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Original Article

Machine learning decision tree algorithm role for predicting mortality in critically ill adult COVID-19 patients admitted to the ICU

Alyaa Elhazmi[a,c,*], Awad Al-Omari[b,c], Hend Sallam[d], Hani N. Mufti[e,f], Ahmed A. Rabie[g], Mohammed Alshahrani[h], Ahmed Mady[g,i], Adnan Alghamdi[j], Ali Altalaq[j], Mohamed H. Azzam[k], Anees Sindi[l], Ayman Kharaba[m], Zohair A. Al-Aseri[n,o], Ghaleb A. Almekhlafi[j], Wail Tashkandi[p,q], Saud A. Alajmi[j], Fahad Faqihi[g], Abdulrahman Alharthy[g], Jaffar A. Al-Tawfiq[r,s], Rami Ghazi Melibari[t], Waleed Al-Hazzani[u,v], Yaseen M. Arabi[w,1]

[a] *Department of Critical Care, Dr. Sulaiman Al-Habib Medical Group, Riyadh, Saudi Arabia*
[b] *Research Center, Dr. Sulaiman Alhabib Medical Group, Riyadh, Saudi Arabia*
[c] *College of Medicine, Alfaisal University, Riyadh, Saudi Arabia*
[d] *Department of Adult Critical Care Medicine, King Faisal Specialist Hospital & Research Centre, Saudi Arabia*
[e] *Section of Cardiac Surgery, Department of Cardiac Sciences, King Faisal Cardiac Center, King Abdulaziz Medical City, MNGHA-WR, Jeddah, Saudi Arabia*
[f] *College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia. King Abdullah International Medical Research Center, Jeddah, Saudi Arabia Intensive Care Department, King Saud Medical City, Riyadh, Saudi Arabia*
[g] *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia*
[h] *Emergency and Critical Care Department, King Fahad Hospital of The University, Imam Abdul Rahman ben Faisal University, Dammam, Saudi Arabia*
[i] *Department of Anesthesiology and Intensive Care, Tanta University Hospitals, Tanta, Egypt*
[j] *Prince Sultan Military Medical City, Military Medical Services, Ministry of Defence, Riyadh, Saudi Arabia*
[k] *Intensive Care Department, King Abdullah Medical Complex, Jeddah, Saudi Arabia*
[l] *Department of Anesthesia and Critical Care, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*
[m] *Department of Critical Care, King Fahad Hospital, Al Medina Al Monawarah, Saudi Arabia*
[n] *Departments Of Emergency Medicine and Critical Care, College of Medicine, King Saud University, Riyadh, Saudi Arabia*
[o] *College Of Medicine, Dar Al Uloom University, Riyadh, Saudi Arabia*
[p] *Department of Critical Care, Fakeeh Care Group, Jeddah, Saudi Arabia*
[q] *Department of Surgery, King Abdulaziz University, Jeddah, Saudi Arabia*
[r] *Infectious Disease Unit, Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia. Infectious Disease Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[s] *Infectious Disease Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA*
[t] *Department of Critical Care, King Abdullah Medical City, Makah, Saudi Arabia*
[u] *Department of Medicine, McMaster University, Hamilton, Canada*
[v] *Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada*
[w] *College of Medicine, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Intensive Care Department, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia*

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ABSTRACT

Background: Coronavirus disease-19 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is currently a major cause of intensive care unit (ICU) admissions globally. The role of machine learning in the ICU is evolving but currently limited to diagnostic and prognostic values. A decision tree (DT) algorithm is a simple and intuitive machine learning method that provides sequential nonlinear analysis of variables. It is simple and might be a valuable tool for bedside physicians during COVID-19 to predict ICU outcomes and help in critical decision-making like end-of-life decisions and bed allocation in the event of limited ICU bed capacities. Herein, we utilized a machine learning DT algorithm to

* Corresponding author at: Department of Critical Care, Dr. Sulaiman Al-Habib Medical Group, Riyadh, Saudi Arabia.
E-mail addresses: a.m.haz@live.com, a.m.haz@live.com (A. Elhazmi), drarabie@ksmc.med.sa (A.A. Rabie).
[1] ORCID: 0000-0001-5735-6241

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Decision tree
ICU
Predictors

describe the association of a predefined set of variables and 28-day ICU outcome in adult COVID-19 patients admitted to the ICU. We highlight the value of utilizing a machine learning DT algorithm in the ICU at the time of a COVID-19 pandemic.

Methods: This was a prospective and multicenter cohort study involving 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 predictors of 28-day ICU mortality were identified using two predictive models: conventional logistic regression and DT analyses.

Results: There were 1468 critically ill COVID-19 patients included in the study. The 28-day ICU mortality was 540 (36.8 %), and the 90-day mortality was 600 (40.9 %). The DT algorithm identified five variables that were integrated into the algorithm to predict 28-day ICU outcomes: need for intubation, need for vasopressors, age, gender, and PaO2/FiO2 ratio.

Conclusion: DT is a simple tool that might be utilized in the ICU to identify critically ill COVID-19 patients who are at high risk of 28-day ICU mortality. However, further studies and external validation are still required.

Introduction

Background

Coronavirus disease 2019 (COVID-19) is caused by severe adult respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first discovered in Wuhan City in late 2019 [1]. The World Health Organization (WHO) announced the disease to be a pandemic on March 11, 2020 [2]. Since then, extensive publications on the epidemiology, characteristics, and outcomes of the disease from different regions and populations showed variable results [3].

The role of machine learning in the intensive care unit (ICU) is evolving. It has been considered in the last few years, typically in oncological and cardiovascular pathologies [4,5]. Yet, its use is limited to diagnostic and prognostic values. During the COVID-19 pandemic, few reports used it as a predictive tool for mortality to identify risk factors. Classical statistical analysis methods utilized to identify such risk factors are limited by their inability to highlight the effect on outcome implicated by possible interactions of these factors.

Machine learning includes many methods that could be utilized in the ICU, and these vary in their complexity [6]. Several studies used different complex machine learning models to predict ICU admission and mortality especially during the COVID-19 pandemic [7,8]. Decision tree (DT) is a simple and intuitive machine learning method that provides sequential nonlinear analysis in algorithmic relationship of combined risk factors to produce a quantitative percentage of sensitivity to mortality. [9]. It might be a useful tool for bedside physicians during COVID-19 to identify critically ill patients and guide important decisions such as ICU resource utilization and clinical management during the COVID-19 pandemic. This study evaluated the predictors of 28-day ICU mortality in COVID-19 adults admitted to the ICU using a machine learning DT algorithm.

Objectives

We highlight the role of machine learning DT algorithms in the ICU at the time of a COVID-19 pandemic.

Methods

Study design

This was a prospective, multicenter national cohort study conducting in 14 hospitals of Saudi Arabia. We included COVID-19 patients admitted to the ICU at the participating centres between March 1, 2020, and October 31, 2020. Institutional review board (IRB) approvals were obtained from the Central Institutional Review Board at the Saudi Ministry of Health and the Ethical Boards for each participating center. The study was designed to be a platform for the COVID-19 patients for research purposes and could address many questions raised during the pandemic.

Setting

The participating ICUs were accredited governmental and non-governmental tertiary hospitals. The multidisciplinary treatment 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. Non- ICU physicians from different specialties joined the critical care team during the COVID-19 surge; their participation was under the supervision of intensivists after receiving basic ICU management training.

Patients

Adult patients above the age of 18 were admitted to the ICU of participating hospitals with confirmed SARS-CoV-2 infection via real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs or tracheal aspirate specimens. Patients who had a Do-Not-Resuscitate code prior to ICU admission were not included in the study. Immunocompromised status was defined as solid organ malignancy, leukemia, current use of steroids (prednisone > 7 mg daily for > 2 weeks), post-organ transplantation at any time, or rheumatological disease on immunomodulators (azathioprine, methotrexate, infliximab, mycophenolate mofetil, or others). Infection was defined by a positive culture in the blood or tracheal aspirate.

Data collection

The data was collected manually according to the clinical record form CRF and entered into the electronic database Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN) [10]. Next, it underwent secondary data validation. The collected data included patient demographics, comorbidities, signs, and symptoms of COVID-19 illness, laboratory values, mechanical ventilation (MV) utilization, adjunctive interventions, medications, complications, and outcomes. FiO_2 was calculated for all spontaneously breathing patients by converting O_2 supply flow to estimated FiO_2 [11].

Measures of outcomes

The primary outcome was 28-day ICU mortality.

Statistical analysis

General analysis

Patient characteristics were summarized for the entire patient cohort using frequencies and percentages for categorical variables. An initial assessment of the variable distribution was made using the Shapiro-Wilk test of normality, histograms, and quantile-quantile plots for continuous variables. If the variable was a customarily distributed continuous variable (Gaussian distribution), the mean and standard deviation (SD) were used to summarize the data. If the variable was not a normally distributed continuous variable (non-Gaussian distribution), then the median and the interquartile range (IQR) were used to summarize the data. A Chi-square or Fisher's exact tests compared the categorical variables. For continuous variables, the Student's t-test was applied for normally distributed variables, and the Wilcoxon rank-sum test was used for non-normally distributed variables. We constructed Kaplan–Meier curves to assess cumulative mortality during the initial 60 days of ICU admission. In the first 28 days of ICU stay, risk factors for mortality were evaluated for the entire cohort using stepwise logistic regression analysis. Variables included in the stepwise logistic regression model were identified based on clinical interest and literature review, and used to generate the predictive models. These included demographics, co-morbid conditions, laboratory data on ICU admission, the respiratory components of the SOFA score [11], and the need for intubation or vasopressors. Regression analysis used variables on the need for intubation within first 48 hours and vasopressors during the first five days of ICU admission. The respiratory component of the SOFA score on ICU admission was classified as category 4 ($PaO_2/FiO_2 < 100$ with respiratory support) or category 0–3 (PaO2/FiO2 > 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 software. This approach maximizes the Youden index, which determines the split point between survivors and non-survivors. The logistic regression model results were reported as odds ratios (OR) with a 95 % confidence interval (95 %CI). All statistical tests were two-tailed, and p-values < 0.05 were considered significant. All of the statistical analyses were done with R software version 4.0.2 (06–22–2020) from the R Foundation for Statistical Computing in Vienna, Austria.

DT analysis

Machine learning DT analysis identified characteristics of COVID-19 patients using the demographics and clinical variables on ICU admission that were predictive of 28-day ICU outcome. The model was generated using the standard setting in an 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). The C4.5 classifier used an information gain ratio split criterion to reduce bias towards multiple values [13].

We used "algorithm accuracy" as a general measure to assess the performance of the classifier. Accuracy is a common performance metric that represents the overall correctness of the algorithm. DT analysis used a ten-fold cross validation to assess the model's generalizability and avoid over-fitting. This approach could be used to calculate the accuracy, area under the receiver operating characteristic (AUROC), and confidence intervals. These models were tuned with a 10-fold cross-validation, fitted in the 75 per cent split of the derivation set and assessed in the remaining 25 per cent. In order to ascertain the model's stability, this training and testing split was randomly repeated 100 times (bootstraps). Finally, to decide which model to select, performance was evaluated through the mean AUROC value. The AUROC can also be used to evaluate the performance of the DT model. It reports 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]. Here, TPR is the true positive cases as determined by the algorithm, divided by the total positive cases (true positive + false positive).

Missing data

Missing data was treated as follows: Variables that had more than 25 % missing were excluded from the analysis unless deemed clinically necessary by the authors. Variables that had fewer than 25 % missing values were treated as missing not at random (MNAR), where the probability of missing depends on unobserved information (e.g., a test/measurement is only performed when the doctor decided that the patient was in a severe condition that justified ordering the test/measurement; however, the severity of the disease can be based on the subjective assessment of the ordering doctor). Based on the above and to avoid the complexity associated with the imputation of missing values, they were treated as unobserved values (also known as missing values).

Results

Patient characteristics and ICU admission data

There were 1468 patients admitted to the ICUs during this study period across the 14 participating hospitals. Table 1 shows the patients' demographics and data over 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 more common in the non-survivors group (p-values of 0.0187, 0.0016, and 0.0333, respectively). SOFA score, median score of 7 (IQR 4–10), was significantly higher in patients who died within the first 28 days of ICU admission. Survivors had a higher PaO_2/FiO_2 ratio on the day of ICU admission than non-survivors at 28 days of ICU admission [142 (IQR 72–176) vs. 92 (IQR 66–138), p-value < 0.001]. (Table 1).

Interventions during the ICU stay

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

Outcomes

Of the 1468 patients, 540 (36.8 %) died within 28 days of ICU admission; 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 nine days (IQR 5–16). The length of hospitalization 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 (Fig. 1).

Table 1
Baseline general characteristics and ICU admission data of 1468 patients according to their 28-day survival status.

Patient characteristic	All Patients (n = 1468) /Denominator	28-day non-survivors (n = 540)	28-day survivors (n = 928)	*p*-value
Age (years), mean (± 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 (± 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 status, 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
Chronic Liver Disease, n (%)	24 (1.8)/1332	10 (2.1)	14 (1.6)	0.557
Chronic Hematological Disease, n (%)	12 (0.9)/1337	3 (0.6)	9 (1.1)	0.553
ICU admission data (first 24 hours)				
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 hours)				
WBC (x 109/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 *
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, 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.

Predictors of 28-day ICU mortality

The results of the decision tree analysis

Five variables were identified and allocated to patients in the final binary outcome (survival versus mortality). These variables arranged according to their significance were the need for intubation or vasopressors, gender, PaO_2/FiO_2 on ICU admission, and age. The resulting DT assigned the root node (start of the tree or first splitting criteria) to the need for intubation. The tree continued to grow, and we then assigned patients into their respective groups sequentially, utilizing the four other variables. The model discrimination, DT model's ability to correctly assign patients to their respective groups, was assessed using the ROC-AUC and 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) (Fig. 2).

The results of the logistic regression

The stepwise logistic regression analysis retained: age groups, gender, the respiratory component of the SOFA score (category 4), need for intubation, or vasopressors, and neutrophil-lymphocytes (NL) ratio as variables that may predict 28-day ICU mortality. (Fig. 3).

Discussion.

We utilized the DT analysis and identified the interaction of five features predictive of 28-day ICU outcomes: the need for intubation, vasopressors, age, gender, and PaO_2/FiO_2 ratio. The COVID-19 pandemic overwhelmed the health care system and led to constrained medical resources, especially in terms of critical care unit capacity; there was even a shortage of mechanical ventilators [15–17].

Many hospitals utilized machine learning analyses by combining clinical, radiological, and laboratory data for the prognostication and rapid risk stratification of PCR-confirmed COVID-19 patients [18–20]. The severity of illness among ICU patients was stratified via different general scoring methods such as the acute physiology and chronic health evaluation (APACHE) II and IV [21,22], the Simplified Acute Physiology Score (SAPS) [23], SOFA scores [11], or COVID-19 specific scores as 4 C mortality scores [24,25].

Machine-learning models have been increasingly utilized in the medical field, especially for cancer outcome predictions [27–29]. Random Forest classifiers, decision trees, and artificial neural

Table 2
Interventions, Respiratory support modalities,Respiratory data following invasive mechanical ventilation and medication 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 h/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_2O)	27.8 (11.2)/152	27 (11.7)	28.6 (10.6)	0.382
Dynamic Compliance (mL/cmH_2O))	22.2 (14.6)/324	20.6 (9.4)	24.1 (19.2)	0.045 *
Peak airway pressure (cmH_2O)	31.2 (6.7)/335	31.7 (7.1)	30.6 (6.2)	0.131
Plateau pressure (cmH_2O)	27.3 (5.7)/156	27 (5.4)	27.5 (5.9)	0.549
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 *
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.

Table 3
Patient's clinical 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
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

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

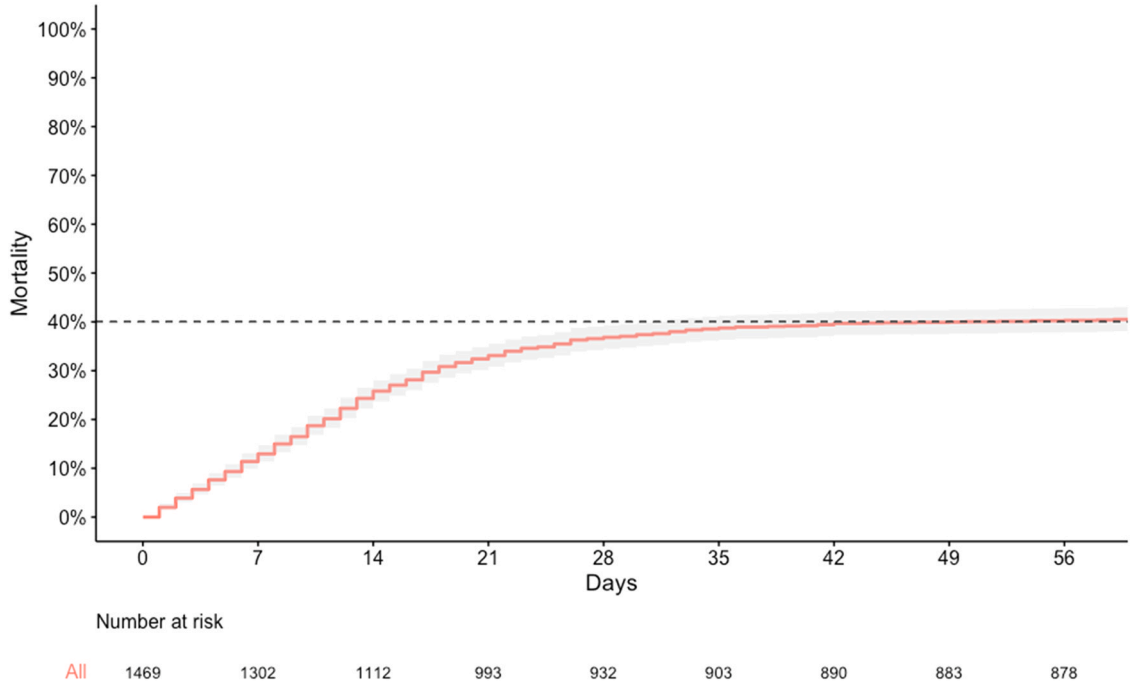

Fig. 1. Kaplan Maier curve for COVID-19 cumulative incidence of mortality.

networks (ANNs) were among the earliest used techniques in medical research [30,31]. DT analysis is an effective classifier and has been applied in many domains [32,33]. DTs are an intuitive non-linear approach and can automatically detect independent variables that predict outcomes as well as the interactions between these variables. DTs also offer an easy-to-understand visual representation of the relationships between the variables and the primary outcome [34].

The standard logistic regression analysis can predict outcomes of interest, but it does not model nonlinear relationships of multiple dimensional data [26]. DT analysis were built using the same predefined set of variables used for stepwise logistic regression. Nevertheless, retained variables were comparable between both models. Our research emphasizes the benefits of DT analysis in terms of providing simple rules-based algorithmic prediction rather than merely identifying associations and relationships between variables, as conventional regression models offer [35,36].

The use of machine learning in the ICU is evolving. It is currently limited to diagnostic and prognostic values. However, DT analysis offers a simple method for the sequential analysis of variables. For example, patients in this cohort who were not intubated nor required vasopressor support early in ICU admission, if they were in the age group younger than 40 years, the true positive rate of survival is 88 % (Fig. 2). This DT provides simple valuable tool for bedside physicians during COVID-19 to guide critical decisions, making decisions on end-of-life and bed allocation easier. The algorithmic relationship of combined risk factors offers a quantitative percentage of sensitivity to outcomes [9].

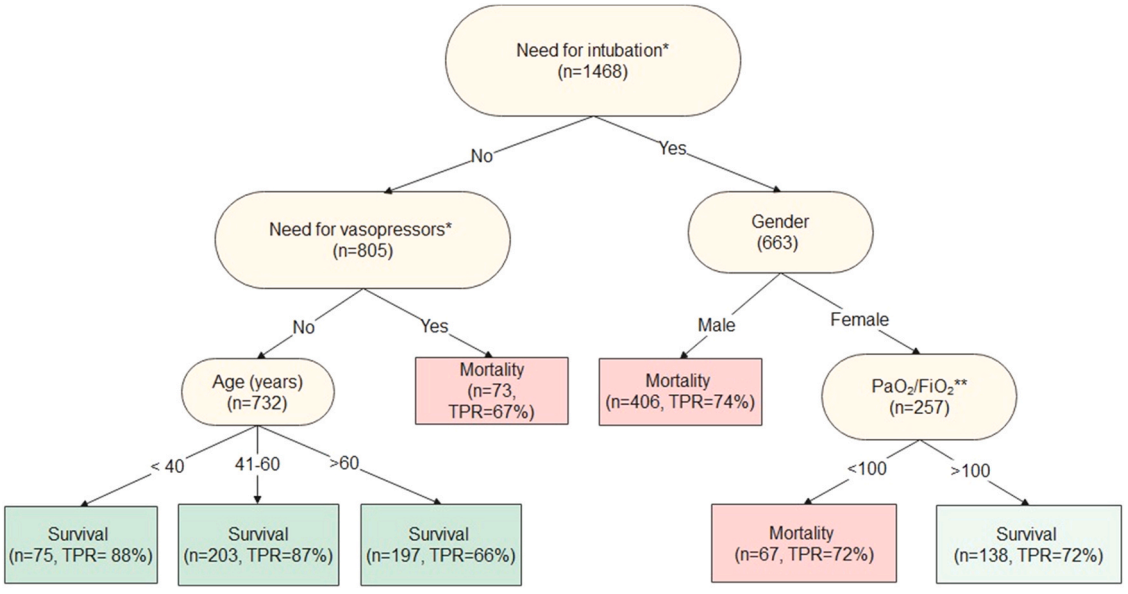

Fig. 2. Decision tree (DT) algorithm for predictors of mortality.

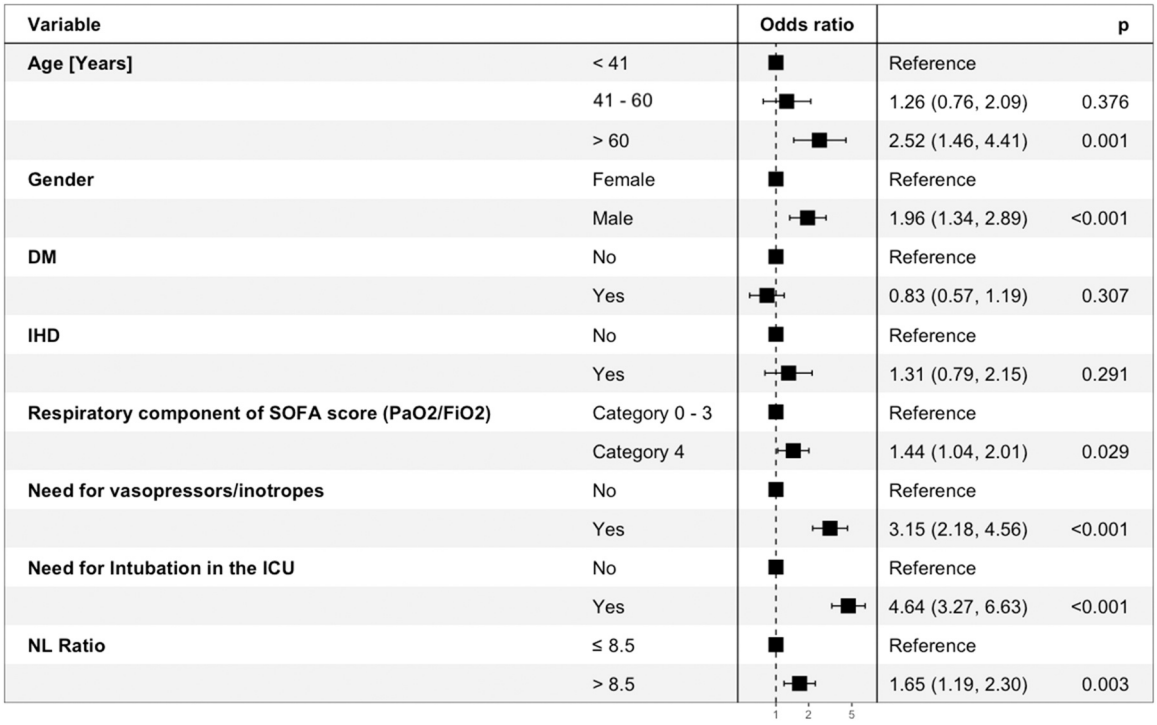

Fig. 3. Stepwise logistic regression of 28-day mortality.

Predictors of mortality in COVID-19 are widely reported in many studies with different settings and designs. These include laboratory and radiological variables [37,38]. However, there are limited reports on clinical variables on ICU admission as predictors of mortality. Such variables can facilitate the early identification of critically ill COVID-19 patients at a higher risk of 28-day mortality [39]. A metaanalysis by Du et al. addressed the predictors of mortality utilizing the classic logistic regression analysis; they showed that advanced age, male gender, comorbidities of chronic respiratory disease, DM, hypertension, and chronic kidney or cardiovascular diseases were associated with severe illness or death among COVID-19 patients [40].

Studies that report predictors of mortality utilizing DT analysis in critically ill COVID-19 patients are quite limited [41–43]. One of these analyses by Yang et al. showed a rapid, simple, and easy-to-interpret DT model built via three biochemical markers on ICU admission (LDH, NLR, and CRP). There was a high true sensitivity rate that could predict death in severe COVID-19 disease [41].

The strengths of this study include different nationalities and a multicenter nature, which improves generalizability. In addition, unlike earlier reported experiences 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]. We used stepwise logistic regression to evaluate the results of the DT analysis (Fig. 3). This is comparable to regression analysis. To our knowledge, the number of patients enrolled here is the largest in the Middle East. Thus, the results offer a valuable analysis to explain the disease and its effects in the Gulf and Middle East regions The performance of DT analysis was comparable to Stepwise Logistic Regression, as both had ROC AUC in the acceptable range, 70–80 %, (79.96 % (95 % CI = 76.91–83.02) 75.42 % (95 % CI = 74.84–78.95), respectively) as well as retraining similar variables as predictors of outcome. DT analysis, on the other hand, used a ten-fold cross validation to assess the model's generalizability and avoid over-fitting. DT analysis provides algorithmic visualization of non-linear interactions between variables that standard logistic regression cannot.

Our study does have some limitations, including the lack of external validation for the proposed model of predictors. We did not include centers as a preset variable for regression and DT analysis; rather, we decided not to adjust for centers in the logistic model or DT models because of the following: 1-The variability of resources available in each center might have an unobserved yet strong effect on 28-day mortality. 2-The number of cases varied significantly between centers and can significantly influence confidence intervals and interpretation of the results. 3-Difficulties in identifying a reference center due to the variability of the patient population presenting to more prominent hospitals in different regions. Finally, the DT model accuracy was 73.1 % (the number of retained patients on the model was 1043 out of 1468), despite being comparable to the analysis of logistic regression, which is not assuring and needs further research to prove that.

Conclusion

Five clinical predictors of 28-day ICU outcomes were identified using DT algorithmic analysis of COVID-19 patients admitted to the ICU. DT is a simple tool that might be utilized in the ICU for early identification of critically ill COVID-19 patients who are at high risk of 28-day mortality. However, further studies are required to validate these results and evaluate the role of DT analysis in the ICU.

Ethics approval

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

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CRediT authorship contribution statement

Design conception: AE, HS, AR. Data collection: AE, HS, AO, AM, AG, AT, M.H.A, AS, AK, ZA, GM, WT, S.A.A, FF, AH, JT, R.G.M, and the Saudi COVID working group. Data validation and cleaning: AE, HS, and HM. Statistical analysis, model development, and Validation: HM. Acquisition, analysis, or interpretation of data: AE. AR, and HM. Drafting and writing of the manuscript: AE & AR. Editing and reviewing: YA, WH, MS, ZA, AO, and HM. Critical revision of the manuscript for important intellectual content, final review, and approval by all authors.

Data Availability

Alyaa Elhazmi, Hend Sallam, and Hani Mufti had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the analysis. They are willing to submit the data for an external review upon request.

Declaration of Competing Interest

None of the authors have a conflict of interest related to this work.

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Consent to participate

Consent was waived because all data are unidentified.

Consent for publication

All authors accept and confirm publication.

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