SUPPLEMENTAL CONTENT

e-Table 1: Sensitivity Analyses Assessing Impact of Inclusion of RASS On GAM Model for Patients with or without RASS Data

	Model 1		**Model 2**		**Model 3**	
	OR [95% CI]	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Race (W)	0.79 [0.77 – 0.82]	0.086	0.77 [0.75 – 0.8]	0.065	0.77 [0.75 – 0.79]	0.060
Age (years)	1.47 [1.41 – 1.54]	< 0.001	1.63 [1.55 – 1.7]	< 0.001	1.63 [1.56 – 1.71]	< 0.001
Creatinine (mmol/L)	1.61 [1.59 – 1.62]	0.025	1.52 [1.5 – 1.54]	0.038	1.50 [1.49 – 1.52]	0.045
Lactate (mmol/L)	2.79 [2.73 – 2.85]	< 0.001	2.79 [2.76 – 2.82]	< 0.001	2.79 [2.76 – 2.82]	< 0.001
SOFA	1.19 [0.86 – 1.65]	< 0.001	0.96 [0.67 – 1.36]	< 0.001	0.97 [0.68 – 1.39]	< 0.001
RASS					1.29 [1.81 – 0.92]	< 0.001
Third vasopressor initiation time after ICU admission (hours)	1.78 [1.69 – 1.87]	< 0.001	2.11 [1.92 – 2.31]	< 0.001	2.08 [1.91 – 2.27]	0.741

Sensitivity analyses were performed to confirm if the presence or absence of RASS had a significant effect on the model's results. The presence or absence of this data did not have a significant effect on our presented model.

Model 1: RASS variable exclusion in the model for patients with or without RASS data (n=1,347).

Model 2: RASS variable exclusion in the model for patients with RASS data (n=1,213).

Model 3: RASS variable inclusion in the model for patients with RASS data (n=1,213).

Reference points were established based on prior literature or, when literature was not available, medians from the analytic sample: Age 60; Creatinine 1.2; Lactate 2.0; SOFA score 0; Third Vasopressor Initiation 12.4 hours (median from analytic sample).[33-34]

e-Table 2: Patient Distribution with Multiple Racial Identities

	MIMIC-IV (*n*=1,347)			**eICU-CRD (*n*=2,100)**		
	Alive (*n*=487)	**Dead (*n*=860)**	**p-value**	**Alive (*n*=976)**	**Dead (*n*=1,124)**	**p-value**
Primary Race (white)	313 (64.3%)	483 (56.2%)	0.003	746 (76.4%)	833 (74.1%)	0.238
Secondary Race (white)	310 (63.7%)	479 (55.7%)	0.005	745 (76.3%)	838 (74.6%)	0.372

The distribution in MIMIC-IV and eICU-CRD were shown for patients who identified multiple races (n=7 from MIMIC-IV, n=18 from eICU-CRD).

e-Table 3: Sensitivity Analysis Assessing Impact of Race Identity Selection on GAM Model for Patients with Multiple Racial Identities

	Model 1		**Model 2**		**Model 3**		**Model 4**	
	OR [95% CI]	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Race (white)	0.79 [0.77 – 0.82]	0.086	0.79 [0.77 – 0.82]	0.086	1.03 [0.99 – 1.06]	0.828	1.03 [0.99 – 1.06]	0.828
Age (years)	1.47 [1.41 – 1.54]	< 0.001	1.47 [1.41 – 1.54]	< 0.001	1.56 [1.5 – 1.62]	< 0.001	1.56 [1.5 – 1.62]	< 0.001
Creatinine (mmol/L)	1.61 [1.59 – 1.62]	0.025	1.61 [1.59 – 1.62]	0.025	1.69 [1.65 – 1.74]	0.007	1.69 [1.65 – 1.74]	0.007
Lactate (mmol/L)	2.79 [2.73 – 2.85]	< 0.001	2.79 [2.73 – 2.85]	< 0.001	3.23 [2.87 – 3.63]	< 0.001	3.23 [2.87 – 3.63]	< 0.001
SOFA	1.19 [0.86 – 1.65]	< 0.001	1.19 [0.86 – 1.65]	< 0.001	3.84 [3.47 – 4.26]	< 0.001	3.84 [3.47 – 4.26]	< 0.001
Third vasopressor initiation time from ICU admission (hours)	1.78 [1.69 – 1.87]	< 0.001	1.78 [1.69 – 1.87]	< 0.001	2.16 [2.02 – 2.31]	< 0.001	2.16 [2.02 – 2.31]	< 0.001

Sensitivity analyses were conducted to determine if selection of one race identity versus another had a significant impact on the GAM model for patients who identified multiple races (n=7 from MIMIC-IV, n=18 from eICU-CRD). The primary race identity selection did not have a significant effect on our presented model.

Model 1: Primary race identity from the MIMIC-IV database.

Model 2: Secondary race identity from the MIMIC-IV database.

Model 3: Primary race identity from the eICU-CRD database.

Model 4: Secondary race identity from the eICU-CRD database.

Reference points were established based on prior literature or, when literature was not available, medians from the analytic sample: Age 60; Creatinine 1.2; Lactate 2.0; SOFA score 0; Third Vasopressor Initiation 12.4 hours (median from analytic sample).[33-34]

e-Table 4: Transitions in Code Status within 24 Hours After Third Vasopressor Initiation, All Patients

		Code Statuses Within 24 Hours After Third Vasopressor				
		Full Code (*n*=2,969)	**DNR (*n*=369)**	**DNI (*n*=8)**	**DNR/DNI (*n*=34)**	**CMO (*n*=67)**
Code Statuses Before the Third Vasopressor	**Full Code (*n*=3,331)**	2,937 (85.2%)	313 (9.1%)	1 (0%)	26 (0.8%)	54 (1.6%)
	DNR (*n*=87)	26 (0.8%)	54 (1.6%)	0 (0%)	1 (0%)	6 (0.2%)
	DNI (*n*=9)	0 (0%)	1 (0%)	7 (0.2%)	0 (0%)	1 (0%)
	DNR/DNI (*n*=17)	5 (0.1%)	1 (0%)	0 (0%)	7 (0.2%)	4 (0.1%)
	CMO (*n*=3)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)

e-Table 5: Transitions in Code Status at Any Point After Initiation of Third Vasopressor Initiation, All Patients

		Code Statuses After Third Vasopressor				
		Full Code (*n*=2,602)	**DNR (*n*=552)**	**DNI (*n*=35)**	**DNR/DNI (*n*=52)**	**CMO (*n*=206)**
Code Status Before the Third Vasopressor	**Full Code (*n*=3,331)**	2,530 (73.4%)	536 (15.5%)	33 (1%)	48 (1.4%)	184 (5.3%)
	DNR (*n*=87)	55 (1.6%)	14 (0.4%)	0 (0%)	2 (0.1%)	16 (0.5%)
	DNI (*n*=9)	6 (0.2%)	0 (0%)	1 (0%)	0 (0%)	2 (0.1%)
	DNR/DNI (*n*=17)	8 (0.2%)	2 (0.1%)	1 (0%)	2 (0.1%)	4 (0.1%)
	CMO (*n*=3)	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

e-Table 6: Transitions in Code Status within 24 Hours After Third Vasopressor Initiation, MIMIC-IV Database

		Code Statuses After Third Vasopressor				
		Full Code (*n*=1,307)	**DNR (*n*=22)**	**DNI (*n*=0)**	**DNR/DNI (*n*=8)**	**CMO (*n*=10)**
Code Status Before the Third Vasopressor	**Full Code (*n*=1,310)**	1,277 (94.8%)	19 (1.4%)	0 (0%)	7 (0.5%)	7 (0.5%)
	DNR (*n*=28)	24 (1.8%)	3 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)
	DNI (*n*=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	DNR/DNI (*n*=8)	5 (0.4%)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.1%)
	CMO (*n*=1)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

e-Table 7: Transitions in Code Status within 24 Hours After Third Vasopressor Initiation, eICU-CRD Database

		Code Statuses After Third Vasopressor				
		Full Code (*n*=1,662)	**DNR (*n*=347)**	**DNI (*n*=8)**	**DNR/DNI (*n*=26)**	**CMO (*n*=57)**
Code Status Before the Third Vasopressor	**Full Code (*n*=2,021)**	1,660 (79%)	294 (14%)	1 (0%)	19 (0.9%)	47 (2.2%)
	DNR (*n*=59)	2 (0.1%)	51 (2.4%)	0 (0%)	1 (0%)	5 (0.2%)
	DNI (*n*=9)	0 (0%)	1 (0%)	7 (0.3%)	0 (0%)	1 (0%)
	DNR/DNI (*n*=9)	0 (0%)	1 (0%)	0 (0%)	6 (0.3%)	2 (0.1%)
	CMO (*n*=2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)

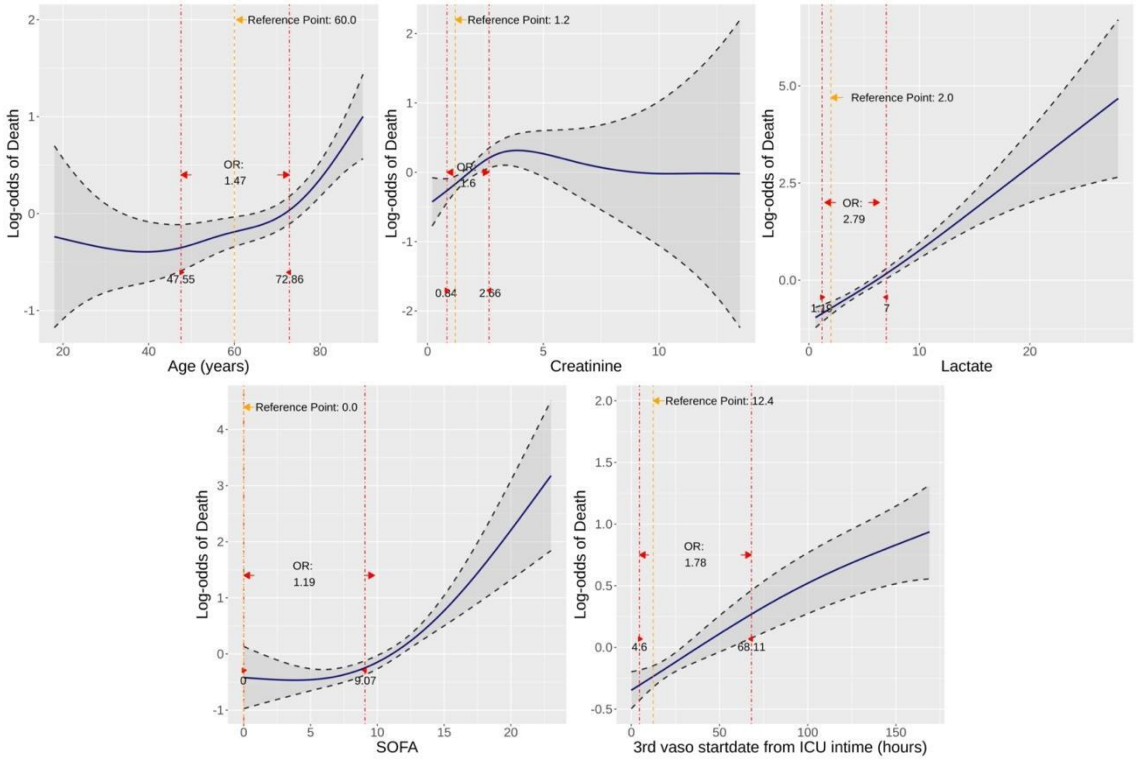
e-Table 8: Transitions in Code Status at Any Point After Initiation of Third Vasopressor Initiation, MIMIC-IV Database

		Code Statuses After Third Vasopressor				
		Full Code (*n*=1,159)	**DNR (*n*=100)**	**DNI (*n*=32)**	**DNR/DNI (*n*=523**	**CMO (*n*=53)**
Code Status Before the Third Vasopressor	**Full Code (*n*=2,021)**	1,135 (84.3%)	93 (6.9%)	31 (2.3%)	3 (0.2%)	48 (3.6%)
	DNR (*n*=59)	18 (1.3%)	7 (0.5%)	0 (0%)	0 (0%)	3 (0.2%)
	DNI (*n*=9)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	DNR/DNI (*n*=9)	5 (0.4%)	0 (0%)	1 (0.1%)	0 (0%)	2 (0.1%)
	CMO (*n*=2)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

e-Table 9: Transitions in Code Status at Any Point After Initiation of Third Vasopressor Initiation, eICU-CRD Database

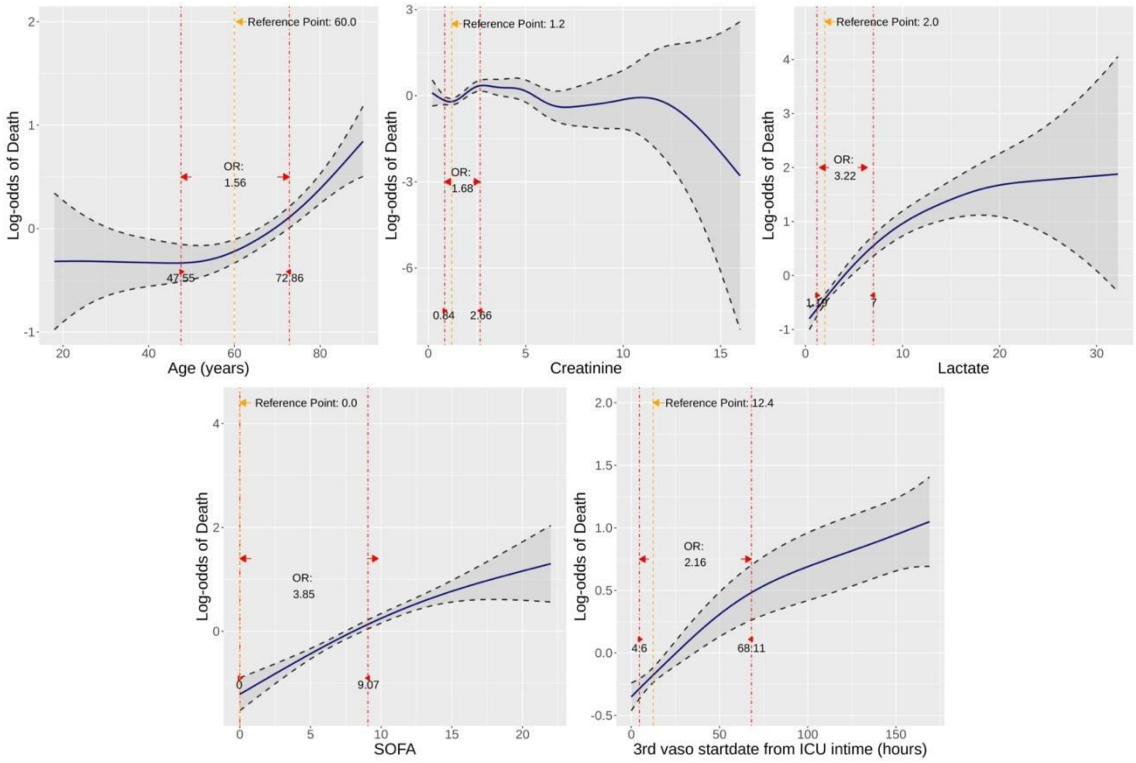
		Code Statuses After Third Vasopressor				
		Full Code (*n*=1,443)	**DNR (*n*=452)**	**DNI (*n*=3)**	**DNR/DNI (*n*=49)**	**CMO (*n*=153)**
Code Status Before the Third Vasopressor	**Full Code (*n*=1,310)**	1,395 (66.4%)	443 (21.1%)	2 (0.1%)	45 (2.1%)	136 (6.5%)
	DNR (*n*=28)	37 (1.8%)	7 (0.3%)	0 (0%)	2 (0.1%)	13 (0.6%)
	DNI (*n*=0)	6 (0.3%)	0 (0%)	1 (0%)	0 (0%)	2 (0.1%)
	DNR/DNI (*n*=8)	3 (0.1%)	2 (0.1%)	0 (0%)	2 (0.1%)	2 (0.1%)
	CMO (*n*=1)	2 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

e-Figure 1: Continuous Variables and Associated Odds Ratios for Mortality, MIMIC-IV Database



Age > 60 years old demonstrates an exponential association with mortality while increasing lactate values, SOFA scores, and time delay between ICU admission and third vasopressor initiation demonstrate a positive linear correlation. The association between rising creatinine and mortality peaks between three and four before leveling off. Solid yellow lines indicate reference points. Reference points were established based on prior literature or, when literature was not available, medians from the analytic sample: Age 60; Creatinine 1.2; Lactate 2.0; SOFA score 0; Third Vasopressor Initiation 12.4 hours (median from analytic sample) (33-34). Dashed red lines indicate 95% confidence bounds.

e-Figure 2: Continuous Variables and Associated Odds Ratios for Mortality, eICU-CRD Database



Age > 60 years old demonstrates an exponential association with mortality while increasing lactate values, SOFA scores, and time delay between ICU admission and third vasopressor initiation demonstrate a positive linear correlation. The association between rising creatinine and mortality follows a complex, bimodal pattern. Solid yellow lines indicate reference points. Reference points were established based on prior literature or, when literature was not available, medians from the analytic sample: Age 60; Creatinine 1.2; Lactate 2.0; SOFA score 0; Third Vasopressor Initiation 12.4 hours (median from analytic sample) (33-34). Dashed red lines indicate 95% confidence bounds.

e-Appendix 1: Vasopressor Search Terms

1. Angiotensin (giapreza)
2. Dopamine (intropin)
3. Epinephrine (adrenalin)
4. Norepinephrine (levophed)
5. Phenylephrine (neosynephrine)
6. Vasopressin (vasostrict)

e-Appendix 2: Intravenous Fluid Search Terms

1. MIMIC-IV
   Itemid: 225158, 225825, 225159, 225823, 225941, 225828, 225827

2. eICU-CRD
   LR

   NS

   NSS

   D5NS

   D10NS

   D5 NS

   1/2 NS

   D10 NS

   D5 LR

   NS+KCl

   0.45 NS

   D5 1/2NS

   LR Bolus

   NS BOLUS

   LR IVF

   NS IVF

   D5 0.2 NS

   0.9 NS_c

   D5LR IVF

   D5NS IVF

   NS + KCL

   NS b IVF

   NS c IVF

   NS d IVF

   NS e IVF

D5 0.45 NS

D5.45NS+KCl

1/2NS IVF

D5NS + KCL

NS with 20KCL

1/2NS + KCL

D51/2NS IVF

D51/4NS IVF

D5NS Volume

NS w/ mEq KCL

D5 LR Volume

LR w/40 mEq KCL

NS w/20 mEq KCL

NS w/40 mEq KCL

D5 1/2NS + KCL

NS 0.9% Volume

D5NS w/20 mEq KCL

D5NS w/40 mEq KCL

D5 1/2 NS Volume

0.45 NS w/20 mEq KCL

0.45 NS w/40 mEq KCL

NS w/40 mEq KCL 500 ml

NS w/KCl 20mEq Volume

0.45 NS w/75 mEq $NaHCO_3$

D5 0.45 NS w/10 mEq KCL

D5 0.45 NS w/20 mEq KCL

D5 0.45 NS w/40 mEq KCL

LR w/20 mEq KCL 1000 ml

LR w/40 mEq KCL 1000 ml

LR w/60 mEq KCL 1000 ml

NS w/20 mEq KCL 1000 ml

NS w/40 mEq KCL 1000 ml

NS w/60 mEq KCL 1000 ml

0.9NS with 20mEq KCL_c

Lactated Ringers Volume

D5NS w/20 mEq KCL 1000 ml

D5NS w/40 mEq KCL 1000 ml

NS w/30 mmol (as PO4) KPO4

NS w/150 mEq NaHCO3 1000 ml

0.45 NS w/20 mEq KCL 1000 ml

0.45 NS w/40 mEq KCL 1000 ml

D5NS w/150 mEq NaHCO3 1000 ml

D5 1/2 NS w/KCl 20mEq Volume

0.45 NS w/75 mEq NaHCO3 1000 ml

D5 0.45 NS w/20 mEq KCL 1000 ml

D5 0.45 NS w/40 mEq KCL 1000 ml

0.45 NS w/100 mEq NaHCO3 1000 ml

NS w/15 mmol (as PO4) KPO4 250 ml

NS w/30 mmol (as PO4) KPO4 250 ml

NS w/30 mmol (as PO4) KPO4 500 ml

NS w/45 mmol (as PO4) KPO4 500 ml

D5 0.45 NS w/75 mEq NaHCO3 1000 ml

NS w/15 mmol (as PO4) NaPO4 250 ml

NS w/45 mmol (as PO4) KPO4 1000 ml

Volume (mL)-lactated ringers infusion

Volume (mL)-SODIUM CHLORIDE 0.9 % IV SOLN

Volume (mL)-lactated ringers bolus 500 mL

Volume (mL)-sodium chloride 0.9% infusion

Volume (mL)-0.9 % sodium chloride solution

Volume (mL)-0.45 % sodium chloride solution

Volume (mL)-lactated ringers bolus 1,000 mL

Volume (mL)-sodium chloride 0.45 % infusion

Volume (mL)-0.45 % sodium chloride infusion

Volume (mL)-0.9 % sodium chloride infusion

Volume (mL)-lactated ringers infusion 1,000 mL

Volume (mL)-lactated ringers infusion 500 mL

Volume (mL)-sodium chloride 0.9 % bolus 250 mL

Volume (mL)-sodium chloride 0.9 % bolus 500 mL

Volume (mL)-sodium chloride 0.9 % 250 mL IV bolus

Volume (mL)-sodium chloride 0.9 % 500 mL IV bolus

D5 0.45 NS w/20 mEq KCL and 10 mmol (as PO4) KPO4

Volume (mL)-sodium chloride 0.9 % bolus 1,000 mL

Volume (mL)-sodium chloride 0.9 % 1,000 mL IV bolus

Volume (mL)-sodium chloride 0.9 % 1,000 mL infusion

Volume (mL)-sodium chloride 0.9 % 2,000 mL IV bolus

Volume (mL)-sodium chloride 0.9 % flush IVPB 250 mL

Volume (mL)-sodium chloride 0.9 % flush IVPB 500 mL

Volume (mL)-dextrose 5 % / lactated ringers infusion

Volume (mL)-dextrose 5 % in lactated ringers infusion

Volume (mL)-sodium chloride 0.45 % 1,000 mL infusion

Volume (mL)-dextrose 5 %-0.9 % sodium chloride infusion

Volume (mL)-SODIUM CHLORIDE 0.9 % IV SOLN Pyxis Override

Volume (mL)-dextrose 5 % / sodium chloride 0.9% infusion

Volume (mL)-dextrose 5 %-0.45 % sodium chloride infusion

Volume (mL)-dextrose 5 % / sodium chloride 0.45% infusion

Volume (mL)-dextrose 5 % and 0.2% sodium chloride infusion

Volume (mL)-sodium chloride 0.9 % with KCl 20 mEq infusion

Volume (mL)-sodium chloride 0.9 % with KCl 40 mEq infusion

Volume (mL)-0.45 % sodium chloride with KCl 20 mEq infusion

Volume (mL)-dextrose 5 % and 0.2 % sodium chloride infusion

Volume (mL)-sodium chloride 0.45 % with KCl 20 mEq infusion

Volume (mL)-sodium chloride (NORMAL SALINE) 0.9 % bolus 250 mL

Volume (mL)-sodium chloride (NORMAL SALINE) 0.9 % bolus 500 mL

Volume (mL)-sodium chloride (NORMAL SALINE) 0.9 % bolus 1,000 mL

Volume (mL)-dextrose 5 % and 0.9 % sodium chloride with KCl 20 mEq/L

Volume (mL)-dextrose 5 % / sodium chloride 0.9% with KCl 20 mEq infusion

Volume (mL)-calcium gluconate 1 g in sodium chloride 0.9 % 100 mL IVPB

Volume (mL)-dextrose 5 % / sodium chloride 0.45% with KCl 20 mEq infusion

Volume (mL)-dextrose 5 % / sodium chloride 0.45% with KCl 40 mEq infusion

Volume (mL)-0.9% sodium chloride with potassium chloride 40 mEq/L infusion

Volume (mL)-Calcium gluconate 10 g in 0.9% sodium chloride 250 ml infusion

Volume (mL)-0.9 % sodium chloride with potassium chloride 20 mEq/L infusion

Volume (mL)-lactated ringers 1,000 mL with potassium chloride 20 mEq infusion

Volume (mL)-dextrose 5 % and 0.45 % sodium chloride with KCl 20 mEq/L infusion

Volume (mL)-dextrose 5 % and 0.45 % sodium chloride with KCl 40 mEq/L infusion

Volume (mL)-sodium chloride 0.225 % with sodium bicarbonate 100 mEq infusion

Volume (mL)-sodium chloride 0.45 % 1,000 mL with sodium bicarbonate 50 mEq infusion

Volume (mL)-sodium chloride 0.45 % 1,000 mL with sodium bicarbonate 75 mEq infusion

Volume (mL)-sodium chloride 0.9 % 1,000 mL with potassium chloride 10 mEq infusion

Volume (mL)-sodium chloride 0.9 % 1,000 mL with potassium chloride 20 mEq infusion

Volume (mL)-sodium chloride 0.9 % 1,000 mL with potassium chloride 40 mEq infusion

Volume (mL)-sodium chloride 0.45 % 1,000 mL with potassium chloride 40 mEq infusion

Volume (mL)-sodium chloride 0.45 % 1,000 mL with sodium bicarbonate 100 mEq infusion

Volume (mL)-dextrose 5 % / sodium chloride 0.45% 1,000 mL with magnesium sulfate 5 g infusion

Volume (mL)-dextrose 5 % and 0.9% sodium chloride 1,000 mL with potassium chloride 40 mEq infusion

Volume (mL)-sodium glycerophosphate (GLYCOPHOS) 10 mmol in sodium chloride 0.9 % 250 mL infusion

Volume (mL)-sodium glycerophosphate (GLYCOPHOS) 20 mmol in sodium chloride 0.9 % 250 mL infusion

Volume (mL)-dextrose 5 % and 0.45% sodium chloride 1,000 mL with sodium bicarbonate 50 mEq infusion

Volume (mL)-dextrose 5 % and 0.45% sodium chloride 1,000 mL with sodium bicarbonate 75 mEq infusion

Volume (mL)-dextrose 5 % and 0.2 % sodium chloride 1,000 mL with sodium bicarbonate 100 mEq infusion

Volume (mL)-lactated ringers 1,000 mL with thiamine 100 mg, folic acid 1 mg, magnesium sulfate 2 g infusion

Volume (mL)-sodium chloride 0.9 % 1,000 mL with thiamine 100 mg, folic acid 1 mg, multivitamins adult 10 mL infusion

Volume (mL)-dextrose 5 % / sodium chloride 0.45% 1,000 mL with potassium chloride 40 mEq, magnesium sulfate 5 g infusion

e-Appendix 3: Feature Selection

1. Characteristics of ICU admission: timing of initiation of third vasopressor relative to ICU admission and relative to initiation of pressors one and two, illness severity at time of third vasopressor initiation
2. Clinical scores: Sequential Organ Failure Assessment, Richmond Agitation-Sedation Scale
3. Laboratory results: lactate, creatinine, hemoglobin
4. Mechanical ventilation
5. Medications: midazolam (versed), lorazepam (ativan), morphine (duramorph), hydromorphone (dilaudid), fentanyl (sublimaze), propofol (diprivan), dexmedetomidine (precedex), phenobarbitol (phenobarbitone), hydrocortisone (solucortef), methylprednisolone (solumedrol), dexamethasone (decadron)
6. Patient comorbidities: Comorbidity list, Charlson Comorbidity, Elixhauser Comorbidity Index
7. Patient demographics: age, sex, race, BMI < 30, BMI 30 to 39, BMI > 40