Machine Learning Identifies ICU Outcome Predictors in a Multicenter COVID-19 Cohort.

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Research

Keywords: COVID-19, critical care, ARDS, outcome, prognostic models

Posted Date: June 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-624809/v1

Version of Record: A version of this preprint was published at Critical Care on August 17th, 2021. See the published version at https://doi.org/10.1186/s13054-021-03720-4.

Abstract

Background. Intensive Care Resources are heavily utilized during the COVID-19 pandemic. However, risk stratification and prediction of SARS-CoV-2 patient clinical outcomes upon ICU admission remain inadequate. This study aimed to develop a machine learning model, based on retrospective & prospective clinical data, to stratify patient risk and predict ICU survival and outcomes.

Methods. A Germany-wide electronic registry was established to pseudonymously collect admission, therapeutic and discharge information of SARS-CoV-2 ICU patients retrospectively and prospectively. Machine learning approaches were evaluated for the accuracy and interpretability of predictions. The Explainable Boosting Machine approach was selected as the most suitable method. Individual, non-linear shape functions for predictive parameters and parameter interactions are reported.

Results. 1,039 patients were included in the Explainable Boosting Machine model, 596 patients retrospectively collected, and 443 patients prospectively collected. The model for prediction of general ICU outcome was shown to be more reliable to predict “survival”. Age, inflammatory and thrombotic activity, and severity of ARDS at ICU admission were shown to be predictive of ICU survival. Patients’ age, pulmonary dysfunction and transfer from an external institution were predictors for ECMO therapy. The interaction of patient age with D-dimer levels on admission and creatinine levels with SOFA score without GCS were predictors for renal replacement therapy.

Conclusions. Using Explainable Boosting Machine analysis, we confirmed and weighed previously reported and identified novel predictors for outcome in critically ill COVID-19 patients. Using this strategy, predictive modeling of COVID-19 ICU patient outcomes can be performed overcoming the limitations of linear regression models.

Trial registration. “ClinicalTrials” (clinicaltrials.gov) under NCT04455451

Background

The COVID-19 pandemic hit Germany in spring 2020 and since then intensive care resources were heavily utilized up to now [1]. Although large numbers of SARS-CoV-2 patients required intensive care unit (ICU) admission, ICU capacity in Germany was not exceeded. However, risk stratification and prediction of outcomes continues to be challenging. Several investigators have reported their ICU COVID-19 experience during this time period, yet these data show great variability in the number of cases and outcomes reported[2–16].

Few of these reports attempted to identify risk factors predicting morbidity, mortality and overall clinical outcome. This may be the result of the reporting of (1) incomplete data sets earlier in the pandemic as many patient were still undergoing ICU care for SARS-CoV-2 infection [10, 13, 15, 16], and (2) data sets biased by the need to triage ICU care to patients in the face of the exhaustion of local/regional ICU capacity [7, 10, 14, 15]. Nonetheless, there was consensus that SARS-CoV-2 ICU patients experienced

lengthy ICU stays with ICU mortality in the range of 25 to 41%[14, 17]. Classical statistical analysis identified risk factors in these patient populations including age, renal function, the degree of pulmonary compromise and severity of acute respiratory distress syndrome (ARDS). But standard statistical techniques are limited in their ability to integrate diverse data types such as past medical history, prior medications, initial ICU admission parameters, therapeutic ICU interventions and many more in relation to clinical outcome variables[18].

To overcome these limitations, we employed machine learning methods to optimize risk stratification and prediction of overall outcomes for individual COVID-19 ICU patients. It has been recently shown that machine learning algorithms in combination with numerous, multidimensional variables with non-linear relationships may have advantages in clinical outcome prediction. Machine learning strategies were found to be superior to classical methods of outcome prediction typically used in cardiovascular pathologies[18, 19].

In the present study, we report on 1,188 PCR-confirmed COVID-19 patients receiving ICU care at 27 German hospitals that were enrolled retrospectively and prospectively. The aim of this study is to investigate whether machine learning can provide additional insights for outcome prediction in COVID-19 ICU patients. Our predictive machine learning models for: (1) ICU survival, (2) need for extra-corporeal membrane oxygenation (ECMO) therapy, and (3) need for renal replacement therapy (RRT). Out model weighs and provides important interpretable insights into these essential patient factors.

Methods

Study design

This multi-center retrospective - prospective cohort study was performed with 27 participating German hospitals (Supplemental Table E1 and Fig. 1). An ethics approval was obtained from the participating hospitals' Institutional Review Boards. The study was registered in "ClinicalTrials" (clinicaltrials.gov) under NCT04455451. COVID-19 patients 18 years and older requiring ICU admission between 1st January 2020 and 4th May 2021 at a participating center were recruited for this study. Patients were recruited either retrospectively (1st January 2020 to 31st July 2020) or prospectively (29th September 2020 to 4th May 2021). Inclusion criteria were the requirement for ICU treatment due to COVID-19 confirmed by a positive SARS-CoV-2 PCR test. The local investigator confirmed the accuracy and completeness of all entered data. A secure electronic research data capture system (REDCap) was used to collect and manage study data in a pseudonymous fashion[20, 21].

Calculations

To allow comparability of intubated and spontaneously breathing patients the Sequential Organ Failure Assessment (SOFA) score was calculated without the Glasgow Coma Scale (GCS)[22]. Murray Lung

blished [23]. Static compliance and driving pressure were

calculated as previously described [24]. Laboratory values were converted to a common unit to permit analysis. Oxygen supply in spontaneously breathing patients was converted to an estimated F_iO_2 (Supplemental Table E2).

Statistical Analyses

Observed parameters were assessed for their distribution. Outliers were excluded by visual assessment of clinical validity based on the distribution plots (excluded data points are provided in Supplemental Table E3). Baseline characteristics of all patients were evaluated. Continuous variables are reported as either means and standard deviation (SD) if normally distributed or as median and interquartile ranges (IQR) if not normally distributed. Shapiro-Wilk-Test was used prior to Student's t test or Wilcoxon rank sum test. Kaplan-Meier estimators were compared using Log-Rank-Test. Categorical variables were compared using the Fisher's Exact Test. All statistical analyses were performed in R (version 4.0.3) and JMP (version 15.2.0, SAS Institute, Cary, USA).

Discontinuation Of Icu Care

107 (8.3%) patients, or their legal representative requested that ICU level care be discontinued during the ICU stay. The majority of these patients died during the ICU stay (n = 95, 88.8%). To avoid bias in predictor analyses this patient group was excluded from further analyses (for patient characteristics please see Supplemental Table E5). For three patients these data were not available, they were excluded from the analyses.

Description Of Machine Learning Process

Variables are referred to as features in machine learning (ML) but for consistency we will refer to them as variables. ML was performed in python (version 3.8.5) with jupyter notebook (jupyter-core 4.63 and jupyter notebook 6.1.5) and pandas (version 1.1.4)[25]. Standard implementations from scikit-learn (version 0.23.2) were used for Random Forest, Support-Vector-Classifier (SVC), and Cross-Validation (CV) [26]. For the EBM, we used Microsoft's open source implementation interpretML (Microsoft Corporation, Redmond, USA, version 0.2.4)[27]. For the visualization of the PR-AUC curves we used matplotlib (version 3.3.3). For all other visualizations, we used R (version 4.0.3) within RStudio (version 1.3.1093); tidyverse (version 1.3.0), latex2exp (version 0.4.0), ggpubr (version 0.4.0), patchwork (version 1.1.0), for the generation of tables finalfit (version 1.0.2), for Kaplan-Meier-Curves finalfit, survminer (version 0.4.8), and survival (version 3.2.7).

Dataset used for ML: Out of the 1,186 patients included in the final study (Table 1), 135 were transferred to another ICU. In four patients, data about the transfer status was not available. Due to study design the ultimate ICU outcome of this subset of patients is unknown. To avoid bias in survival prediction these

patients were excluded, thus ML models were trained on 1,039 (complete cohort), 596 (retrospective cohort) and 443 (prospective cohort) patients.

Table 1
Clinical characteristics of N = 1,186 patients included in the study; clinical and laboratory parameters

Parameter	Total N	Missing N	non-survival	survival	total
Total N (%)			403 (34.0)	783 (66.0)	1,186
Age (years)	1,186	0	66.0 (58.0 to 75.5)	62.0 (53.0 to 72.0)	63.0 (54.0 to 73.0)
Age groups	1,186	0			
18–29 years			2 (0.5)	26 (3.3)	28 (2.4)
30–39 years			8 (2.0)	37 (4.7)	45 (3.8)
40–49 years			32 (7.9)	75 (9.6)	107 (9.0)
50–59 years			75 (18.6)	196 (25.0)	271 (22.8)
60–69 years			130 (32.3)	202 (25.8)	332 (28.0)
70–79 years			105 (26.1)	187 (23.9)	292 (24.6)
80–89 years			48 (11.9)	57 (7.3)	105 (8.9)
> 90 years			3 (0.7)	3 (0.4)	6 (0.5)
Sex	1,186	0			
female			92 (22.8)	241 (30.8)	333 (28.1)
male			311 (77.2)	542 (69.2)	853 (71.9)
BMI (kg/m²)	1,120	66	28.1 (25.1 to 33.1)	28.4 (25.2 to 32.7)	28.3 (25.2 to 32.8)
BMI groups	1,120	66			
below 20 kg/m²			8 (2.1)	16 (2.2)	24 (2.1)
20–25 kg/m²			88 (22.8)	164 (22.3)	252 (22.5)
25–30 kg/m²			141 (36.5)	267 (36.4)	408 (36.4)

All values are reported as absolute numbers and percentages for categorical variables, and as median and interquartile ranges (IQR) if not distributed normally for continuous variables.

Abbreviations: BMI: body-mass-index (kg/m²); COPD: chronic-obstructive pulmonary disease; ICU: intensive care unit; LOS: length-of-stay; NIDDM: Non-insulin dependent diabetes mellitus; NOAC: novel oral anticoagulants; RASS: Richmond agitation sedation scale; SOFA score without GCS: sequential organ failure assessment score without Glasgow coma scale (GCS); n/a not available.

[1] Prior thrombotic events: e.g. deep vein thrombosis, pulmonary embolism.

[2] Sedation at day of ICU admission.

Parameter	Total N	Missing N	non-survival	survival	total
above 30 kg/m²			149 (38.6)	287 (39.1)	436 (38.9)
Bloodgroup	755	431			
0			121 (40.2)	158 (34.8)	279 (37.0)
A			124 (41.2)	213 (46.9)	337 (44.6)
AB			10 (3.3)	24 (5.3)	34 (4.5)
B			46 (15.3)	59 (13.0)	105 (13.9)
Past medical history and chronic medications					
Arterial hypertension	1,186	0	255 (63.3)	479 (61.2)	734 (61.9)
Cardiovascular disease	1,186	0	124 (30.8)	187 (23.9)	311 (26.2)
Chronic arrhythmia	1,186	0	61 (15.1)	84 (10.7)	145 (12.2)
COPD	1,186	0	38 (9.4)	69 (8.8)	107 (9.0)
Other lung disease	1,186	0	44 (10.9)	80 (10.2)	124 (10.5)
Nicotine abuse	1,186	0	36 (8.9)	78 (10.0)	114 (9.6)
History of solid organ transplant	1,186	0	9 (2.2)	14 (1.8)	23 (1.9)
History of bone marrow transplant	1,186	0	3 (0.7)	5 (0.6)	8 (0.7)
Alcoholism	1,186	0	13 (3.2)	23 (2.9)	36 (3.0)
Chronic kidney failure	1,186	0	53 (13.2)	92 (11.7)	145 (12.2)
Diabetes mellitus	1,186	0	126 (31.3)	218 (27.8)	344 (29.0)
NIDDM	1,186	0	88 (21.8)	132 (16.9)	220 (18.5)

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Abbreviations: BMI: body-mass-index (kg/m²); COPD: chronic-obstructive pulmonary disease; ICU: intensive care unit; LOS: length-of-stay; NIDDM: Non-insulin dependent diabetes mellitus; NOAC: novel oral anticoagulants; RASS: Richmond agitation sedation scale; SOFA score without GCS: sequential organ failure assessment score without Glasgow coma scale (GCS); n/a not available.

[1] Prior thrombotic events: e.g. deep vein thrombosis, pulmonary embolism.

[2] Medication at day of ICU admission.

Parameter	Total N	Missing N	non-survival	survival	total
Prior thrombotic events[1]	1,186	0	24 (6.0)	35 (4.5)	59 (5.0)
ACE inhibitors	1,186	0	95 (23.6)	172 (22.0)	267 (22.5)
AT2 receptor blocker	1,186	0	47 (11.7)	117 (14.9)	164 (13.8)
Beta blockers	1,186	0	116 (28.8)	227 (29.0)	343 (28.9)
Anti-platelet medication	1,186	0	95 (23.6)	165 (21.1)	260 (21.9)
NOAC	1,186	0	29 (7.2)	56 (7.2)	85 (7.2)
Corticosteroids	1,186	0	44 (10.9)	63 (8.0)	107 (9.0)
Immunosuppressive drugs	1,186	0	21 (5.2)	31 (4.0)	52 (4.4)
Opioids	1,186	0	19 (4.7)	38 (4.9)	57 (4.8)
Status at ICU admission					
Admission/Transfer status	1,186	0			
External transfer			206 (51.1)	336 (42.9)	542 (45.7)
Internal or direct admission			197 (48.9)	447 (57.1)	644 (54.3)
Ventilatory status at admission	1,186	0			
intubated			217 (53.8)	278 (35.5)	495 (41.7)
non-invasive assisted ventilation			40 (9.9)	91 (11.6)	131 (11.0)
spontaneous breathing			146 (36.2)	414 (52.9)	560 (47.2)
Prior days of non-invasive ventilation	1,016	170	0.0 (0.0 to 1.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Days prior invasive ventilation	1,099	87	0.0 (0.0 to 3.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)

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Abbreviations: BMI: body-mass-index (kg/m²); COPD: chronic-obstructive pulmonary disease; ICU: intensive care unit; LOS: length-of-stay; NIDDM: Non-insulin dependent diabetes mellitus; NOAC: novel oral anticoagulants; RASS: Richmond agitation sedation scale; SOFA score without GCS: sequential organ failure assessment score without Glasgow coma scale (GCS); n/a not available.

[1] Prior thrombotic events: e.g. deep vein thrombosis, pulmonary embolism.

[2] Ventilatory status: ventilation at day of ICU admission.

Parameter	Total N	Missing N	non-survival	survival	total
RASS	1,100	86	-2 (-5 to 0)	0 (-4 to 0)	0 (-4 to 0)
SOFA (w/o GCS)	1,186	0	7 (4 to 9)	5 (3 to 7)	5 (3 to 8)
Murray Lung Injury Score	1,156	30	3.2 (2.5 to 3.5)	3.0 (2.2 to 3.5)	3.0 (2.5 to 3.5)
ARDS grading according to PaO2/FiO2 quotient	1,154	32			
Mild (PaO2/FiO2 201 to 300)			45 (11.3)	147 (19.4)	192 (16.6)
Moderate (PaO2/FiO2 101 to 200)			189 (47.6)	357 (47.2)	546 (47.3)
Severe (PaO2/FiO2 < = 100)			142 (35.8)	186 (24.6)	328 (28.4)
no ARDS			21 (5.3)	67 (8.9)	88 (7.6)
Static compliance (ml/mbar)[2]	612	574	34.6 (24.7 to 44.4)	37.9 (29.3 to 49.4)	36.7 (27.5 to 47.3)
Driving pressure (mbar)[2]	636	550	13.0 (10.0 to 16.0)	12.0 (10.0 to 15.0)	12.0 (10.0 to 15.0)
Hemoglobin (g/dl)	1,179	7	11.0 (9.5 to 12.9)	11.9 (10.1 to 13.3)	11.6 (9.9 to 13.2)
Platelets (x10³µl-1)	1,178	8	203.0 (146.0 to 282.0)	232.0 (177.0 to 316.0)	223.0 (164.0 to 304.0)
Leucocytes (n/nl)	1,177	9	10.7 (7.1 to 14.5)	8.8 (6.1 to 12.1)	9.4 (6.3 to 12.9)
Lymphocytes (n/nl)	971	215	0.7 (0.4 to 1.1)	0.8 (0.6 to 1.2)	0.8 (0.5 to 1.2)

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Abbreviations: BMI: body-mass-index (kg/m²); COPD: chronic-obstructive pulmonary disease; ICU: intensive care unit; LOS: length-of-stay; NIDDM: Non-insulin dependent diabetes mellitus; NOAC: novel oral anticoagulants; RASS: Richmond agitation sedation scale; SOFA score without GCS: sequential organ failure assessment score without Glasgow coma scale (GCS); n/a not available.

[1] Prior thrombotic events: e.g. deep vein thrombosis, pulmonary embolism.

[2] ...pation at day of ICU admission.

Parameter	Total N	Missing N	non-survival	survival	total
Neutrophiles (n/nl)	886	300	8.7 (5.6 to 12.7)	6.8 (4.7 to 9.4)	7.3 (4.9 to 10.5)
Platelet/neutrophile ratio	882	304	23.3 (15.5 to 36.0)	34.6 (24.9 to 53.2)	31.4 (21.2 to 47.5)
Platelet/lymphocyte ratio	965	221	278.1 (158.3 to 473.9)	280.4 (181.8 to 425.7)	280.3 (174.1 to 436.6)
C-reactive protein (mg/dl)	1,141	45	17.5 (9.6 to 27.9)	14.1 (7.6 to 22.5)	14.8 (8.4 to 24.3)
Procalcitonin (ng/ml)	1,153	33	0.7 (0.3 to 2.4)	0.3 (0.1 to 0.9)	0.4 (0.1 to 1.4)
Interleukin-6 (pg/ml)	851	335	161.0 (63.0 to 429.5)	89.4 (39.8 to 189.5)	104.0 (43.2 to 268.9)
Ferritin (µg/dl)	623	563	154.0 (88.3 to 272.8)	114.2 (59.2 to 195.5)	126.3 (68.8 to 210.8)
D-Dimer (µg/ml)	905	281	4.2 (1.7 to 14.9)	2.2 (1.1 to 5.0)	2.8 (1.2 to 8.0)
Total bilirubin (mg/dl)	1,160	26	0.7 (0.4 to 1.1)	0.6 (0.4 to 0.8)	0.6 (0.4 to 0.9)
Creatinine (mg/dl)	1,172	14	1.2 (0.8 to 2.1)	0.9 (0.7 to 1.4)	1.0 (0.8 to 1.6)
ICU outcomes					
Mortality n/%			403 (34.0)		
LOS ICU (days)	1,186	0	14.0 (8.0 to 24.0)	16.0 (6.0 to 34.0)	15.0 (7.0 to 30.0)
Transfer destination	1,180	6			
intermediate care			n/a	51 (6.6)	n/a
normal ward			n/a	489 (62.9)	n/a

All values are reported as absolute numbers and percentages for categorical variables, and as median and interquartile ranges (IQR) if not distributed normally for continuous variables.

Abbreviations: BMI: body-mass-index (kg/m²); COPD: chronic-obstructive pulmonary disease; ICU: intensive care unit; LOS: length-of-stay; NIDDM: Non-insulin dependent diabetes mellitus; NOAC: novel oral anticoagulants; RASS: Richmond agitation sedation scale; SOFA score without GCS: sequential organ failure assessment score without Glasgow coma scale (GCS); n/a not available.

[1] Prior thrombotic events: e.g. deep vein thrombosis, pulmonary embolism.

[2] ...pation at day of ICU admission.

Parameter	Total N	Missing N	non-survival	survival	total
other ICU			n/a	125 (16.1)	n/a
REHA			n/a	112 (14.4)	n/a

All values are reported as absolute numbers and percentages for categorical variables, and as median and interquartile ranges (IQR) if not distributed normally for continuous variables.

Abbreviations: BMI: body-mass-index (kg/m²); COPD: chronic-obstructive pulmonary disease; ICU: intensive care unit; LOS: length-of-stay; NIDDM: Non-insulin dependent diabetes mellitus; NOAC: novel oral anticoagulants; RASS: Richmond agitation sedation scale; SOFA score without GCS: sequential organ failure assessment score without Glasgow coma scale (GCS); n/a not available.

[1] Prior thrombotic events: e.g. deep vein thrombosis, pulmonary embolism.

[2] At ICU admission or first value after intubation at day of ICU admission.

Variable representation: We transformed the following laboratory values to their log10(x + 1)-scale (based on visual inspection) prior to their use as ML variables: lymphocytes, leucocytes, neutrophils, creatinine, procalcitonin, d-dimers, IL-6, ferritin, platelets, platelets/neutrophils ratio, platelets/lymphocytes ratio, bilirubin.

Machine Learning Methods: We trained SVC, Random Forest Classifier (RF), and EBM with a 5-fold stratified CV by using 80% of the data for training and 20% of the data for testing. We excluded variables with more than 30% of data missing (see Supplemental Table E7). For all ML-methods, we applied one-hot encoding for categorical data, i.e. creating indicator columns for each category (including missing values). We converted Boolean data to numerical values zero and one. We performed a hyper-parameter optimization across all ML-algorithms with nested CV techniques[28]. Performance of the models was evaluated as the average of balanced accuracy and the area under precision-recall curve (PR-AUC) per fold of CV. A regular accuracy or AUC would be biased towards the overrepresented class (“survival”). In order to verify the robustness of our results in light of the imbalanced outcome variable, we used both over-sampling and under-sampling for the outcome “survival”. For over-sampling, the observations from the under-represented class (here: “non-survival”) were added at random to the data set. For under-sampling, the over-represented class (here ”survival”) was reduced at random to the same size as the underrepresented class. We compared the ranking of variable importance and the shape function with the results from each of the 5-fold stratified CV runs on the retrospective dataset. The results of each run were the same (data not shown). We further validated the results by training the ML-models with a 5-fold CV for hyper-parameter optimization (RF and SVC) on the retrospective data and predicting the outcome on the prospective data (see Table 2).

Table 2
Overall performance of the machine learning models for ICU outcome prediction

Prediction variable	**ICU survival** **N = 1,053**		**ECMO therapy** **N = 1,053**		**Renal Replacement Therapy** **N = 1,000**	
ML model	Balanced accuracy	PR-AUC	Balanced accuracy	PR-AUC	Balanced accuracy	PR-AUC
RF	0.65	0.84	0.72	0.75	0.69	0.66
SVC	0.65	0.81	0.79	0.53	0.7	0.64
EBM	0.61		0.72		0.68	
EBM (10 interactions)	0.64	0.81	0.73	0.69	0.7	0.69

EBM: Explainable Boosting Machine; ICU: intensive care unit, ML: machine learning, RF: Random Forest Classifier; SVC: Support Vector Classifier

For the results presented in this paper, we trained the EBM on the entire dataset (retrospective and prospective).

Rationale for the use of the Explainable Boosting Machines model: EBMs are built on a generalized additive model (GAM) of the form $g(y) = f_1\left(x_1\right) + f_2\left(x_2\right) + ::: + f_p\left(x_p\right)$, where g is the link function and $f_i\left(x_i\right)$ the shape function for variable x_i. In a classification problem, the link function g is a logistic function[29]. As the model is additive, each variable contributes in a modular way. This allows for an easy interpretation about the influence of a variable to the prediction. The idea of using shape functions for each variable allows for complex relationships (even non-linear) between the variable and the outcome prediction. Therefore, GAMs can be significantly more accurate than simple linear models[30]. We use EBMs as they additionally employ modern machine learning techniques such as bagging and boosting and have a comparable performance to state-of-the art ML techniques such as RF [30, 31]. Overall performance of the ML models was assessed by balanced accuracy and PR-AUC (Table 2).

Results

Participating Centers and Level of Care

27 ICUs participated in this observational study including 24 ICUs from university hospitals and three ICUs from regional primary and secondary care hospitals (Supplemental Table E1, Supplemental Figure E1). All patients requiring ICU treatment could receive the full treatment possibilities including ventilation, renal replacement therapy (RRT), and extracorporeal membrane oxygenation (ECMO).

Patient Characteristics And Status At Icu Admission

1,186 patients were recruited into the study (patient selection chart, Supplemental Figure E2) with 713 patients in the retrospective and 473 patients in the prospective cohort. Overall patient characteristics, severity of the disease, and organ failure are given in Table 1 and Supplemental Table E4. Twice as many males (71.9%) than females (28.1%) were treated at the participating ICUs. The median age was 63 (IQR 54 to 73), 180 patients (15.2%) had an age below 50 years, and 6 patients (0.5%) had an age above 90 years. For age distribution and baseline parameters please see Fig. 1. Kaplan Meier Curves for probability of ICU survival according to patient age are provided in Supplemental Figure E3a. At ICU admission spontaneous breathing via oxygen mask, non-invasive assisted ventilation or invasive ventilation were present in 47.2%, 11%, 41.7% patients, respectively. Data for the grading of the ARDS severity were available for 1,154 patients (97.3%). According to the Berlin definition ARDS was graded using the P_aO_2/F_iO_2 index as mild (16.6%), moderate (47.3%), or severe (28.4%) [32]. Supplemental Figure E3b provides the Kaplan Meier Curves for probability of ICU survival according to ARDS severity.

Patient Outcome

Overall ICU mortality was 34% for all recruited patients. Median length of ICU stay was 15 days (IQR 7 to 30 days). Mortality was significantly lower in female patients (27.6%) than in male patients (36.5%) ($p = 0.0041$). Mortality was highest in octogenarians with an observed mortality of 45.7% (Supplemental Figure E3a). 22% patients received ECMO therapy (21% in the retrospective cohort and 23.5% in the prospective cohort) with a median duration of 16 days (IQR 9 to 26). Patients receiving ECMO therapy were significantly younger than those not receiving ECMO (57 (IQR 49 to 65) years vs. 66 (IQR 56 to 76) years; $p < 0.0001$). 39.3% patients, not receiving chronic dialysis prior to ICU admission, received RRT/dialysis therapy during their ICU stay (41.7% in the retrospective cohort and 35.8% in the prospective cohort).

Prediction Of Icu Survival By Ebm Models

Overall performance of the different ML models including results for balanced accuracies and precision recall area under the curve (PR-AUC) are given in Table 2. The EBM model based on variables reflecting status at ICU admission (Supplemental Table E8), resulted in a high precision recall area under the curve (PR-AUC) of 0.81 and a moderate balanced accuracy of 0.64 (Supplemental Figure E4a). The ten most important predictive variables in the admission model were: age, platelet/neutrophil ratio, D-dimer, Horowitz quotient, hemoglobin, procalcitonin, Murray lung injury score, platelet count, interaction of c-reactive protein and interleukin-6 and absolute lymphocyte count (Fig. 2). As shown in the shape function for the variable age, there is a transition from improved survival to worsened survival at the age of 61 years (confidence interval (CI) 60 to 62) with a first worsening at the age of 34.7 (CI 31 to 35) years. The platelet/neutrophil ratio was the second most important parameter showing a worsened outcome above

a ratio of 43.7 (CI 19.6 to 44.1). Elevated D-Dimers, for instance, affect ICU survival negatively at levels above 4.06µg/ml (CI 3.78 to 4.07). Low Horovitz quotients demonstrated a negative impact on ICU survival with transitions for the worst impact at P_aO_2/F_iO_2 quotients below 85 (CI 84 to 86) and improved survival above 163 to 172. Overall performance and results of the EBM model was similar for the different datasets (complete, prospective and retrospective) (Supplemental Table E9, Supplemental Figure E5a).

Predicting The Need For Ecmo Therapy By Ebm Models

EBM models for the prediction of ECMO therapy resulted in a good PR-AUC of 0.69 and a good balanced accuracy of 0.73. The five most important parameters associated with ECMO therapy were: age, ventilatory status “intubated” at ICU admission, admission by external transfer, Murray lung injury score, and admission by internal transfer (reduced risk) (Fig. 3a). The shape function for the factor age showed a higher risk for ECMO therapy below the age of 70 (CI 69 to 75) years. A Murray Lung injury score above a level of 2.8 (no CI) resulted in a higher risk for ECMO therapy. Patients admitted by external transfer had a higher risk to receive ECMO therapy. Comparison of the EBM models and selected shape functions of important variables revealed similar results (Supplemental Table E9 and Supplemental Figure E5b).

Prediction Of Renal Replacement Therapy By Ebm Models

Patients on chronic dialysis were excluded prior to EBM model generation. The EBM model on the complete dataset resulted in a good PR-AUC (Supplemental Figure E4c). The five most important parameters were: interaction of age with D-dimer level, creatinine level, SOFA score w/o GCS, interaction of BMI with creatinine, and platelet/neutrophile ratio (Fig. 3b). Patients with an age below approximately 65 years combined with elevated D-dimers had a higher risk for the need of RRT (see heatmap of interaction of age and D-dimers in Fig. 3b). An elevated creatinine level above 1.3mg/dl (no CI) at ICU admission, as well as a SOFA score w/o GCS above 5 (no CI) resulted in a higher risk to receive RRT during ICU stay. Throughout all EBM models, creatinine and bilirubin levels showed a reverse correlation relationship.

Discussion

In this multi-center retrospective - prospective cohort study we identified and weighed possible predictive factors on COVID-19 outcome. We used a machine learning based approach, since that allows for interpretability of the results by weighing the importance of each variable and by providing a shape-function for each variable. Moreover, the influence of interactions between different variables can be included. Using this ML approach, we confirmed previously reported factors and extend knowledge to novel factors likely predicting outcome in COVID-19 patients. For ICU survival these include age, platelet/neutrophil ratio, D-dimers, and ARDS severity.

Prediction of positive outcome (“survival”) and factors predicting adverse outcome (“mortality”) are important information for cohorts with a large number of intensive care admissions. Here, we optimized the model for the prediction of “survival”. This is on the one hand relevant to resource planning for health care systems taking care of COVID-19 patients, and on the other hand, essential to risk stratification of the individual patient. Previous studies have shown that older age, obesity, diabetes, being immunocompromised, lower P_aO_2/F_iO_2, higher hemodynamic and renal SOFA score at ICU admission were independently associated with 90-day mortality in COVID-19 [14]. This has also been reported by other investigators, yet they did not show individual cutoff values nor weigh the individual importance for the identified factors[33, 34]. To exclude an early effect or a late effect as seen when logistic regression is performed, we included almost all admission variables collected for our cohort. Variable selection influencing outcome can be performed in ML models but is less crucial than for logistic regression. We refrained from such a variable selection in our EBM model’s decision process. In our analysis we were able to confirm that age and pulmonary function on admission are important predictors in COVID-19 ICU patients. The present shape functions clearly show a non-linear association between the predictive factors and the outcome variable. Patient’s age, for instance, as the most important predictive factor, shows a higher chance for ICU survival below 61 years. Additionally, the ML approach identified the D-dimer level and platelet/neutrophil ratio at ICU admission as important factors. This is especially interesting in the context of reported thrombotic complications of COVID-19 patients [35, 36]. When activated, neutrophils complex with platelets to form platelet-neutrophil complexes (PNCs) activating both cell types. These PNCs enhance inflammation, increases neutrophil extracellular trap formation, and result in micro-thrombosis [37, 38]. The same is applicable when looking at D-dimer levels. High D-dimer levels reflect an activation of inflammation and the formation of micro-thrombi with neutrophil extracellular trap formation. We can therefore say that our data reflects the inflammatory markers known from translational science and confirm their relevance to outcome [38].

In everyday clinical practice, it is of great interest to assess the further course of patients in intensive care, such as a necessity for renal replacement or ECMO therapy. The present ML model predicting the need for ECMO therapy identified age and pulmonary compromise (Murray lung injury score) as important factors. Admission both from an external hospital and already in an intubated state are associated with the need for ECMO therapy. This result is not surprising, as both younger and more severely pulmonary compromised patients were typically transferred for ECMO therapy to our participating centers [39]. Our ML models assessing the need for RRT include age as an important factor as well as variables quantifying disease severity (SOFA score) or inflammatory and thrombotic activity (D-dimers and Platelet/neutrophil ratio). Our models do not only permit the identification of risk factors in COVID-19 patients, they also provide insights to the weight of each individual variable for the selected ICU outcome of the individual patient [18, 40]. The ML models chosen allow for transparent assessment of various variables in a non-linear fashion which overcomes limitations of currently employed regression models. The superiority of this approach has been shown in cardiovascular pathologies, where machine learning based models overcame the limitations of current analytical approaches of risk prediction [19]. This is possible since machine learning models take a different non-linear approach for the evaluation of the

individual patient as compared to cohort based logistic regression. Generalized additive models (GAM) and linear regression models are both additive models, hence every variable contributes in a modular way[30]. This allows for an easy interpretation of the impact of a variable on the prediction. The use of shape functions in GAMs for each variable allows for complex relationships (even non-linear) between the variable and the outcome prediction. Therefore, EBMs can be significantly more accurate than simple linear models [30]. Interactions of different variables extend the analyzing capabilities of the ML approach. Therefore, the results from the GAM offer a greater degree of interpretability than a p-value of a linear regression, or an odds ratio analysis. As shown in Figs. 2 and 3 the visualizations offer insight into transition values from positive to negative impact, plateaus, as well as confidence intervals as a certainty measure. By employing modern machine learning techniques such as bagging and boosting, the EBM proves to work well in comparison to state-of-the-art ML models such as Random Forest and SVCs, while preserving the interpretability of predictions that Random Forest and SVCs are unable to deliver[30, 31].

A limitation of the present study is that we were not able to include even more patients into the analysis. This is of course a valid point of criticism, yet the data used for our analyses were manually collected and curated. The data was not simply exported from an electronic medical record where missing data are prevalent and validity of the information has not been confirmed. Missing data often needs to be imputed prior to analysis. As a result of the design of our study, we were largely able to reduce imputation of missing data, again adding to the significance of our findings. Another strength of our approach is the ability to determine a weight for individual patient factors with respect to an individual prediction. Whereas a logistic regression approach identifies factors of importance for an outcome in a cohort, the analysis does not allow the individual weighing of factors that are identified. Due to the imbalanced dataset (more patients survived ICU therapy, more patients did not need ECMO or RRT), our model is more reliable for predicting “survival” than “mortality”.

Conclusions

Yet, we present individual risk factors that can be combined for a prediction of “survival” during COVID-19 treatment and ICU course and these factors are weighed for importance. This has been done for the first time and will allow clinicians to weigh clinical criteria for outcome prediction in the patients treated.

List Of Abbreviations

CI confidence interval

CV cross-validation

DIVI German interdisciplinary association for intensive care and emergency medicine

EBM Explainable Boosting Machine

ECMO extracorporeal membrane oxygenation

GAM generalized additive model

GCS Glasgow Coma Scale

ICU Intensive Care Unit

IQR inter-quartile range

PCR Polymerase chain reaction

PEEP positive end expiratory pressure

RF Random Forest Classifier

RRT renal replacement therapy

SD standard deviation

SOFA Sequential organ failure assessment

SVC Support Vector Classifier

Declarations

Ethics approval and consent to participate

An ethics approval was obtained by all participating centers from their Institutional Review Boards (IRB) prior to data acquisition. German privacy regulations do not require individual patient consent for retrospective data acquisition or use. All prospectively enrolled patients gave informed consent.

Consent for publication

Not applicable.

Data availability

Data can be obtained from the authors upon reasonable request.

Competing interests

Harry Magunia	HM received a speaker's honorarium from CSL Behring (Germany) outside the submitted work.
Simone Lederer	SL has no competing interests to report.
Raphael Verbuecheln	RV has no competing interests to report.
Bryant Joseph Gilot	BJG has no competing interests to report.
Michael Koeppen	MK has no competing interests to report.
Helene A Haeberle	HH has no competing interests to report.
Valbona Mirakaj	VM has no competing interests to report.
Pascal Hoffmann	PH has no competing interests to report.
Gernot Marx	GM reports personal fees from Philips Health Care, personal fees from B. Braun, during the conduct of the study; and GM is co-founder of Clinomics GmbH, Germany.
Johannes Bickenbach	JB reports personal fees from Biotest AG , Germany, during the conduct of the study.
Boris Nohe	BN has no competing interests to report.
Michael Lay	ML has no competing interests to report.
Claudia Spies	CS reports no conflicts of interests within the submitted manuscript, she reports grants from outside the submitted manuscript from Drägerwerk AG & Co. KGaA, grants from Deutsche Forschungsgemeinschaft / German Research Society, grants from Deutsches Zentrum für Luft- und Raumfahrt e. V. (DLR) /German Aerospace Center, grants from Einstein Stiftung Berlin/ Einstein Foundation Berlin, grants from Gemeinsamer Bundesausschuss / Federal Joint Committee (G-BA), grants from Inneruniversitäre Forschungsförderung / Inner University Grants, grants from Projektträger im DLR / Project Management Agency, grants from Stifterverband/Non-Profit Society Promoting Science and Education, grants from WHOCC, grants from Baxter Deutschland GmbH, grants from Cytosorbents Europe GmbH, grants from Edwards Lifesciences Germany GmbH, grants from Fresenius Medical Care, grants from Grünenthal GmbH, grants from Masimo Europe Ltd., grants from Pfizer Pharma PFE GmbH, personal fees from Georg Thieme Verlag, grants from Dr. F. Köhler Chemie GmbH, grants from Sintetica GmbH, grants from Stifterverband für die deutsche Wissenschaft e.V. / Philips, grants from Stiftung Charité, grants from AGUETTANT Deutschland GmbH, grants from AbbVie Deutschland GmbH & Co. KG, grants from Amomed Pharma GmbH, grants from InTouch Health, grants from Copra System GmbH, grants from Correvio GmbH, grants from Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V., grants from Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin (DGAI, grants from Stifterverband für die deutsche Wissenschaft e.V. / Metronic, grants from Philips ElectronicsNederland BV, grants from BMG, grants from BMBF, grants from BMBF, grants from Deutsche Forschungsgemeinschaft / German Research Society, [illegible]vork; In addition, Dr. Spies has a patent 10 2014 215 211.9

	licensed, a patent 10 2018 114 364.8 licensed, a patent 10 2018 110 275.5 licensed, a patent 50 2015 010 534.8 licensed, a patent 50 2015 010 347.7 licensed, and a patent 10 2014 215 212.7 licensed.
Andreas Edel	AE has no competing interests to report.
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Thea Koch	TK has no competing interests to report.
Timo Brandenburger	TBra has no competing interests to report.
Detlef Kindgen-Milles	DKM has co competing interests to report.
Thorsten Brenner	TBre reports grants from Deutsche Forschungsgemeinschaft (DFG), Dietmar Hopp Stiftung and Stiftung Universitätsmedizin Essen, personal fees from CSL Behring GmbH, Schöchl medical education GmbH, Boehringer Ingelheim Pharma GmbH, Biotest AG, Baxter Deutschland GmbH, Astellas Pharma GmbH, B. Braun Melsungen AG and MSD Sharp & Dohme GmbH outside the submitted work.
Marc Berger	MB has no competing interests to report.
Kai Zacharowski	KZ has no competing interests to report.
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Christian S. Scheer	CS has no competing interests to report.
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Markus A. Weigand	MW has no competing interests to report.
Falk Fichtner	FF has no competing interests to report.
Carla Nau	CN has no competing interests to report.
Florian	FP has no competing interests to report.

Thomas Wiesmann	TW reports personal fees from Pajunk, Germany, personal fees from Vygon, Germany, outside the submitted work.
Christian Koch	CK has no competing interests to report.
Gerhard Schneider	GS has no competing interests to report.
Tobias Lahmer	TL has no competing interests to report.
Andreas Straub	AS reports personal fees from CSL Behring GmbH (Munich, Germany), personal fees from Schöchl Medical Education GmbH (Mattsee, Austria), personal fees from Aspen Germany GmbH (Munich, Germany), outside the submitted work.
Andreas Meiser	AM reports personal fees from Sedana Medical, Danderyd, Sweden, outside the submitted work.
Manfred Weiss	MW has no competing interests to report.
Bettina Jungwirth	BJ has no competing interests to report.
Frank Wappler	FW has no competing interests to report.
Patrick Meybohm	PM has no competing interests to report.
Johannes Herrmann	JH has no competing interests to report.
Nisar Malek	NM has no competing interests to report.
Oliver Kohlbacher	OK has no competing interests to report.
Stephanie Biergans	SB has no competing interests to report.
Peter Rosenberger	PR has no competing interests to report.

Funding

This work was funded by a grant from the Deutsche Forschungsgemeinschaft DFG RO 3671/8-1 to P.R. O.K. received funding from the Bundesministerium für Bildung und Forschung (BMBF) (DIFUTURE, 01ZZ1804D).

Funding of the participating centers:

Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Goethe University, Frankfurt, Germany: This work was funded by the grant Horizon 2020 Framework Programme, Call: H2020-SC1-PHE-CORONAVIRUS-2020-2-CNECT; Project: 101015930 — ENVISION to K.Z.

Authors' contributions

HM and PR developed the concept of this study including study design, data handling, data analysis, interpretation of results and drafting of the first manuscript. SB performed database planning and set-up. SL, SB and RV performed data analysis, statistics, and visualization. HM, PR, SL and SB verified the underlying data. SL and RV performed the machine-learning analysis. BJG supported database planning and data analysis. OK supported database planning and setup. BJG, SL, SB and NM critically reviewed the manuscript. MK, HH, VM, PM, GM, JB, BN, ML, CD, AE, FS, TR, CP, TS, TK, TBra, DKM, TBre, MB, KZ, EA, MP, OM; CS, DS, MW, FF, CN, FP, TW, CK, GS, TL, AS, AM, MW, BJ, FW, PM and JH reviewed patient charts, entered data into the electronic database and critically reviewed the manuscript. HM and PR finalized the manuscript. All authors approved the final version.

Acknowledgments

The authors and collaborators thank the employees of the participating intensive care units for their immeasurable efforts in the care of COVID-19 patients. The authors thank Nico Pfeifer, Medical Informatics, University of Tübingen, Germany, for the numerous fruitful discussions and valuable input on the application of ML methods. The authors thank Sascha Rehm and Christian Erhardt (meDIC, University Hospital of Tübingen, Germany) for server and REDCap administration and support.

The authors also greatly appreciate the contributions of the assistant scientists, data scientists, study nurses and physicians towards all aspects of data collection, data analysis and the general support of this study, namely: H. Gloeckner & M. Keim (Department of Anaesthesiology and Intensive Care Medicine, University Hospital Tübingen, Eberhard-Karls-University Tübingen, Tübingen, Germany), T. Simon (Department of Intensive Care Medicine, University Hospital RWTH Aachen, Aachen, Germany), S. Winands & N. Andrees & G. Vorderwülbecke & K. Steinecke (Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité - Universitätsmedizin Berlin, , corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Germany), K. Willemsen & B. Rahmel (Department of Anesthesiology/Intensive Care Medicine/Pain Therapy, Knappschaftskrankenhaus Bochum, Bochum, Germany), N. Theuerkauf & C. Bode & C.J. Schewe & U. Lohmer (Department of Anaesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn,

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Figures

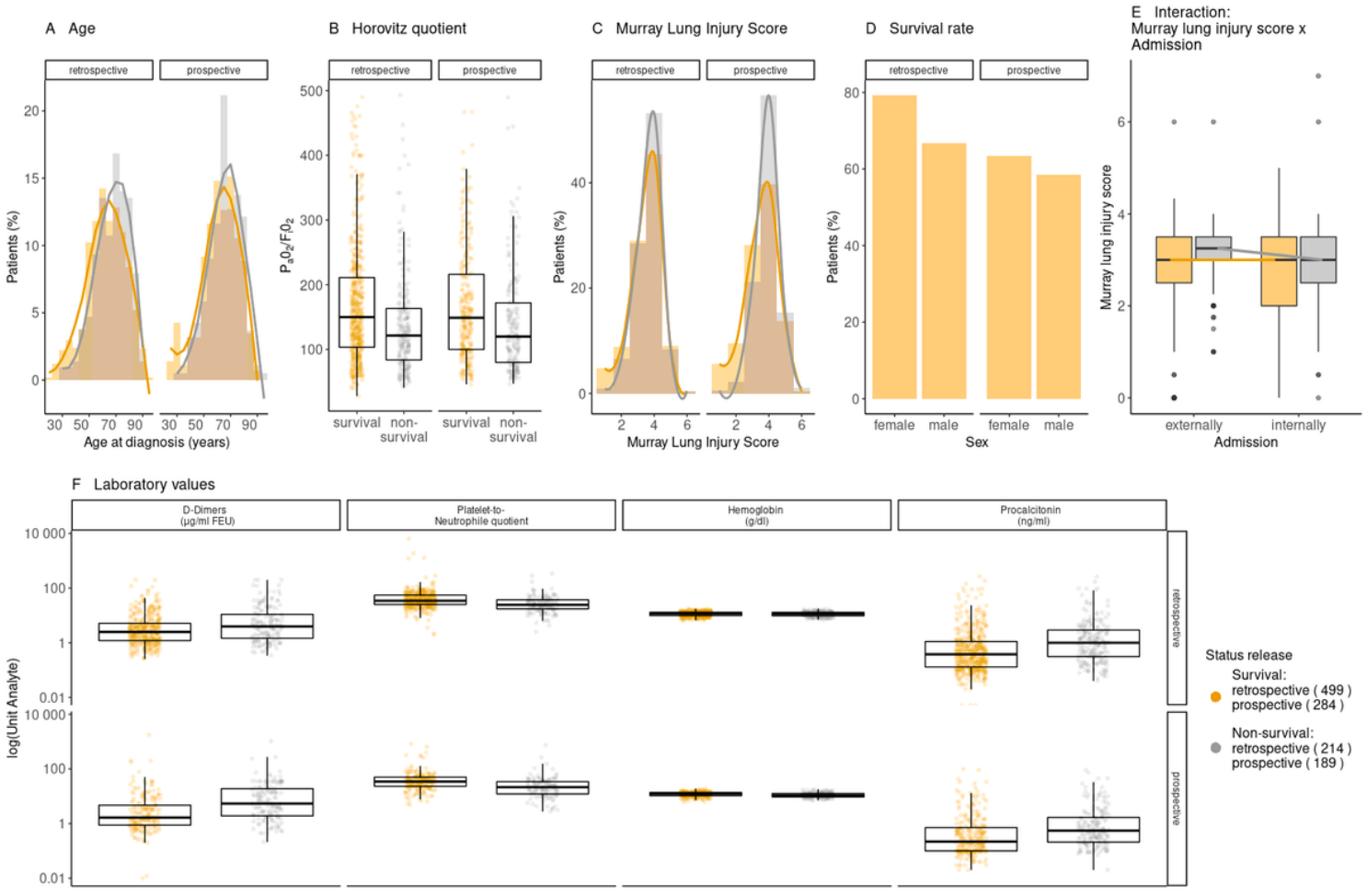


Figure 1

Descriptive data of patients included into the study population. (n=596 retrospective cohort and n=443 prospective cohort) A) Distribution Age B) Horovitz quotient at admission C) Murray lung injury score and SOFA score without GCS at admission D) Survival rates E) Interaction of Murray long injury score and admission status F) Laboratory values. Grey indicates patients that did not survive ICU therapy, orange indicates patients that did survive ICU therapy.

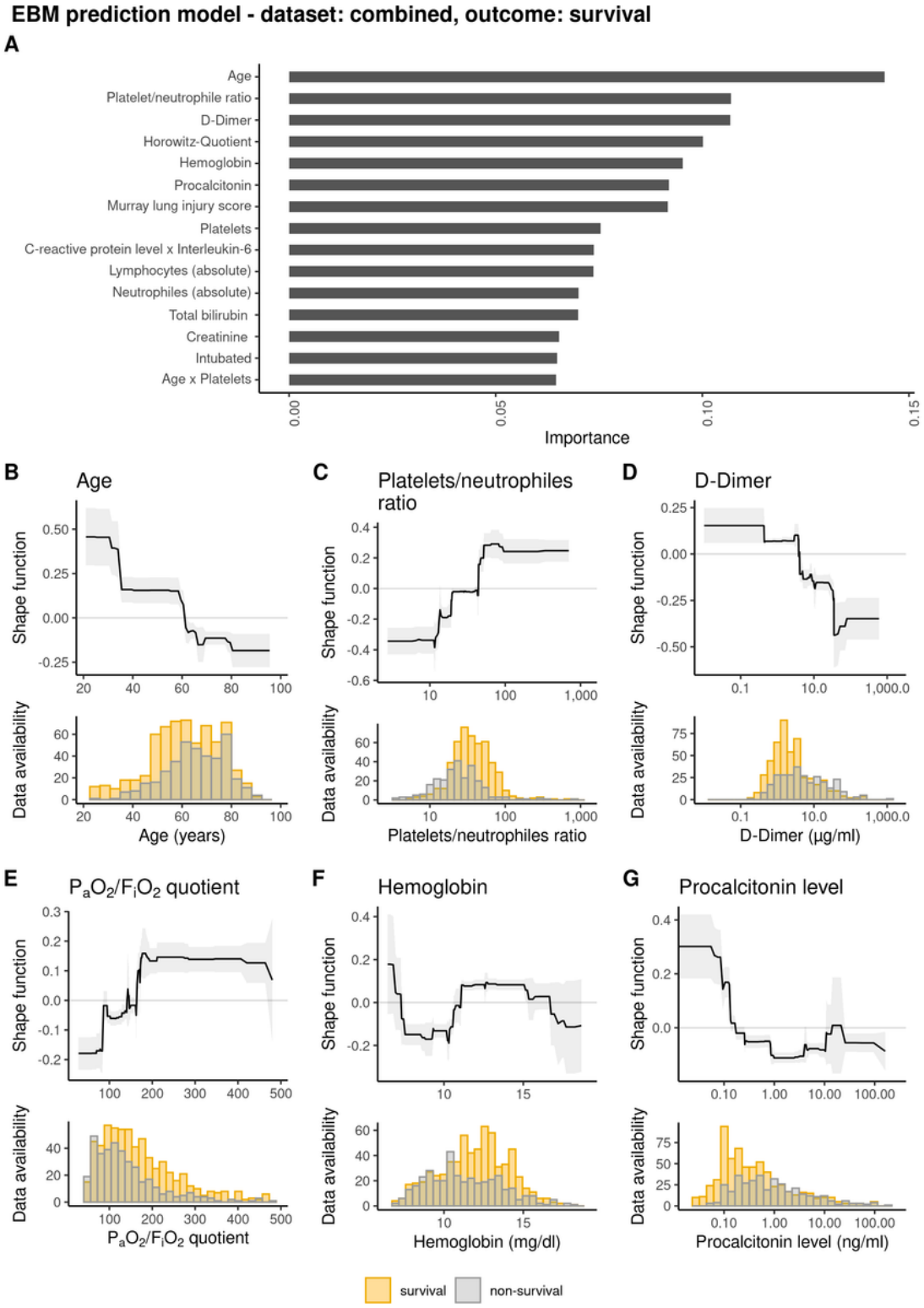
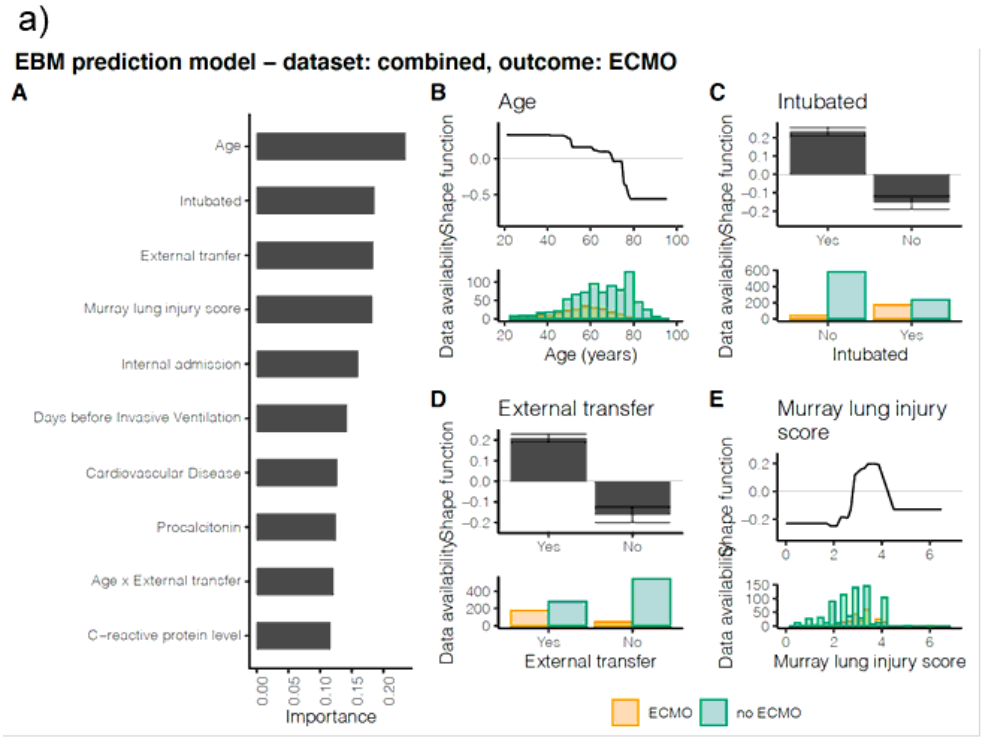


Figure 2

EBM prediction model showing importance of risk factors predicting “survival” in COVID-19 ICU patients including admission data. top) A) significant risk factors for outcome after analysis of admission data and weighed according to their importance for outcome. bottom) B) importance of age for outcome and distribution of age data C) platelet/neutrophil ratio and distribution of data on admission D) initial D-

determined on admission E) importance of Horovitz quotient

(PaO2/FiO2) for outcome and distribution of data on admission F) initial hemoglobin values and distribution of data on admission G) initial procalcitonin (PCT) serum values and distribution of data on admission. Grey indicates patients that did not survive ICU therapy, orange indicates patients that did survive ICU therapy.



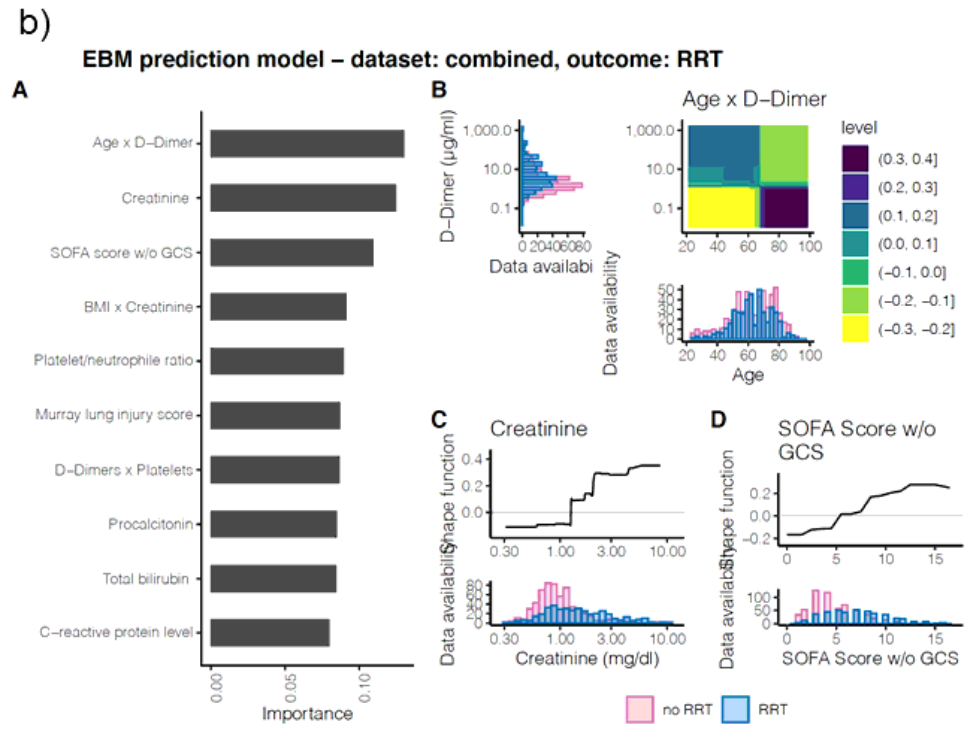


Figure 3

EBM prediction model showing importance of risk factors predicting need for ECMO or RRT in COVID-19 ICU patients including admission data. a) ECMO therapy left) A) significant risk factors for outcome after analysis of admission data and weighed according to their importance for outcome. right) B) importance of age for outcome and distribution of age data C) importance of status “intubated” on ICU admission and distribution of status D) importance of status “external transfer” on ICU admission and distribution of status E) importance of Murray lung injury score and distribution of MLIS data. Green indicates patients that did not receive ECMO therapy, orange indicates patients that did receive ECMO therapy. b) Renal Replacement Therapy (RRT) left) A) significant risk factors for outcome after analysis of admission data and weighed according to their importance for outcome. right) B) importance of the interaction of age and D-dimer level for outcome and distribution of data C) initial creatinine values and distribution of data determined on admission D) initial SOFA score w/o GCS and distribution of data determined on ICU admission. Blue indicates patients that did not receive RRT, red indicates patients that did receive RRT.

Supplementary Files

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