CHEST Online Supplement

Late Vasopressor Administration in Patients in the ICU

A Retrospective Cohort Study

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e-Appendix 1: Exclusion criteria

Patients were excluded if they were under the age of 18, documented to have a pre-existing neuromuscular disease (**e-Table 1**) which inherently contribute to prolonged recoveries, were previously in a VA ICU in the past 12 months in order to more reliably distinguish early and later time periods of critical illness, or if they had a pre-existing tracheostomy because of the association with the need for prolonged mechanical ventilation.[17] Those with new tracheostomies were included if they remained in the ICU.

e-Table 1. ICD-9 and ICD-10 codes

	ICD-9 codes	ICD-10 codes
Myasthenia gravis	358.00, 358.0	G70.00, G70.01
Amyotrophic lateral sclerosis	335.20	G12.21
Multiple sclerosis	340, 341.9	G35, G37.9
Tracheostomy	V44.0, 519.09	Z93.0, J95.01, J95.03, J95.04
Cerebral vascular accident	434.91, 433, 436, 434.11, 430, 431, 432, 435	I63.50, I63.40, I67.89, I60.9, I61.9, I60*, I61*, I62*, I63*
Spinal cord injuries	952, 336.9, 344	S14*, S24*, S34*, G82*

e-Appendix 2: Sepsis present on admission

Patients were identified as having sepsis on ICU admission utilizing the CDC definition.

Only 9.2% (N=14,854/160,855) of the hospitalizations from 2014-2017 had sepsis on ICU admission. Of the hospitalizations with an ICU LOS of at least four days, 14.5% (N=9,048/62,206) of the hospitalizations had sepsis on ICU admission. Late vasopressor administration patterns were similar among all patients admitted to the ICU for a minimum of 4 days, patients admitted with sepsis and patients not admitted with sepsis (**e-Figure 1**).

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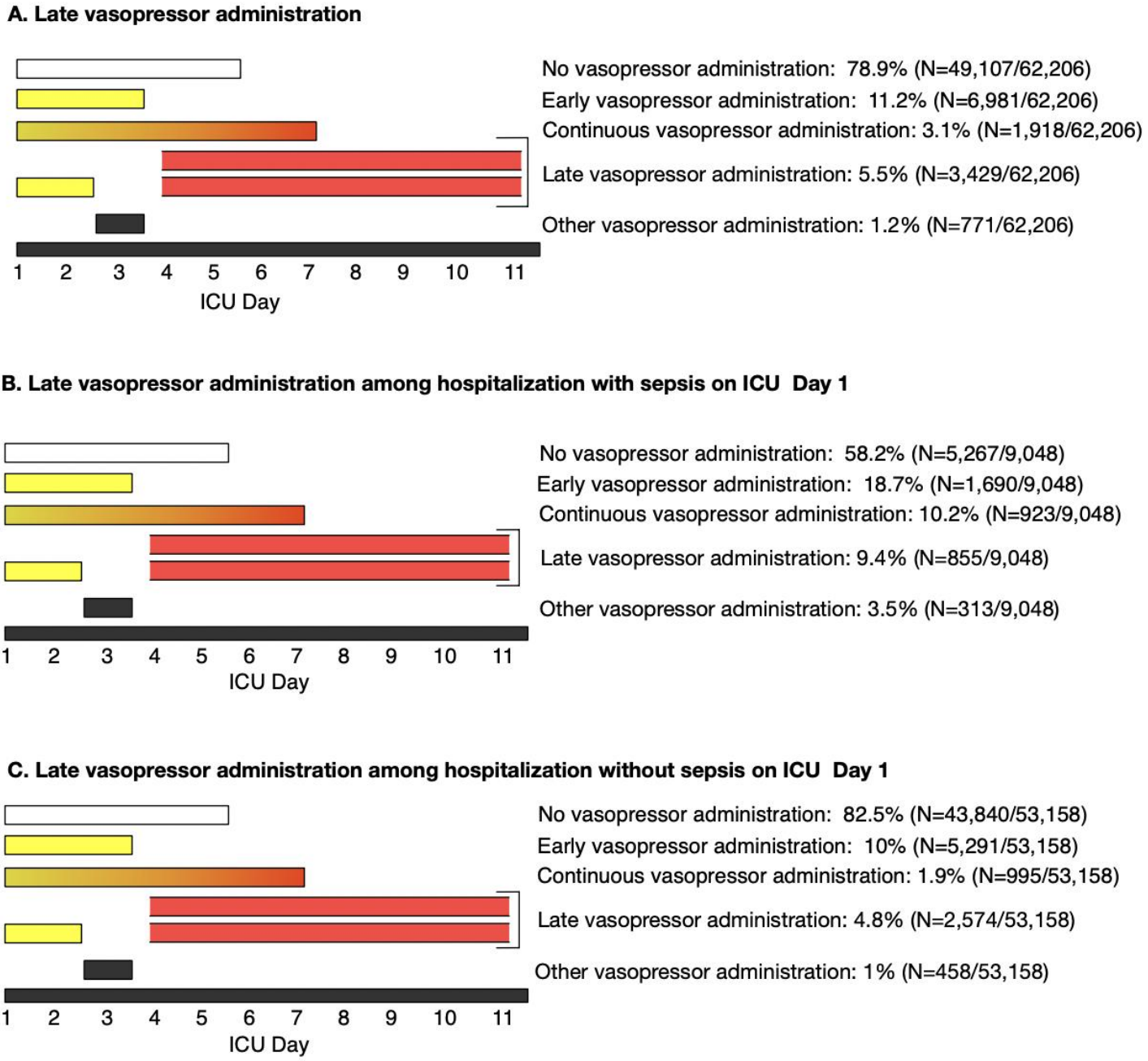
e-Figure 1. Late vasopressor administration stratified by the presence of sepsis on ICU admission among hospitalizations with an ICU LOS of at least 4 days. **A**. Late vasopressor administration among all hospitalizations. **B**. Late vasopressor administration among hospitalizations with sepsis on ICU admission. **C.** Late vasopressor administration among hospitalizations without sepsis.



e-Appendix 3: Identifying Persistent Critical Illness in the Veterans Administration (VA) Healthcare System

Study Population

The VA cohort represented patients admitted to a VA ICU from 2014-2017. We included all patients ≥18 years of age admitted to an ICU. We excluded patients transferred from another hospital because of previous ICU exposure making it impossible to accurately date onset of ICU exposure. We considered only the patient's first ICU admission during a hospital stay.

Statistical Analysis

All statistical analyses were carried out in R version 3.5.1, using Multivariate Adaptive Regression Splines (MARS) models from the Earth R package version 4.6.3. For simple tests of differences between groups, Kruskal-Wallis tests were used for numeric variables and Pearson Chi-square for all categorical covariates with a p-value of < 0.05 considered significant.

We first examined whether key variables in our dataset were differently distributed between patients with short or long stays. (**e-Tables 2a-c**) We specifically present differences between patients with ICU stays 6+ days (**e-Table 2a**) with additional splits 11+ days (**e-Table 2b**) and 16+ days (**e-Table 2c**)—for comparability with data published from Australia, New Zealand, and Alberta, Canada (11+ days) and with data (under review, not yet published) from Scotland (6+).

For the primary analyses, the outcome was in-hospital mortality. Single imputation was applied to all continuous acute and antecedent physiological predictors replacing missing values with the median value for each predictor.

A full logistic MARS model was fit combining both the acute and antecedent covariates, enabling a complete risk of in-hospital mortality to be calculated across all patients. The MARS model automatically allowed nonlinearities in continuous variables. All included variables are shown in **e-Table 3**. The full dataset was categorised into three mortality risk groups: high (≥66%), moderate (between 33%-66%), and low (<33%).

Subsequently, separate logistic MARS models were built consisting of either acute or antecedent variables and predicted probability of in-hospital mortality was generated for both models for every hospitalization. All MARS models were fit using backwards variable selection allowing for two-way interactions. These models are equivalent to logistic regressions with stepwise parameter selection allowing for non-linear trends in the continuous covariates via hinge function splines. Allowing for non-linearity within continuous predictors enables a better fit due to the complex nature of most physiological processes.

Our primary assessment metric, discrimination, as measured by the area under the curve of the receiver operating characteristic (AUROC), was then produced for the acute and antecedent models. To estimate discrimination the data was split into 28 reduced sets based on ICU length of stay, each split containing only those patients still in the ICU on or after the given length of stay (LOS). For each of these reduced datasets the AUROC and its 95% confidence interval were estimated using the baseline acute and antecedent model predictions of in-hospital mortality. Bootstrap replicates were used to estimate the confidence intervals with 2000 replicates for each interval. This provides a measure of how the discrimination of each model changed when looking at patients with progressively longer ICU stays. The AUROC for each of the reduced datasets were extracted and plotted per day in the given LOS for the acute and antecedent model.

Results

The acute characteristics on admission were more predictive of inpatient mortality with an AUROC curve of 0.843 (95% CI: 0.839-0.848). The antecedent model had an AUROC of 0.773 (95% CI: 0.768-0.778) on the first day of ICU. For patients with longer ICU stays, the acute characteristics on admission were no more predictive of inpatient mortality as compared to the antecedent characteristics on ICU day 16 and crossed over on ICU day 24. (**e-Figure 2**)

When comparing the patient's risk of mortality on admission, patients categorized as high (>66%) or moderate (33-66%) risk on admission, their mortality risk decreased the longer they remained in the

ICU. However, patients who were low risk (<33%) on admission had an increased risk of death the longer they remain in the ICU, plateauing around days 15-20 by visual inspection. (**e-Figure 3**).

e-Table 2a: Variable summary comparing hospitalizations for ICU stays ≤5 days and 6+ days.

Variable	ICU LOS ≤5 days	ICU LOS 6+ days	p-value
	N = 131,138	N = 29,717	
Age: median (IQR)	67 (60, 72)	68 (62,74)	<0.01
Female: N (%)	6252 (4.77)	998 (3.36)	<0.01
ICU LOS: median (IQR)	3 (2, 3)	8 (6, 11)	<0.01
Hospital Mortality: N (%)	5520 (4.21)	3387 (11.4)	<0.01
Race			
Black: N (%)	27164 (20.71)	6053 (20.37)	0.19
White: N (%)	93965 (71.65)	21510 (72.38)	0.01
Other: N (%)	10009 (7.63)	2154 (7.25)	0.03
Primary admission diagnosis (multilevel CCS) related to:			
Blood Disease: N (%)	1297 (0.99)	178 (0.6)	<0.01
Circulatory System: N (%)	44455 (33.9)	9777 (32.9)	<0.01
Digestive System: N (%)	12921 (9.85)	2808 (9.45)	0.04
Endocrine or Metabolic System: N (%)	7418 (5.66)	543 (1.83)	<0.01
Genitourinary System: N (%)	4171 (3.18)	688 (2.32)	<0.01
Infectious or Parasitic Disease: N (%)	7514 (5.73)	3011 (10.13)	<0.01
Mental Illness: N (%)	5287 (4.03)	884 (2.97)	<0.01
Musculoskeletal System: N (%)	4946 (3.77)	538 (1.81)	<0.01
Neoplasms: N (%)	14712 (11.22)	4108 (13.82)	<0.01
Nervous System: N (%)	2218 (1.69)	430 (1.45)	<0.01
Respiratory System: N (%)	13329 (10.16)	4504 (15.16)	<0.01
Other: N (%)	1177 (0.9)	247 (0.83)	0.285
Hospitalization Information			
Given pressor during hospitalization: N (%)	5143 (3.92)	2733 (9.2)	<0.01
Readmissions within 30 days: N (%)	14103 (10.75)	4024 (13.54)	<0.01
Used mechanical ventilation: N (%)	5865 (4.47)	7449 (25.07)	<0.01
Outcomes			
30-day mortality: N (%)	9526 (7.26)	4252 (14.31)	<0.01
90-day mortality: N (%)	14713 (11.22)	6617 (22.27)	<0.01

IQR: Interquartile range; LOS: Length of stay; ICU: Intensive care unit

e-Table 2b: Variable summary comparing hospitalizations for ICU stays ≤ 10 days and 11+ days.

Variable	ICU LOS ≤ 10 days	ICU LOS 11+ days	p-value
	N = 152,854	N = 8,001	
Age: median (IQR)	67 (60, 73)	68 (62, 73)	<0.01
Female: N (%)	6993 (4.57)	257 (3.21)	<0.01
ICU LOS: median (IQR)	3 (2, 4)	15 (12, 20)	<0.01
Hospital Mortality: N (%)	7258 (4.75)	1649 (20.61)	<0.01
Race			
Black: N (%)	31516 (20.62)	1701 (21.26)	0.17
White: N (%)	109754 (71.8)	5721 (71.5)	0.57
Other: N (%)	11584 (7.58)	579 (7.24)	0.27
Primary admission diagnosis (multilevel CCS) related to:			
Blood Disease: N (%)	1441 (0.94)	34 (0.42)	<0.01
Circulatory System: N (%)	52168 (34.13)	2064 (25.8)	<0.01
Digestive System: N (%)	14908 (9.75)	821 (10.26)	0.14
Endocrine or Metabolic System: N (%)	7847 (5.13)	114 (1.42)	<0.01
Genitourinary System: N (%)	4718 (3.09)	141 (1.76)	<0.01
Infectious or Parasitic Disease: N (%)	9394 (6.15)	1131 (14.14)	<0.01
Mental Illness: N (%)	5937 (3.88)	234 (2.92)	<0.01
Musculoskeletal System: N (%)	5365 (3.51)	119 (1.49)	<0.01
Neoplasms: N (%)	17728 (11.6)	1092 (13.65)	<0.01
Nervous System: N (%)	2477 (1.62)	171 (2.14)	<0.01
Respiratory System: N (%)	16342 (10.69)	1491 (18.64)	<0.01
Other: N (%)	1369 (0.9)	55 (0.69)	0.06
Hospitalization Information			
Given pressor during hospitalization (%)	7010 (4.59)	866 (10.82)	<0.01
Readmissions within 30 days (%)	17027 (11.14)	1100 (13.75)	<0.01
Used mechanical ventilation (%)	9530 (6.23)	3784 (47.29)	<0.01
Outcomes			
30-day mortality: N (%)	12173 (7.96)	1605 (20.06)	<0.01
90-day mortality: N (%)	18749 (12.27)	2581 (32.26)	<0.01

IQR: Interquartile range; LOS: Length of stay; ICU: Intensive care unit

e-Table 2c: Variable summary comparing hospitalizations for ICU stays ≤ 15 days and 16+ days.

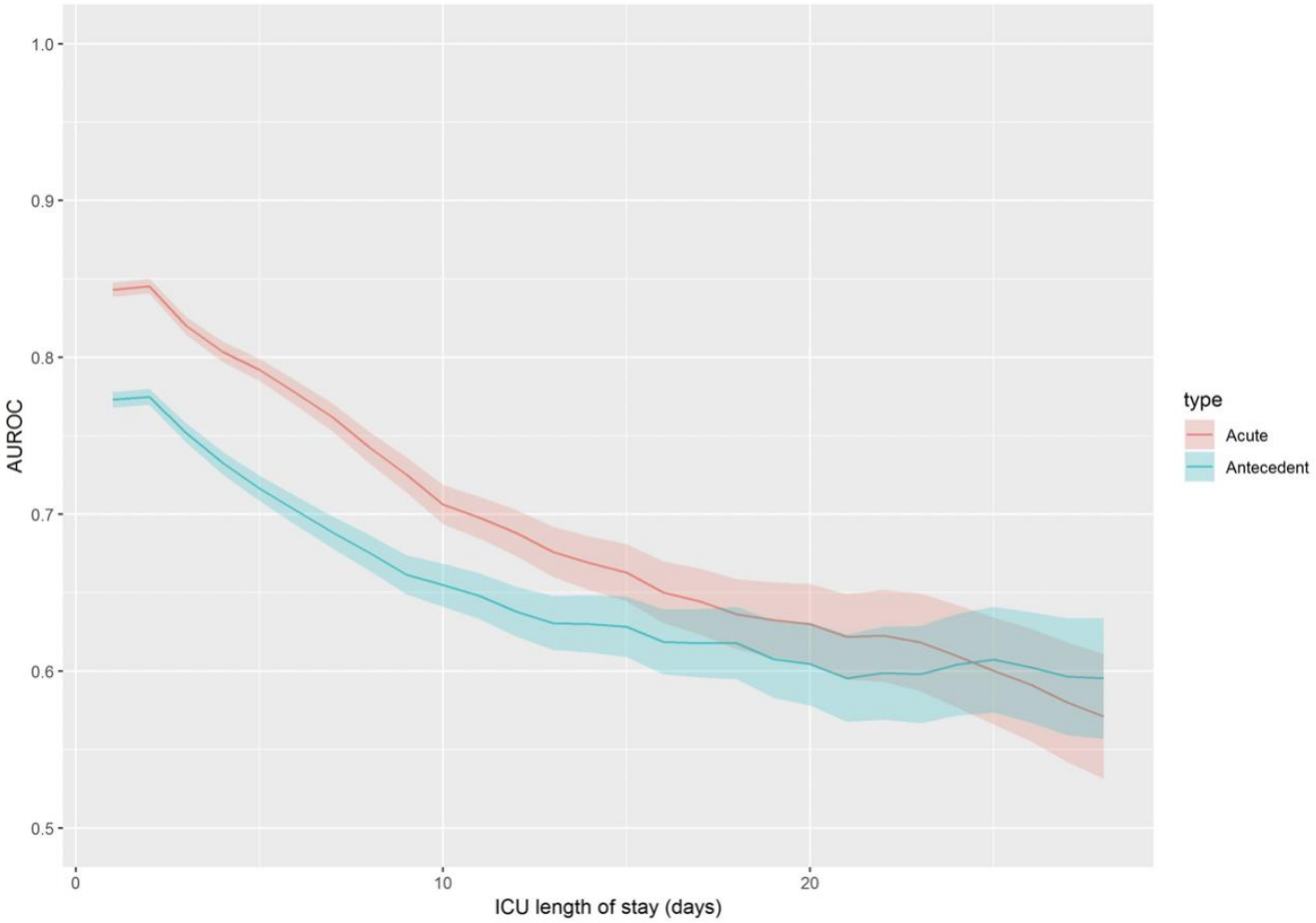
Variable	ICU LOS ≤15 days	ICU LOS 16+ days	p-value
	N = 157,227	N = 3,628	
Age: median (IQR)	67 (60, 73)	68 (62, 73)	<0.01
Female: N (%)	7150 (4.55)	100 (2.76)	<0.01
ICU LOS: median (IQR)	3 (2, 4)	21 (18, 29)	<0.01
Hospital Mortality: N (%)	7966 (5.07)	941 (25.94)	<0.01
Race			
Black: N (%)	32407 (20.61)	810 (22.33)	0.01
White: N (%)	112903 (71.81)	2572 (70.89)	0.23
Other: N (%)	11917 (7.58)	246 (6.78)	0.08
Primary admission diagnosis (multilevel CCS) related to:			
Blood Disease: N (%)	1461 (0.93)	14 (0.39)	<0.01
Circulatory System: N (%)	53419 (33.98)	813 (22.41)	<0.01
Digestive System (%)	15341 (9.76)	388 (10.69)	0.06
Endocrine or Metabolic System: N (%)	7913 (5.03)	48 (1.32)	<0.01
Genitourinary System: N (%)	4803 (3.05)	56 (1.54)	<0.01
Infectious or Parasitic Disease: N (%)	9963 (6.34)	562 (15.49)	<0.01
Mental Illness: N (%)	6077 (3.87)	94 (2.59)	<0.01
Musculoskeletal System: N (%)	5426 (3.45)	58 (1.6)	<0.01
Neoplasms: N (%)	18316 (11.65)	504 (13.89)	<0.01
Nervous System: N (%)	2550 (1.62)	98 (2.7)	<0.01
Respiratory System: N (%)	17096 (10.87)	737 (20.31)	<0.01
Other: N (%)	1404 (0.89)	20 (0.55)	0.04
Hospitalization Information			
Given pressor during hospitalization: N (%)	7449 (4.74)	427 (11.77)	<0.01
Readmissions within 30 days: N (%)	17609 (11.2)	518 (14.28)	<0.01
Used mechanical ventilation: N (%)	11095 (7.06)	2219 (61.16)	<0.01
Outcomes			
30-day mortality: N (%)	13073 (8.31)	705 (19.43)	<0.01
90-day mortality: N (%)	20017 (12.73)	1313 (36.19)	<0.01

IQR: Interquartile range; LOS: Length of stay; ICU: Intensive care unit

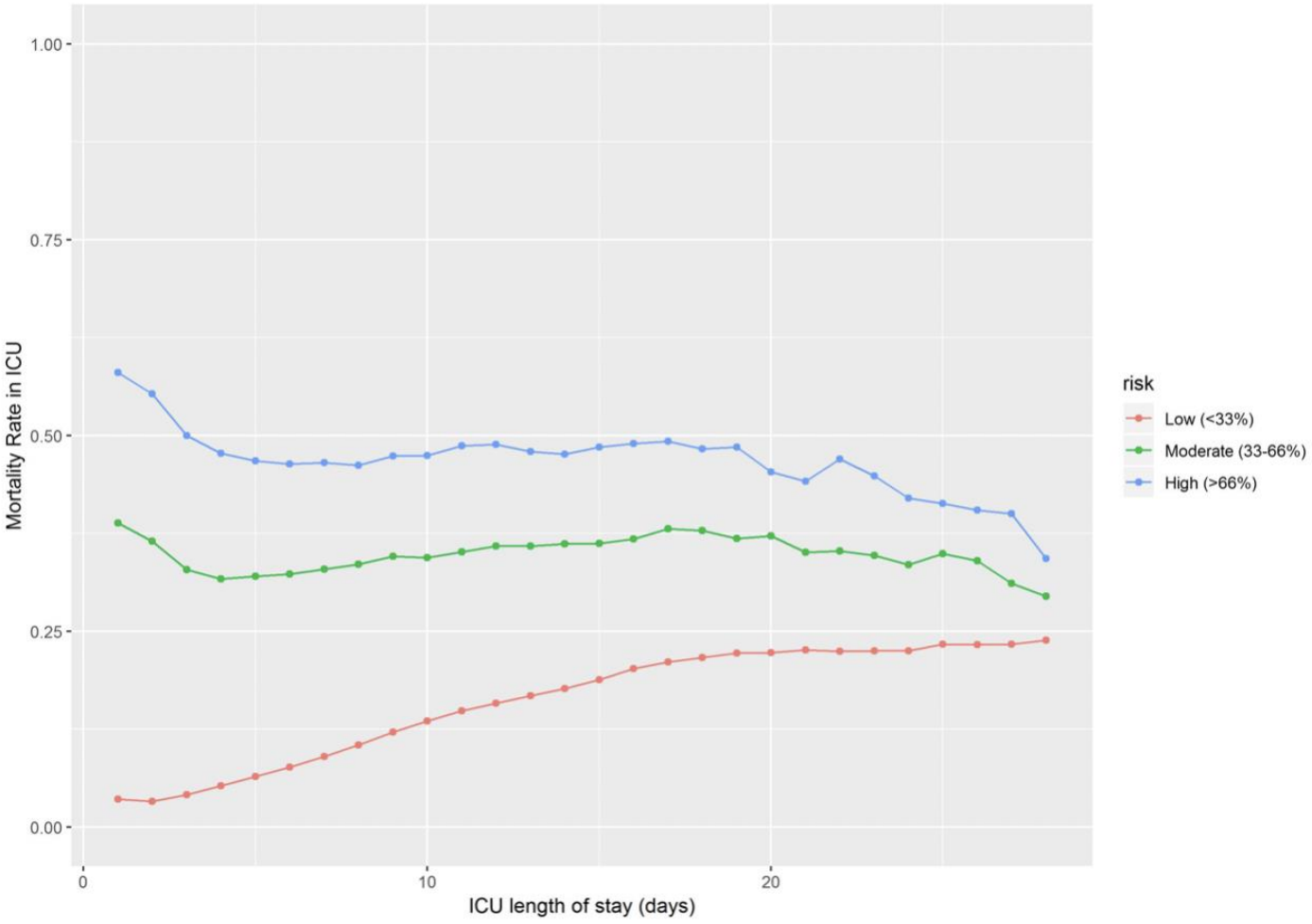
e-Table 3: List of variables included in acute and antecedent logistic MARS models

Acute Model	Antecedent Model	
Blood Laboratory Scores	Age	
Albumin	Sex	
Glucose	Race	
Creatinine	White	
Bilirubin	Black	
Blood urea nitrogen	Other	
Sodium	Comorbidity indicators	
White blood cells count	Congestive heart failure	AIDS/HIV
Hematocrit	Cardiac arrhythmia	Lymphoma
Partial pressure of oxygen	Valvular disease	Metastatic cancer
pH	Pulmonary circulation disorder	Non-metastatic cancer
Indicators for 20 most common admission diagnoses	Peripheral valvular disorder	Rheumatoid arthritis
Multilevel CCS diagnosis code	Hypertension	coagulopathy
Use of vasopressors during hospitalization	Paralysis	Obesity
Use of mechanical ventilation during hospitalization	Neurological disorder	Weight loss
Readmission status	Chronic pulmonary disease	Fluid and electrolyte disorder
	Diabetes uncomplicated	Blood loss anemia
	Diabetes complicated	Deficiency anemia
	Hypothyroidism	Alcohol abuse
	Renal failure	Drug abuse
	Liver disease	Psychosis
	Peptic ulcer disease	Depression

e-Figure 2: AUROC comparison for logistic MARS models including either Acute or Antecedent hospitalization/patient information



e-Figure 3. Risk is assessed using predictions from a logistic MARS model as described above.



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