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Predictive value of the preliminary findings in the severity of COVID-19 disease and the effect on therapeutic approaches

Hamid Reza Khayat Kashani[1] | Mohamad Hajijafari[2] | Fereshte Khayat Kashani[3] | Sohrab Salimi[4]

[1]Department of Neurosurgery, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Anaesthesiology, Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran
[3]Clinical Research and Development Unit, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
Sohrab Salimi, Department of Anesthesiology, Imam Hossein Hospital, Madani Street, Tehran, Iran.
Email: salimi.sohrab@gmil.com

Abstract

In this retrospective multicenter case series study, the predictive value of initial findings of confirm COVID-19 cases in determining outcome of the disease was assessed. Patients were divided into two groups based on the outcome: low risk (hospitalization in the infectious disease ward and discharge) and high risk (hospitalization in ICU or death). A total of 164 patients with positive PCR-RT were enrolled in this study. About 36 patients (22%) were in the high-risk group and 128 (78%) were in the low-risk group. Results of statistical analysis revealed a significant relationship between age, fatigue, history of cerebrovascular disease, organ failure, white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), and derived neutrophil-to-lymphocyte ratio (dNLR) with increased risk of disease. The artificial neural network (ANN) could predict the high-risk group with an accuracy of 87.2%. Preliminary findings of COVID-19 patients can be used in predicting their outcome and ANN can determine the outcome of patients with appropriate accuracy (87.2%). Most treatment in Covid-19 are supportive and depend on the severity of the disease and its complications. The first step in treatment is to determine the severity of the disease. This study can improve the treatment of patients by predicting the severity of the disease using the initial finding of patients and improve the management of disease with differentiating high-risk from low-risk groups.

KEYWORDS

artificial neural network (ANN), biomarkers, COVID-19, derived neutrophil-to-lymphocyte ratio (dNLR), neutrophil-to-lymphocyte ratio (NLR), SARS virus

1 | INTRODUCTION

The novel viral pneumonia, known by the World Health Organization (WHO) as Coronavirus 2019 (COVID-19), began in late December 2019 as an epidemic in Wuhan, China. The virus causes fever, dry cough, dyspnea, weakness, and lymphopenia. It can also lead to pneumonia, SARS, and death in severe cases.[1,2]

COVID-19 is the third zoonotic virus that leads to the involvement of the respiratory system. Like its counterparts, SARS-CoV and MERS-CoV, it uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter the cell, creating pneumonia and bilateral pulmonary infiltrates. The virus is very similar to the bat coronavirus, and although its exact origin is unknown, an influential theory suggests that it is transmitted from wild animals.[3] According to the experiences from SARS and MERS, its complete virus genome was identified in less than a month.[4,5]

COVID-19 is a single positive-stranded RNA virus coated with two lipid layers. The layer that covers the virus contains S protein. S-protein is fused to cell membrane receptors called ACE2. RNA is injected into the cell to make virus proteins. Once the virus multiplies, the cell explodes, and the viruses are released and penetrate other cells. ACE2 receptors are more commonly found in tissues of the lungs, heart, kidneys, and adipose tissue; these organs consequently are more at higher risk of infection.[6,7] COVID-19 virus is 10-20 times more likely to bind ACE2 than is SARS-CoV. These two viruses have up to 40% similarity of amino acids in S protein.[8,9]

The disease is asymptomatic in most cases but can be accompanied by mild to moderate or severe clinical symptoms. COVID-19 can cause acute respiratory syndrome and possibly death.[10-12] The virus has spread rapidly to other countries and caused a pandemic. According to WHO, on May 31, 2020, more than 5 934 000 people were infected, and 367 000 people died in 225 countries and territories.

Many studies have been performed on clinical and laboratory symptoms and chest CT scans of COVID-19 patients. Given the importance of severe and critical types of the disease, the present study investigates not only the clinical, laboratory symptoms, and underlying diseases, but also the relationship between these findings and the course of the disease and patients' outcome. The studied variables are statistically analyzed, and then, the ANN efficiency in predicting the patients' outcome was explicitly investigated.

2 | METHOD

2.1 | Study design and participants

In this study, COVID-19 patients that have been hospitalized were studied consecutively. The present project was approved by the Imam Hussein Hospital Research Office. The study was conducted at Imam Hossein Hospital of Tehran and Shahid Beheshti Hospital of Kashan from February 10, 2019, to March 10, 2019. Patients with positive PCR-RT tests, based on the WHO protocol, included in the study. The clinical outcome of the patients was evaluated according to the patient's transfer to the ICU and the mortality.

2.2 | Data collection

The inclusion criteria included the following: (a) Positive PCR-RT test for COVID-19 disease; (b) Hospital admission due to coronavirus complications; (c) Informed consent form; and (d) Completion of patient's data.

The data was collected using patients' electronic files and patient follow-up until discharge or death. Demographic information, clinical symptoms at admission, underlying comorbidities, duration of pre-hospital symptoms, and the results of the first laboratory tests were extracted. The patients were treated using the WHO recommendations. Patients with severe respiratory distress or vital organ damage were transferred to the ICU.

The present study aimed to determine the predictive effect of demographic characteristics, clinical and laboratory symptoms, and underlying diseases upon the first referral, on the clinical outcome of the patients. Patients were divided into two groups. The first group included patients who were hospitalized in the infectious disease ward and were discharged without serious complications (low-risk group). The second group included patients who were transferred to the ICU upon referral or during hospitalization or death (high-risk group).

2.3 | Statistical analysis

Data analysis was performed using SPSS (version19.0, IBM, The United States). To investigate the statistical distribution, Kolmogorov-Smirnov test was applied. *T*-test was used in order to investigate the mean value of continuous variables that had a normal distribution. To compare the other groups in terms of the mean value of noncontinuous variables and abnormal distribution, Mann-Whitney *U*-test was used. Univariate and multivariate logistic regression analyses were used to examine the predictors of the patients' outcome. In the case of the normal distribution, the Pearson correlation coefficient was applied, and the Spearman statistical correlation coefficient test was used in the case of the abnormal distribution. ROC curve and AUC were applied to assess the diagnostic value of the preliminary findings of the disease outcome. In the present research, both-sided *P*-value <.05 was considered statistically positive.

2.4 | Artificial neural network

An artificial neural network (ANN) can be used in cases to predict the disease outcome by multiple variables. One of the most widely used ANNs is a multilayer perceptron (MLP). MLP involves a three-layer structure, including the input, the middle, and the output layers. The middle layer consists of one or more layers. Besides the input layer nodes, each node in the other layers uses a nonlinear activation function. MLP uses a supervised learning technique where a set of inputs and outputs is sent to the system, and the system tries to learn a function to convert the input to the output. Backpropagation is the training method in MLP. In this method, first, the network error is determined, and the weights are then corrected so that the mean squares of the difference between the actual output and desired output of the network are reduced.

In the present research, the training set for each case includes demographic characteristics and laboratory results of patients with positive COVID-19 test as the input and disease outcome as the output. Each person has one of the following two outcomes. (a) Infectious disease ward admission and discharge (Class 0); and (b) ICU admission or death (Class 1). The MLP network is trained using the available data, and its classification accuracy of patients in two groups of Class 0 or Class 1 is evaluated.

The evaluation was performed using the *k*-fold cross-validation method. In this method, the whole data set is divided into *k* parts, and each part is considered as a fold. In this study, $k = 10$ was used. The results of MLP are presented in the confusion matrix table, in which the accuracy and precision of the data placement are determined. The predictive value of the neural network in determining the disease outcome is shown using the ROC curve.

3 | RESULTS

3.1 | Demographic characteristics

A total of 164 patients with positive PCR-RT results were included in the study. As presented in Table 1, 79 patients were female and 85 were male. The mean age of patients was 58.8 years (range of 20-86 years). The average prereferral duration of symptoms was 6.5 days. Of the total patients, 128 were hospitalized in the infectious disease ward and were discharged from the same ward, thus did not require ICU admission and intensive care (low-risk patients); 36 patients required ICU admission from the beginning or during hospitalization or died due to the disease complications (high-risk patients). The mortality rate was 10 individuals (6.1%). The most common symptoms upon admission were cough and dyspnea (65.2%), followed by fever (55.5%) and anorexia (53.7%). Diarrhea (7.3%) was the rarest symptom in patients. A total of 52.3% of patients had comorbidities, being higher in the high-risk patient group. The most common comorbidity was hypertension (25%), followed by cardiovascular (13.4%) and respiratory disorders (11%).

Intergroup comparison concerning demographic characteristics showed that age was significantly higher in high-risk patients ($P < .001$). A significant relationship between the patient's sex and the disease severity was observed so that it was more severe in men ($P < .004$). Comparison of clinical symptoms upon referral in the two low-risk and high-risk patient groups showed a significant relationship between fatigue ($P < .03$) and the disease severity; however, other clinical symptoms were not significantly different in the two groups. Concerning comorbidities, cerebrovascular disease (.007) and organ failure (.002) were significantly related to increased risk of being in the high-risk group, and there was no significant relationship between the two groups concerning other types of underlying diseases. Further, results showed no relationship between the prereferral duration of the symptoms and the disease severity.

TABLE 1 Demographic characteristic, clinical symptoms, and comorbidities of COVID-19 patients

	Outcome			
	Low risk	High risk	Total	*P* value
Age	56.3(20-96)	67.7(31-59)	58.8(20-96)	<.001
Sex				<.044
Female	67	12	79	
Male	61	24	85	
Mortality	0	10(27.8)	10(6.1)	
Sign and symptoms				<.25
Fever	68(53.1)	23(63.9)	91(55.5)	<.55
Cough	82(64.1)	25(69.4)	107(65.2)	<.32
Dyspnea	81(63.3)	26(72.2)	107(65.2)	<.32
Headache	28(22.9)	5(13.9)	33(20.1)	<.29
Anorexia	65(50.8)	23(63.9)	88(53.7)	<.16
Myalgia	53(41.4)	10(27.8)	63(38.4)	<.13
Nausea and vomiting	30(23.4)	6(16.7)	36(21.9)	<.38
Pharyngalgia	17(13.3)	3(8.3)	20(12.2)	<.42
Diarrhea	10(7.8)	2(5.6)	12(7.3)	<.64
Fatigue	17(13.3)	3(8.3)	20(12.2)	<.033
Chest pain	16(12.5)	2(5.6)	18(11)	<.24
Anosmia	16(12.5)	1(2.8)	17(10.4)	<.16
Hypogeusia	32(25)	9(25)	41(25)	<.062
Comorbidities	24(66.7)	91(55.5)	67(52.3)	<.12
Cardiovascular disease	16(12.5)	6(16.7)	22(13.4)	<.51
COPD	14(10.9)	4(11.1)	18(11)	<.97
Hypertension	32(25)	9(25)	41(25)	<1
Cerebrovascular disease	2(1.6)	4(11.1)	6(3.7)	<.007
Diabetes	8(6.3)	4(11.1)	12(7.3)	<.32
Malignancy	2(1.6)	0	2(1.2)	<.45
Organ failure	7(6.5)	8(22.2)	15(9.2)	<.002
Symptoms before hospitalization	6.6	6.2	6.5	<.41

3.2 | Laboratory parameters and blood markers

The laboratory findings of the patients are shown in Table 2. In the present study, in addition to the patient's tests, the blood markers were also calculated to examine their relationship with the degree of risk of the disease. Among blood cells, the mean leukocyte, neutrophil, and monocyte counts are higher, and platelet and lymphocyte counts are lower in the high-risk group.

Hemoglobin levels are slightly lower in high-risk patients, and the mean erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are higher in high-risk patients. In this study, there were significant differences between high-risk and low-risk groups of patients in terms of WBC ($P < .001$), neutrophil ($P < .001$), NLR ($P < .001$), and dNLR ($P < .001$). Pearson correlation test was used to examine the relationship between blood markers and disease severity; the results revealed a positive relationship between NLR ($r = .21$, $P < .007$), dNLR ($r = .22$, $P < .005$), WBC ($r = .31$, $P < .001$), and neutrophil count ($r = .31$, $P < .005$) with the disease severity. Univariate logistic regression showed a significant difference between the two groups in terms of WBC ($P < .004$), neutrophil ($P < .004$), and CRP ($P < .003$). Multivariate logistic regression analysis of the relationship between laboratory findings and disease severity showed no significant relationship between blood markers as an independent predictor and disease severity. Figure 1 shows the ROC curve of the predictive value of neutrophil, WBC, NLR, and dNLR for the disease severity. Among these blood markers, WBC was the best predictor of disease severity (AUC = 0.646), followed by neutrophil and dNLR, respectively.

3.3 | Artificial neural network

In the present work, the data set consisted of blood markers, age, and sex of 164 COVID-19 patients. The blood markers used included WBC, neutrophil, lymphocyte, monocyte, platelet, NLR, LMR, PLR, and dNLR1.

The outcome of each individual was classified into two categories: low-risk (class 0) or high-risk (class 1). A total of 128 patients were placed in Class 0 and 36 patients in Class 1. The patient data set was used for training and testing of MLP.

As shown in the confusion matrix of the artificial neural network (Figure 2), the classification accuracy of the ANN is 87.2%, so that 143 cases are categorized correctly, and there are 21 classification errors.

As given in Table 3, Recall for class 0 ($Recall^0$) is 0.961. In other words, in the low-risk group, 96.1% of cases are classified correctly, which indicates the proper efficiency of the system in the classification for low-risk group members. Recall in the high-risk group (Class 1) is 0.556%, indicating that the MLP network has been able to properly classify more than half of critically ill samples in the right class. Comparison of $Recall^0$ and $Recall^1$ is indicative of better MLP performance for Class 0.

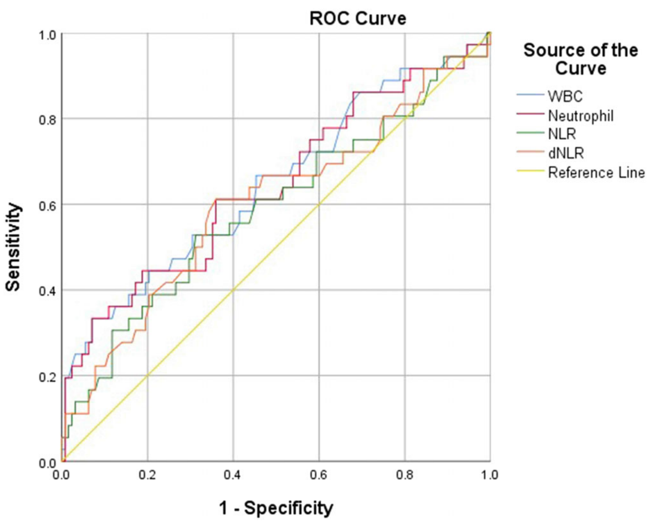

FIGURE 1 ROC curves demonstrate the predictive values of blood markers in differentiation between low and high risk patients. The AUC of the markers are as follows: WBC = 0.646, neutrophil = 0.641, NLR = 0.590, and dNLR = 0.602

TABLE 2 Laboratory findings of COVID-19 patients

	Outcome			
	Low risk	High risk	Total	*P* value
White blood cell count, $\times 10^9$/L	6.7(2.1-22.6)	9.9(2.6-27.5)	7.4(2.1-27.5)	.001
Neutrophil count, $\times 10^9$/L	4.8(.49-23)	7.3(.68-19.9)	5.3(.49–23)	.001
Lymphocyte count, $\times 10^9$/L	1.4(.16-7.4)	1.3(.46-4.2)	1.4(.46–4.2)	.13
Monocyte count, $\times 10^9$/L	.19(.03-1.4)	.2(.04-1.4)	.18(.3-.96)	.147
Platelet count, $\times 10^9$/L	205(74-633)	204(30-608)	205(30-633)	.90
NLR	3.9(.17-19)	6.2(.17-32)	4.4(.17-32)	.001
LMR	15.7(.89-187.5)	14.9(2.8-54.5)	15.5(.89-187)	.589
PLR	159(14-745)	149(9-443)	157(9-745)	.79
dNLR	3.2(.14-15.6)	5.1(.14-24)	3.7(.14-24)	.001
Hb	14.8(9.2-21.2)	14.5(9.2-21.2)	14.4(7.6-21.2)	.76
ESR	42.6(1-132)	45.3(1-139)	43.2(1-139)	.07
CRP	36.7(2-142)	56.5(13-97)	43.1(2-197)	.48

Precision refers to the ratio of the correct items of a given class to the total number of those classes; in other terms, this parameter shows the output performance of the designed MLP. The precision results for Class 0 samples (Precision^0) is equal to 0.885, which indicates that if the MLP classifies a person in Class^0, correct classification has been performed in 88.5% of cases, and it is equal to ($\text{Percision}^1 = 0.80$) for Class^1.

F_{Measure} provides a simultaneous evaluation of both Recall and precision parameters and shows the quality of MLP performance, and its value is between 0 and 1. Comparing F_{Measure0} and F_{Measure1} shows better network performance in Class 0. The MCC value can be between −1 and 1, with values +1, 0, and −1 indicating an accurate and error-free, accidental prediction, and a mismatch between the predicted and the observed cases, respectively. The MCC value in the present research is 0.596, specifying that the results are not accidental.

Figure 3 shows the ROC curve of MLP used in this study. The predictive value of the neural network is acceptable (AUC = 0.736), indicating the acceptable efficacy of the neural network in predicting the disease severity using preliminary findings of patients.

4 | DISCUSSION

Despite its high contamination, COVID-19 is currently untreatable. Most cases are asymptomatic but can lead to clinical symptoms of varying degrees and acute respiratory failure and death.[6,13,14] In epidemic crises, a lack of medical equipment and ventilators can lead to an increase in the mortality rate. Clinical symptoms, laboratory findings, and underlying diseases have been identified as risk factors for the disease in various studies. Accordingly, predicting the severity of the disease using the above indicators can be effective in admission indication and patient care levels.[15-17]

The present study investigates the predictive value of disease severity using clinical symptoms, underlying diseases, and laboratory findings. The predictive value of the variables is examined in two sections: statistical analysis and artificial neural network. The statistical analysis revealed that there was no significant difference in clinical symptoms between two groups except fatigue. Among the underlying diseases, there was a difference between the two groups in terms of organ failure and cerebrovascular diseases. There was also a difference between low-risk and high-risk patient groups in terms of laboratory findings, that is, WBC, neutrophil, NLR, and dNLR and these lab tests were significantly higher in the high-risk patient group. The predictive value of laboratory findings using the ROC curve showed that NLR, among these findings, has the highest AUC level (0.64), which is weak predictive value, and other lab tests had lower AUC levels.

Higher WBC, neutrophil, and NLR levels have been shown in other similar studies. The high neutrophil count can have a proactive or pathological effect. It seems that higher neutrophil count is associated with an increase in the incidence of the disease complication.[17] Numerous

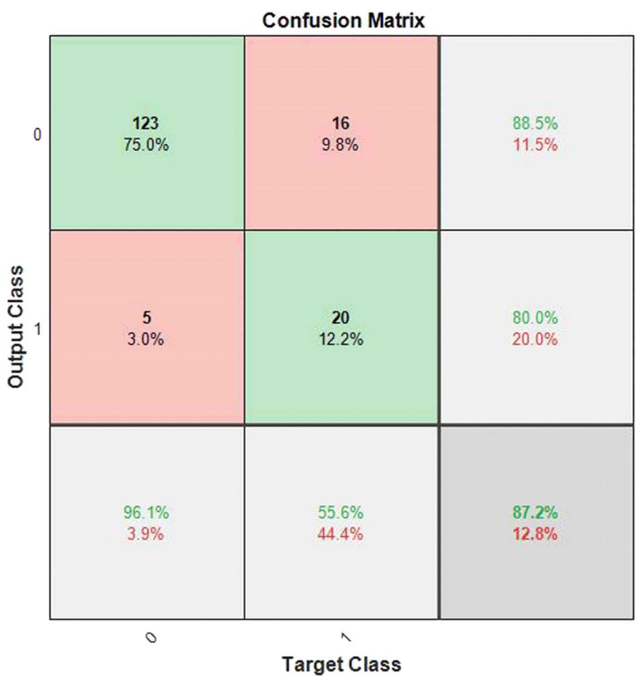

FIGURE 2 Confusion matrix (Class 0: low-risk patients, Class 1: high-risk patients)

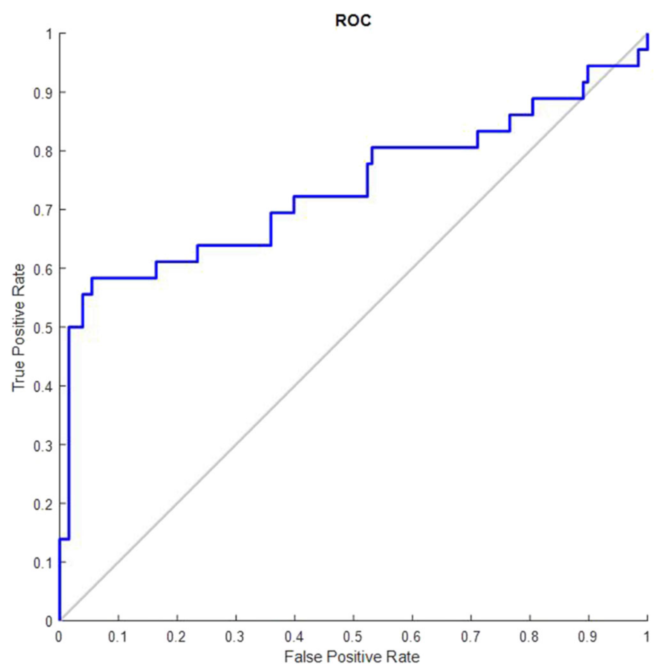

FIGURE 3 Artificial neural network ROC plot. AUC = 0.736

TABLE 3 Specifications of artificial neural network designed to determine COVID-19 severity

Recall^0	Recall^1	Precision^0	Precision^1	F_Measure^0	F_Measure^1	MCC	AUC
0.961	0.556	0.885	0.800	0.921	0.655	0.594	0.736

Notes: $0 \le \text{F\_Measure} \le 1$, $-1 \le \text{MCC} \le +1$.
Abbreviations: AUC, area under the curve; MCC, Matthews correlation coefficient.

studies have shown a decrease in the lymphocyte count in association with the increased risk of the disease; however, the present study showed no significant relationship in this regard.[2,10,17-19] This may be due to the fact that laboratory findings used in the present study are related to the first test of hospitalized patients, and the gradual decrease in lymphocyte count during hospitalization is associated with an increase in the disease risk. Many studies have considered changes in platelet and PLR levels as effective factors in disease severity; however, in the present research, this difference was not statistically significant.[19]

The advantage of the present study is the use of ANN in predicting the disease severity using the patient admission data. This research results showed that MLP could determine the disease severity with an accuracy of 87.2%. The characteristics of ANN (MLP), used in the present study, showed acceptable predictive value of disease severity based on the ROC curve (AUC = 0.736), and the ANN had a good classification (MCC = 0.594).

5 | CONCLUSION

Most treatment in COVID-19 are supportive and depend on the severity of the disease and its complications. The first step in treatment is to determine the severity of the disease. This study can improve the treatment of patients by predicting the severity of the disease using the initial finding of patients and improve the management of disease with differentiating high-risk from low-risk groups. The higher WBC, neutrophil, NLR, and dNLR in the first lab test of hospitalized COVID-19 patients is associated with an increased risk of the disease. The artificial neural network could accurately predict the risk of disease (87.2%), and it is reliable (AUC = 0.736).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly in different area of the research and drafting the manuscript. In addition, none of the authors listed on the manuscript are employed by a government agency of Iran that has a primary function other than research and/or education.

DATA AVAILABILITY STATEMENT

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

ORCID

Sohrab Salimi https://orcid.org/0000-0002-9464-2703

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