coronavirus disease 2019; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartic transaminase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.
[a] Data are the median [interquartile range], mean ± standard deviation or n (%).
[b] P-values were calculated by Mann–Whitney U-test, t-test or χ^2 test, as appropriate.
[c] Data were missing for some patients for 'Signs and symptoms' and 'Treatments'.

count, neutrophil count, lactate dehydrogenase, CRP, interleukin-6 (IL-6), PCT, BUN and D-dimer levels were significantly higher in the non-survivor group ($P < 0.0001$). Antibiotics (95.3%), antivirals (96.1%) and corticosteroids (43.5%) were the three most common medications in patients with COVID-19, and the percentage of treatment with mechanical ventilation, corticosteroids and immunoglobulins ($P < 0.0001$) was significantly higher in the non-survivor group. The antibiotics used were mainly cephalosporins (46.9%), quinolones (87.2%) and penicillins (15.3%). Arbidol (83.6%), lopinavir (10.4%), oseltamivir (21.3%) and Lianhua Qingwen granules (60.8%) were the commonly used antiviral medications.

3.2. Performance of blood urea nitrogen and D-dimer levels in the COVID-19 patient cohort

In the univariable regression analysis, the risk of death was higher in elderly and male patients with co-morbidities ($P < 0.001$). Patients with co-morbidities of hypertension [hazard ratio (HR) = 2.13, 95% confidence interval (CI) 1.35–3.37; $P < 0.0001$] and cardiovascular disease (HR = 3.05, 95% CI 1.77–5.26; $P < 0.0001$) had a significantly higher risk of death. Elevated levels of neutrophil count, lactate dehydrogenase, CRP, IL-6, prothrombin time, creatinine and PCT were also associated with in-hospital

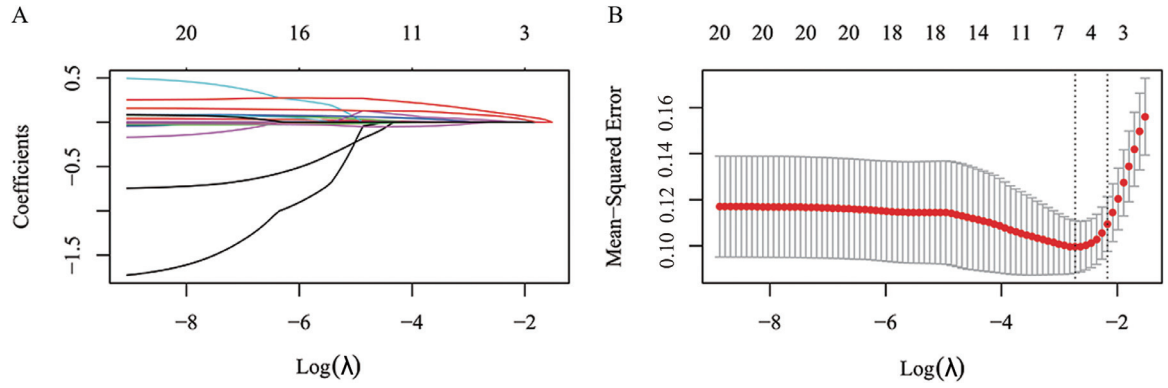


Fig. 1. The prognostic factors of blood urea nitrogen (BUN) and D-dimer were selected by least absolute shrinkage and selection operator (LASSO) regression analyses. (A) LASSO coefficient profiles of the non-zero variables of COVID-19. A coefficient profile plot was produced against the log (λ) sequence. A vertical line was drawn at the value selected using 10-fold cross-validation, where optimal λ resulted in three non-zero coefficients. (B) Mean-squared error plot of the lowest point of the red curve, which corresponds to a three-variable model. Tuning parameter (λ) selection in the LASSO model used 10-fold cross-validation via minimum criteria. The mean-squared error was plotted versus log (λ). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 standard error (SE) of the minimum criteria (the 1-SE criteria). A λ value of 0.114, with log (λ) −2.172 was chosen (1-SE criteria) according to 10-fold cross-validation.

Table 2
Cox regression analysis for the association of blood urea nitrogen (BUN) and D-dimer categories with risk of in-hospital mortality in COVID-19 patients

Model[a]	D-dimer < 0.845 μg/mL and BUN < 4.6 mmol/L (n = 97)	D-dimer ≥ 0.845 μg/mL and BUN < 4.6 mmol/L (n = 55)		D-dimer < 0.845 μg/mL and BUN ≥ 4.6 mmol/L (n = 55)		D-dimer ≥ 0.845 μg/mL and BUN ≥ 4.6 mmol/L (n = 98)	
	aHR (95% CI)	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Model 1	Ref. (0.0)	4.01 (1.07–15.06)	0.040	4.48 (1.18–16.94)	0.027	22.28 (6.81–72.94)	<0.001
Model 2	Ref. (0.0)	3.87 (1.03–14.55)	0.045	4.56 (1.20–17.26)	0.026	19.70 (5.92–65.51)	<0.001
Model 3	Ref. (0.0)	5.96 (1.27–28.01)	0.024	6.02 (1.27–28.50)	0.024	22.94 (5.33–98.77)	<0.001

aHR, adjusted hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.
[a] Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, co-morbidities and eGFR; and Model 3; adjusted for age, sex, co-morbidities, eGFR and CRP.

death (Supplementary Table S1). In particular, it was observed that increasing levels of BUN (HR = 1.11, 95% CI 1.09–1.13; P < 0.001) and D-dimer (HR = 1.15, 95% CI 1.11–119; P < 0.0001) were associated with an increased risk of mortality. Furthermore, LASSO regression analysis was performed to select optimal predictive factors. A total of 20 variables that were associated with in-hospital death in the univariate Cox regression analysis were included and the results showed that BUN, CRP and D-dimer levels were predictive factors for in-hospital death (Fig. 1). In addition, in the multivariable Cox regression model (forward LR), BUN (adjusted HR = 1.06, 95% CI 1.03–1.09; P < 0.0001) and D-dimer (adjusted HR = 1.11, 95% CI 1.08–1.14; P < 0.0001) remained significantly associated with in-hospital mortality after adjustment for age, sex, co-morbidity, neutrophil count, lymphocyte count, platelet count, albumin, lactate dehydrogenase, PCT and IL-6, which was consistent with the LASSO analysis results (Supplementary Table S2). According to the median of BUN and D-dimer, BUN ≥ 4.6 mmol/L combined with D-dimer ≥ 0.845 μg/mL were significant predictors of all-cause mortality after adjusting for age, sex, co-morbidity, eGFR and CRP (HR = 22.94, 95% CI 5.33–98.77; P < 0.001) (Table 2). A subgroup analysis for age, eGFR, CRP and co-morbidities was also conducted. Elevated BUN or D-dimer was associated with an increased risk of mortality stratified by normal or abnormal eGFR, which was more evident among patients aged >65 years (Supplementary Fig. S1).

Kaplan–Meier survival curves in hospitalised patients are given in Fig. 2. COVID-19 patients were divided into two strata according to the median value of BUN (low, <4.6 mmol/L; and high, ≥4.6 mmol/L) and D-dimer (low, <0.845 μg/L; and high ≥0.845 μg/L). Kaplan–Meier analysis showed statistically significant differences between the two groups (P < 0.0001) (Fig. 2A,B). Furthermore, patients with COVID-19 were stratified by BUN and D-dimer (stratum 1, D-dimer < 0.845 μg/mL and BUN < 4.6 mmol/L; stratum 2, D-dimer ≥ 0.845 μg/mL and BUN < 4.6 mmol/L; stratum 3, D-dimer < 0.845 μg/mL and BUN ≥ 4.6 mmol/L; and stratum 4, D-dimer ≥ 0.845 μg/mL and BUN ≥ 4.6 mmol/L). There were significant differences in poor outcomes among these strata (P < 0.0001). Moreover, the mortality incidence was significantly higher in stratum 4 compared with strata 2 and 3 (Fig. 2C).

3.3. Predictive power of blood urea nitrogen combined with D-dimer in COVID-19 patients

The risk factors of BUN, D-dimer and CRP mentioned above were further analysed by ROC curve analysis to evaluate the predictive ability for in-hospital mortality in COVID-19 patients. The area under the curve (AUC) was 0.88 for BUN (95% CI 0.83–0.93), 0.88 for D-dimer (95% CI 0.83–0.92) and 0.87 for CRP (95% CI 0.83–0.91). It was found that the predictive effect of BUN combined with D-dimer had significantly better AUC values than that of the BUN or D-dimer alone or CRP+BUN, with a sensitivity of 85% and a specificity of 91% (Fig. 3).

3.4. Development of an individualised prediction model and apparent performance to indicate poor prognosis

To predict the clinical effect of BUN and D-dimer on individuals, a prediction model for outcomes was established using the nomogram analysis. The model incorporated the potential predictors BUN and D-dimer that were screened by the LASSO regression model and incorporated individuals' age. The prediction model was presented as the nomogram (Fig. 4A). The calibration curve

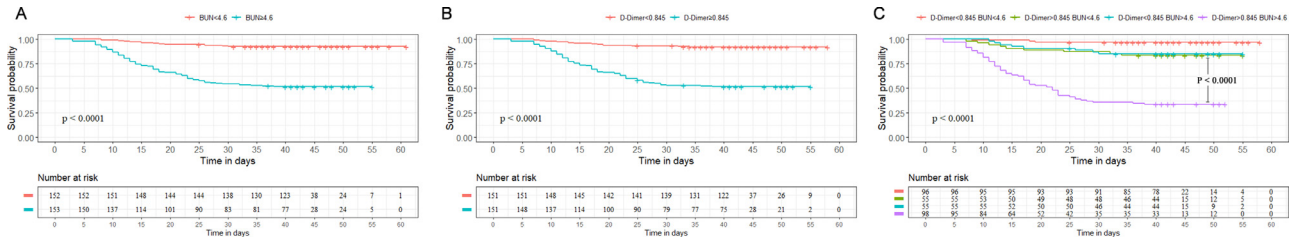
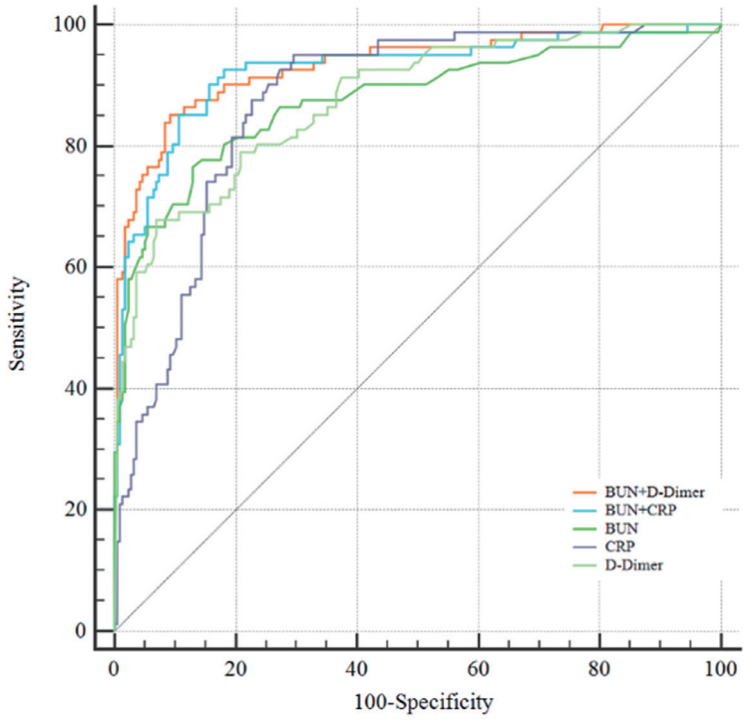


Fig. 2. Kaplan–Meier survival estimates according to blood urea nitrogen (BUN) and D-dimer levels. (A) Risk group stratification with the median of BUN concentration (4.6 mmol/L). (B) Risk group stratification with the median of D-dimer concentration (0.845 μg/mL). (C) Stratification with BUN and D-dimer.



Variables	AUC (95%CI)	Sensitivity	Specificity	Cut-off value	P value
D-Dimer	0.88 (0.83-0.92)	0.68	0.93	2.56	<0.001
BUN	0.88 (0.83-0.93)	0.77	0.87	5.95	<0.001
CRP	0.87 (0.83-0.91)	0.95	0.70	26.15	<0.001
CRP+BUN	0.92 (0.89-0.96)	0.85	0.82		<0.001
D-Dimer + BUN	0.94 (0.90-0.97)	0.85	0.91		<0.001

Abbreviations: CRP, C-reactive protein; BUN, blood urea nitrogen; AUC: area under curve.

Fig. 3. Receiver operating characteristic curves for in-hospital mortality. The AUC increased significantly when BUN and D-dimer levels were combined. CI, confidence interval.

of the nomogram for the probability of poor prognosis in COVID-19 demonstrated good agreement between prediction and observation in the COVID-19 patient cohort. The Hosmer–Lemeshow test showed a non-significant statistic ($P = 0.574$), which suggested that there was no departure from a perfect fit. The C-index for the prediction nomogram was 0.94 (95% CI 0.90–0.97). Through bootstrapping validation, the bias-adjusted C-index was confirmed to be 0.929 (Fig. 4B). These results suggested the perfect discriminative capacity of this model.

4. Discussion

In this study, serum levels of BUN and D-dimer were found to be significantly higher in non-survivor COVID-19 patients compared with survivor cases. LASSO and multivariable Cox regression analysis suggested that BUN and D-dimer levels were independent predictive factors for in-hospital mortality. Meanwhile, high levels of BUN and D-dimer were associated with high mortality independent of other covariates and had a robust predictive ability for poor outcome. Further analysis found that BUN combined with D-dimer had a stronger predictive ability, with an ideal sensitivity and specificity.

Several recent studies have investigated serum markers closely associated with the severity of COVID-19 patients, such as neutrophil-to-lymphocyte ratio, D-dimer, PCT, IL-6 and lactate dehydrogenase [17–19]. However, only a few studies have focused on the prognostic role of laboratory findings for mortality in these patients so far. In the current study, we found more than 20

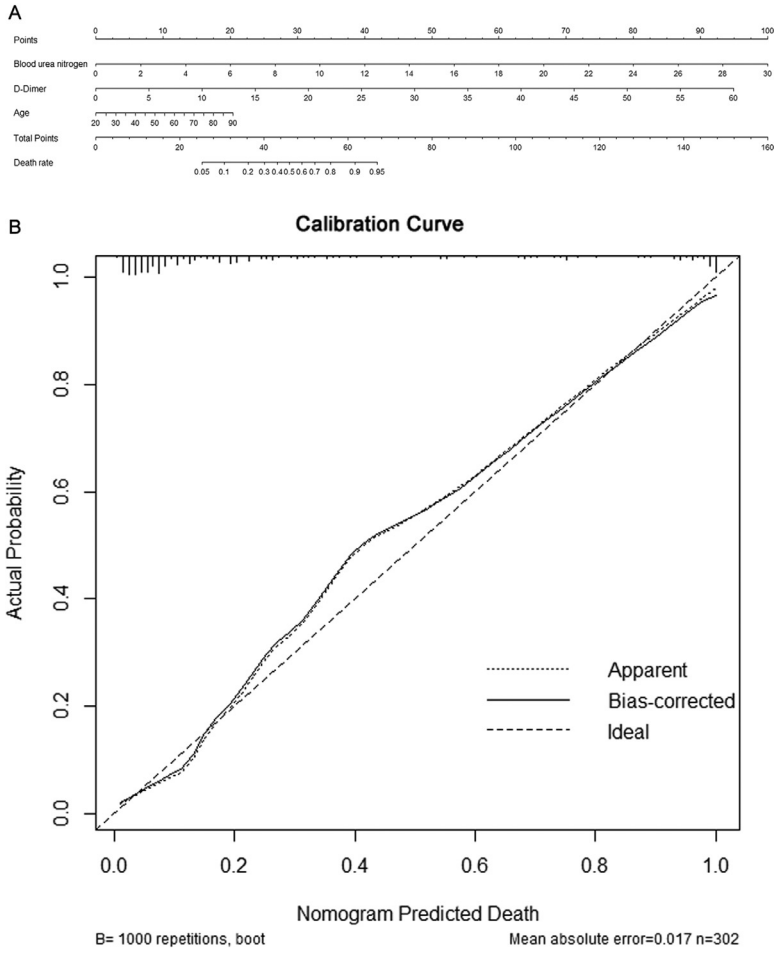


Fig. 4. (A) Nomogram predicting mortality of patients with COVID-19. (B) Calibration plot of the nomogram for patients with COVID-19.

variables significantly related to mortality among the COVID-19 patients. Considering the sparse data and multicollinearity problem, the LASSO method was suitable for the regression of high-dimensional data and to select optimal predictive features [20]. Finally, BUN, D-dimer and CRP were screened as optimal risk factors associated with COVID-19 in-hospital mortality. BUN is a renal function marker and is also a potential parameter of neurohormonal activity. A recent study showed that high BUN levels at admission were robustly associated with adverse outcomes in critically ill patients admitted to the ICU, even after correction for co-founders, including renal failure [21]. Besides, elevated levels of BUN are independent predictors of mortality in patients with heart failure or myocardial infarction [7,22]. In line with previous studies, we found that elevated BUN was an independent risk factor for an unfavourable prognosis after adjustment for eGFR and had a high ability to predict mortality in patients with COVID-19. This finding is similar to that of a study which identified the relationship between higher serum BUN concentration and mortality in patients with H1N1-confirmed pneumonia [23]. Although serum creatinine is also a renal marker, it was not considered as a risk associated with worse prognosis in the COVID-19 patients in this study. The precise difference between BUN and creatinine to COVID-19 prognosis needs to be studied further.

Recently, D-dimer was reported to be closely related to the severity of COVID-19 patients, and when combined with IL-6 detection it had the highest specificity and sensitivity for its early prediction [16]. An elevated level of D-dimer was also associated with ICU admission and lower survival in CAP patients [13,24]. In the current study, the D-dimer levels at admission were lower in survivors compared with non-survivors, with an AUC of 0.88 for predicting in-hospital mortality. Although CRP also had almost the same clinical value to predict poor outcomes, the specificity of D-dimer was higher than that of CRP. CRP is an acute-phase reactant associated with the severity of inflammation, and its serum levels are unstable and are susceptible to anti-inflammatory factors, especially in some COVID-19 patients who have been treated with antibiotics before hospital admission. Also, previous studies indicated that there is some controversy about the prognostic significance of CRP in pneumonia. Some studies reported that CRP was associated with mortality in patients with CAP [25]. However, other studies showed a non-significant correlation between CRP levels at admission and the prognosis of CAP [26]. Moreover, the current study found that among the prognostic factors, D-dimer levels had a higher hazard ratio than CRP for patients with COVID-19. Meanwhile, BUN combined with D-dimer had a higher AUC value and specificity than BUN or CRP alone or BUN+CRP to predict in-hospital mortality in patients with COVID-19. Therefore, the parameters BUN and D-dimer were selected for better prediction of in-hospital mortality among COVID-19 patients.

Based on BUN and D-dimer levels and integrating patient age on admission, a nomogram-individualised model was developed for predicting mortality in patients with COVID-19. The C-index of the calibration curve of the nomogram was 0.94 in the current cohort, which suggested it had a robust ability to predict mortality. However, the only drawback was that internal and independent validation of the nomogram was not performed. Therefore, to jus-

tify the clinical usefulness, we need to validate the nomogram in other COVID-19 patients and assess whether it could be applied directly to the clinic in future studies.

Nevertheless, this study has some limitations. First, it is a retrospective analysis based on the initial BUN and D-dimer levels on admission. Kinetic analysis of serum BUN and D-dimer levels in the COVID-19 patients was not performed. Therefore, the relationship between prognostic significance and time-dependent changes in BUN and D-dimer remains unknown. Second, only uraemia patients or regular maintenance dialysis patients were excluded and we did not consider the possibility of patients with chronic kidney disease to have high baseline BUN levels. Third, as Tongji Hospital was assigned as a designed hospital for severely or critically ill patients with COVID-19, and the critical patient selection bias for prognostic research, the case fatality rate in this study cannot reflect the true mortality of COVID-19. Last but not least, this was a retrospective observational single-centre study; whether the results of this study are replicable in the other regions is questionable. As it is limited by the sample size, validation of the individualised prediction model for patient outcomes requires further investigation.

5. Conclusion

Initial serum BUN and D-dimer levels were associated with in-hospital mortality in patients with COVID-19. A useful individualised nomogram was developed that incorporated initial levels of BUN and D-dimer as well as patient age and can be conveniently used to predicate mortality in COVID-19 patients. The predictive model can help clinicians to improve individual treatment, make timely clinical decisions, and make optimal use of limited clinical resources.

Availability of data and materials

The data sets generated and analysed during the current study are available from the corresponding authors on reasonable request.

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Ethical approval: This study was approved by the Research Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology (Wuhan, China) [TJ-IRB20200353] to Dr. Tao Wang. Consent to participate is not applicable because this was a retrospective study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106110.

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