Risk Factors for Mortality in Critically Ill Patients with COVID-19 in Huanggang, China: A Single-Centre Multivariate Pattern Analysis

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Research Article

**Keywords:** COVID-19, Risk factor, Machine learning, Clinical indicators, Self-evaluation

**Posted Date:** May 18th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-29429/v1

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**Version of Record:** A version of this preprint was published at Journal of Medical Virology on October 14th, 2020. See the published version at [https://doi.org/10.1002/jmv.26572](https://doi.org/10.1002/jmv.26572).
Abstract

To date, the coronavirus disease 2019 (COVID-19) has a worldwide distribution. Risk factors for mortality in critically ill patients, especially detailed self-evaluation indicators and laboratory-examination indicators, have not been well described. In this paper, a total of 192 critically ill patients (142 were discharged and 50 died in the hospital) with COVID-19 were included. Self-evaluation indicators including demographics, baseline characteristics and symptoms and detailed lab-examination indicators were extracted. Data were first compared between survivors and non-survivors. Multivariate pattern analysis (MVPA) was performed to identify possible risk factors for mortality of COVID-19 patients. MVPA achieved a relatively high classification accuracy of 93% when using both self-evaluation indicators and laboratory-examination indicators. Several self-evaluation factors related to COVID-19 were highly associated with mortality, including age, duration (time from illness onset to admission), and the Barthel index score. When the duration, age and Barthel index increased by one day, one year and one point, the mortality increased by 3.6%, 2.4% and 0.9% respectively. Laboratory-examination indicators including C-reactive protein (CRP), white blood cell (WBC) count, platelet count, fibrin degradation products (FDP), oxygenation index (OI), lymphocyte count and D-dimer were also risk factors. Among them, duration was the strongest predictor of all-cause mortality. Several self-evaluation indicators that can simply be obtained by questionnaires and without clinical examination were the risk factors of all-cause mortality in critically ill COVID-19 patients. The prediction model can be used by individuals to improve health awareness, and by clinicians to identify high-risk individuals.

Introduction

Coronavirus disease 2019 (COVID-19) has been reported in the Wuhan area of China's Hubei Province since the end of December 2019. Huanggang was the second city in China to be locked down only next to Wuhan. As of April 10, more than 1.5 million confirmed cases of COVID-19, including more than 92,000 deaths, had been reported to the World Health Organization (WHO) [1]. COVID-19 not only causes pneumonia, but can also damage other organs such as the heart, liver, kidney, blood system and immune system. Patients eventually die of multiple organ failure (MOF), shock, acute respiratory distress syndrome (ARDS), heart failure, arrhythmia, or renal failure [2-4]. With the increasing number of deaths, clinicians are most concerned about the following questions: [1] What are the differences in the clinical characteristics between surviving and non-surviving critically ill patients? [2] What are the risk factors for mortality in critically ill COVID-19 patients? [3] Is there a quick and feasible way for COVID-19 patients to perform risk self-assessments?

To date, there have been many studies on the clinical courses, outcomes, mortality of and risk factors for critically ill patients, but those studies were retrospective observational studies or cohort studies using descriptive analyses. As reported by Huang [5], older patients and those with chronic underlying conditions may have worse outcomes. Patients with severe illness may develop dyspnea and hypoxemia
within 1 week after disease onset, which may quickly progress to ARDS or MOF. Yang reported that compared with survivors, non-survivors were older, more likely to develop ARDS and more likely to receive mechanical ventilation [6]. Zhou proposed 3 clinical features of COVID-19 non-survivors: older age, higher sequential organ failure assessment (SOFA) score and high D-dimer levels [7]. Although these studies indicated the clinical courses of and risk factors for severe patients, they did not provide a quantitative ranking of the importance of risk factors, so for a given severe patient, it was impossible to predict the probability of mortality.

Multivariate pattern analysis (MVPA), based on machine learning, decodes different patterns by learning a discrimination rule from a data-set and can subsequently categorize new samples. Compared with the univariate approach, MVPA considers multiple variables together to take better advantage of the inherent multivariate nature of high-dimensional data [8], and it can identify the features that contribute the most to the classifier [9]. Among many MVPA methods, support vector machine (SVM) method is widely used for its excellent classification performance and its ability to handle very high-dimensional data.

In this paper, the SVM method is performed to establish a mortality prediction model for critically ill patients with COVID-19. The main aims were to: [1] assess the differences in the clinical characteristics between survivors and non-survivors based on systematic comparison of predictors; [2] detect the possible risk factors associated with mortality in critically ill COVID-19 patients and [3] identify risk factors that were consistently good discriminators for mortality. The identified characteristics or risk factors can help clinicians to identify high risk patients quickly and patients to do self-monitoring through risk assessment.

Methods

Study design and participants

This single-center study was performed at Dabie Mountain Regional Medical Center (Huanggang, Hubei Province), which is a designated hospital for the treatment of patients with COVID-19. We screened all adult patients who had been diagnosed with COVID-19, according to WHO interim guidance, and those who were critically ill, who died or who were discharged between January 28, 2020 (when the first patients were admitted) and March 13, 2020, were included in our study. Identification of critically ill patients was achieved by reviewing and analyzing admission logs and histories from all available electronic medical records and patient care resources.

A total of 1500 adult COVID-19 patients were discharged or died in the Dabie Mountain Regional Medical Center before March 13, 2020. After excluding 1272 patients who were not critically ill or who were still hospitalized, 6 patients who died within 24 hours after admission, and 7 inpatients without available key information in their medical records, we included the maximum number of patients who met the inclusion criteria. In total, 215 inpatients were included in the following analysis. Of them, 51 patients died during hospitalization and 164 were discharged (Figure 1 (A)). Two kinds of indicators were collected on admission: self-assessment indicators and laboratory-examination indicators. Self-assessment
indicators included information on demographics, baseline characteristics and symptoms. Laboratory-
examination indicators included results of routine tests such as routine blood indicators, etc.

Data preprocessing

Because not all patients had undergone all the laboratory-examinations, we needed to preprocess the raw
data. First, subjects for whom more than 15% of information was missing and those for whom more than
15% of variable values were missing were excluded. Accordingly, 192 patients (50 non-survivors vs 142
survivors) and 47 indicators (17 self-assessment indicators and 30 laboratory-examination indicators)
were finally included in the following analysis, see Table S1 for abbreviations of the laboratory-
examination indicators.

Imputation of the rest missing values was then conducted utilizing multivariate imputation by chained
equations (MICE) implemented in the R package “mice”. The method is based on fully conditional
specification, where each incomplete variable is imputed by a separate model [10]. The MICE algorithm
can impute mixes of continuous, binary categorical data. MICE is a robust method for imputation
compared with other methods such as mean imputation or complete case analysis which can bias
results. We imputed missing data for CRP (2.11%), PCT (2.11%), ESR (4.74%), and etc. (See Table S2).
Furthermore, the outliers were reset as the boundaries of the data. Specifically, the quantile of 1% and
99% of each continuous variable was calculated, replacing the data less than 1% quantile and more than
99% quantile, respectively.

SVM modeling

SVM is a popular classifier among many machine learning technologies because of its ability to handle
small samples with high-dimensional features. To alleviate the risk of overfitting and facilitate follow-up
characterization of contributing features, we chose linear-SVM as the classifier [11].

Our dataset contained unbalanced sample sizes (50 non-survivors vs. 142 survivors), which could cause
serious bias in our classification model if we trained the model with the unbalanced data. To overcome
this challenge, we used the random under-sampling algorithm for the majority class group (i.e., the
survival group). Specifically, for each repetition, we randomly selected the under-sampling dataset from
the survival group with the same sample size (50 subjects) as the non-survival group. We repeated the
under-sampling procedure 10 times to obtain the final result. We applied a nested 10-fold cross-validation
(CV), with the outer 10-fold CV loop estimating the generalizability of the model and the inner 10-fold CV
loop determining the optimal parameter set C for the linear-SVM model. The outer 10-fold CV served as
the primary mechanism to prevent overfitting, with the inner 10-fold CV for model selection. We applied
the R package e1071 to implement the SVM in the present study.

In the outer 10-fold CV, all subjects were randomly divided into 10 subsets according to their group labels.
Each feature was linearly scaled to zero mean and unit variance across the training dataset; and the
scaling parameters were also used for later predictions. The training and testing procedures were
repeated 10 times, with each subset used once as the testing set. For all the testing subjects for each fold, the accuracy sensitivity, specificity, precision, recall and F1 were computed to quantify the performance of the classifier.

Within each loop of the outer 10-fold CV, we applied an inner 10-fold CV to determine the optimal cost C. Specifically, the training set for each loop of the outer 10-fold CV was further partitioned into 10 subsets according to group labels. Nine subsets were selected to train the model under a given parameter set of C values \( C = [0.01, 0.1, 1, 10, 100] \) and the remaining subset was used to test the model. For each C value, accuracies were measured for each inner 10-fold CV loop, and a mean value for all the 10-fold inner loops was then obtained to indicate the inner prediction accuracy. The C with the highest inner prediction accuracy among the 5 inner 10-fold CVs was chosen as the optimal parameter. Finally, all data of the inner 10-fold CV were trained with the best parameter C, and the testing subjects of the outer 10-fold CV were predicted.

Accordingly, for each under-sampling repetition, each loop of the outer 10-fold CV resulted in a specific optimal parameter C, and a corresponding SVM model. After establishing a 10-fold outer CV, 10 SVM models were generated, and the performance of each SVM model was evaluated. The final performance measures were averaged across the 10-fold performances to produce the under-sampling performance metrics.

**Contributing indices**

A crucial aspect of linear SVM is displaying and analyzing the features that drive the multivariate classifier. Here, we calculated the feature weights \( \omega \) (i.e., the coefficient for each indicator) for each SVM model, and the sum of the feature weights of all 10 SVM models was defined as the final feature weight for each data set. Then, the feature weights were linearly scaled to \([0, 1]\). The indices with the highest weights were deemed the contributing indices for the non-survival and survival predictions. The flow diagram of the SVM analysis is shown in Figure 1 (B).

**Results**

**Statistical analysis**

We expressed descriptive data as means (stds) for continuous variables and numbers (%) for categorical variables. Of the 192 critically ill patients with COVID-19, the mean age was (mean ), and 124 were male (64.6%). The most common clinical symptoms were fever (155 patients, 80.7%), cough (134 patients, 69.8%) and chest-pain (77 patients, 40.1%). A total of 134 (69.8%) patients had at least one basic disease. Among the non-survivors, 14 (28%) patients died of respiratory failure, 3 (6%) patients died of circulatory failure, 35 (70%) patients died of MOF, and 5 (10%) patients died of other causes, such as carcinoma, and severe immunological disorders secondary to rheumatic diseases.
We assessed the differences between survivors and non-survivors using a two-sample $t$ test for continuous variables and a test of independence in a contingency table for categorical variables. The obtained test statistics and corresponding two-sided p values are listed in Table 1 and Table 2. Table 1 demonstrates the statistical analysis results of all self-evaluation indicators. Compared with survivors, non-survivors were older ($t=-4.65, p=5.73\times 10^{-6}$), had a longer time from illness onset to admission ($t=-13.2, p=1.2\times 10^{-28}$) and had a lower Barthel index score ($t=7.75, p=2.1\times 10^{-13}$). There were significant differences between survivors and non-survivors in the distribution of age ($\chi^2=33.8, p=2.5\times 10^{-6}$, Figure S1). Patients with chronic underlying conditions had worse outcomes, such as digestive disease ($\chi^2=6.93, p=0.0085$), cardiovascular disease ($\chi^2=6.66, p=0.01$), cerebrovascular disease ($\chi^2=15.3, p=8.9\times 10^{-5}$) and chronic obstructive pulmonary disease (COPD) ($\chi^2=5.6, p=0.018$) than those without underlying conditions. The non-survivors were more likely to have dyspnea ($\chi^2=7.82, p=5.1\times 10^{-4}$) than the survivors among all critically ill patients with COVID-19.

Table 2 demonstrates the statistical analysis results of all laboratory-examination indicators. As summarized in Table 2, the levels of inflammation or infection-related indices (C-reactive protein (CRP), white blood cell (WBC), Procalcitonin (PCT)) and hypercoagulability-related indicators (D-dimer, fibrin degradation products (FDP)) were significantly higher in the non-survivors than in the survivors. More prominent thrombocytopenia was found in non-survivors. Blood gas analysis and respiratory parameters revealed higher rates of hypoxia (lower PO$_2$, SO$_2$) and acidosis (lower pH values); higher CO$_2$ levels; and greater lactate accumulation (higher PCO$_2$, lat.) and respiratory impairment (lower oxygenation index (OI) values) in the non-survivors than in the survivors. The levels of albumin and calcium ions and lymphocyte counts (LYMPH) were significantly lower, and aspartate aminotransferase (AST), the international normalized ratio (INR), blood sugar and sodium ions were higher in the survivors than in the non-survivors. There were no significant differences in alanine aminotransferase (ALT), total bilirubin (TBIL), creatinine, blood urea nitrogen (BUN), or markers of hepatic or renal function between the survivors and non-survivors. There were no differences in the hemoglobin (Hb) level, erythrocyte sedimentation rate (ESR), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB) level or potassium ions between the two groups.

**Classification performance and risk factors for mortality**

To predict the prognosis of critically ill patients with COVID-19 according to indicators at admission, we constructed an SVM model with all the self-evaluation indicators and laboratory-examination indicators as input features. Over the 10 undersampling iterations, the classifiers achieved a mean test accuracy of 93% ± 2% between survivors and non-survivors from 10-fold CV, as shown in Figure 2 (A) (inner plot). Permutation testing showed that the accuracies reported by real-label samples were significantly different from those reported by random-label samples ($p=0.019$, Table S3).

Figure 2 (A) (outer plot) is the plot of all indicators sorted by weight. The greater the weight, the more likely the indicator was to be a risk factor for mortality. Duration (time from illness onset to admission)
had the highest weight of 1, which meant it was the strongest predictor of all-cause mortality. The weights (ω) of 11 indicators were greater than 0.3, including 3 self-evaluation indicators: duration (ω=1±0), the Barthel index score (ω=0.45±0.11) and age (ω=0.33±0.12). For the non-survivors, the median time from illness onset to admission was 22.5 (IQR 15-28) days, and the median age was 71 (IQR 61-78) years, the median Barthel index score was 45 (IQR 10-70). When the duration, age and the Barthel index score increased by one day, one year and one point, the mortality increased by 3.6%, 2.4% and 0.9% respectively, as shown in black dashed lines in Figure 2 (B).

Eight laboratory-examination indicators with weights greater than 0.3, including CRP (ω=0.54±0.08), WBC (ω=0.5±0.09), Ca⁺ (ω=0.40±0.07), PLT (ω=0.39±0.08), FDP (ω=0.33±0.05), OI (ω=0.33±0.12), LYMPH (ω=0.31±0.08), and D-dimer (ω=0.30±0.06), were considered to be important risk factors. The detailed weights are listed in Table S4.

**Predictive ability of self-evaluation indicators and laboratory-examination indicators**

To estimate the predictive ability of the self-evaluation indicators and laboratory-examination indicators in predicting a poor prognosis, we constructed an SVM model with the self-evaluation indicators and laboratory-examination indicators as individual input features. Over the 10 under-sampling iterations, the classifiers achieved a mean test accuracy of 87.8% ± 1.8% between survivors and non-survivors from 10-fold CV when using the self-evaluation indicators and 85.6% ± 2.5% when using the laboratory-examination indicators. Duration (ω=1±0), the Barthel index score (ω=0.57±0.14) and age (ω=0.37±0.11) were still the most important risk factors when considering the self-evaluation indicators, as shown in Figure 3 (A). WBC (ω=0.96 ± 0.08), CRP (ω=0.91 ± 0.1), LYMPH (ω=0.65 ± 0.1), Ca⁺ (ω=0.59 ± 0.15), FDP (ω=0.56 ± 0.08), D-dimer (ω= 0.56 ± 0.12), and PLT (ω=0.55 ± 0.18) were risk factors when considering the laboratory-examination indicators, as shown in Figure 3 (B).

**Discussion**

In this study, MVPA was used to identify risk factors for mortality in critically ill COVID-19 patients. A relatively high classification accuracy of 93% was achieved when using both self-evaluation indicators and laboratory-examination indicators. Self-evaluation indicators, such as time from illness onset to hospital, age and the Barthel index score were risk indicators that can simply be obtained by questionnaires and they helped preliminarily and conveniently assess disease severity, even by the patients themselves. Laboratory-examination indicators, such as CRP, WBC, Ca⁺, PLT, FDP, OI, LYMPH and D-dimer, were risk factors as well; these factors may help us stratify patients based on possible requirements for the level of care to improve outcomes and find potential targets for therapeutic interventions.

Many studies have noted that age is a risk factor [3, 12,13] for COVID-19 severity, but for the first time, our results showed that the time from symptom onset to admission and the Barthel index (BI) score were risk factors. The longer time from symptom onset to admission in the non-survivors than in the survivors
suggests that these patients tend to wait longer before admission, voluntary or involuntary, and might miss the best treatment opportunity. In Italy, nearly 10% of infected patients required intensive care management [14], which placed considerable strain on the health care system [15,16]. Some critically ill patients could not get prompt and effective treatments due to limited resources [17]. This may be one of the reasons for the high mortality (12.6%) in patients in Italy. The situation is worse in Iran because of the large epidemic scale of COVID-19, and greatly reduced access to medical care, which is partly influenced by US punitive policies [18]. All these data suggest that early and effective access to medical care is vital for improving the chance of survival, especially for high-risk or critically ill patients. The BI was 10-item ordinal scale (range: 0 to 100) which was widely used for evaluating patients’ independence in activities of daily living [19]. We found that BI was a strong predictor of mortality in critically ill patients with COVID-19 and might be applied to risk stratification, therapy optimization and patients’ self-assessment.

High PCT levels (p=1.4×10^{-5}) combined with increased WBC counts (p= 6.1×10^{-14}), which were strongly suggestive of bacterial coinfection, were observed in the non-survivors and correlated with a high mortality rate. This was consistent with our clinical observations and some reports on other viral diseases. Among critically ill patients with Middle East respiratory syndrome (MERS), 18% had bacterial coinfections [20]. As mentioned in previous studies, nearly 100% of COVID-19 patients died in ICU had sepsis [7]. The non-survivors tended to suffer from severe coinfection, partly because of the need for invasive treatments such as tracheal intubation, tracheotomy, mechanical ventilation, central venous catheterization. Though the treatment of COVID-19 with glucocorticoids is controversial [2,13, 21], it is still used to suppress cytokine storms in critically ill patients based on existing therapeutic strategies for community-acquired pneumonia, ARDS, and other viral infections [22-25]. However, these patients are at a high risk of glucocorticoid-related secondary infection. Empiric antimicrobial treatment is recommended on the basis that superinfection is reasonably common in this population, as in pandemic influenza [26-28]. However, the high rates (100%), long courses (19.2 days), and combined use (94.3%) of broad-spectrum antibiotics might lead to the emergence of drug-resistant bacteria that render combating bacterial infections increasingly difficult. Positive rate on etiological examinations was extremely low (5.6%) in our center. This might be influenced by the prior use of antibiotics before sample collection and relatively limited medical human resources at the time of opening of the medical center. How to optimize antibiotic usage in this population is still a challenge. Timely etiological testing may be essential.

The D-dimer (p=1.7×10^{-7}) and FDP (p=2.6×10^{-8}) levels in non-survivors were dramatically elevated, reflecting the hypercoagulable and hyperfibrinolytic states of blood in vivo, which have been previously reported by Zhou [7]. A recent study reported that anticoagulant therapy appears to be associated with an improved prognosis in severe COVID-19 patients with markedly elevated D-dimer levels [29]. Furthermore, we found an increased rate of obvious thrombocytopenia in non-survivors (p=0.011), which might result from consumption by the thrombus, decreased production, and accelerated destruction. Thrombocytopenia occurred in some patients with viral infections and was identified as a risk factor for mortality [30-31], but this relationship was not previously clear in COVID-19 patients. Our study is the first
to report that thrombocytopenia can be used as a risk factor for mortality in critically ill patients with COVID-19.

MOF was observed in both groups (survivor 20.1% vs non-survivor 23.5%). Respiratory failure was often the earliest and most severe form of organ dysfunction [2,6], followed by renal, cardiac and liver function impairment. The reported prevalence of MOF is highly variable (from 3 to 35%) [4,22]. We infer that acute organ failure or exacerbation of chronic dysfunction could partly result from prolonged hypoxia secondary to respiratory insufficiency. However, we did not find any statistically significant differences in indicators of renal, cardiac and liver functions (BUN, creatinine, B-type natriuretic peptide (BNP), ALT, TBIL) between the two groups or myocardial injury indicators (creatine kinase (CK)); these results were unexpected. OI, a marker of oxygenation, was significantly higher in survivors than in non-survivors. Our data showed that respiratory function, not comorbidities, was the most important determinant of prognosis in critically ill COVID-19 patients. A recent study in Italy reported that among 1591 patients, the majority were admitted to the ICU because of respiratory failure had a mortality rate of 26% at 5 weeks after the first admission; and could eventually be higher [16]. This may partially explain a significantly lower mortality in uremic patients (3.8%) than in nonuremic patients (26.4%) with COVID-19 in our study. The pathophysiological mechanisms warrant further investigation.

This study has several limitations. First, only patients classified as having severe COVID-19 were included, and all the others were excluded from the analyses. Second, this study was conducted at a single-center hospital with a limited sample size. As such, this study may have included disproportionately more patients with poor outcomes. There may also be selection bias when identifying factors that influence clinical outcomes. A large-cohort study of patients with COVID-19 pneumonia from Wuhan, China, other cities in China, and other countries would help to further define the clinical characteristics of and risk factors for the disease.

**Declarations**

**Study approval**

The Ethics Commission of Hunan Provincial People's Hospital approved this study. Registration number: ChiCTR2000030941. The Ethics Commission exempted from the need for patient consent.

**Data availability statement**

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

**Conflicts of interest**

All authors declare no competing interests.

**Author Contribution**
Drs Chen and Linli equally contributed to this work. The study was designed by Chen, Guo and Linli. Chen, Lei, Yang, Liu, Xia, Liang, Zhu collected the data, had full access to all of the data in the study and takes responsibility for the integrity of the data. Linli, Guo developed the analytical plan. Guo, Linli, and Zhao undertook the statistical analyses and took responsibility for its accuracy. Guo, Chen, and Linli wrote the first draft of the paper. All authors contributed to writing the manuscript.

Acknowledgments

Dr Guo was supported by the National Natural Science Foundation of China (NSFC) grant (No.11671129). Dr Chen was supported by the Health and Family Planning Commission of Hunan Province, China (No. B20180428), Hunan Provincial Natural Science Foundation for Outstanding Youth.

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Tables

Table 1: Demographics, baseline characteristics and symptoms of patients with critically ill COVID-19 patients.

| Demographics | Survivors (n=142) | Non-survivors (n=50) | Statistics /p value |
|--------------|-------------------|----------------------|---------------------|
| Age, years   | 56.4(17.2)       | 68.45(11.7)          | t=-4.65, p=5.73×10^{-6} |
| Sex (Female/Male) | 52/90          | 16/34                | χ²=0.34, p=0.56    |
| Duration    | 7.9(5.3)         | 21.1(7.8)            | t=-13.2, p=1.2×10^{-28} |
| Barthel Index | 80.3(27.6)     | 44(30.8)             | t=7.75, p=2.1×10^{-13} |

| Baseline characteristics | | |
|--------------------------| | |
| Digestive disease        | 5(3.5%) | 7(14%) | χ²=6.93, p=0.0085 |
| Cardiovascular disease   | 58(40.8%) | 31(62%) | χ²=6.66 p=0.01 |
| Cerebrovascular disease  | 16(11.3%) | 18(36%) | χ²=15.3, p=8.9×10^{-5} |
| COPD                     | 21(14.8%) | 15(30%) | χ²=5.6, p=0.018 |
| Chronic kidney disease   | 29(20.4%) | 7(14%) | χ²=0.98, p=0.31 |
| Diabetes                 | 29(20.4%) | 6(12%) | χ²=1.76 p=0.18 |
| Other                    | 26(18.3%) | 8(16%) | χ²=0.13, p=0.71 |

| Symptoms | |
|----------|-------------------|-------------------|
| Fever    | 113(79.6%)        | 42(84%)           | χ²=0.46, p=0.49 |
| Cough    | 96(67.6%)         | 38(76%)           | χ²=1.24, p=0.27 |
| Myalgia  | 38(26.7%)         | 9(18%)            | χ²=1.54, p=0.22 |
| Diarrhea | 6(4.2%)           | 5(10%)            | χ²=2.28, p=0.13 |
| Chest pain | 51(35.9%)   | 26(52%)           | χ²=3.98, p=0.046 |
| Dyspnea  | 22(15.5%)         | 17(34%)           | χ²=7.82, p=5.1×10^{-4} |

Note: Duration: Time from illness onset to admission; COPD: Chronic obstructive pulmonary disease.
Table 2: Differences in clinical medical records between survivors and non-survivors of critically ill COVID-19 patients.

|                                | Survivors   | Non-survivors | T statistics/p value |
|--------------------------------|-------------|---------------|----------------------|
| T statistics/p value          |             |               |                      |
| WBC (4-10×10⁹/L)              | 6.3(2.8)    | 12.2(8.09)    | t=-8, p=6.1×10⁻¹⁴    |
| Hb (120-160 g/L)               | 117.1(22.1) | 122.6(23.6)   | t=-1.54, p=0.12      |
| PLT (100-400×10⁹/L)           | 202.7(102.4)| 161.6(92)     | t=2.56, p=0.011      |
| LYMPH (0.8-4×10⁹/L)           | 1.23(0.67)  | 0.73(0.79)    | t=4.43, p=1.5×10⁻⁵   |
| Alb (35-55 g/L)                | 35.8(6.5)   | 31.7(5.4)     | t=4.07, p=1.5×10⁻⁵   |
| ALT (0-50 U/L)                 | 29.1(34.1)  | 32.3(41.5)    | t=-0.55, p=0.58      |
| AST (0-50 U/L)                 | 25.4(25.8)  | 37.2(19.9)    | t=-2.99, p=0.0031    |
| TBIL (0-20 umol/L)             | 15.9(13.2)  | 19.6(12.4)    | t=1.74, p=0.083      |
| Bun (1.7-8.2 mmol/L)           | 8.98(10.4)  | 11.2(9.2)     | t=1.37, p=0.17       |
| Crea (38-120 umol/L)           | 223.6(417.2)| 124.9(123.4)  | t=1.66, p=0.098      |
| UA (204-428 umol/L)            | 228(131.9)  | 310.3(163.9)  | t=0.99, p=0.32       |
| CRP (0-10 mg/L)                | 29.9(29.3)  | 73.4(42.3)    | t=-7.7, p=8.1×10⁻¹³ |
| PCT (0-0.1 ng/ml)              | 0.47(1.4)   | 3.4(6.7)      | t=4.5, p=1.4×10⁻³    |
| ESR (0-25 mm/h)                | 39.6(28.2)  | 48.4(26.7)    | t=1.87, p=0.06       |
| PT (8.6-12 s)                  | 12.6(10.1)  | 13.2(1.66)    | t=0.4, p=0.68        |
| INR (0.8-1.1)                  | 1.1(0.16)   | 1.2(0.16)     | t=0.3, p=3.2×10⁻⁵    |
| APTT (26-42s)                  | 31.7(8.3)   | 31.5(8.2)     | t=0.1, p=0.91        |
| D-Dimer (0-243 ng/ml)          | 605.4(2162) | 4341.8(7338)  | t=-5.5, p=1.7×10⁻⁷  |
| FDP (0-5 ug/ml)                | 4.5(12.8)   | 39.4(70.9)    | t=-5.8, p=2.6×10⁻⁸   |
| Fib (1.9-4.6 g/L)              | 3.98(1.1)   | 4.3(1.7)      | t=1.6, p=0.11        |
| PH                             | 7.4(0.08)   | 7.3(0.17)     | t=3.06, p=0.0025     |
| PCO₂ (mmHg)                    | 38.6(5.4)   | 47.1(23.9)    | t=3.96, p=0.0001     |
| PO₂ (mmHg)                     | 76.4(27.6)  | 59.9(27.3)    | t=3.55, p=0.0005     |
| SO₂ (%)                        | 93.4(8.3)   | 85.1(15.2)    | t=4.7, p=4.9×10⁻⁶   |
| Lat (0.18-3mmol/L)             | 2.7(1.3)    | 3.7(3.2)      | t=4.5, p=1.4×10⁻³    |
| K⁺ (3.8-5.4 mmol/L)            | 4.03(0.7)   | 4.2(1.4)      | t=1.37, p=0.17       |
| Na⁺ (135-148 mmol/L)           | 138.6(5.4)  | 142.2(8.7)    | t=3.38, p=0.0009     |
| Ca²⁺ (2.25-3 mmol/L)           | 2.01(0.29)  | 1.8(0.44)     | t=3.7, p=0.0003      |
| BG (3.9-11.1 mmol/L)           | 9.3(3.4)    | 10.5(4.15)    | t=1.99, p=0.05       |
| OI (400-500 mmHg)              | 327.2(134.8)| 255.8(66.8)   | t=3.63, p=0.0004     |

Note: Brackets represent the range of reference values.

Figures
Figure 1

The study flow diagram of the participants (A) and the SVM analysis (B).
Figure 2

(A) Performance of SVM results. Mean accuracy, sensitivity and specificity were shown in inner plot for all 10 repetitions. The risk factors were shown in the outer plot in order of weight. (B) Kaplan Meier plot was drawn for duration, age and Barthel index. Red dashed lines represented 95% CIs. When the duration (time from illness onset to hospital), age and the Barthel index score increased by one day, one year and
one point, the mortality increased by 3.6%, 2.4% and 0.9%, respectively, as shown in black dashed lines in (B).

Figure 3
Performance of SVM results when using self-evaluation indicators (A) and laboratory-examination indicators (B) as input features individually.

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- SupplementalMaterial.docx