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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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 death4,5.
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 studies6,7 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 report8 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 reports7,9. According to the interim criteria of WHO10 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 al7. 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. Sepsis and septic shock were defined based on the 2016 Third International Consensus Definition. Sequential Organ Failure Assessment (SOFA) score was calculated as previously reported. Definitions of various organ injuries were described in the additional file: 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, x² 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. Principal component analysis (PCA) was then conducted by using the R package “factoextra” 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” 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), °C | 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|
| CO₂, 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**

|                          | All patients, n/N (%) | Non-critical patients, n/N (%) | Critical patients, n/N (%) | P value |
|--------------------------|-----------------------|--------------------------------|-----------------------------|---------|
| Discharged               | 949/1150 (82.5)       | 854/854 (100.0)                | 95/296 (32.1)               | < 0.0001|
| Deceased                 | 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|
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
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) \( \text{(abbreviations are too many, which have been shown in the list of abbreviations on page 15–16).} \)

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, \textit{additional file 1: Figure S5-S7 and supplementary notes}).

\textbf{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 \textit{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 (\textit{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 \( (46.9 \ [4.95] \text{mg/L}, P < 0.0001) \), glucose \( (7.83 \ [0.2] \text{mmol/L}, P = 0.0066) \), D-dimer \( (6.08 \ [0.28] \mu g/L, P < 0.0001) \), LDH \( (461 \ [13.95] \text{U/L}, P = 0.0008) \), and BUN \( (6.51 \ [0.55] \text{mmol/L}, P < 0.0001) \), 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 these 47 indicators after the critical illness onset (CIO) have been shown in \textit{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    | 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, ×10⁹/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, ×10⁹/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, ×10⁹/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    |
| CO₂, 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    |
| Preadalbumin, 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)**

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

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; 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 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. Previous studies 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. Pneumonia area was larger in patients who died from COVID-19. Overall, the risk-factors based nomogram 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. 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. 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\textsuperscript{24–26}, there are still no special and effective treatments\textsuperscript{27,28}. Intensifying multidisciplinary treatments, such as enhanced nutritional support, anticoagulation (low molecular weight heparin [LMWH]), anti-inflammatory (\(\gamma\)-globulin, etc.), respiratory support (mechanical ventilation), and replacement therapy (continuous renal replace therapy [CRRT]) are adopted to save lives of critical COVID-19 patients\textsuperscript{1,29,30}. But the implementation of the above-mentioned intensive treatments usually started after the occurrence of critical illness. A recent study\textsuperscript{23} about COVID-19 proposed that early initiation of intravenous \(\gamma\)-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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References

1. Grasselli G, Zaninello A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81.

2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory medicine. 2020;8(5):475-81.
3. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*. 2020;382(21):2012-22.

4. N C, M Z, X D, J Q, F G, Y H, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. 2020;395(10223):507-13.

5. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA internal medicine*. 2020.

6. Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China. *Clin Infect Dis*. 2020.

7. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. *JAMA internal medicine*. 2020.

8. Yan L, Zhang H-T, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction model for COVID-19 patients. *Nature Machine Intelligence*. 2020;2(5):283-8.

9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-62.

10. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected [updated March 13, 2020. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

11. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-33.

12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-10.

13. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793-800.

14. L. B. Manual for Setting Up, Using, and Understanding Random Forest V4.0 [Available from: https://www.stat.berkeley.edu/~breiman/Using_random_forests_v4.0.pdf.

15. Kassambara A MF. Factoextra: extract and visualize the results of multivariate data analyses [1.0.7: [Available from:https://CRAN.R-project.org/package=factoextra.

16. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of statistical software*. 2015;67(1).
17. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. *Am J Respir Crit Care Med.* 2020;201(11):1380-8.

18. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study. 2020:2000524.

19. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. *Chest.* 2020.

20. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect.* 2020.

21. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol.* 2020.

22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020;368:m1091.

23. L L, L L, W C, microbes LTJE, infections. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. 2020;9(1):727-32.

24. Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet.* 2020.

25. Cao Y, Su B, Guo X, Sun W, Deng Y, Bao L, et al. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. *Cell.* 2020.

26. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. *Cell.* 2020.

27. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020.

28. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2020;395(10236):1569-78.

29. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int.* 2020.

30. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. *J Allergy Clin Immunol.* 2020.

**Figures**
Figure 1

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