

# Machine learning-based prognostic model for in-hospital mortality of aortic dissection: Insights from an intensive care medicine perspective

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## Abstract

**Objective:** Aortic dissection (AD) is a severe emergency with high morbidity and mortality, necessitating strict monitoring and management. This retrospective study aimed to identify prognostic factors and establish predictive models for in-hospital mortality among AD patients in the intensive care unit (ICU).

**Methods:** We retrieved ICU admission records of AD patients from the Medical Information Mart for Intensive Care (MIMIC)-IV critical care data set and the eICU Collaborative Research Database. Functional data analysis was further applied to estimate continuous vital sign processes, and variables associated with in-hospital mortality were identified through univariate analyses. Subsequently, we employed multivariable logistic regression and machine learning techniques, including simple decision tree, random forest (RF), and eXtreme Gradient Boosting (XGBoost) to develop prognostic models for in-hospital mortality.

**Results:** Given 643 ICU admissions from MIMIC-IV and 501 admissions from eICU, 29 and 28 prognostic factors were identified from each database through univariate analyses, respectively. For prognostic model construction, 507 MIMIC-IV admissions were divided into 406 (80%) for training and 101 (20%) for internal validation, and 87 eICU admissions were included as an external validation group. Of the four models tested, the RF consistently exhibited the best performance among different variable subsets, boasting area under the receiver operating characteristic curves of 0.870 and 0.850. The models highlighted the mean 24-h fluid intake as the most potent prognostic factor.

**Conclusions:** The current prognostic models effectively forecasted in-hospital mortality among AD patients, and they pinpointed noteworthy prognostic factors, including initial blood pressure upon ICU admission and mean 24-h fluid intake.

## Keywords

Aortic dissection, in-hospital mortality, machine learning, blood pressure, fluid balance

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## Introduction

Aortic dissection (AD) is a severe medical condition marked by the separation of layers within the aortic wall, resulting in the formation of a false lumen, and demands swift diagnosis and intervention. Its incidence is relatively rare, estimated at approximately two to three cases per 100,000 individuals annually, and it rises to about 15 cases per 100,000 individuals annually in the elderly population.<sup>1</sup> Nevertheless, AD is associated with a significant mortality, reaching 20% within 24 h and 45%–56% within 30 days, even taking into account that approximately 17.6% patients died before hospital arrival.<sup>2</sup> Given the potential for hemodynamic instability, end-organ malperfusion, and complications such as rupture or expansion of the dissection, AD patients often require admission to the intensive care unit (ICU).

Effectively managing AD has been an intricate task, necessitating a multidisciplinary approach and tailored treatment strategies. Surgical interventions, including open repair or endovascular stent grafting, are the mainstay of treatment for dissections.<sup>3</sup> Previous studies have predominantly focused on the efficacy of interventions and certain parameters related to aortic lesions, such as diameter and false lumen volume.<sup>4</sup> Although these factors hold confirmed implications for patients' long-term prognosis, they fall short in addressing the imminent and potentially fatal risks associated with the rapidly evolving nature of AD in its acute phase.<sup>5,6</sup> Importantly, there is a lack of standardized severity risk scoring system for AD, which poses challenges in identifying patients' mortality risks during acute inpatient management. For both perioperative patients and individuals who are not candidates for CT angiography and surgery, early detection and monitoring of mortality risks may facilitate timely adjustment of treatment strategies and enable interventions at the appropriate juncture, thereby stabilizing the patients' condition and improve their prognosis.

However, such clinical decision-making heavily relies on the judgment of experienced clinicians and can lead to variations in clinical practice. Despite advances in both diagnosis and treatment, there remains a dearth of a comprehensive risk assessment scale for AD mortality. In this study, we focus on critically ill AD patients who require immediate and frequent assessment, aiming to provide insights into the determinants of mortality outcomes and promote the development of effective risk assessment strategies and planned interventions to improve patients' survival and in-hospital prognosis.

## Method

### Data source and ethics

This study is based on the Medical Information Mart for Intensive Care (MIMIC)-IV critical care data set<sup>7,8</sup> and

the eICU Collaborative Research Database.<sup>9,10</sup> One of the authors (XL) underwent the necessary credentialing process (Record ID 50038775) and obtained authorized access to the databases. XL signed the data use agreement and all authors were responsible for data extraction.

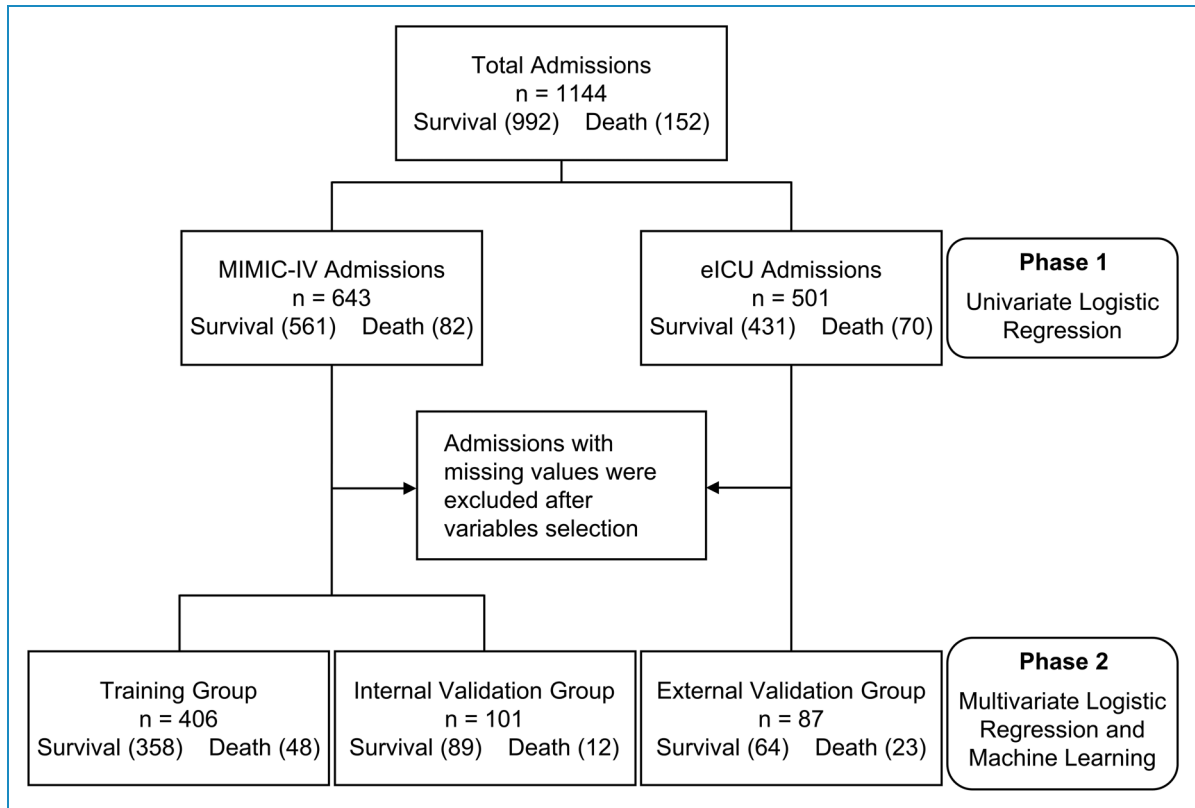
MIMIC-IV and eICU data were acquired from the PhysioNet<sup>11</sup> by PostgreSQL, version 13.8. Briefly, MIMIC-IV includes data on 76,540 ICU admissions at Beth Israel Deaconess Medical Center between 2008 and 2019. The eICU encompasses over 200,000 ICU admissions at critical care units across 208 hospitals throughout the United States from 2014 to 2015.

### Study population and data collection

The cohort included all AD patients over 18 years with the ICD codes: 44100–44103 and I7100–I7103. Some important etiological factors were identified using specific ICD codes: bicuspid aortic valve with 7464 and Q231, Marfan syndrome with 75982 and Q874, and Ehlers-Danlos syndrome with 75683 and Q796. A total of 1144 admissions were acquired in this study, with 643 ICU admissions from the MIMIC-IV and 501 from the eICU.

This study consisted of two phases (Figure 1). In phase 1, we screened the risk factors associated with in-hospital mortality using MIMIC-IV and eICU datasets, disregarding the missing data. In phase 2, known as the model-associated phase, the 506 ICU admissions from the MIMIC-IV dataset were randomly partitioned into a training group (80%) and an internal validation group (20%). The eICU dataset was utilized for external validation and 87 admissions were enrolled considering the data integrity. The training group was used to assess the combined effect of significant risk factors identified in phase 1, while the internal and external validation groups were employed to validate model predictability on in-hospital death.

We collected age, sex, weight, height, ethnicity at admission, the first laboratory examinations (blood gas, blood routine, basic metabolic panel, coagulation panel as well as some special items including total iron binding capacity (TIBC) and ferritin), comorbidity, dynamic heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). The acute physiology score III was calculated based on the first day examinations. The Charlson comorbidity index was acquired according to comorbidities. The mean 24-h fluid balance (intake or output) was calculated by dividing the total fluid intake or output by the number of days in the ICU. Given the discrete observation of patients' vital signs (i.e., HR, SBP, DBP, MAP), to mitigate the potential impact of vital sign fluctuations in the moments leading up to cardiac arrest on the prediction of ultimate mortality, we excluded data during the last 30 min before death. Meanwhile, we applied functional data analysis (FDA) to consistently estimate the continuous underlying vital sign



**Figure 1.** Study flowgram. Intensive care unit admissions of AD patients and subsequent disposition.

processes.<sup>12,13</sup> The FDA method has been shown to be a reliable estimation tool that can automatically recover the true underlying structure from discretely observed data, and has been used in various medical studies in dealing with vital signs.<sup>14,15</sup> The process of estimating the continuous-time underlying vital sign procedure resembled that of the previous study<sup>13</sup> and we then computed patients' vital signs on a per-minute basis after their admission to the ICU. From these data, we extracted the subsequent variables to characterize the dynamic risk factors of AD patients. The baseline (Base) vitals corresponded to the initial vital measurements taken after patients' admission. The average (Avg) vitals were calculated as the mean of the fitted vital observations over a 24-h period. Our previous study also indicated that variations in BP and HR have a potential role in predicting AD adverse events. Therefore, we also calculated indices reflecting changes in vital signs. The Delta vitals were determined as the average difference between the maximum and minimum vital sign values recorded within a 24-h span. The standard deviation (SD) of vitals was computed as the 24-h mean dispersion from the average of vital values. In-hospital death was defined as the occurrence of death during the patient's hospital stay, not limited to the ICU stay. It should be noted that patients might have multiple ICU admissions during a single hospitalization.

### Statistical analysis

Chi-square test (sex) and Fisher's exact test (ethnicity) were conducted for categorical variables, and Student's t test or ANOVA was utilized for continuous variables. The variables exclusion criteria for subsequent multivariable logistic regression included: (1) variables that show linear separability; (2) variables with missing values exceeding 20%; (3) variables that are not statistically significantly correlated to in-hospital death in univariate analysis ( $p$ -value > .05). Variables such as white blood cell (WBC) counts, red blood cell (RBC) counts and comorbidities like hypertension, diabetes and obstructive lung disease were specifically included in the final models due to their potential clinical relevance.<sup>16–18</sup> Among all these analyses,  $p$ -value < .05 was considered statistically significant.

To analyze the model's effectiveness, mitigate potential multicollinearity among predictors, and enhance understanding of the connections between variables and outcomes, we employed multiple statistical models using different subsets of variables. In particular, we opted for either MAP or separate measures of SBP and DBP as the blood pressure parameter(s), considering that distinct types of blood pressure could potentially have varying effects on AD.<sup>19</sup> For each analytical set, we employed five distinct variable subsets to investigate, refine, and

tailor our models. Subset (1) encompassed solely patients' baseline characteristics and laboratory test attributes, excluding any vital signs from the analysis. Subset (2) introduced baseline vital information, while subset (3) incorporated average vital measurements. In subsets (4) and (5), we utilized either Delta or SD to represent vital variations.

The four statistical algorithms used are: logistic regression, simple-decision tree, random forest (RF), and eXtreme Gradient Boosting (XGBoost). Among these, logistic regression is the benchmark model. It assumes a linear relationship between the independent variables (features) and the logarithm of the odds ratio, and uses the logistic to map the predicted values to the range [0, 1], which can be interpreted as the probability of death in this study. Despite its simplicity, interpretability, and computational efficiency, the logistic regression model is limited by its strict assumptions concerning the functional relationship between predictors and the log-odds of the response variable,<sup>20</sup> and hence, we also included several more flexible machine learning methods for this study. A simple decision tree represents a flowchart-like structure where each internal node corresponds to a feature, each branch represents a decision based on that feature, and each leaf node represents a predicted outcome. The tree is built by recursively splitting the data based on the feature that optimally separates the classes or reduces the variance. Decision trees are intuitive, interpretable, and can handle both categorical and numerical data. However, they can be prone to overfitting and might not capture complex relationships in the data.<sup>21</sup> RF is an ensemble learning technique that improves upon the decision tree's limitations. It constructs multiple decision trees and combines their predictions to achieve better accuracy and generalization, and the final prediction is made by aggregating the predictions of individual trees through voting.<sup>22</sup> On the other hand, XGBoost is an advanced gradient boosting algorithm that excels in predictive accuracy and efficiency. It builds an ensemble of weak prediction models, usually decision trees, in a sequential manner. Each new tree is trained to correct the errors made by the previous trees. XGBoost employs regularization techniques to prevent overfitting and includes features like handling missing values, cross-validation, and early stopping to enhance model performance.<sup>23</sup> All analyses were performed using R, version 4.2.0, and involved the following packages: "readxl," "stargazer," "xgboost," "caret," "pROC," "ggplot2," "rpart," "rpart.plot," "randomForest," "dplyr," "tidyr," "gbm," "sandwich," "gtsummary," and "lmtest."

## Results

### *Patients characteristics and risk factors screening*

Out of the 643 admissions for AD patients identified in the MIMIC-IV datasets, 82 resulted in in-hospital deaths. In the eICU datasets, out of the 501 admissions, 70 led to

in-hospital deaths. A total of 71 items were included to assess their association with in-hospital death (Table 1, Supplemental Table S1). No significant differences were observed in age, sex, weight and height. Based on the MIMIC-IV dataset, we identified 29 items as significant risk factors ( $p < .05$ ), including blood pH, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), mean 24-h fluid intake and output. Additional analyses were also performed using the eICU database, uncovering 28 significantly different items.

### *Multivariable logistic regression based on risk factors*

Given the inherent heterogeneity between the eICU and MIMIC-IV databases, the former was employed as an external validation group. The latter was divided into training and internal validation groups, with no significant differences observed in most variables (Supplemental Table S2). Importantly, among the admissions, 48 out of 406 (11.82%) in the training group, 12 out of 101 (11.88%) in the internal validation group and 23 out of 87 (26.44%) in the external validation group experienced in-hospital death.

To compare the sensitivity and specificity among different variable subsets, the area under the ROC curves (AUCs) were calculated. However, we did not identify an optimal subset that demonstrated superior performance in both the internal and external validation groups (Table 2, Supplemental Table S3). Notably, it was found that the mean 24 h intake, mean 24 h output, congenital disorders and aortic rupture showed significant associations with in-hospital mortality in all these subsets. These regressions also revealed the potential significance of heart failure, Base MAP and Base DBP.

### *Model comparison*

In both univariate and multivariate logistic regression analyses, we did not observe significant relationships between many BP and HR parameters and in-hospital mortality. Acknowledging the potential nonlinearity between vital sign parameters and in-hospital death, these variables were subsequently applied in the training of simple decision tree, RF and XGboost model. The sensitivity and specificity were also evaluated by AUC. Among the distinct types of blood pressure related regression, the AUCs for MAP in predicting in-hospital death were comparable to those of SBP combined with DBP. The RF models for SBP/DBP (3) and MAP (3) subsets exhibited the best performance in both the internal and external validation groups (Table 3, Supplemental Table S4). Therefore, the initial vital signs at admission and mean vital signs during ICU stay seemed critical to in-hospital death rather than variations in vital signs.

**Table 1.** Demographic and clinical characteristics of patients in MIMIC-IV.

Variable	MIMIC-IV				p-value <sup>a</sup>
	Survival (n = 561) excluding missing data	Missing (%)	Death (n = 82) excluding missing data	Missing (%)	
<b>Demographics</b>					
Age (years)	67.98 ± 14.60	0 (0.00)	70.89 ± 14.04	0 (0.00)	.08
Sex (%)					.58
Female	248 (44.21%)	0 (0.00)	33 (40.24%)	0 (0.00)	
Male	313 (55.79%)	0 (0.00)	49 (59.76%)	0 (0.00)	
Weight (kg)	82.37 ± 22.15	19 (3.39)	82.57 ± 26.50	7 (8.54)	.95
Height (cm)	170.64 ± 11.15	178 (31.73)	169.16 ± 11.18	24 (29.27)	.35
Ethnicity (%)					<.001
African	94 (16.76%)	0 (0.00)	6 (7.32%)	0 (0.00)	
Asian	17 (3.03%)	0 (0.00)	5 (6.10%)	0 (0.00)	
Hispanic	34 (6.06%)	0 (0.00)	1 (1.22%)	0 (0.00)	
Indian	3 (0.53%)	0 (0.00)	0 (0.00%)	0 (0.00)	
White	321 (57.22%)	0 (0.00)	35 (42.68%)	0 (0.00)	
Other <sup>b</sup> /unknown	92 (16.40%)	0 (0.00)	35 (42.68%)	0 (0.00)	
Location of dissection					.88
Abdominal	93 (16.58%)	0 (0.00)	12 (14.63%)	0 (0.00)	
Thoracic	331 (59.00%)	0 (0.00)	48 (58.54%)	0 (0.00)	
Both	111 (19.79%)	0 (0.00)	17 (20.73%)	0 (0.00)	
Unspecified	26 (4.63%)	0 (0.00)	5 (6.10%)	0 (0.00)	
<b>First laboratory examinations</b>					
pH	7.37 ± 0.09	191 (34.05)	7.28 ± 0.15	8 (9.76)	<.001
Basophils (K/ $\mu$ L)	0.03 ± 0.03	159 (28.34)	0.03 ± 0.03	25 (30.49)	.34
Eosinophils (K/ $\mu$ L)	0.12 ± 0.16	159 (28.34)	0.07 ± 0.10	25 (30.49)	.005
Lymphocytes (K/ $\mu$ L)	1.38 ± 0.80	159 (28.34)	1.40 ± 1.29	25 (30.49)	.89
Monocytes (K/ $\mu$ L)	0.59 ± 0.39	159 (28.34)	0.71 ± 0.54	25 (30.49)	.14

(continued)

Table 1. Continued.

Variable	MIMIC-IV				<i>p</i> -value <sup>a</sup>
	Survival ( <i>n</i> = 561) excluding missing data	Missing (%)	Death ( <i>n</i> = 82) excluding missing data	Missing (%)	
Neutrophils (K/ $\mu$ L)	9.16 $\pm$ 5.19	159 (28.34)	10.31 $\pm$ 5.62	25 (30.49)	.15
Basophils (%)	0.33 $\pm$ 0.28	158 (28.16)	0.28 $\pm$ 0.24	25 (30.49)	.12
Eosinophils (%)	1.23 $\pm$ 1.69	158 (28.16)	0.80 $\pm$ 1.24	25 (30.49)	.02
Lymphocytes (%)	14.11 $\pm$ 8.90	158 (28.16)	12.59 $\pm$ 9.64	25 (30.49)	.27
Monocytes (%)	5.55 $\pm$ 3.16	158 (28.16)	5.62 $\pm$ 3.04	25 (30.49)	.88
Neutrophils (%)	77.64 $\pm$ 11.45	158 (28.16)	78.72 $\pm$ 10.77	25 (30.49)	.49
Platelets (K/ $\mu$ L)	212.88 $\pm$ 105.16	5 (0.89)	195.68 $\pm$ 80.31	2 (2.44)	.09
WBC counts (K/ $\mu$ L)	11.29 $\pm$ 10.78	5 (0.89)	12.66 $\pm$ 5.84	2 (2.44)	.09
RBC counts (M/ $\mu$ L)	3.79 $\pm$ 0.82	5 (0.89)	3.61 $\pm$ 0.89	2 (2.44)	.09
Hematocrit (%)	34.32 $\pm$ 6.96	5 (0.89)	33.20 $\pm$ 7.61	2 (2.44)	.22
Hemoglobin (g/dL)	11.33 $\pm$ 2.44	5 (0.89)	10.77 $\pm$ 2.54	2 (2.44)	.07
MCH (pg)	29.99 $\pm$ 2.51	5 (0.89)	30.11 $\pm$ 2.36	2 (2.44)	.68
MCHC (g/ $\mu$ L)	32.97 $\pm$ 1.62	5 (0.89)	32.47 $\pm$ 1.83	2 (2.44)	.02
MCV (fL)	91.04 $\pm$ 6.51	5 (0.89)	92.88 $\pm$ 6.74	2 (2.44)	.02
RDW (%)	14.48 $\pm$ 1.82	5 (0.89)	15.15 $\pm$ 2.01	2 (2.44)	.006
Fibrinogen (mg/dL)	217.40 $\pm$ 128.39	333 (59.36)	227.55 $\pm$ 172.94	35 (42.68)	.70
INR	1.39 $\pm$ 0.62	23 (4.10)	1.73 $\pm$ 1.62	1 (1.22)	.07
PT (s)	15.26 $\pm$ 6.56	23 (4.10)	18.75 $\pm$ 16.53	1 (1.22)	.06
APTT (s)	37.14 $\pm$ 22.58	23 (4.10)	47.25 $\pm$ 35.29	1 (1.22)	.01
Creatinine (mg/dL)	1.28 $\pm$ 1.22	5 (0.89)	2.01 $\pm$ 2.23	2 (2.44)	.005
ALT (IU/L)	54.91 $\pm$ 175.03	225 (40.11)	377.42 $\pm$ 1284.31	17 (20.73)	.05
AST (IU/L)	79.76 $\pm$ 221.06	220 (39.22)	487.55 $\pm$ 1572.22	17 (20.73)	.04
Albumin (g/dL)	3.34 $\pm$ 0.68	281 (50.09)	2.87 $\pm$ 0.76	31 (37.80)	<.001
Bicarbonate (mmol/L)	23.89 $\pm$ 3.62	5 (0.89)	20.77 $\pm$ 5.66	2 (2.44)	<.001
Calcium (mg/dL)	8.65 $\pm$ 0.74	28 (4.99)	8.70 $\pm$ 1.15	3 (3.66)	.67
Chloride (mmol/L)	103.65 $\pm$ 5.34	5 (0.89)	104.45 $\pm$ 5.87	2 (2.44)	.25

(continued)

Table 1. Continued.

Variable	MIMIC-IV				p-value <sup>a</sup>
	Survival (n = 561) excluding missing data	Missing (%)	Death (n = 82) excluding missing data	Missing (%)	
Sodium (mmol/L)	138.93 ± 4.00	5 (0.89)	139.29 ± 6.03	2 (2.44)	.60
Potassium (mmol/L)	4.26 ± 0.77	5 (0.89)	4.52 ± 1.08	2 (2.44)	.03
Phosphate (mg/dL)	3.75 ± 1.00	30 (5.35)	4.85 ± 2.17	3 (3.66)	<.001
Magnesium (mg/dL)	2.08 ± 0.42	16 (2.85)	2.18 ± 0.53	3 (3.66)	.13
Iron (µg/dL)	45.19 ± 40.15	530 (94.47)	68.44 ± 59.39	73 (89.02)	.30
TIBC (µg/dL)	226.44 ± 79.20	534 (95.19)	130.00 ± 34.47	73 (89.02)	<.001
Ferritin (ng/mL)	1691.77 ± 5137.53	539 (96.08)	6259.00 ± 10557.00	73 (89.02)	.25
APSIII	44.37 ± 21.31	0 (0.00)	71.84 ± 30.18	0 (0.00)	<.001
<b>Comorbidity (%)</b>					
Congenital disorders <sup>c</sup>	27 (4.81%)	0 (0.00)	2 (2.44%)	0 (0.00)	.49
Aortic rupture	12 (2.14%)	0 (0.00)	1 (1.22%)	0 (0.00)	.90
Shock	36 (6.42%)	0 (0.00)	22 (26.83%)	0 (0.00)	<.001
Hypertension	362 (64.53%)	0 (0.00)	44 (53.66%)	0 (0.00)	.06
Diabetes	79 (14.08%)	0 (0.00)	16 (19.51%)	0 (0.00)	.20
Heart failure	114 (20.32%)	0 (0.00)	33 (40.24%)	0 (0.00)	<.001
Obstructive lung disease	93 (16.58%)	0 (0.00)	14 (17.07%)	0 (0.00)	.91
CCI	5.76 ± 2.28	0 (0.00)	6.66 ± 2.65	0 (0.00)	.004
<b>Heart rate (bpm)</b>					
Base HR	79.79 ± 15.68	6 (1.07)	84.56 ± 20.45	4 (4.88)	.0504
Avg HR	79.29 ± 13.83	6 (1.07)	83.85 ± 16.69	4 (4.88)	.02
Delta HR	26.32 ± 14.92	6 (1.07)	34.64 ± 24.18	4 (4.88)	.004
Sd HR	6.42 ± 3.51	7 (1.25)	8.58 ± 5.50	4 (4.88)	.001
<b>Blood pressure (mmHg)</b>					
Base SBP	124.13 ± 23.60	6 (1.07)	120.69 ± 24.78	4 (4.88)	.25
Base DBP	66.25 ± 15.89	6 (1.07)	67.81 ± 21.64	4 (4.88)	.54
Base MAP	83.04 ± 16.71	6 (1.07)	85.47 ± 25.55	4 (4.88)	.42

(continued)

Table 1. Continued.

Variable	MIMIC-IV				p-value <sup>a</sup>
	Survival (n = 561) excluding missing data	Missing (%)	Death (n = 82) excluding missing data	Missing (%)	
Avg SBP	121.76 ± 16.72	6 (1.07)	119.17 ± 25.84	4 (4.88)	.39
Avg DBP	61.97 ± 11.64	6 (1.07)	63.52 ± 22.37	4 (4.88)	.55
Avg MAP	78.88 ± 12.48	6 (1.07)	78.03 ± 21.41	4 (4.88)	.73
Delta SBP	49.09 ± 22.46	6 (1.07)	57.31 ± 28.74	4 (4.88)	.02
Delta DBP	34.00 ± 21.07	6 (1.07)	38.06 ± 24.60	4 (4.88)	.17
Delta MAP	38.28 ± 21.91	6 (1.07)	45.81 ± 30.15	4 (4.88)	.04
Sd SBP	11.36 ± 4.45	6 (1.07)	13.72 ± 6.03	4 (4.88)	.001
Sd DBP	7.64 ± 4.42	6 (1.07)	8.70 ± 5.59	4 (4.88)	.11
Sd MAP	8.54 ± 4.49	6 (1.07)	10.38 ± 6.92	4 (4.88)	.03
<b>Others</b>					
Mean 24 h intake (mL)	3214.76 ± 2016.14	84 (14.97)	5602.02 ± 4851.19	20 (24.39)	<.001
Mean 24 h output (mL)	1956.65 ± 1134.89	90 (16.04)	1548.35 ± 1358.78	21 (25.61)	.03

WBC, white blood cell; RBC, red blood cell; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TIBC, total iron binding capacity; APSIII, acute physiology score III; CCI, Charlson comorbidity index.

<sup>a</sup>Chi-squared test (sex) and Fisher's exact test (ethnicity) for categorical variables and Student's t-test for continuous variables.

<sup>b</sup>The other category included Pacifier islander and patient with multiple ethnicity.

<sup>c</sup>Congenital disorders include bicuspid aortic valve, Marfan syndrome, and Ehlers-Danlos syndrome.

### Final predictive models and online calculator

Considering the best performance of RF models for SBP/DBP (3) and MAP (3) among all models, the two variable importance plots depicting the contribution of different features to the outcome were generated based on how often a feature is used for splitting nodes in the trees and how much those splits improve the model's performance. In brief, a higher number implies a higher importance of the variable. The mean 24-h fluid intake consistently remained the most important factor in both models, followed by vital sign parameters and blood phosphate (Figure 2). Partial dependence plots illustrate the marginal effect of a variable on the predicted probability while controlling for the effects of other variables in the model. In both RF models, we observed a nonlinear U-shaped relationship between BP and HR parameters and the risk of mortality, indicating that both excessively high and low BP and HR are associated with increased mortality, consistent with clinical practice (Supplemental Figures S1 and S2). Therefore, we

chose the RF models for SBP/DBP (3) and MAP (3) as the final predictive models.

Notably, the entire models essentially evaluate the risk of mortality within a specific period, rather than being limited to the moment of ICU admission. Therefore, by comparing differences in mortality risk between adjacent time intervals, clinicians can comprehensively assess the recent treatment effects and determine whether treatment strategies need adjustment. Based on our best RF models trained on SBP/DBP(3) and MAP(3) subsets, we have developed an online calculator available at <https://aortic-disease-model.com/>. This tool allows users to input the values of 26 variables for SBP/DBP(3) or 24 variables for MAP(3) and automatically calculates the mortality risk for the specific period of the AD patient.

### Discussion

This study comprehensively compiled the relationships between various laboratory test results as well as vital

**Table 2.** Multivariable logistic regression among different variable subsets about systolic and diastolic blood pressure.

SBP/DBP subsets					
	(1)	(2)	(3)	(4)	(5)
Age	0.018 (0.016) <sup>a</sup>	0.024 (0.016)	0.023 (0.016)	0.016 (0.017)	0.015 (0.017)
Location: thoracic <sup>b</sup>	0.843 (0.990)	1.008 (1.010)	1.035 (1.016)	1.322 (0.979)	1.134 (1.020)
Location: both	0.851 (1.062)	0.834 (1.080)	0.814 (1.085)	1.318 (1.081)	1.189 (1.104)
Location: unspecified	0.598 (1.016)	0.753 (1.036)	0.738 (1.050)	1.125 (1.012)	0.962 (1.053)
WBC counts	0.019 (0.029)	0.026 (0.030)	0.026 (0.030)	0.027 (0.032)	0.033 (0.031)
RBC counts	0.035 (0.223)	-0.059 (0.227)	-0.057 (0.229)	-0.130 (0.244)	-0.143 (0.238)
MCV	0.014 (0.031)	0.009 (0.030)	0.009 (0.030)	0.011 (0.030)	0.013 (0.029)
RDW	0.086 (0.094)	0.091 (0.094)	0.089 (0.095)	0.147 (0.100)	0.147 (0.101)
APTT	0.001 (0.006)	0.001 (0.006)	0.001 (0.006)	-0.002 (0.008)	0.0004 (0.007)
Creatinine	0.026 (0.096)	-0.016 (0.099)	-0.007 (0.101)	-0.029 (0.104)	-0.033 (0.103)
Bicarbonate	-0.059 (0.042)	-0.061(0.043)	-0.059(0.043)	-0.048(0.048)	-0.059 (0.050)
Potassium	-0.276 (0.273)	-0.205(0.293)	-0.209(0.292)	-0.244(0.308)	-0.227 (0.288)
Phosphate	0.225 (0.163)	0.246(0.169)	0.235(0.173)	0.284(0.170)	0.270 (0.175)
Mean 24 h intake	0.0003*** (0.0001)	0.0004*** (0.0001)	0.0004*** (0.0001)	0.0004*** (0.0001)	0.0003*** (0.0001)
Mean 24 h output	-0.001** (0.0002)	-0.001** (0.0002)	-0.001** (0.0002)	-0.001** (0.0002)	-0.001** (0.0002)
Congenital disorders	-14.875*** (0.725)	-14.593*** (0.729)	-14.612*** (0.733)	-14.800*** (0.705)	-14.663*** (0.656)
Aortic rupture	-15.067*** (0.921)	-14.689*** (0.992)	-14.743*** (1.031)	-14.109*** (0.976)	-13.919*** (0.957)
Shock	-0.024 (0.861)	0.085 (0.798)	0.041 (0.815)	0.004 (0.884)	0.038 (0.847)

(continued)

Table 2. Continued.

SBP/DBP subsets					
(1)	(2)	(3)	(4)	(5)	(5)
Hypertension	-0.047(0.455)	-0.112 (0.441)	-0.112 (0.444)	-0.189 (0.476)	-0.142 (0.486)
Diabetes	-0.410 (0.515)	-0.403 (0.537)	-0.407 (0.536)	-0.232 (0.517)	-0.176 (0.516)
Heart failure	0.909* (0.429)	0.907* (0.423)	0.943* (0.455)	0.911* (0.459)	0.876 (0.459)
Obstructive lung disease	0.779 (0.501)	0.741 (0.543)	0.740 (0.546)	0.761 (0.564)	0.755 (0.592)
Base HR	∖	0.004 (0.015)	0.004 (0.015)	-0.007 (0.014)	-0.007 (0.015)
Base SBP	∖	0.0002 (0.010)	-0.0003 (0.011)	-0.003 (0.011)	-0.003 (0.012)
Base DBP	∖	0.029*(0.013)	0.030* (0.015)	0.037* (0.017)	0.036* (0.017)
Avg HR	∖	∖	0.002 (0.016)	-0.010 (0.017)	-0.014 (0.017)
Avg SBP	∖	∖	0.001 (0.015)	-0.0003 (0.012)	-0.014 (0.014)
Avg DBP	∖	∖	-0.005 (0.018)	-0.010(0.016)	0.002 (0.017)
Delta HR	∖	∖	∖	0.042** (0.015)	∖
Delta SBP	∖	∖	∖	0.009 (0.008)	∖
Delta DBP	∖	∖	∖	-0.007 (0.011)	∖
Sd HR	∖	∖	∖	∖	0.198** (0.063)
Sd SBP	∖	∖	∖	∖	0.112* (0.045)
Sd DBP	∖	∖	∖	∖	-0.106* (0.046)
Constant	-5.897 (4.493)	-8.525 (4.668)	-8.465 (4.978)	-8.486 (5.188)	-7.433 (5.156)
AUC in the internal validation group	0.720 (0.522-0.918) <sup>c</sup>	0.739 (0.552-0.926)	0.726 (0.536-0.916)	0.735 (0.545-0.925)	0.718 (0.527-0.909)

(continued)

**Table 2.** Continued.

SBP/DBP subsets					
(1)	(2)	(3)	(4)	(5)	
AUC in the external validation group	0.614 (0.479–0.749)	0.575 (0.6–0.714)	0.581 (0.442–0.720)	0.590 (0.454–0.727)	0.578 (0.437–0.719)

SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; RDW, red cell distribution width; APTT, activated partial thromboplastin time; HR, heart rate.

<sup>a</sup>Data were shown as coefficients (standard error of coefficients).

<sup>b</sup>Compared to abdominal aortic dissection.

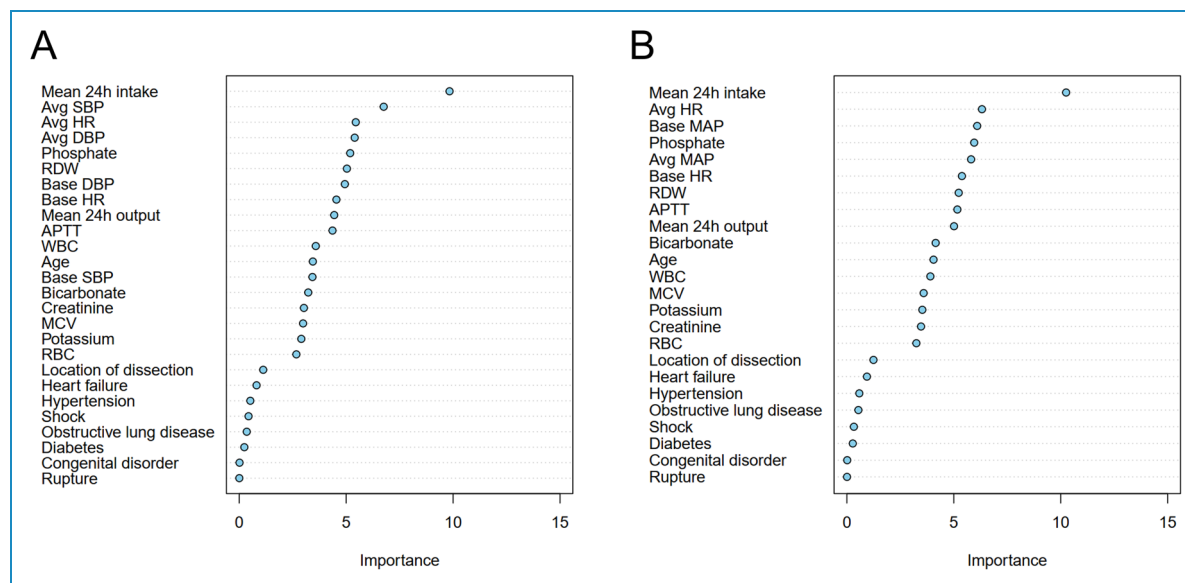
<sup>c</sup>Data were shown as AUC (95% confidence interval).

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .

**Table 3.** Model comparison among four different analyses about systolic and diastolic blood pressure.

		AUC of SBP/DBP subsets				
		(1)	(2)	(3)	(4)	(5)
Internal validation group	Logistic regression	0.720 [0.522–0.918] <sup>a</sup>	0.739 [0.552–0.926]	0.726 [0.536–0.916]	0.735 [0.545–0.925]	0.718 [0.527–0.909]
	Simple decision tree	0.644 [0.426–0.861]	0.812 [0.673–0.951]	0.619 [0.491–0.748]	0.619 [0.491–0.748]	0.619 [0.491–0.748]
	Random forest	0.844 [0.663–1.00]	0.858 [0.724–0.991]	0.870 [0.744–0.996]	0.841 [0.708–0.974]	0.833 [0.685–0.981]
	XGBoost	0.835 [0.669–1.00]	0.789 [0.603–0.975]	0.739 [0.563–0.915]	0.856 [0.739–0.974]	0.842 [0.722–0.962]
External validation group	Logistic regression	0.614 [0.479–0.749]	0.575 [0.6–0.714]	0.581 [0.442–0.720]	0.590 [0.454–0.727]	0.578 [0.437–0.719]
	Simple decision tree	0.487 [0.347–0.628]	0.628 [0.486–0.77]	0.492 [0.477–0.507]	0.492 [0.477–0.507]	0.492 [0.477–0.507]
	Random forest	0.730 [0.622–0.839]	0.765 [0.659–0.871]	0.767 [0.658–0.876]	0.756 [0.638–0.874]	0.753 [0.637–0.869]
	XGBoost	0.666 [0.537–0.795]	0.665 [0.526–0.804]	0.671 [0.529–0.812]	0.671 [0.548–0.794]	0.646 [0.511–0.78]

<sup>a</sup>Data were shown as AUC [95% confidence interval].

**Figure 2.** Random forest variable importance plots. (A) Variables in SBP/DBP (3) subset. (B) Variables in MAP (3) subset.

signs and in-hospital death in AD patients from public critical care databases. Within the scope of multivariable logistic regression, we identified the potential predictability of parameters such as 24-h intake and output, heart

failure, baseline MAP and DBP on in-hospital death. Furthermore, our study employed machine learning techniques to develop and optimize the predictive model for AD patients, highlighting the significance of baseline

and mean blood pressure and heart rate in predicting patient outcomes.

AD is a critical medical emergency with high mortality, necessitating prompt treatment to prevent acute and chronic complications. Apart from open surgery and endovascular repair, early initiation of medical treatment and close monitoring also hold significance in improving survival rates.<sup>24,25</sup> Research efforts have been dedicated to exploring biomarkers for AD and predictive indicators of disease severity to enable timely diagnosis and identification of high-risk patients.<sup>26–28</sup> In addition to recognizing high-risk clinical signs and symptoms,<sup>29</sup> the relationship between laboratory examinations (such as blood gas, blood routine, blood electrolyte and basic metabolic panel) and AD has been a subject of interest in medical research. These laboratory tests play crucial roles in differential diagnosis and detecting complications and can provide valuable insights into disease progression and prognosis. However, most existing studies focusing on the laboratory tests are single-center studies, lacking external validation.<sup>30,31</sup> In line with the recommended tests for patients with acute AD according to ESC 2014 guideline, our study identified creatinine, ALT, and AST as important factors for AD prognosis, indicating impaired renal and liver perfusion.<sup>18</sup> However, we did not observe significant differences in WBC and RBC counts in the multivariable logistic regressions, consistent with the previous study.<sup>30</sup> Meanwhile, based on the impact of serum mixtures of metals on AD incidence,<sup>32</sup> we explored the relationship between various blood electrolytes as well as metal ions and mortality. Although calcium and magnesium levels were lower in AD patients compared to healthy individuals,<sup>33</sup> our results did not show significant differences between the death and survival groups.

Through multivariable analyses, our research identified the optimal variable subset and the best machine learning model. While XGBoost is renowned for its exceptional predictive accuracy and efficiency in some medical-related topics, such as the study conducted by Klaudel et al., which compared five advanced machine learning methods when identifying the most significant predictors of dissection and found that XGBoost achieves the optimal balance between positive predictive value (precision) and sensitivity (recall),<sup>34</sup> it's important to note that no single method is universally superior for all problems. Unlike studies focusing on a single dataset, which allow for tailoring hyperparameters specific to that dataset, our study explored five subsets using XGBoost while sharing hyperparameters across them. However, achieving a high level of performance with XGBoost necessitates meticulous hyperparameter tuning for each dataset.<sup>23</sup> Consequently, the RF algorithm, known for its robustness, emerges as a superior method for some subsets in our study.<sup>22</sup> Furthermore, our goal is to select a model with wide applicability across different datasets

and the robustness of RF aligns well with our objective of achieving generalizability and practical utility.

Consistent with current perspectives, effective blood pressure management in AD patients remains crucial, as highlighted in the ACC/AHA 2022 guideline where anti-impulse therapy with invasive monitoring of blood pressure is recommended as the initial treatment to reduce aortic wall stress.<sup>35</sup> In this study, we conducted multivariable logistic regression and machine learning analyses to compare the predictive efficacy of different blood pressure parameters. In contrast to blood pressure variability (standard deviations and ranges), baseline blood pressure at ICU admission and mean blood pressure during ICU stay were more significant in predicting in-hospital mortality.

In the final model, there are indicators that we cannot control, such as initial BP, which has relatively clear predictive significance. However, for those modifiable factors, we need to proceed with caution to determine whether they could be treatment targets to improve AD prognosis. The relationship between BP and the progression of AD has been well-recognized,<sup>19</sup> enabling antihypertensive medications to be an effective therapy in treating AD. Although our study revealed that 24-h fluid intake remained consistently the most significant risk factor across different variable subsets, it is important to clarify whether it is the compromised circulatory system caused by severe AD that prompts clinicians to increase fluid intake, or if excessive fluid intake exacerbates AD. Thus, before considering restricting fluid intake as a potential treatment measure, further prospective clinical trials are needed to compare AD prognosis by implementing different fluid management strategies.

While our study drew upon data from reputable public databases, it is important to note certain limitations in the data structure, primarily designed for ICU patients. The ICD diagnosis and procedure codes constrained our access to specific features relevant to AD, such as the Stanford/Debaquey classification and detailed aneurysm imaging parameters, as well as information on surgical or endovascular repair procedures. Consequently, our findings are better suited for monitoring and intensive care of a broad range of critically ill patients rather than targeted specialized management. Additionally, the diagnostic information of all these records is based on discharge diagnoses, which presented challenges in establishing the timing of AD and associated complications, such as heart failure. This complexity posed difficulties for causal inference in our study. Furthermore, the data structure limited our ability to identify the extensive resuscitative fluid administered in the final moments of life. Consequently, the role of fluid intake, considered a pivotal factor in our predictive model, may not entirely reflect its anticipated significance. These limitations could introduce bias to our analyses. As such, the findings warrant further validation through well-designed prospective studies.

## Conclusion

In summary, our study validated certain risk factors associated with in-hospital death in patients with AD, such as creatinine, ALT, and AST. Through multivariable logistic regression and machine learning techniques, we found the RF models exhibited the best performance and identified that initial and mean blood pressure and heart rate demonstrated the highest predictive efficacy. Notably, the mean 24-h fluid intake was the most important variable. The final models aimed to serve as both an initial inpatient risk assessment tool upon admission and as a real-time monitoring system for assessing the evolving mortality risk during the treatment process based on temporal data.

**Authors' Notes:** Jiahao Lei, Zhuojing Zhang, Yixuan Li, Zhaoyu Wu have contributed equally to this work.

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**Author contributions:** JL, XY, GL, PQ, TC, and XL conceived and designed the study, JL, ZW, HP, JH, and XL acquired the data, ZZ, YL, ZX, and PQ conducted the analyses, JL, ZZ, JY, ZW, and PQ drafted the manuscript, HP, ZX, XY, JH, GL, TC, and XL revised it critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

**Data availability:** The original data were public in PhysioNet (<https://physionet.org/content/mimiciv/2.0/>; <https://physionet.org/content/eicu-crd/2.0/>) and the codes used for data extraction and analyses were available from the corresponding authors upon reasonable request.

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**Ethics approval:** Permission to use the data was obtained for both databases (Record ID 50038775) and the data use agreement was available in Supplemental Material. The patient consent was waived as the data are wholly deidentified and retrospective from public databases.

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