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Explainable machine learning reveals key predictors of ICU mortality in COVID-19: functional outcomes and physiotherapy interventions in cardiovascular patients

Aprendizado de máquina explicável revela principais preditores de mortalidade em UTI por COVID-19: resultados funcionais e intervenções fisioterapêuticas em pacientes cardiovasculares

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Abstract

Background: Cardiovascular diseases are a leading cause of mortality worldwide, with the COVID-19 pandemic intensifying their impact on intensive care unit outcomes. Functional impairments and reduced mobility among critically ill cardiovascular patients are linked to adverse outcomes, but their predictive value for mortality during intensive care hospitalization with COVID-19 remains underexplored. **Aim**: This study employs machine learning and explainable artificial intelligence to identify key predictors and optimize intervention strategies. **Methods**: This retrospective study analyzed data from 100 critically ill patients with cardiovascular diseases and COVID-19 admitted to a private hospital in Brazil. Functional assessments included scores of global muscle strength and mobility at admission. Machine learning models—Logistic Regression, Decision Tree, Random Forest, CatBoost, and Explainable Boosting Machine—were developed in Python. Interpretability analyses were performed using Shapley Additive Explanations to determine the most relevant predictors. **Results**: The best-performing model, Random Forest, achieved a sensitivity of 90.5% and specificity of 83.9%, with an accuracy of 0.92 (95% confidence interval: 0.83–1.00). Passive kinesiotherapy, restricted mobility, and invasive mechanical ventilation were strongly associated with in-hospital mortality, while active mobilizations such as walking and standing predicted better survival outcomes. Feature relevance analysis revealed critical feature interactions involving oxygenation levels, sedation, and mobility variables on mortality risks. **Conclusion**: Machine learning approaches identified predictors of mortality and reinforced the protective effects of active physiotherapy interventions for critically ill cardiovascular patients with COVID-19. These findings support the application of data-driven strategies to optimize rehabilitation practices in intensive care units and suggest the need for validation in larger populations.

Keywords: Critical care; Physical Therapy; Machine Learning.

Resumo

Introdução: As doenças cardiovasculares são uma das principais causas de mortalidade em todo o mundo, com a pandemia de COVID-19 intensificando seu impacto nos desfechos em unidades de terapia intensiva. Comprometimentos funcionais e mobilidade reduzida em pacientes críticos com doença cardiovascular estão associados a desfechos adversos, mas seu valor preditivo para mortalidade durante a internação na unidade de terapia intensiva devido à COVID-19 ainda não foi explorado. **Objetivo**: Este estudo utiliza aprendizado de máquina e inteligência artificial explicável (XAI) para identificar os principais preditores e otimizar estratégias de intervenção. **Métodos**: Este estudo retrospectivo analisou dados de 100 pacientes críticos com doenças cardiovasculares e COVID-19 internados em um hospital privado no Brazil. As avaliações funcionais incluíram escores de força muscular global e mobilidade no momento da admissão. Modelos de aprendizado de máquina—Regressão Logística, Árvore de Decisão, Random Forest, CatBoost e Explainable Boosting Machine—foram desenvolvidos em Python. A interpretação dos modelos foi realizada com base na técnica de Shapley Additive Explanations para identificar os preditores mais relevantes. **Resultados**: O modelo com melhor desempenho, Random Forest, obteve uma sensibilidade de 90,5% e especificidade de 83,9%, com acurácia de 0,92 (intervalo de confiança de 95%: 0,83–1,00).

A cinesioterapia passiva, mobilidade restrita e ventilação mecânica invasiva foram fortemente associadas à mortalidade hospitalar, enquanto mobilizações ativas, como caminhar e ficar em pé, previram melhores desfechos de sobrevivência. A análise de relevância das variáveis revelou interações críticas envolvendo níveis de oxigenação, sedação e métricas de mobilidade. **Conclusão**: Técnicas de aprendizado de identificaram preditores de mortalidade e reforçaram o efeito protetor das intervenções fisioterapêuticas ativas em pacientes críticos com doença cardiovascular e COVID-19. Esses achados apoiam adoção de estratégias de reabilitação orientadas por dados clínicos em unidades de terapia intensiva, com necessidade de validação em populações maiores.

Palavras-chave: Cuidado Crítico; Fisioterapia; Aprendizado de Máquina.

INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of death globally, accounting for an estimated 31% of all mortalities, or about 17.9 million deaths annually[1]. In Brazil, CVD contributed to 267,635 deaths in 1990 and 424,058 deaths in 2015[2]. Despite global trends indicating a reduction in CVD-related mortality risks, recent data show a plateauing of this decline in Brazil[3,4]. Population aging and therapeutic advancements have extended survival rates but increased the prevalence of CVD and related hospitalizations[5].

The emergence of the new coronavirus disease (COVID-19) pandemic further exacerbated the burden of CVD. Patients with pre-existing CVD were found to have higher susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, longer hospital stays, and increased mortality rates[6-8]. In ICU settings, older adults often experience functional declines, with reduced musculoskeletal strength and mobility contributing to poorer outcomes[9,10].

Patients with COVID-19 can improve their mobility at hospital discharge and have a higher probability of discharging home with increased frequency and longer mean duration of physiotherapy visits[11]. In a previous study, we found that admission-impaired functional characteristics and specific physiotherapy interventions were associated with a higher risk of in-ICU death[12]. However, the specific impacts of functional status and physiotherapy interventions in CVD patients hospitalized with COVID-19 remained insufficiently explored.

Machine learning has been applied in predicting COVID-19 outcomes. Dan et al.[13] demonstrated the utility of artificial neural networks in predicting ICU admissions based on clinical severity scores and white blood cell counts. Similarly, Akram et al.[14] employed discrete wavelet transform and extended segmentation-based fractal texture analysis methods to extract relevant features from CT images and Naive Bayes classifiers to distinguish COVID-19 from other respiratory diseases. Exploratory Spatial Data Analysis (ESDA) by Scarpone et al.[15] revealed significant socio-economic and infrastructural variables influencing COVID-19 case distributions. Cheng et al.[16] utilized Random Forest algorithms to predict ICU transfers in COVID-19 patients, achieving predictive accuracy of 90%.

Building on the findings of our previous study[12], which highlighted the association between functional characteristics and physiotherapy interventions with ICU outcomes in patients with CVD, this study employs advanced machine learning models and explainable artificial intelligence to revisit and expand upon these findings. We aim to provide deeper insights into their association with in-ICU mortality in older adults with CVD and COVID-19. Furthermore, this study introduces the novel application of attribute machine learning analysis to evaluate the impact of physiotherapy interventions.

METHODS

Ethics

The study protocol follows national resolution No. 466/2012 and the World Medical Association Declaration of Helsinki. The Institutional Ethics Committee approved this research protocol (No. 19966919.7.0000.5235), waiving the informed consent form because patient data were de-identified before subsequent analysis and the research protocol did not affect the hospital's treatment protocols of the inpatients.

Study design and reporting

This retrospective, single-center study analyzed data from February to November 2020, collected from ICU patients at a private hospital in Curitiba, Paraná, Brazil. Inclusion criteria encompassed CVD diagnosis confirmed by clinical and laboratory tests, functional assessment by a physiotherapist, and SARS-CoV-2 testing at admission. Hospitalizations were included if ICU stays exceeded 12 hours, considering a minimum time necessary for an initial physiotherapeutic evaluation and to ensure clinical stability for functional assessments. Re-admissions within the study period were excluded. Data were obtained by the principal investigator through information previously contained in electronic medical records, examination reports, and notes of the health professional staff involved in the care of the patients. This study is reported following the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement[17].

No prospective sample size calculation was performed for this secondary analysis. The present study used data from a previous retrospective cohort[12], whose sample size calculation determined that a minimum of 96 participants would be required to estimate overall risk with a margin of error ≤ 10% and a true outcome proportion equal to 50%.

Setting and participants

This study retrospectively analyzed all data from patients consecutively hospitalized at the ICU. Patients who had a primary diagnosis of CVD after a complete clinical exam and laboratory testing—including laboratory blood tests, electrocardiogram, blood pressure, and/or echocardiography as prescribed—admission assessment by a physiotherapist, and tested for SARS-CoV-2 infection at admission were included. Length of ICU stay was defined as admissions exceeding 12 hours. Re-admissions to the ICU within the study period were excluded from the analysis.

Clinical measurements

All admission data were collected within <24 h of ICU hospitalization. Data were collected retrospectively from electronic medical recordings regarding demographics, vital signs, laboratory, gasometry, presence of CVD and comorbidities, and drugs in continuous use. Date of hospital admission and discharge from the ICU or death were collected for computing the total length of ICU stay. Overall muscle strength was assessed by the Medical Research Council (MRC) scale that uses a 6-point scale of 6 muscle groups bilaterally. Representative scores comprised the sum of points observed for each muscle group, ranging from 0 (no muscle activity) to 30 (maximal muscle strength)[18]. Mobility was assessed by the ICU Mobility Scale (IMS). The score varies between 0 expressing low mobility (patient who only performs passive exercises in bed) and 10 expressing high mobility (the patient who presents independent walking, without assistance)[19].

Physiotherapy interventions

Exposure to each routine physiotherapy intervention was defined as using a given therapeutic resource at any time during the total length of stay in the ICU, thus registered as dichotomous variables ('yes' = 1; 'no' = 0). Ventilatory support was characterized by the use of non-invasive mechanical ventilation, through an orofacial or facial interface connected to the mechanical ventilator in one (CPAP) or two (BiPAP) pressure levels ventilation modes; or invasive ventilatory support, in which the patient was connected through an orotracheal or tracheal prosthesis in controlled ventilatory modes, controlled assistance and/or spontaneous; patients diagnosed with acute respiratory distress syndrome, even when COVID-19 negative, were used protective strategy ventilatory parameters, which may require alveolar recruitment through the prone position or recruitment through the gradual increase of PEEP up to 35 cmH_2O and subsequent titration of ideal PEEP, whereas that they presented clinical stability for such; when they needed oxygen therapy, it was performed using a low-flow system (nasal catheter, face mask with reservoir, tracheostomy mask); spontaneous prone was also used, in which the patient lay in the frontal decubitus position for at least 1h. In the supine position, the head was elevated between 30° and 45°. In the prone position, the head was elevated between 10° and 20°. Mobility activities were categorized as complete bed restriction; passive kinesiotherapy (the physiotherapists passively mobilized the wrist, elbow, shoulder, hip, knee and ankle joints, stretching and positioning the individual to bed); active kinesiotherapy (active free, active resisted or assisted active mobilization of the wrist, elbow, shoulder, hip, knee and ankle joints, dynamic or static global stretches, trunk control work); assisted or active sitting out of bed; standing; and walking.

Study outcomes

The primary outcome was in-ICU mortality as well as admission functional assessments of MRC and IMS scores. A standardized census was conducted at the rehabilitation center by the principal investigator through the medical information system. In-ICU mortality was calculated from the admission date and confirmed using electronic medical records. The study only considered deaths due to COVID-19 or complications resulting from it.

Data cleaning and feature engineering methods

The initial dataset contained 108 patients and 72 features. Patients with less than 80% of the features available were excluded, reducing the dataset to 103 patients. Features with less than 80% availability were removed, leaving 62 features. Certain features that directly predicted outcomes, such as ICU discharge dates equal to death dates, were excluded. Additional features were synthesized, including patient age from birthdates, ICU length of stay from admission and discharge dates, and categorical variables such as "systemic arterial hypertension." Missing categorical data were imputed with the "Missing" category, while missing numeric data were replaced with median values. This strategy aimed to preserve the original data distribution and minimize the introduction of bias during modeling.

Machine learning methods

Five classifier algorithms were selected to evaluate predictive performance for in-ICU mortality among patients with cardiovascular diseases and COVID-19. The first algorithm, Logistic Regression (LR), uses maximum likelihood estimation to predict binary outcomes.

The second, Decision Tree (DT), constructs a tree-like model of decisions based on data features to predict outcomes. Random Forest (RF), the third algorithm, employs an ensemble of decision trees to enhance prediction accuracy and reduce overfitting[20]. The fourth algorithm, CatBoost (CB), optimizes boosting algorithms for categorical data[21]. Finally, the Explainable Boosting Machine (EBM) combines machine learning interpretability and high predictive accuracy[22].

Hyperparameter tuning and model evaluation

Hyperparameters for each algorithm were optimized using a Tree-structured Parzen Estimator (TPE) from the Optuna framework[23]. Stratified K-fold cross-validation (K=5) was employed to ensure robust evaluation, balancing bias and variance in model performance estimates given the moderate sample size. The primary metric for model performance was the area under the receiver operating characteristic curve (AUC). Secondary metrics included sensitivity and specificity.

Data augmentation methods

To address class imbalances and improve model generalization, the Synthetic Minority Oversampling Technique for Nominal and Continuous features (SMOTE-NC) was used during training[24]. SMOTE-NC generates synthetic samples for minority classes while preserving the original feature space.

Attribute relevance analysis

Attribute relevance analysis was conducted to identify the most influential features for predicting mortality. Techniques included Weight of Evidence (WoE) and Information Value (IV) to quantify feature importance. Features with high IV scores were prioritized for model training. Explainable Artificial Intelligence (XAI) methods, such as Shapley Additive Explanations (SHAP), were employed to interpret feature contributions to model predictions.

Chi-square, Cramér's V, and weight of evidence

Chi-Square tests were used to evaluate the association between categorical features and the outcome variable (in-ICU mortality). A p-value threshold of <0.05 was used to determine statistical significance. Cramér's V was calculated to measure the strength of association for significant relationships, with values ranging from 0 (no association) to 1 (perfect association). Weight of Evidence (WoE) was applied to transform categorical variables into numeric representations based on their relationship with the target variable. Variables with high predictive value were identified through Information Value (IV) analysis, where IV scores above 0.3 indicated strong predictive power.

Explainable artificial intelligence

It is hard to mathematically define interpretability, but there are non-mathematical definitions: interpretability is the degree to which a human can understand the cause of a decision[25]. Another one is interpretability is the degree to which a human can consistently predict the model's result[26]. Explainable Artificial Intelligence (XAI) methodologies were applied to enhance the interpretability of machine learning model predictions. Shapley Additive Explanations (SHAP) values were used to attribute contributions of individual features to predicted outcomes, offering insights into how different clinical and functional features influenced in-ICU mortality. For instance, mobility features such as IMS scores and active physiotherapy interventions were consistently identified as protective factors, while indicators of disease severity, such as PaO_2 levels and sedation status, increased mortality risk. XAI visualizations provided by SHAP summary plots and dependence plots enabled clinicians to understand model decision-making processes and integrate findings into patient care strategies.

All analyses were conducted using Python programming language, with the use of Scikit-learn, Optuna, and SHAP libraries.

Machine learning experiments

Experiment 1 consisted of classifying whether the patient died or not based only on the admission data. The dataset is divided into train and test sets. The train set was used to train the models and find the best hyperparameters, and the test set was used to evaluate the generalization performance. Hyperparameters and their search range are described in Table 1. Due to the small train set, we applied SMOTE to add synthetic data. The categorical features we encoded using the WoE and numerical features were scaled to have 0 mean and variance equal to 1. We included the ventilation treatments in the patient admission data for *Experiment 2*. The preprocessing and feature engineering were the same as in Experiment 1. For *Experiment 3*, mobility treatments were added. Finally, in *Experiment 4*, we exploit attribute relevance analysis. It serves two crucial purposes: first, identifying the variables that have the most prominent effects on the target variable; second, figuring out how the most significant predictor and the target variable are related. This analysis can be performed using the information value and weight of evidence technique. We used it to select the most suitable mobility and ventilation treatments to add to patient admittance data.

Table 1. Hyperparameter and their search range.

Model	Hyperparameter	Searching range
Decision Tree	max_depth	1 – 10
	min_samples_split	2 – 40
	min_samples_leaf	1 – 20
Logistic Regression	C	1E-4 – 100.0
	penalty	‘l2’
	max_iter	1000
	class_weights	‘balanced’
Explainable Boosting Machine	max_depth	1 – 10
	max_bins	10 – 100
	learning_rate	0.001 – 1.0
	interactions	1 – 10
	max_leaves	10 – 1000
Random Forest	max_depth	1 – 10
	n_estimators	10 – 1000
CatBoost	depth	1 – 10
	border_count	1 – 255
	iterations	10 – 1000
	learning_rate	0.01 – 1.0
	random_strength	1E-9 – 10.0
	l2_leaf_reg	2.0 – 30.0
	bagging _temperature	0.0 – 1.0

Source: The authors.

RESULTS

Sample characteristics

Table 2 compares clinical and demographic characteristics of sample. Patients with COVID-19 had significantly longer ICU stays (14.5 vs. 6.2 days, $p = 0.0071$), higher body mass (81.9 vs. 72.3 kg, $p = 0.0101$), and taller stature (1.7 vs. 1.6 m, $p = 0.0061$). Functional outcomes on admission showed COVID-19+ patients had higher MRC and IMS scores (48.3 vs. 43.8, $p = 0.0211$; 5.5 vs. 3.9, $p = 0.0391$, respectively). COVID-19+ patients were younger on average (68.1 vs. 80.4 years, $p < 0.001$). Leukocyte counts were lower in the COVID-19+ group (9564.6 vs. 13,456.8 per mcL, $p = 0.0021$), and PCO2 and bicarbonate levels were also reduced ($p < 0.001$, $p = 0.0441$, respectively). Regarding comorbidities, congestive heart failure ($p = 0.0402$) and atrial fibrillation ($p = 0.0152$) were more prevalent in the COVID-19− group. Sedation use was more frequent among COVID-19+ patients (52.4% vs. 29.3%, $p = 0.0202$).

Table 2. Characteristics of the studied sample.

	COVID-19−	COVID-19+	Total	*p* Value
	(*n* = 58)	(*n* = 42)	(*n* = 100)	
Length of ICU stay, days	6.2 (6.8)	14.5 (21.7)	9.7 (15.5)	0.0071
Glasgow, score	13 (3.0)	14 (1.5)	14 (2.5)	0.0561
APACHE II, score	30.3 (4.8)	30.2 (4.9)	30.2 (4.8)	0.9171
Admission functional outcomes				
MRC, score	43.8 (10.4)	48.3 (7.9)	45.7 (9.6)	0.0211
IMS, score	3.9 (3.8)	5.5 (4.0)	4.6 (3.9)	0.0391
Age, years	80.4 (13.4)	68.1 (16.2)	75.2 (15.8)	<0.001[1]
Sex, *n*				0.1472
Female	32 (55.2%)	17 (40.5%)	49 (49.0%)	
Male	26 (44.8%)	25 (59.5%)	51 (51.0%)	
Body mass, kg	72.3 (17.4)	81.9 (18.7)	76.3 (18.5)	0.0101
Body height, m	1.6 (0.1)	1.7 (0.1)	1.7 (0.1)	0.0061
Body mass index, kg/m²	26.4 (4.7)	28.2 (5.4)	27.1 (5.1)	0.0791
Body mass index category, *n* (%)				0.4512
Thin	3 (5.2%)	1 (2.4%)	4 (4.0%)	
Eutrophic	19 (32.8%)	11 (26.2%)	30 (30.0%)	
Overweight	25 (43.1%)	15 (35.7%)	40 (40.0%)	
Obesity I	7 (12.1%)	10 (23.8%)	17 (17.0%)	
Obesity II	4 (6.9%)	4 (9.5%)	8 (8.0%)	
Obesity III	0 (0.0%)	1 (2.4%)	1 (1.0%)	
Vital signs				
Heart rate, beat/min	84.4 (21.8)	85.5 (17.6)	84.9 (20.0)	0.7941
Respiratory rate, cycle/min	21.9 (5.5)	21.9 (5.3)	21.9 (5.4)	0.9961
Systolic pressure, mmHg	137.5 (26.1)	129.5 (25.0)	134.1 (25.8)	0.1271
Diastolic pressure, mmHg	76.9 (18.8)	75.2 (16.6)	76.2 (17.9)	0.6431
Pulse pressure, mmHg	60.6 (23.1)	54.3 (17.4)	58.0 (21.0)	0.1391
Mean pressure, mmHg	97.1 (18.6)	93.3 (18.0)	95.5 (18.3)	0.3111
Laboratory exams				
Sodium, mEq/L	135.8 (6.4)	135.5 (6.4)	135.6 (6.3)	0.8131
Potassium, mEq/L	4.3 (0.8)	4.2 (0.8)	4.3 (0.8)	0.5531
Urea, mg/L	69.6 (56.0)	71.5 (69.7)	70.4 (61.8)	0.8821
Creatinine, mg/L	1.7 (1.8)	1.5 (1.3)	1.6 (1.6)	0.6541
Lactate, mg/L	1.9 (1.3)	1.6 (0.9)	1.7 (1.1)	0.1891
Reactive-C protein, CP/μL	75.9 (90.7)	108.8 (96.0)	89.7 (93.9)	0.0841
Hemoglobin, g/dL	13.0 (2.2)	12.7 (2.3)	12.9 (2.2)	0.5821
Hematocrit, %	37.6 (6.2)	37.2 (7.2)	37.4 (6.6)	0.7751
Leukocyte, per mcL	13,456.8 (6443.9)	9564.6 (5472.5)	11822.1 (6327.6)	0.0021
Platelets, per mcL	193,869 (80,822)	177,255 (73,991)	186,891 (78,078)	0.2961
Lymphocytes, %	15.5 (9.3)	15.7 (9.2)	15.6 (9.2)	0.9221
Neutrophiles, %	78.4 (10.3)	77.4 (11.1)	78.0 (10.6)	0.6661
Gasometry				
pH	7.4 (0.1)	7.4 (0.1)	7.4 (0.1)	0.0591
PCO_2, mmHg	37.7 (8.5)	31.7 (6.5)	35.2 (8.2)	<0.001[1]
Bicarbonate, mEq/L	23.8 (4.9)	21.9 (4.5)	23.0 (4.8)	0.0441
PaO_2, mmHg	100.2 (43.6)	89.4 (38.6)	95.7 (41.7)	0.2031
Base excess, mEq/L	−0.5 (5.3)	−1.5 (5.1)	−0.9 (5.2)	0.3341
O_2 saturation, %	95.1 (5.0)	93.9 (6.0)	94.6 (5.4)	0.2891
Comorbidities, *n* (%)				
Hypertension	55 (94.8%)	36 (85.7%)	91 (91.0%)	0.1162
Stroke	15 (25.9%)	7 (16.7%)	22 (22.0%)	0.2732
Coronary artery disease	14 (24.1%)	7 (16.7%)	21 (21.0%)	0.3652
Congestive heart failure	13 (22.4%)	3 (7.1%)	16 (16.0%)	0.0402
Atrial fibrillation	13 (22.4%)	2 (4.8%)	15 (15.0%)	0.0152
Drugs, *n* (%)				
Vasoactive drug	20 (34.5%)	22 (52.4%)	42 (42.0%)	0.0732
Sedation	17 (29.3%)	22 (52.4%)	39 (39.0%)	0.0202

Data shown as mean (SD) or absolute frequency (relative frequency %). [1]Linear Model analysis of variance; [2]Pearson's Chi-squared test. APACHE: acute physiology and chronic health evaluation; PaO_2: partial pressure of oxygen. Bold formatting represents grouped variables. Italic formatting represents individual variables within a group.
Source: The authors.

Experiment 1

Table 3 summarizes the results of Experiment 1, which evaluates the performance of machine learning models using only patient admission data. The table includes the Area Under the ROC Curve (AUC), the Standard Error (SE), and the 95% Confidence Interval (95% CI) for each classifier. None of the models achieved an AUC greater than 0.9, indicating limited predictive performance using admission data alone.

Experiment 2

Table 4 presents the results of Experiment 2, which examines the performance of machine learning models incorporating patient admission data and ventilation-related features. The table highlights the AUC, SE, and 95% CI for each classifier. While there is a slight improvement in the AUC from 0.88 to 0.89, no model surpasses the AUC threshold of 0.9, suggesting incremental predictive enhancements with the addition of ventilation-related features.

Table 3. Performance of machine learning models using only patient admission data.

	Sensitivity (%)	Specificity (%)	Area under the curve
CatBoost	85.7	83.9	0.88 (0.05)
	(70.7 - 100.7)	(70.9 - 96.8)	(0.78 - 0.98)
Random Forest	85.7	83.9	0.88 (0.05)
	(70.7 - 100.7)	(70.9 - 96.8)	(0.77 - 0.98)
Explainable Boosting Machine	85.7	80.6	0.86 (0.06)
	(70.7 - 100.7)	(66.7 - 94.6)	(0.75 - 0.97)
Logistic Regression	81.0	77.4	0.83 (0.06)
	(64.2 - 97.7)	(62.7 - 92.1)	(0.71 - 0.95)
Decision Tree	76.2	83.9	0.80 (0.07)
	(58.0 - 94.4)	(70.9 - 96.8)	(0.67 - 0.93)

Performance metrics include sensitivity (true positive rate), specificity (true negative rate), and area under the receiver operating characteristic curve (AUC). All metrics are presented with their respective 95% confidence intervals (CI). Machine learning algorithms evaluated include: CatBoost (Categorical Boosting), Random Forest, Logistic Regression, and Decision Tree.

Source: The authors.

Table 4. Performance of machine learning models using patient admission data plus the ventilation-related features.

	Sensitivity (%)	Specificity (%)	Area under the curve
Random Forest	85.7	83.9	0.89 (0.05)
	(70.7 - 100.7)	(70.9 - 96.8)	(0.79 - 0.99)
Explainable Boosting Machine	85.7	80.6	0.88 (0.05)
	(70.7 - 100.7)	(66.7 - 94.6)	(0.78 - 0.98)
Logistic Regression	85.7	87.1	0.86 (0.06)
	(70.7 - 100.7)	(75.3 - 98.9)	(0.75 - 0.97)
CatBoost	90.5	77.4	0.86 (0.06)
	(77.9 - 103.0)	(62.7 - 92.1)	(0.75 - 0.97)
Decision Tree	76.2	83.9	0.85 (0.06)
	(58.0 - 94.4)	(70.9 - 96.8)	(0.73 - 0.96)

Performance metrics include sensitivity (true positive rate), specificity (true negative rate), and area under the receiver operating characteristic curve (AUC). All metrics are presented with their respective 95% confidence intervals (CI). Machine learning algorithms evaluated include: CatBoost (Categorical Boosting), Random Forest, Logistic Regression, and Decision Tree.

Source: The authors.

Experiment 3

Table 5 shows the results of Experiment 3, which evaluates machine learning models using patient admission data combined with mobility-related features. The inclusion of mobility-related features enables the (EBM to achieve an AUC of 0.92, surpassing the 0.9 threshold. The top six critical features identified are sedation, passive kinesiotherapy, vasoactive drugs, sitting, IMS at admission, and sitting (repeated due to interaction effects). EBM's feature importance analysis reveals significant interactions among features, such as $SatO_2$*Sitting, Sedation*IMS at Admission, PaO_2*Sitting, Sedation*Age, and Passive Kinesiotherapy*Active Kinesiotherapy*Vasoactive Drugs.

Experiment 4

Table 6 provides the results of IV and SS interpretations for ventilation-related features. Features with IV > 0.1 are considered to have medium predictive power. The most predictive features include invasive mechanical ventilation, mechanical ventilation in the prone position, and non-invasive mechanical ventilation. While IV identifies feature importance, WoE analysis reveals that performing these procedures is associated with patient mortality.

Table 7 summarizes the IV and SS interpretations for mobility-related features. Predictive features include sitting, walking, active physiotherapy, passive kinesiotherapy, and restricted mobility. WoE analysis indicates that sitting, walking, and active kinesiotherapy are associated with ICU discharge, whereas passive kinesiotherapy and restricted mobility correlate with ICU mortality.

Table 8 displays the results of Experiment 4, which evaluates machine learning models using patient admission data enriched with mobility-related features. The best model achieves an AUC of 0.92, with critical features identified as passive kinesiotherapy, sedation, invasive mechanical ventilation, vasoactive drugs, sitting, and walking. EBM, an intrinsically interpretable model, also provides superior accuracy (AUC > 0.9). EBM's global explanation highlights key feature interactions, including PaO2*Sitting, Sitting*Admission IMS, Hemoglobin*Sedation, COVID-19*Sitting, and Leucocytes*Passive Kinesiotherapy.

Table 5. Performance of machine learning models using patient admission data plus the mobility-related features.

	Sensitivity (%)	Specificity (%)	Area under the curve
Random Forest	90.5	83.9	0.92 (0.04)
	(77.9 - 103.0)	(70.9 - 96.8)	(0.83 - 1.01)
CatBoost	85.7	87.1	0.92 (0.04)
	(70.7 - 100.7)	(75.3 - 98.9)	(0.83 - 1.00)
Explainable Boosting Machine	90.5	83.9	0.90 (0.05)
	(77.9 - 103.0)	(70.9 - 96.8)	(0.81 - 1.00)
Logistic Regression	81.0	87.1	0.90 (0.05)
	(64.2 - 97.7)	(75.3 - 98.9)	(0.80 - 0.99)
Decision Tree	76.2	83.9	0.88 (0.05)
	(58.0 - 94.4)	(70.9 - 96.8)	(0.77 - 0.98)

Performance metrics include sensitivity (true positive rate), specificity (true negative rate), and area under the receiver operating characteristic curve (AUC). All metrics are presented with their respective 95% confidence intervals (CI). Machine learning algorithms evaluated include: CatBoost (Categorical Boosting), Random Forest, Logistic Regression, and Decision Tree.

Source: The authors.

Table 6. Attribute relevance analysis ventilation-related treatment on Experiment 4.

Feature	IV	p-value	Effect size	IV interpretation	SS interpretation
Invasive mechanical ventilation	5.191	1.18 e-34	0.87	very strong	very strong
Mechanical ventilation in prone	0.607	8.59 e-07	0.34	very strong	medium
Non-invasive ventilation	0.413	6.28e-05	0.28	strong	medium
Spontaneous breath in prone	0.035	4.13e-01	0.06	weak	useless
Oxygen therapy	0.004	1.00e-01	0.11	useless	weak
Alveolar recruitment	0.002	1.00	0.00	useless	useless

IV: Information Value; SS: Strength Score. Interpretations: very strong (IV > 0.5), strong (IV 0.3–0.5), medium (IV 0.1–0.3), weak (IV < 0.1).

Source: The authors.

Table 7. Attribute relevance analysis of mobility-related treatment in Experiment 4.

Feature	IV	p-value	Effect size	IV interpretation	SS interpretation
Sitting	3.950	2.01e-26	0.75	very strong	very strong
Walking	2.577	2.00e-16	0.58	very strong	strong
Active kinesiotherapy	2.287	6.86e-21	0.66	very strong	very strong
Passive kinesiotherapy	1.945	1.56e-32	0.84	very strong	very strong
Restricted mobility	0.226	1.72e-09	0.42	medium	strong

IV: Information Value; SS: Strength Score. Interpretations: very strong (IV > 0.5), strong (IV 0.3–0.5), medium (IV 0.1–0.3), weak (IV < 0.1).
Source: The authors.

Table 8. Performance of machine learning models using patient admission data plus the mobility-related features.

	Sensitivity (%)	Specificity (%)	Area under the curve
Random Forest	90.5	83.9	0.92 (0.04)
	(77.9 - 103.0)	(70.9 - 96.8)	(0.83 - 1.00)
Explainable Boosting Machine	90.5	83.9	0.90 (0.05)
	(77.9 - 103.0)	(70.9 - 96.8)	(0.81 - 1.00)
Logistic Regression	90.5	87.1	0.90 (0.05)
	(77.9 - 103.0)	(75.3 - 98.9)	(0.81 - 1.00)
CatBoost	90.5	87.1	0.89 (0.05)
	(77.9 - 103.0)	(75.3 - 98.9)	(0.79 - 0.99)
Decision Tree	76.2	83.9	0.82 (0.06)
	(58.0 - 94.4)	(70.9 - 96.8)	(0.69 - 0.94)

Performance metrics include sensitivity (true positive rate), specificity (true negative rate), and area under the receiver operating characteristic curve (AUC). All metrics are presented with their respective 95% confidence intervals (CI). Machine learning algorithms evaluated include: CatBoost (Categorical Boosting), Random Forest, Logistic Regression, and Decision Tree.
Source: The authors.

DISCUSSION

Our analysis revealed that inpatient exposure to invasive mechanical ventilation, prone positioning, and passive kinesiotherapy were strong predictors of in-ICU mortality, while active mobilizations such as kinesiotherapy, standing, and walking were associated with ICU discharge. These findings have important clinical implications, reinforcing the role of early active mobilization to improve survival outcomes among critically ill cardiovascular patients with COVID-19. Furthermore, the integration of explainable machine learning models enhanced the precision and interpretability of these results, achieving high predictive accuracy (AUC ≥ 0.9) when mobility-related features were included or when treatments were selected based on attribute relevance analysis (Experiment 4). These findings expand upon our previous study,[12] providing deeper insights into how functional and therapeutic factors impact patient outcomes.

Building on these findings, Experiment 4 specifically highlighted the Explainable Boosting Machine (EBM) model, emphasizing the importance of passive kinesiotherapy, sedation, and sitting activities. Significant interactions identified by the model included PaO2*sitting, sedation*IMS admission, hemoglobin*sedation, COVID-19*sitting, and leucocytes*passive kinesiotherapy. Although EBM did not achieve the best overall result, its ability to assign importance to individual features and their interactions makes it valuable for further analysis. Similarly, Experiment 3 corroborated these observations, as the EBM model emphasized the significance of sedation, sitting, and passive kinesiotherapy, further identifying key interaction effects among clinical features. Additionally, it identified interactions such as sedation*IMS admission, sitting*SatO2, sitting*PaO2, and sedation*age, which warrant further investigation.

These findings are consistent with international studies that have identified demographic and clinical risk factors for hospitalization and mortality in patients with cardiovascular diseases (CVD) and COVID-19. These risk factors include older age, overweight, low lymphocyte count, and pre-existing comorbidities[6-8,27-29]. In Brazil, the aging population helps explain the predominance of non-communicable chronic diseases as the leading causes of hospitalization and death in older individuals[30].

The overall length of stay in our sample was similar to that in other studies of patients with COVID-19, ranging from less than one week to two months[31]. A retrospective study of 88 older adults hospitalized for COVID-19 in an ICU in Brazil reported hypertension as the most common comorbidity, with a median ICU stay of 23 days (range: 4–38)[32]. The link between pre-existing CVDs, worse outcomes, and increased risk of death in patients with COVID-19 is further supported by our findings[33]. Together, these results support the external validity of our findings, while highlighting the significant role of demographic characteristics and COVID-19 diagnosis in predicting in-ICU death in this population.

Emerging clinical algorithms[34] and consensus guidelines[35] for the respiratory management of COVID-19 patients were developed. Our findings contribute to these efforts by suggesting that inpatients with CVD and COVID-19 were more likely to be exposed to ventilatory support techniques, particularly alveolar recruitment (concomitant with invasive ventilation) and awake prone positioning. While the role of early mobilization in COVID-19 patients is already acknowledged[35,36], algorithms incorporating mobility interventions for this population remain scarce. Although similar exposure to all mobility interventions reinforces the general need for early mobilization in hospitalized patients[37], the higher exposure to passive kinesiotherapy in COVID-19 patients may serve as a proxy for disease severity in this group.

In line with this, our results revealed that in-ICU mortality was higher among patients who tested positive for COVID-19, were exposed to invasive mechanical ventilation, or had lower mobility scores at ICU admission. These characteristics may serve as proxies for disease severity. Interestingly, exposure to physiotherapy interventions had two distinct effects on in-ICU mortality. While restricted mobility and passive kinesiotherapy were associated with in-ICU death, active mobilizations (such as kinesiotherapy, standing, or walking) were linked to in-ICU discharge. This finding is consistent with previous studies showing improved mobility at hospital discharge and a higher likelihood of returning home with increased frequency and longer duration of physical therapy visits for COVID-19 patients in acute care hospitals[11]. Given that the interventions investigated here can be viewed as part of a continuum of recovery—progressing from restricted mobility to passive kinesiotherapy and eventually to active kinesiotherapy—it can be argued that transitioning from "passive to active kinesiotherapy" may be a critical factor influencing clinical outcomes. Further studies are needed to explore whether different sequences of physiotherapy interventions are associated with in-ICU mortality and, if so, to determine which specific sequence is most likely to lead to in-ICU discharge.

Despite the strengths of the current study, limitations should be acknowledged. Due to its retrospective design, data regarding functional outcomes at admission were missing for some participants. Additionally, physiotherapy interventions were delivered based on the clinical decisions of the rehabilitation team, which introduces variability. The sample, derived from a single center during the initial "wave" of COVID-19 cases in Brazil[38], may not be representative of the broader Brazilian healthcare system, warranting further investigation.

CONCLUSION

Functional outcomes at ICU admission and exposure to routine physiotherapy interventions are significantly associated with in-ICU mortality in older adults with cardiovascular diseases. Machine learning enabled the identification of key predictive features and their interactions, achieving high predictive accuracy. Future studies should further explore the application of machine learning to validate and refine these findings across diverse populations and settings.

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CONFLICT OF INTEREST

None do declare.

RESEARCH DATA AVAILABILITY

Research data is only available upon request.

AUTHOR CONTRIBUTIONS

Conceptualization: JA, LFR, CAS, ASF; Data curation: JA, GRCS, LMT, CAS, ASF; Formal Analysis: JA, GRCS, LMT; Funding acquisition: ASF; Investigation: CAS, ASF; Methodology: JA, LFR, CAS, ASF; Project administration: ASF; Resources: ASF; Software: JA, GRCS, LMT; Supervision: JA, ASF; Validation: JA, LFR, ASF; Visualization: GRCS, LMT; Writing – original draft: GRCS, LMT, CAS, ASF; Writing – review & editing: JA, LFR, ASF.

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