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Predicting ICU Length of Stay in COVID-19 patients Using a Multivariable Model Incorporating Clinical, Laboratory, and Imaging Features

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Research Article

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Abstract

Objective: To predict ICU length of stay (LOS) using a multivariable model incorporating clinical, and laboratory and imaging features in hospitalized COVID-19 patients, thereby stratifying patients and allocating resources accordingly.

Methods: In this retrospective cohort study, 139 hospitalized patients (aged between 3 to 99) with rRT-PCR confirmed COVID-19 pneumonia requiring intensive care, who had been discharged or deceased, were enrolled. Demographic, clinical, and laboratory findings of eligible patients were all extracted from electronic medical records and, if needed, through phone calls. Semi-quantitative CT severity score (CTSS) was calculated and assigned to each encoded patient independently and blindly. We used cox regression model to investigate the prognostic role of semi-quantitative CTSS, clinical and laboratory features to anticipate ICU-LOS.

Results: 139 patients with rRT-PCR confirmed COVID-19 pneumonia (including 60 females and 79 males) with a mean age of 58.52 ± 20.58 (ranging from 3 to 99) were included. CTSS was not predictive of ICU-LOS. Additionally, CTSS of more than 11 was predictor of mortality (sensitivity, 60.3%; specificity, 58%; AUC, 0.605; 95% confidence interval, 0.508-0.702; P-value, 0.034), and CTSS of above 10 was predictor of oxygen therapy dependency (sensitivity, 70.2%; specificity, 68%; AUC, 699 / 0; 95% confidence interval, 0.580-0.818; P-value, 0.002). CTSS was not significantly associated with respiratory rate and on-admission dyspnea, while it was inversely related to air-room SpO2 on the first day of admission (P <0.0001, r = -0.341).

Conclusion: CTSS is capable of anticipating mortality rate and the chance of undergoing supportive oxygen therapy during ICU hospitalization, while it does not predict ICU-LOS, rate of mechanical ventilation, or corticosteroid therapy.

Keywords: COVID-19, SARS-CoV-2, Intensive Care Units (ICU), CT severity score (CTSS)

Introduction

In mid-December 2019, several cases of pneumonia with unidentified cause were reported in Wuhan City, Hubei Province, China [1]. Afterward, it was attributed to a new strain of coronavirus, which leads to an acute respiratory infectious disease [2]. On February 12th 2020, The International Committee on Virus Taxonomy declared that severe acute respiratory syndrome coronavirus 2 is the approved classification of the new coronavirus (SARS-CoV-2) [3]. On the same date, the World Health Organization (WHO) announced Corona Virus Disease 2019 (COVID-19)as the official name of the disease caused by SARS-CoV-2 [4]. On March 11th 2020, WHO declared a SARS-CoV-2 pandemic[5]. New strains of the virus spreading across the planet at a surprising pace still heralds COVID-19 as a serious challenge to international health. The spectrum of clinical symptoms varies widely from asymptomatic infection or mild

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upper respiratory tract symptoms to a critical viral pneumonia leading to respiratory failure, multiorgan failure, and death [1, 6-10]. According to previous studies, The median time between the symptoms onset and the progression of pneumonia is about 5 days [7, 9], and the median time from symptoms onset to extreme hypoxemia and ICU admission is about 7-12 days [1, 9, 11-13]. Although COVID-19 infection might be associated with serious organ(s) failure, most patients show moderately severe symptoms and a good prognosis [8, 14].

The gold standard for diagnosing COVID-19 infection is widely known to be the real-time reverse transcriptase polymerase chain reaction (rRT-PCR); although chest computed tomography (CT) has been confirmed to be diagnostic in cases of false-negative RT-PCR result. Not only is CT a dependable screening modality, but it also is of a great assistance in tracking the course of illness and assessing treatment strategy effectiveness [15]. Given its high sensitivity, availability, and quickness, computed tomography (CT) has been granted a key role in patient stratification in both China and Europe [16]. Basically, CT Scan findings of COVID-19 patients include ground-glass opacities and consolidation [17, 18].

Up to date, CTSS has been a major prognostic indicator in patients admitted to ICU [19] . Successful treatment of critically ill patients is substantially essential to minimize death and poor clinical outcomes (5). Accordingly, determining factors related to disease severity and clinical outcome is very crucial. Herewith, we aim to explore the prognostic value of CTSS, clinical and laboratory characteristics of COVID-19 infected patients, individually and in concert, to predict ICU-LOS.

Methods

Study population

This is a retrospective cohort study of 139 patients aged between 3 and 99 years with rRT-PCR confirmed COVID-19 pneumonia, ICU hospitalized in our affiliated tertiary teaching care. The local institutional review board approved this retrospective study, and the need for obtaining patient informed consent was waived. According to the data extracted from the hospital registry system, patients were admitted from 20 February 2021 to 20 June 2021. To run rRT-PCR on patients, samples were collected either through oropharyngeal or nasopharyngeal swabs. Only patients who underwent chest CT scan within the first day of admission were included in this study.

Procedures

Clinical and laboratory data were extracted and enlisted independently and blindly. Two radiologists with 6 and 8 years of experience in thoracic imaging analyzed and reported CT images of encoded patients unaware of clinical and laboratory data of corresponding participants. All chest CT scans were obtained using a 16-row multidetector scanner (Toshiba, Canonn, Alexia, Japan) with the following parameters:100-120 kVp, 100 mA, sharp kernel, reconstruction matrix of 512×512, and slice thickness of 1.0mm to 3.0mm in axial section.

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (version 20.0, IBM). Categorical variables were described as frequency rates and percentages, and quantitative variables were presented as mean (SD) or median (interquartile range, IQR) values. Quantitative variables were tested for normality using Shapiro-Wilk tests. Kaplan-Meier analysis with Log-Rank test was used to evaluate the factors effective on the duration of ICU admission. To model variables predicting ICU hospitalization duration (demographic data, comorbidities including DM, HTN, cancer, kidney disease, liver disease, heart disease, laboratory data, clinical findings and chest CT features), cox regression was implemented. The relation of comorbidities, demographic,

Table 1. demographic, clinical, laboratory and imaging data, comorbidities and outcome of participants.

Frequency/distribution		Variable		
58.52 ± 20.58		**Age (year)**		
60 (43.2%)		Female	**Gender**	**Demographic data**
79 (56.8%)		Male		
61 (44.8%)		**HTN**		
48 (35.8%)		**Heart disease**		
45 (33.6%)		**DM**		
38 (27.3%)	28 (73.7%)	Acute[1]	**Kidney disease**	**Comorbidities**
	10 (26.3%)	Chronic		
8 (5.8%)	8 (5.8%)	Acute[1]	**Liver disease**	
	0	Chronic		
7 (5.4%)	4 (57.1%)	Hematopoietic tissues	**Cancer**	
	2 (14.3%)	Gastrointestinal		
	1 (14.3%)	Brain		
3 (50%)		Chemotherapy		
0		Radiotherapy		
41 (32%)		0	**# of comorbidities[#]**	
40 (31.2%)		1		
24 (18.8%)		2		
17 (13.3%)		3		
6 (4.7%)		4		
88.75 ± 9.34				**SpO_2 (%)**
62 (42.6%) 12.09 ± 4.77		Early stage (0-4 days)		**CTSS**
41 (32.8%) 13.26 ± 4.42		Progressive stage (5-8 days)		
10 (8%) 11.90 ± 5.70		Peak stage day (9-13 days)		
12 (9.6%) 11.75 ± 5.17		Absorption stage (≥14 days)		
	58 (41.7%)	Expiration		**Outcomes**
	64 (40%)	Intubation		
	114 (82%)	O2 therapy		
	52 (37.4%)	GC prescription		
	6 (2, 10)[**]	ICU-LOS (day)		

Data distribution are presented as mean ± SD, median (Q1-Q3), or frequency (percent)

[*] in last 6 months

[#] including: DM, HTN, cancer, kidney disease, liver disease, heart disease

[**]Calculated using Kaplan-Meier analysis

CKD, chronic kidney disease; CTSS, CT severity score; DM, diabetes mellitus; GC, glucocorticoid; HTN, hypertension; ICU-LOS, intensive care unit length of stay.

clinical and laboratory data, and CTSS with patient's prognosis were evaluated by Mann-Whitney U and Chi-square tests. The relation of demographic, clinical, and laboratory data with semi-quantitative CTSS and pleural effusion was evaluated by Mann-Whitney U, Chi-square, and Spearman's rank correlation tests. Variables with p-values < 0.25 were incorporated into the model, while the significance level was considered at p-values < 0.05.

Results

The median age of participants enrolled in this investigation was 58.52±20.58 (IQR,3-99 years), 79 of those (56.8%) were male. The average time interval between symptoms onset and hospitalization was 5.28±4.44 days (ranging between 0-20 days). Ninety-five patients (68.84%) had dyspnea on admission. eighty-seven patients (62.58%) had one or more comorbidities. Hypertension was the most common comorbidity (n=61, 44.85%), followed by cardiovascular disorders (n=48, 35.82%) and diabetes mellitus (n=45, 33.58%). Fifty-eight patients (41.72%) had pleural effusion, and 41 patients (32.8%) had CTSS of more than 11. Fifty-eight patients (41.72%) died eventually, 47 of which (81.03%) deceased during ICU stay, while others died after being transferred to general wards. In general, 114 patients (82.01%) required oxygen therapy (through nasal cannula or simple mask) during hospitalization and 64 patients (46.04%) underwent mechanical ventilation. Corticostreoids were given to 52 patients (37.41%) (for average period of 10.13±8.17 days). Table 1 shows Descriptive characteristics of patients in terms of demographic, clinical, laboratory and imaging data, comorbidities and clinical outcome in hospitalization coarse.

Table 2 shows relation of demographic features, clinical, and laboratory data with ICU-LOS. ICU LOS was significantly longer in patients older than 60 (7 vs.5 days in younger patients). No meaningful gender difference was observed comparing ICU-LOS in males and females. Hypertension, Chronic Kidney Disease (CKD), diabetes mellitus, on-admission SpO_2 of 93% or lower were associated with longer ICU-LOS; whereas cardiovascular disorders (other than hypertension), on-admission dyspnea or respiratory rates of >30 were not associated with a significantly longer ICU-LOS. Lymphopenia, elevated ESR and CRP levels and 3-fold elevated liver enzymes, was associated with an extended ICU stay; unlike being under glucocorticoids therapy, which didn't significantly affect ICU-LOS.

To design a model predicting ICU LOS, Cox regression analysis was implemented. This analysis revealed that age predicts a longer ICU stay (p value= 0.018), while CTSS and pleural effusion are not strong predictors of duration of ICU stay (Table 3).

According to our results, age and CKD predict a higher mortality rate in ICU admitted COVID-19 patients, i.e. advanced age by one year increases the probability of death by 1.059 times. CKD patients infected with COVID-19 and hospitalized in ICU, have 11.609- fold increased risk of death compared to non-CKD patients with same situation. Meanwhile, advanced age and CKD are not predictors of mechanical ventilation and corticosteroid therapy.

On-admission laboratory indices including wight blood cell (WBC) count, erythrocyte sedimentation rate (ESR), creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), random blood sugar (BS), Troponin, blood urea nitrogen (BUN), and creatinine were not significant predictors of mechanical ventilation, supplemental oxygen therapy or corticosteroid therapy. C-reactive protein (CRP) predicted the need for supplemental oxygen and corticosteroid therapy, however, was not predictive of mortality rate or the need for mechanical ventilation. CTSS was directly correlated with ESR, CRP, LDH, AST, and neutrophil to lymphocyte ratio (NLR); while inversely correlated with SpO2. Furthermore, pleural effusion was positively associated with increased creatinine, BUN, WBC and Neutrophil count, while inversely correlated with ESR.

Table 2. association between demographic, clinical, and laboratory features with ICU-LOS.

Variable	Risk factor		ICU-LOS (median)	CI 95%	Log Rank (Chi square)	P-value
Demographic data	Age	60≥	5 (1, 8)	3.695 - 6.305	11.550	0.001
		60<	7 (3, 23)	4.006 - 9.994		
	Gender	Female	8 (3, 11)	5.342 -10.658	2.830	0.093
		Male	5 (2, 9)	3.667 - 6.333		
Comorbidities	DM	Yes	8 (4, 10)	6.334 - 9.666	4.090	0.043
		No	5 (2, 10)	3.663 - 6.337		
	HTN	Yes	8 (2, 14)	6.232 - 9.768	5.383	0.020
		No	5 (2, 9)	3.415 - 6.585		
	CKD	Yes	*	*	6.712	0.010
		No	6 (2, 9)	4.781 - 7.219		
	Heart disease	Yes	7 (2, 14)	4.507 - 9.493	2.182	0.140
		No	6 (2, 9)	4.533 - 7.467		
	# of comorbidities	2>	5 (2, 9)	3.865 - 6.135	5.544	0.019
		2≤	8 (3, 23)	6.481 - 9.519		
SPO2		94≤	4 (1, 8)	2.434 - 5.566	7.683	0.006
		94>	7 (4, 12)	5.066 - 8.934		
		1<	4 (1,9)	2.281 - 5.719		
Laboratory	ESR	22≥	5 (2, 9)	2.715 - 7.285	4.246	0.039
		22<	7 (4, 13)	4.351 - 9.649		
	LDH	550>	5 (1, 9)	2.462 - 7.538	2.109	0.146
		550≤	6 (3, 10)	4.263 - 7.737		
	Troponin	19≥	7 (3, 10)	5.574 - 8.426	0.674	0.412
		19<	4 (2,9)	1.865-6.135		
CTSS		11≥	6 (2, 10)	3.551 - 7.449	1.135	0.287
		11<	6 (5, 12)	1.954 - 10.046		
GC prescription		Yes	8 (4, 12)	5.359 - 10.641	2.483	0.115
		No	5 (2, 10)	2.734 - 7.266		

CKD, chronic kidney disease; CTSS, CT severity score; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HTN, hypertension; LDH, lactate dehydrogenase.

Table 3. Covariates incorporated in model designed for prediction of ICU-LOS.

Variable	Risk factor	Univariate OR	95% CI	P-value	Multivariate OR	95% CI	P-value
Demographic data	Age	0.981	0.971 - 0.992	0.000	0.972	0.949 - 0.995	0.018
	Gender	0.710	0.465 - 1.084	0.112	0.854	0.383 - 1.901	0.699
Comorbidities	DM	0.641	0.406 - 1.013	0.057	0.639	0.167 - 2.453	0.514
	HTN	0.619	0.403 - 0.952	0.029	0.893	0.134 - 5.940	0.906
	CKD	0.300	0.109 - 0.826	0.020	0.733	0.152 - 3.537	0.699
	Heart disease	0.728	0.466 - 1.137	0.162	2.258	0.582 - 8.765	0.239
	# of comorbidities	0.802	0.670 - 0.960	0.016	1.222	0.361 - 4.139	0.747
	SpO_2	1.024	0.990 - 1.061	0.171	0.995	0.936 - 1.057	0.868
	ESR	0.991	0.982 - 0.999	0.022	0.998	0.984 - 1.013	0.807
	LDH	1.000	0.999 - 1.000	0.227	1.000	0.999 - 1.001	0.406
	Troponin	1.000	1.000 - 1.000	0.000	1.000	1.000 - 1.000	0.105
CTSS		0.969	0.927 - 1.013	0.167	1.002	0.905 - 1.109	0.973

CKD, chronic kidney disease; CTSS, CT severity score; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HTN, hypertension; LDH, lactate dehydrogenase.

Discussion

COVID -19 is a newly emerged pandemic disease threatening global health [20]. Management of ICU-admitted COVID-19 patients is of a great importance regarding all human and technical resources shortages which raise the need for resource allocation [21].The aim of our study was to use the Semi-Quantitative CTSS

to predict length of ICU hospitalization in patients with COVID-19, individually and in concert with laboratory findings and clinical data.

A study on 380 COVID-19 patients revealed that CTSS of greater than 12 is predictor of higher mortality rate in patients (sensivity :75.82%,specificity:75.78%) [22]. Likewise, Francon et al. showed that CTSS of 18 and higher is significantly associated with higher mortality rate [23]. Mahdjoub et al. demonstrated that CTSS of 13 and higher is associated with poor overall 5-day outcomes regarding the need for intubation or death (sensitivity:80%-specificity:85.2%) [24]. The results of our study revealed that in ICU-admitted COVID-19 patients, CTSS >11 within the first day of admission is an independent predictor of higher mortality rate (sensitivity:60.3%-specificity:58%), while it does not predict the ICU-LOS. Likewise, CTSS >10 independently predicts the need for oxygen therapy during hospitalization with the sensitivity of 70.2% and specificity of 68%. This study demonstrated that CTSS is unable to predict the need for endotracheal intubation and corticosteroid therapy during hospitalization. This controversy over CTSS capability of predicting mortality rate can be related to higher chance of death for causes other than merely pulmonary involvement (e.g. thromboembolic events and multi-organ failure) in patients enrolled in our investigation, given that we only studied ICU-admitted patients.

Our study found a longer ICU stay and a higher mortality rate in elderly patients, as advanced age was most important factor to predict ICU-LOS and mortality. These findings were in keeping with results from previous studies [19, 23, 26, 28]. We did not find a meaningful association between advanced age and the need for respiratory supportive care or glucocorticoid therapy, but some other studies reported that old age patients more commonly undergo mechanical ventilation [26].

We found that female gender need Glucocorticoid (GC) therapy more frequent than male gender, as Ma et al. study [29]. According to our study, need for respiratory supportive therapy, ICU-LOS, and mortality were gender independent.

In current study, HTN was not predictive of the need for mechanical ventilation, GC or respiratory supportive therapy, ICU-LOS, or mortality. Likewise, Zhang et al. study on critically ill COVID-19 patients reported no significant association between HTN and mortality rate [19].

However, some other researches showed opposite results as they reported that HTN patients have a higher chance of mortality and developing in-hospital complications [26, 30].

There is some controversy on association between heart disease and poor out-come or mortality in COVID-19 patients; as in our study we did not appreciate any significant relationship between heart disease and need for GC/respiratory supportive therapy or mortality, and heart disease was not predictive of ICU-LOS, that is in line with some previous researches (28). In contrary, some studies have suggested a significant relationship between heart disease and poor final outcome/mortality [26, 31].

Diabetic patients had a higher mortality rate (although not significant); but DM could not predict ICU-LOS and the need for supportive respiratory care. Same results were documented in previous studies [26, 28, 30, 32]. Colombi et al. reported no significant association between DM and mortality or ICU-LOS. We found a significant association between CKD and higher ICU-LOS/ mortality as Xu et al. study [26]; however, unlike our study they found a higher rate of mechanical ventilation in CKD patients.

Our study showed that on-admission SpO_2 of less than 88% independently predicts a higher rate of mortality and higher chance of undergoing mechanical ventilation, which is in line with previous studies [27, 33]. Respiratory rate and dyspnea on admission were not significant predictors of ICU-LOS or need for O2/GC therapy or in-hospital mortality, unlike Carlino et al. study, where they reported a significant association between tachypnea and dismal prognosis and mortality [33].

According to our data, Troponin was an independent predictor of ICUC-LOS, and CRP level was an independent predictor of the need for supplemental O_2 therapy and GC therapy. No other association was demonstrated between laboratory findings and ICU-LOS, GC or respiratory supportive therapy, and final outcomes.

Interestingly, patients with pleural effusion had higher levels of WBC, neutrophil count, BUN and creatinine, and more frequently presented with tachypnea on admission. On the other hand, higher ESR, CRP, LDH and AST levels and higher NLR were predictive of higher CTSS. Presence and severity of pleural effusion was not meaningfully related to need for GC or respiratory supportive therapy, ICU-LOS, and mortality. Same findings were reported in literature [25, 26]. Davarpanah et al. reported a higher rate of ICU admission among patients with pleural effusion in imaging [27].

This study was subjected to some limitations. First, considering its retrospective design, missing data and lack of homogeneity could serve as sources of bias; although through phone calls we collected as many missing data as we could. Second, length of general ward stay was not taken into consideration, as the main focus of this study was on IC-LOS. Third, ICU admitted patients may develop with variety of complication (e.g. multiorgan failure and thromboembolic events) which potentially can lead to death; thus, specifying final outcome in more detail may reveal new associations. Finally, these findings are limitedly applicable to ICU-admitted COVID-19 patients, and for investigating predicting factors which anticipate hospital LOS, one should study patients admitted to general wards as well.

Conclusion

We founded that Semi-quantitative CTSS of higher than 11 within the first day of admission is an independent predictor of mortality, while it doesn't predict ICU-LOS. Additionally, CTSS of higher than 10 predicts the need for oxygen therapy independently. Moreover, CTSS doesn't predict the need for mechanical ventilation or GC therapy during hospitalization and is not significantly correlated with on-admission dyspnea or patient respiratory rate, whereas it is inversely correlated with on-admission SpO_2.

Declaration of Competitive Interest

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