ORIGINAL ARTICLE



Risk factors associated with intensive care unit (ICU) admission and in-hospital death among adults hospitalized with COVID-19: a two-center retrospective observational study in tertiary care hospitals

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Received: 20 November 2020 / Accepted: 19 January 2021 / Published online: 3 February 2021 © American Society of Emergency Radiology 2021, corrected publication 2021

Abstract

Background The COVID-19 pandemic is straining the health care systems worldwide. Therefore, health systems should make strategic shifts to ensure that limited resources provide the highest benefit for COVID-19 patients.

Objective This study aimed to describe the risk factors associated with poor in-hospital outcomes to help clinicians make better patient care decisions.

Material and methods This retrospective observational study enrolled 176 laboratory-confirmed COVID-19 patients. Demographic characteristics, clinical data, lymphocyte count, CT imaging findings on admission, and clinical outcomes were collected and compared. Two radiologists evaluated the distribution and CT features of the lesions and also scored the extent of lung involvement. The receiver operating characteristic (ROC) curve was used to determine the optimum cutoff point for possible effective variables on patients' outcomes. Multivariable logistic regression models were used to determine the risk factors associated with ICU admission and in-hospital death.

Result Thirty-eight (21.5%) patients were either died or admitted to ICU from a total of 176 enrolled ones. The mean age of the patients was 57.5 ± 16.1 years (males: 61%). The best cutoff point for predicting poor outcomes based on age, CT score, and O_2 saturation was 60 years (sensitivity: 71%, specificity: 62%), 10.5 (sensitivity: 73%, specificity: 58%), and 90.5% (sensitivity: 73%, specificity: 59%), respectively. CT score cutoff point was rounded to 11 since this score contains only integer numbers. Multivariable-adjusted regression models revealed that ages of \geq 60 years, CT score of \geq 11, and O_2 saturation of \leq 90.5% were associated with higher worse outcomes among study population (odds ratio (OR): 3.62, 95%CI: 1.35–9.67, P = 0.019; OR: 4.38, 95%CI: 1.69–11.35, P = 0.002; and OR: 2.78, 95%CI: 1.03–7.47, P = 0.042, respectively).

Conclusion The findings indicate that older age, higher CT score, and lower O₂ saturation could be categorized as predictors of poor outcome among COVID-19-infected patients. Other studies are required to prove these associations.

Keywords COVID-19 · Coronavirus · Risk factor · Poor outcome

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Introduction

COVID-19 is a novel coronavirus that was first reported in January 2020 as the causative organism of clusters of pneumonia in Wuhan, China, and quickly spread throughout the world [1]. According to the virus's high infectivity, the World Health Organization (WHO) announced its pandemic on March 11, 2020. The clinical spectrum of COVID-19 seems to be broad, including asymptomatic infection, mild upper respiratory tract illness, severe pneumonia, acute respiratory distress syndrome (ARDS), and even death [2].



The standard of reference for COVID-19 diagnosis is realtime polymerase chain reaction (RT-PCR), which can detect a viral nucleic acid. A person with a positive RT-PCR result regardless of clinical signs and symptoms is considered a confirmed case [3].

There is no definite consensus on the use of chest imaging for the management of suspected COVID-19 pneumonia. CXR is not sensitive to COVID-19 infection in the early disease course with mild symptoms [4].

Based on RSNA (Radiologic Society of North America) and STR (Society of Thoracic Radiology) consensus statement, a chest CT scan should not be performed for routine screening of suspected COVID-19 pneumonia; it should be reserved for hospitalized, symptomatic patients [5]. However, several studies have been performed on the relationship of parenchymal involvement in CT scan and the severity of clinical symptoms and patient outcome [6].

Nowadays, due to the limited number of ICU beds and ventilators and the increasing number of patients with COVID-19 infection, an important challenge for healthcare systems is to determine the prognostic factors that significantly influence the clinical outcome of the patients.

Some studies are indicating old age, the presence of comorbidities, higher serum levels of D-dimer, lactate dehydrogenase (LDH), and C-reactive protein (CRP) as predictors of severity and prognosis of COVID-19 [7, 8].

This study analyzed the demographic characteristics, clinical data, lymphocyte count, and imaging findings of admitted COVID-19 patients to describe these patients' clinical characteristics and outcomes.

Materials and methods

Patients

In this study, we retrospectively reviewed the patients hospitalized at two tertiary care hospitals (Al-Zahra Hospital and Noor Hospital) in Isfahan, located in the center of Iran. The admission criteria were according to guidelines published by the Iranian Ministry of Health for the management of patients with suspected COVID-19 pneumonia based on a combination of clinical, laboratory, and radiologic information [9]. The demographic data (age and gender), comorbidity (ischemic heart disease, chronic respiratory disease, etc.), the clinical symptoms, and lymphocyte count at the admission time were retrospectively collected from patients' records.

This study was approved by the ethical committee of the Radiology Department, Isfahan University of Medical Sciences, Isfahan, Iran, and with a waiver of informed consent.



Clinical symptoms

The patients' clinical data at the time of admission, including the history of cough, fever, dyspnea, the time of symptoms initiation, the respiratory rate, and O_2 saturation, were extracted from patients' records.

According to WHO classifications, all patients were classified into mild and severe pneumonia based on their clinical data at admission. The presence of respiratory rate > 30 breaths/min, severe respiratory distress, or $SpO_2 \le 93\%$ with fever or suspected respiratory infection was considered as severe pneumonia. Mild pneumonia was considered non-severe pneumonia and no need for supplemental oxygen [10].

CT images

All chest CT images were acquired using Phillips Scanner with the patients in a supine position and at full inspiration and without the injection of contrast. Two board-certificate radiologists reviewed the images (AS and SH). In the disagreement between the two primary radiologists, a third radiologist adjudicated the final decision. The two radiologists were blinded to the clinical and laboratory findings.

The CT images were evaluated for the presence of the following: (1) pattern characteristics including ground-glass opacity, consolidation, centrilobular nodules, bronchial wall thickening, reticulation, and vascular enlargement; (2) distribution characteristics including craniocaudal distribution (upper lobe predominant, lower lobe predominant, none), transverse distribution (central predominant or peripheral predominant, none), scattered (focal, multifocal, diffuse), and region (unilateral, bilateral); (3) ancillary findings including lymphadenopathy and pleural effusion.

A semi-quantitative scoring system was used to evaluate the extent of lung parenchymal involvement. A total of 5 lobes in both lungs were evaluated. The lobes were individually weighted based on parenchymal involvement. If no involvement was revealed, 0 was assigned. The involvement of less than 5%, 5% to 25%, 26% to 49%, 50% to 75%, and $\geq 75\%$ was scored as 1 to 5, respectively. The final score was calculated, and a total score of 0 (no involvement) to 25 (diffuse interstitial involvement) was assigned for each patient (Fig. 1) [11].

Short-term outcome

In-hospital death and the need for ICU care are considered poor short-term outcomes. The discharge criteria were the presence of improvement in chest X-ray findings and clinical symptoms, the absence of fever for at least three days, and $\rm O_2$ saturation > 93% without mechanical ventilation.

Fig. 1 An 81-year-old man with positive RT-PCR; symptoms: severe; CT findings: ground-glass opacities in both central and peripheral zones of both lungs without craniocaudal predilection; CT score: 14; outcome: mechanical ventilation



Statistical analysis

All the data were entered into the SPSS21 (SPSS Inc., Chicago, IL, USA). The quantitative data were reported using the mean value. Percentage and frequency were used to report the qualitative data. Independent sample t-test and chi-square tests were utilized used to examine the relation between numerical and nominal variables, respectively. The receiver operating characteristic (ROC) curve was used to determine the optimum cutoff point for possible effective variables on patients' outcomes. The relation between the pre-defined risk factors with the outcome was assessed with crude and adjusted models. In model 1, age and gender were adjusted. We further adjusted other confounding variables, including CT score, lymphocytes, O₂ saturation, hypertension (HTN), diabetes mellitus (DM), chronic respiratory disease, cancer, chronic kidney disease (CKD), and hyperlipidemia (HLP) in the last model. The significance level was set at 0.05.

Results

Of 176 recruited patients, 38 (21.5%) subjects died or were admitted to ICU. Table 1 shows the characteristics of the study population according to discharge or ICU/death status. The study sample had a mean age of 57.5 ± 16.1 years, and 61% were male patients. Participants with poor outcomes had significantly higher means of age than the discharge group (67 ± 13.2 years vs. 54.9 ± 15.9 years, P < 0.001). Those who died

or were admitted to ICU had more prevalence of cardiovascular diseases (CVD) and lowered O_2 saturation in comparison to discharged patients (36.8% vs. 14.5%, P = 0.002, and 85.21 \pm 8.6% vs. 90.29 \pm 5.9, P < 0.001). In terms of radiology findings and in comparison to patients with a good outcome, those with poor outcomes had significantly higher CT scores, higher bilateral lung involvement, but with lower consolidation rates (14.39 \pm 5.8 vs. 9.53 \pm 5.1, P < 0.001, 97.4% vs. 84.8%, P = 0.038, and 0 vs. 12.3%, P = 0.023). There was no significant association in terms of other radiologic findings between groups.

The area under the curve (AUC) for age based on the ROC curve was 0.703 (95% confidence interval (CI): 0.611–0.794, P < 0.001) (Fig. 2), and the best cutoff point for this variable was 60 years with the sensitivity of 71% and specificity of 62%.

We also performed a ROC curve for the CT score and found that the AUC was 0.732 (95%CI: 0.642–0.821, P < 0.001) (Fig. 3). The optimum cutoff value was set to be 10.5 (sensitivity: 73%, specificity: 58%). The cutoff point is rounded to the next integer number (11) since the CT score contains only integer numbers. The most common findings were mixed ground-glass opacity (ground-glass opacity and consolidation), which was seen among 82 (46.6%) patients. The second most common finding was reticulation detected in 73 (41.5%) patients. The most common distribution of pneumonia was peripherally (61.4%), bilaterally (87.5%), and multifocal (88.1%) involvement. None of the patients had lymphadenopathy. Pleural effusion was detected in 9 (5.1%) patients.



 Table 1
 Baseline characteristics of the study population according to discharge or ICU/death status

Variables		Total $(n = 176)$	Discharge $(n = 138)$	ICU/death $(n = 38)$	P
Age(years)		57.5 ± 16.1	54.9 ± 15.9	67 ± 13.2	< 0.001
Age group (%)	20–30 30–40	8 (4.5) 18 (10.2)	8 (5.8) 17 (12.3)	0 1 (2.6)	0.001
	40–50	26 (14.8)	24 (17.4)	2 (5.3)	
	50–60	45 (25.6)	37 (26.8)	8 (21.1)	
	60–70	38 (21.6)	25 (18.1)	13 (34.2)	
	70–80	24 (13.6)	19 (13.8)	5 (13.2)	
	80–90	17 (9.7)	8 (5.8)	9 (23.7)	
Gender	Males (%) Females (%)	108 (61.4) 68 (38.6)	81 (58.7) 57 (41.3)	27 (71.1) 11 (28.9)	0.166
Previous medical history					
HTN		54 (30.7)	43 (31.2)	11 (28.9)	0.793
Cardiovascular disease (%)		34 (19.3)	20 (14.5)	14 (36.8)	0.002
DM (%)		39 (22.2)	31 (22.5)	8 (21.1)	0.853
Chronic respiratory disease (%)		16 (9.1)	12 (8.7)	4 (10.4)	0.728
Cancer (%)		3 (1.7)	2 (1.4)	1 (2.6)	0.618
CKD (%)		15 (8.5)	10 (7.2)	5 (13.2)	0.248
HLP (%)		12 (6.8)	11 (8)	1 (2.6)	0.248
Clinical and laboratory data					
Lymphocyte (%)		1119.15 ± 1418.8	1179.05 ± 1579.3	893.26 ± 389.2	0.291
O ₂ saturation (%)		89.19 ± 6.9	90.29 ± 5.9	85.21 ± 8.6	< 0.001
Respiratory rates (rates/minute)		21.42 ± 5.1	21.13 ± 5.1	22.44 ± 5	0.162
CT findings					
CT score		10.58 ± 5.6	9.53 ± 5.1	14.39 ± 5.8	< 0.001
Ground-glass opacity (%)		70 (39.8)	51 (37)	19 (50)	0.146
Mixed ground-glass opacity and consolidation (%)		82 (46.6)	64 (46.4)	18 (47.4)	0.914
Consolidation (%)		17 (9.7)	17 (12.3)	0	0.023
Centrilobular nodules (%)		8 (4.5)	7 (5.1)	1 (2.6)	0.522
Bronchial wall thickening (%)		14 (8)	10 (7.2)	4 (10.5)	0.508
Reticulation (%)		73 (41.5)	57 (41.3)	16 (42.1)	0.929
Vascular enlargement (%)		13 (7.4)	11 (8)	2 (5.3)	0.572
Pleural effusion (%)		9 (5.1)	8 (5.8)	1 (2.6)	0.433
Upper or lower involvement (%)	Upper Lower	5 (2.8) 89 (50.6)	5 (3.6) 74 (53.6)	0 15 (39.5)	0.101
	None	82 (46.6)	59 (42.8)	23 (60.5)	
Unilateral/bilateral (%)	Unilateral Bilateral	22 (12.5) 154 (87.5)	21 (15.2) 117 (84.8)	1 (2.6) 37 (97.4)	0.038
Central/peripheral/none (%)	Central Peripheral	9 (5.1) 108 (61.4)	7 (5.1) 86 (62.3)	2 (5.3) 22 (57.9)	0.880
	None	59 (33.5)	45 (32.6)	14 (36.8)	
Focal/multifocal/diffuse (%)	Focal Multifocal	17 (9.7) 155 (88.1)	16 (11.6) 120 (87)	1 (2.6) 35 (92.1)	0.107
	Diffuse	4 (2.3)	2 (1.4)	2 (5.3)	

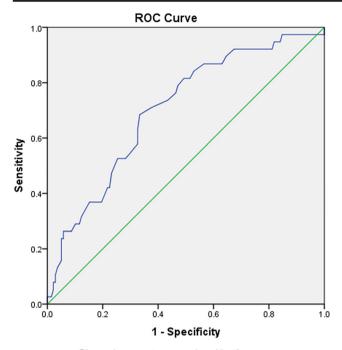
Also, no difference between discharge or ICU/death status was seen regarding lymphopenia lymphocyte count (p = 0.291).

Finally, we calculated the AUC for $\rm O_2$ saturation and the result was 0.713 (95%CI: 0.618–0.808, P < 0.001) (Fig. 4)

with the best cutoff point of 90.5% (sensitivity: 73%, specificity: 59%).

Table 2 presents the multivariable-adjusted odds ratio of death/ICU status according to age, CT score, and O₂

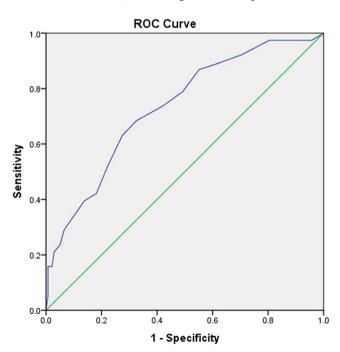




Diagonal segments are produced by ties.

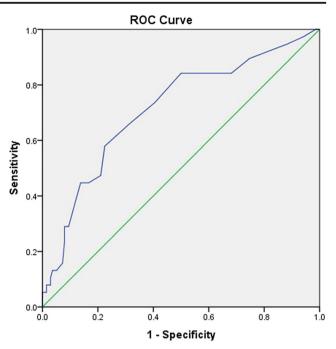
Fig. 2 ROC curve based on age among the study population

saturation. In comparison to patients with less than 60 years, those with higher ages had a significantly higher likelihood of poor outcome both in crude and adjusted models (crude: 4.05 (95%CI: 1.85-8.86, P < 0.001), model 1: 3.95 (95%CI: 1.80-8.66, P = 0.001), model 2: 3.62 (95%CI: 1.35-9.67, P = 0.019)). Patients with higher CT scores had 3.86 (95%CI: 1.74-8.57, P = 0.001) times higher risks of poor outcomes



Diagonal segments are produced by ties.

Fig. 3 ROC curve based on CT score among the study population



Diagonal segments are produced by ties.

Fig. 4 ROC curve based on O₂ saturation among the study population

than the reference group in the crude model. This higher like-lihood remained significant after adjusting all potential confounders (OR: 4.38, 95%CI: 1.69–11.35, P = 0.002). In terms of O_2 saturation, patients with the saturation of less than 90.5% had 4.10 (95%CI: 1.84–9.10, P = 0.001) and 2.78 (95%CI: 1.03–7.47, P = 0.042) times higher odds of worse clinical outcome compared to those with higher O_2 saturation in the crude and adjusted model, respectively.

Discussion

This study evaluated the clinical data, lymphocyte count, and chest CT findings of 176 patients with a positive RT-PCR for COVID-19 to determine significant prognostic factors for short-term outcomes.

We found that among a sample of adults hospitalized with laboratory-confirmed COVID-19, almost one-fifth required ICU admission or died during hospitalization. The most prevalent comorbidities were HTN (30.7%), DM (22.2%), and CVD (19.3%), respectively. Older age, higher CT score, and lower O_2 saturation were associated with higher ICU admission risks and in-hospital mortality.

ICU admissions and death due to COVID-19 have been shown to occur more often with increasing age [12, 13]. In our study, the age of \geq 60 years was the strongest independent predictor of ICU admission and in-hospital mortality. These findings are in concordance with other studies from China, Europe, and the USA [13–17]. Our findings showed that older patients are particularly vulnerable to worse outcomes from



P Models CT score O₂ saturation Age < 60 ≥ 60 < 10.5 ≥ 10.5 > 90.5 ≤ 90.5 Crude 1.00 4.05 (1.85-8.86) < 0.001 1.00 3.86 (1.74-8.57) 0.001 1.00 4.10 (1.84-9.10) 0.001 Model 1* 1.00 3.95 (1.80-8.66) 0.001 1.00 3.69 (1.61-8.46) 0.002 1.00 2.99 (1.28-6.95) 0.011 Model 2** 1.00 3.62 (1.35-9.67) 0.019 1.00 4.38 (1.69-11.35) 0.002 1.00 2.78 (1.03-7.47) 0.042

Table 2 The multivariable-adjusted odds ratio of death/ICU status according to age, CT score, and O₂ saturation

COVID-19 disease and should be targeted for aggressive preventive measures [18].

We showed that the extent of lung parenchymal involvement in chest CT was associated with the disease's severity. In terms of radiology findings, those patients with poor outcomes had significantly higher CT scores, higher bilateral lung involvement, but with lower consolidation rates (P < 0.001, P = 0.038, and P = 0.023, respectively). The results are in concordance with the results reported by Li et al., suggesting the quantitative CT image analysis as an accurate method for clinical severity assessment and associated with poor outcome [19]. Another study done on 101 patients with COVID-19 reported that the extension of parenchymal lung involvement was significantly higher in patients with severe and fatal disease types [20].

We found an association between CVD and poor shortterm outcomes; however, we cannot find any significant association between DM, CKD, HTN, or chronic respiratory disease, and ICU admission or in-hospital mortality. In this regard, Kim et al., in their study on the US population, showed an association between DM and CKD with ICU admission. They also cannot found any association between HTN and poor outcomes [21]. Like our study, Killerby et al., in another study on the US population, reported no significant association between HTN and poor outcomes; however, they showed that HTN was a more prevalent comorbidity in the US population. [22]. On the other hand, several Chinese studies reported that HTN to be associated with more severe clinical outcomes [17, 23, 24]. Further studies are needed to determine whether HTN, which is highly prevalent in the admitted COVID-19 patients, increases the risk of in-hospital complications in these patients. Similarly, the associations between the duration and degree of blood pressure control in HTN and outcomes of COVID-19 disease require further investigation.

In this study, we also assessed the role of clinical characteristics, lymphocyte count, and CT imaging features in predicting the patients' short-term prognosis. The results indicated that O_2 saturation $\leq 90.5\%$, age ≥ 60 , and CT score ≥ 11 were associated with increased odds of ICU admission or in-hospital death. Because COVID-19 primarily affects the respiratory system, markers that reflect respiratory function would more likely relate

to outcomes. Therefore, systemic oxygenation is a potential prognostic biomarker. On the other hand, hypoxemia was associated with an increase of inflammatory biomarkers (higher D-dimer levels, WBC counts, neutrophil counts, and CRP levels) and acute inflammation of the respiratory system [25].

Davarpanah et al. showed that older age, $\operatorname{SpO}_2 < 88\%$, and higher chest CT scores were significant predictors for ICU admission or in-hospital death [9]. In another study by Li et al., chest CT score > 7 and age > 50 years indicated critical COVID-19 pneumonia [26]. Tan et al. suggested that lymphopenia could be considered a useful indicator of severe COVID-19 disease [27]. However, we do not find a significant association between poor in-hospital outcomes and lymphopenia. In a study by Xu et al., \geq 2 comorbidities, leukocytosis, lymphopenia, chest CT score > 14, and older age were associated with increased odds of poor outcome [28].

Altogether, due to the rapid growth of critically ill COVID-19 patients and limited health resources, especially ICU beds, we need effective triage strategies for identifying patients at higher risk for poor outcomes to achieve effective resource allocation.

This study's limitations were the retrospective nature of the study and the relatively small sample size. Additionally, it is probably that not all COVID-19-associated hospitalizations were captured because of the lack of widespread testing capability during the study period and because the recognition of COVID-19 patients was mostly dependent on clinician directed testing. Finally, due to the study's retrospective nature, we did not record the time between the onset of symptoms and the CT examination date.

Conclusion

We found that older age, higher CT severity score, and hypoxemia were risk factors for poor in-hospital outcomes in COVID-19 PCR-positive patients. Further studies are required to prove these associations.

Availability of data and material All data will be made available based on reasonable request.



^{*}Adjusted for age and sex

^{**}Adjusted for age, sex, CT score, lymphocytes, O2 saturation, HTN, DM, COPD, cancer, CKD, HLP with the exception of the desired variable

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and data analysis were performed by A. Shayganfar, S. Hajiahmadi, R. Sami, S. Sadeghi, M. Dehghan, N. Khademi, R. Basiratnia, and F. Ferdosi. The first draft of the manuscript was written by S. Hajiahmadi and supervised by A. Shayganfar. Statistics analysis was performed by R. Rikhtegaran. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethical approval IR.MUI.MED.REC.1398.720.

Consent to participate A waiver of informed consent was granted for this retrospective study.

Consent for Publication The included CT images are not necessary to obtain consent as without any identifying information.

Conflict of interest The authors declare that they have no conflict of interest.

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