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A comparative analysis of clinical, laboratory findings, and HRCT score in ICU and non-ICU admitted COVID19- patients: identifying predictive markers for ICU admission

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ABSTRACT

Introduction: Health care systems all over the world face numerous challenges as a result of the rapid spread of the COVID-19 virus that has resulted in increased mortality rates. About 40% of ICU-admitted COVID-19 patients were not severely ill at the time of admission. Thus, by using appropriate ICU admission predictors, clinicians can identify potential critical patients early on. It can also result in suitable resource allocation and consideration for these patients. Therefore, the current study was done with the aim of identifying clinical characteristics and laboratory data that could predict ICU admission in cases with COVID-19.

Methods: This two-center retrospective observational study was done in Imam Reza and Ghaem Hospitals, Mashhad, Iran. Overall, 334 COVID-19 patients who referred to these hospitals from February to May 2020 were enrolled in this study. The participants were separated into two groups according to ICU admission status. All demographic, clinical, and paraclinical information were extracted from the medical records of the patients.

Results: The present study composed of 88 ICU and 246 non-ICU-admitted COVID-19 patients. No significant differences were found in age between the two groups of patients (P=0.154). Multivariate regression analysis revealed that higher levels of CRP (OR=1.01, 95%CI 1.001-1.010, P=0.016), WBC (OR=1.11, 95% CI 1.01-1.22, P=0.03), and HRCT scores (OR=1.08, 95%CI=1.01-1.16, P=0.037) were linked to higher odds of ICU admission.

Conclusion: This study suggests that higher levels of CRP, WBC, and LDH, as well as the HRCT score at the time of admission, were potential independent predictors of ICU admission during inpatient treatment in COVID-19 patients.

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Introduction

The COVID-19 outbreak, as a global health emergency, began in Wuhan, China in December 19, 2019, and has spread rapidly worldwide (1). Those with COVID-19 present with various

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clinical manifestations varying from asymptomatic to life-threatening (2). Most patients experience mild flu-like symptoms such as fever, cough, loss of taste and smell, tiredness, diarrhea, and shortness of breath (3). However, 15-20% of patients with prominent abnormal laboratory findings develop severe forms of the disease that may result in intensive care unit (ICU) admission (4,5).

Previous studies have reported that ICU-related complications like acute respiratory distress syndrome (ARDS), shock, and acute cardiac and renal damage were observed in only 5% of severe COVID-19 patients (3, 4). This indicates that the identification of predictive factors is necessary to determine the patients who will be most likely be eligible for ICU admission. It has been reported that ICU requirement in patients with COVID-19 varies from 5% to 32% among different countries (6).

Moreover, it has been proposed that some factors such as age, sex, and accompanying comorbidities can serve as potential predictors of ICU admission requirements (6,7). Obviously, timely ICU admission is vital in the appropriate management of critically ill COVID-19 patients. Mortality rates among ICU-admitted patients in China, Italy, and the US were reported to vary between 60% to 85% (8-10).

These wide differences in mortality rates can be due to variable ICU admission thresholds and different health care system services, but also differences in socioeconomic status and patient characteristics (11). Health care systems face many different challenges because of COVID-19's nature to spread rapidly. This situation has caused an increased load of COVID-19 patients referring to health care systems, reduced quality of medical services, and subsequently increased mortality rates. Due to these reasons and the fact that ICU treatment can enhance the outcome of gravely ill COVID-19 patients, it is important to identify those at risk of developing the critical form of the disease at an early stage, and distinguish COVID-19 cases who require ICU admission from mild cases with good prognosis (12-14).

Therefore, we conducted the present study with the aim of comparing clinical, para-clinical, and laboratory factors in ICU and non-ICU admitted COVID-19 patients, and to single out predictive factors for ICU admission.

Materials and Method

Study population

This two-center retrospective observational study was conducted in Imam Reza and Ghaem Hospitals, Mashhad, Iran. In total, 334 consecutive COVID-19 patients were enrolled in the current study. All patients were diagnosed as having the disease by RT-PCR (by using oropharyngeal or nasopharyngeal swap) and HRCT (high-resolution computed tomography). The principal outcome of the study was to compare clinical and laboratory findings, and the high resolution computed tomograph (HRCT) score amid ICU and non-ICU admitted COVID-19 patients. The participants were placed into two groups in accordance with ICU admission status.

All patients were admitted to the COVID ward on the first day of admission, and patients with the ensuing criteria were admitted to the ICU: (a) developing respiratory failure (developing ARDS and requiring mechanical ventilation); (b) any organ failure that required ICU admission (e.g., acute kidney failure, acute liver failure, cardiac arrest, heart failure, encephalopathy, stroke, or sepsis) (12).

Follow-up of these patients was done from the first day of admission to the day of discharge. The ethics committee of the Mashhad University of Medical Sciences gave ethical approval based on the Helsinki Declaration (IR.MUMS.MEDICAL.REC.1399.414).

Data collection

Patients' data collection was done from February 2020 until May 2020 and the following data were extracted from the patients' medical records: demographic data (age, gender), clinical presentation (cough, dyspnea, fever, headache, arthralgia, and myalgia), laboratory data (complete blood count: CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), blood gasometry (Po2 and Pco2), O2 saturation, comorbidities (diabetes, hypertension, cerebrovascular events, renal disease, liver disease, cancer, asthma, hyperlipidemia, and Alzheimer's disease), HRCT score, and patients' mortality. In ICU-admitted patients, symptoms of headache, arthralgia, myalgia, or lethargy were recorded in conscious and responsive patients. All of these tests were done on the first day of hospitalization.

All patients underwent a HRCT scan when admitted to the hospital and a semi-quantitive HRCT severity scoring suggested by Pan et al. was used for all patients (scoring from 0 to 25) (13). All the data were compared between non-ICU and ICU admitted patients.

Statistical analysis

Continuous variables were reported as mean±SD and categorical variables were recorded as percentages. All consecutive COVID-19 patients who were admitted to the hospital between February to May 2020 were enrolled in this study.

The Mann-Whitney U test was used to compare the continuous variables and the chi square test was used to compare categorical variables. The significant

variables were included in the univariate logistic regression, which was used to identify ICU admission risk factors. The multivariate logistic regression model was used with the following parameters: myalgia, diarrhea, diabetes, and CRP, WBC, LDH, and HRCT scores. The ROC curve was done to evaluate the accuracy of significant ICU predictors. SPSS software (version 26) was used to do all analyses, and two-tailed p<0.05 was considered statistically significant.

Results

Overall, 334 consecutive COVID-19 patients (with positive PCR and HRCT scan) were entered in this study between February 2020 and May 2020. Their mean age was 62.22±16.59 years (range: 16-96 years), and 57.78% of patients were male. The mortality rate of all study patients was 13.77%. Table 1 presents an overview of the patients' demographic, clinical presentations, comorbidities, laboratory results, and imaging findings. The ICU group consisted of 88 COVID-19 patients and the non-ICU admitted group consisted of 246 COVID-19 patients. The mean age of ICU (60.1±17.5) and non-ICU patients (63±16.1) was not significantly different. Moreover, 2.39% of ICU admitted and 6.89% of non-ICU admitted patients were smokers (P value=0.94). The mortality rate of ICU patients was 8.98% and for non-ICU-admitted patients it was 4.79% (P value <0.001).

Table 1. Characteristics data in ICU and non-ICU admitted patients

Variable	All N=334 (Percentage)	COVID-19 Patients		P valeu
		Admitted to ICU N=88	Not admitted to ICU N=246	
DEMOGRAPHICS				
Age (years)	62.2±16.6	60±17.5	63±16.1	0.154
Sex (male)	193 (57.78)	49 (14.67)	144 (43.11)	0.642
Weight (kg)	71.57±17.88	73.42±14.91	70.95±18.78	0.450
Height (cm)	164.02±13.78	165.2±9.23	163.63±15.01	0.535
Smoking	31 (9.28)	8 (2.39)	23 (6.89)	0.94
Addiction	24 (7.18)	6 (1.79)	18 (5.39)	0.88
Death	46 (13.77)	30 (8.98)	16 (4.79)	<0.001
Time in hospital (days)	12.02±7.57	16.86±9.41	10.49±6.16	<0.001
VITAL SIGNS AND CLINICAL PRESENTATIONS				
O2 saturation (%)	84.54±8.76	83.58±12.08	84.15±9.4	0.7
Respiratory rate (breaths per minute)	22.30±7.46	23.69±5.23	21.45±8.46	0.56
Cough	91 (27.24)	28 (8.38)	63 (18.86)	0.27
Excessive sputum	9 (2.69)	1 (0.30)	8 (2.39)	0.29
Fever	184 (55.09)	42 (12.57)	142 (42.52)	0.11
Dyspnea	264 (79.04)	66 (19.76)	198 (59.28)	0.25
Chest pain	3 (0.9)	0	3 (0.9)	0.3
Myalgia	60 (17.96)	9 (2.69)	51 (15.27)	0.028
Arthralgia	66 (19.76)	14 (4.19)	52 (15.57)	0.28
Weakness and lethargy	39 (11.68)	7 (2.10)	32 (9.58)	0.2
Diarrhea	69 (20.66)	7 (2.10)	62 (18.56)	0.001
Nausea and vomiting	17 (5.09)	0	17 (5.09)	0.011
Headache	55 (16.47)	12 (3.60)	43 (12.87)	0.59
COMORBIDITIES				
Cancer	30 (8.98)	6 (1.80)	24 (7.18)	0.25
Liver diseases	17 (5.09)	3 (0.9)	14 (4.19)	0.11
Renal diseases	48 (14.37)	13 (3.89)	35 (10.48)	0.33
Diabetes	102 (30.54)	18 (5.39)	84 (25.15)	0.037
Cerebrovascular accident	25 (7.48)	7 (2.10)	18 (5.38)	0.24

Asthma	35 (10.48)	10 (3.00)	25 (7.48)	0.36
Hyperlipidemia	39 (11.67)	11 (3.29)	28 (8.38)	0.29
Alzheimer's disease	15 (4.49)	4 (1.20)	11 (3.29)	0.37
LABORATORY AND IMAGING FINDINGS				
RBC (106/mm3)	4.42±1.09	4.28±1.01	4.47±1.11	0.15
Hb (g/dl)	12.34±2.69	11.96±2.97	12.48±2.57	0.121
Hct (%)	35.86±7.64	34.70±9.00	36.28±7.07	0.101
PLT (1000/per µL)	209.69±111.34	212.07±120.32	208.95±108.69	0.84
CR (mg/dL)	1.33±1.13	1.54±1.41	1.26±1.01	0.06
CRP (mg/L)	118.05±84.50	146.23±90.77	107.26±79.59	>0.001
ESR (mm/hr)	58.83±37.04	62.41±42.87	57.6±34.85	0.37
WBC (1000/per µL)	9.01±4.42	10.47±5.07	8.47±4.03	>0.001
Lymphocyte count (1000/per µL)	1.23±0.69	1.14±0.65	1.26±0.70	0.189
LDH (U/L)	586.92±236.56	669.57±271.10	560.15±218.44	0.02
AST (U/L)	37.99±34.94	42.41±35.09	36.28±34.82	0.213
ALT (U/L)	30.20±21.9	28.65±19.12	30.79±22.89	0.50
PCO2 (mmHg)	41.98±12.21	42.11±12.29	41.94±12.22	0.926
PO2 (mmHg)	40.78±19.48	41.27±19.63	40.66±19.49	0.847
Radiologic score	9.38±5.88	11.26±6.74	8.42±5.23	<0.001

Summary statistics are means ± SD or n (%). The Mann-Whitney U test was used for continuous variables and the chi-square test was used for categorical variables (Hb: hemoglobin, Hct: hematocrit, RBC: red blood cell, PLT: platelet, CR: creatinine, CRP: c reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cells, LDH: lactate dehydrogenase, AST: aspartate transaminase, ALT: alanine transaminase

Clinical presentations and comorbidities

Clinical presentations among patients were mostly dyspnea (79%), fever (55%), and cough (27.24%). Also, hypertension (31%), diabetes (30%), and renal diseases (14.37%) were the most frequent comorbidities among patients. Myalgia was significantly higher in non-ICU admitted patients (P value=0.028).

In addition, diarrhea (P value=0.001) and nausea and vomiting (P value=0.011) were significantly higher among non-ICU patients. ICU-admitted patients had significantly higher rates of type 2 diabetes (P value=0.037); however, other underlying diseases were not significantly different.

Laboratory and imaging findings

The results (as shown in Table 1) indicate that ICU-admitted patients had significantly higher levels of CRP (P value< 0.001).

Also, WBC (P value <0.001) and LDH (P value=0.02) levels were significantly higher in ICU-admitted patients. The HRCT scan of the patients showed that ICU-admitted patients had a higher score of lung involvement compared to non-ICU admitted patients (P value < 0.001).

Univariate and multivariate analysis and AUC analysis

In univariate analysis, as represented in Table 2, myalgia was significantly associated with ICU admission (P value=0.031, OR=0.44, 95% CI=0.21-0.93). Also, diarrhea (P value=0.001, OR=0.26, 95% CI=0.11-0.59) and diabetes (P value=0.011, OR=0.44, 95% CI=0.24-0.83) were associated with ICU admission.

In laboratory findings, CRP (P value<0.001, OR=1.005, 95% CI=1.001-1.010), LDH (P value=0.003, OR=1.002, 95% CI=1.001-1.003), and WBC levels (P value<0.001, OR=1.10, 95% CI=1.04-1.16) were associated with increased risk of ICU admission. Furthermore, the HRCT score were associated with a risk of ICU admission (P value=0.001, OR=1.08, 95% CI=1.04-1.14).

The multivariable model consisted of CRP, WBC, LDH, myalgia, radiologic score, diarrhea, and diabetes. CRP (P value=0.016, OR=1.006, 95%=1.001-1.010) and WBC levels (P value=0.03 OR=1.11 95% CI=1.01-1.22) were significantly associated with a higher risk of ICU admission. Also, the HRCT score was significantly related to ICU admission (P value=0.037, OR=1.08, 95% CI=1.005-1.16).

Table 2. Factors associated with ICU admission (univariate and multivariate logistic regression)

Characteristics	Univariate Logistic Regression			Multivariate Logistic Regression		
	Odd ratio (OR)	CI (95%)	P value	Odd ratio (OR)	CI (95%)	P value
CRP (mg/L)	1.005	1.002-1.008	<0.001	1.01	1.001-1.010	0.016
Myalgia	0.44	0.21-0.93	0.031	0.480	0.148-1.558	0.22
Diarrhea	0.26	0.11-0.59	0.001	0.265	0.064-1.098	0.067
Diabetes	0.44	0.24-0.83	0.011	0.81	0.289-2.269	0.69
HRCT score	1.08	1.04-1.14	0.001	1.08	1.005-1.16	0.037
WBC (1000/per µL)	1.10	1.04-1.16	<0.001	1.11	1.01-1.22	0.03
LDH (U/L)	1.002	1.001-1.003	0.003	1.002	1.000-1.003	0.033

(CRP: c-reactive protein, WBC: white blood cell, LDH: lactate dehydrogenase)

Table 3 presents the value of factors associated with ICU admission. The area under the curve (AUC) of CRP is 0.63 (P value=0.001, 95% CI=0.56-0.7). Also, the AUC of WBC (P value=0.001, 95% CI=0.545-0.69) and LDH (P value=0.013, 95% CI=0.52-0.69) are 0.62 and 0.61. The AUC for the HRCT score is 0.62 (P value=0.003, 95% CI=0.54-0.70).

Table 3. The value of predictors of ICU admission

Prognostic Factor	AUC (95% CI)	Sensitivity	Specificity	P value
CRP (mg/L)	0.63	71	52	0.001
Radiologic score	0.62	62	56	0.003
WBC (1000/per µL)	0.62	62	57	0.001
LDH (U/L)	0.61	60	47	0.013

Discussion

The present study was conducted to determine clinical, para-clinical, and laboratory factors in ICU and non-ICU admitted COVID-19 patients. Given that the ICU capacity is limited, it is important to find predicting factors to identify patients who need ICU admission to optimize resources and patients' management. Also, developing ICU admission predictors can lead to decreased ICU requirement and improve the patients' outcome (14).

In the current study, we showed that the CRP, WBC, LDH, and HRCT scores at baseline were significant independent predictors of ICU admission in hospitalized patients with COVID-19. This finding can contribute to improving patients outcomes and management, and resources conservation.

CRP, as marker of systemic inflammation, can bind to phosphocholine in pathogens and the membrane of host cells, and enhance phagocytosis (15). In a recent study, the initial CRP level was 10-fold higher in patients who died in comparison to survivors, and the CRP level was associated with COVID-19 mortality with the area under the curve of 0.896 (16). In this study, we found that ICU-admitted patients had significantly higher CRP levels than non-ICU patients; hence, the CRP level was associated with a higher probability of ICU admission. However, the AUC of CRP was only 0.63. In a cohort study done by Liao et al., it was shown that CRP>10 (mg per liter) is an independent predicting factor of COVID-19 severity (17), which was also reported by Sadeghi et al. The authors examined 214 COVID-19 patients and found CRP levels to be a predictor of the inflammatory phase and ICU admission (18).

In addition, Yitao et al. stated that CRP is a predictor of clinical deterioration in COVID-19 patients (19). Earlier researches have indicated that CRP levels have a strong association with critical illness, mortality, venous thromboembolism, and acute kidney damage in COVID-19 patients (20).

Also, Liu et al. has observed that CRP levels were elevated in severe COVID-19 patients, and can independently predict COVID-19 severity. They also showed that patients with CRP levels above 41.8 mg/L were more likely to have severe complications (21). A possible explanation for this finding might be that CRP is capable of activating complement and enhancing phagocytosis, which is the possible mechanism for inflammatory

cascade and can induce cytokine storm and organ dysfunction (22).

Moreover, a higher concentration of pro-inflammatory cytokines was found in COVID-19 patients requiring ICU admission, and these findings suggest an association among cytokine storm, disease severity, and ICU admission (3,23).

In our study, we also showed that WBC level, as another inflammatory marker, was significantly higher in ICU-admitted patients, and can thus be a potential predicting factor of COVID-19 ICU admission, which is in agreement with previous studies. Sadeghi et al. concluded that WBC count could be considered as a predictor of ICU admission in COVID-19 patients (18).

Also, in line with our results, in a study done by Carlino et al. in Italy, it was found that WBC levels could serve as a very good predictor of ICU admission (AUC=0.847) (24). Although, in this study, lymphocyte count was lower in ICU-admitted patients and the statistical difference was not significant. Contrary to our results, a recent study has shown that reduced lymphocyte count can predict ICU admission (25).

Moreover, it has been demonstrated that WBC and especially lymphocyte count, as a reflection of COVID-19 severity, can predict mortality in COVID-19 patients (26).

This discrepancy can be explained by the effects of patient-associated factors, such as the patient's medication, disease severity, or differences regarding pre-existing comorbidities.

Furthermore, in the current study, LDH level was significantly higher in ICU-admitted patients, and was described as a promising predictor of ICU admission in COVID-19 patients. This finding is in harmony with Zhao et al., who ascertained that elevated LDH levels can forecast ICU admission and mortality in COVID-19 patients (25).

Moreover, it was shown that an elevated LDH level was an independent risk factor for clinical deterioration in mild COVID-19 patients (27). In a pooled analysis done by Henry et al., it was demonstrated that elevated LDH is associated with increased odds of severity (six-fold) and mortality (more than 16-fold) in COVID-19 patients (28).

We also studied the HRCT score and extent of lung involvement in COVID-19 patients. Previous researches have shown that clinical staging and disease severity of COVID-19 are vastly correlated with the extent of CT damage (29). Also, Ayoobi Yazdi et al. mentioned a higher HRCT score, and that consolidation opacity in HRCT was associated with ICU admission (18).

In consistency with the mentioned studies, we found that a higher HRCT score and extent of lung involvement were associated with ICU admission, and can be used as potential predicting factor for a patient's ICU admission requirement.

We found that a lower rate of myalgia is associated with ICU admission although unaccompanied it could not be regarded as a predictor of ICU admission. In accordance with our results, it was shown that myalgia was higher among non-ICU COVID-19 patients (15).

Interestingly, other studies have shown inconsistent results on this topic. Myalgia was associated with an increase odd of COVID-19 disease severity and ICU admission (11,12). Larger studies with more focus on myalgia are needed to disclose the exact connection between myalgia and COVID-19 ICU admission. Furthermore, about 40% of ICU-admitted COVID-19 patients were not severely ill in initial admission. Thus, by using proper ICU admission predictors, clinicians can identify potential critical patients faster. It can also lead to proper resource allocation and better consideration for these patients (4,27).

Some limitations exit in this study. First, data such as those related to CT scan detailed findings were missing, which can cause bias. Second, some of the laboratory tests were not performed due to the lack of medical resources.

Third, the laboratory data were measured only once with potential measurement errors. Fourth, although CRP, WBC, LDH, and HRCT scores were independent predicting factors of ICU admission, the area under the curve of these variables was poor. Multicenter studies with a greater population should be done to substantiate these results.

Despite these limitations, our study presented potential factors to predict ICU admission and assist medical workers in identifying patients who require ICU admission.

Conclusion

We found that CRP, WBC, LDH, and HRCT scores were associated with the odds of ICU admission. Hence, these scores can be potential predicting factors for ICU admission, and used for improving patients' management and optimizing healthcare resources and plans although the area under the curve of these factors was poor.

Furthermore, these results can assist clinicians to detect patients who have the greatest risk of turning critical; thus, providing the necessary care as soon as possible to improve patient outcomes.

Conflicts of interest

None to be declared.

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Author's contribution

KH, MS, FE, and ZM, and conducted the study. AE, KT, HMM, MHJ, MKH, MS, BA, DO, and MGH contribute to the data collection and writing the article. All the authors contributed to the manuscript revision and final approval.

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