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Prediction Strength of Some Risk Factors for Severe COVID-19 Course at hospital Admission in Al-Nasiriyah City -Iraq : A Cohort Retrospective Single center Study

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Abstract
Background: The early prediction of the clinical course of COVID-19 helps health professionals to discriminate the severe cases that need ICU admission from those with no risk of worsening outcomes.
Materials & methods: This cohort retrospective study included 389 COVID-19 patients admitted to Al-Hussein Teaching Hospital during the period from March to August 2021. Demographic characteristics, clinical symptoms, and laboratory findings upon hospital admission were analyzed by univariate analysis to determine their association with the severity of COVID-19; only those variables with (P>0.05) were included in the multivariable logistic regression to find the strong predictors of severity in term of Odd ratios.
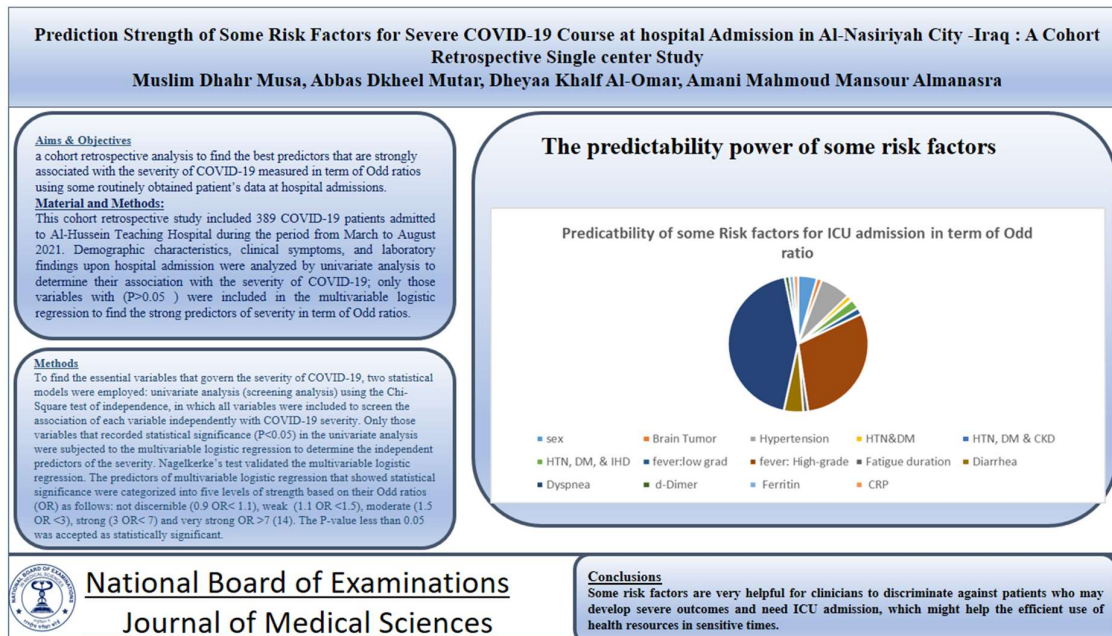**Results**: The mean age of the 389 patients was 33.6 ± 14.8; there were 231(59.4%) severe cases (admitted to ICU), and 158(40.6%) were non-severe cases (admitted to regular wards). Univariate analysis revealed that gender (male) presence of co-morbidities and all clinical symptoms and laboratory findings were associated with severe outcomes of COVID-19. However, multivariate logistic regression revealed that dyspnea [O.R 42.58 (12.22; 148.36)] and high grad fever [O.R 29.25 (5.34; 160.24)] were very strong predictors for severity, while male gender [O.R4.26 (1.95; 9.33)] and hypertension [O.R6.83 (2.4; 19.54)] were strong predictors of the severity. On the other hand, Ferritin gave an indiscernible predictive value [O.R1.003 (1.001; 1.006)].
Conclusion: Some risk factors are very helpful for clinicians to discriminate against patients who may develop severe outcomes and need ICU admission, which might help the efficient use of health resources in sensitive times.

Keywords: Risk factors, Severity, COVID-19, Iraq

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Graphical Abstract

Prediction Strength of Some Risk Factors for Severe COVID-19 Course at hospital Admission in Al-Nasiriyah City -Iraq : A Cohort Retrospective Single center Study

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Aims & Objectives
a cohort retrospective analysis to find the best predictors that are strongly associated with the severity of COVID-19 measured in term of Odd ratios using some routinely obtained patient's data at hospital admissions.

Material and Methods:
This cohort retrospective study included 389 COVID-19 patients admitted to Al-Hussein Teaching Hospital during the period from March to August 2021. Demographic characteristics, clinical symptoms, and laboratory findings upon hospital admission were analyzed by univariate analysis to determine their association with the severity of COVID-19; only those variables with (P>0.05) were included in the multivariable logistic regression to find the strong predictors of severity in term of Odd ratios.

Methods
To find the essential variables that govern the severity of COVID-19, two statistical models were employed: univariate analysis (screening analysis) using the Chi-Square test of independence, in which all variables were included to screen the association of each variable independently with COVID-19 severity. Only those variables that recorded statistical significance (P<0.05) in the univariate analysis were subjected to the multivariable logistic regression to determine the independent predictors of the severity. Nagelkerke's test validated the multivariable logistic regression. The predictors of multivariable logistic regression that showed statistical significance were categorized into five levels of strength based on their Odd ratios (OR) as follows: not discernible (0.9 OR< 1.1), weak (1.1 OR <1.5), moderate (1.5 OR <3), strong (3 OR< 7) and very strong OR >7 (14). The P-value less than 0.05 was accepted as statistically significant.

The predictability power of some risk factors

Predicatbility of some Risk factors for ICU admission in term of Odd ratio

■ sex ■ Brain Tumor ■ Hypertension ■ HTN&DM ■ HTN, DM & CKD
■ HTN, DM, & IHD ■ fever:low grad ■ fever: High-grade ■ Fatigue duration ■ Diarrhea
■ Dyspnea ■ d-Dimer ■ Ferritin ■ CRP

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Conclusions
Some risk factors are very helpful for clinicians to discriminate against patients who may develop severe outcomes and need ICU admission, which might help the efficient use of health resources in sensitive times.

Introduction

Late 2019 was an extraordinary global event in public health; the emerging new respiratory viral disease, COVID-19, caused by *betacoronavirus* SRAS-Cov-2, began in China and spread worldwide, hitting 229 countries and leaving behind more than 6 million deaths [1]. The clinical presentation of the disease is widely varied from asymptomatic/mild to fatal respiratory distress and multi-organ failure [2,3]. Although about 80% of infected patients experienced mild symptoms, resolved entirely by the end of the disease course, a subset of the patients developed severe symptoms [4,5]. However, due to the surge in the number of patients, especially during the first and second waves of the pandemic, this subset of severe patients constitutes a massive burden on health systems, even those in developed countries, particularly the intense care units (ICU) [6]. One of the biggest challenges was the early prediction of the clinical course or identifying the risk factors that worsened the clinical course. The importance of early prediction of the clinical course helps health professionals to arrange their priorities in dealing with the vast numbers of hospital attendances and to discriminate the severe cases that need ICU admission from those with no risk of worsening outcome [7], Additionally, strengthening early prediction of COVID-19 severity is one of the fundamental approaches for lowering the death rate [8]. Since then, many efforts have gone into determining the best risk factors the clinician can use to assess the severity of hospital admission. Many previous studies have undertaken the topic of risk factors for severe forms of COVID-19 using demographic, clinical, and laboratory results variables. Nevertheless, most of those studies only apply their prediction models to estimate in-hospital mortality [7,9]. Other studies used the prediction models to assess the severity upon hospital presentation; however, these studies' results are difficult to generalize due to

small sample sizes or variations in the demographic characteristics of populations in different countries [7-12]. Studying the possible risk factors that may play a role in the path of COVID-19 clinical course in the Iraqi population has not been fully covered; thus, in this study, we perform a cohort retrospective analysis to find the best predictors that are strongly associated with the severity of COVID-19 measured in term of ICU admission using some routinely obtained patient's data at hospital admissions.

Materials and Methods

Study Design and Setting

This retrospective cohort study included 389 COVID-19 patients admitted to Al-Hussien Teaching Hospital (the main hospital for COVID-19 management) in Thi-Qar province, south of Iraq, for five months (March to August 2021). The outcome of the study was the severity of the disease defined in terms of clinical symptoms at hospital admission time according to WHO, 2021 [13], and the demand for ICU admission based on the decisions of emergency physicians; thus, the study population divided into two groups as severe cases and non-severe cases

Definitions

- *Severe cases*: are those patients that are characterized by low oxygen saturation (<90%) on room air, low respiratory rate (<30 breaths/minute), and signs of respiratory distress, besides the physician's decision to ICU admission.
- *Non-severe cases* are those patients without any criteria signs as mentioned above of severe cases; thus, the physician decides to be admitted to regular hospital wards.

- *Primary education*: patients who have accomplished primary school.
- *Intermediate education*: patients who have accomplished secondary school.
- *High education*: patients who have a Bachelor's or higher degrees.

Data collection

All data were obtained retrospectively from the biostatic department of Al-Hussien Teaching Hospital, based on approved written permission from the Thi-Qar Health Directory. Each participant had three parts of information: demographic included; age, gender, smoking habit, residence (stratified into rural and urban), education levels (stratified into primary, intermediate, and high), blood group, and presence of co-morbidities; hypertension (HTN), diabetes mellitus (DM), ischemic heart diseases (IHD), chronic kidney diseases (CKD), and cancers. The clinical information included fever, fatigue duration, dyspnea, and diarrhea. The laboratory data included D-dimer, Ferritin, and CRP serum levels. All patients' data regarded the clinical symptoms, and the laboratory findings represented the patient's health status during the first 24 hours of hospital admission.

Statistical Analysis

Descriptive statistics were conducted to illustrate the characteristics of the cohort. Categorical variables were expressed as numbers and percentages (%). Continuous variables were expressed as mean and standard deviation (SD) or median (IQR: Inter-quartile Range) based on the normality test (Kolmogorov-Smirnov). To find the essential variables that govern the severity of COVID-19, two

statistical models were employed: univariate analysis (screening analysis) using the Chi-Square test of independence, in which all variables were included to screen the association of each variable independently with COVID-19 severity. Only those variables that recorded statistical significance (P<0.05) in the univariate analysis were subjected to the multivariable logistic regression to determine the independent predictors of the severity. Nagelkerke's test validated the multivariable logistic regression. The predictors of multivariable logistic regression that showed statistical significance were categorized into five levels of strength based on their Odd ratios (OR) as follows: not discernible (0.9 OR< 1.1), weak (1.1 OR <1.5), moderate (1.5 OR <3), strong (3 OR< 7) and very strong OR >7 (14). The P-value less than 0.05 was accepted as statistically significant.

Results
Cohort characteristics

The cohort characteristics are illustrated in Table 1. Our cohort included 389 patients; 231 (59.4%) were severe cases (admitted to ICU), and 158 (40.6%) were recognized as non-severe cases(admitted to regular wards). The mean age of the entire cohort was 36.6±14.8 ranging from 7 years to 78 years old. Most of the cohort 255 (65.6%) were in the age group 19-40 years old, while only 18 (4.6%) were older than 65 years. Most participants, 238 (61.2%), lived in urban regions. Regarding education levels, most participants (48.6%) have a high education level. The majority of individuals, 244(62.7%), were non-smokers. Thirty-four percent of the cohort had comorbid conditions; the most common were HTN & DM (13.4%) and HTN alone (13.1%), whereas brain tumors were the least common, reported in 0.8% of cases. Patients with over three co-morbidities (DM, HTN, IHD, and CKD) constitute 2.3% of the study population.

Table 1. The Demographic Characteristics, Clinical Features and Laboratory findings of the Study Cohort

Type of character	Characters	Categories	No (%)
Demographic	Age Mean ± SD (Min-Max) 33.6 ± 14.8 (9-78)		
	Age categories	≤18 years	22 (5.7%)
		19-40 years	**255 (65.6%)**
		41-64 years	94 (24.2%)
		≥65 years	18 (4.6%)
	Gender	Male	189 (48.6%)
		Female	200 (51.4%)
	Residence	Rural	151 (38.8%)
		Urban	238 (61.2%)
	Education levels	Primary	66 (17%)
		Intermediate	134 (34.4%)
		High	189 (48.6%)
	Smoking status	Smoker	79 (20.3%)

		Non-Smoker	244(62.7%)
		X-Smoker	66 (17%)
	Blood Group	A	105 (27%)
		AB	76 (19.5%)
		B	72 (18.5%)
		O	136 (35%)
	Co-Morbidity	Without Co-Morbidity	256 (65.8 %)
		With Co-morbid	133(34.2%)
		Brain Tumor	3 (0.8 %)
		HTN	51 (13.1 %)
		HTN&DM	52 (13.4 %)
		HTN, DM, CKD	4 (1 %)
		HTN, DM, IHD	14 (3.6 %)
		HTN, DM, IHD, CKD	9 (2.3 %)
Clinical Symptoms	Fever (˚C) Mean ± SD (Min-Max) 38.8 ± 0.6 (38- 40)		
	Fever categories	No fever	40 (10.3%)
		Low grade (38-39.3)	281 (72.2%)
		High grade (>= 39.4)	68 (17.5%)
	Fatigue duration (days) Mean ± SD (Min-Max) 18.9 ± 8.2 (3-35)		
	Fatigue categories	Less than one week	6 (1.5%)
		1-2 weeks	79 (20.3%)
		2-3 weeks	171 (44%)
		More than three weeks	133 (34.2%)
	Diarrhoea	Yes	153 (39.3%)
		No	236 (60.7%)
	Dyspnea	Yes	161 (41.4%)
		No	228 (58.6%)
	Severity	Yes	231 (59.4%)
		No	158 (40.6%)
Laboratory findings	d-Dimer (µg/ml)	Median (IQR)	680 (230-1600)
	Ferritin (ng/ml)	Median (IQR)	460 (260-840)
	CRP (mg/l)	Median (IQR)	46 (24-96)

Regarding the patient's clinical symptoms, most study participants (89.7%) had a fever. Most of them (72.2%) have a low-grade fever. The highest recorded fever was 40°C. Additionally, 60.7% reported having diarrhea. All the study participants reported being fatigued, with the mean duration of fatigue18.9±8.2 days.

The largest group (44%) reported fatigue for two to three weeks. Dyspnea was reported among 41.4% of the cohort. The laboratory findings included the CRP, d-Dimer, and ferritin values. Their median readings were 46 mg/l, 680 g/ml, and 460 ng/ml.

The Association of the variables with the severity

The univariate analysis illustrated in Table 2 revealed that among seven demographic variables, only gender and the presence of co-morbidities were significantly associated with severe cases (*P-value* =0.001). As among 231 severe cases, 135 (58.4%) accounted for male's sex, while 96 (41.6%) were females. For the age variable, although 145 (62.8%) of the severe cases belonged to the age group (19-40 years old), no significant association was found (*P-value* 0.47). Nearly two-thirds (61.5%) of the patients with severe infection lived in urban regions. Yet, the association between the geographic region and the symptoms' severity was insignificant *(P value* 0.88). Regarding the education levels, higher education levels were found to have more severe infections as nearly half (48.9%) of those severe cases were among this category and the lowest group (18.6%) of severe cases were primarily educated. Again, the relationship between education and severity was insignificant (*P-value* 0.45). Surprisingly, the non-smoker was found to have a more severe infection (61%) when compared with both the smoker (22.5%) and X-Smoker groups (16.5%). However, the association was not significant (*P-value* 0.42). Similarly, patients with different blood groups tend to have different responses to the COVID infection, as our study reported that those with blood group O were more likely to have a severe infection (37.2%) when compared with other groups, followed by blood group A (25.1%), moreover, blood group AB and B nearly making the same contribution among the severe group, (19%) and (18.6%) respectively. Nevertheless, the association was not statistically significant (*P-value 0.64*). Patients without underlying comorbidities were found to have a higher percentage (79.7%) in the non-severe group than in the severe group (56.3%). Yet, the percentage of patients without comorbidities was still higher than those with comorbidities in the severe group. Among patients with underlying diseases, those with double burden (DM & HTN) and those with HTN alone contributed to 17% and 16% of the severe group. Those with HTN, DM &IHD constituted nearly 5% of the severe group. Patients with HTN, DM, IHD and CKD contribute to approximately 4% of the severe group, and the lowest group was those with a brain tumour. Regarding the clinical features, fever found to be significantly associated with the severity of infection, as 97% of the patients with severe infection were had fever at presentation (P value .00). Those with low-grade fever (less than $39.4°$ C) constituted the majority of the severe group (69.3%). Additionally, increasing the duration of fatigue was found to be significantly associated with the severity of COVID-19 infection (P value 0.00), as those who reported being fatigued for more than three weeks were found to be the largest contribution to the severe group (52.8%), followed by those whose duration of fatigue was between 2-3 weeks (38.5%), and none of those whose fatigue duration was less than one week found to have a severe infection. Patients with diarrhoea similarly being more likely to have a severe infection (50.2%), and the association is statistically significant (P value 0.00). Dyspnea was linked with COVID severity, and the relationship is statistically significant (P value 0.00) as 65.4% of the severe group had dyspnea.

Table 2. Univariate analysis of fourteen variables that included in this study

Variable	Categories	Non-severe (Regular ward) n= 158	Severe (ICU admitted) n= 231	P-value
Demographic characteristics				
Age categories	<= 18 years	8 (5.1%)	14 (6.1%)	0.47
	19-40 years	110 (69.6%)	145 (62.8%)	
	41-64 years	35 (22.2%)	59 (15.1%)	
	>= 65 years	5 (3.2%)	13 (5.6%)	
Gender	Male	54 (34.2%)	135 (58.4%)	**0.00**
	Female	104 (65.8%)	96 (41.6%)	
Geographic region	Rural	62 (39.2%)	89 (38.5%)	0.88
	Urban	96 (60.8%)	142 (61.5%)	
Education level	Primary education	23 (14.6%)	43 (18.6%)	0.45
	Intermediate education	59 (37.3%)	75 (32.5%)	
	High-level education	76 (48.1%)	113 (48.9%)	
Smoking status	Smoker	27 (17.1%)	52 (22.5%)	0.42
	Non-Smoker	103 (65.2%)	141 (61%)	
	X-Smoker	28 (17.7%)	38 (16.5%)	
Blood Group	A	47(29.7%)	58 (25.1%)	0.64
	AB	32 (20.3%)	44 (19%)	
	B	29 (18.4%)	43 (18.6%)	
	O	50 (31.6%)	86 (37.2%)	
Co-Morbidity	Brain Tumor	1(0.6%)	2 (0.8%)	**0.00**
	HTN	14 (8.9 %)	37 (16%)	
	HTN&DM	13 (8.2 %)	39 (16.9%)	
	HTN, DM, CKD	1(0.6 %)	3 (1.3%)	
	HTN, DM, IHD	3 (1.9 %)	11 (4.8%)	
	HTN, DM, IHD, CKD	0 (0 %)	9 (3.9%)	
	No comorbidity	126 (79.7%)	130 (56.3%)	
Clinical features*				
Fever categories	No fever	33 (20.9%)	7 (3%)	**0.00**
	Low grade (38-39.3)	121 (76.6%)	160 (69.3%)	
	High grade (>= 39.4)	4 (2.5%)	64 (27.7%)	
Fatigue categories	Less than one week	6 (3.8%)	0 (0%)	**0.00**
	1-2 weeks	59 (20.3%)	20 (8.7%)	
	2-3 weeks	82(51.9%)	89 (38.5%)	
	More than three weeks	11(7%)	122 (52.8%)	
Diarrhoea	Yes	37 (23.4%)	116 (50.2%)	**0.00**
	No	121 (76.6%)	115 (49.8%)	
Dyspnea	Yes	10 (6.3%)	151 (65.4%)	**0.00**
	No	148 (93.7%)	80 (34.6%)	

Laboratory Findings			
D-Dimer (µg/ml), Mean value	618.2	1435.8	0.00
Ferritin (ng/ml), Mean value	386.9	721.6	0.00
CRP (mg/l), Mean value	37.6	73.9	0.00

When comparing the two groups (severe and non-severe) based on their laboratory findings, we found that the mean of d-Dimer for the severe group is 1435.8 µg/ml, which is significantly higher than the mean of the non-severe group 618.2 µg/ml (t 879.6= -8.036, P value < .001). Similarly, among the severe group, the mean of the ferritin level is 721.6 ng/ml, which is significantly higher than the mean for the non-severe group, 386.9 ng/ml (t 376.9= -9.65, P value < .001). The CRP level was also considerably higher among the severe group, 73.9 mg/l versus 37.6 mg/l for the non-severe group (t 377.9 = -9.94, p < .001).

Predictors of COVID-19 Severity

The multivariable logistic regression model was created with the following variables: sex, co-morbidities, fever, fatigue duration, diarrhoea, dyspnea, CRP, ferritin, and D-Dimer levels. In general, the model's overall classification accuracy was 85.9%, and Nagelkerke's R2 was .715, which suggests that the model explains roughly 71.5% of the variation in the outcome. Also, there is no multicollinearity between the independent variables.

The results showed that among the nine included variables, eight were statistically significant independent predictors of COVID-19 severity, as illustrated in Table 3. Developing severe COVID-19 infection was significantly higher among male patients; the odds of developing severe infection were more than four times that of the female group (OR 4.5,[95% CI 2.05; 9.87]). Among comorbid patients, HTN was the only comorbidity found to be a statistically significant predictor in that developing severe infection among patients with HTN was more than six times (OR 6.83, [95% CI 2.4; 19.54]). Additionally, fever was a significant predictor of the severity of COVID-19 infection. Patients with high-grade fever were 29 times more likely to develop a severe infection when compared with patients without fever (OR 29.3, 95% CI 5.34; 160.24). Similarly, diarrhoea and dyspnea were found to be a statistically significant predictor of COVID-19 severity as they increased the odds of developing a severe infection by more the 4, 42, and 18 times (ORs 4.4, 42.6, 18.4), respectively, when compared with the reference groups (No diarrhoea, No dyspnea). Increasing fatigue duration was also a significant predictor of the severity of COVID-19 infection, as it increased the odds of severity by 8% (OR 1.08, 95% CI 1.01; 1.16). Of the three studied laboratory findings, elevated ferritin level was a significant predictor of the severity of infection. As for every one ng/ml increase in ferritin level, the odds of severity are increased by 0.3 (OR 1.003, 95% CI 1.001; 1.006).

Table 3. Multivariable binary logistic regression of ten risk factors for the severe course of COVID-19 in the study cohort

Variable	β Coefficient	SE	P value	Odds Ratios (95% CI)
Sex (Female = reference)	**1.45**	**.40**	**.000***	**4.26 (1.95; 9.33)**
Underlying disease (No= reference)			.019	
Brain Tumor	.12	1.94	.952	1.12 (.03; 49.97)
Hypertension	**1.92**	**.54**	**.000***	**6.83 (2.4; 19.54)**
HTN&DM	.12	.54	.823	1.13 (.39; 3.27)
HTN, DM & CKD	-1.63	2.50	.515	.196 (.001; 26.32)
HTN, DM, & IHD	.81	1.06	.446	2.24 (.28;17.9)
Fever categories (No fever= reference)			.000	
Low-grade fever	.43	.60	.478	1.53 (.47; 4.96)
High-grade fever	**3.3**	**.87**	**.000***	**29.25 (5.34; 160.24)**
Fatigue duration (continuous)	**.080**	**.034**	**.021***	**1.08 (1.01; 1.16)**
Diarrhea (No diarrhea = reference)	**1.47**	**.44**	**.001***	**4.36 (1.85; 10.28)**
Dyspnea(No dyspnea = reference)	**3.75**	**.64**	**.000***	**42.58 (12.22; 148.36)**
d-Dimer (μg/ml)	.000	.000	.377	1.00 (.99; 1.00)
Ferritin (ng/ml)	**.003**	**.001**	**.013***	**1.003 (1.001; 1.006)**
CRP (mg/l)	-.012	.01	.198	.99 (.97; 11.01)
Constant	-2.92	1.11	.008	

To summarise, the logistic regression model identified that male gender, HTN as underlying disease, high-grade fever, increasing fatigue duration, diarrhoea, dyspnea, and higher ferritin level were significantly associated with the severity of COVID-19 infection, and indeed can explain 67.2 % of the variance in outcome. Furthermore, sorting the significant predictors based on their odds ratios revealed that dyspnea and high grad fever were very strong predictors of severity. At the same time, male gender and hypertension were strong predictors of severity. On the other hand, Ferritin gave indiscernible predictive value.

Discussion

This study focuses on the predictability of some routinely and easily obtained patient data upon hospital admission that might govern the severity of COVID-19 in an attempt to early discrimination between the severe and non-sever cases. Since it is not reasonable to perform physical examinations and laboratory tests for the vast numbers of hospital-attending individuals, it is important to find the strong predictors of the possibility of getting a severe course and required ICU admission.

Different previous studies documented that older age (above 60 years) has been associated with the worse outcome; however, in our research and through univariate analysis, the age variable did not show a significant association with the severity. Our cohort characteristics can account for this inconsistency, as the older participants (above 65 years) constitute only 4%, and the cohort mean age is 33.6 years. This study found that male gender was the important risk factor for a severe course of

the disease; in this regard, our finding was in agreement with a large-scale global study conducted by Peckham and his colleagues, 2020 (15), who found that male gender was significantly associated with severe outcome measured in term of ICU admission with OD=4.26 (1.95; 9.33); furthermore, Jin et al., 2020(16) conclude that male gender was a significant risk factor and independent of age and susceptibility to COVID-19 infection; also many other global studies stated the association of gender (male) with severe cases of COVID-19 [8,10,17,18]. However, in contrast to our findings, other studies found no significant association of the gender variable with the severe course of the disease [10,12,19]. The gender-biased prognosis is attributed to the gender differences in the genetic makeup, hormonal factors and immune response. Male gender had a higher expression level of TMPRSS2, the main protease involved in SARS-Cov-2 entry, many genes that play a crucial role in both innate and adaptive immune responses are located on the chromosomes X since females have two X chromosomes; they are protected from an inherent mutation in contrast to males that have only one chromosome [20] . Estrogen may also protect females against worse outcomes [21,22]. Regarding the immunological aspect, the differences between males and females accounted for the females' advantages, as a higher number of CD4-T cells and increased B-cell production of antibodies were found in females [23].

For smoking status, in this study, the univariate analysis found no significant differences between smokers, non-smokers, and X-smokers regarding COVID-19 severity; a similar finding was also reported previously [24,25]; ABO-system has been linked to the susceptibility and severity of many infectious diseases like; Rotavirus, Norovirus Malaria, Cholera and E.coli [26]. Nevertheless, the results of previous studies that proposed such an association with COVID-19 severity were heterogeneous. Our study found that blood group O was more likely to have a severe infection (37.2%); however, no statistical significance between the blood groups and the severity of COVID-19 was found. Our finding in this regard was in line with [27]. In agreement with our result, Almadhi et al., 2021 [28] found that the ABO-blood groups were not ideal predictors of severity. Regarding the co-morbidities, previous studies [29-32] showed a higher prevalence of hypertension than other comorbidities. However, our study's prevalence rate of hypertension was 13.1% lower than what was previously documented in international studies [8,10,17]. It has been stated that the prevalence rates of hypertension among COVID-19 patients varied from 15% [29] to 58% [30]. To explain this difference, the age variable should be considered, as there is a high correlation between older ages (above 65 years) and hypertension. Furthermore, the prevalence of hypertension is affected by the age of the patients included [31], with the keeping in mind that the mean age of our cohort was 33.6 years, lower than the mean ages (>65 years) of previous studies.

The univariate analysis of the current study indicated a significant association of the co-morbidities with the severity; this finding was in line with many severity prediction studies [10,17,32,33]. However, the multivariable logistic regression model indicated that only hypertension was the solid independent

risk factor of severity(OR. 6.83), a finding that was also recorded in China (8,30), USA [34], Spain [22] and Bangladesh [35]. Hypertension has been considered a risk factor for the poor prognosis of COVID-19 in many previous meta-analysis studies [36,37]. It is widely accepted that some comorbidities frequently coexist, and the best example is the coexistence of hypertension with diabetes, which was noticed in this study. However, in contrast to Guan et al. (2020) [33], who found a correlation between the number of comorbidities and the severity of COVID-19, such a finding was not recorded in our study. Our results indicated that the prevalence of CKD and tumors among COVID patients were relatively low in consistency with other reports [33,35,38]. The association of the comorbidities with the severe outcome in this study represents an interesting finding since the confounding effect of age did not exist.

Regarding the clinical features at presentation, this study found that dyspnea, and high-grade fever, were very strongly (OR >7) predicted the severe outcome. Previous meta-analysis studies also recorded a similar finding [39-41]. The result of this study in this regard is significant since both dyspnea and fever can easily be measured at the house, and the patient can judge if they need hospitalization or not. Ding, 2021 [42] documented that fever significantly predicted longer hospitalization. Gastrointestinal symptoms, particularly diarrhea, have frequently been reported among COVID-19 patients; in our study, the prevalence of diarrhea was 30.3%. Although the prevalence of diarrhea among the COVID-19 population was subjected to regional variation, sample size, and the number of involved study sites, our finding

was within the global prevalence range (10-50%) of diarrhea among COVID-19 patients stated in the previous meta-analysis studies [43-45]. Several studies have associated diarrhea with a severe course of COVID-19; our study found that diarrhea increases the chance of a severe course about four times [OR: 4.36 (1.85; 10.28)]. However, our finding was in line with [45,46]. Gastrointestinal symptoms are not uncommon in COVID-19 patients since the SARS-Cov-2 receptors, ACE2, are expressed on the enterocytes of the ileum and colon; attachment of the virus to enterocytes causes alteration in the absorption function through dysregulation of the sodium-dependent glucose transport and hence diarrhea ensues [47]. The association of diarrhea with the severe COVID-19 course could be explained as the massive release of proinflammatory cytokines during cytokine storms could damage the digestive tract [48].

Regarding the laboratory findings, in the current study, the univariate analysis revealed a significant association between laboratory findings and the COVID-19 severity as the levels of d-Dimer, ferritin and CRP in the severe group were higher than those of the non-sever group (1435.8, 721,6 and 73.9 vs 618.2, 386.9 and 37.6), findings were agreed with previous studies [7,49-52]. On the other hand, Multivariable logistic regression showed that only ferritin level was significantly associated with the severity of COVID-19; moreover, the prediction strength of all laboratory findings (measured by OR) was not Discernable. In this regard, our results disagreed with a previous Iraqi study conducted by Mohammed et al. (2022) [51] as they found that the elevated levels of biomarkers (Ferritin, CRP, and d-Dimer) are essential predictors of severity;

this disagreement could be attributed to differences in the statistical models as they used only one statistical model (Two Step Cluster analysis) while in our study, two tests were used (Univariate and Multivariable logistic regression), in addition we used 14 different types of variable (demographic, clinical presentation and laboratory findings), while they used only laboratory findings of some biomarkers, so the confounding effect of other variables was considered in our study. It has been stated that no reliable biomarkers can be used for precise prediction of the prognosis and the severity of COVID-19 [53]. However, in agreement with our study, Omran 2021 [10] and Zayed 2022 [54] documented ferritin as a significant predictor for severe COVID-19 [10]. In the same context, [55] concluded that early assessment of ferritin level may help identify the patients with increasing risk of poor outcomes. The high level of proinflammatory cytokines (IL-6) stimulates the production of hepcidin, which regulates the ferritin level [56].

The strength of this study was: I- the use of routinely obtained patient data at hospital admission time (within the first 24 hours) that are applicable in different hospitals. II- Relatively good sample size, representative of the entire population of Al-Nasiriyah city, since the study was conducted in the main COVID-19 hospital specialized for diagnosing and managing COVID-19. III- The study was conducted during peak COVID-19 cases recorded in the city. IV- in contrast to many previous studies, which used only demographic or clinical signs or laboratory findings to predict the severity, our study combined all demographic, clinical symptoms, and laboratory findings in which the confounding effects of different variables

were considered. V- Since the age variable was not included in our logistic regression model, the prediction power of comorbidities was isolated from the confounding effect of the age. VI- Instead of previous predicting studies, which only named the risk factors without determining the strength of prediction, this study arranged the risk factors according to their power of prophecy in terms of OR. However, the interpretation of the findings of this study should consider the following limitations that could not be overcome, including the I-missing of some important host-specific data like; MI and some essential clinical symptoms like cough and radiological findings. The laboratory findings represented the patient's status within the first 24 hours of admission. Our study did not include mortality due to the study design focusing on hospital admission, not follow-up studies.

Conclusions

In this study, some risk factors are found to have strong prediction power for the severity of COVID-19; these factors include; high grad fever, dyspnea, male gender, diarrhoea and presence of comorbidities, particularly hypertension. This work is constructive for clinicians to early discriminate the patients who may develop severe outcomes, which might help efficiently use health resources in sensitive times.

in the categorization of the cases based on the clinical features.

Ethical Approval

This study was approved by the scientific committee of the community health department of AL-Nasiriyah Technical Institute/ Southern Technical University and the scientific committee of the College of Medicine/ Thi-Qar University. The data were collected according to written approval permission from the Thi-Qar Health Directory. Patient's consensuses were not required as personal information was unidentified.

Competing Interests and Funding

All authors of this manuscript have no conflict of interest with this publication, and no financial support was received that might affect the research outcome

References

1. WHO. COVID-19 Weekly Epidemiological Update. 2023. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2023

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497–506.

3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China : a descriptive study. The Lancet. 2020;395(10223):507–13.

4. Epidemiological Group of Emergency Response Mechanism of Novel Coronavirus Pneumonia CC for DC and P. Analysis of Epidemiological Characteristics of Novel Coronavirus Pneumonia. Chinese Journal of Epidemiology. 2020;41(02):145–51. Available from: doi: 10.3760/cma.j.issn.0254-6450.2020.02.003

5. Wang Y, Wang Y, Chen Y QQ. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020;92(6):568–76.

6. Requia WJ, Kondo EK, Adams MD, Gold DR, Struchiner CJ. Risk of the Brazilian health care system over 5572 municipalities to exceed health care capacity due to the 2019 novel coronavirus (COVID-19). Science of the Total Environment. 2020;730.

7. Pramono A, Setiawan YB, Maryani N. Risk Factors for Mortality in Indonesian COVID-19 Patients. Open Access Maced J Med Sci. 2022;9(T5):181–4.

8. Fang L, Xie H, Liu L, Lu S, Lv F, Zhou J, et al. Early predictors and screening tool developing for severe patients with COVID-19. BMC Infect Dis. 2021;21(1):1–8. Available from: https://doi.org/10.1186/s12879-021-06662-y

9. Abolfotouh MA, Musattat A, Alanazi M, Alghnam S, Bosaeed M. Clinical characteristics and outcome of Covid-19 illness and predictors of in-hospital mortality in Saudi Arabia. BMC Infect Dis. 2022;22(1):1–11. Available from: https://doi.org/10.1186/s12879-022-07945-8

10. Omran D, Soda M Al, Bahbah E, Esmat G, Shousha H, Elgebaly A, et al. Predictors of severity and development of critical illness of Egyptian COVID-19 patients: A multicenter study. PLoS One. 2021;16(9 September):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0256203

11. Alrajhi AA, Alswailem OA, Wali G, Alnafee K, Alghamdi S, Alarifi J, et al.

Data-Driven Prediction for COVID-19 Severity in Hospitalized Patients. Int J Environ Res Public Health. 2022;19(5).

12. Cantero-Quintero S, Sáez-Martínez M, Castellanos-Garrido AB. Risk factors for severity and mortality in adults testing positive for COVID-19 in the VI Health Area of Albacete. Enferm Clin. 2022;32(4):217–24.

13. WHO. Clinical management Clinical management Living guidance COVID-19. 2021B. 2021;(January):16–44.

14. Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, et al. Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. Cancer Causes and Control. 2000;11(6):477–88.

15. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11(1):1–10. Available from: http://dx.doi.org/10.1038/s41467-020-19741-6

16. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 2020;8(April):1–6.

17. Martínez-Martínez MU, Alpízar-Rodríguez D, Flores-Ramírez R, Portales-Pérez DP, Soria-Guerra RE, Pérez-Vázquez F, et al. An Analysis COVID-19 in Mexico: a Prediction of Severity. J Gen Intern Med. 2022;37(3):624–31.

18. Chen J, Bai H, Liu J, Chen G, Liao Q, Yang J, et al. Distinct Clinical Characteristics and Risk Factors for Mortality in Female Inpatients with Coronavirus Disease 2019 (COVID-19): A Sex-stratified, Large-scale Cohort Study in Wuhan, China. Clinical Infectious Diseases. 2020;71(12):3188–95.

19. Ramadan HK-A, Mahmoud MA, Aburahma MZ, Elkhawaga AA, El-Mokhtar MA, Sayed IM et al. Predictors of Severity and Co-Infection Resistance Profile in COVID-19 Patients: First Report from Upper Egypt. Infect Drug Resist. 2020;13:3409–3422. Available from: https://doi.org/10.2147/IDR.S272605

20. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: Sex differences in immune response and cardiovascular comorbidities. Cardiovasc Res. 2020;116(14):2197–206.

21. Roved J, Westerdahl H HD. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. Horm Behav. 2017;88:95–105.

22. Klein SL FK. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–38.

23. Abdullah M et al. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell Immunol. 2012;272:214–219.

24. Rachmawati E, Nurmansyah MI, Suraya I, Listiowati E, Kurniawan DW, Ahsan A. Association between cigarette smoking patterns and severity of COVID-19: Findings from a study in 15 private Hospitals in Indonesia. Tob Induc Dis. 2023;21:2021–4.

25. Ismail N, Hassan N, Abd Hamid MHN, Yusoff UN, Khamal NR, Omar MA, et al. Association of Smoking and Severity of Covid-19 Infection Among 5,889 Patients in Malaysia: a Multi-Center Observational Study. International Journal of Infectious Diseases. 2022;116(February 2020):189–96. Available from: https://doi.org/10.1016/j.ijid.2022.01.011

26. L. C. Blood groups in infection and host susceptibility. Clin Microbiol. 2015;28(3):801–70.

27. Kabrah SM, Kabrah AM, Flemban AF AS. Systematic review and meta-analysis of the susceptibility of ABO blood group to COVID-19 infection. Transfusion and Apheresis Science. 2021;60(4):103169.

28. Almadhi MA, Abdulrahman A, Alawadhi A, Rabaan AA, Atkin S, AlQahtani M. The effect of ABO blood group and antibody class on the risk of COVID-19 infection and severity of clinical outcomes. Sci Rep. 2021;11(1):19–23. Available from: https://doi.org/10.1038/s41598-021-84810-9

29. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708–20.

30. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - Journal of the American Medical Association. 2020;323(11):1061–9.

31. Sisnieguez CEL, Espeche WG, Salazar MR. Arterial hypertension and the risk of severity and mortality of COVID-19. European Respiratory Journal. 2020;55(6):6–9. Available from: http://dx.doi.org/10.1183/00000000.00000000

32. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. Clinical Immunology. 2020;217(May):108509.

33. Guan WJ, Liang WH, Zhao Y et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a Nationwide Analysis. Eur Respir J. 2020;55(5):2000547. Available from: doi:10.1183/13993003.00547-2020

34. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. The BMJ. 2020;369.

35. Ganguli S, Howlader S, Dey K, Barua S, Islam MN, Begum A, et al. Association of food habit with the COVID-19 severity and hospitalization: A cross-sectional study among the recovered individuals in Bangladesh. Nutr Health. 2022;28(4):771–82.

36. Fathi M, Vakili K, Sayehmiri F, Mohamadkhani A, Hajiesmaeili M, Rezaei-Tavirani M, et al. The prognostic value of comorbidity for the severity of COVID-19: A systematic review and meta-analysis study. PLoS One. 2021;16(2 February):1–25. Available from: http://dx.doi.org/10.1371/journal.pone.0246190

37. Yang J. et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. International Journal of Infectious Diseases. 2020;

38. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025–31.

39. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. International Journal of Infectious Diseases. 2020;94:91–5.

40. Jain V, Yuan J min. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission : a systematic review and meta- analysis. Int J Public Health. 2020;65(5):533–46. Available from: https://doi.org/10.1007/s00038-020-01390-7

41. Hu X, Hu C, Yang Y, Chen J, Zhong P, Wen Y, et al. Clinical characteristics and risk factors for severity of COVID-19 outside Wuhan: a double-center retrospective cohort study of 213 cases in Hunan, China. Ther Adv Respir Dis. 2020;14(April):1–15.

42. Ding FM, Feng Y, Han L, Zhou Y, Ji Y, Hao HJ, et al. Early Fever Is Associated With Clinical Outcomes in Patients With Coronavirus Disease. Front Public Health. 2021;9(August).

43. Klopfenstein, T.; Kadiane-Oussou, N.D.J.; Royer PYD. Diarrhea: An underestimated symptom in Coronavirus disease 2019. Clin Res Hepatol Gastroenterol. 2020;44:282–283.

44. Ozkurt, Z.; Çınar Tanrıverdi E. Gastrointestinal manifestations, liver injury and recommendations. World J Clin Cases. 2022;10:1140–1163.

45. Ghimire S, Sharma S, Patel A, Budhathoki R, Khan HM, Lincoln M, et al. Diarrhea Is Associated With Increased Disease Severity in COVID-19: Systematic Review and Meta-Analysis. American Journal of Gastroenterology. 2020;115(1):S68–S68.

46. Dhakal S, Charoen P, Pan-ngum W, Luvira V, Sivakorn C, Hanboonkunupakarn B, et al. Severity of COVID-19 in Patients with Diarrhoea: A Systematic Review and Meta-Analysis. Trop Med Infect Dis. 2023;8(2).

47. Gu, J., Han, B., & Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission See. Gastroenterology. 2020;7(2):33–48. Available from: http://repository.radenintan.ac.id/11375/1/PERPUS PUSAT.pdf%0Ahttp://business-law.binus.ac.id/2015/10/08/pariwisata-syariah/%0Ahttps://www.ptonline.com/articles/how-to-get-better-mfi-results%0Ahttps://journal.uir.ac.id/index.php/kiat/article/view/8839

48. Wang, M.-K.; Yue, H.-Y.; Cai J. COVID-19 and the digestive system. World J Clin Cases. 2021;9:3796–3813.

49. Assal HH, Abdel-hamid HM, Magdy S, Salah M, Ali A, Elkaffas RH, et al. Predictors of severity and mortality in COVID-19 patients. The Egyptian Journal of Bronchology. 2022;16(1). Available from: https://doi.org/10.1186/s43168-022-00122-0

50. Cueto-Manzano AM, Espinel-Bermúdez MC, Hernández-González SO, Rojas-Campos E, Nava-Zavala AH, Fuentes-Orozco C, et al. Risk factors for mortality of adult patients with COVID-19 hospitalised in an emerging country: A cohort study. BMJ Open. 2021;11(7):1–9.

51. Mohammed SK, Taha MM, Taha EM, Mohammad MNA. Cluster Analysis of Biochemical Markers as Predictor of COVID-19 Severity. Baghdad Science Journal. 2022;19(6):1423–9.

52. Ghweil AA, Hassan MH, Khodeary A, Mohamed AO, Mohammed HM, Abdelazez AA, et al. Characteristics, outcomes and indicators of severity for covid-19 among sample of esna quarantine hospital's patients, egypt: A retrospective study. Infect Drug Resist. 2020;13:2375–83.

53. Yan L, Zhang HT, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell. 2020;2(5):283–8. Available from: http://dx.doi.org/10.1038/s42256-020-0180-7

54. Zayed NE, Abbas A, Lutfy SM. Criteria and potential predictors of severity in patients with COVID-19. The Egyptian Journal of Bronchology. 2022;16(1). Available from: https://doi.org/10.1186/s43168-022-00116-y

55. Para O, Caruso L, Pestelli G, Tangianu F, Carrara D, Maddaluni L, et al. Ferritin as prognostic marker in COVID-19: the FerVid study. Postgrad Med. 2022;134(1):58–63. Available from: https://doi.org/10.1080/00325481.2021.1990091

56. Velavan TP MC (Mild versus severe COVID-19): laboratory markers. Int J Infect Dis. 2020;95:304–7.