

Predicting Mortality and ICUs Transfer in Hospitalized COVID-19 Patients Using Random Forest Model

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ABSTRACT

Background: The objective of the present study was to identify prognostic factors associated with mortality and transfer to intensive care units (ICUs) in hospitalized COVID-19 patients using random forest (RF). Also, its performance was compared with logistic regression (LR).

Methods: In this retrospective cohort study, information of 329 COVID-19 patients were analyzed. These patients were hospitalized in Besat hospital in Hamadan province, the west of Iran. The RF and LR models were used for predicting mortality and transfer to ICUs. These models' performance was assessed using area under the receiver operating characteristic curve (AUC) and accuracy.

Results: Of the 329 COVID-19 patients, 57 (15.5%) patients died and 106 (32.2%) patients were transferred to ICUs. Based on multiple LR model, there was a significant association between age (OR=1.02; 95% CI=1.00-1.05), cough (OR=0.24; 95% CI=0.10-0.56), and ICUs (OR=7.20; 95% CI=3.30-15.69) with death. Also, a significant association was found between kidney disease (OR=3.90; 95% CI=1.04-14.63), decreased sense of smell (OR=0.28; 95% CI=0.10-0.73), Kaletra (OR=2.53; 95% CI=1.39-4.59), and intubation (OR=8.32; 95% CI=3.80-18.24) with transfer to ICUs. RF showed that the order of variable importance has belonged to age, ICUs, and cough for predicting mortality; and age, intubation, and Kaletra for predicting transfer to ICUs.

Conclusion: This study showed that the performance of RF provided better results compared to LR for predicting mortality and ICUs transfer in hospitalized COVID-19 patients.

Introduction

Here In late 2019, a new type of Coronavirus (COVID-19) called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first appeared in Wuhan, China. Since then, it has rapidly spread around the world and become a worldwide epidemic [1-2]. The SARS-CoV-2 infection has led to extensive morbidity and mortality throughout the world [3]. Approximately 20% to 30% of patients experience a

moderate to severe form of the disease that may lead to hospitalization or death [4]. In addition, 5% to 12% of all COVID-19 patients and up to 33% of hospitalized patients require intensive care units (ICUs) [4-6].

Studies have shown that most COVID-19 patients experience mild symptoms such as fever, dry cough, weakness, shortness of breath, and diarrhea [7]. However, elderly patients and those with diabetes, hypertension, and cardiovascular disease may experience worse outcomes, such as hospitalization [8-9]. Some features, such as age, body temperature, lymphocyte

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count, and lung imaging features, have been reported as the most common predictors in the diagnosis and prognosis of COVID-19 [10]. Several prognostic factors such as older age, male sex, obesity, smoking, cardiovascular disease, diabetes, hypertension, and chronic respiratory disease are related to severe illness and death from COVID-19. However, the results of several studies have been inconsistent [11-15].

In the past decade, machine learning models have been widely applied to many fields [16-20]. Among them, the random forests (RF) is well-known as one of the best models, which is widely employed for classification and regression problems. This model can improve predictions by considering the complex nonlinear relationships between variables [19-21]. However, RF cannot determine the direction of association of variables on outcome. To overcome this problem can be applied to the logistic regression (LR) model [22].

Despite the several studies that have used machine learning models for predicting the prognosis of COVID-19 patients [10, 14, 15, 23-28], only a few of them have been performed in Iran [29-31]. Furthermore, COVID-19 is still widely spreading in Asian countries such as Iran. Hence, this study's main goal was to identify prognostic factors associated with mortality and transfer to intensive care units (ICUs) in hospitalized COVID-19 patients using RF. Also, its performance was compared with LR.

Methods

In this retrospective cohort study, information of 329 COVID-19 patients was analyzed. These patients were hospitalized in Besat hospital in Hamadan, Iran. Data were extracted from hospital records using a checklist of items according to the context of the patient's records. The checklist included data on demographic variables, medical history, co-morbidities, laboratory tests, and clinical symptoms. Missing values of these variables were imputed with the multiple imputations method. The outcome was mortality and transfer to ICUs.

RF is a tree-based model that was applied to determine important prognostic factors. This model has proved its success in classification and regression problems. In RF, data were randomly divided into two parts. The learning part (2/3 of the data set) was used for developing the model, and the test part was used (1/3 of the data set) to check the data validity. Totally, 1000 bootstrap samples were constructed from the learning part. Then decision trees for each bootstrap sample were grown. In each tree node, a subset of p variables was selected randomly and among which, the best variables are chosen for splitting. The RF Final estimate was the average of all results from each tree. The variables were ranked using the Gini Index [21]. LR model was performed to assess the effect of prognostic factors on mortality and transfer to ICUs. In the univariate LR model, significant variables were selected and entered into the multiple LR model. Crude and adjusted odds ratios (ORs) were reported to address

the effect of prognosis factors associated with mortality and transfer to ICUs. A p -value less than 0.05 was considered statistically significant.

The cross-validation method was used in the performance evaluation of RF and LR models, in which the dataset was randomly divided into training (70%) and test (30%) sets. Then, the discrimination ability of both models was assessed using the area under the receiver operating characteristic curve (AUC) and accuracy. This procedure was repeated 100 times and the average values of AUC and accuracy were computed.

The statistical analyses were performed using R Version 3.6.3 [32], with the following packages "randomForest", "CORElearn" and "pROC".

Results

During the study period, 57 (15.5%) patients died and 106 (32.2%) patients were transferred to ICUs. The mean age (standard deviation) of all patients was 43.11(28.89) years old. The majority of them were men (60.9%) and married (65.5%). The characteristics of COVID-19 patients and results from the univariate LR analysis of the prognostic factors associated with mortality and transfer to ICUs are given in (Table 1).

Data are expressed as Mean (SD) or N (%); CI: confidence interval.

The results of the multiple LR model for mortality and transfer to ICUs are presented in (Table 2-3), respectively.

The risk of death increased significantly with age ($P<0.001$). There was a significant association between marital and death, and the OR of death in COVID-19 married patients was 2.10 (95% CI: 1.03-4.28) compared to single patients. The OR estimate of death among patients with heart disease was 3.14 (95% CI=1.37-7.19) compared to those patients without heart disease. The COVID-19 patients who had symptoms such as fever ($P=0.001$), headache ($P=0.017$), and cough ($P<0.001$) were significantly at a lower risk of death. However, the patients who had a weakness ($P<0.001$) were significantly at a higher risk of death. Compared to COVID-19 patients without hypertension, the OR estimate of death was 2.40 (95% CI=1.31-4.40) in patients with hypertension. There was an association between WBC and death. The OR estimate of the death of COVID-19 patients was 1.98 (95% CI=1.08-3.63) for $WBC \geq 11000$ compared to $WBC < 11000$ (Table 1). Transfer to ICUs was the strongest risk factor for COVID-19 patients' mortality. The OR estimate of death in those who transfer to ICUs was 5.72 (95% CI=3.01-0.86) compared to those without transfer to ICUs. After controlling for the potential confounding effect of other variables, the association became stronger and reached 7.87 (95% CI=3.47-17.86).

There was an association between age and transfer to ICUs in COVID-19 patients ($p=0.032$). Compared to married COVID-19 patients, single patients were at a lower risk of transfer to ICUs($p=0.009$). There was a

direct association between transfer to ICUs and WBC. Compared to COVID-19 patients with WBC <11000, the OR estimate of transfer to ICUs was 2.14 (95% CI=1.32-3.47) in patients with WBC >=11000. The COVID-19 patients who had headaches (P=0.008), and decreased sense of smell (P<0.001) were significantly at a lower risk of transfer to ICUs (Table 1). The risk of transfer to ICUs was higher in COVID-19 patients with kidney disease than in those without kidney disease (p=0.043). Treatment with Kaletra increased the risk of transfer to ICUs in COVID-19 patients (P=0.002). This OR estimate increased to 2.53 (95% CI=1.39-4.59) when adjusted for other variables. Intubation was the strongest risk factor for transfer to ICUs in COVID-19 patients. The OR estimate of transfer to ICUs in those who had intubation was 5.59 (95% CI=2.90-10.78) compared to those without intubation. After controlling for the potential

confounding effect of other variables, the association became stronger and reached 8.32 (95% CI=3.80-18.24). (Figure 1) displays the top ten variable importance obtained from RF for mortality and transfer to ICUs in COVID-19 patients.

The results showed that age, ICUs, and cough as the three most important variables for predicting mortality in COVID-19 patients (Figure-1 (A)). Also, RF identified that age, intubation, and Kaletra as the three most important variables for predicting transfer to ICUs in COVID-19 patients (Figure 1 (B)).

(Table 4) shows the performance of LR and RF models for Predicting mortality and ICUs transfer in hospitalized COVID-19 patients in training and testing datasets. As seen, the performance of RF compared to LR was better for both outcomes in the training and testing datasets, respectively.

Table 1- The characteristics of COVID-19 patients and results of univariate logistic regression model for mortality and transfer to ICUs.

Variables	Patient status			P value	ICUs Transfer			P value
	Died N=51	Alive N=278	Unadjusted OR (95% CI)		Yes N=106	No N=223	Unadjusted OR (95% CI)	
Age (Year)	56.67 (24.74)	40.62 (28.94)	1.02 (1.00-1.03)	<0.001	38.14 (30.77)	45.47 (27.71)	0.99 (0.98-0.99)	0.032
Sex								
Male	36 (70.6)	164 (59.0)	1		63 (60.6)	135 (61.1)	1	
Female	15 (29.4)	114 (41.0)	0.59 (0.31-1.14)	0.122	41 (49.4)	86 (38.9)	1.08 (0.67-1.74)	0.728
Marital status								
Single	11 (21.6)	102 (36.7)	1		47 (46.1)	63 (29.0)	1	
Married	40 (78.4)	176 (63.3)	2.10 (1.03-4.28)	0.040	55 (53.9)	154 (71.0)	0.52 (0.32-0.85)	0.009
Heart disease								
No	41 (80.4)	258 (92.8)	1		94 (88.7)	205 (91.9)	1	
Yes	10 (19.6)	20 (7.2)	3.14 (1.37-7.19)	0.007	12 (11.3)	18 (8.1)	1.45 (0.63-3.14)	0.341
Hypertension								
No	25 (49.0)	194 (69.8)	1		72 (67.9)	147 (65.9)	1	
Yes	26 (51.0)	84 (30.3)	2.40 (1.31-4.40)	0.005	34 (32.1)	76 (34.1)	0.91 (0.55-1.49)	0.719
Respiratory disease								
No	48 (94.1)	265 (95.3)	1		102 (96.2)	211 (94.6)	1	
Yes	3 (5.9)	13 (4.7)	1.27 (0.35-4.64)	0.713	4 (3.8)	12 (5.4)	0.69 (0.21-2.19)	0.529
Kidney disease								
No	48 (94.1)	268 (96.4)	1		98 (92.5)	218 (97.8)	1	
Yes	3 (5.9)	10 (3.6)	1.67 (0.44-6.31)	0.446	8 (7.5)	5 (2.2)	3.55 (1.13-1.15)	0.029
Liver disease								
No	49 (96.1)	272 (97.8)	1		104 (98.1)	217 (97.3)	1	
Yes	2	6	1.85	0.459	2	6	0.69	0.660

	(3.9)	(2.2)	(0.36-9.43)		(1.9)	(2.7)	(0.13-3.50)	
Digestive disease								
No	50 (98.0)	242 (87.1)	1		99 (93.4)	193 (86.5)	1	
Yes	1 (2.0)	36 (12.9)	0.13 (0.01-1.00)	0.050	7 (6.6)	30 (13.5)	0.45 (0.19-1.07)	0.072
Diabetes								
No	39 (76.5)	231 (83.1)	1		87 (82.1)	183 (82.1)	1	
Yes	12 (23.5)	47 (16.9)	1.51 (0.73-3.10)	0.260	19 (17.9)	40 (17.9)	0.99 (0.54-1.82)	0.998
Anemia								
No	48 (94.1)	267 (96.0)	1		99 (95.2)	212 (95.9)	1	
Yes	3 (5.9)	11 (4.0)	1.51 (0.40-5.64)	0.534	5 (4.8)	9 (4.1)	1.17 (0.38-3.60)	0.775
LDH								
<400	11 (21.6)	55 (19.8)	1		6 (12.2)	20 (21.1)	1	
>=400	40 (78.4)	223 (80.2)	0.89 (0.43-1.86)	0.770	43 (87.8)	75 (78.9)	1.22 (0.67-2.20)	0.505
WBC								
<11000	27 (52.9)	192 (69.1)	1		58 (55.2)	159 (73.6)	1	
>=11000	24 (47.1)	86 (30.9)	1.98 (1.08-3.63)	0.027	47 (44.8)	57 (26.4)	2.14 (1.32-3.47)	0.002
ESR								
<50	33 (64.7)	202 (72.7)	1		51 (68.0)	88 (70.4)	1	
>=50	18 (35.3)	76 (27.3)	1.45 (0.77-2.72)	0.249	24 (32.0)	37 (29.6)	1.12 (0.67-1.86)	0.721
Blood pressure								
Normal	49 (96.1)	272 (97.8)	1		94 (98.9)	212 (97.2)	1	
Abnormal	2 (3.9)	6 (2.2)	1.85 (0.36-9.43)	0.459	1 (1.1)	6 (2.8)	0.69 (0.13-3.50)	0.660
PR								
Normal	47 (92.2)	254 (91.3)	1		94 (89.5)	206 (92.4)	1	
Abnormal	4 (7.8)	24 (8.7)	0.90 (0.29-2.71)	0.853	11 (10.5)	17 (7.6)	1.40 (0.63-3.11)	0.405
SPO2								
Normal	47 (92.2)	268 (96.4)	1		98 (93.3)	216 (96.9)	1	
Abnormal	4 (7.8)	10 (3.6)	2.28 (0.68-7.57)	0.178	7 (6.7)	7 (3.1)	2.18 (0.74-6.38)	0.155
Fever								
No	30 (58.8)	95 (34.2)	1		48 (45.3)	77 (34.5)	1	
Yes	21 (41.2)	183 (65.8)	0.36 (0.19-0.66)	0.001	58 (54.7)	146 (65.5)	0.63(0.39-1.02)	0.061
Headache								
No	40 (78.4)	168 (60.4)	1		78 (73.6)	130 (58.3)	1	
Yes	11 (21.6)	110 (39.6)	0.42 (0.20-0.85)	0.017	28 (26.4)	93 (41.7)	0.50 (0.30-0.83)	0.008
Sore throat								
No	45 (88.2)	234 (84.2)	1		94 (88.7)	185 (83.0)	1	

Yes	6 (11.8)	44 (15.8)	0.70 (0.28-1.76)	0.459	12 (11.3)	38 (17.0)	0.62 (0.31-1.24)	0.180
Decreased sense of smell								
No	42 (82.4)	227 (81.7)	1		99 (93.4)	170 (76.2)	1	
Yes	9 (17.6)	51 (18.3)	0.95 (0.43-2.08)	0.906	7 (6.6)	53 (23.8)	0.22 (0.09-0.51)	<0.001
Gastrointestinal disorders								
No	44 (86.3)	207 (74.5)	1		85 (80.2)	166 (74.4)	1	
Yes	7 (13.7)	71 (25.5)	0.46 (0.20-1.07)	0.074	21 (19.8)	57 (25.6)	0.72 (0.40-1.26)	0.253
Shortness of breath								
No	24 (47.1)	108 (38.8)	1		43 (40.6)	89 (39.9)	1	
Yes	27 (52.9)	170 (61.2)	0.71 (0.39-1.30)	0.273	63 (59.4)	134 (60.1)	0.97 (0.60-1.55)	0.910
Cough								
No	39 (76.5)	118 (42.4)	1		51 (48.1)	106 (47.5)	1	
Yes	12 (23.5)	160 (57.6)	0.27 (0.11-0.45)	<0.001	55 (51.9)	117 (52.5)	0.97 (0.61-1.55)	0.922
Diarrhea								
No	49 (96.1)	237 (85.3)	1		95 (89.6)	191 (85.7)	1	
Yes	2 (3.9)	41 (14.7)	0.23 (0.05-1.00)	0.051	11 (10.4)	32 (14.3)	0.69 (0.33-1.43)	0.320
Weakness								
No	35 (68.6)	249 (89.6)	1		88 (83.0)	196 (87.9)	1	
Yes	16 (31.4)	29 (10.4)	3.92 (1.93-7.94)	<0.001	18 (17.0)	27 (12.1)	1.48 (0.77-2.83)	0.231
Myalgia								
No	50 (98.0)	248 (89.2)	1		98 (92.5)	200 (89.7)	1	
Yes	1 (2.0)	30 (10.8)	0.16 (0.02-1.24)	0.080	8 (7.5)	23 (10.3)	0.71 (0.30-1.64)	0.424
Hydroxychloroquine								
No	24 (47.1)	94 (33.8)	1		34 (32.1)	84 (37.3)	1	
Yes	27 (52.9)	184 (66.2)	0.57 (0.31-1.05)	0.072	72 (67.9)	139 (62.3)	1.28 (0.78-2.08)	0.323
Azithromycin								
No	36 (70.6)	234 (84.2)	1		83 (78.3)	187 (83.9)	1	
Yes	15 (29.4)	44 (15.8)	2.21 (1.11-4.38)	0.022	23 (21.7)	36 (16.1)	1.43 (0.80-2.58)	0.221
Kaletra								
No	36 (70.6)	206 (74.1)	1		66 (62.3)	176 (78.9)	1	
Yes	15 (29.4)	72 (25.9)	1.19 (0.61-2.30)	0.601	40 (37.3)	47 (21.1)	2.27 (1.36-3.77)	0.002
Intubation								
No	3 (5.9)	278 (100)	-	-	74 (69.8)	207 (92.8)	1	
Yes	48 (94.1)	0	-	-	32 (30.2)	16 (7.2)	5.59 (2.90-10.78)	<0.001

ICUs							
No	17 (33.3)	206 (74.1)	1		-	-	-
Yes	34 (66.7)	72 (25.9)	5.72 (3.01-0.86)	<0.001	-	-	-

Table 2- The odds ratio (OR) estimates of Covid-19 patients mortality by different variable using multiple logistic regression model.

Variables	Adjusted OR(95% CI)	P value
Age (Year)	1.02 (1.00-1.05)	0.044
Marital status		
Single	1	
Married	0.70 (0.17-2.83)	0.626
Heart disease		
No	1	
Yes	1.04 (0.33-3.21)	0.940
Hypertension		
No	1	
Yes	1.71 (0.66-4.43)	0.267
WBC		
<11000	1	
>=11000	1.91 (0.89-4.08)	0.095
Fever		
No	1	
Yes	0.76 (0.33-1.75)	0.531
Headache		
No	1	
Yes	0.71 (0.29-1.76)	0.467
Cough		
No	1	
Yes	0.24 (0.10-0.56)	0.001
Weakness		
No	1	
Yes	1.58 (0.61-4.11)	0.342
Azithromycin		
No	1	
Yes	1.37 (0.56-3.37)	0.483
ICUs		
No	1	
Yes	7.20 (3.30-15.69)	<0.001

CI: confidence interval.

Table 3- The odds ratio (OR) estimates of Covid-19 patients transfer to ICUs by different variable using multiple logistic regression model.

Variables	Adjusted OR (95% CI)	P value
Age (Year)	0.99 (0.97-1.00)	0.220
Marital status		
Single	1	
Married	0.69 (0.27-1.76)	0.447
Kidney disease		
No	1	
Yes	3.90 (1.04-14.63)	0.043
WBC		
<11000	1	
>=11000	1.62 (0.94-2.81)	0.080
Headache		
No	1	
Yes	0.93 (0.51-1.72)	0.840
Decreased sense of smell		

No	1	
Yes	0.28 (0.10-0.73)	0.009
Kaletra		
No	1	
Yes	2.53 (1.39-4.59)	0.002
Intubation		
No	1	
Yes	8.32 (3.80-18.24)	<0.001

CI: confidence interval.

Table 4- The performance criteria of models

Models	Data set	Mortality		Transfer to ICUs	
		AUC	Accuracy	AUC	Accuracy
Logistic regression	Train	0.93±0.01	0.90±0.01	0.85±0.03	0.83±0.02
	Test	0.76±0.06	0.83±0.03	0.83±0.07	0.81±0.04
Random Forest	Train	0.97±0.01	0.87±0.01	0.88±0.04	0.88±0.02
	Test	0.82±0.04	0.85±0.03	0.87±0.05	0.89±0.04

AUC: Area under the receiver operating characteristic curve.

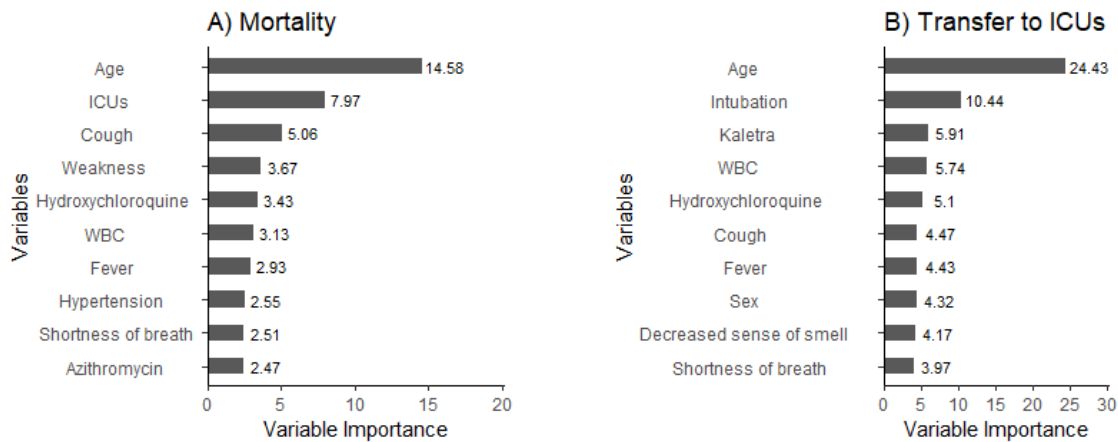


Figure 1- The top ten variable importance for mortality and ICUs transfer in hospitalized COVID-19 patients.

Discussion

In this study, the effects of several variables on mortality and transfer to ICUs were assessed using RF and LR models. The results of RF indicated that age, ICUs, and cough as the top three most important variables for predicting death; and age, intubation, and Kaletra for predicting transfer to ICUs. Also, the multiple LR model indicated a significant association between age, cough, and ICUs with death; and kidney disease, decreased sense of smell, Kaletra, and intubation with transfer to ICUs.

We found a strong association between age and death. So that the risk of death increased with age. Also, the results of RF showed that age was an important variable for death and transfer to ICUs in hospitalized COVID-19 patients. These results are in agreement with previous studies [33-35]. Zhao et al. also reported that age was an important risk factor for death and transfer to ICUs in hospitalized COVID-19 patients [33].

According to the results, kidney disease was another important risk factor for transfer to ICUs. in COVID-19

patients. Subudhi et al. and Flythe et al. reported that kidney disease can lead to a severe prognosis of COVID-19 and even death in them [3, 36]. In this study, intubation was another significant variable for predicting transfer to ICUs in COVID-19 patients. This may be due to disease progression and worsening symptoms in these patients. Previous studies have confirmed this result in these patients [37-38].

In this study, we also compared the performance of RF and LR models using cross-validation. According to the results, the comparison between these models showed that the performance of RF was better than LR for predicting mortality and ICUs transfer in hospitalized COVID-19 patients. Various studies have investigated mortality and ICUs transfer among COVID-19 patients using different models. Yadaw et al. [39] compared the performance of LR, RF, support vector machine, and XGBoost to predict COVID-19 mortality. They found that XGBoost had better performance than other models. In another study, Gao et al. [40] showed that the neural network had the highest performance for predicting

COVID-19 patient's physiological deterioration and death. Moulaei et al. [38] also found the performance of RF was better than LR for predicting COVID-19 mortality. This finding is consistent with our results.

Based on our analysis, the RF had better performance than LR in predicting the ICUs transfer in COVID-19 patients. These results are in agreement with previous studies [24, 41-42]. Subudhi et al. compared the performance of machine learning algorithms for predicting ICU admission and mortality in COVID-19 patients. They found that ensemble-based methods had better performance than other machine learning algorithms [3]. Similar results were also reported in a study conducted by Orooji et al. [31].

The limitations of this study were the retrospective design and the absence of some data in patients' records. Despite these limitations, our study showed that RF had a good performance in predicting mortality and transfer to ICUs in COVID-19 patients. The results of this study can help better manage patients with COVID-19.

Conclusion

This study showed that the performance of RF provided better results compared to LR for predicting mortality and ICUs transfer in hospitalized COVID-19 patients.

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