Predictive Risk Factors at Admission and a "Burning Point" During Hospitalization Serve as Sequential Alerts for Critical Illness in COVID-19 Patients

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Research

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Abstract

Background In critically ill COVID-19 patients, the crucial turning point before critical illness onset (CIO) remain largely unknown, and the combination of baseline risk factors with the turning point during hospitalization was rarely reported.

Methods In this retrospective cohort study, 1150 consecutively admitted patients with confirmed COVID-19 were enrolled, including 296 critical and 854 non-critical patients. We compared the differences of all the clinically tested indicators and their dynamic changes between critical and non-critical patients. Three prediction models were established and validated based on the risk factors at admission, and an online baseline predictive tool was developed. Linear mixed model (LMM) was applied for longitudinal data analysis in 296 critical patients throughout the hospitalization, to predict the likelihood and possible time of critical illness in COVID-19 patients. A crucial turning point, where several indicators will experience a greater and significantly continuous change before CIO, was defined as “burning point” in our study. This point indicates the deterioration of patient’s condition before CIO.

Results We established a novel two-checkpoint system to predict critical illness for COVID-19 patients in which the first checkpoint happened at patient admission was assessed by a baseline prediction model to project the likelihood of critical illness based on the variables selected from random forest and LASSO regression analysis, including age, SOFA score, neutrophil-to-lymphocyte ratio (NLR), D-dimer, lactate dehydrogenase (LDH), International Normalized Ratio (INR), and pneumonia area derived from CT images, which yields an AUC of 0.960 (95% confidence interval, 0.941-0.972) and 0.958 (0.936-0.980) in the training and testing sets, respectively. This model has been translated into a public web-based risk calculator. Furthermore, the second checkpoint (designated as “burning point” in our study) could be identified as early as 5 days preceding the CIO, and 12 (*IQR*, 7-17) days after illness onset. Seven most significant and representative “burning point” indicators were SOFA score, NLR, C-reactive protein (CRP), glucose, D-dimer, LDH, and blood urea nitrogen (BUN).

Conclusions With this two-checkpoint prediction system, the deterioration of COVID-19 patients could be early identified and more intensive treatments could be started in advance to reduce the incidence of critical illness.

Introduction

SARS-CoV-2 is known to cause severe acute respiratory illness in humans. Currently, the pandemic triggered by SARS-CoV-2 is still quickly unfolding in many countries. According to real-time statistics released by WHO, as of August 26, 2020, more than 24 million cases of COVID-19 were confirmed and over 800,000 patients died. Five to twenty percent of hospitalized patients with COVID-19 were admitted to the intensive care unit (ICU), with mortality rate reportedly standing between 26% and 61.5%[1–3]. The condition of critically ill patients tends to deteriorate over a very short period of time, frequently leading to acute respiratory distress syndrome (ARDS) or multiple-organ failure, and even death[4,5].

Ongoing pandemic necessitates the discovery of reliable prognostic predictors and dynamic changes of certain laboratory variables to help guide clinical decision making tailored to the patient characteristics. Identifying patients' characteristics and dynamic changes associated with critical illness in patients diagnosed with COVID-19 can provide therapeutic targets as well as improve the design and analysis of future clinical trials. Similarly, the deciphering of prognostic predictors and their dynamic changes that have an adverse effect on the disease progression may provide new insights into the disease pathogenesis.

So far, several studies[6,7] have reported prediction models for critically ill patients with COVID-19. However, these models were solely-based on baseline characteristics, and therefore did not involve longitudinal analysis and were unable to predict disease progression during hospitalization. A recent report[8] was able to predict the mortality of patients more than 10 days in advance using laboratory indicators during hospitalization. Nevertheless, only blood samples from 485 patients were used for modeling and this model didn't involve the dynamic changes of all the indicators. Here, we introduced a novel two-checkpoint prediction system based on both baseline characteristics at patient admission and longitudinal data collected during hospitalization. A crucial turning point - "burning point" was found before patients deteriorated to a critical condition (such as ICU admission), which was incorporated into this warning system. The two-checkpoint prediction system is a workable early warning system, including the first warning at admission and the second alert as early as five days before critical illness onset (CIO), to predict the occurrence and possible time of critical illness in COVID-19 patients.

Methods

Study design and participants

A total of 1224 Laboratory-confirmed COVID-19 adult patients (≥ 18 years old) were consecutively admitted to Wuhan West Union Hospital between January 12 and February 25, 2020. Among which 74 patients were excluded including 57 patients transferred to other hospitals and 17 patients who died within 24 h after admission. The remaining 1150 participants were included in our study and they all had a definite clinical outcome (death or discharge) as of early-May, 2020 **(study flowchart in Fig. 1A)**.

Criteria and definitions

The diagnosis and discharge criteria for COVID-19 were consistent with previous reports[7,9]. According to the interim criteria of WHO[10] and the guidelines by the National Health Commission (trial version 7.0), critical COVID-19 illness was evaluated retrospectively and confirmed based on respiratory infection, plus one of the following: 1) acute respiratory distress syndrome (ARDS) needing mechanical ventilation; 2) sepsis leading to life-threatening organ dysfunction; 3) septic shock. All of these critical patients either was admitted to ICU or received invasive mechanical ventilation or died, which met the definition of critical COVID-19 by Liang et al[7]. Otherwise, the patients were seen as non-critical patients. The critical illness onset (CIO) was recorded as the beginning time of moderate/severe ARDS requiring mechanical

ventilation, or the time point at which sepsis caused the life-threatening multiple organ dysfunction or the septic shock developed or patient was admitted to ICU. We introduced a new concept - “burning point” and defined it as a critical turning point at which the condition exacerbated before CIO and some indicators started to change significantly and continuously. The period from the burning point to CIO was deemed as the high-risk period of CIO. The first alert comes from the baseline warning system at admission and the second alert comes from the “burning point” warning system during hospitalization. ARDS was diagnosed according to the Berlin definition[11]. Sepsis and septic shock were defined based on the 2016 Third International Consensus Definition[12]. Sequential Organ Failure Assessment (SOFA) score was calculated as previously reported[13]. Definitions of various organ injuries were described **in the additional file 1: supplementary notes**.

Data Collection

A total of 87 baseline variables, covering demographics, comorbidities, symptoms, laboratory findings, imaging features, SOFA score, and admission time, were collected from electronic medical documents. The baseline CT images were interpreted independently by two senior radiologists experienced in chest radiology. For all participants, the SOFA score and all laboratory data (47 items in total) were recorded from admission to discharge or death. At least two experienced doctors carefully went through the medical records of each critical patient to determine the time of CIO. All of these data were summed up in a standardized form.

Descriptive analysis

Categorical variables were presented as frequencies (n) and percentages (%). The continuous variables with normal or non-normal distribution were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]). To compare the differences of baseline variables between critical and non-critical participants, we used the independent sample t-test or Mann-Whitney U test for continuous variables, x^2 test, Fisher’s exact test, or Mann-Whitney U test were employed for categorical (binary or ordinal) variables wherever appropriate.

Variable selection and model construction

To ensure the data integrity and avoid potential selection bias, variables or patients with missing rate of less than 40% were all included. As a result, 81 variables and 1118 patients remained. The random forest machine learning method was employed to impute the missing values[14]. Principal component analysis (PCA) was then conducted by using the R package "factoextra"[15] to evaluate the distribution of patients and the most relevant variables for critical illness. No cases were labeled as outliers and excluded in this process. Thereafter, a total of 1118 remaining patients were randomized into training and testing sets at a ratio of 7:3 (Training set, N = 783 [Non-critical/Critical: 587/196]; Testing set, N = 335 [Non-critical/Critical: 241/94]).

Three prediction models (i.e. the machine-learning based random forest, the Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression, and the multivariable logistic regression models)

were built to predict, at admission, the likelihood of progression to critical illness in COVID-19 patients. Briefly, we chose the predictors selected by both the random forest and LASSO regression models as candidate risk factors to conduct multivariable logistic regression analysis, and then developed a nomogram scoring system. Finally, the three models were further compared and validated. (**See details in additional file 1: supplementary methods, Table S1-6, Figure S1-4**). The nomogram scoring system was finally transformed into an online predictive tool:

https://hust-covid19.shinyapps.io/Critical-illness-Predictive-Tool/ (**Figure S4**).

Longitudinal data analysis

SOFA score and 46 laboratory markers (47 indicators in total) were recorded successively in all the 1150 hospitalized COVID-19 patients. To find out the indicators that changed significantly during the period of critical illness development, the liner mixed model (LMM) implemented in the R package "lme4"[16] was used to explore the association between time and indicators by taking the age, sex and comorbidities as fixed effects.

All tests were two-sided, and a *P* value less than .05 was considered statistically significant. R software (version 3.6.2, R Foundation) was used for all analyses.

Results

Features and Outcomes of non-critical and critical COVID-19 Patients

In our study, we collected data from the 1150 consecutively admitted patients. All the participants were studied until discharge or death **(Fig. 1A)**. Among them, 296 of 1150 patients (25.7%) were identified to be critically ill. As shown in Table 1, the overall mortality was 17.5% (201/1150), while up to 67.9% in critically-ill patients. All non-critical patients were discharged, and their hospital stay time was significantly shorter than critical patients discharged (23.0 *vs.* 43.0, $P < 0.0001$). The median age of non-critical and critical patients were 59.0 (IQR, 48.0–68.0) and 68.0 (61.0–76.0) years respectively. And there were more male patients in critical group than in non-critical group (64.2% *vs.* 46.6%, $P < 0.0001$). Over half of the patients had fever (81.4%) and cough (68.3%) at admission. 778 (68.7%) patients had at least one comorbidity, including hypertension (33.6%), diabetes (20.4%), and coronary heart disease (10.9%) as the top three comorbidities. Sepsis (48.1%) was the most frequent complication, followed by acute liver injury (31.4%), ARDS (31.1%), acute cardiac injury (13.5%), and acute kidney injury (13.1%). The frequencies of complications were significantly higher in critical patients (all $P < 0.0001$). Both the SOFA score at admission (3.00 *vs.* 1.00, $P < 0$ .0001) and highest SOFA score during hospitalization (6.00 *vs.* 1.00, $P < 0.0001$) were significantly higher in critical patients. The baseline CT features and laboratory findings among critical and non-critical patients were also summarized in Table 1. The time from illness onset to admission, "burning point", critical illness onset (CIO), death or discharge was listed in **Fig. 1B**.

Table 1
Baseline characteristics and outcomes of critical and non-critical patients with COVID-19

Variables	All patients, [n = 1150]	Non-critical patients, [n = 854]	Critical patients, [n = 296]	*P* value
Demographics				
Age, median (IQR), years	62.0 (52.0, 70.0)	59.0 (48.0, 68.0)	68.0 (61.0, 76.0)	< 0.0001
Sex				
Male, n (%)	588 (51.1)	398 (46.6)	190 (64.2)	< 0.0001
Female, n (%)	562 (48.9)	456 (53.4)	106 (35.8)	
Clinical characteristics				
Initial symptoms, n/N (%)				
Fever	912/1120 (81.4)	688/844 (81.5)	224/276 (81.2)	0.895
Highest temperature, median (IQR),℃	38.20 (37.50, 39.00)	38.00 (37.50, 39.00)	38.50 (37.63, 39.00)	0.065
Sore throat	44/1091 (4.0)	34/828 (4.1)	10/263 (3.8)	0.817
Fatigue	531/1104 (48.1)	390/835 (46.7)	141/269 (52.4)	0.150
Myalgia	238/1096 (21.7)	192/832 (23.1)	46/264 (17.4)	0.057
Cough	759/1113 (68.3)	576/842 (68.4)	184/271 (67.9)	0.868
Sputum production	361/1104 (32.7)	262/836 (31.3)	99/268 (36.9)	0.095
Chest tightness	348/1104 (31.5)	241/835 (28.9)	107/269 (39.8)	0.0008
Dyspnea	307/1099 (27.9)	184/831 (22.1)	123/268 (45.9)	< 0.0001
Running nose	22/1095 (2.0)	14/828 (1.7)	8/267 (3.0)	0.191
Vomiting	83/1100 (7.5)	71/833 (8.5)	12/267 (4.5)	0.036
Nausea	71/1100 (6.5)	60/838 (7.2)	11/262 (4.2)	0.083
Diarrhea	171/1103 (15.5)	131/834 (15.7)	40/269 (14.9)	0.800
Headache	69/1098 (6.3)	59/828 (7.1)	10/270 (3.7)	0.052
Asymptomatic	13/1120 (1.2)	12/870 (1.4)	1/250 (0.4)	0.291
Comorbidities, n/N (%)				

Variables	All patients, [n = 1150]	Non-critical patients, [n = 854]	Critical patients, [n = 296]	*P* value
Hypertension	381/1133 (33.6)	249/837 (29.7)	132/296 (44.6)	< 0.0001
Diabetes	231/1133 (20.4)	139/837 (16.6)	92/296 (31.1)	< 0.0001
Coronary heart disease	123/1133 (10.9)	76/837 (9.1)	47/296 (15.9)	0.0012
Cerebrovascular disease	49/1133 (4.3)	16/837 (1.9)	33/296 (11.1)	< 0 .0001
Malignancy	64/1133 (5.6)	40/837 (4.8)	24/296 (8.1)	0.033
Chronic bronchitis	27/1133 (2.4)	21/837 (2.5)	6/296 (2.0)	0.640
Asthma	14/1133 (1.2)	12/837 (1.4)	2/296 (0.7)	0.479
Chronic obstructive pulmonary disease	19/1133 (1.7)	9/837 (1.1)	10/296 (3.4)	0.017
Kidney disease	50/1133 (4.4)	32/837 (3.8)	18/296 (6.1)	0.104
Liver disease	54/1133 (4.8)	45/837 (5.4)	9/296 (3.0)	0.105
Others	360/1133 (31.8)	258/837 (30.8)	102/296 (34.5)	0.248
Number of comorbidities, n/N (%)				
≥ 1	778/1133 (68.7)	524/837 (62.6)	254/296 (85.8)	< 0.0001
≥2	392/1133 (34.6)	250/837 (29.9)	142/296 (48.0)	
≥3	150/1133 (13.2)	94/837 (11.2)	56/296 (18.9)	
≥4	36/1133 (3.2)	18/837 (2.2)	18/296 (6.1)	
Complications, n/N (%)				
Sepsis	553/1149 (48.1)	258/854 (30.2)	295/295 (100)	< 0.0001
Acute respiratory distress syndrome	358/1150 (31.1)	66/854 (7.7)	292/296 (98.6)	< 0.0001
Acute liver injury	361/1149 (31.4)	187/854 (21.9)	174/295 (59.0)	< 0.0001
Acute cardiac injury	155/1149 (13.5)	31/854 (3.6)	124/295 (42.0)	< 0 .0001
Acute kidney injury	150/1149 (13.1)	42/854 (4.9)	108/295 (36.6)	< 0.0001

Variables	All patients, [n = 1150]	Non-critical patients, [n = 854]	Critical patients, [n = 296]	*P* value
Baseline CT findings, n/N (%)				
Pneumonia area (Lesion ratio to lung)				
Small area (≤ 35%)	485/1109 (43.7)	450/849 (53.0)	35/260 (13.5)	< 0.0001
Medium area (35%-65%)	493/1109 (44.5)	347/849 (40.9)	146/260 (56.2)	
Large area (> 65%)	131/1109 (11.8)	52/849 (6.1)	79/260 (30.4)	
Uni-/Bilateral pneumonia				
Unilateral pneumonia	164/1109 (14.8)	137/849 (16.1)	27/260 (10.4)	0.022
Bilateral pneumonia	945/1109 (85.2)	712/849 (83.9)	233/260 (89.6)	
Central/Peripheral lesion location				
Central	2/1109 (0.2)	1/849 (0.1)	1/260 (0.4)	< 0.0001
Peripheral	282/1109 (25.4)	240/849 (28.3)	42/260 (16.2)	
Both	825/1109 (74.4)	608/849 (71.6)	217/260 (83.5)	
Consolidation	858/1109 (77.4)	623/849 (73.4)	235/260 (90.4)	< 0.0001
Patchy exudation	1030/1109 (92.9)	784/849 (92.3)	246/260 (94.6)	0.218
Ground-glass opacity	964/1109 (86.9)	722/849 (85.0)	242/260 (93.1)	0.0008
White lung	42/1109 (3.8)	9/849 (1.1)	33/260 (12.7)	< 0.0001
Pleural effusion	152/1109 (13.7)	98/849 (11.5)	54/260 (20.8)	0.0002
Lymph node enlargement	91/1109 (8.2)	73/849 (8.6)	18/260 (6.9)	0.389
SOFA score, median (IQR)				
SOFA score at admission	1.00 (0.00, 2.00)	1.00 (0.00, 1.00)	3.00 (2.00, 4.00)	< 0.0001
Highest SOFA score during hospitalization	1.00 (1.00, 3.00)	1.00 (0.00, 2.00)	6.00 (4.00, 11.00)	< 0.0001
Baseline Laboratory findings, median (IQR) or mean (± SD)				
White blood cells, $x10^9$/L	5.75 (4.34, 7.55)	5.33 (4.22, 6.88)	7.39 (5.12, 10.26)	< 0.0001

Variables	All patients, [n = 1150]	Non-critical patients, [n = 854]	Critical patients, [n = 296]	*P* value
Red blood cells, $x10^{12}$/L	4.10 (± 0.58)	4.10 (± 0.55)	4.09 (± 0.67)	0.950 *
Hemoglobin, g/L	125.65 (± 17.36)	125.22 (± 16.00)	126.90 (± 20.73)	0.212 *
Platelet, $x10^9$/L	211.0 (153.00, 278.00)	222.00 (166.00, 287.75)	166.00 (115.00, 239.00)	< 0.0001
Neutrophil count, $x10^9$/L	3.96 (2.82, 5.97)	3.68 (2.65, 5.10)	6.29 (3.96, 8.87)	< 0 .0001
Lymphocyte count, $x10^9$/L	0.99 (0.68, 1.36)	1.09 (0.80, 1.47)	0.65 (0.46, 0.91)	< 0 .0001
Neutrophil-to-lymphocyte ratio	3.80 (2.23, 6.93)	3.18 (1.99, 5.24)	8.48 (5.02, 13.07)	< 0 .0001
Monocyte count, $x10^9$/L	0.37 (0.27, 0.51)	0.39 (0.29, 0.53)	0.30 (0.20, 0.48)	< 0 .0001
Eosinophil count, $x10^9$/L	0.02 (0, 0.07)	0.03 (0.01, 0.08)	0.01 (0, 0.02)	< 0 .0001
Basophil count, $x10^9$/L	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.01 (0, 0.03)	0.247
Total bilirubin, μmol/L	10.80 (8.20, 14.30)	10.30 (7.80, 13.30)	12.40 (9.05, 17.50)	< 0 .0001
Direct bilirubin, μmol/L	3.30 (2.50, 4.70)	3.20 (2.30, 4.30)	4.40 (3.10, 5.90)	< 0 .0001
Alanine aminotransferase, U/L	31.00 (19.00, 49.00)	29.00 (19.00, 48.00)	33.40 (23.00, 52.00)	0.0025
Aspartate aminotransferase, U/L	30.00 (22.00, 43.00)	28.00 (20.00, 40.00)	40.00 (27.25, 55.00)	< 0 .0001
Alkaline phosphatase, U/L	57.00 (44.00, 73.00)	55.00 (44.00, 69.00)	65.50 (48.00, 87.25)	< 0 .0001
γ-glutamyl transpeptidase, U/L	28.00 (18.00, 45.00)	26.00 (17.00, 43.00)	36.00 (24.00, 59.00)	< 0 .0001
Total protein, g/L	63.10 (± 6.06)	63.47 (± 5.86)	62.04 (± 6.51)	0.0006 *
Albumin, g/L	31.48 (± 5.53)	32.42 (± 5.47)	28.83 (± 4.81)	< 0 .0001 *
Globin, g/L	31.54 (± 5.22)	30.99 (± 4.92)	33.10 (± 5.72)	< 0 .0001 *

Variables	All patients, [n = 1150]	Non-critical patients, [n = 854]	Critical patients, [n = 296]	*P* value
Albumin/globin	1.00 (0.80, 1.20)	1.10 (0.90, 1.30)	0.90 (0.70, 1.10)	< 0 .0001
Prealbumin, mg/L	139.90 (92.55, 208.05)	156.30 (111.40, 225.90)	90.50 (66.15, 132.17)	< 0 .0001
Total bile acid, μmol/L	2.70 (1.70, 4.40)	2.60 (1.60, 4.30)	3.20 (2.00, 5.10)	0.0004
Total cholesterol, mmol/L	3.96 (3.40, 4.57)	4.02 (3.44, 4.58)	3.83 (3.27, 4.47)	0.028
Triglyceride, mmol/L	1.29 (1.00, 1.69)	1.27 (0.99, 1.67)	1.33 (1.10, 1.72)	0.054
High density lipoprotein cholesterol, mmol/L	0.90 (0.76, 1.09)	0.92 (0.78, 1.11)	0.84 (0.71, 1.01)	< 0 .0001
low density lipoprotein cholesterol, mmol/L	2.36 (± 0.77)	2.39 (± 0.74)	2.26 (± 0.85)	0.037 *
Creatinine, μmol/L	69.52 (± 18.99)	68.24 (± 18.30)	73.48 (± 20.52)	0 .0001 *
Blood urea nitrogen, mmol/L	4.47 (3.48, 6.01)	4.25 (3.26, 5.45)	5.97 (4.25, 8.10)	< 0 .0001
Uric acid, μmol/L	240.70 (183.90, 303.40)	242.60 (189.10, 303.40)	233.80 (173.40, 304.60)	0.280
Cystatin-C, mg/L	0.84 (0.72, 0.97)	0.81 (0.71, 0.93)	0.91 (0.78, 1.07)	< 0 .0001
Glucose, mmol/L	6.00 (5.30, 7.29)	5.84 (5.24, 6.86)	6.90 (5.87, 8.48)	< 0 .0001
Creatine kinase, U/L	73.00 (46.00, 126.00)	68.00 (44.00, 111.75)	94.00 (55.00, 186.50)	< 0 .0001
Lactate dehydrogenase, U/L	256.00 (195.00, 362.75)	234.00 (187.00, 308.00)	412.00 (301.00, 558.50)	< 0 .0001
CO_2, mmol/L	25.13 (± 5.01)	25.55 (± 4.90)	23.90 (± 5.15)	< 0 .0001 *
C-reactive protein, mg/L	24.39 (4.36, 65.35)	13.70 (3.13, 43.72)	69.17 (34.15, 109.97)	< 0 .0001
Procalcitonin, ng/mL	0.08 (0.05, 0.14)	0.06 (0.04, 0.12)	0.16 (0.10, 0.29)	< 0 .0001
Ferritin, ng/ml	543.28 (228.13, 1128.53)	400.24 (195.84, 805.12)	1047.6 (569.77, 2084.3)	< 0 .0001

Variables	All patients, [n = 1150]	Non-critical patients, [n = 854]	Critical patients, [n = 296]	*P* value
D-dimer, μg/mL	0.51 (0.25, 1.00)	0.44 (0.22, 0.87)	0.83 (0.42, 1.73)	< 0 .0001
Prothrombin time, s	13.26 (± 1.20)	13.08 (± 1.05)	13.81 (± 1.41)	< 0 .0001*
International normalised ratio	1.02 (0.95, 1.10)	1.01 (0.95, 1.07)	1.08 (1.00, 1.19)	< 0 .0001
Activated partial thromboplastin time, s	36.00 (32.50, 40.10)	35.50 (32.40, 39.20)	37.30 (32.85, 42.40)	0.001
Fibrinogen, g/l	4.16 (± 1.25)	4.15 (± 1.14)	4.18 (± 1.51)	0.813 *
Thrombin time, s	15.62 (± 1.17)	15.53 (± 1.06)	15.90 (± 1.42)	0.0002*
Brain natriuretic peptide, pg/ml	30.90 (12.90, 94.60)	21.90 (5.00, 66.15)	59.60 (30.90, 130.10)	< 0 .0001
Myoglobin, ng/ml	45.30 (31.27, 76.90)	39.30 (27.40, 62.20)	75.20 (42.60, 132.50)	< 0 .0001
Creatine kinase muscle-brain isoform, ng/ml	0.80 (0.50, 1.30)	0.70 (0.40, 1.10)	1.00 (0.70, 1.80)	< 0 .0001
hypersensitive cardiac troponin I, ng/L	4.50 (1.90, 10.30)	3.90 (1.90, 8.10)	7.55 (2.59, 16.45)	0.0008
Outcomes and timeline				
Discharged, n/N (%)	949/1150 (82.5)	854/854 (100.0)	95/296 (32.1)	< 0 .0001
Deceased, n/N (%)	201/1150 (17.5)	0/854 (0.0)	201/296 (67.9)	
Time from illness onset to admission, median (IQR), days	11.0 (7.0, 15.0)	11.0 (8.0, 15.0)	10.0 (7.0, 15.0)	0.045
Time from admission to death, median (IQR), days	10.0 (6.0, 18.0)	–	10.0 (6.0, 18.0)	–
Time from admission to discharge, median (IQR), days	25.0 (17.0, 37.0)	23.0 (16.0, 34.0)	43.0 (31.0, 50.0)	< 0.0001

Note: Data were presented as n/N (%), median (IQR) or mean (±SD). P values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact, if not specified;
* t-test. Abbreviations: IQR: interquartile range; SD: standard deviation; SOFA: Sequential Organ Failure Assessment.

Baseline predictor Selection in the Training Set

The random forest and LASSO regression analysis were conducted in the training set respectively, with top 20 important variables remaining after random forest analysis and 19 variables selected by the latter (**Table S3-S4, Figure S2 in additional file 1**). The nine variables selected by both random forest and LASSO regression models were used in the subsequent multivariable logistic regression analysis, with two variables (neutrophils and CRP) excluded for their high correlation, respectively, with NLR and LDH and relatively lower AUC value (Fig. 2A). These seven variables included age (*OR* [95% confidence interval (CI)]: 1.028 [1.004–1.052], $P = 0.023$), SOFA score (4.367 [3.230, 5.903], $P < 0.001$), NLR (1.094 [1.024, 1.168], $P = 0.008$), D-dimer (1.476 [1.107, 1.968], $P = 0.008$), LDH (1.004 [1.001, 1.006], $P = 0.003$), INR (1.027 [0.999, 1.055], $P = 0.059$) and pneumonia area interpreted from CT images (medium *vs.* small, 4.358 [2.188, 8.678], $P < 0.001$; large *vs.* small, 9.567 [3.982, 22.986], $P < 0.001$) (Fig. 2A**).**

First alert: A baseline nomogram model for the prediction at admission of the risk for critical illness

For easy clinical application, we developed a nomogram scoring system in the training set based on the seven aforementioned variables to predict, at admission, the likelihood of progression to critical illness in COVID-19 patients **(**Fig. 2B**)**. Internal 10,000 bootstrap resamples exhibited that the nomogram had a good distinguishing power, with its *AUC* reaching 0.960 (95%*CI*, 0.941–0.972), comparable to the other two models (random forest: 1.000 [1.000–1.000] and LASSO regression: 0.971 [0.955–0.981]) **(**Fig. 2C**)**. The non-parametric bootstrap test in the validation dataset showed that there was no statistically significant differences in AUCs among the three models (all $P > 0.05$) **(additional file 1: Table S5)**. In addition, the calibration curve of this nomogram model indicated that the predictive probability for critical illness fitted very well with the actual probability, in both the training and the testing set **(**Fig. 2D**)**. In the testing set, the H-L test further confirmed the good performance of this model ($P = 0.863$) **(additional file 1: Table S6, Figure S3)**. Importantly, we performed a sensitivity analysis for this nomogram model based on the variables without missing values, yielding an *AUC* of 0.948 ($P = 0.43$) and 0.929 ($P = 0.26$) respectively in the training and testing set **(**Fig. 2C, **additional file 1: Table S5)**. As shown in Fig. 2E-F, the Decision curve analysis (DCA) and clinical impact curves proved that this nomogram worked well in supporting clinical decision-making, not much different from the other two prediction models.

Differences in dynamic changes of SOFA score and laboratory markers between critical and non-critical patients

We compared the change patterns of SOFA score and 46 laboratory variables in 296 critical and 854 non-critical patients from illness onset to 26 days later by plotting line charts **(**Fig. 3, **additional file 1: Figure**

S5-S7). Most of the indicators were substantially higher in critical patients than in non-critical patients during the whole observation period, including a sustained high level of SOFA score, inflammatory biomarkers (NLR, CRP, WBCs, neutrophils, PCT, Ferritin), coagulation indices (D-dimer, PT, INR, APTT), organ dysfunction indicators (LDH; CK, BNP, CK-MB, myoglobin, hsTNI; TBIL, DBIL, ALP, AST, Globin, TBA, GGT, ALT; BUN, Cys-C) and metabolism parameter (glucose) **(abbreviations are too many, which have been shown in the "list of abbreviations" on** page 15–16**)**. However, some indicators were persistently lower in critical patients than their non-critical counterparts, and these indicators were indicative of immune damage (lymphocytes and eosinophils), coagulation disorder (platelets), impaired liver function (A/G), and malnutrition (hemoglobin, RBCs, TP, prealbumin, albumin). Importantly, several laboratory markers started to rise or drop on the 8th (7th-9th) day after illness onset in critical patients, such as neutrophils, NLR, D-dimer, LDH, BUN, PCT, myoglobin, globin (all rose), and lymphocyte, albumin, A/G, HDL-C (all dropped) (Fig. 3, **additional file 1: Figure S5-S7 and supplementary notes**).

Second alert: A "burning point" - identified by studying the dynamic changes before CIO in critically ill patients

We further examined the dynamic changes of these 47 indicators before and after the CIO in 296 critical patients. As shown in Fig. 3 **and additional file 1: Figure S5-S7**, boxplots showed the dynamic changes of laboratory findings and SOFA score starting from the CIO in critical patients. Indicators, including SOFA score, NLR, CRP, PCT, ferritin (four inflammatory biomarkers), lymphocytes (immune indicator), D-dimer (coagulation index), LDH (organ dysfunction variable), glucose (metabolic indicator), TP and albumin (two nutrient indicators), were abnormal from the beginning, and started to progress substantially and continuously on the 5th day before the CIO. Some other indices, including WBCs, neutrophils, hemoglobin, RBCs, platelet, BUN, CK, BNP, DBIL, were virtually within normal range from the beginning but become abnormal upon approaching CIO, also showing the same change pattern within five days before CIO. Moreover, indicators, including PT, INR, and ALP, were constantly within the reference value range but also began to change persistently on the 5th day before CIO **(all in** Fig. 3, **additional file 1: Figure S5-S7)**. Based on the above facts, the "burning point" was identified to be at the 5th day before CIO, a critical turning point indicating that CIO was only five days away, at which several indicators would experience further clear and continuous changes. This "burning point" appeared 12 (*IQR*, 7–17) days after illness onset **(Fig. 1B)**. As shown in Table 2, LMM analysis revealed 26 out of 47 indicators changed significantly and continuously within five days before CIO, involving aspects of hematology, coagulation function, inflammation, energy and metabolism, cardiac, liver and renal function. Seven most significant and representative indicators were selected as reference indicators for clinical judgment. They were SOFA score (2 [+ 0.49], $P < .001$), NLR (10.61 [+ 2.07], $P < 0.0001$), CRP (46.9 [+ 4.95] mg/L, $P < 0.0001$), glucose (7.83 [+ 0.2] mmol/L, $P = 0.0066$), D-dimer (6.08 [+ 0.28] μg/L, $P < 0.0001$), LDH (461 [+ 13.95] U/L, $P = 0.0008$), and BUN (6.51 [+ 0.55] mmol/L, $P < 0.0001$), each being presented as median value at the 5th day before CIO plus average daily increment between burning point and CIO [in square bracket]. **(**Fig. 3, Table 2**)**. The dynamic changes of all theses 47 indicators after the critical illness onset (CIO) have been shown in **additional file 1: Table S7**.

Table 2
Dynamic changes of SOFA score and laboratory findings before the critical illness onset (CIO).

Variables	Day − 5	Day − 3	Day − 1	Day 0 Critical illness onset	Estimate	Std. Error	Pr (>|t|)
Representative variables, median (IQR)							
SOFA score	2.00 (2.00–4.00)	3.00 (3.00–4.00)	4.00 (2.00–5.00)	4.00 (3.00–6.00)	0.492	0.033	< 0.0001
NLR	10.61 (7.25–17.99)	16.33 (7.96–24.03)	18.19 (11.58-27.00)	18.29 (9.59–30.55)	2.068	0.264	< 0.0001
CRP, mg/L	46.90 (16.23–73.52)	54.93 (35.62–111.10)	78.20 (41.03-111.97)	78.00 (37.36-128.24)	4.951	0.958	< 0.0001
Glucose, mmol/L	7.83 (6.10-11.09)	8.01 (6.37–10.55)	8.96 (7.45–11.36)	8.50 (6.62–12.12)	0.201	0.074	0.0066
D-dimer, μg/mL	6.08 (1.01–8.50)	8.00 (1.93–8.50)	8.00 (3.73–8.50)	8.00 (2.60–8.50)	0.282	0.067	< 0.0001
LDH, U/L	461.00 (278.50-594.50)	431.00 (287.00-616.00)	489.00 (383.00-702.50)	467.50 (339.00-625.50)	13.951	4.157	0.0008
BUN, mmol/L	6.51 (4.39–9.67)	8.36 (5.96–11.32)	8.45 (6.27–12.75)	8.25 (6.20-13.52)	0.547	0.096	< 0.0001
Hematology, median (IQR)							
WBC, $\times 10^9$/L	8.14 (6.39–10.73)	9.23 (6.58–11.57)	12.80 (9.48–15.07)	11.12 (7.71–16.48)	0.799	0.097	< 0.0001
Neutrophil count, $\times 10^9$/L	7.10 (5.12–9.82)	8.29 (5.68–10.58)	10.84 (7.30-13.75)	9.96 (6.69–15.20)	0.766	0.093	< 0.0001
Lymphocyte count, $\times 10^9$/L	0.73 (0.46–0.96)	0.56 (0.42–0.75)	0.53 (0.34–0.76)	0.55 (0.36–0.81)	-0.026	0.006	< 0.0001
Hemoglobin, g/L	124.50 (114.00-141.75)	125.00 (109.00-140.00)	122.00 (104.00-133.00)	118.50 (103.00-133.25)	-2.106	0.303	< 0.0001

Variables	Day − 5	Day − 3	Day − 1	Day 0 Critical illness onset	Estimate	Std. Error	Pr (>|t|)
RBC, $\times 10^{12}$/L	4.14 (3.57–4.51)	3.95 (3.59–4.51)	3.90 (3.36–4.32)	3.93 (3.33–4.39)	-0.065	0.009	< 0.0001
Monocyte count, $\times 10^{9}$/L	0.38 (0.21–0.51)	0.30 (0.17–0.53)	0.32 (0.20–0.54)	0.37 (0.22–0.54)	0.008	0.005	0.107
Eosinophil count, $\times 10^{9}$/L	0.01 (0-0.02)	0.01 (0-0.03)	0.01 (0-0.02)	0.01 (0-0.03)	0.0002	0.0009	0.798
Coagulation function, median (IQR)							
PLT, $\times 10^{9}$/L	188.50 (121.75–241.50)	134.00 (96.00-208.00)	136.00 (85.00-215.00)	141.50 (85.00-221.00)	-4.987	1.104	< 0.0001
PT, s	13.40 (12.70-14.25)	14.35 (13.67–16.35)	14.60 (13.50–16.40)	14.50 (13.40–15.60)	0.141	0.045	0.0016
INR	1.05 (0.99–1.12)	1.15 (1.07–1.29)	1.17 (1.07–1.31)	1.16 (1.05–1.25)	0.009	0.004	0.035
TT, s	15.70 (14.75–16.75)	16.30 (14.70–17.30)	15.95 (14.67–17.52)	15.60 (14.60–16.60)	-0.038	0.045	0.393
FIB, g/l	4.01 (2.85–5.01)	3.42 (2.39–4.69)	3.85 (2.46–4.84)	3.95 (2.80–5.01)	0.014	0.032	0.657
APTT, s	34.05 (30.12–38.75)	36.90 (32.70–41.80)	37.25 (30.98–43.35)	37.05 (32.12–41.70)	0.064	0.167	0.702
Inflammation, median (IQR)							
PCT, ng/mL	0.14 (0.10–0.36)	0.21 (0.12–0.49)	0.38 (0.18–0.69)	0.31 (0.13–0.62)	0.026	0.014	0.066
Ferritin, ng/ml	1259.0 (935.9-1991.4)	1980.0 (1378.0-2000.5)	1232.4 (707.4-2000.5)	1086.0 (540.1-2000.5)	-36.202	33.047	0.277
Energy and metabolism, median (IQR)							

Variables	Day − 5	Day − 3	Day − 1	Day 0 Critical illness onset	Estimate	Std. Error	Pr (>|t|)
LDL-C, mmol/L	2.28 (1.69–2.66)	2.07 (1.55–2.69)	2.23 (1.82–2.84)	2.03 (1.45–2.77)	-0.030	0.015	0.051
Tch, mmol/L	3.81 (3.44–4.62)	3.61 (3.06–4.26)	4.08 (3.22–4.75)	3.56 (3.05–4.53)	-0.032	0.018	0.086
HDL-C, mmol/L	0.80 (0.71–0.91)	0.76 (0.64–0.87)	0.76 (0.66–0.85)	0.77 (0.64–0.93)	-0.010	0.006	0.104
TG, mmol/L	1.52 (1.15–2.17)	1.34 (1.19–2.13)	1.66 (1.25–2.01)	1.35 (1.1–1.89)	-0.010	0.017	0.558
CO_2, mmol/L	27.60 (23.45–29.60)	27.30 (22.95–29.45)	26.05 (21.60-31.68)	27.30 (23.10–30.10)	0.115	0.113	0.308
Cardiac function, median (IQR)							
CK, U/L	70.00 (41.00-179.75)	94.00 (62.00-236.00)	139.50 (63.50-395.50)	111.50 (57.00-281.00)	16.331	4.355	0.0002
BNP, pg/ml	49.15 (29.83–95.30)	134.10 (64.28-218.35)	131.75 (54.50-276.12)	95.00 (38.90-230.45)	13.250	6.386	0.039
CK-MB, ng/ml	1.00 (0.65–1.70)	1.55 (1.02–2.70)	1.25 (0.72–2.63)	1.70 (0.90–3.10)	0.115	0.061	0.063
Myoglobin, ng/ml	92.50 (37.65-192.55)	77.70 (56.26-139.12)	81.40 (50.73-168.95)	84.30 (55.88-175.22)	8.214	6.090	0.179
hsTNI, ng/L	16.20 (7.80–24.70)	10.10 (1.38–40.85)	11.40 (4.79–50.95)	16.65 (6.88–53.85)	1.232	1.522	0.420
Liver function, median (IQR)							
TBIL, μmol/L	11.90 (9.50–21.80)	16.00 (10.95–21.33)	14.25 (9.97–22.96)	15.20 (10.55–23.25)	0.649	0.179	0.0003
DBIL, μmol/L	4.20 (2.90–6.60)	5.70 (3.30–8.40)	4.85 (3.03–10.57)	5.50 (3.60–8.30)	0.402	0.082	< 0.0001

Variables	Day − 5	Day − 3	Day − 1	Day 0 Critical illness onset	Estimate	Std. Error	Pr (>|t|)
ALP, U/L	69.00 (52.00–92.00)	71.00 (57.00–96.00)	80.00 (63.00-103.50)	79.00 (59.00-101.00)	1.807	0.484	0.0002
TP, g/L	60.95 (57.00-65.78)	61.80 (56.00-66.18)	60.30 (56.10-64.47)	59.40 (55.75–65.68)	-0.298	0.131	0.023
Albumin, g/L	27.25 (26.18–31.32)	25.90 (23.62–30.45)	26.85 (23.52–29.32)	27.70 (23.90–30.10)	-0.202	0.093	0.030
Prealbumin, mg/L	119.00 (78.35-167.02)	96.00 (59.40-136.30)	100.70 (64.30–134.00)	98.05 (70.00-135.82)	-0.820	0.903	0.364
AST, U/L	44.00 (23.40–58.00)	36.00 (28.00–52.00)	38.00 (28.00–61.00)	34.00 (25.00–52.00)	-1.070	0.491	0.030
Globin, g/L	33.10 (28.95–37.10)	32.75 (29.50-38.75)	33.80 (30.10–37.50)	32.15 (29.00-37.45)	-0.065	0.100	0.519
A/G	0.80 (0.70-1.00)	0.78 (0.60–0.90)	0.80 (0.70–0.92)	0.80 (0.70-1.00)	-0.005	0.004	0.215
TBA, μmol/L	3.00 (2.00-4.40)	2.90 (1.60–5.65)	3.50 (1.60–5.80)	3.10 (1.80-5.00)	0.053	0.065	0.410
GGT, U/L	40.00 (25.25-65.00)	47.00 (26.00–74.00)	46.55 (29.02-83.00)	42.50 (28.00–64.00)	-0.332	0.426	0.436
ALT, U/L	37.00 (21.00–56.00)	40.00 (21.80–59.50)	34.00 (22.50–57.00)	37.00 (24.00-55.50)	-0.185	0.496	0.709
Renal function, median (IQR)							
Cys-C, mg/L	0.97 (0.81–1.21)	0.98 (0.84–1.28)	1.03 (0.87–1.39)	0.97 (0.80–1.33)	0.027	0.008	0.0007
Creatinine, μmol/L	67.05 (56.70-81.17)	73.50 (59.95–86.05)	72.20 (58.20-98.55)	68.00 (55.50-90.05)	1.053	0.505	0.038

Variables	Day − 5	Day − 3	Day − 1	Day 0 Critical illness onset	Estimate	Std. Error	Pr (>|t|)
UA, μmol/L	220.85 (118.37-298.15)	234.90 (158.45–316.20)	227.35 (143.90-299.40)	213.15 (146.90-311.1)	2.483	2.118	0.242

Note: The linear mixed model has been adjusted for age, sex and comorbidities.
Abbreviations: SOFA, Sequential Organ Failure Assessment; PLT, platelet; NLR, neutrophil to lymphocyte ratio; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; RBC, red blood cell; WBC, white blood cell; PT, prothrombin time; INR, international normalised ratio; TT, thrombin time; FIB, fibrinogen; APTT, activated partial thromboplastin time; CRP, C-reactive protein; PCT, procalcitonin; LDL-C, low density lipoprotein cholesterol; Tch, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; CK, creatine kinase; BNP, brain natriuretic peptide; CK-MB, creatine kinase muscle-brain isoform; hsTNI, hypersensitive cardiac troponin I; TBIL, total bilirubin; DBIL, direct bilirubin; ALP, Alkaline phosphatase; TP, total protein; AST, Aspartate aminotransferase; A/G, Albumin/globin; TBA, total bile acid; GGT, γ-glutamyl transpeptidase; ALT, Alanine aminotransferase; Cys-C, cystatin C; UA, uric acid.

Discussion

In this study, on the basis of the analysis of 1150 COVID-19 consecutive patients who were admitted to Wuhan West Union Hospital from January 12 to February 25, 2020, we established a reliable baseline prediction model and developed an online tool to predict, at admission, the risk for the development to critical illness, which can be used as the first warning sign (the first alert). Moreover, in critical patients, we retrospectively identified a “burning point”, a warning sign that CIO was only five days away and several indicators would experience significant and continuous changes. The “burning point” can serve as a second warning sign (the second alert) which can give clinicians precious time to take proactive measures before CIO. The two-checkpoint system can tell us “who” and “when” the critical illness will be developed in COVID-19 patients.

The predictors incorporated into the baseline prediction model were selected based on the random forest and LASSO regression analysis, which can provide a double guarantee for the selected predictors, ensuring the accuracy of the baseline model. Meanwhile, the model was translated into a nomogram system. Actually, the differentiating power of this nomogram scoring system was comparable to that of the aforementioned two models, yielding an AUC of 0.960 (95%*CI*, 0.941–0.972]) (*vs.* 1.00 [1.00–1.00] *vs.* 0.971 [0.955–0.981]) in the training set and an AUC of 0.958 (0.936–0.980) (*vs.* 0.963 [0.941–0.986] *vs.* 0.956 [0.934–0.978]) in the testing set. The accuracy of this model was also fully validated by the internal 10,000 bootstrap and external testing set through the H-L test and calibration plots. The sensitivity analysis in the training ($P = 0.43$) and testing set ($P = 0.26$) further proved the good performance of this nomogram model. Besides, the DCA and clinical impact curves verified that this

model worked effectively in supporting clinical decision- making. The nomogram system contained seven risk factors, including age, SOFA score, NLR, D-dimer, LDH, INR, and pneumonia area. All of them are easily obtained since they are included in the essential examinations at admission. Several studies[5, 17–19] have demonstrated that advanced age was an independent risk factor for death in COVID-19 patients. Higher SOFA score at admission was associated with increased odds of in-hospital death for COVID-19 patients[9]. Previous studies[9,20,21] showed that NLR, D-dimer, and LDH were risk factors for the fatal outcome related to COVID-19. INR was reportedly higher in deceased patients than in convalescent patients with COVID-19[22]. Pneumonia area was larger in patients who died from COVID-19[9]. Overall, the risk-factors based nomgram model is simple, effective and amenable to clinical application, especially when transformed into a web-risk calculator, which can serve as the first alert for predicting critical illness in COVID-19 patients.

In addition, the longitudinal data analysis of critical and non-critical patients with COVID-19 demonstrated that almost all indicators showed conspicuous differences between those two groups and several laboratory markers started to rise or drop on the 8th (7th-9th) day after illness onset in critical patients, supporting the hypothesis that the acute phase starts from the 7th-10th day after illness onset of COVID-19, as proposed by a previous study[23]. Collectively, differences in the aforementioned laboratory markers between critical and non-critical populations suggested that critical patients experienced a long-term of coagulopathy, inflammatory activation, lymphocyte exhaustion, malnutrition, metabolic disorders, myocardial injury, liver dysfunction, and kidney injury. These findings can help us gain insight into the pathogenesis of COVID-19 and distinguish between critical and non-critical patients.

What's more, we further looked into the dynamic changes in these 47 indicators before and after the CIO in 296 critical patients. The median time from illness onset to CIO was 17.0 (*IQR*, 12.0–22.0) days. We found that, prior to CIO, critical patients also suffered from severe coagulopathy (elevated D-dimer and declined PLT), inflammatory activation (elevated neutrophils), lymphocyte exhaustion, myocardial damage (ascendant LDH and BNP), impaired liver function (elevated TBIL, AST, GGT, and ALT), kidney injury (ascendant BUN and Cys-C), malnutrition (reduced TP, albumin and hemoglobin) and metabolic disorders (elevated glucose). Most importantly, we noticed that many laboratory markers started to have further and continuous changes on the 5th day before CIO. It indicates a turning point, at which the patient's condition began to deteriorate before the CIO, appeared. We designated this point as the "burning point", which occurred 12 (*IQR*, 7–17) days after illness onset. This "burning point" corresponded exactly to a point in the early acute phase of COVID-19 proposed by Lin et al[23]. Furthermore, results of LMM revealed that 26 out of 47 indicators changed significantly and continuously within the five days before CIO, covering almost all the aspects of abnormities mentioned above. For clinical application, we selected seven most significant and representative indicators as reference indicators and calculated their median values at the "burning point" (at the 5th day before CIO) and their average daily increments from "burning point" to CIO. These indicators were SOFA score, LDH, BUN (two organ-dysfunction indicators), CRP (inflammatory biomarkers), NLR (immune indicator), glucose (metabolism index), and D-dimer (coagulation indicator). In practice, we can judge whether a patient has

passed the "burning point" on the basis of the time after illness onset, value of each indicator at the “burning point” and its daily change increment. The appearance of “burning point” indicates that CIO is only five days away, which can serve as the second alert before critical illness developed in COVID-19 patients.

Until now, although the vaccine against COVID-19 is in full swing[24–26], there are still no special and effective treatments[27,28]. Intensifying multidisciplinary treatments, such as enhanced nutritional support, anticoagulation (low molecular weight heparin [LMWH]), anti-inflammatory (γ-globulin, *etc.*), respiratory support (mechanical ventilation), and replacement therapy (continuous renal replace therapy [CRRT]) are adopted to save lives of critical COVID-19 patients[1,29,30]. But the implementation of the above-mentioned intensive treatments usually started after the occurrence of critical illness. A recent study[23] about COVID-19 proposed that early initiation of intravenous γ-globulin and LMWH anticoagulant therapy was effective in improving the prognosis of COVID-19 patients. Since the "burning point" in this study represented the starting point at which the patient's condition began to deteriorate before CIO, the high-risk period between the “burning point” and CIO might provide a precious time window for earlier intensive care and multidisciplinary interventions, thereby avoiding the aggravation to critical illness and improving survival.

Our study had several limitations. First, it was a single-center study. However, the participants in our study were consecutively enrolled from the beginning of the outbreak to the near end in the epicenter and very few patients were excluded (74/1224). All 1150 patients were observed until death or discharge and the data during hospitalization were collected continuously. Second, data generation was clinically driven and not prospective. Third, since all data were from China, the conclusion should be further validated in other countries.

Conclusions

In conclusion, the baseline risk factors based nomogram (the first alert) can be employed at admission to identify the high-risk patients who might progress to critical illness. During hospitalization, the “burning point” (the second alert) could be identified in COVID-19 patients based on the time after illness onset, value of each indicator at “burning point”, and their daily change increments. The appearance of “burning point” indicates that CIO was only five days away. The two sequential alerts allow early identification of deterioration of patients’ condition, which is critical in optimizing medical intervention and reducing the mortality rate of COVID-19 patients.

List Of Abbreviations

COVID-19: coronavirus disease 2019

ICU: intensive care unit

CIO: critical illness onset

LASSO: Least Absolute Shrinkage and Selection Operator

LMM: linear mixed model

IQR: interquartile range

SD: standard deviation

OR: odds ratio

95% CI: 95% confidential interval

COPD: chronic obstructive pulmonary disease

ARDS: acute respiratory distress syndrome

SOFA: sequential organ failure assessment

CT: computed tomography

WBC: white blood cell

RBC: red blood cell

PLT: platelet

NLR: neutrophil to lymphocyte ratio

TBIL: total bilirubin

DBIL: direct bilirubin

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

ALP: Alkaline phosphatase

GGT: γ-glutamyl transpeptidase

TP: total protein

A/G: Albumin/globin

TBA: total bile acid

Tch: total cholesterol

TG: triglyceride

HDL-C: high density lipoprotein cholesterol

LDL-C: low density lipoprotein cholesterol

BUN: blood urea nitrogen

UA: uric acid

Cys-C: cystatin C

CK: creatine kinase

LDH: lactate dehydrogenase

CO2: carbon dioxide

CRP: C-reactive protein

PCT: procalcitonin

PT: prothrombin time

INR: international normalised ratio of prothrombin time

APTT: activated partial thromboplastin time

FIB: fibrinogen

TT: thrombin time

BNP: brain natriuretic peptide

CK-MB: creatine kinase muscle-brain isoform

hsTNI: hypersensitive cardiac troponin I

Declarations

Ethical Approval and Consent to participate

This study was approved by the institutional review board of Medical Ethics Committee of Union Hospital, Huazhong University of Science and Technology (NO.0036). Written informed consent was waived by the Committee for this critical situation of emerging infectious diseases.

Consent for publication

No individual participant data is involved.

Availability of supporting data

Anonymized clinical and laboratory data are available for researchers on request, subject to an internal review by YJ, MZ, JX, ZY to ensure that the participants' anonymity and confidentiality are protected, with completion of a data-sharing agreement, and in accordance with the Wuhan Union hospital's institutional review boards and institutional guidelines. Please submit requests for participant-related clinical and other data to YJ (whuhjy@126.com).

Competing interests

The authors declare no competing interests.

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Author Contributions

YJ and MZ designed the study, JX, HL, FW, GM, LD, and YA collected and summarized the clinical data. ZY, XT, and CD checked all the data. XH, KW, MZ, and ZW cleaned and analyzed all data. MZ, ZY, XT, KW drafted the manuscript. YH, YJ, JX, XH revised the final manuscript. All authors approved the final draft of the manuscript. Yang Jin is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figures

Figure 1

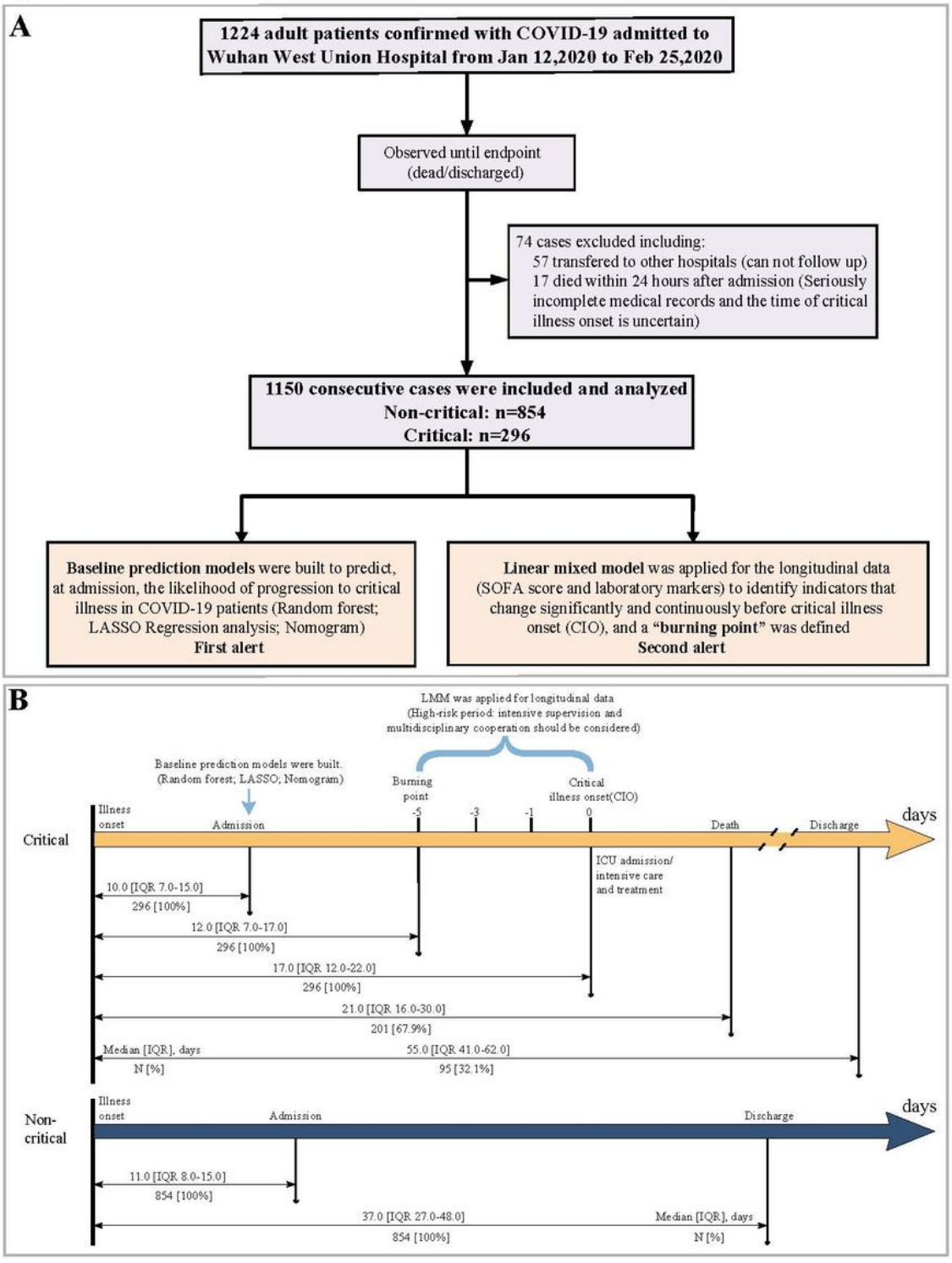

Figure 1

Study flow chart (A) and schematic diagram (B).

Figure 2

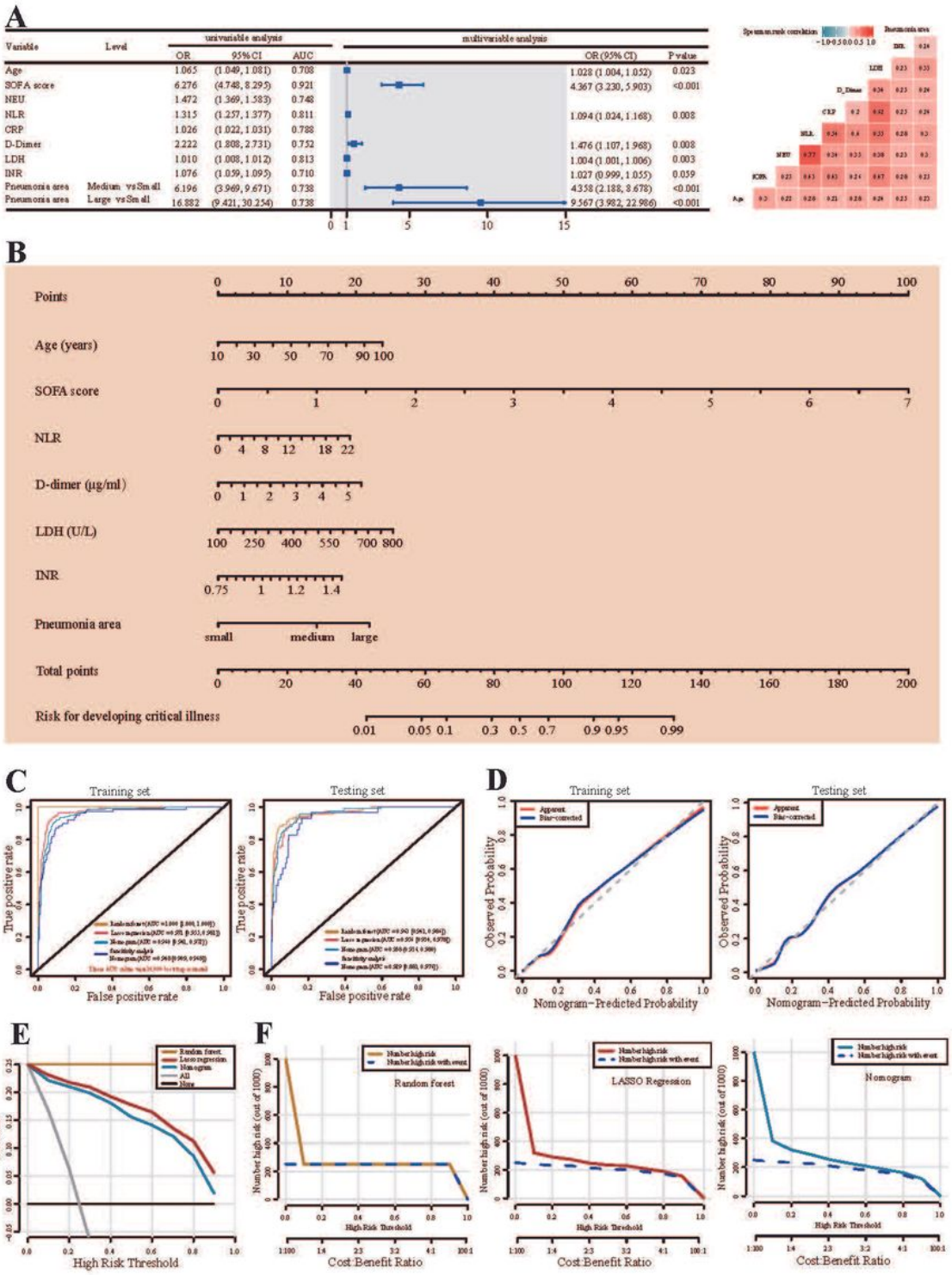

Figure 2

Construction of and comparison among the three baseline prediction models. (A) Univariable logistic analysis of the nine variables selected by both random forest and LASSO predictive models. Multivariable logistic analysis of the seven remained variables, with NEU and CRP excluded according to the spearman rank correlation for the nine variables. (B) The predictive nomogram model was developed in the training set, with age, SOFA score, NLR, D-dimer, LDH, INR, and pneumonia area interpreted from CT images

incorporated. (C) Receiver operating characteristic curve (ROC) plots of the three predictive models and the sensitivity analysis for nomogram model in training and testing set. The AUCs and 95% CIs for these models were computed with 10,000 bootstrap resample in the training set. (D) Calibration plots of the nomogram model in training and testing set. The ideal calibration curve (gray dotted line), raw calibration curve (red curve) and the bootstrap corrected calibration curve (blue curve) were displayed. (E) Decision curve analysis (DCA) comparing the clinical utility of the random forest (yellow line), LASSO (red line), and nomogram (ocean blue line) models. The gray line and horizontal solid black line reflect the corresponding net benefit if some intervention strategies conducted in all or no patients across the full range of threshold probabilities at which a patient would undergo special intervention to avoid critical illness. (F) Clinical impact curves of random forest (yellow line), LASSO regression (red line), and nomogram (ocean blue line) model. They were evaluated by the predictive performance of risk stratification for 1000 people and the corresponding Cost-Benefit Ratio. The yellow, red, and ocean blue lines represent the number of people classified as high risk by each model under different threshold probability; the blue dotted curve is the number of truly positive people under different threshold probability.

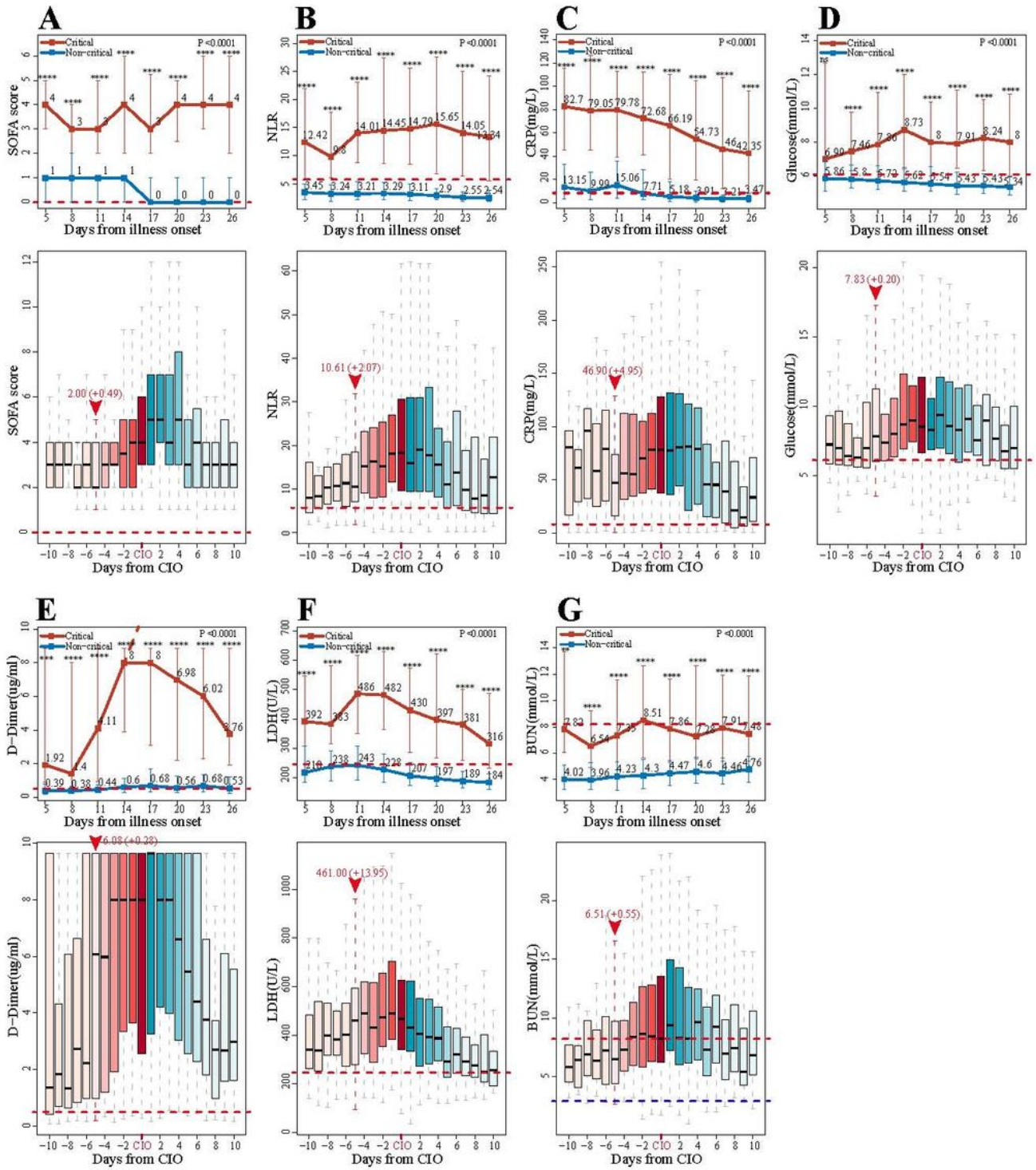

Figure 3

Change patterns of seven representative indicators in critical and non-critical COVID-19 patients. The dynamic changes of (A) SOFA score, (B) NLR, (C) CRP, (D) glucose, (E) D-dimer, (F) LDH, and (G) BUN, starting from illness onset between critical and non-critical patients (line chart), and those starting from critical illness onset (CIO) in critical patients (boxplot). The horizontal red dotted line and the horizontal blue dotted line represent the upper and lower limits of the reference value range of each indicator,

respectively. In line chart, the results are reported as median (IQR). The values of D-dimer after day 14 exceeded the upper limit of detection, as indicated by the dashed line. In the boxplot, the day of “burning point” is highlighted by vertical red dotted line and red arrow, above which are indicator's median value at the “burning point” and its average daily increment from “burning point” to CIO estimated by linear mixed model, they are expressed in the form of median (+increment).

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