Online Data Supplement

Vasopressor-resistant hypotension, combination vasopressor therapy, and shock phenotypes in critically ill adults with vasodilatory shock

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Table of Contents

eMethods 1: Study Population

For each patient, the following information were extracted: age, sex, primary diagnosis and patient comorbidities (coded according to the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision [ICD-9]). For patients with multiple ICU admissions, the first ICU admission was considered as the reference point for our analyses. Severity of illness was computed from electronic abstraction of all physiologic variables comprising the Acute Physiologic and Chronic Health Evaluation (APACHE)-III score.[1] We used ICD-9 codes, for reported cases of sepsis. We extracted hourly mean arterial pressure (MAP) and vasopressor type and dose for each patient during the 6 hours for meeting criteria for vasopressor-resistant hypotension (VRH) and within the first 6 hours of vasopressor use among those with vasopressor-sensitive hypotension (VSH).

eTable 1: Vasopressor Standardization to Norepinephrine Equivalents

Drug	Dose	Norepinephrine Equivalent
Epinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Norepinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Dopamine	15 mcg/kg/min	0.1 mcg/kg/min
Phenylephrine	1.0 mcg/kg/min	0.1 mcg/kg/min
Vasopressin	0.04 U/min	0.1 mcg/kg/min

All vasopressors were standardized according to the following conversion scale. The conversion scale was developed based on the cardiovascular Sequential Organ Failure Assessment score and the medical literature.[2,3] Vasopressin equivalence to norepinephrine was developed with the use of the Vasopressin and Septic Shock Trial data set.[4]

eTable 2: Vasopressor Type and Dose

Vasopressor Type [a]	VRH (n=1,291)	VSH (n=4,022)	All (N=5,313)
Dopamine	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)
Norepinephrine	2.2 (3.3)	0.2 (0.8)	0.7 (1.9)
Phenylephrine	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Epinephrine	0.3 (1.6)	0.1 (0.4)	0.1 (0.8)
Vasopressin	0.3 (1.9)	0.0 (0.5)	0.1 (1.0)
Total norepinephrine equivalents [b]	2.9 (4.0)	0.4 (1.0)	1.0 (2.4)

[a] Shown are Mean (SD) of cumulative vasopressor dose was calculated for each patient during the 6-hour time period for patients with VRH and the first six hours of vasopressor use for patients with VSH

[b] All vasopressor dose were standardized in terms of norepinephrine equivalents

eTable 3: Patient Characteristics by Cluster

Characteristics	No. (%)					
	All (N=5,313)	Cluster 1 (N=2,931)	Cluster 2 (N=873)	Cluster 3 (N=673)	Cluster 4 (N=836)	P value
Age, median (IQR)	61.0 (50.0-72.0)	63.0 (52.0-74.0)	61.0 (52.0-70.0)	56.0 (46.0-67.0)	58.0 (47.0-70.0)	<0.001
BMI, median (IQR)	26.6 (23.0-30.9)	26.8 (23.3-31.0)	26.9 (23.5-30.9)	25.6 (22.2-30.7)	25.9 (22.4-30.4)	<0.001
Female	2,261 (42.6)	1,434 (48.9)	186 (21.3)	244 (36.3)	397 (47.5)	<0.001
APACHE-III score, Median (IQR)	75.0 (54.0-99.0)	73.0 (52.0-94.0)	69.0 (50.0-95.0)	100.0 (75.0-121.0)	74.0 (54.0-97.0)	<0.001
Mechanical ventilation	4,152 (78.1)	2,267 (77.3)	681 (78.0)	558 (82.9)	646 (77.3)	0.015
Baseline serum creatinine	1.0 (0.8-1.4)	1.0 (0.7-1.3)	1.0 (0.8-1.4)	1.0 (0.8-1.6)	1.0 (0.8-1.4)	0.01
Estimated Glomerular Filtration Rate	75.0 (68.9-94.7)	75.0 (70.3-93.9)	75.0 (65.7-93.5)	75.0 (66.4-94.3)	75.0 (70.7-103.1)	0.03
Sepsis admission	5,192 (97.7)	2,857 (97.5)	857 (98.2)	658 (97.8)	820 (98.1)	0.5
Trauma	487 (9.2)	279 (9.5)	60 (6.9)	69 (10.3)	79 (9.4)	0.07
Cardiac Disease	1,260 (23.7)	660 (22.5)	250 (28.6)	148 (22.0)	202 (24.2)	0.002
Liver Disease	528 (9.9)	260 (8.9)	97 (11.1)	96 (14.3)	75 (9.0)	<0.001
Diabetes	1,093 (36.6)	615 (21.0)	186 (21.3)	133 (19.8)	159 (19.0)	0.5
Vascular Disease	566 (10.7)	338 (11.5)	90 (10.3)	56 (8.3)	82 (9.8)	0.07
Hypertension	1,946 (36.6)	1,090 (37.2)	346 (39.6)	240 (35.7)	270 (32.3)	0.01

Characteristics	No. (%)					P value
	All (N=5,313)	Cluster 1 (N=2,931)	Cluster 2 (N=873)	Cluster 3 (N=673)	Cluster 4 (N=836)	
Malignancy	177 (3.3)	96 (3.3)	25 (2.9)	32 (4.8)	24 (2.9)	0.1
COPD	607 (11.4)	319 (10.9)	110 (12.6)	75 (11.1)	103 (12.3)	0.4
Liver transplant history	200 (3.8)	103 (3.5)	36 (4.1)	37 (5.5)	24 (2.9)	0.04
Liver transplant admission	377 (7.1)	217 (7.4)	64 (7.3)	47 (7.0)	49 (5.9)	0.5
Surgical admission	3,734 (70.3)	2,151 (73.4)	642 (73.5)	381 (56.6)	560 (67.0)	<0.001
Oliguria	90 (1.7)	32 (1.1)	11 (1.3)	22 (3.3)	25 (3.0)	<0.001
MAP during the first 6 hours of vasopressor use, mmHg, Median (IQR)[b]	72.5 (66.5-79.5)	73.0 (67.0-80.5)	72.0 (67.0-79.0)	69.0 (63.0-75.0)	72.0 (66.0-80.0)	<0.001
Fluid received in the preceding 24 hr, mL, Median (IQR)	4,192 (2,150-6,711)	4,070 (2,056-6,397)	4,207 (2,210-6,707)	4,523 (2,192-7,321)	4,479.5 (2,557.5-7,508)	<0.001
Cumulative fluid balance, Liters, Median (IQR)	4,447.0 (1,286.0-9,954.0)	4,108.0 (1,240.0-9,090.0)	3,663.0 (810.0-7,568.0)	7,150.0 (2,530.0-14,244.0)	5,165.3 (1,249.5-12,207.5)	<0.001
Cardiac Index 24 hours before vasopressors, Liters/min, Median (IQR)	3.6 (3.0-4.5)	3.6 (3.0-4.3)	3.6 (3.0-4.5)	4.1 (3.3-5.2)	3.6 (3.0-4.6)	<0.001

Characteristics	No. (%)					P value
	All (N=5,313)	Cluster 1 (N=2,931)	Cluster 2 (N=873)	Cluster 3 (N=673)	Cluster 4 (N=836)	
CVP 24hr before vasopressor, cm H_20, Median (IQR)	17 (13-22)	17 (13-22)	17 (13-21)	20 (15-26)	18 (14-23)	<0.001
ICU admission to vasopressor initiation, hours, Median (IQR)	12.3 (3.8-64.5)	11.7 (3.6-52.9)	9.9 (3.4-37.6)	10.4 (1.4-86.4)	21.7 (7.1-127.9)	<0.001
Digital Ischemia	779 (14.7)	415 (14.2)	141 (16.2)	89 (13.2)	134 (16.0)	0.2
Necrosis	288 (5.4)	168 (5.7)	49 (5.6)	27 (4.0)	44 (5.3)	0.3

eTable 4: Patient Outcomes by Cluster

Outcomes	No. (%)					
	All (N=5,313)	**Cluster 1 (N=2,931)**	**Cluster 2 (N=873)**	**Cluster 3 (N=673)**	**Cluster 4 (N=836)**	**P value**
Length of ICU stay, median (IQR)	6.0 (3.0-15.0)	6.0 (3.0-13.0)	6.0 (3.0-12.0)	8.0 (4.0-18.0)	9.0 (4.0-19.0)	<0.001
Length of hospital stay, median (IQR)	18.0 (9.0-33.0)	17.0 (9.0-30.0)	17.0 (10.0-34.0)	17.0 (6.0-34.0)	23.0 (11.0-40.0)	<0.001
Use of KRT	780 (14.7)	342 (11.7)	107 (12.3)	182 (27.0)	149 (17.8)	<0.001
1-year mortality	2,236 (42.1)	1,119 (38.2)	294 (33.7)	437 (64.9)	386 (46.2)	<0.001

eTable 5: Vasopressor dose by Cluster

Vasopressor dose	Mean (SD)					P value
	All (N=5,313)	Cluster 1 (N=2,931)	Cluster 2 (N=873)	Cluster 3 (N=673)	Cluster 4 (N=836)	
Dopamine	0.06 (0.15)	0.054 (0.15)	0.04 (0.08)	0.11 (0.21)	0.07 (0.15)	<0.001
Norepinephrine	0.72 (1.93)	0.555 (2.33)	0.29 (0.44)	1.63 (1.91)	0.99 (0.82)	<0.001
Phenylephrine	0.001(0.02)	0.000 (0.002)	0.002 (0.02)	0.003 (0.06)	0.001 (0.01)	0.035
Epinephrine	0.12 (0.84)	0.12 (1.09)	0.13 (0.24)	0.15 (0.49)	0.10 (0.25)	0.66
Vasopressin	0.08 (1.02)	0.08 (1.17)	0.10 (0.36)	0.14 (1.41)	0.05 (0.18)	0.26
Cumulative nor-epinephrine equivalent dose	0.99 (2.40)	0.81 (2.93)	0.57 (0.69)	2.04 (2.34)	1.22 (0.75)	<0.001

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