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ORIGINAL RESEARCH

Clinical Risk Factors of Need for Intensive Care Unit Admission of COVID-19 Patients; a Cross-sectional Study

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Abstract: Introduction: It could be beneficial to accelerate the hospitalization of patients with the identified clinical risk factors of intensive care unit (ICU) admission, in order to control and reduce COVID-19-related mortality. This study aimed to determine the clinical risk factors associated with ICU hospitalization of COVID-19 patients. **Methods:** The current research was a cross-sectional study. The study recruited 7182 patients who had positive PCR tests between February 23, 2020, and September 7, 2021 and were admitted to Afzalipour Hospital in Kerman, Iran, for at least 24 hours. Their demographic characteristics, underlying diseases, and clinical parameters were collected. In order to analyze the relationship between the studied variables and ICU admission, multiple logistic regression model, classification tree, and support vector machine were used. **Results:** It was found that 14.7 percent (1056 patients) of the study participants were admitted to ICU. The patients' average age was 51.25±21 years, and 52.8% of them were male. In the study, some factors such as decreasing oxygen saturation level (OR=0.954, 95%CI: 0.944-0.964), age (OR=1.007, 95%CI: 1.004-1.011), respiratory distress (OR=1.658, 95%CI: 1.410-1.951), reduced level of consciousness (OR=2.487, 95%CI: 1.721-3.596), hypertension (OR=1.249, 95%CI: 1.042-1.496), chronic pulmonary disease (OR=1.250, 95%CI: 1.006-1.554), heart diseases (OR=1.250, 95%CI: 1.009-1.548), chronic kidney disease (OR=1.515, 95%CI: 1.111-2.066), cancer (OR=1.682, 95%CI: 1.130-2.505), seizures (OR=3.428, 95%CI: 1.615-7.274), and gender (OR=1.179, 95%CI: 1.028-1.352) were found to significantly affect ICU admissions. **Conclusion:** As evidenced by the obtained results, blood oxygen saturation level, the patient's age, and their level of consciousness are crucial for ICU admission.

Keywords: COVID-19; intensive care units; logistic models; decision trees; support vector machine

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1. Introduction

The current COVID-19 pandemic caused by SARS-CoV-2 was first detected in December 2019 in Wuhan, China (1, 2). As the number of new cases of COVID-19 increased unexpectedly and the disease rapidly spread throughout the world, the World Health Organization declared a Coronavirus pandemic on March 11, 2020 (3). To date, more than 640 million cases and 6.61 million deaths have been reported worldwide (4). Many COVID-19 patients experience a relatively severe illness after a period of mild symptoms, and it is crucial to make quick and accurate diagnoses and to provide high-quality care to those who require admission to the intensive care unit (ICU) (5, 6). According to previous studies, hospitalization in the ICU plays a very important role in the treatment of COVID-19 patients, as it has been proven to be very effective on reducing mortality among these patients (1). Several studies have reported that gender, age, and underlying diseases are associated with severe disease and hospitalization in an ICU. Among patients with severe disease, acute kidney injury, acute respiratory distress syndrome, and heart diseases are the most commonly reported complications (7-10). Based on the need and capacity of the medical center in various countries, the rate of COVID-19 patients admitted to

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ICU varies from 5% to 32% (11). As a result of the increased patient numbers and the lengthening of hospital stays, the hospital's capacity to admit new patients is severely limited (12). The severely-limited capacity of the hospital to admit new patients may negatively affect patient care quality and also increase mortality rates (13). By identifying and classifying patients with high risks, a greater number of beds can be saved in the ICU. Studies have shown that accelerating the admission of patients with the identified major clinical risk factors for ICU admission can reduce mortality rate. In addition to other nations, Iran has also been affected by COVID-19. It has been estimated that approximately 7.55 million cases and more than 145,000 deaths have occurred since the first case of COVID-19 was identified on February 18, 2020 (4, 14). It is noteworthy that approximately more than 500,000 people live in the city of Kerman, located in southeastern Iran (15).

The city of Kerman is one of those in Iran where many patients require admission to the ICU (16). More than half of the hospital's capacity for ICU admissions is used during ordinary times in Kerman's hospitals (17). Similar to all hospitals and ICUs throughout the world, Kerman's hospitals and their ICUs face some limitations during a crisis like the COVID-19 epidemic (18). Identifying significant clinical risk factors in the early stages of this disease is crucial for predicting which patients will require admission to the ICU (19). Based on a patient's disease symptoms, this study aimed to assist physicians in quickly identifying patients who will need ICU admission.

2. Methods

2.1. Study design and settings

The present study was a cross-sectional study conducted in Afzalipour Hospital, Kerman, Iran (700 beds), with focus on patients who had been hospitalized with COVID-19 disease (20). The admission rules were defined by the guidelines published by the Iranian Ministry of Health for managing COVID-19 patients and based on a combination of clinical data (1). The required data were collected from electronic medical records of 7182 patients with a positive COVID-19 PCR test, who were admitted to Afzalipour Hospital in Kerman, Iran, between February 23, 2020, and September 7, 2021, using the census method. Research Ethics Committee of Kerman University of Medical Sciences approved this study (No. IR.KMU.REC.1400.451).

2.2. Participants

The present study included all COVID-19 patients who had been hospitalized for more than 24 hours and were diagnosed using SARS-COV-2 nucleic acid RT-PCR (7, 21). Patients with a negative PCR test for COVID-19 were excluded from the study. Also, hospitalized patients whose test status was unclear and were suspected to having COVID-19 were excluded from the study. The patients were admitted to the ICU directly or after being admitted to the general ward.

2.3. Data collection

For this study, the primary data source was electronic medical records from the Medical Care Monitoring Center (MCMC) system, which are frequently used in emergency situations. The patients' data were accurately recorded in the MCMC system. The data for 10 patients were missing and they were excluded from the study.

The dependent variable was receiving ICU care, for patients who were hospitalized either in the ICU or in the general ward (2).

In this study, studied variables included age, gender, heart diseases, chronic kidney disease, chronic pulmonary disease, chronic liver disease, diabetes, cancer, hypertension, chronic neurological diseases, blood diseases, immunodeficiency (Acquired or congenital), fever, myalgia, cough, chest pain, diarrhea, respiratory distress, vomiting and nausea, headache, loss of consciousness, smell or taste disorders, anorexia, seizures, dizziness, opium abuse, smoking, oxygen therapy, oxygen saturation level, and the time between the onset of symptoms and admission to the hospital.

2.4. Statistical analyses

In order to analyze the obtained data, the mean, standard deviation, frequency, and percentage were calculated. To control the effect of confounding variables, Univariate and multiple logistic regression analyses were run and the effect of each variable was evaluated by adjusting for other variables.

At first, univariate regression was performed, and variables with p-values less than 0.2 were considered as important and then added to multiple regression model. Finally, p-values less than 0.05 were used to identify significant variables in the multiple logistic regression model and the backward approach. Additionally, the odds ratios and 95% confidence intervals were reported (22, 23).

The classification and regression trees (CART) model was used to classify the investigated variables, identify specific ICU admission groups, and evaluate the interaction between the variables (24). A tree model was built with 10-fold cross-validation, with 100 cases in the parent node and 50 subjects in the child node, and 10 maximum levels for the Classification and Regression Trees model (CART) (25). The misclassification cost for patients who were wrongly admitted to the general ward instead of the ICU was 5 times more than patients admitted to the ICU instead of the general ward. Therefore, it was considered that an effective strategy to solve the imbalanced classification problem is to maximize the sum of sensitivity and specificity (26, 27). Moreover, support vector machine method was used to investigate and control the non-linear effect of confounding variables and separation of the variables affecting hospitalization in the ICU.

Support vector machine method provides a powerful separator margin among classes using the kernel trick and converting the data into another dimension. This study used the radial basis function (RBF) as the kernel, and 10-fold cross-validation was applied to estimate model parameters (28, 29). Afterward, the accuracy of support vector machine model and the importance of each variable regarding ICU admission were determined (30).

2.5. Sensitivity and specificity of models

The data in this study were validated using the K-fold validation method. In the K-fold method, the data are divided into K subsets.

Besides, each sample is used once for validation and k-1 times for training. This process is repeated K times and all the data are used once for validation. Finally, the average of these K validation times is reported. K was equal to 10 in the present study (31).

Accuracy, sensitivity, and specificity of the model was evaluated by comparing the prediction of the model regarding patients' need for ICU hospitalization with the reality (32).

In the present study, descriptive analysis, univariate and multiple logistic regression, and Classification Tree model were conducted using SPSS.25 software and analysis of support vector machine was done using R software packages (caret and e1071).

3. Results

3.1. Patient characteristics

The current study recruited 7,182 COVID-19 patients with the mean age of 51.25 ± 21.00 (range: 0.02 (7 days)-102) years (52.8% male). The number of the patients admitted to the ICU was 1056 (14.7%). Among the patients, 413 (5.8%) cases were smokers and 898 (12.5%) cases were opium abusers. There were 1211 (16.9%) patients with hypertension, 976 (13.6%) patients with diabetes, 694 (9.7%) patients with heart diseases, and 608 (8.5%) patients with chronic pulmonary disease. The most prevalent signs and symptoms of these patients were respiratory distress with 4952 (69.0%), fever with 3426 (47.7%), and cough with 3603 (50.2%) cases. Oxygen therapy was provided to 5684 (71.9%) of the hospitalized patients. According to this analysis, the patients were hospitalized at an average oxygen saturation level of 90.51±5.61 percent, and the time from the onset of symptoms to hospitalization was 5.7±3.59 days. Table 1 shows the association between studied clinical variables with need for ICU admission.

3.2. Multiple logistic regression analysis of clinical risk factors for ICU admission

Table 2 shows the results of multiple regression analysis of independent clinical risk factors of COVID-19 patients' need for ICU admission. In multiple logistic regression, male cases had 1.179 times the odds of being admitted to the ICU compared to females (OR=1.179, 95%CI:1.028-1.352). In addition, being admitted to the ICU was associated with age (OR=1.007, 95%CI: 1.004-1.011). Patients with heart diseases (OR=1.250, 95%CI=1.009-1.548), chronic pulmonary disease (OR=1.250, 95%CI=1.006-1.554), chronic kidney disease (OR=1.515, 95%CI=1.111-2.066), hypertension (OR=1.249, 95%CI=1.042-1.496), and cancer (OR=1.682, 95%CI=1.130-2.50) had higher odds of being admitted to the ICU. There was a higher chance of admission to the ICU among the patients with signs and symptoms of loss of consciousness (OR=2.487, 95%CI=1.721-3.596), seizures (OR=3.428, 95%CI=1.615-7.274), respiratory distress (OR=1.658, 95%CI=1.410-1.951), and a decrease in oxygen saturation level (OR=0.954, 95%CI=0.944-0.964). Moreover, the patients who had myalgia (OR=0.847, 95%CI=0.733-0.978), cough (OR=0.827, 95%CI=0.722-0.949), diarrhea (OR=0.727, 95%CI=0.561-0.941), headache (OR=0.708, 95%CI=0.593-0.844), and smell or taste disorders (OR=0.622, 95%CI=0.474-0.816) had a lower chance of being admitted to the ICU.

The total sensitivity and specificity of the model were maximized with a cut point of 0.145 in predicted probability of receiving ICU care. Multiple logistic regression model had 62.4% (95%CI=59-65) accuracy, 59.7% (95%CI=51.2-68.2) sensitivity, and 62.7% (95%CI=58.2-67.3) specificity.

3.3. Classification Tree

The estimated tree model depicts a tree with five levels and eight nodes (Figure 1). Using the tree structure, it was determined that oxygen saturation level, age, and level of consciousness were the variables affecting ICU hospitalization. There were four high-risk groups of patients admitted to the ICU: The first group consisted of the patients with oxygen saturation levels less than 86.5%, the second group consisted of the patients younger than 0.196 years (72 days) whose oxygen saturation was greater than 86.5%, the third group consisted of patients older than 66.5 years with oxygen saturation level greater than 86.5%, and the fourth group consisted of the patients with a lowered level of consciousness aged between 0.196 and 66.5 years (Figure 1). A cost of misclassification of 5 led both the sensitivity and specificity of the model to reach their maximum levels.

Classification Tree Model had an accuracy of 68.5% (95%CI=66.6-70.4), a sensitivity of 56.7% (95%CI=53.4-59.9), and a specificity of 70.5% (95%CI=68.0-73.0).

Table 1: The association between clinical characteristics of COVID-19 cases with need for ICU admission based on univariate analysis

Variables	Need for ICU care		OR	95%CI	P
	No	Yes			
Age (year)					
Mean ± SD	50.39±20.47	56.20±23.23	1.014	1.011-1.017	<0.001
Gender					
Female	2935 (86.6)	454 (13.4)	1		
Male	3191 (84.1)	602 (15.9)	1.220	1.069-1.391	0.003
Underlying disease					
Heart diseases	544 (78.4)	150 (21.6)	1.699	1.399-2.062	<0.001
Chronic kidney disease	197 (75.8)	63 (24.2)	1.909	1.427-2.556	<0.001
Chronic pulmonary disease	472 (77.6)	136 (22.4)	1.771	1.445-2.169	<0.001
Chronic liver disease	67 (81.7)	15 (18.3)	1.303	0.742-2.290	0.357
Diabetes	799 (81.9)	177 (18.1)	1.343	1.124-1.604	0.001
Cancer	112 (75.7)	36 (24.3)	1.895	1.294-2.775	<0.001
Hypertension	970 (80.1)	241 (19.9)	1.572	1.340-1.843	<0.001
Blood diseases	33 (73.3)	12 (26.7)	2.122	1.093-4.122	0.02
Immunodeficiency	22 (75.9)	7 (24.1)	1.851	0.789-4.345	0.157
Chronic neurological diseases	139 (84.8)	25 (15.2)	1.044	0.679-1.607	0.843
Fever	2980 (87.0)	446 (13.0)	0.772	0.676-0.881	<0.001
Myalgia	2428 (87.3)	354 (12.7)	0.768	0.669-0.881	<0.001
Cough	3123 (86.7)	480 (13.3)	0.801	0.703-0.914	0.001
Chest pain	518 (87.1)	77 (12.9)	0.852	0.664-1.092	0.205
Diarrhea	635 (89.4)	75 (10.6)	0.661	0.516-0.848	0.001
Respiratory distress	4117 (83.1)	835 (16.9)	1.844	1.575-2.158	<0.001
Vomiting and nausea	1269 (88.6)	164 (11.4)	0.704	0.589-0.840	<0.001
Headache	1545 (89.3)	185 (10.7)	0.630	0.532-0.764	<0.001
Loss of consciousness	91 (65.0)	49 (35)	3.227	2.226-4.596	<0.001
Smell or taste disorders	568 (89.7)	65 (10.3)	0.642	0.492-0.837	0.001
Seizures	24 (66.7)	12 (33.3)	2.92	1.457-5.862	0.003
Anorexia	2277 (85.8)	376 (14.2)	0.935	0.816-1.017	0.331
Dizziness	857 (83.7)	167 (16.3)	1.155	0.964-1.383	0.118
Opium abuse	739 (82.3)	159 (17.7)	1.292	1.074-1.555	0.007
Smoking	352 (85.2)	61 (14.8)	1.006	0.760-1.331	0.969
Oxygen therapy	4896 (86.1)	788 (13.9)	0.739	0.634-0.860	<0.001
Oxygen saturation (%)					
Mean ± SD	90.88±5.4	88.4±7.8	0.945	0.936-0.954	<0.001
Symptoms to admission (days)					
Mean ± SD	5.80±3.49	5.679±4.14	0.990	0.972-1.009	0.296

Data are presented as mean ± standard deviation (SD) or frequency (%). OR: Odds ratio; CI: confidence interval.

3.4. Support vector machine

A vector machine model was constructed after cross-validation using the radial basis kernel function and parameters "sigma=0.0279, cost=2". In order to separate the classes and reduce data error, support vector machine used non-linear variable separation as well as the best margin. As a result of using the vector machine model (Figure 2), the variable importance graph indicated that oxygen saturation level had the greatest impact (100%) on the classification of hospitalized patients in ICUs and general wards followed by age (43.62%), respiratory distress (37.54%), and the decreased level of consciousness (29.72%). Heart diseases, chronic pulmonary disease, and hypertension were found to have a significant effect on patients with about 18 to 20 percent, while myalgia, fever, vomiting and nausea, oxygen therapy, and chronic kidney disease were found to have a significant impact between 9 and 12 percent.

In general, the importance of gender, seizures, diabetes, diarrhea, smell or taste disorders, and cancer variables ranged from 5 to 7 percent, while the importance of other variables was ranked to be lower. There was 99.8% (95%CI=99.6-100.0) accuracy, 99.6% (95%CI=99.3-100.0) sensitivity, and 99.9% (95%CI=99.7-100.0) specificity for the support vector machine model.

4. Discussion

This study aimed to determine the clinical risk factors associated with COVID-19 patients who require admission to the

Table 2: The association between clinical characteristics of COVID-19 cases with need for ICU admission based on multiple regression analysis

Variables	**OR**	**95% CI**	**P**
Age (years)	1.007	1.004-1.011	<0.001
Gender			
Male	1.179	1.028-1.352	0.018
Underlying disease			
Heart diseases	1.250	1.009-1.548	0.042
Chronic pulmonary Disease	1.250	1.006-1.554	0.044
Chronic kidney disease	1.515	1.111-2.066	0.009
Cancer	1.682	1.130-2.505	0.010
Hypertension	1.249	1.042-1.496	0.016
Myalgia	0.847	0.733-0.978	0.024
Cough	0.827	0.722-0.949	0.007
Diarrhea	0.727	0.561-0.941	0.015
Respiratory distress	1.658	1.410-1.951	<0.001
Headache	0.708	0.593-0.844	<0.001
Loss of consciousness	2.487	1.721-3.596	<0.001
Smell or taste disorders	0.622	0.474-0.816	0.001
Seizures	3.428	1.615-7.274	0.001
Oxygen saturation (%)	0.954	0.944-0.964	<0.001

Data are presented as mean ± standard deviation (SD) or frequency (%). OR: Odds ratio; CI: confidence interval.

ICU. By employing results of statistical methods, this cross-sectional study identified some clinical risk factors associated with ICU admission (33). One of the study's strengths was the use of univariate and multiple logistic regression, classification tree, and support vector machine to develop a list of clinical risk factors that could be used to distinguish ICU patients from general ward patients. According to the results of this study, amongst the demographic characteristics affecting hospitalization in the ICU, gender is an important factor that is relevant and influential, and it was shown that the majority of patients admitted in the ICU are men. Age is one of the most significant clinical risk factors associated with ICU hospitalization. As the age of patients increases, their chances of being hospitalized in the ICU and experiencing a worsening of their disease's condition also increase. Even with acceptable oxygen saturation levels, newborns (less than 0.196 years old (72 days)) and the elderly (over 66.5 years old) require ICU care. A meta-analysis of 59 studies involving 36,470 patients concluded that men and patients aged over 70 years old are more likely to be admitted to the ICU compared to other patients (34). This study was consistent with the current study.

Since the results of the current study identified underlying diseases such as hypertension, chronic pulmonary disease, heart diseases, chronic kidney disease, and cancer as clinical risk factors, it can be said that patients with these underlying diseases experience a more severe form of COVID-19 and require special care. The most important underlying disease was hypertension. A meta-analysis of 30 original articles found that high blood pressure is significantly associated with increased mortality and need for intensive care, which is consistent with the results of this research (35). In some cases, certain signs and symptoms are strongly related to the possibility of admission to the ICU. These factors may worsen a patient's condition and also increase their need for intensive care.

A low oxygen saturation level is considered to be the most significant risk factor in this study, and patients with low oxygen saturation levels must be admitted to ICU. Additionally, patients with oxygen saturation below 86.5% require immediate admission to the ICU. In a previous study conducted on 641 patients at Stony Brook University Hospital, it was found that patients with an oxygen saturation level of less than 92% are at high risk, and ICU hospitalization was recommended due to the danger of low oxygen saturation levels and these findings are consistent with the findings of the present study (5). Seizures, respiratory distress, and decreased level of consciousness are factors affecting the severity of the disease and the need for hospitalization in an ICU. Headache, myalgia, cough, diarrhea, and smell or taste disorders do not increase the severity of the disease, and most patients with these symptoms are admitted to the hospital's general ward. The effects of diabetes, oxygen therapy, fever, vomiting, and nausea are not significant in multiple logistic regression model; whereas, they are considered to be important in the vector machine model. The reason for this difference may be related to the fact that vector machines consider non-linear relationships between variables, which can be used as a predictor of hospitalization ICUs (36).

There is a higher chance of admission to the ICU if the patient

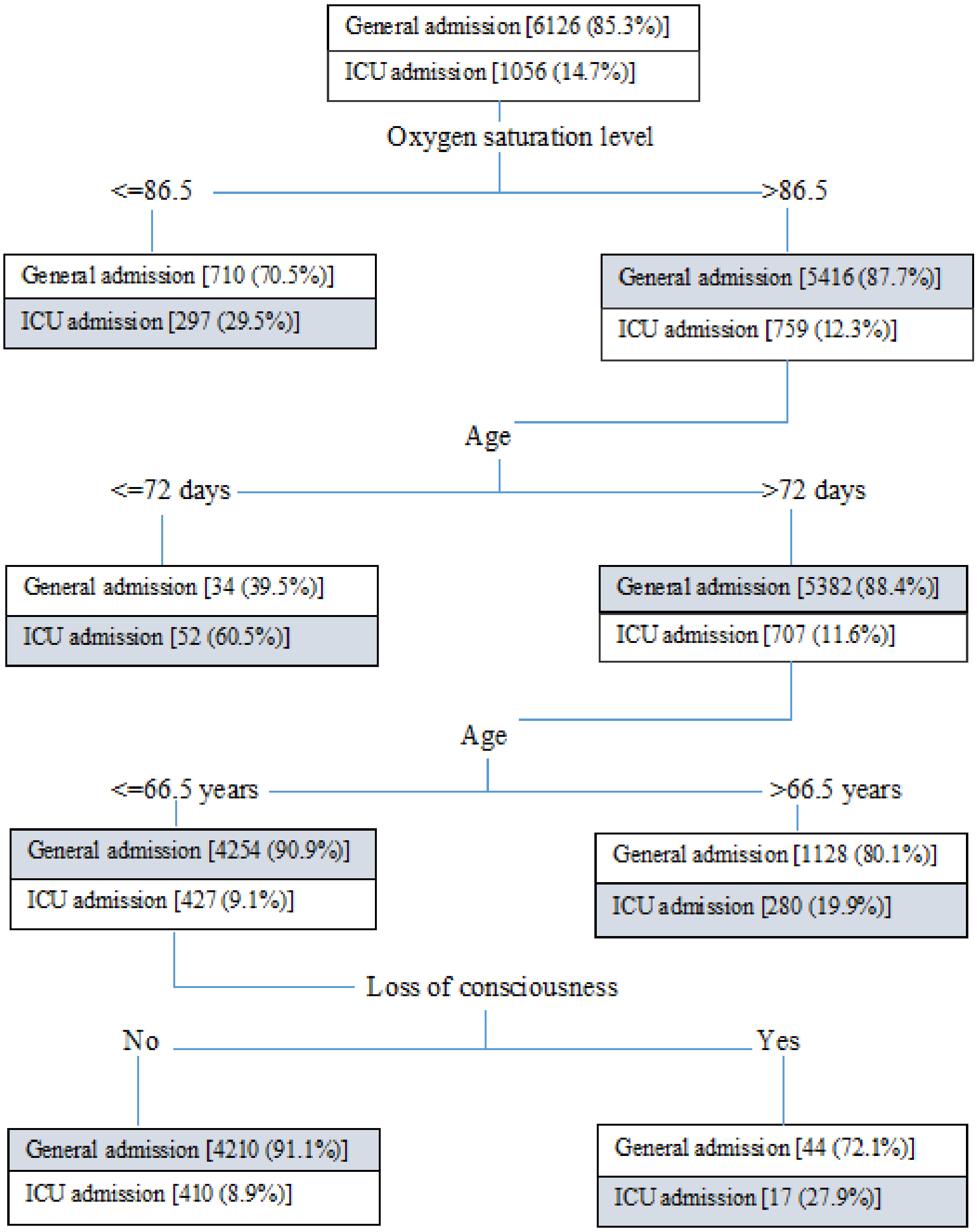

Figure 1: Factors affecting patients' intensive care unit (ICU) admission according to the classification tree model. Misclassification costs of the patients admitted to the general ward instead of the ICU were five times more than the patients admitted to the ICU instead of the general ward. So, in each node, the tree model predicts that the patient will be admitted to the ICU if the proportion of admissions to the ICU exceeds 16.6%.

has an underlying disease like diabetes. A meta-analysis of 33 studies involving 16,003 patients confirmed that diabetes is significantly associated with COVID-19-related mortality and disease severity, which is in agreement with our finding (37). Symptoms such as fever, vomiting, and nausea do not worsen the disease, and patients with these symptoms are mostly ad-

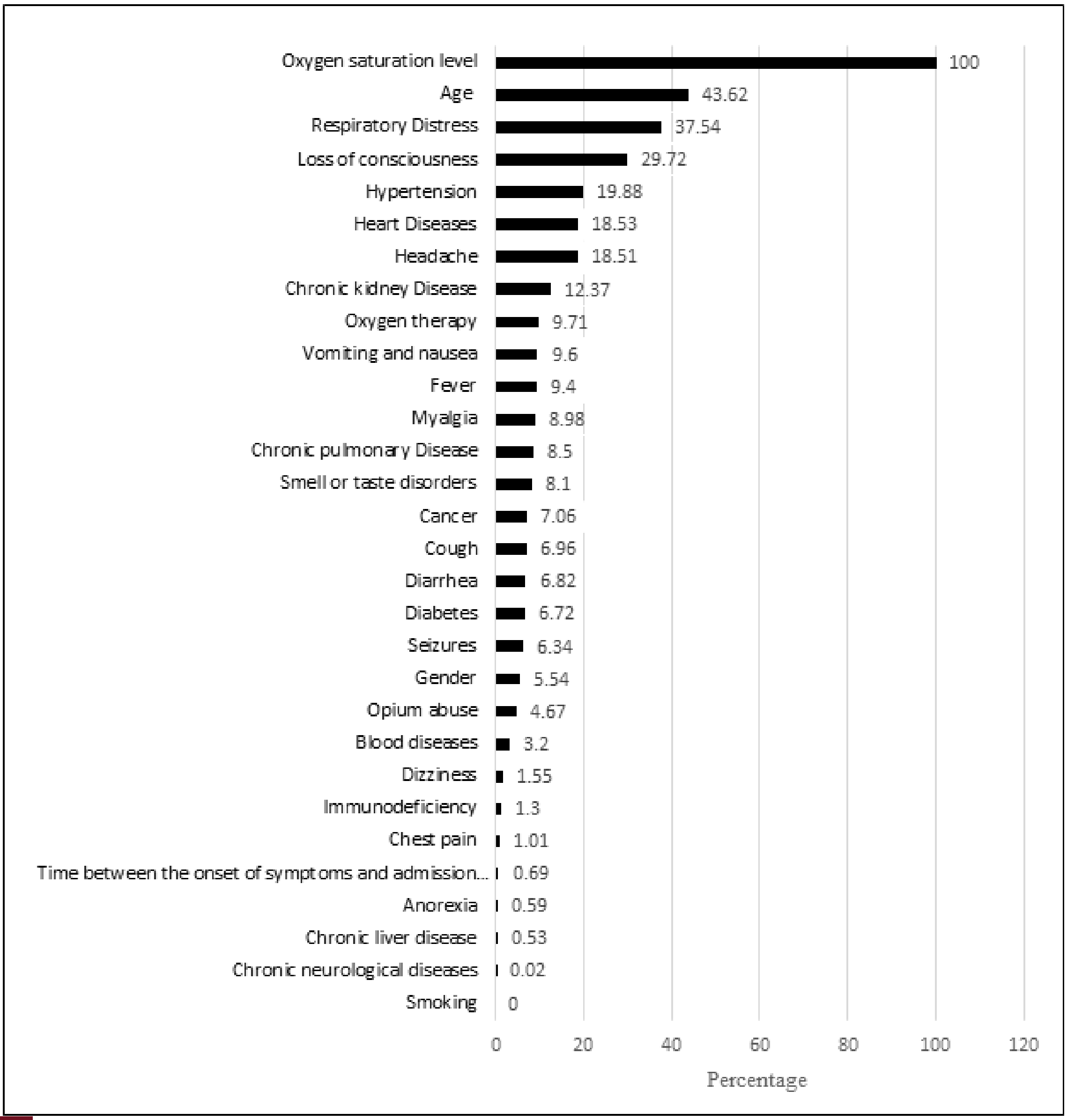

Figure 2: The importance graph of the effective intensive care unit (ICU) admission variables as calculated by the vector machine model.

mitted to the general ward. Patients with COVID-19 who receive oxygen therapy are less likely to require admission to an ICU.

Physicians can utilize this research results to be provided with a simple and accurate stratification tool that will enable them to manage patients with COVID-19 and similar diseases in a timely manner (1). In general, the combined results of all the models revealed that a number of factors such as decreasing oxygen saturation level (the risk is higher for patients whose oxygen saturation level is less than 86.5%), aging (66.5 years and older), age under 72 days in infants, respiratory distress, decreased level of consciousness, hypertension, chronic pulmonary disease, heart diseases, chronic kidney disease, cancer, diabetes, and seizures are associated with severe type of illness and ICU admission in COVID-19 patients. Additionally, these factors may guide physicians to make a better decision. For instance, if a patient aged 66.5 years or older is recommended to seek medical advice at the early stage of their illness, and if hospitalization is required, physicians should be aware of the high risk of severe disease in these groups (34). A combination of the results of the three models and the K-fold cross-validation increased the external validity of the study, and the comparison of model accuracy revealed that logistic model accuracy was

62.7 percent, classification tree model accuracy was 64.3%, and support vector machine model accuracy was 99%. Support vector machine model was the most accurate one. For clinical researchers, predicting COVID-19 patients' hospitalization in the ICU is essential. Accordingly, it is better to use the support vector machine model, which is more accurate. Researchers should use classification tree if they need a simple algorithm for classifying the hospitalization of COVID-19 patients. In order to examine the association among the variables and severity of COVID-19 disease and hospitalization in the ICU, it is recommended to use logistic regression model(33).

5. Limitations

The type of treatment and different strains of COVID-19 have changed over time and these may affect receiving or not receiving intensive medical care. These two variables were not addressed in this study. Thus, they may cause bias and reduce the generalizability of the findings to the community. Accordingly, they need to be addressed in future studies.
It is possible that additional confounding factors exist that we have not included in the models. The criteria for admission of patients in ICU of different hospitals are different, which it may affect the generalizability of the result. Additionally, this study only focused on some clinical variables and laboratory data of hospitalized patients were unavailable, which it is recommended to consider them for future research.

6. Conclusions

The results of our study showed that clinical risk factors such as hypertension, chronic pulmonary disease, heart disease, chronic kidney disease, cancer, diabetes, seizures, and gender were predictors of patients' admission to the ICU, but oxygen saturation level, increasing age, respiratory distress, and reduced level of consciousness were identified as independent predictors of need for ICU admission among COVID-19 patients. The results of this study can help physicians and hospital staff to assign timely special care services to patients with COVID-19.

7. Declarations

7.1. Acknowledgments

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7.2. Conflict of interest

No potential conflict of interest relevant to this article was reported.

7.3. Fundings and supports

The study did not receive any funding from any organization.

7.4. Authors' contribution

Study concept and design: YJ. Analysis and interpretation of data: YJ, FS and MA. Data collection: MHM. Writing the original draft of the manuscript: FS and YJ. All authors reviewed, edited, and approved the final article.

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