Savable but Lost Lives when ICU Is Overloaded: a Model from 733 Patients in Epicenter Wuhan, China

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Abstract

Coronavirus Disease 2019 (COVID-19) causes a sudden turnover to bad at some checkpoints and thus needs the 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 into the ICU will be valuable to optimize the management and assignment of ICU. Retrospective, 733 in-patients diagnosed with COVID-19 at a local hospital (Wuhan, China), as of March 18, 2020. Demographic, clinical and laboratory results were collected and analyzed using machine learning to build a predictive model. 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 needing ICU care yet they did not as Missing-ICU (MI)-mortality. To estimate MI-mortality, a prognostic classification model was built to identify the in-patients who may need ICU care. Its predictive accuracy was 0.8288, with an AUC of 0.9119. On our cohort of 733 patients, 25 in-patients who have been predicted by our model that they should need ICU, yet they did not enter ICU due to lack of shorting ICU wards. Our analysis had shown that the MI-mortality is 41%, yet the mortality of ICU is 32%, implying that enough bed of ICU in treating patients in critical conditions.

Introduction

Coronavirus Disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the world. As of December 10th, 68, 165, 877 have been diagnosed and 1, 557, 385 deaths have occurred, with a mortality rate of 2.3%. At the peak of the outbreak, the mortality was increasing in an upward trend every day, posing a serious challenge to medical resources around the world (Chai et al. 2020). This has aroused extreme attention from the World Health Organization (WHO) (https://www.who.int/) and all national health organizations. Currently, a new round of epidemic seems to be coming quietly, to mitigate the spread of the virus, most countries have taken measures of lockdown, whereas it has undoubtedly caused indelible losses to the economy.

The genetic characterization of the SARS-CoV-2 is significantly different from SARS-CoV and MERS-CoV (Voo, Clapham, and Tam 2020). The most worrying aspect is that the virus of SARS-CoV-2 has super spreadability, 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 (Hessami et al. 2020; Onder, Rezza, and Brusaferro 2020; Suleyman et al. 2020; Tong et al. 2020; Wu, Leung, and Leung 2020; Zeng et al. 2020; Zhang et al. 2020; Zheng et al. 2020; Zhu et al. 2021).

The COVID-19 costed average mortality of 2.3% worldwide. Yet the reported mortality is largely different, with as high as 29.1% in Yemen and as low as 0.05% in Singapore (Updated on December 10th) (Dong, Du, and Gardner 2020). 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 the hope of survival in serious conditions. Estimate the mortality of the critical patients who 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 beds needed for early preparation.

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Materials and 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 has been described elsewhere (Huang et al. 2020; Zhou et al. 2020). 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 (Zhou et al. 2020). All patients obtained the throat-swab specimens and reviewed them every other day via treatment.

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 (no. 2020 (KY-E-083)).

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 + C-reactive protein), respiratory tract infection pathogen Immunoglobulin M nine items and influenza A/B virus antigen detection. Considering, 173 examination indicators extracted from the inpatients were collected.

Study Definitions

Fever was defined as an axillary temperature of at least 37.3°C. The illness severity of COVID-19 was defined according to the Chinese management guide for COVID-19 (version 7.0), (http://www.nhc.gov.cn/cms-search/downFiles/f9ea38ce2c2d4352bf61ab0feada439f.pdf) mentioned in (Dan et al. 2020). 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 been 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) (Guan et al. 2020). 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 the true positive rate (TPR) and the 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 MI-mortality for 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. To this end, the clinical data of the patients were extracted 1-15 days before they

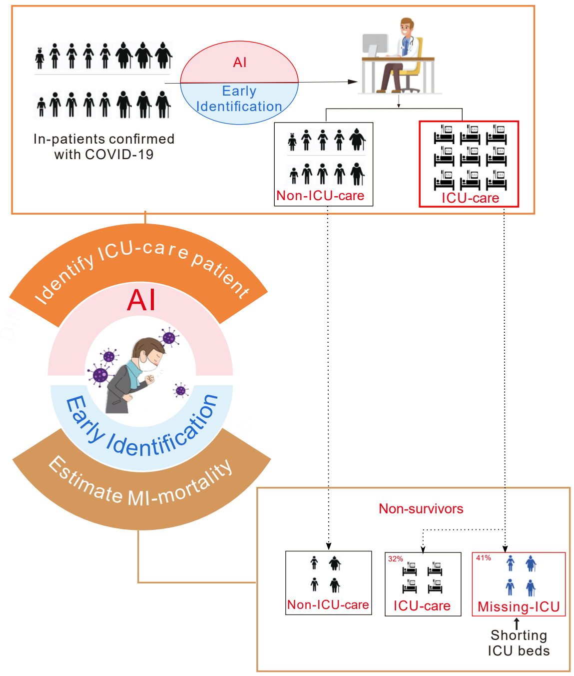


Figure 1: The work firstly identifies the in-patients who need ICU care through machine learning on the patients' clinical variables. The mortality related to ICU care is categorized and analyzed.

were actually admitted into ICU. We involved the patients who were first admitted into the hospital and then received ICU care. Such patients were labeled "ICU-care". Those in-hospital patients who were not received in ICU until discharge were labeled "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 patients (20 ICU-care and 566 Non-ICU-care) and 147 patients (5 ICU-care and 142 Non-ICU-care), 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 the support vector machine (SVM) (Cortes and Vapnik 1995). We employed the balance-sampling with ensemble learning strategy (Guo et al. 2017), given that the dataset was severely class-imbalanced. We divided 566 Non-ICU-care samples into 29 groups, each of which was consisted of 20 ICU-care samples. Thus, the 29 groups of balanced training subset, was utilized for training 29 SVM classifiers. After training, 29 classifiers were obtained via the bootstrap sampling scheme. The obtained 29 classifiers were applied to 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 2.3% worldwide. In a radical time of shorting ICU beds, a very tough decision needs are 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 predicting 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 (MI)-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 been admitted into ICU was also estimated for comparing the difference between 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.

Results

Statistics on Collected Patients

733 collected in-patients were identified as laboratory-confirmed COVID-19 in Huangpi Hospital of Traditional Chinese Medicine (Wuhan, China). 25 in-patients were admitted to ICU. Fig. 2 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.

Common abbreviations of indicators: Lactate Dehydrogenase (LDH), High sensitivity troponin I (hs-cTnI), Myoglobin (Mb), Hypersensitive C-reactive protein (hs-CRP), Creatine Kinase Isoenzyme-MB (CK-MB), Immunoglobulin M (IgM).

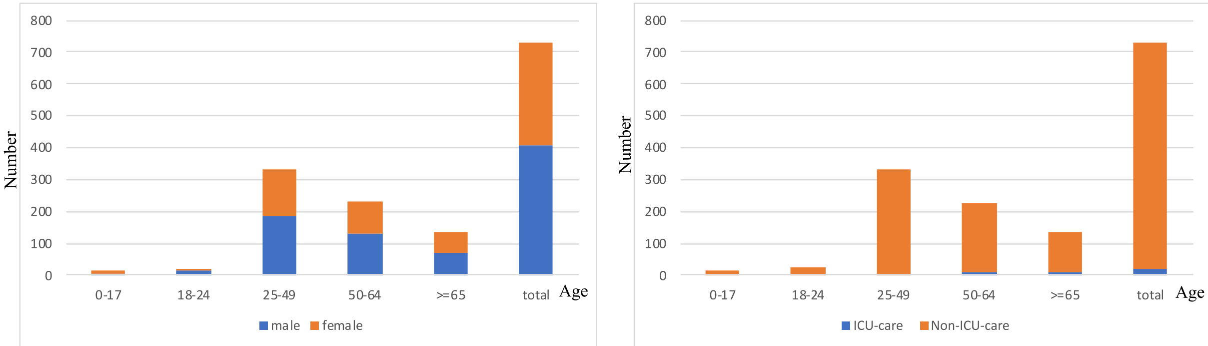
As of March 2020, 717 (97.8%) of 733 patients have been discharged and 16 (2.2%) patients have died. 16 inpatients were declared dead after the rescue failed and 8 (50%) of whom were enrolled in ICU.

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

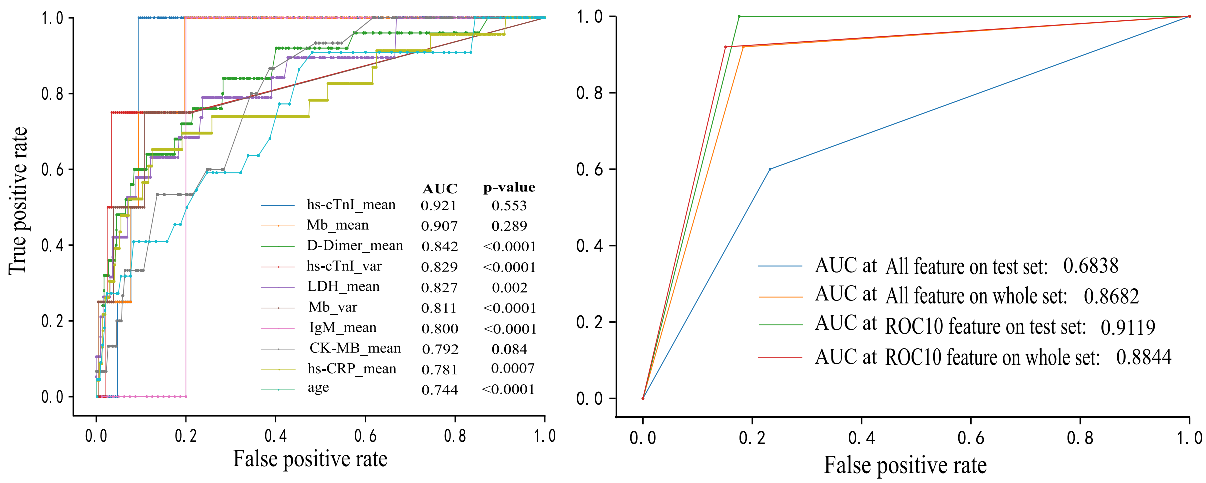
	Total (n=733)	ICU care (n=25)	Non-ICU care (n=708)	p-value
Demographics and clinical characteristic				
Age, years	49.6 (1-95)	53.1 (35-69)	49.4 (1-95)	< 0.0001
Sex				0.7499
Female	329 (44.9%)	12 (48%)	317 (44.8%)	
Male	404 (55.1%)	13 (52%)	391 (55.2%)	
Any comorbidity				
Hypertension	108 (14.7%)	7 (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 I				< 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
> 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 M				< 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-MB				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%)	

Table 1: Demographic, clinical, laboratory and course of inpatients. Data were denoted by median (IQR), n (%), or n/N (%). p-values were calculated by Mann Whitney-U test, T test, χ^2 test, or Fishers exact test, as appropriate.



(A) (B)

Figure 2: The distribution of in-patients with laboratory-confirmed COVID-19.



(A) (B)

Figure 3: (A) The top ten single variable ROC curves. '_mean' and '_var' denote the mean and variance of the measured values for 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 ROC10 (10) on the whole and test dataset.

ten key factors were identified according to their predictive power measured by ROC. The factors included the mean value of hs-cTnI (hs-cTnI_mean), the mean value of M-b (Mb_mean), the mean of D-Dimer (D-Dimer_mean), the variance of hs-cTnI (hs-cTnI_var), the mean of LDH (LD-H_mean), the variance of Mb (Mb_var), the mean of IgM (IgM_mean), the mean of CK-MB (CK_mean), the mean of hs-CRP (hs-CRP_mean) and age, achieved a high AUC of 0.9213, 0.9067, 0.8416, 0.8286, 0.8271, 0.8106, 0.8000, 0.7916, 0.7807 and 0.7440, respectively (as shown in Fig. 3-A). Their corresponding boxplots with respect to the t-wo types of patients were also visualized in Fig. 4. Their p-values and the performance measurements were summarized in Table 1. Expect for CK-MB, they were indicated to be statistically different (p-value ≤ 0.001). On 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 M-b were larger. 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 0.9119 for predicting whether inpatients will need ICU care. From the confusion matrices, shown in Table 3, 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 (MI). The caused reason was that the resources of ICU were limited, which did not guarantee that all critical in-patients, even satisfying the criteria of ICU care, could not be admitted to the ICU.

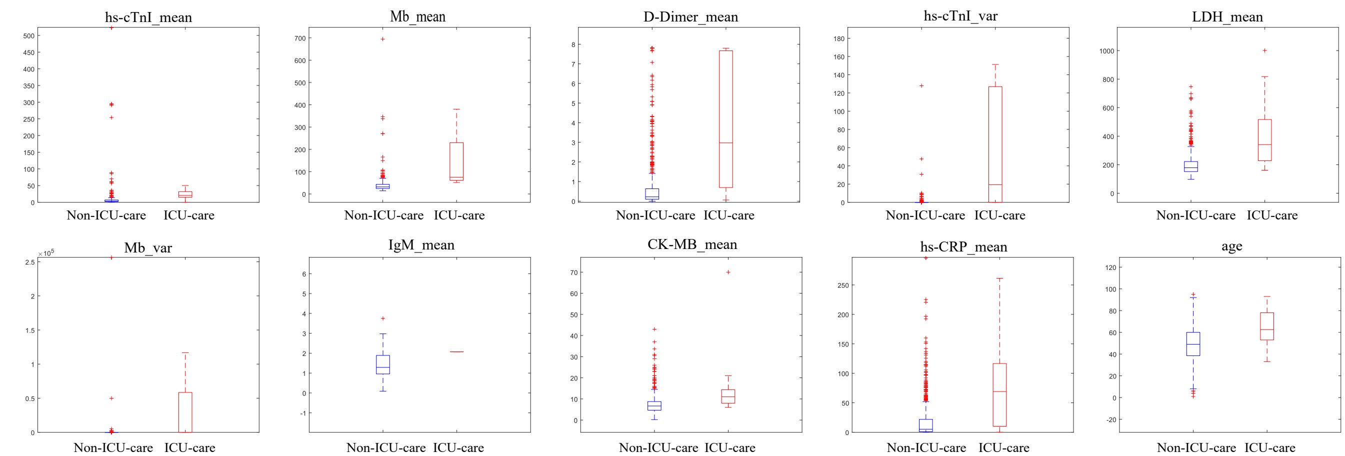


Figure 4: The boxplots of the top ten factors for predicting the patients who need ICU care.

	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	0.9119	0.8844

Table 2: The results in prediction whether the patients who need ICU care. Each patient was characterized by 909 clinical features. The prediction is based on all features, and the top ten features are selected based on their AUC values.

All feature (909)				ROC10 (10)			
Training set		Testing set		Training set		Testing set	
566	0	109	33	533	33	117	25
2	578	2	3	89	491	0	5

Table 3: Confusion matrices of predicting the patients who need ICU care.

The Estimated MI-mortality Is 41%

In the previous 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 patients over a 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 classier in the first step is relatively stable. The patients recommended being admitted in ICU by the model in the 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. 3-B).

Discussion

The study aimed to estimate the mortality of critical patients who 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 (shown in Table 3), the trained model identified all the patients who should have entered and have entered the ICU. It indicates the proposed model possesses the 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 $\leq$ 0.0001), to serve as key prognostic factors for identifying the patients who need ICU care in early time. The temporal changes of two-group patients on these indi-

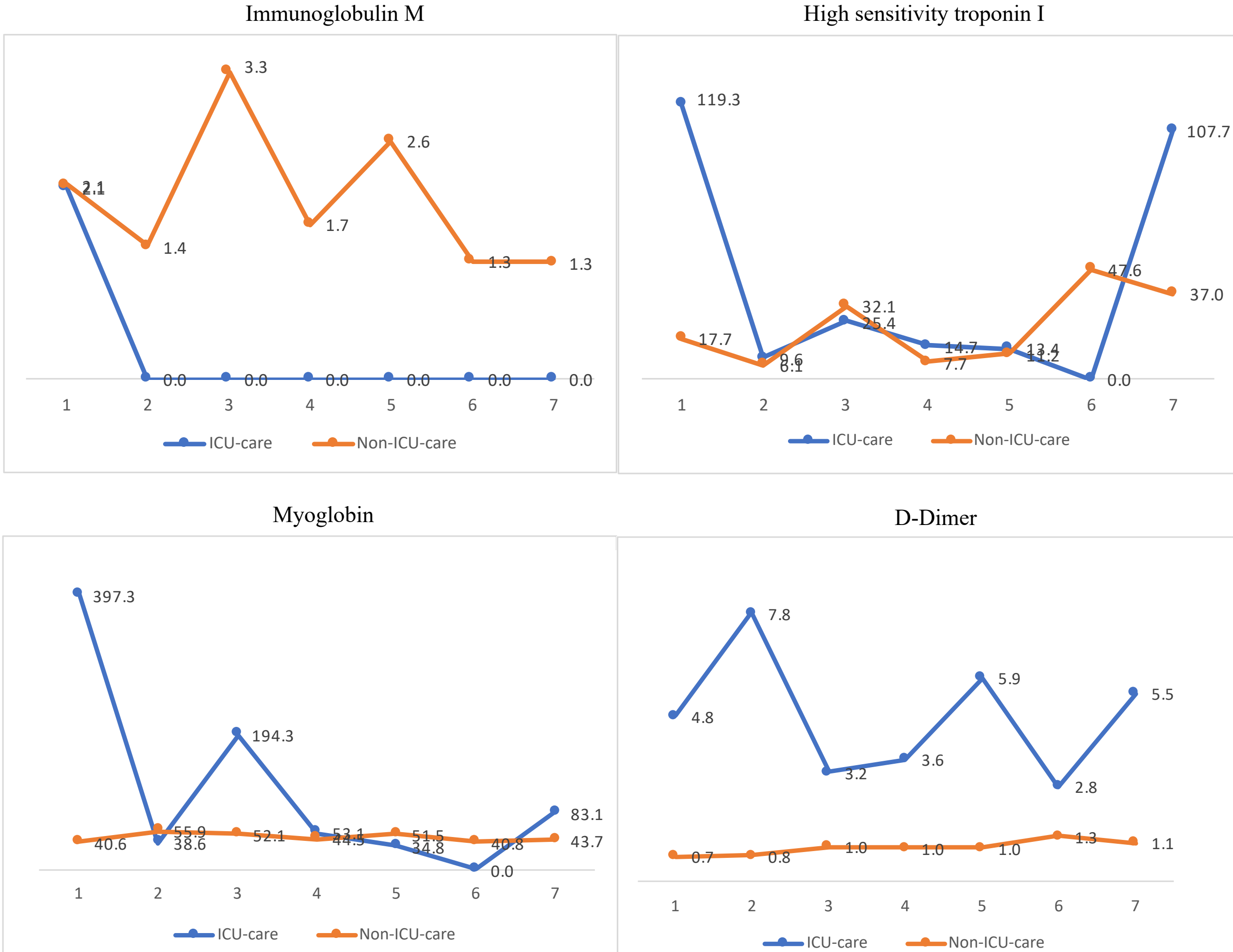


Figure 5: Temporal changes in four key factors from the onset in patients hospitalized with COVID-19. To quantitatively count the time series of clinical courses and indicators for all patients, the results of seven tests were extracted.

cators were tallied, the optimal thresholds can be obtained, as shown in Fig. 5.

The built prognostic model was demonstrated to be quite 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 who 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 a complete sample in a short time. Second, the positive sample size is a tiny fraction of the 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%. The prediction can be done by using the clinical data collected within 1-15 days before the actual ICU admission for achieving early identification.

Acknowledgments

This work was partially supported by the Key-Area Research and Development of Guangdong Province under Grant (2020B010166002, 2020B1111190001), the National Natural Science Foundation of China (61472145, 61771007), Guangdong Natural Science Foundation

(2017A030312008), and the Health & Medical Collaborative Innovation Project of Guangzhou City (201803010021, 202002020049). The authors thank the volunteers from the School of Computer Science and Engineering, South China University of Technology for manually tiding the clinical course data.

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