Development and validation of clinical risk score model for predicting progression of COVID-19 among Iranian patients

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Abstract

There are few scoring systems within the clinical setting for early figuring out high-risk COVID-19 patients for severe illness and negative consequences. The present study aimed to create a risk prediction score that could identify patients whose disease is probably to progress at the time of hospitalization. From April to June 2021, 171 confirmed COVID-19 patients admitted to Bohlool hospital, Iran, were consecutively enrolled in this prospective study. First, the risk score prediction model was constructed the use of a logistic regression model. Then, the validation of the risk score was assessed in an independent sample of patients. 141 (82.5%) were recovered or showed symptomatic improvement. Nine patients (5.2%) had progressed to severe disease, while 21 patients (12.3%) died. Three independently significant variables, including IL-6, NLR, and lung involvement were included in the risk score. The discrimination ability of the risk score was good, with the area under the receiver operating characteristic curve (ROC) 0.970 (95% CI: 0.935, 1.00) in the discovery dataset and 0.973 (95% CI: 0.923, 1.00) in the validation dataset. We discovered a risk score that might be utilized as a clinical diagnostic tool to identify COVID-19 individuals who are at increased risk of illness progression.

Introduction

The coronavirus illness 2019 (COVID-19) first appeared in China in late December 2018 and quickly spread throughout the world [1, 2]. As of 4 February 2022, a total of 386,548,962 confirmed cases of COVID-19, including 5,705,754 deaths, have been reported to the world health organization [3]. So far, the strain that COVID-19 has imposed on global health and economic systems is unprecedented. There have been increased challenges and concerns with the emergence of new SARS-CoV-2 variants such as Delta and Omicron due to their much higher viral transmissibility, harder to detect by real-time reverse transcription-polymerase chain reaction (RT-PCR) methods, and resistance to vaccines [4]. Health resources are limited and could still be influenced by severe cases due to new highly infectious SARS-CoV-2 variants, leading to more hospitalizations and deaths [5].

Early identification of COVID19 patients at increased risk of disease progression, more severe illness and death is a high priority. It could help clinical decision-making on the optimal allocating of limited resources and capacity to patients who are most likely to benefit from early therapeutic intervention. As a result, it could prevent disease progression, reduce the risk of death, and diminish the disease burden on healthcare systems [5]. So far, several models have been proposed based on a combination of demographic, clinical, and radiological features to predict and identify patients at risk early for severe pneumonia, intubation, ICU transfer, and patient death [4-7]. However, these models are currently not generally used in clinical practice. They are prone to bias (5) for reasons, such as limited selected samples, being the retrospective nature of the study design, and unclear details of the model development and validation. On the other hand, considering the emergence of new variants of SARS_CoV-2 with different characteristics, these models need to be updated. Despite being one of the countries most affected by the COVID-19 outbreak, there are very little research and limited available clinical experience

in this context from Iran. Therefore, this study aimed to create a risk prediction score that could identify patients whose disease is probably to progress at the time of hospitalization.

Methods

Study Design, Participants, and data collection

This descriptive-analytical study was performed on 171 consecutive COVID-19 patients admitted to Bohlool hospital in Gonabad, Iran, between April 4 and June 5, 2021. Inclusion criteria included a definitive diagnosis of COVID-19 by RT-*PCR test* and a minimum age of 18 years. All patients were treated according to the physician's diagnosis, and interleukin 6 (IL-6), C - reactive protein (CRP), Lactate Dehydrogenase (LDH), and Ferritin tests were performed as a supplement for all patients. Other data were extracted using hospital information system (HIS) resources. Patients with incomplete records were excluded from the study.

Ethical considerations

The study was approved by the ethics committee of Gonabad University of Medical Sciences. The ethical principles of human medical research (Helsinki declaration) was observed in all phases of the study. Data of all patients were extracted confidentially and encrypted from the HIS system. The patient's diagnosis process was carried out under the guidelines published by the World Health Organization and the Iranian Ministry of Health.

Potential Predictive Variables

Potential predictor variables were: age, sex, pregnancy, use tobacco, use opium, history of COVID-19, inpatient department, Pao2, temperature, Computed Tomographic (CT) imaging score, signs, and symptoms at admission (fever, cough, muscular pain, respiratory distress, loss of consciousness, decreased sense of smell, decreased sense of taste, seizure, abdominal pain, nausea, vomiting, diarrhea, anorexia, headache, vertigo, paresthesia, paraplegia, chest pain, skin lesion, comorbidities (liver diseases, diabetes, hematologic diseases, HIV/ AIDS, autoimmune diseases, heart diseases, kidney diseases, asthma, chronic lung diseases, nervous diseases, hypertension, and other), laboratory values (WBC, NLR, CRP, IL-6, LDH, Ferritin), Clinical management & pharmacological treatment (tracheal intubation, O2 therapy, drugs).

Outcome

Patients were divided into two groups based on the outcomes: 1) without disease progression: patients who fully recovered and discharged or showed stable symptomatic improvement, 2) with disease progression: patients who had progressed to severe illness and stayed in ICU or dead.

Statistical Analysis

Data were analyzed by SPSS software version 16.

Descriptive statistics and bivariate analysis

The Kolmogorov-Smirnov test was used to examine if the normal distribution for quantitative variables, including age, Pao2, temperature, duration of hospitalization, and laboratory values, are met or not. The age distribution was normal and reported as the mean (standard deviation) and was compared between the two groups with and without disease progression using the independent t-test. Median (25th percentile, 75th percentile) and the Mann-Whitney test were used to describe and compare other quantitative variables between the two groups, respectively. Describing and statistical comparison for qualitative variables were carried out using number (percentage) and the Chi-square test, respectively. A two-sided P-value less than 0.05 was considered significant.

Development and validation of risk score prediction model

After randomly dividing data into two parts (discovery dataset (80% of data) and validation dataset (20% of data)), to develop a risk score prediction model for disease progression in patients with COVID-19, the prediction model was developed using a logistic regression model on the discovery dataset. The variables with a p-value less than 0.2 in the simple logistic regression model were entered into a multiple logistic regression model. We considered a backward removal method with $p < 0.05$ for entering variables and $p < 0.1$ for removing variables into/from the model. The coefficients obtained from the multiple logistic regression model were converted to an integer risk score. The highest value of sensitivity and specificity were used to determine the optimum cut-point for the risk score model. Assessment of model calibration was performed using the Hosmer-Lemeshow test with a P-value greater than 0.05, indicating acceptable goodness of fit to the data. The area under the receiver operator curve (AUC), with the minimum value of 0.70 as a desirable discrimination ability, was used to evaluate the discrimination ability of the risk score model in both discovery and validation datasets. The performance of the risk score prediction model was compared with each of the predictors of the model and also other statistically significant laboratory variables in bivariate analyses alone. The significance level was considered 0.05.

Results

Individual and clinical characteristics of patients

Data were analyzed from 171 patients with COVID-19, of which 149 (87.13%) were hospitalized in the isolation ward and 22 (12.86%) were in the ICU. Of 171 patients, 30 (17.54%) worsened or died. The individual and clinical characteristics of the patients are shown in Table 1.

Table 1
Demographic and clinical characteristics of hospitalized COVID-19 patients

Characteristics		Disease progression		P-value
		Yes	No	
Age, Mean (SD)		71.90 (14.3)	59.33 (17.7)	**< 0.001**‡
Sex, n (%)	Man	18 (60.0)	68 (48.2)	0.315 †
	Woman	12 (40.0)	73 (51.8)	
Pregnancy, n (%)	Yes	1 (3.3)	0 (0.0)	0.175 †
	No	29.0 (96.7)	141 (100.0)	
Use tobacco, n (%)	Yes	1 (3.3)	1 (0.7)	0.321 †
	No	26 (96.7)	140 (99.3)	
Use opium, n (%)	Yes	2 (6.7)	4 (2.8)	0.592 †
	No	28 (93.3)	137 (97.2)	
Inpatient department	Isolation room	15 (50.0)	134 (95.0)	**< 0.001** †
	ICU	15 (50.0)	7 (5.0)	
History of COVID-19, n (%)	Yes	2 (6.7)	13 (9.2)	0.745 †
	No	28 (93.3)	128 (90.8)	
Radiological finding				
Lung involvement, n (%)	< 25%	6 (20)	38 (27)	**< 0.001** †
	25–50%	7 (23.3)	50 (35.5)	
	51–75%	14 (46.7)	8 (5.7)	
	> 75%	2 (6.7)	1 (0.7)	
Signs and symptoms at admission				
Fever, n (%)	Yes	6 (20.0)	61 (43.3)	**0.018 †**
	No	24 (80.0)	80 (56.7)	
Cough, n (%)	Yes	9 (30.0)	54 (38.3)	0.392 †

Notes: SD, Standard Deviation; PaO_2, Partial Pressure of Oxygen; CT, Computed Tomographic; WBC, White Blood Cells; NLR, Neutrophil-to-lymphocyte Ratio; CRP, C-Reactive Protein; IL-6, Interleukin 6; LDH, Lactate Dehydrogenase; ‡ Independent T-test; * Mann-Whitney test; † Chi-square test; Bold values indicate $p < 0.05$.

Characteristics		Disease progression		P-value
		Yes	No	
	No	21 (70.0)	87 (61.7)	
Muscular pain, n (%)	Yes	3 (10.0)	17 (12.1)	0.777 †
	No	27 (90.0)	124 (87.9)	
Respiratory distress, n (%)	Yes	24 (80.0)	80 (56.7)	**0.018 †**
	No	6 (20.0)	61 (43.3)	
Loss of consciousness, n (%)	Yes	3 (10.0)	6 (4.3)	0.363 †
	No	27 (90.0)	135 (95.7)	
Decreased sense of smell, n (%)	Yes	0 (0.0)	4 (2.8)	0.601 †
	No	30 (100)	137 (97.2)	
Decreased sense of taste, n (%)	Yes	0 (0.0)	4 (2.8)	0.601 †
	No	30 (100)	137 (97.2)	
Seizure, n (%)	Yes	1 (0.70)	4 (2.8)	1.000 †
	No	140 (99.30)	137 (97.2)	
Abdominal pain, n (%)	Yes	1 (3.3)	4 (2.8)	1.000 †
	No	29 (96.7)	137 (97.2)	
Nausea, n (%)	Yes	0 (0.0)	17 (12.1)	0.084 †
	No	30 (100)	124 (87.9)	
Vomiting, n (%)	Yes	0 (0.0)	5 (3.5)	0.588 †
	No	30 (100)	136 (96.5)	
Diarrhea, n (%)	Yes	0 (0.0)	4 (2.8)	0.601 †
	No	30 (100)	137 (97.2)	
Anorexia, n (%)	Yes	2 (6.7)	20 (14.2)	0.374 †
	No	28 (93.3)	121 (85.8)	
Headache, n (%)	Yes	0 (0.0)	9 (6.4)	0.220 †

Notes: SD, Standard Deviation; PaO_2, Partial Pressure of Oxygen; CT, Computed Tomographic; WBC, White Blood Cells; NLR, Neutrophil-to-lymphocyte Ratio; CRP, C-Reactive Protein; IL-6, Interleukin 6; LDH, Lactate Dehydrogenase; ‡ Independent T-test; * Mann-Whitney test; † Chi-square test; Bold values indicate $p < 0.05$.

Characteristics		Disease progression		P-value
		Yes	No	
	No	30 (100)	132 (93.6)	
Vertigo, n (%)	Yes	0 (0)	2 (1.4)	1.000 †
	No	30 (100)	139 (98.6)	
Paresthesia, n (%)	Yes	0 (0.0)	0 (0.0)	—
	No	30 (100)	141 (100)	
Paraplegia, n (%)	Yes	0 (0.0)	0 (0.0)	—
	No	30 (100)	141 (100)	
Chest pain, n (%)	Yes	1 (3.3)	3 (2.1)	1.000 †
	No	29 (96.7)	138 (97.9)	
Skin lesion, n (%)	Yes	0 (0.0)	0 (0.0)	—
	No	30 (100)	141 (100)	
PaO_2, Median (25th, 75th)		87.00 (77.75, 91.00)	92.00 (89.00, 95.00)	**< 0.001***
Temperature, Median (25th, 75th)		37.00 (36.50, 37.72)	37.00 (36.70, 37.80)	0.458 *
Comorbidities				
Liver diseases, n (%)	Yes	0 (0.0)	1 (0.7)	1.000 †
	No	30 (100)	140 (99.3)	
Diabetes, n (%)	Yes	6 (20.0)	19 (13.5)	0.394 †
	No	24 (80.0)	122 (86.5)	
Hematologic diseases, n (%)	Yes	0 (0.0)	2 (1.4)	1.000 †
	No	30 (100)	139 (98.6)	
HIV/ AIDS, n (%)	Yes	0 (0.0)	0 (0.0)	—
	No	30 (100)	141 (100)	
Autoimmune diseases, n (%)	Yes	0 (0.0)	0 (0.0)	—

Notes: SD, Standard Deviation; PaO_2, Partial Pressure of Oxygen; CT, Computed Tomographic; WBC, White Blood Cells; NLR, Neutrophil-to-lymphocyte Ratio; CRP, C-Reactive Protein; IL-6, Interleukin 6; LDH, Lactate Dehydrogenase; ‡ Independent T-test; * Mann-Whitney test; † Chi-square test; Bold values indicate $p < 0.05$.

Characteristics		Disease progression		P-value
		Yes	No	
	No	30 (100)	141 (100)	
Heart diseases, n (%)	Yes	5 (16.7)	18 (12.8)	0.570 †
	No	25 (83.3)	123 (87.2)	
Kidney diseases, n (%)	Yes	0 (0.0)	0 (0.0)	—
	No	30 (100)	141 (100)	
Asthma, n (%)	Yes	3 (10)	4 (2.8)	0.104 †
	No	27 (90)	137 (97.2)	
Lung diseases, n (%)	Yes	6 (20)	5 (3.5)	**0.004 †**
	No	24 (80)	136 (96.5)	
Nervous diseases, n (%)	Yes	1 (3.3)	1 (0.7)	0.321 †
	No	29 (96.7)	140 (99.3)	
Hypertension, n (%)	Yes	16 (53.3)	38 (27.0)	**0.005 †**
	No	14 (46.7)	103 (73.0)	
Other's diseases, n (%)	Yes	5 (16.67)	19 (13.47)	1.000 †
	No	25 (83.3)	122 (86.5)	
Laboratory values				
WBC, Median (25th, 75th)		58.50 (44.75, 91.25) $*10^2$	53.00 (40.00, 72.50)$*10^2$	0.144 *
NLR, Median (25th, 75th)		4.93 (2.51, 12.08)	3.63 (2.37, 5.65)	**0.032 ***
CRP, Median (25th, 75th)		47.36 (16.51, 101.43)	20.49 (5.66, 45.77	**0.005 ***
IL-6, Median (25th, 75th)		23.90 (17.85, 33.50)	10.80 (9.10, 13.15)	**< 0.001 ***
LDH, Median (25th, 75th)		381.50 (320.00, 586.00)	339.00 (265.00, 438.00)	**0.027 ***

Notes: SD, Standard Deviation; PaO_2, Partial Pressure of Oxygen; CT, Computed Tomographic; WBC, White Blood Cells; NLR, Neutrophil-to-lymphocyte Ratio; CRP, C-Reactive Protein; IL-6, Interleukin 6; LDH, Lactate Dehydrogenase; ‡ Independent T-test; * Mann-Whitney test; † Chi-square test; Bold values indicate $p < 0.05$.

Characteristics		Disease progression		P-value
		Yes	No	
Ferritin, Median (25th, 75th)		237.30 (143.40, 374.22)	217.00 (101.80, 352.25)	0.542 *
Clinical management & pharmacological treatment				
Tracheal intubation, n (%)	Yes	19 (63.3)	3 (2.1)	**< 0.001** †
	No	11 (36.7)	138 (97.9)	
O_2 therapy, n (%)	Yes	6 (20)	40 (28.4)	0.348 †
	No	24 (80)	101 (71.6)	
Remdesivir, n (%)	Yes	20 (66.7)	117 (83.0)	**0.042 †**
	No	10 (33.3)	24 (17.0)	
Interferon, n (%)	Yes	7 (23.3)	45 (31.9)	0.354 †
	No	23 (76.7)	96 (68.1)	
Dexamethasone, n (%)	Yes	21 (70.0)	101 (71.6)	0.858 †
	No	9 (30.0)	40 (28.4)	
Methylprednisolone, n (%)	Yes	14 (46.7)	46 (32.6)	0.143 †
	No	16 (53.3)	95 (67.4)	
Neurobion, n (%)	Yes	2 (6.7)	16 (11.3)	0.448 †
	No	28 (93.3)	125 (88.7)	
Favipiravir, n (%)	Yes	1 (3.3)	2 (1.4)	1.000 †
	No	29 (96.7)	139 (98.6)	
Hydrocortisone, n (%)	Yes	4 (13.3)	3 (2.1)	**0.019 †**
	No	26 (86.7)	138 (97.9)	
Atorvastatin, n (%)	Yes	19 (63.3)	87 (61.7)	0.867 †
	No	11 (36.7)	54 (38.3)	
Aspirin, n (%)	Yes	17 (56.7)	77 (54.6)	0.837 †

Notes: SD, Standard Deviation; PaO_2, Partial Pressure of Oxygen; CT, Computed Tomographic; WBC, White Blood Cells; NLR, Neutrophil-to-lymphocyte Ratio; CRP, C-Reactive Protein; IL-6, Interleukin 6; LDH, Lactate Dehydrogenase; ‡ Independent T-test; * Mann-Whitney test; † Chi-square test; Bold values indicate $p < 0.05$.

Characteristics		Disease progression		P-value
		Yes	No	
	No	13 (43.3)	64 (45.4)	
Chloroquine, n (%)	Yes	4 (13.3)	20 (14.2)	1.000 †
	No	26 (86.7)	121 (85.8)	
Famotidine, n (%)	Yes	18 (60.0)	105 (74.5)	0.109 †
	No	12 (40.0)	36 (25.5)	
Zinc, n (%)	Yes	8 (26.7)	45 (31.9)	0.572 †
	No	22 (73.3)	96 (68.1)	
Heparin, n (%)	Yes	27 (90.0)	124 (87.9)	0.777 †
	No	3 (10.0)	17 (12.1)	
Vitamin C, n (%)	Yes	12 (40.0)	54 (38.3)	0.862 †
	No	18 (60.0)	87 (61.7)	
Outcomes				
Duration of hospitalization, Median (25th, 75th)		9.00 (3.00, 18.25)	5.00 (4.00, 7.00)	**0.014 ***
Final outcome of COVID-19, n (%)	Fully recover	0 (0.0)	15 (10.6)	
	Improved	0 (0.0)	126 (89.4)	
	Exacerbation	9 (30.0)	0 (0.0)	
	Death	21 (70.0)	0 (0.0)	

Notes: SD, Standard Deviation; PaO_2, Partial Pressure of Oxygen; CT, Computed Tomographic; WBC, White Blood Cells; NLR, Neutrophil-to-lymphocyte Ratio; CRP, C-Reactive Protein; IL-6, Interleukin 6; LDH, Lactate Dehydrogenase; ‡ Independent T-test; * Mann-Whitney test; † Chi-square test; Bold values indicate $p < 0.05$.

Bivariate analysis

The results showed that the mean age of patients with disease progression was significantly higher ($p < 0.001$). The median Pao2 on admission was significantly lower in these patients ($p < 0.001$). The severity of lung involvement based on CT scan imaging findings was significantly higher in this group ($p < 0.001$). Fever and respiratory distress symptoms were significantly different between the two groups at admission ($ps = 0.018$), and no significant difference was observed for other symptoms. Also, in terms of underlying diseases, these patients suffered more from lung diseases ($p = 0.004$) and hypertension ($ps = 0.005$). Among Laboratory findings, NLR, ($p < 0.001$), CRP, ($p = 0.005$), IL -6, ($p = 0.032$), and LDH ($p =$

0.027) were significantly higher in these patients. Also, taking the Remedsivir in these patients was significantly less (p = 0.042), and hydrocortisone was more (p = 0.019).

Development and validation of risk score prediction model

Sixteen variables including age, sex, use of opium, inpatient department, fever, respiratory distress, loss of consciousness, lung involvement, HTN, chronic lung disease, Remedsivir, hydrocortisone, IL-6, CRP, LDH, and NLR in the simple logistic regression model with p-values less than 0.2 and were selected as potential predictor variables to enter the multiple logistic regression model. Of them, three variables, including lung involvement, NLR, and IL-6, were significant in the multiple logistic regression model and were used to establish the risk score (Table 2). The risk score for disease progression was developed based on the regression coefficients of the logistics model. The following formula was used to calculate the probability of disease progression.

Table 2
Logistic Regression Model results of associated factors with adverse in Patients Hospitalized with COVID-19

Variable	Simple		Multiple	
	Unadjusted OR (95% CI)	P- value	Adjusted OR (95% CI)	P- value
IL-6	1.41 (1.25, 1.59)	< 0.001	1.54 (1.26, 1.89)	< 0.001
NLR	1.13 (1.05, 1.22)	0.001	1.23 (1.06, 1.43)	0.008
Long invovement	1.05 (1.03, 1.08)	< 0.001	1.07(1.03, 1.12)	0.001
Notes: IL-6, Interleukin 6; NLR, Neutrophil-to-lymphocyte Ratio; OR, Odds ratio; CI, Confidence Interval.				

$$Riskscore = (0.433 \times IL-6) + (0.205 \times NLR) + (0.072 \times Longinvolvement)$$

$$Probability = \exp(Riskscore)/(1+\exp(riskscore))$$

The Hosmer - Lemeshow test statistic indicated a well-fitting risk score model to the data (p = 0.681).

The Performance and validation of Risk Score

The AUC was 97.0 (95% CI: 93.5, 1.00) in the discovery dataset and 97.3 (95% CI: 92.3, 100.0) in the validation dataset, indicating a good performance in both discovery and validation datasets. The performance of combined variables of IL-6, NLR, and lung involvement as predictors of disease progression in the risk score prediction model was significantly higher than IL-6, NLR, lung involvement, CRP, and LDH alone (Fig. 1). The cut-off values, sensitivity, specificity, positive and negative predictive values of each of mentioned variables, and the Z-score of the established prediction model are listed in Table 3.

Table 3
Sensitivity, specificity, NPV, PPV, and AUC of CRP, LDH, NLR, Lung involvement, and IL-6 in discovery and validation datasets.

Discovery dataset						
Marker (cut-off)	CRP (33.22)	LDH (356.50)	NLR (4.54)	Long involvement (42.5)	IL-6 (14.45)	Long involvement + IL-6 + NLR (-2.45)
Sensitivity % (95% CI)	66.7 (44.7, 84.4)	58.3 (36.6, 78.0)	54.2 (32.8, 74.5)	70.8 (48.6, 86.6)	91.7 (73.0,99.0)	91.7 (73.0, 99.0)
Specificity % (95% CI)	65.5 (55.8, 74.3)	56.4 (47.0, 65.8)	60.0 (50.2, 69.2)	85.5 (77.1, 91.2)	84.5 (76.4, 90.7)	88.2 (80.6, 93.6)
NPV % (95% CI)	90.0 (83.4, 94.1)	86.1 (79.0, 91.1)	85.7 (79.1, 90.5)	93.1 (85.8, 96.9)	97.9 (92.4, 99.4)	98.0 (92.8, 99.5)
PPV % (95% CI)	29.6 (22.3, 38.1)	22.6 (16.4, 91.1)	22.8 (16.1, 31.3)	51.5 (33.6, 68.8)	56.4 (45.1, 67.1)	62.9 (50.0, 74.1)
AUC % (95% CI)	68.8 (56.7, 81.0)	61.8 (48.9, 74.7)	64.6 (50.6, 78.6)	78.7 (66.7, 90.7)	93.4 (87.7, 99.1)	97.0 (93.5, 100.0)
Validation dataset						
Sensitivity % (95% CI)	66.7 (22.3, 95.7)	50.0 (11.8, 88.2)	50.0 (11.8, 88.2)	66.7 (24.1,94.0)	83.3 (35.9, 99.6)	100.0 (54.1, 100.0)
Specificity % (95% CI)	64.5 (45.4, 81.0)	58.1 (39.1, 75.5)	67.7 (48.6, 83.3)	80.6 (61.9, 91.8)	71.0 (52.0, 85.8)	87.1 (70.2, 93.4)
NPV % (95% CI)	90.9 (75.8, 97.0)	85.7 (71.9, 93.4)	87.5 (75.2, 94.2)	92.6 (74.2, 98.7)	95.7 (78.4, 99.3)	100.0 (100.0, 100.0)

Notes: NPV, negative predictive value; PPV, positive predictive value; AUC, Area Under the receiver operator Curve; CRP, C-Reactive Protein; LDH, Lactate Dehydrogenase; NLR, Neutrophil-to-lymphocyte Ratio; IL-6, Interleukin 6; CI, Confidence Interval.

Discovery dataset						
PPV %	26.7	18.8	23.1	41.3	35.7	60.0
(95% CI)	(14.8, 43.2)	(8.6, 36.2)	(10.4, 43.7)	(13.3, 100.0)	(22.4, 51.7)	(37.5, 78.9)
AUC %	58.1	66.9	53.8	84.1	88.7	97.3
(95% CI)	(26.2, 90.0)	(38.1, 95.7)	(24.5, 83.0)	(67.1, 100.0)	(68.2, 100.0)	(92.3, 100.0)

Notes: NPV, negative predictive value; PPV, positive predictive value; AUC, Area Under the receiver operator Curve; CRP, C-Reactive Protein; LDH, Lactate Dehydrogenase; NLR, Neutrophil-to-lymphocyte Ratio; IL-6, Interleukin 6; CI, Confidence Interval.

Discussion

In this study, to identify risk factors for disease progression and establish a risk prediction model, demographics, clinical, laboratory, and imaging features of 171 consecutive newly admitted COVID-19 patients were evaluated.

The bivariate analyses' results showed that disease progression was significantly associated with older age, which was consistent with other studies (8–10). Older adults have an increased risk of developing more severe COVID-19 complications due to comorbidities, reduced physical functioning, poor body resistance, and decline in ACE2 expression levels and anti-inflammatory response [5, 10].

Fever and respiratory distress were also associated with the risk of disease progression. Fever is the most frequent symptom in COVID-19 patients, which occurs in response of the immune system to virus infections in the body [11]. Delay in seeking medical attention and the rapid disease progression in patients with COVID-19 could lead to an excessive inflammatory condition called a cytokine storm, which appears with an unlimited fever [12], promoting further inflammation and further immune activation with undesired effects [11]. Respiratory symptoms are also important indicators of the severity of the infection.

Similar to other studies [13, 14], patients with preexisting hypertension or chronic lung disease comorbidities were more susceptible to COVID-19 progression. Severe COVID-19 outcome in patients with preexisting hypertension could be related to endothelial dysfunction and renin-angiotensin system (RAS) imbalance that favors a pro-inflammatory state causing a higher level of IL-6 and tumor necrosis factor-α (TNF-α) [15, 16]. Elevating respiratory problems in COVID-19 patients with preexisting chronic lung diseases could worsen the condition and increase mortality [17].

Bivariate analyses' results demonstrated a significant association between elevated NLR, CRP, LDH, and IL-6 values and disease progression in patients with COVID-19. In line with the findings of our study, numerous research (18–20) proposed that increased IL-6, NLR, CRP, and LDH values are related to higher levels of severity of COVID-19 and poorer outcomes. Cytokines play critical roles in regulating

immunological and inflammatory responses. IL-6 is a major inflammatory cytokine with pleiotropic effects implicated in coronavirus-induced storms [21, 22]. The cytokine storm, i.e., high and uncontrolled levels of cytokines, triggers following the inflammatory responses induced in immune, epithelial and endothelial cells due to SARSCoV2 invasion in the body [22]. Cardiovascular collapse, and dysfunction syndromes of various organs, including renal and liver failure, are the consequences of high concentrations of the cytokine storm [23]. The increase in NLR values is related to the decrease in lymphocytes, which have a crucial role in battling SARS-infected cells. The direct effect of SARS-CoV-2 on lymphocytes and causing cell death, increasing lactic acid and inhibiting lymphocyte proliferation, and directly invading the lymphatic organs and destroying them are the main reasons for decreasing lymphocytes in patients with severe COVID-19 [24]. CRP is a plasma protein clinically used as a biomarker to identify disease severity in various inflammatory conditions [25]. COVID19 progression may be accompanied by a cytokine storm and activation of the complement system and amplifying inflammatory insults because of increasing CRP production through stimulating hepatocytes by cytokines such as IL-6 and TNFα. However, it is difficult to effectively state adaptive immunity in severe or critically ill COVID19 patients due to severe damage to the integrity of the alveolar epithelial and endothelial barrier and significant decreases in lymphocyte counts with T cell-mediated immunosuppression. Therefore, it leads to severe macrophage infiltration and worsens acute lung injury [26]. LDH is an intracellular enzyme found in almost all body cells, and increasing its concentration may indicate damage to tissue/cells and viral infections or lung damage [27]. Nevertheless, the pathogenic mechanism by LDH on COVID-19 progress and prognosis remains unclear [28].

To date, corticosteroids and Remdesivir are considered as two most promising treatments for COVID-19 [29]. Nevertheless, As a result of the scarcity of randomized trials and inconclusive observational studies, the efficacy and safety of corticosteroids in viral pneumonia patients, and Remdesivir's risk and benefit for COVID-19 patients who require high-flow oxygen or mechanical ventilation are not certain [30, 31]. In this study, take the Remdesivir in patients with poorer outcomes was statistically significant less, and hydrocortisone was more.

Based on the multivariate logistic regression model results, IL-6, NLR, and lung involvement on admission are the only independent biomarker associated with COVID-19 progression. Our risk prediction model with these three variables achieved an acceptable ROC-AUC of 0.90 in the discovery dataset and 0.89 in the validation dataset for disease progression prediction. However, for the validation dataset, confidence intervals were wider for indices, especially for sensitivity, which may be related to the smaller sample size in the validation dataset. Therefore, a larger sample size is needed to assess its applicability in future research.

Strengths and limitations

This study had some strengths. One of the strengths of this study was the prospective nature of the study design, which added to the validity of data and findings. In this study, validation of the risk score was performed and all indices of assessing the risk score performance were reported with confidence interval.

The Simplicity of the achieved risk score was another strength. The study had some limitations, too. A single-center study and a small sample size weakened the generalizability of the study. Therefore, future studies with national data and larger sample sizes are needed.

Conclusion And Future Development Directions

We identified a risk score that may represent a potential diagnostic tool in the clinical setting to identify COVID-19 patients who are at a higher risk of disease progression. Considering other changes in biomarkers and clinical and diagnostic symptoms of patients with Covid − 19 can help us determine the exact indicators of the disease progression.

Abbreviations

NLR: Neutrophil-Lymphocyte Ratio; IL-6: Interleukin-6; TNFα: Tumor necrosis factor; LDH: Lactate Dehydrogenase; CRP: C - reactive protein; HIS: hospital information system; ACE2: Angiotensin-converting enzyme 2; AUC: Area under the ROC Curve; RAS: renin-angiotensin system; WBC: White Blood Cell; PaO2: Partial Pressure of Oxygen.

Declarations

Acknowledgement

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Authors' Contribution

MS, SSB, and ADN conceived the presented idea.FM, MT, and JH contributed to the design and concepts of the work. Data were collected by MS, SSB, ADN, and HA. FM analyzed data and prepared the draft manuscript. All authors reviewed the manuscript and made amendments before submission.

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Availability of data and materials

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Gonabad University of Medical Sciences (Ethical

code No: IR.GMU.REC.1399.079). All phases of this study were based on the ethical principles of human medical research (Helsinki declaration). For all patients and/or their legal guardians, described the steps of the research and how the patient's participation in the study was explained, assured that all information was confidential, no cost would be imposed on the patient, at any time it could continue to participate in Research has declined and each question can ask the researcher. The informed consent form of Persian is prepared and signed by the from all study participants and/or their legal guardians, researcher and a witness.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

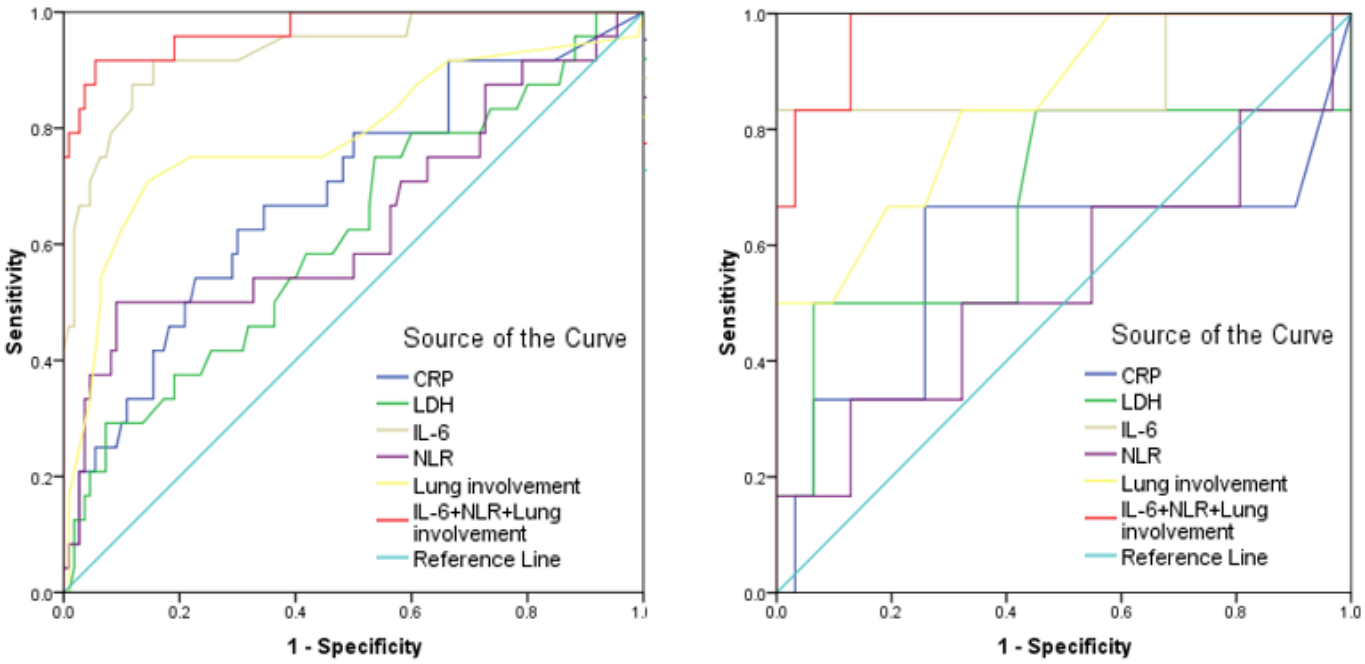

Figure 1

ROC curve of CRP, LDH, NLR, Lung involvement, and IL-6 in a) Left: discovery dataset, b) Right: validation datasets.