

Savable but lost lives when ICU is overloaded: a model from 733 patients in epicenter Wuhan, China

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Abstract

Background. Coronavirus Disease (COVID-19) causes a sudden turn over to bad at some check-point and thus needs intervention of intensive care unit (ICU). This resulted in urgent and large needs of ICUs posed great risks to the medical system. Estimating the mortality of critical in-patients who were not admitted to the ICU (MI-mortality) will be valuable to optimize the management and assignment of ICU.

Methods. Retrospective, of the 733 in-patients diagnosed with COVID-19 at Huangpi Hospital of Traditional Chinese Medicine (Wuhan, China), as of March 18, 2020. This study aims to estimate the MI-mortality and build a model to identify the critical in-patients. Demographic, clinical and laboratory results were collected and analyzed. The mortality rate for the patients who failed to receive ICU and unfortunately died was analyzed. To this end, the key factors for prognostic of patients who may need ICU care were found. A prognostic classification model using machine learning was built to identify the patient who may need ICU.

Results. Considering the shortage of ICU beds at the beginning of disease emergence, we defined the mortality for those patients who were predicted to be in need of ICU treatment yet they did not as MI-mortality. Patients who entered the ICU and died were defined as ICU-mortality. To estimate MI-mortality, a prognostic classification model was built to identify the in-patients who may need ICU care based on the medical factors collected in-hospital. Its predictive accuracies on whole patient set (733 [25 708]), training set (586 [20 566]) and testing set (147 [5 142]) dataset were 0.8513, 0.8935 and 0.8288, with the AUC of 0.8844, 0.8941 and 0.9120, respectively. Our analysis had shown that the MI-mortality is 41% and the ICU-mortality is 32%, implying that enough bed of ICU in treating patients in critical conditions.

Conclusions. On our cohort of 733 patients, 25 in-patients were admitted to ICU, among them 8 patients died. 25 in-patients who have been predicted by our model that they should need ICU care, yet they did not enter ICU due to lack of shorting ICU wards. The MI-mortality is 41%.

Background

Coronavirus Disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the world. As of June 18th 2020, 8,434,977 have been diagnosed and 449,787 deaths have occurred, with a mortality rate of 5.3%. It is worth noting that there is no slight downward trend in mortality, yet an upward trend, posing a serious challenge to medical resources around the world [1]. This has aroused extreme attention from the World Health Organization (WHO) [2] and all national health organizations. To mitigate the spread of the virus, most countries have taken measures to isolate at home (study and work at home), whereas it has undoubtedly caused indelible losses to the economy.

The genetic characterization[3] of the SARS-CoV-2 is significantly different from SARS-CoV and MERS-CoV [4]. The most worrying aspect is that the virus of SARS-CoV-2 has super spread ability, which seems to spread by any means (respiratory droplet transmission, close contact transmission, air aerosol

transmission, etc.). The analysis, modeling and forecasting of clinical characteristics for patients diagnosed with COVID-19, are of great significance for the evaluation of new severe patients. Many scholars have done abundantly research on the clinical manifestations, epidemiological characteristics and treatment methods of infected patients [3, 5–15].

The COVID-19 costed average mortality of 5.3% worldwide. Yet the reported mortality is largely different, with as high as 27.3% in Yemen and as low as 0.1% in Singapore and Qatar (Updated on June 19) [16]. It remains unknown on such differences. The plausible explanation includes the low ratio of infected people among the whole population, high level of medical standard and ICU ward per capita. In a radical time of shorting ICU beds, a very tough decision needs be made to grant high priority for the patient with hope of survival in serious conditions. Estimate the mortality of the critical patients failed to receive ICU will further help to explain the differences in mortality rate across countries, and optimize the assignment on ICU resources.

In this study, 733 patients from Huangpi Hospital of Traditional Chinese Medicine (Wuhan, China) were collected and analyzed by benchmark machine learning methods. The patients were systematically reviewed and the disease progression was carefully quantified. The study aimed to estimate the mortality for the critical patient who should be admitted into the ICU intervention in early time yet did not due to various causes. To this end, a prognostic system was built to identify those patients who were more likely to need ICU care, thereby helping to estimate the number of ICU bed needed for early preparation.

Methods

Study Design and Participants

The retrospective cohort study consists of 733 patients diagnosed with COVID-19, the collected patients were admitted to Huangpi Hospital of Traditional Chinese Medicine (Wuhan, China) from January to March 2020 by the Guangxi Medical Team joined the battle against COVID-19. Method for laboratory confirmation of SARS-CoV-2 infection have been described elsewhere [17] [18]. Briefly, the methods of next-generation sequencing, real-time reverse-transcriptase polymerase chain reaction (RT-PCR) or Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies can be utilized to diagnose patients with COVID-19 [18]. All patients obtained the throat-swab specimens and reviewed every other day via treating.

This study had been approved by the First Affiliated Hospital of Guangxi Medical University Hospital Ethics Committee and the requirement for informed consent was waived.

Data Collection

The data were extracted from electronic medical records. For each patient, three types of factors including demographic, clinical and laboratory results were extracted. The demographic factors include the medical history and census information, such as gender, age, presence or absence of comorbidities,

time from onset to admission, time from admission to ICU care and death, main symptoms at admission. The clinical and laboratory examination includes chest radiographs or CT scans, treatment measurement, and daily routine tests minutely recorded (12 factors such as pulse, respiration rate, blood pressure, body temperature, oxygen saturation, heart rate, etc.). The symptoms present referred to the first symptoms related to the main complaint such as fever, cough, fatigue, diarrhea, etc. There are in total 909 factors are indexed for each patient, resulting in a comprehensive characterizing the disease progression. All data were handled by computer professionals and checked by two physicians (HW and JZ).

Laboratory Procedures

Routine blood examinations include complete blood count, coagulation profile, serum biochemical tests (including liver function (twelve items), renal function electrolyte (twelve items), blood lipid and blood glucose (three items), procalcitonin detection and fluorescence, glucose determination (various enzymatic methods), six sets of coagulation, five categories of complete blood count + CRP), respiratory tract infection pathogen IgM 9 items and influenza A/B virus antigen detection. Considering, 173 examination indicators extracted from the inpatients were collected.

Study Definitions

Fever was defined as axillary temperature of at least 37.3°C. The illness severity of COVID-19 was defined according to the Chinese management guide for COVID19 (version 7.0) [4]. The critical patients indicate that they should be admitted into the ICU. The criteria for inclusion in the ICU were 1) respiratory failure and requires mechanical ventilation, 2) shock, 3) combined with other organ failures. Due to the limited medical resources, it is not guaranteed that those who meet the above three conditions can be included in the ICU. The critical patients who should be admitted into ICU yet they did not due to the lack of ICU beds, herein this type of patient is named Missing ICU. All patients in the ICU meet the aforementioned three conditions or even serious. The mortality of the patients who have admitted into ICU was named by ICU-mortality. Hepatorenal insufficiency indicated liver or kidney dysfunction, such as cirrhosis, hepatic carcinoma, renal cyst, etc. CT scan for double lung infection indicates abnormal CT manifestations, such as Ground-glass Opacity, Consolidation, Reversed Halo Sign, Fibrosis, Septal Thickening, etc.

Continuous variables were quantified by six statistical measurements, including median value, mean value, maximum value, minimum value, standard deviation, and interquartile range (IQR) [10]. The six measurements are enough comprehensive for variables following normal distribution. Categorical variables were expressed as 0 or 1. All features (909) were extracted from demographic, clinical and laboratory results for modeling, analysis and forecasting. Statistics reveal that 143 factors were continuous variables (858 features) and 51 factors were categorical variables (51 features).

The patients were dichotomized into two subgroups by thresholds. Accordingly, we calculated the resulted values including true positive rate (TPR) and false positive rate (FPR) and draw its receiver operating characteristic curve (ROC). The area under the curve (AUC) was calculated to measure the

prognostic power for each factor. The value the close to 1, the better prognostic power. The top ten factors with the largest AUCs were extracted to build a prognostic classification model.

Statistical Analysis

The Mann Whitney-U test, T-test, χ^2 test, or Fisher's exact test were utilized to compare the differences between the identified two subgroups where it applies. We involved the top ten factors which have the largest AUC value. Boxplots were drawn to illustrate the statistical differences.

Estimating the MI-mortality for the patients who may survive

This study aimed to estimate the mortality for the critical patient who should be admitted into the ICU intervention in early time yet did not due to various causes. To this end, we firstly built a prognostic model for identifying the patients who were critical patients, i.e., who need ICU care. The study chart is demonstrated in Fig. 1.

The building of a prognostic model for identifying the critical in-patients who need ICU care. We involved the patients who were firstly admitted in-hospital and then received ICU care. Such patients were labeled by "ICU-care". Those in-hospital patients who were not received in ICU until discharge were labeled by "Non-ICU-care". For the two types of patients, their clinical measures collected during in-hospital were extracted. The whole samples were randomly divided into two datasets. One was used to build a classifier while the other one was used to test the prognostic performance of the classifiers. The training and testing dataset consisted of 586 [20 566] patients and 147 [5 142] patients, respectively. We considered the prognostic prediction on whether a patient needs ICU care as a supervised learning problem. We firstly involved the top ten factors which have the largest AUC when evaluated its prognostic power individually. The found ten factors were then used to build a composite classification model by the benchmark model of support vector machine (SVM) [19]. We employed balance-sampling with ensemble learning strategy [20], given that the dataset was severely class-imbalanced. We divided 566 Non-ICU-care samples into 29 groups, each of which was consisted by 20 ICU-care samples. Thus, the 29 groups of balanced training subset, was utilized to train 29 SVM classifiers. After training, 29 classifiers were obtained via the bootstrap sampling scheme. The obtained 29 classifiers were applied on the test samples and the prediction of its label was obtained by majority voting.

Estimating the MI-mortality for the patients who may survive. The COVID-19 costed average mortality of 6.9% worldwide. In a radical time of shorting ICU beds, a very tough decision needs be made to grant high priority for the solvable patient. However, it remains unknown the mortality for the patients should be treated in ICU, as predicted by the first step, yet not been admitted to ICU due to various causes. Given the high sensitivity or specificity of 1 and 0.8239 (Table 2) of the classification model in the first step in prediction whether a patient should be admitted to ICU, we reasoned that the predicted positive patients do need ICU care. Consequently, we involved the dying patients who were classified as the one should receive ICU care yet not. We defined the ratio of a number of such patients over a total number of dead people as Missing-ICU-mortality. MI-mortality measured the necessity of ICU in selecting patients in

critical conditions. It also measured the reliability of the model built in the first step. Furthermore, the mortality of the patients who have admitted into ICU was also estimated for comparing the difference of MI-mortality and ICU-mortality. This difference can not only help us to understand the difference in mortality between countries, but also help us to rationally plan ICU resources in emergencies.

Table 2

The results in prediction whether the patients who need ICU care. Each patient was characterizing by 909 clinical features. The prediction is based on all features, and the top ten features selected based on their AUC value.

	All features (909)			ROC (10)		
	Train	Test	Whole	Train	Test	Whole
Sensitivity	0.9966	0.6000	0.9200	0.8465	1.0000	0.9200
Specificity	1.0000	0.7676	0.8164	0.9417	0.8239	0.8489
Accuracy	0.9983	0.7619	0.8199	0.8935	0.8299	0.8513
AUC	0.9983	0.6838	0.8682	0.8941	0.9120	0.8844

Results

Statistics on Collected Patients

733 collected inpatients were identified as laboratory-confirmed COVID-19 in Huangpi Hospital of Traditional Chinese Medicine (Wuhan, China). 25 in-patients were admitted to ICU. Additional file 1 shows the statistics on all inpatients. The median age of the patients was 50 years (IQR 39–61; Table 1). There were 404 (55.1%) males. Less than half had comorbidities (222 [30.3%]), including diabetes (48 [6.5%]), hypertension (108 [14.7%]), hyperlipidemia (5 [0.7%]), cerebral infarction (11 [1.5%]), hepatorenal insufficiency (17 [2.3%]) and heart disease (33 [4.5%]). The most comm symptoms at onset of illness were fever, dry cough or fatigue ((595 [81.2%]), sputum production (578([78.9%]), food refusal or feeding difficulties (29 [4.0%]) and CT scan for double lung infection ((499 [68.1%]). Table 1 listed the specific statistical results of the demographic, clinical characteristics, symptoms and laboratory findings.

Table 1

Demographic, clinical, laboratory and course of inpatients. Data were median (IQR), n (%), or n/N (%). *p*-values were calculated by Mann-Whitney U test, T test, χ^2 test, or Fisher's exact test, as appropriate.

	Total (n = 733)	ICU care (n = 25)	Non-ICU care (n = 708)	<i>p</i>-value
Demographics and clinical characteristic				
Age, years	49.6(1–95)	53.1(35–69)	49.4(1–95)	< 0.0001
Sex				0.7499
Female	329(44.9%)	12(48%)	317(44.8%)	
Male	404(55.1%)	13(52%)	391(55.2%)	
Any comorbidity				
Hypertension	108(14.7%)	7(28%)	101(14.3%)	0.0569
Diabetes	48(6.5%)	4(16%)	44(6.2%)	0.0519
Cerebral infarction	11(1.5%)	0(0%)	11(1.6%)	0.5300
Hepatorenal insufficiency	17(2.3%)	2(8%)	15(2.1%)	0.0548
Heart disease	33(4.5%)	3(12%)	30(4.2%)	0.0658
Hyperlipidemia	5(0.7%)	0(0%)	5(0.7%)	0.6733
Signs and symptoms				
Fever, dry cough and fatigue	595(81.2%)	19(76.0%)	576(81.4%)	0.5008
Sputum production	578(78.9%)	19(76.0%)	559(79.0%)	0.7221
CT scan for double lung infection	499(68.1%)	18(72%)	481(68.0)	0.6685
Food refusal or feeding difficulties	29(4.0%)	1(4.0%)	28(4.0%)	0.9909
Laboratory findings				
High sensitive troponin \boxtimes				< 0.0001
> 34.2	13(1.8%)	1(4%)	12(1.7%)	
<=34.2	223(30.4%)	3(12%)	220(31.8%)	
Myoglobin				< 0.0001
> 154.9	7(1%)	1(4%)	6(0.8%)	
<=154.9	230(31.4%)	3(12%)	227(32.1%)	
D-Dimer				< 0.0001

	Total (n = 733)	ICU care (n = 25)	Non-ICU care (n = 708)	p-value
> 0.5	225(30.7%)	21(84%)	204(28.8%)	
<=0.5	486(66.3%)	4(16%)	482(68.1%)	
Lactate dehydrogenase				0.0017
> 245	107(14.6%)	12(48%)	95(13.4%)	
109–245	424(57.9%)	7(28%)	417(58.9%)	
<=109	8(1.0%)	0(0%)	8(1.1%)	
Immunoglobulin IgM				< 0.0001
> 3.44	1(0.1%)	0(0%)	1(0.1%)	
0.29–3.44	78(10.6%)	1(4%)	77(10.9%)	
<=0.29	2(0.2%)	0(0%)	2(0.3%)	
Creatine kinase isoenzyme				0.0846
> 5.2	367(50.0%)	15(60%)	352(49.7%)	
<=5.2	178(24.3%)	0(0%)	178(25.1%)	
Hypersensitive C-reactive protein				0.0007
> 5	368(50.2%)	18(72%)	350(49.4%)	
<=5	345(47.1%)	5(20%)	340(48.0%)	

As of March 2020, 717 (97.8%) of 733 patients have been discharged and 16 (2.2%) patients have died. 16 inpatients were declared dead after the rescue failed and 8 (50%) of whom were enrolled in ICU.

Can Identify the In-patients who may need ICU care

This first step aimed to identify the in-patients who could possibly be transferred to ICU to seek treatment. The top ten key factors were identified according to its predictive power measured by ROC. The factors included the mean value of high sensitivity troponin I (hs-cTnI_mean), the mean value of myoglobin (Mb_mean), the mean of D-Dimer (D-Dimer_mean), the variance of high sensitivity troponin I (hs-cTnI_var), the mean of lactate dehydrogenase (LDH_mean), the variance of myoglobin (Mb_var), the mean of Immunoglobulin M (IgM_mean), the mean of creatine kinase isoenzyme-MB (CK-MB_mean), the mean of hypersensitive C-reactive protein (hs-CRP_mean) and age, achieved a high AUC of 0.9213, 0.9067, 0.8406, 0.8286, 0.8271, 0.8106, 0.8000, 0.7916, 0.7807 and 0.7440, respectively (as shown in Fig. 2-A). Their corresponding boxplots with respect to the two types of patients were also visualized in the Additional file 2. Their p-values and the performance measurements were summarized in Table 1. LDH and hs-CRP were

indicated to be statistically different (p -value ≤ 0.001). One will observe that the mean values of hs-cTnI, Mb, D-Dimer, LDH, IgM, CK-MB and hs-CRP on ICU-care were higher than non-ICU-care. The fluctuation (variance) of hs-cTnI and Mb were larger. The age was also a significant factor. Older patients tended to need ICU care more than young patients (p -value ≤ 0.0001). Statistics illustrated that those older than 60 (more than half of the total) were easily admitted to ICU. Table 2 indicated the numerical results with accuracy and AUC of 0.8299 and 0.9120 for predicting whether inpatients will need ICU care. From the confusion matrices (refer to the Supplementary Table 1), 25 patients were judged to be admitted to the ICU care, whereas in fact they did not enter the ICU. We named such patients group as Missing-ICU. The caused reason was that the resources of ICU were limited, which did not guarantee that all critical in-patients, even satisfying criteria of ICU care, could not be admitted to the ICU.

The estimated MI-mortality is 41%

In the aforementioned step, we involved the patient who died before admitted to ICU and they were identified that patients should receive ICU by the classifier. We defined the MI-mortality to measure the ratio of number of such patient over total number of deaths. We repeated the sampling and training scheme 100 times to ensure a full coverage of the whole patients' dataset. The averaged and standard deviation of the MI-mortality were obtained with values of 0.41 and 0.30, respectively. The mean MI-mortality value of 0.41 implies that the patients who did not receive adequate ICU treatment will be forcing high mortality of 41%. The standard deviation of 0.3 demonstrates that the built classifier in first step is relatively stable. The patients recommended being admitted in ICU by the model in first step were accurate.

On the whole, of the 16 non-survivors, the MI-mortality rate is 41%. The predicted results of ROC (10) involved by the machine learning technology outperform the results using all features (909) (as shown in Fig. 2-B).

Discussion

The study aims to estimate the mortality of the critical patients failed to receive ICU by performing early prognostic using machine learning. Currently, with the epidemic continuing to spread in many countries, our strategy provides quantitative evidence and method to estimate the ICU admission and MI-mortality for maximum rescuing of patients who are hopeful to survive. It helps to explain the differences in mortality rate across countries, and optimize the assignment on ICU resources.

In the current study, our model identified the patients who should be admitted into the ICU. When inspecting the confusion matrices by the prediction (Additional file 3), the trained model identified all the patients who should have entered and have entered the ICU. It indicates the proposed model possess nice capability of identifying the patients with critical conditions. Our model also involved patients who were not treated in ICU care and died in-hospital. For such patients, we have estimated their mortalities in different trials. Our model also identified four statistically significant factors, including hs-cTnI, Mb, D-Dimer and IgM (p -values ≤ 0.0001), to serve as key prognostic factors for identifying the patients need

ICU care in early time. The temporal changes of two-group patients on these indicators were tallied, the optimal thresholds can be obtained, as shown in Fig. 3. More concretely, once the value of IgM was 0 g/L, the patients were at risk and the immune system was forced by the virus. The values of hs-cTnI (ICU-care: 17.7 pg/ml² – 37.0 pg/ml²; Non-ICU-care: 6.1 pg/ml² – 47.6 pg/ml²) and Mb (ICU-care: 0 ng/ml² – 397.7 ng/ml²; Non-ICU-care: 38.6 ng/ml² – 55.9 ng/ml²) were unstable in ICU-care group. The value of D-Dimer in the blood of the ICU-care patients (2.8 ug/ml -7.8 ug/ml) is significantly increased after infection, which indicates that the circulatory system is in a state of high coagulation, which can easily lead to pulmonary embolism. It is worth noting that the elevated D-Dimer of COVID-19 patients is related to the poor prognosis of patients.

The built prognostic model was demonstrated to be very accurate in the first step. It predicted the Missing-ICU patients according to the early warning of these key factors. Consequently, the expected MI-mortality rate was as high as 41%. In comparison, the mortality for the patients received ICU care was 32% (8/25). The current study proved in the first time that ICU care can effectively reduce the mortality caused by COVID-19 infections. For the patient need ICU care as classified by the proposed model, they should admit to the ICU in early time to reduce the survival risk.

The study has some notable limitations. First, independent cross-institutional samples for model evaluation are missing. Due to the chaos as well as other factors such as patient privacy, it is very difficult to collect such complete sample in short time. Second, the positive sample size is a tiny fraction of total sample size. The caused data imbalance yields difficulties in training a model. To relieve the problem, we used an effective and mature learning method to deal with it.

Conclusion

On our cohort of 733 patients, the mortality of patients admitted in ICU was 32%. There were 25 in-patients who have been predicted by our model that they should need to enter ICU, yet they did not enter ICU due to short of ICU beds. The MI-mortality was 41%.

Abbreviations

COVID-19

Coronavirus Disease 2019; ICU:intensive care unit; SARS-CoV-2:severe acute respiratory syndrome coronavirus 2; WHO:World Health Organization; RT-PCR:positive real-time reverse-transcriptase polymerase chain reaction; IQR:interquartile range; TPR:true positive rate; FPR:false positive rate; ROC:interquartile range; receiver operating characteristic curve; AUC:area under the curve; SVM:support vector machine; LDH:lactate dehydrogenase; hs-cTnI:high sensitivity troponin I; Mb:myoglobin; hs-CRP:hypersensitive C-reactive protein; CK-MB:creatin kinase isoenzyme-MB; IgM:Immunoglobulin M.

Declarations

Ethics approval and consent to participate:

This study was approved by the First Affiliated Hospital of Guangxi Medical University Hospital Ethics Committee, with the informed consent being waived.

Consent for publication:

Not applicable.

Availability of data and materials:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

ZZ, YL and TD contributed equally to this study and are considered as joint first authors. YO and HC conceived and designed the study. HC, YL, YH and TD developed the algorithms with the help of clinical input from XC, WQ, GT and ZZ. HW, JZ, YJ, LL, CL and DC collected, anonymized, and prepared the data from Wuhan and Guangxi, China. HC, YO, TD and YL contributed to the protocol of the study. XC, YL, LZ and WQ did the statistical analysis. TD, ZZ and HC wrote the initial draft. All authors subsequently critically edited the report. All authors read and approved the final report. HC, HW, and YO had final responsibility for the decision to submit for publication.

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Figures

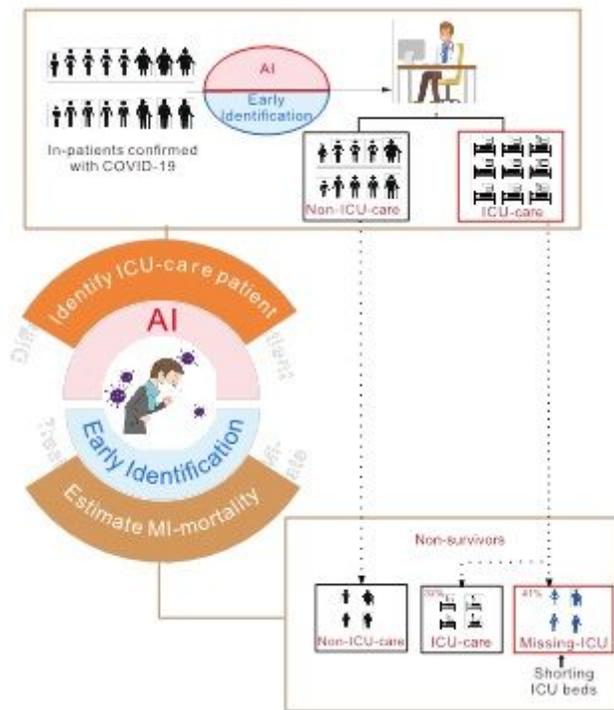


Figure 1

The work firstly identify the in-patients who need ICU care through machine learning on the patients' clinical variable. The mortality related with ICU care are categorized and analyzed.

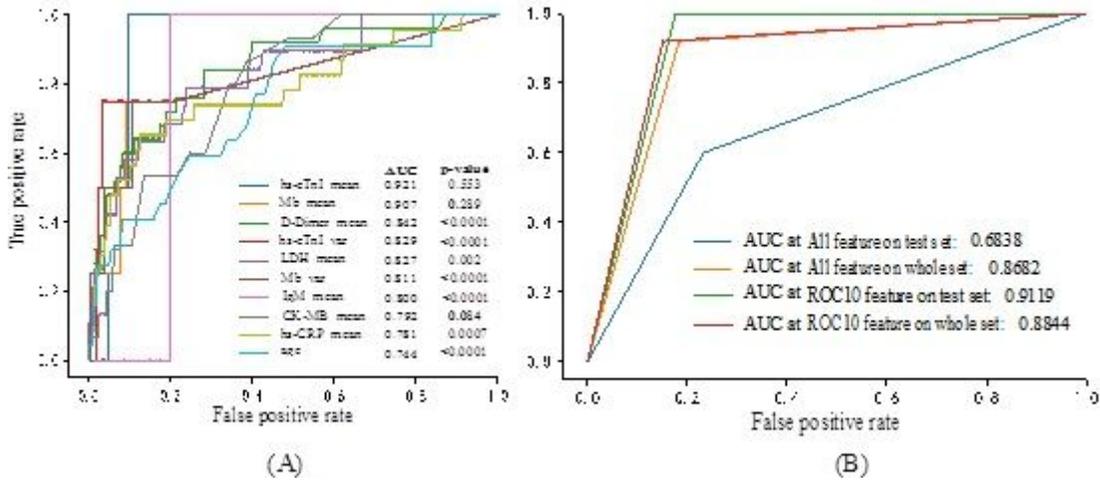


Figure 2

(A) The top ten single variable ROC curves. ‘_mean’ and ‘_var’ denote the mean and variance of factors. (B) Comparison of the experimental results of predicting the patients who need ICU care for the performances of early identification using all features (909) and ROC (10) on whole and test dataset.

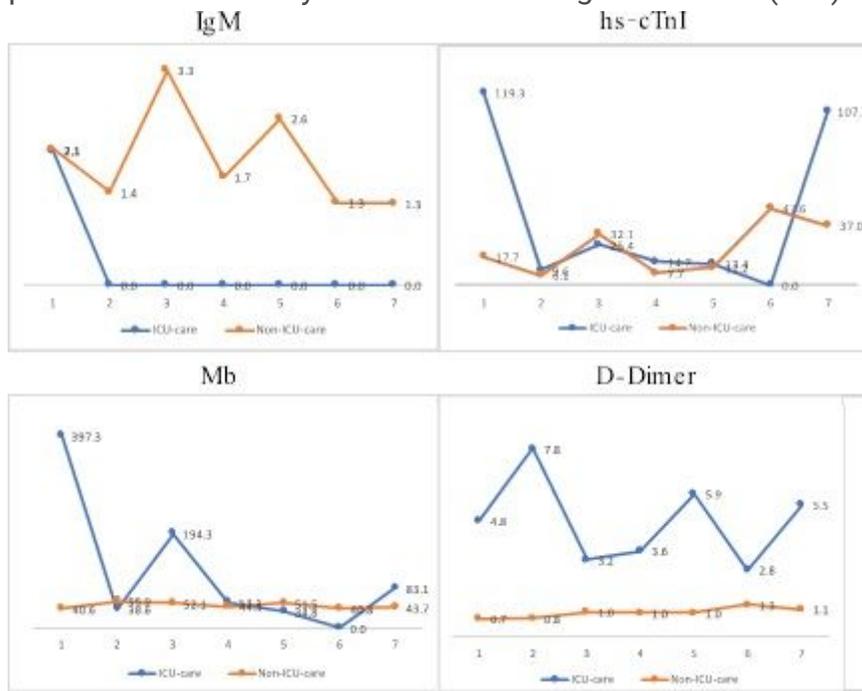


Figure 3

Temporal changes in four key factors from onset in patients hospitalized with COVID-19. In order to quantitatively count the time series of clinical courses and indicators for all patients, the results of seven tests were extracted.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S3.docx
- S2.docx
- S1.docx