

Predictors of Mortality Using Machine Learning Decision Tree Algorithm in Critically Ill Adult Patients with COVID-19 Admitted to the ICU.

Alyaa Elhazmi (✉ a.m.haz@live.com)

Dr Sulaiman AlHabib Medical Center: Dr Sulaiman Al Habib Medical Group <https://orcid.org/0000-0001-8315-7393>

Awad Alomari

Dr Sulaiman AlHabib Medical Center: Dr Sulaiman Al Habib Medical Group

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Yaseen Arabi

King Abdulaziz University Faculty of Medicine

Research

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Abstract

Background:

The Coronavirus Disease-19 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a major cause of intensive care unit (ICU) admissions globally. Robust data of epidemiology, characteristics, and disease outcomes from different regions and populations showed considerable variations. However, limited number of reports addressed predictors of mortality utilizing machine learning methods. Herein, we aimed to describe the association and relationship of a predefined set of variables found to be predictive of 28-day ICU outcome among adults COVID-19 patients admitted to the ICU using a machine learning decision tree (DT) algorithm.

Methods:

This was a prospective/retrospective, multicenter cohort study from 14 hospitals in Saudi Arabia. We included critically ill COVID-19 patients admitted to the ICU between March 1, 2020, and October 31, 2020. The primary outcome was 28-day ICU mortality. Secondary outcomes were 90-day mortality and ICU length of stay. The predictors of mortality were identified using two predictive models, the conventional logistic regression and DT analysis.

Results:

A total of 1468 critically ill COVID-19 patients were included. The mean age was 55.9 (SD±15.1) years, with 74% of the patients were males. The 28-day ICU mortality was 540 (36.8%), while 90-day mortality was 600 (40.9%). The multivariable logistic regression model demonstrated that the PaO₂/FiO₂ ratio on ICU admission and the need for intubation or vasopressors could strongly predict 28-day ICU mortality. The DT algorithm identified five variables [need for intubation, need for vasopressors, age, gender, and PaO₂/FiO₂ ratio] provided in an algorithmic fashion to predict 28-day ICU outcome.

Conclusion:

Five clinical predictors of 28-day ICU outcome were identified using DT algorithmic analysis of COVID-19 patients admitted to ICU. The findings of this DT analysis may be used in ICU for early identification of critically ill COVID-19 patients who are at high risk of 28-day mortality.

Background

The Coronavirus disease 2019 (COVID-19) caused by Severe Adult Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first discovered in Wuhan city in late 2019 [1]. The World Health Organization (WHO) announced the disease to be pandemic on March 11, 2020 [2]. Since then, many investigators have addressed robust data of epidemiology, characteristics, and outcome of the disease from different regions and populations that showed variable results [3–8]. However, a limited number of reports addressed predictors of mortality utilizing machine learning methods [9]. Herein, we conducted this study

to evaluate predictors of 28-day ICU mortality based on a predefined set of variables among COVID-19 adults admitted to the intensive care unit (ICU) using a machine learning decision tree (DT) algorithm.

Methods

Study design

This was a prospective/retrospective, multicenter national study. We included COVID-19 patients admitted to ICU between March 1, 2020, and October 31, 2020. Institutional review boards (IRB) approvals were obtained from the Central Institutional Review Board at the Saudi Ministry of Health and the Ethical Boards of each participating center.

Setting

The study was conducted in 14 participating centers across the Kingdom of Saudi Arabia. The participating ICUs were in accredited governmental and non-governmental tertiary hospitals. The multidisciplinary treating team included critical care physicians (consultants, specialists, and residents), registered ICU nurses, respiratory therapists, clinical pharmacists, and other ICU care providers who practiced according to national and international published protocols and guidelines. In addition, during the time of the COVID-19 surge, non-ICU physicians from different specialties joined the critical care team under the supervision of intensivists after receiving basic ICU management training.

Patients

Adult patients admitted to the ICU of participating hospitals with confirmed COVID-19 by detecting SARS-CoV-2 using real-time polymerase chain reaction (RT-PCR) in nasopharyngeal swabs or tracheal aspirate specimens. Immunocompromised status was defined as solid organ malignancy, leukemia, current use of steroids (prednisone >7mg daily for >2 weeks), post organ transplantation at any time, or rheumatological disease on immunomodulators (as azathioprine, methotrexate, infliximab, mycophenolate mofetil or others). Infection was defined by the positive culture in blood or tracheal aspirate.

Data collection

The data was collected using the Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN) [10]. The collected data included patients' demographics, comorbidities, signs, and symptoms of COVID-19 illness, laboratory abnormalities, mechanical ventilation (MV) utilization, adjunctive interventions, medications, complications, and outcomes.

Outcomes measures

The primary outcome was 28-day ICU mortality. Secondary outcomes were 90-day ICU mortality and hospital length of stay.

Statistical analysis

General analysis

Patients' characteristics were summarized using frequencies and percentages for categorical variables and as medians and interquartile ranges (IQR) or mean and standard deviation (SD) for continuous variables. Chi-square or Fisher's exact tests compared categorical variables. The Wilcoxon rank-sum test was used for continuous variables. We constructed Kaplan–Meier curves to assess cumulative mortality during the initial 60 days from ICU admission.

In the first 28 days of ICU stay, risk factors of mortality were evaluated in the whole cohort using univariate and multivariable logistic regression analyses. Variables included in the multivariable logistic regression model were identified based on literature review and used to generate the predictive models included demographics, co-morbid conditions, laboratory data on ICU admission, the respiratory component of SOFA score [11] and the need for intubation or vasopressors. In the regression analysis, variables of the need for intubation and vasopressors included patients during the first five days of ICU admission, and the respiratory component of SOFA score on ICU admission was classified as (category 4 was $\text{PaO}_2/\text{FiO}_2 < 100$ with respiratory support, while category 0-3 was $\text{PaO}_2/\text{FiO}_2 > 100$). Continuous variables were categorized using cut-off points based on either previous literature review or optimal cut-off points statistically identified using the cut pointer library in R, maximizing the Youdin index that determines the split point between survivors and non-survivors. The logistic regression model results were reported as odds ratio (OR) with a 95% confidence interval (95%CI). All statistical tests were two-tailed, and p values < 0.05 were considered significant. All statistical analyses were performed using R software, version 4.0.2 (06-22-2020) (R Foundation for Statistical Computing, Vienna, Austria).

Decision Tree (DT) analysis

Machine learning DT analysis was used to identify characteristics of patients with COVID-19 that were predictive of 28-day ICU outcome. The model was generated using the standard setting in the open-source software library Waikato Environment for Knowledge Analysis (WEKA, University of Waikato) [12] using the C 4.5 classification algorithm (J48) with 20 cases as the minimum number of cases at the leaf of each branch (end of the tree). C4.5 classifier used the information gain ratio split criterion to reduce bias towards multivalued [13]. In addition, we used "Algorithm Accuracy" as a general measure to assess the performance of the classifier. Accuracy is one of the most used performance measures representing the overall correctness of the algorithm. The Area Under the Receiver Operating Characteristic Curve (AUROC) is also used to evaluate the performance of the decision tree model, which represents the predictive performance of the model across different thresholds of sensitivity (true positive rate (TPR)) plotted over different ranges of 1- specificity (false positive rate) [14]. Ten-fold cross validation was applied to generate the accuracy, AUROC, and its confidence intervals. TPR is the true positive cases by the algorithm divided by the total positive cases (true positive + false positive). To assess the model's generalizability and avoid over-fitting, 10-folds cross validation was applied.

Results

Patient characteristics and ICU admission data

During the study period, 1468 patients were admitted to the ICUs in the 14 participating hospitals. Table 1 described the patients' demographics and data in the first 24 hours of ICU admission among the 28-day ICU survivors vs. non-survivors. The mean age was 55.9 (SD±15.1) years, (74%) of the patients were males, and 69 patients (4.8%) were healthcare workers. Hypertension, ischemic heart disease, and smoking were significantly associated with higher 28-day ICU mortality (P value 0.0187, 0.0016, and 0.0333, respectively). The SOFA score, 7 (IQR 4-10), was significantly higher in patients who died within the first 28 days of ICU admission. Survivors had a higher PaO₂/FiO₂ ratio compared to non-survivors at 28-day of ICU admission [142 (IQR 72-176) vs. 92 (IQR 66-138), p value <0.001]. (Table 1)

Table 1
Baseline general characteristics and ICU admission data.

Patient characteristic	All Patients (n=1468) /Denominator	28-day non- survivors (n= 540)	28-day survivors (n= 928)	p-value
Age (years), mean (\pm SD)	55.9 (15.1)/1423	58.4 (15.2)	54.3 (14.9)	<0.001*
Gender, n (%)				
Male gender, n (%)	1085 (74)/1467	413 (76.6)	672 (72.4)	0.0765
Female Gender, n (%)	382 (26)/1467	126 (23.4)	256 (27.6)	
Pregnancy, n (%)	19 (5.1)/372	2 (1.6)	17 (6.8)	0.0425*
Healthcare worker, n (%)	69 (4.8)/1436	15 (2.9)	54 (5.9)	0.009 *
BMI (kg/m ²), mean (\pm SD)	30.1 (6.8)/1369	29.5 (6.5)	30.5 (7)	0.009 *
Comorbidity				
Diabetes mellitus, n (%)	770 (54.8)/1405	297 (58.1)	473 (52.9)	0.0589
Hypertension, n (%)	676 (48.6)/1391	267 (52.8)	409 (46.2)	0.0187*
Ischemic heart disease, n (%)	184 (13.8)/1333	85 (17.8)	99 (11.6)	0.0016*
Bronchial Asthma, n (%)	128 (9.6)/1333	37 (7.7)	91 (10.6)	0.0845
Chronic Kidney Disease, n (%)	123 (9.2)/1339	47 (9.7)	76 (8.9)	0.656
Smoker, n (%)	85 (7.2)/1180	21 (5)	64 (8.4)	0.0333*
Left ventricular failure, n (%)	74 (5.6)/1331	32 (6.7)	42 (4.9)	0.181
Immunocompromised, n (%)	72 (5.4)/1332	19 (4)	53 (6.2)	0.079
Renal Replacement therapy, n (%)	54 (4.1)/1332	25 (5.2)	29 (3.4)	0.12
Cancer, n (%)	48 (3.6)/1333	17 (3.5)	31 (3.6)	0.913
Chronic Lung Disease, n (%)	38 (2.9)/1327	14 (2.9)	24 (2.8)	0.891
Solid-organ transplant, n (%)	29 (2.2)/1334	8 (1.7)	21 (2.5)	0.337
COPD, n (%)	26 (2)/1327	12 (2.5)	14 (1.6)	0.27

COPD, chronic obstructive pulmonary disease. BMI, *body mass index*. COPD, *chronic obstructive pulmonary disease*. CRP, *C - reactive protein*. GCS, *Glasgow coma scale*. HR, *heart rate*. LDH, *Lactic Acid Dehydrogenase*. MAP *mean arterial pressure*. NL ratio, *Neutrophil-to-lymphocyte ratio*. RR, *respiratory rate*. SOFA, *Sequential Organ Failure Assessment*. WBC, *white blood cells*.

Patient characteristic	All Patients (n=1468) /Denominator	28-day non- survivors (n= 540)	28-day survivors (n= 928)	p-value
Chronic Liver Disease, n (%)	24 (1.8)/1332	10 (2.1)	14 (1.6)	0.557
Chronic Hematological Disease (%)	12 (0.9)/1337	3 (0.6)	9 (1.1)	0.553
ICU admission data (first 24 hs)				
Use of inotropes, n (%)	189 (15.3)/1235	120 (29.4)	69 (8.3)	<0.001*
New AKI on ICU admission, n (%)	98 (8.6)/1137	60 (14.4)	38 (5.3)	<0.001*
MAP (mmHg), mean (±SD)	86.1 (16.1)/1299	84.7 (16.7)	86.8 (16.3)	0.0246*
HR (beat/min), mean (±SD)	91.2 (20.4)/1294	95.1 (20.7)	89.3 (20)	<0.001*
RR (per min), mean (±SD)	27.9 (7.2)/1274	28.3 (7.1)	27.8 (7.3)	0.196
GCS, median (±IQR)	15 (14-15)/1259	15 (9-15)	15 (15-15)	<0.001*
SOFA, median (±IQR)	4 (3-8)/1333	7 (4-10)	4 (2-6)	<0.001*
PO ₂ /FiO ₂ ratio, median (IQR)	134 (71-163)/1217	92 (66-138)	142 (72-176)	<0.001*
PO ₂ /FiO ₂ ratio, n (%)				<0.001*
< 100	550 (50)/1099	210 (57.9)	340 (46.2)	
100 - <200	361 (32.8)/1099	110 (30.3)	251 (34.1)	
200 - 300	116 (10.6)/1099	27 (7.4)	89 (12.1)	
>300	72 (6.6)/1099	16 (4.4)	56 (7.6)	
ICU admission laboratory data (first 24 hs)				
WBC (x 10 ⁹ /L), mean (±SD)	10.7 (6.3)/1378	12.3 (7.8)	9.7 (5)	<0.001*
NL Ratio, mean (±SD)	10.3 (8.7)/1126	11.8 (9.4)	9.4 (8.1)	<0.001*
Creatinine (nmol/L), median (IQR)	83 (63-130)/1289	106 (71-187)	75 (60-105)	<0.001*
Lactate (mmol/L), median (IQR)	1.5 (1.1-2.2)/652	1.8 (1.2-3)	1.5 (1.1-2)	<0.001*

COPD, chronic obstructive pulmonary disease. BMI, *body mass index*. COPD, *chronic obstructive pulmonary disease*. CRP, *C - reactive protein*. GCS, *Glasgow coma scale*. HR, *heart rate*. LDH, *Lactic Acid Dehydrogenase*. MAP *mean arterial pressure*. NL ratio, *Neutrophil-to-lymphocyte ratio*. RR, *respiratory rate*. SOFA, *Sequential Organ Failure Assessment*. WBC, *white blood cells*.

Patient characteristic	All Patients (n=1468) /Denominator	28-day non- survivors (n= 540)	28-day survivors (n= 928)	p-value
Procalcitonin (ng/mL), median (IQR)	0.36 (0.15-1.5)/669	0.96 (0.27-3.6)	0.3 (0.13-0.64)	<0.001*
LDH (IU/L) (, median (IQR)	504 (363-706)/1028	584 (411-826)	467 (353-641)	<0.001*
D-Dimer (mcg/mL), median (IQR)	1.51 (0.8-2.8)/1060	2.38 (1.2-5.4)	1.2 (0.7-2.8)	<0.001*
Ferritin (ng/mL), median (IQR)	802 (396-1295)/850	915 (486-1166)	772 (370-1295)	<0.001*
CRP (mg/l), median (IQR)	104 (33-196)/937	117 (40-198)	99 (30-194)	0.0524
COPD, chronic obstructive pulmonary disease. BMI, <i>body mass index</i> . COPD, <i>chronic obstructive pulmonary disease</i> . CRP, <i>C - reactive protein</i> . GCS, <i>Glasgow coma scale</i> . HR, <i>heart rate</i> . LDH, <i>Lactic Acid Dehydrogenase</i> . MAP <i>mean arterial pressure</i> . NL ratio, <i>Neutrophil-to-lymphocyte ratio</i> . RR, <i>respiratory rate</i> . SOFA, <i>Sequential Organ Failure Assessment</i> . WBC, <i>white blood cells</i> .				

Interventions during ICU stay

Out of the study cohort, 778 patients (52.9%) required invasive mechanical ventilation (IMV) during the ICU admission, of whom 128 patients were intubated prior to transfer to the ICU of the participating centers. High flow nasal cannula (HFNC) was used in 446 patients (35.3%) with median duration of 3 (IQR 2-6) days. In non-intubated patients, awake prone position was utilized in 350 patients (27.7%), of whom 194 patients (57.4 %) utilized it for a duration longer than 4 hours/day. Of patients who required IMV, 506 patients (75.3 %) received neuromuscular blockade, and 319 patients (47.8 %) received prone positioning (Table 2).

Table 2
Interventions during ICU stay.

Patient characteristic	All Patients (n= 1468) /Denominator	28-day non- survivors (n= 540)	28-day survivors (n= 928)	p-value
Vasopressors n (%)	395 (26.9)/1468	246 (45.5)	149 (16)	<0.001*
Oxygen delivery modes				
HFNC, n (%)	446 (35.3)/1264	105 (25.1)	341 (40.4)	<0.001*
HFNC days, median (IQR)	3 (2-6)/429	2 (1-4)	4 (2-6)	<0.001*
NIPPV, n (%)	205 (16.2)/1267	96 (22.8)	109 (12.9)	<0.001*
NIPPV days, median (IQR)	2 (1-4)/198	2 (1-4)	2 (2-6)	0.527
Awake prone positioning, n (%)	350 (27.7)/1263	86 (20.6)	264 (31.2)	<0.001*
Awake prone days, median (IQR)	3 (2-5)/316	2 (1-4)	4 (2-6)	<0.001*
Awake prone >4 hours/day, n (%)	194 (57.4)/338	49 (60.5)/81	145 (56.4)	0.518
IMV, n (%)	778 (52.9)/1468	454 (83.9)	324 (34.9)	<0.001*
First 24 hs of intubation, mean (±SD)				
PaO ₂ /FiO ₂	125.5 (80)/535	115 (76)	137.7 (83)	0.001*
PCO ₂ (mmHg)	46.6 (14.7)/558	48 (15.5)	45 (13.5)	0.015*
Static Compliance (ml/cmH ₂ O)	27.8 (11.2)/152	27 (11.7)	28.6 (10.6)	0.382
Dynamic Compliance (ml/cmH ₂ O))	22.2 (14.6)/324	20.6 (9.4)	24.1 (19.2)	0.045*
Peak airway pressure (cmH ₂ O)	31.2 (6.7)/335	31.7 (7.1)	30.6 (6.2)	0.131
Plateau pressure (cmH ₂ O)	27.3 (5.7)/156	27 (5.4)	27.5 (5.9)	0.549

HFNC, high flow nasal cannula. IVIG, Intravenous immunoglobulin. NIPPV, non-invasive positive pressure ventilation. IMV, Invasive Mechanical Ventilation. PaO₂/FiO₂, Partial pressure of oxygen to fraction of inspired oxygen ratio. PCO₂, Partial pressure of Co₂. Fio₂, fraction of inspired oxygen. MV, mechanical ventilator. APRV, Airway pressure release ventilation. ECMO, extracorporeal membrane oxygenation. HFOV, high-frequency oscillatory ventilation. iNO, inhaled nitric oxide.

Patient characteristic	All Patients (n= 1468) /Denominator	28-day non-survivors (n= 540)	28-day survivors (n= 928)	p-value
Tidal Volume (ml per IBW)	6.94 (1.34)/601	6.87 (1.2)	7.04 (1.51)	0.135
Interventions during IMV, n (%)				
Neuromuscular blockade infusion	562 (74.8)/751	332 (76.1)	230 (73)	0.329
Recruitment maneuvers use	91 (12.3)/737	50 (11.6)	41 (13.4)	0.482
iNO use	64 (8.6)/742	37 (8.5)	27 (8.7)	0.927
Prone positioning during MV	350 (47)/745	194 (44.6)	156 (50.3)	0.123
Rescue APRV use	20 (2.7)/739	10 (2.3)	10 (3.2)	0.444
Rescue HFOV use	12 (1.6)/740	8 (1.8)	4 (1.3)	0.563
Tracheostomy	60 (7.7)/778	8 (1.5)	52 (5.6)	<0.001*
ECMO	71 (9.1)/778	40 (7.5)	31 (3.4)	<0.001*
Medications and interventions, n (%)				
Azithromycin	1069 (74.2)/1440	366 (68.9)	703 (77.3)	<0.001*
Corticosteroids	1048 (73.1)/1433	401 (75.8)	647 (71.6)	0.081
Chloroquine	429 (30.5)/1406	152 (29.2)	277 (31.3)	0.403
Tocilizumab	426 (30.1)/1414	126 (24)	300 (33.7)	<0.001*
Favipiravir	316 (22.4)/1441	111 (21.2)	205 (23.1)	0.401
Ribavirin	241 (17.2)/1402	79 (15.3)	162 (18.3)	0.141
Convalescent plasma	53 (3.8)/1409	12 (2.3)	41 (4.6)	0.026*
IVIG	51 (3.6)/1401	18 (3.5)	33 (3.7)	0.792
Plasmapheresis	26 (1.8)/1409	17 (3.2)	9 (1)	0.002*

HFNC, high flow nasal cannula. IVIG, Intravenous immunoglobulin. NIPPV, non-invasive positive pressure ventilation. IMV, Invasive Mechanical Ventilation. PaO₂/FiO₂, Partial pressure of oxygen to fraction of inspired oxygen ratio. PCO₂, Partial pressure of Co₂. Fio₂, fraction of inspired oxygen. MV, mechanical ventilator. APRV, Airway pressure release ventilation. ECMO, extracorporeal membrane oxygenation. HFOV, high-frequency oscillatory ventilation. iNO, inhaled nitric oxide.

Patient characteristic	All Patients (n= 1468) /Denominator	28-day non-survivors (n= 540)	28-day survivors (n= 928)	p-value
Remdesivir	13 (0.9)/1399	5 (1)	8 (0.9)	0.91

HFNC, *high flow nasal cannula*. IVIG, *Intravenous immunoglobulin*. NIPPV, *non-invasive positive pressure ventilation*. IMV, *Invasive Mechanical Ventilation*. PaO₂/FiO₂, *Partial pressure of oxygen to fraction of inspired oxygen ratio*. PCO₂, *Partial pressure of Co2*. Fio₂, *fraction of inspired oxygen*. MV, *mechanical ventilator*. APRV, *Airway pressure release ventilation*. ECMO, *extracorporeal membrane oxygenation*. HFOV, *high-frequency oscillatory ventilation*. iNO, *inhaled nitric oxide*.

Outcomes:

Out of 1468 patients, 540 (36.8%) died within 28-day of ICU stay, while 757 (51.6%) were discharged alive from the hospital. The 90-day ICU mortality was 600 patients (40.9%), and the median ICU length of stay was 9 (IQR 5-16) days, while the hospital length of stay was 15 (IQR 9-24) days. Blood cultures were positive in 267 patients (24.3%) and respiratory samples in 227 patients (33.4%) (Table 3). The Kaplan Maier curve for COVID-19 cumulative incidence of mortality showed 40% mortality at day 60 of ICU admission. (Figure 1)

Table 3
Patients Outcomes

	All Patients (n=1468) /Denominator	28-day non- survivors (n= 540)	28-day survivors (n= 928)	p- value
ICU Mortality at 28 days, n (%)	540 (36.8)			
90-day mortality, n (%)	600 (40.9)			
Discharge from ICU alive, n (%)	869 (59.1)			
Discharged from hospital alive, n (%)	757 (51.6)			
Transfer to another institution, n (%)	94 (6.5)			
Mortality Subgroup analysis according to time of death				
0-28 days, n (%)	540 (90.05)			
29-60 days, n (%)	54(8.9)			
61-90 days, n (%)	6 (0.06)			
ICU length of stay (days), Median (IQR)	9 (5-16)/1468	10 (5-16)	9 (5-17)	0.356
Hospital length of stay, (days) Median (IQR)	15 (9-24)/1468	13 (7-18)	18 (11-31)	<0.001 *
Mechanical ventilation duration (days) Median (IQR)	7 (0-14)/1082	10 (4-15)	3 (0-11)	<0.001 *
Infection (positive culture, respiratory), n (%)	227 (33.4)/679	131 (46.6)	96 (24.1)	<0.001 *
Infection (positive culture, blood), n (%)	267 (24.3)/1100	151 (34.2)	116 (17.6)	<0.001 *
AKI requiring RRT, n (%)	178 (14.1)/1259	130 (28.6)	48 (6)	<0.001 *
Pneumothorax, n (%)	89 (6.2)/1440	55 (10.4)	34 (3.7)	<0.001 *
Myocardial infarction, n (%)	64 (4.5)/1433	40 (7.6)	24 (2.6)	<0.001 *
GI Bleeding, n (%)	52 (3.6)/1438	27 (5.1)	25 (2.7)	0.019 *
Pulmonary embolism, n (%)	44 (3.1)/1435	20 (3.8)	24 (2.6)	0.215

AKI, *acute kidney injury* ICU, *intensive care unit*. GI, *gastrointestinal*. RRT, *renal replacement therapy*.

	All Patients (n=1468) /Denominator	28-day non- survivors (n= 540)	28-day survivors (n= 928)	p- value
Deep vein thrombosis, n (%)	33 (2.3)/1435	17 (3.2)	16 (1.8)	0.070
Intracranial hemorrhage, n (%)	33 (2.3)/1432	15 (2.9)	18 (2)	0.277
Ischemic Stroke, n (%)	32 (2.2)/1438	14 (2.7)	18 (2)	0.39
<i>AKI, acute kidney injury ICU, intensive care unit. GI, gastrointestinal. RRT, renal replacement therapy.</i>				

Predictors of 28-day ICU mortality

Results of the logistic regression:

The multivariable logistic regression analysis retained the respiratory component of SOFA score (category 4) and the need for intubation and vasopressors as predictors of 28-day ICU mortality [(OR 2.12 (95% CI 1.21-3.7), P value <0.008), (OR 3.25 (95%CI 1.76-5.99), P value <0.001); and (OR 3.11 (95%CI 1.66-5.82), P value <0.001)] respectively. (Table 4)

The stepwise logistic regression analysis retained eight variables: age groups, gender, diabetes mellitus (DM), ischemic heart disease (IHD), the respiratory component of SOFA score (category 4), need for intubation, or vasopressors, and neutrophils-lymphocytes (NL) ratio. (Figure 3)

Results of the decision tree analysis:

Five variables were identified and allocated the patients into the final binary outcome (Survival versus Mortality). These variables were: the need for intubation or vasopressors, Gender, PaO₂/FiO₂ on ICU admission, and age categories. The constructed DT assigned the root node (start of the tree or first splitting criteria) to the need for intubation. Then, the tree continued to grow and assign patients into their respective groups utilizing the other four variables in a sequential manner. The DT model's ability to correctly assign patients to their respective groups (model discrimination), assessed using the ROC-AUC, was 75.42 % (95% CI= 74.84-78.95). The DT model accuracy was 73.1% (number of retained patients on the model 1043 out of 1468). (Figure 2).

Discussion

We utilized the DT analysis and identified five features that are predictive of 28-day ICU outcomes. These features are the need for intubation, vasopressors, age, gender, and PaO₂/FiO₂ ratio.

The COVID-19 pandemic overwhelmed the health care system leading to constraints of medical resources, mainly in critical care unit capacity, and a shortage of mechanical ventilators. [15–17]. Many hospitals utilized machine learning-based analyses combining clinical, radiological and laboratory data for the prognostication and rapid risk stratification of PCR confirmed COVID-19 patients [18–20]. The evaluation of the severity of illness for patients admitted to the ICU has been applied by different general scoring methods such as the acute physiology and chronic health evaluation (APACHE) II and IV [21, 22], Simplified Acute Physiology Score (SAPS) [23], and SOFA scores [11] or COVID-19 specific scores as 4C mortality score [24]. APACHE-II score, the most commonly utilized score on ICU admission, is subjective, time-consuming, and depends mainly on laboratory indicators which are not comprehensive enough to predict the outcome of the newly emerged COVID-19 [25]. Standard logistic regression analysis is useful in predicting outcomes of interest; however, it does not model a nonlinear relationship of multiple dimensional data [26].

The application of machine-learning models in the medical field has been increasingly utilized, especially in outcome prediction of cancer outcomes [27–29]. Random Forest classifiers, decision trees, and artificial neural networks (ANNs) specifically were among the earliest used techniques in medical research [30, 31]. DT analysis is an effective classifier that has been applied in many domains [32, 33] and is considered an intuitive nonlinear approach that can automatically detect independent variables that predict outcomes and the interactions between these variables. Moreover, it allows an easy-to-understand visual representation of the relationships between the variables and the primary outcome [34]. The multivariable, stepwise logistic regression, and DT analyses in our study were built using the same predefined set of variables. Nevertheless, our study demonstrates the advantage of DT analysis in providing prediction in an algorithmic fashion rather than merely identifying associations and relations between the variables and the outcome achieved by most regression models [35, 36]. In this context, DT algorithms are very intuitive, easy to understand and explain while producing simple rules that simulate a human logic-like approach.

Predictors of mortality in COVID-19 have been widely reported in many studies with different settings and designs, including mainly laboratory and radiological variables [37, 38]. Limited reports, however, studied clinical variables on ICU admission as predictors of mortality that may facilitate the early identification of critically ill COVID-19 patients at higher risk of 28-day mortality [39]. In metanalysis reported by (Pengqiang Du. et al. 2021) addressed the predictors of mortality utilizing the classic logistic regression analysis showed that advanced age, male gender, and comorbidities of chronic respiratory disease, DM, hypertension, and chronic kidney or cardiovascular diseases were associated with severe illness or death for COVID-19 patients [40].

On the other hand, studies that reported predictors of mortality utilizing DT analysis in critically ill COVID-19 patients were very limited [41–43]. One of these analyses by (Qiao Yang et al. 2021) showed a rapid, simple, and easy to interpret decision tree model built of three biochemical markers on ICU admission (LDH, NLR, and CRP) with a high true sensitivity rate to predict death in severe COVID-19 disease [41].

Strengths of the study include the multicenter nature, which improves generalizability. In addition, unlike the earlier reported experience from the Middle East [44], the 28-day ICU mortality of 36.8% in this cohort was comparable to reported experiences during the pandemic [45–47]. Our study has limitations, including a low retained number of patients in the multivariable logistic regression in the provided model (409 out of 1468 (27.82%)). However, this low number depends on the clinically dependent variables utilized in the model that is limited to a small number of critically ill patients on ICU admission as the need for intubation and vasopressors.

Conclusion

Five clinical predictors of 28-day ICU outcome identified using DT algorithmic analysis of COVID-19 patients admitted to ICU. DT analysis may be used in ICU for early identification of critically ill COVID-19 patients who are at high risk of 28-day mortality. Further studies are required to validate these results.

Declarations

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Ethics approval: Approval was obtained from the Central Institutional Review Board at the Saudi Ministry of Health approved this study [20-80E]. Individual ethical board approvals of the participating centers were obtained.

Consent to participate was waived as all data are unidentified.

Consent for publication all authors accept and confirm publication.

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Figures

KSA COVID-19 ICU Cummulative Incidence of Mortality

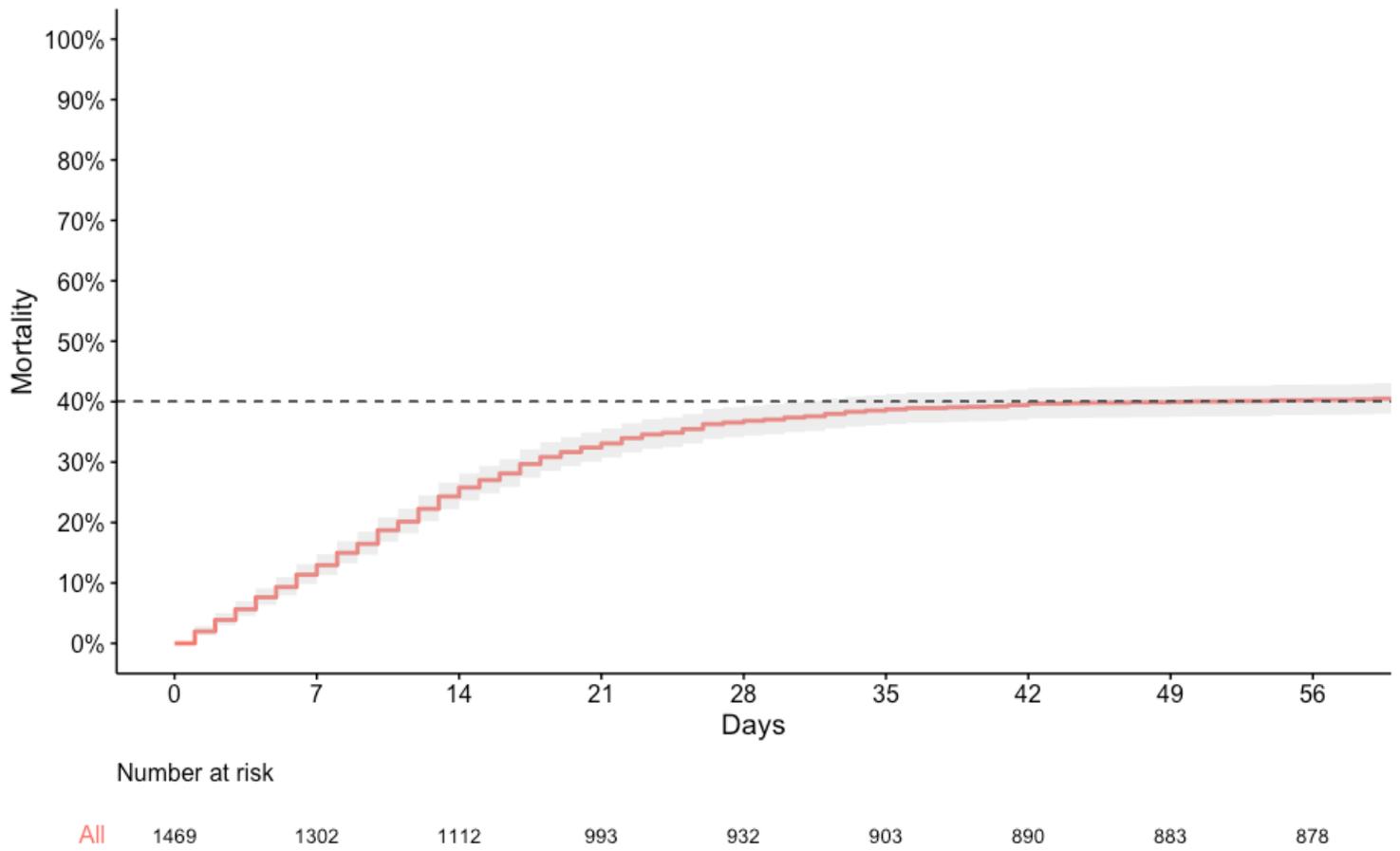


Figure 1

Kaplan Maier curve for COVID-19 cumulative incidence of mortality.

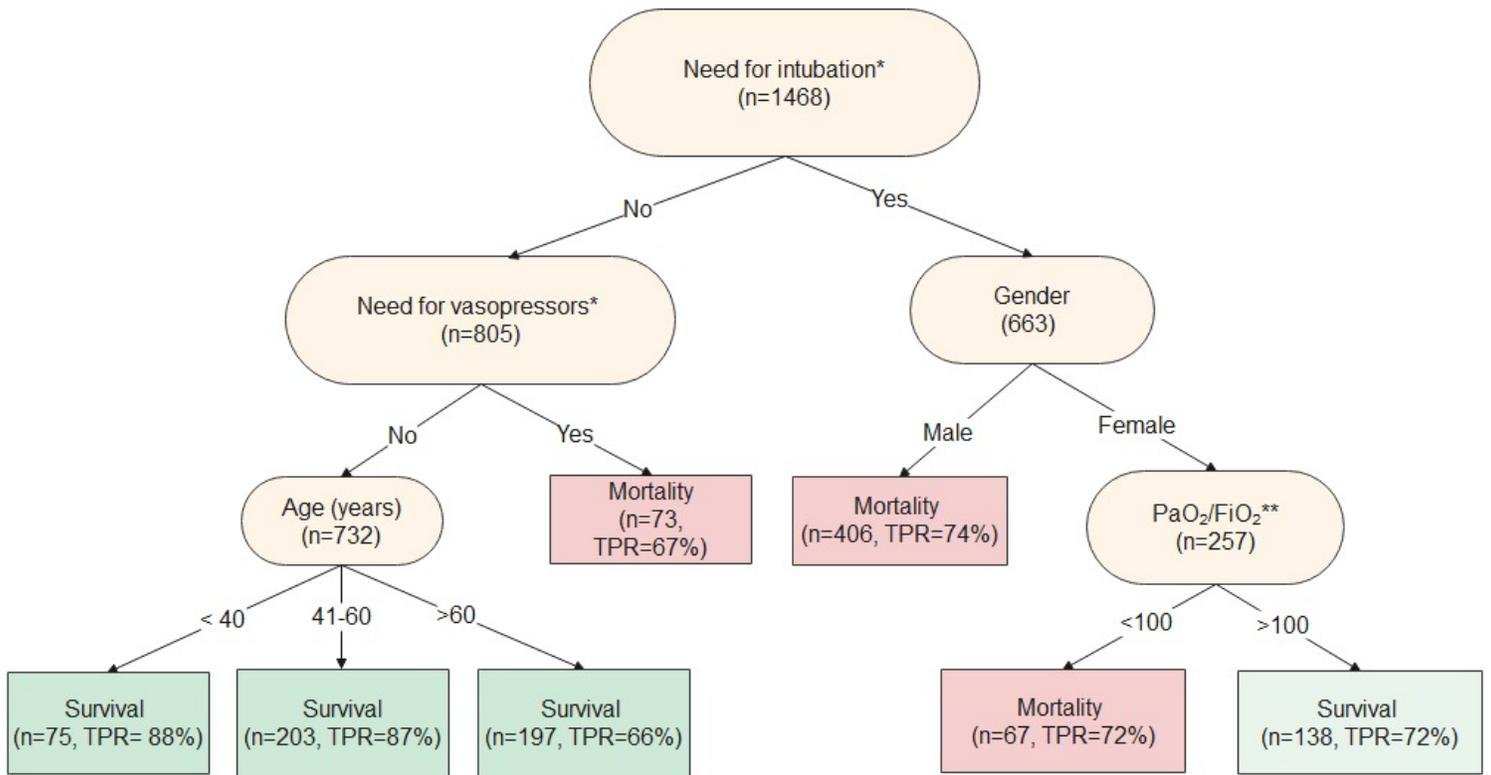


Figure 2

Decision Tree (DT) algorithm for predictors of mortality. - n: number of subjects in the leaf, TPR: true positive rate (sensitivity). - *During five days of ICU admission - ** In the first 24 hours of ICU admission. - DT algorithm with ROC-AUC= 75.42 % (95% CI= 74.84-78.95). - Number of patients retained in the model= 1043 out of 1468 (71.04%). - The need for intubation during the first five days of ICU admission was the first splitting variable (Root node); in those who required intubation, gender was the next splitting step. If the patient was a Male, a high probability of mortality with 74% accuracy is anticipated. While if female gender, the PaO₂/FiO₂ ratio <100 had a high probability of mortality with an accuracy of 72%. On the other hand, for those who did not require intubation nor vasopressors during the first five days, age affected the outcome widely (e.g., high probability of survival with an 88% accuracy in age group less than 40).

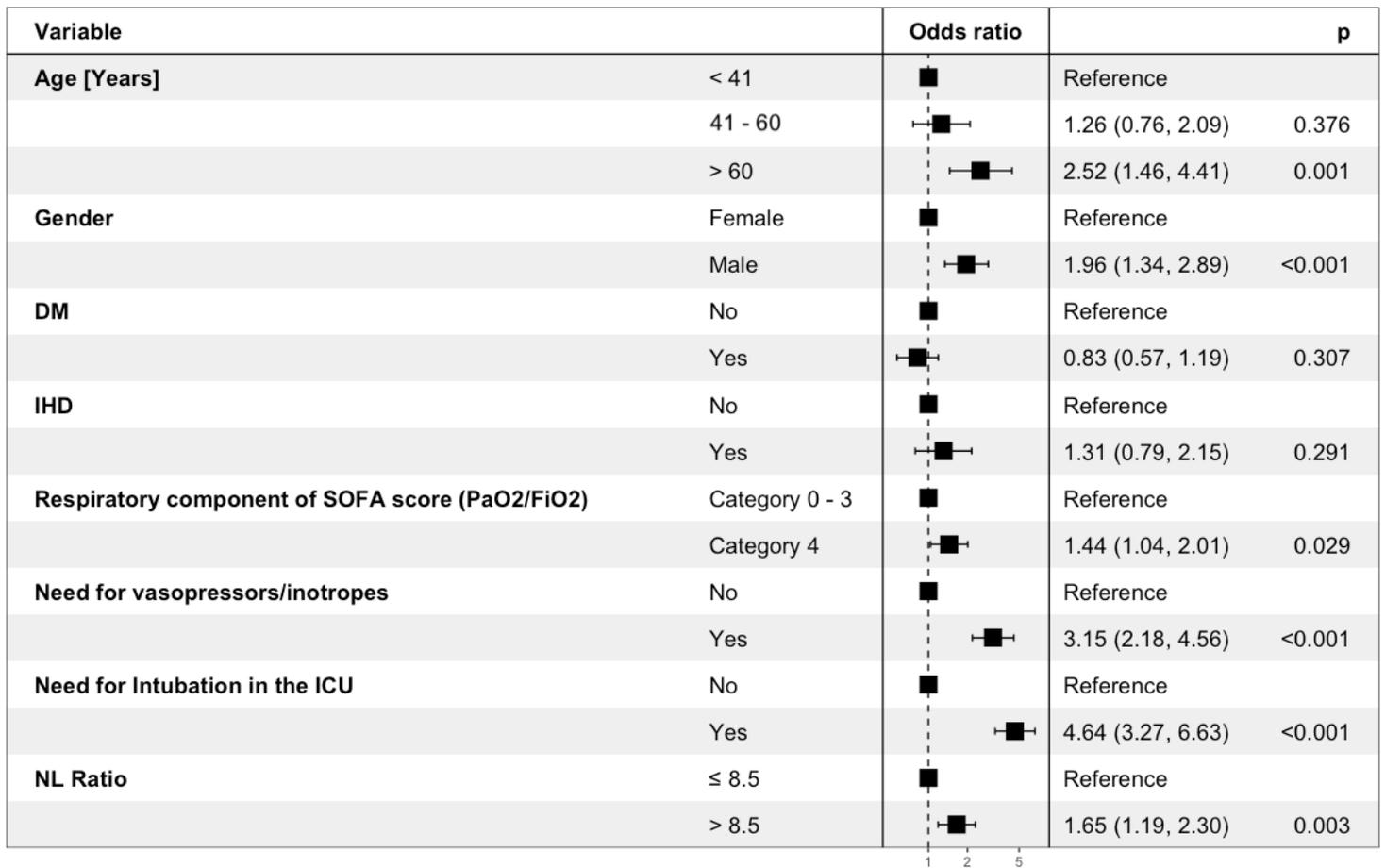


Figure 3

Stepwise logistic regression of 28-day mortality PaO₂/ FiO₂, Partial pressure of oxygen to fraction of inspired oxygen ratio. DM: Diabetes mellitus. IHD: Ischemic heart disease, LDH: lactate dehydrogenase. Stepwise Logistic Regression: ROC-AUC= 79.96% (95% CI= 76.91-83.02). Number of patients retained in the model= 843 Out of 1468 (57.35%)