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DATABASE ANALYSIS

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Norepinephrine, Dopamine, and Vasopressin in Patients with Sepsis and Preexisting or Acute Heart Failure: A Retrospective Cohort Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to assess the impact of norepinephrine (NE), norepinephrine plus vasopressin (NE+VAS) and dopamine in patients with sepsis and heart failure.

Material/Methods: Data were extracted from the Medical Information Mart for Intensive Care III database, v1.4. Adults aged >18 years in an Intensive Care Unit (ICU) who had heart failure and took vasopressors were included. The patients were divided into 3 groups: NE, NE+VAS, and dopamine. Differences in survival, treatment time, and organ function among the 3 groups were compared. Propensity score matching (PSM) was used to screen for possible prognostic differences, and regression analysis was used to further analyze and predict prognoses.

Results: A total of 1864 patients were included. There were significant differences among the 3 groups in 7-, 28-, and 90-day mortality after PSM. The 5-year survival rates among the 3 groups also were significantly different ($P<0.001$). After Cox regression analysis, NE+VAS was an independent risk factor affecting 5-year survival ($P<0.001$). After multiple linear regression, dopamine was the factor related to ICU and hospital lengths of stay.

Conclusions: Compared with NE or dopamine alone, NE+VAS can reduce survival in patients with sepsis and heart failure who need vasopressors. Compared with the other 2 treatment options, dopamine can shorten ICU and hospital stays for these patients.

MeSH Keywords: Dopamine • Heart Failure • Norepinephrine • Sepsis • Vasopressins

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/927716

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Background

Sepsis is well-recognized as a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection. It is a life-threatening organ dysfunction that results from a dysregulated host response to infection. The clinical manifestations depend on the site of infection and the response of the host to the infection. Patients with sepsis often present with general malaise and nonspecific signs such as fever (although hypothermia can be present, too), tachycardia, or altered mental status [1]. As the disease progresses, arterial hypotension, gas exchange disorders (even when the focus of infection is outside the chest), oliguria, and increased capillary recanalization time can occur (**Figure 1**) [1].

In the United States, admissions for sepsis have overtaken those for myocardial infarction and stroke [2]. Although outcomes in patients with sepsis have improved, the mortality rate ranges from 25% to 30%, and when shock is present, it can approach 40% to 50% [3]. Sepsis-associated multiorgan dysfunction is the predominant cause of death. Clinical identification of organ dysfunction is based largely on surrogates such as serum creatinine, serum bilirubin, blood pressure, PaO_2/FiO_2 ratio, Glasgow Coma Scale, platelet count, and respiratory rate [4]. However, little is known about the pathobiology of dysfunction in individual organ systems or prognosis.

Heart failure (HF) is a major cause of cardiovascular morbidity and mortality and affects 5.7 million US adults, and the prevalence is predicted to increase by 46% in the next 15 years [5]. In nearly 70% of patients with sepsis, the condition is severe, and it can manifest as hemodynamic instability, cardiac biomarker elevation, myocardial dysfunction on echocardiography, and end-organ hypoperfusion [6]. In about 1% of cases of severe sepsis, infective endocarditis, the most important cause of cardiac dysfunction, is associated with a mortality rate of 33% [7]. The onset of HF in sepsis greatly increases the risk of mortality and it is a major cause of therapy failure.

Currently, norepinephrine (NE), dopamine, and vasopressin (VAS) are commonly used as vasoactive drugs in the clinic. Most studies of these drugs have focused on their use in populations with sepsis or cardiogenic shock, and few have focussed on patients with sepsis and HF. Therefore, we conducted the present retrospective cohort study to evaluate these 3 drugs in patients with sepsis and HF.

Material and Methods

Data sources

Data were obtained from the Medical Information Mart for Intensive Care (MIMIC)-III database, v1.4, which is an open-access database containing information on patients admitted to Beth Israel Deaconess Medical Center (BIDMC) (Boston, Massachusetts, U.S.A.) between 2001 and 2012 [8]. Use of the MIMIC-III database was approved by the Institutional Review Boards of BIDMC and Massachusetts Institute of Technology (certification number: 36300529).

Study population and stratification

Patients older than age 18 years admitted to the Intensive Care Unit (ICU) for more than 24 h were included. For patients with multiple ICU admissions, only the first stay was analyzed. Because there was no criterion standard for sepsis, the diagnosis was identified in patients in the present study based on:

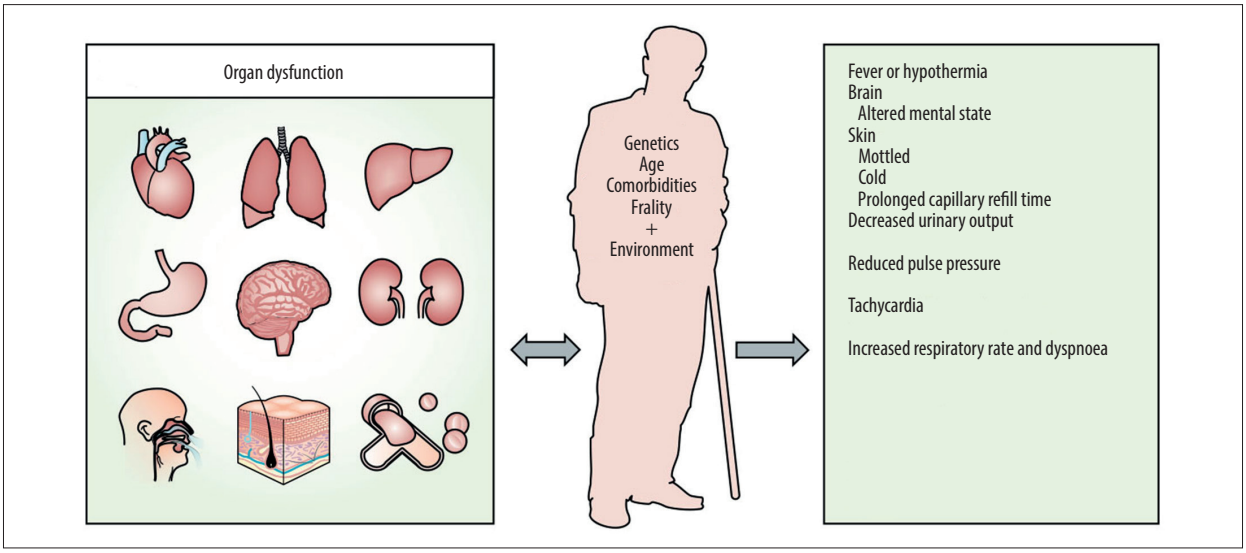

Figure 1. Clinical manifestations and organs involved in sepsis.

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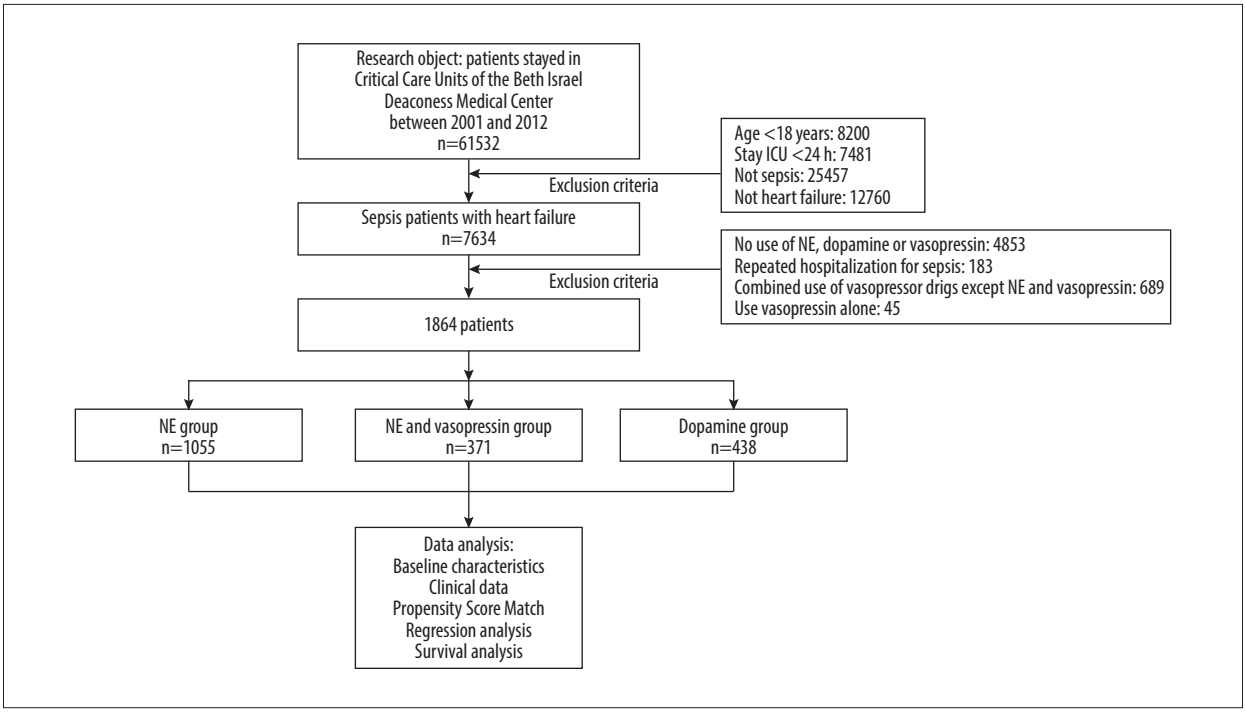

Figure 2. The process of inclusion and exclusion of research objects. NE – norepinephrine; VAS – vasopressin.

- The Sepsis-3 criteria for an infection with associated organ dysfunction (Sequential Organ Failure Assessment [SOFA] score ≥2) [9];
- International Classification of Diseases, 9th revision (ICD-9) codes 955.95 (sepsis) or septic shock (785.52);
- The Angus method for extracting patients with sepsis [10]; or
- The ICD-9 codes proposed by Martin et al. [11].

The following ICD-9 codes were used to identify a diagnosis of HF with comorbidities: 4280, 4281, 4289, 39891, 40201, 40211, 40291, 40401, 40403, 40411, 40491, 40493, 42820, 42821, 42822, 42823, 42830, 42831, 42832, 42833, 42840, 42841, 42842, and 42843.

Exclusion criteria were age <18 years; ICU length of stay <24 h; no sepsis; no HF; no exposure to NE, VAS or dopamine; use of combinations of vasoactive drugs other than NE combined with VAS; and repeated hospitalization for sepsis. Based on our clinical practice, we included patients taking NE combined with VAS (NE+VAS) and excluded those taking VAS alone (**Figure 2**).

Definitions and outcomes

Congestive HF (CHF) was defined as HF with limb edema or pulmonary congestion. Preexisting HF was defined as preexisting chronic HF or various cardiomyopathies, including acute exacerbations of chronic HF. The remainder of the population was patients who were originally heart-healthy and had a diagnosis of acute cardiac dysfunction during their current hospitalization. Information on heart rate (HR), temperature, laboratory tests, and scores were collected on admission to the ICU.

The primary endpoint of the study was all-cause mortality (7-, 28-, and 90-day mortality). Secondary endpoints included the following indicators: hospital length of stay (Hos LOS), ICU length of stay (LOS), incidence of mechanical ventilation (MV), MV duration, incidence and duration of new renal replacement therapy (RRT), incidence of acute kidney injury (AKI), increased HR, emerging arrhythmia, emerging malignant arrhythmia, and decreased hemoglobin level and platelet count. AKI was diagnosed using the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine-based criterion, which was defined as an absolute increase of ≥1.5 times baseline [12]. New ventricular tachycardia, ventricular fibrillation, and asystole were described as emerging malignant arrhythmias. Increased HR was calculated as the difference between the maximum and baseline HR during ICU treatment, as measured by electrocardiogram. Hemoglobin and platelet declines were the baseline level minus the minimal value during a patient's ICU stay.

Statistical analysis

For continuous variables, mean ± standard error of mean, median, or interquartile range are given. Categorical variables are expressed as absolute and relative frequencies. Analysis of variance, the Wilcoxon rank sum test, or the Kruskal-Wallis test were used wherever applicable. Propensity score matching

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Table 1. Demographic characteristics and clinical baseline data for the patients.

Variables	NE group (n=1055)	NE+VAS group (n=371)	Dopamine group (n=438)	*P* value
Demographics				
Age (y, mean±SD)	72.54±13.6	69.06±14.11	74.58±12.28	<0.001*
Sex (% Male)	555 (52.6%)	217 (58.5%)	208 (47.5%)	0.008
Weight (kg)	81.75±25.12	86.3±29.27	81.18±25.82	0.016*
Ethnicity (% White)	785 (74.4%)	275 (74.1%)	296 (67.6%)	0.021
Comorbidity (%)				
CHF	852 (80.8%)	282 (76%)	212 (48.4%)	<0.001
Preexisting HF	1026 (97.3%)	362 (97.6%)	432 (98.6%)	0.278
Valvular disease	168 (15.9%)	65 (17.5%)	54 (12.3%)	0.097
Peripheral vascular	137 (13%)	49 (13.2%)	60 (13.7%)	0.934
Hypertension	236 (22.4%)	82 (22.1%)	71 (16.2%)	0.023
Chronic pulmonary	280 (26.5%)	104 (28%)	121 (27.6%)	0.822
Neurological	151 (14.3%)	34 (9.2%)	39 (8.9%)	0.002
Diabetes	376 (35.6%)	136 (36.7%)	143 (32.6%)	0.431
Hypothyroidism	167 (15.8%)	36 (9.7%)	57 (13%)	0.011
Chronic kidney disease	306 (29%)	107 (28.8%)	103 (23.5%)	0.083
Liver disease	67 (6.4%)	45 (12.1%)	19 (4.3%)	<0.001
Lymphoma	24 (2.3%)	9 (2.4%)	7 (1.6%)	0.654
Tumor	31 (2.9%)	13 (3.5%)	10 (2.3%)	0.583
Rheumatoid arthritis	33 (3.1%)	14 (3.8%)	11 (2.5%)	0.588
Coagulopathy	241 (22.8%)	129 (34.8%)	56 (12.8%)	<0.001
Temperature (°C)	36.1 (35.56, 37.5)	36.06 (35.4, 37.5)	36 (35.56, 37.13)	0.047
Heart rate (bpm)	87.29±18.44	91.68±21.39	82.56±18.26	<0.001*
Dobutamine	66 (6.3%)	51 (13.7%)	47 (10.7%)	<0.001
Microbiology information (%)				
Bacteria	704 (66.7%)	254 (68.5%)	299 (68.3%)	0.758
Fungi	192 (18.2%)	70 (18.9%)	61 (13.9%)	0.095
Virus	10 (0.9%)	0 (0%)	2 (0.5%)	0.147**
Laboratory tests				
Lactate (mmol/L)	2.09±1.498	3.19±2.91	2.18±1.74	<0.001*
Bilirubin (mg/dL)	1.36±3.59	2.24±4.44	0.93±2.08	<0.001*
sCR (μmol/L)	1.81±1.58	2.01±1.60	2.04±1.55	0.015*
BUN (mmol/L)	37.18±25.12	38.83±24.91	42.29±26.74	0.003*
Platelets (k/uL)	226.91±127.06	211.99±127.92	241.21±109.97	0.002*
Hemoglobin (g/dL)	10.14±1.82	10.18±1.85	10.56±1.90	<0.001*

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Table 1 continued. Demographic characteristics and clinical baseline data for the patients.

Variables	NE group (n=1055)	NE+VAS group (n=371)	Dopamine group (n=438)	*P* value
Scores				
SOFA	7 (5, 9)	9 (6, 11)	6 (4, 8)	<0.001
APS-III	55 (43, 68)	65 (50, 86)	52.5 (42, 65)	<0.001
SAPS II	46 (38, 54)	51 (41, 61)	44 (36, 53)	<0.001
GCS	11 (8, 14)	10 (6, 14)	14 (9, 15)	<0.001
PaO_2/FiO_2	217 (140, 323)	200 (119, 298.3)	202.77 (136.65, 301.36)	0.019

Data are presented as n (%), mean±SD, or median and interquartile range. *P* values are comparisons between the NE, NE+VAS, and dopamine groups. * Using Welch's *t* test; ** Using Fisher's exact test. APS-III – Acute Physiology Score III; CHF – congestive heart failure; GCS – Glasgow Coma Scale, HF – heart failure; HR – heart rate; NE – norepinephrine; Preexisting HF – preexisting heart failure; SAPS II – Simplified Acute Physiology Score II; sCR – serum creatinine; SD – standard deviation; SOFA – Sequential Organ Failure Assessment; VAS – vasopressin.

Table 2. Outcomes in the patients.

Variable	Group			*P* value
	NE (n=1055)	NE+VAS (n=371)	Dopamine (n=438)	
Mortality rate (%)				
7-d	105 (10%)	85 (22.9%)	45 (10.3%)	<0.001
28-d	284 (26.9%)	189 (50.9%)	107 (24.4%)	<0.001
90-d	409 (38.8%)	232 (62.5%)	161 (36.8%)	<0.001
ICU LOS (h)	231.76±235.84	347.52±312.16	171.52±171.93	<0.001*
Hos LOS (d)	15.58±12.9	17.44±14.53	13.07±10.62	<0.001*
Mechanical ventilation (%)	758 (71.8%)	336 (90.6%)	259 (59.1%)	<0.001
Vent durations (h)	47.77 (0, 173.8)	148.3 (44,307)	12.38 (0, 87.17)	<0.001
New RRT (%)	21 (2%)	50 (41.5%)	4 (0.9%)	<0.001**
AKI (%)	257 (24.4%)	154 (35.6%)	91 (20.8%)	<0.001
Increased heart rate (bpm)	37.99±26.52	45.84±29.39	32.02±23.11	<0.001
Emerging arrhythmias (%)	392 (37.2%)	164 (44.2%)	216 (49.3%)	<0.001
Emerging malignant arrhythmias (%)	46 (4.4%)	42 (11.3%)	22 (5%)	<0.001
Reduced hemoglobin (g/dL)	1.69±1.50	2.08±1.73	1.66±1.52	<0.001
Platelet decline (k/μL)	71.48±80.32	100.09±97.51	70.21±76.81	<0.001

Data are presented as n (%), mean±SD, or median and interquartile range. *P* values are comparisons between the NE, VAS, NE+VAS, and dopamine groups. * Using the Welch's *t* test; ** Using Fisher's exact test. AKI – acute kidney injury; Hos LOS –time from transfer to ICU to discharge; ICU LOS – Intensive Care Unit length of stay; NE – norepinephrine; RRT – renal replacement therapy; SD – standard deviation; VAS – vasopressin; Vent durations – mechanical ventilation time.

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Table 3. Demographic characteristics of and clinical baseline data for patients in the NE, NE+VAS, and dopamine groups after propensity score matching.

Variable	Group			*P* value
	NE (N=231)	NE& VAS (N=231)	Dopamine (N=231)	
Demographics				
Age (y, mean±SD)	69.53±14.07	70.97±13.58	72.04±12.86	0.192
Sex (% Male)	126 (54.5%)	133 (57.6%)	124 (53.7%)	0.676
Weight (kg)	83.40±27.45	83.80±25.60	83.07±28.11	0.792
Temperature (°C)	36.11 (35.6, 37.56)	36 (35.44,37.56)	36.11 (35.61, 37.7)	0.294
Heart rate (bpm)	88.76±18.06	87.82±19.39	85.58±19.33	0.831
CHF	180 (77.9%)	165 (71.4%)	160 (69.3%)	0.093
Preexisting HF	219 (94.8%)	226 (97.8%)	226 (97.8%)	0.100
Dobutamine	16 (6.9%)	27 (11.7%)	22 (10%)	0.211
Laboratory tests				
Lactate (mmol/L)	2.23±1.39	2.35±1.42	2.42±1.92	0.474*
Bilirubin (mg/dL)	1.71±4.44	1.33±2.04	1.06±1.97	0.083*
sCR (μmol/L)	2.01±1.82	2.07±1.72	2.09±1.60	0.744
BUN (mmol/L)	38.08±24.87	39.87±25.78	40.03±26.92	0.652
Platelets (k/μL)	223.24±135.05	226.20±128.63	234.30±109.10	0.124
Hemoglobin (g/dL)	10.20±1.79	10.28±1.79	10.44±2.03	0.159
Scores				
SOFA	8 (6, 10)	8 (5,10)	7 (5,10)	0.232
APS-III	58 (46, 71)	58 (46, 73)	54 (44, 68)	0.153
SAPS II	47 (39, 53)	48 (39, 56)	45 (35,55)	0.154
GCS	10 (7, 14)	11 (8, 14)	11 (8, 14)	0.412
PaO_2/FiO_2	207 (118.6, 313.3)	206 (122.5, 315)	199 (135, 298)	0.800

Matching variables: Age, sex, weight, temperature, HR, CHF, preexisting HF, dobutamine, APS-III, SAPS II, SOFA, GCS, lactate, bilirubin, PaO_2/FiO_2, platelets, creatinine, BUN, hemoglobin. Matching tolerance: NE+VAS: NE=0.02, NE+VAS: Dopamine=0.1. * Using Welch's *t* test. APS-III – Acute Physiology Score III; BUN – blood urea nitrogen; CHF – congestive heart failure; GCS – Glasgow Coma Scale; HF – heart failure; NE – norepinephrine; SAPS II –Simplified Acute Physiology Score II; sCR – serum creatinine; SD – standard deviation; SOFA – Sequential Organ Failure Assessment; VAS – vasopressin.

(PSM) was used for variables with baseline differences. Kaplan-Meier curves were plotted for survival analysis and log-rank tests were used as appropriate. A Cox proportional hazards model and a multiple linear regression model were used as follows. First, multivariate analyses were used to test all variables with $P<0.1$ in univariate analysis; then, a stepwise elimination procedure was used to remove variables with $P>0.1$; then, variables with latent multicollinearity were included in the 2 models for retrospective analysis. All statistical analyses were carried out with SPSS software (IBM SPSS Statistics v26). In all tests, the α level was set at 0.05 (2-sided).

Results

Initially, 61 532 records were identified in the MIMIC-III database, of which 53 898 were excluded (8200 were patients aged <18 years; 7481 spent <24 h in the ICU; 25 457 did not have sepsis; 12 760 were patients without HF). Of the remaining

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Table 4. Outcomes after PSM in patients in the NE, NE+VAS, and dopamine groups.

Variable	Group			*P* value
	NE (n=231)	NE+VAS (n=231)	Dopamine (n=231)	
Mortality rate (%)				
7-d	26 (11.3%)	40 (17.3%)	21 (9.1%)	0.022
28-d	61 (26.4%)	106 (45.9%)*	55 (23.8%)	<0.001
90-d	87 (37.7%)	130 (56.3%)*	88 (38.1%)	<0.001
ICU LOS (h)	255.14±274.2	345.62±295.39	189.32±189.63	<0.001**
Hos LOS (d)	16.9±15.88	17.54±12.71	14.16±10.74*	0.005**
Mechanical ventilation (%)	178 (77.1%)	203 (87.9%)	149 (64.5%)	<0.001
Vent durations (h)	56 (2.25, 206)	140 (38.67, 285.5)*	32.32 (0, 143.8)	<0.001
New RRT (%)	6 (2.6%)	24 (10.4%)*	1 (0.4%)	<0.001
AKI (%)	66 (28.6%)	91 (39.4%)*	51 (22.1%)	<0.001
Increased heart rate (bpm)	37.27±23.42	48.18±30.19*	34.24±24.99	<0.001
Emerging arrhythmias (%)	136 (58.9%)	107 (46.3%)	131 (56.7%)	0.015
Emerging malignant arrhythmias (%)	15 (6.5%)	31 (13.4%)*	9 (3.9%)	<0.001
Reduced hemoglobin (g/dL)	1.70±1.40	2.14±1.74*	1.67±1.54	0.003**
Platelet decline (k/μL)	72.03±85.88	107.65±98.13*	68.29±67.88	<0.001

* Significant difference between this group and the other 2 groups; ** Using Welch's *t* test. AKI – acute kidney injury; Hos LOS – hospital length of stay; NE – norepinephrine; PSM – propensity score matching; RRT – renal replacement therapy; VAS – vasopressin.

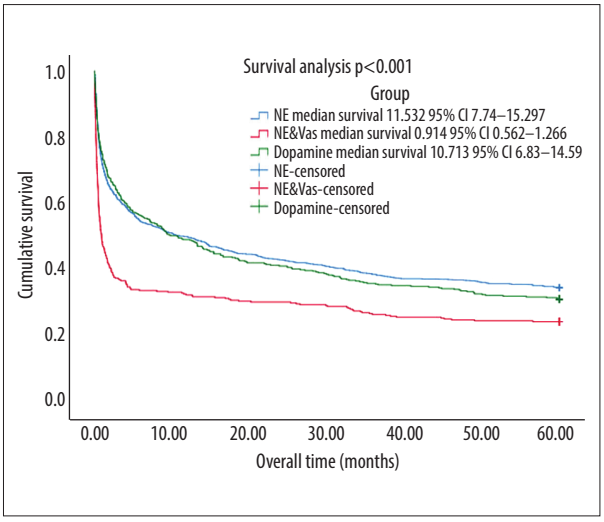

Figure 3. The 5-year survival rates in the norepinephrine, NE+VAS, and dopamine groups were 34.6%, 24.3%, and 31.1%, respectively.

7634 patients with sepsis and HF, 4853 were excluded for not using NE, dopamine, or VAS; 689 patients were excluded for using vasopressors other than NE combined with VAS; and 183 were excluded for repeated hospitalization for sepsis.

Finally, 1864 patients with sepsis and HF were included: 1055 in the NE group, 371 in the NE+VAS group, and 438 in the dopamine group (**Table 1**). The mean age was 72.32±13.52 years, 980 patients (52.58%) were male, and 1356 (72.7%) were White. There were 1592 patients (85.4%) in this study for whom microbiological results were available (**Supplementary Table 1**). They were distributed across 5 types of ICUs: 977 (52.41%) in the medical ICU, 396 (21.24%) in the coronary care unit, 242 (12.98%) in the cardiac surgery recovery unit, 165 (8.85%) in the surgical ICU, and 84 (4.99%) in the trauma/surgical ICU. Significant differences were noted among the 3 groups in terms of 7-, 28-, and 90-day mortality; treatment duration (ICU and Hos LOS, and MV duration); and organ function (MV, new RRT, AKI, emerging arrhythmias, emerging malignant arrhythmias, increased HR, and reduced hemoglobin level and platelet count (**Table 2**).

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Table 5. Associations with 5-year mortality in patients with sepsis and heart failure in the NE, NE+VAS, and dopamine groups.

	Unadjusted (n=1864)		*P* value	Adjusted (n=1864)		*P* value
	Composite endpoint HR (95% CI)			HR (95% CI)		
Sex (Male)	1.003	(0.899, 1.120)	0.952			
Age	1.019	(1.014–1.023)	<0.001	1.019	(1.015–1.024)	<0.001
Weight (kg)	0.995	(0.993–0.998)	<0.001	0.997	(0.995–0.999)	0.028
Race (White)	1.009	(0.892–1.143)	0.883			
Group (NE reference)						
NE+VAS	1.585	(1.379–1.821)	<0.001	1.466	(1.266–1.697)	<0.001
Dopamine	1.056	(0.922–1.209)	0.432	1.053	(0.915–1.212)	0.474
SOFA	1.060	(1.042–1.079)	<0.001	0.983	(0.959–1.009)	0.199
APS-III	1.016	(1.013–1.018)	<0.001	1.010	(1.008–1.013)	<0.001
GCS	0.981	(0.968–0.994)	0.004	0.991	(0.976–1.007)	0.266
Lactate (mmol/L)	1.068	(1.039–1.097)	<0.001	1.017	(0.985–1.049)	0.300
PaO_2/FiO_2	1.000	(0.999–1.000)	0.097	1.000	(0.999–1.000)	0.076
Bilirubin	1.048	(1.034–1.063)	<0.001	1.036	(1.021–1.052)	<0.001
Platelets (k/μL)	1.000	(0.999–1.000)	0.163			
sCr (μmol/L)	1.067	(1.036–1.099)	<0.001	1.016	(0.972–1.062)	0.478
BUN	1.008	(1.007–1.010)	<0.001	1.004	(1.001–1.007)	0.002
Hemoglobin	0.939	(0.911–0.968)	<0.001	0.963	(0.933–0.993)	0.017
Heart rate (bpm)	1.005	(1.002–1.008)	0.001	1.005	(1.002–1.008)	0.002
CHF	1.515	(1.331–1.724)	<0.001	1.418	(1.235–1.629)	<0.001
Preexisting HF	0.887	(0.625–1.260)	0.505			
Temperature	0.904	(0.870–0.940)	<0.001	0.948	(0.912–0.985)	0.011
Dobutamine	1.447	(1.206–1.736)	<0.001	1.458	(1.212–1.754)	<0.001

APS-III – Acute Physiology Score III; BUN – blood urea nitrogen; CHF – congestive heart failure; GCS – Glasgow Coma Score; HF – heart failure; NE – norepinephrine plus vasopressin; sCr – serum creatinine; SOFA – Sequential Organ Failure Assessment; VAS – vasopressin.

PSM was used to balance the differences among the 3 groups at baseline (**Table 3**). After PSM, all outcome variables were significantly different among the 3 groups, especially the primary endpoint (**Table 4**). A 5-year survival analysis suggested a significant difference in cumulative survival among the NE, dopamine, and NE+VAS groups ($P<0.001$, **Figure 3**). The combination of NE and VAS was negatively associated with 5-year cumulative survival in both unadjusted and adjusted Cox regression models (**Table 5**). For the secondary endpoints, we focused on analysis of ICU and Hos LOS. A multivariate linear retrospective model was constructed to examine whether dopamine was an important negative factor associated with ICU and Hos LOS (**Tables 6, 7**; Simplified Acute Physiology Score II may have multiple collinearity problems with other variables, so it was not included in the multifactor analysis model). In addition, we performed a multiple linear regression analysis of mechanical ventilation duration in these patients and showed that dopamine was a negative factor (**Supplementary Table 2**).

Finally, it is well known that there is an ambivalent dose-effect role for dopamine. Therefore, we divided the dopamine group into low-, moderate-, and high-dose groups [13] and analyzed patient baselines and outcome variables. There were no significant differences in the baseline conditions, except for the criticality scores in the low- and high-dose groups (**Table 8**). No significant differences in any outcome variables were observed between the high- and low-dose groups (**Table 9**).

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Table 6. Multiple linear regression analysis of differences in ICU LOS among the NE, NE+VAS, and dopamine groups.

Parameter	Univariate (n=1864)			Multivariate (n=1864, stepwise elimination)		
	Unstandardized B	95% CI	*P* value	Unstandardized B	95% CI	*P* value
Sex (Male)	7.562	−14.947~30.070	0.510			
Age	−2.879	−3.700~−2.058	<0.001	−2.286	−3.081~−1.491	<0.00
Weight (kg)	0.788	0.360–1.215	<0.001			
Race (White)	−7.801	−33.044~17.441	0.544			
Group (NE reference)						
NE+VAS	133.43	105.94~160.92	<0.001	113.38	85.2~141.5	<0.001
Dopamine	−90.363	−116.55~−64.171	<0.001	−28.89	−56.214~−1.569	0.038
SOFA	−0.189	−3.635~3.256	0.914	−10.57	−14.124~−7.017	<0.001
APS-III	0.432	−0.089~0.954	0.104			
GCS	−11.605	−14.326~−8.884	<0.001	−12.42	−15.232~−9.608	<0.001
Lactate (mmol/L)	2.454	−3.280~8.188	0.401			
PaO_2/FiO_2	−0.061	−0.146~0.023	0.155			
Bilirubin	3.010	−0.178~6.198	0.064			
Platelets(k/μL)	−0.034	−0.125~0.057	0.462			
sCr (μmol/L)	−6.515	−13.617~0.587	0.072			
BUN	−0.117	−0.557~0.324	0.603			
Hemoglobin	−1.831	−7.894~4.232	0.554			
Heart rate (bpm)	0.393	−0.191~0.977	0.187			
CHF	68.027	43.125~92.928	<0.001	61.615	36.778~86.452	<0.001
Preexisting HF	−47.310	−121.32~26.7	0.210			
Temperature	16.562	8.780~24.344	<0.001	9.362	1.910~16.813	0.014
Dobutamine	14.139	−25.537~53.815	0.485			

APS-III – Acute Physiology Score III; BUN – blood urea nitrogen; CHR – congestive heart failure; GCS – Glasgow Coma Scale; HF – heart failure; ICU LOS – Intensive Care Unit length of stay; NE – norepinephrine; SOFA – Sequential Organ Failure Assessment; VAS – vasopressin.

Discussion

In the present study, 3 main findings were elicited. First, the outcomes in the NE+VAS group were significantly worse than in the NE and dopamine groups in terms of all-cause mortality, treatment duration, and safety measures in patients with sepsis and HF who needed vasopressors (the incidence of emerging arrhythmias was lower, but the incidence of emerging malignant arrhythmias was higher.) Furthermore, after PSM, the dopamine group did not show a higher incidence of emerging arrhythmias, especially malignant arrhythmias, than the NE group. Last but not least, dopamine can shorten ICU and Hos LOS in these patients compared with the LOS in the NE and NE+VAS groups.

In the clinic, NE, VAS, and dopamine are the most commonly used vasoactive drugs. An intriguing and important question is regarding the best approach for patients with sepsis. NE was recommended as the first-choice vasopressor for sepsis in the Surviving Sepsis Campaign (SSC) guidelines [14]. An earlier systematic review and meta-analysis suggested that NE has more advantages than dopamine related to the occurrence of all-cause mortality and arrhythmia in septic shock [15]. Therefore, it is recommended that use of NE be prioritized in

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Table 7. Multiple linear regression analysis of differences in hospital length of stay among the NE, NE+VAS, and dopamine groups.

Parameter	Univariate (n=1864)			Multivariate (n=1864, stepwise elimination)		
	Unstandardized B	95% CI	*P* value	Unstandardized B	95% CI	*P* value
Sex (Male)	0.952	–0.216~2.119	0.11			
Age	–0.195	–0.237~–0.153	<0.001	–0.189	–0.231~–0.147	<0.00
Weight (kg)	0.047	0.025–0.069	<0.001			
Race (White)	–0.061	–1.371~1.249	0.927			
Group (NE reference)						
NE+VAS	2.598	1.142~4.054	<0.001	113.38	85.2~141.5	<0.001
Dopamine	–2.993	–4.362~–1.625	<0.001	–1.461	–2.879~–0.043	0.043
SOFA	0.064	–0.114~0.243	0.479	–0.236	–0.423~–0.049	0.014
APS-III	0.011	–0.016~0.038	0.420			
GCS	–0.380	–0.523~–0.238	<0.001	–0.419	–0.569~–0.269	<0.001
Lactate (mmol/L)	0.07	–2.228~0.367	0.646			
PaO_2/FiO_2	0.001	–0.004~0.005	0.728			
Bilirubin	0.076	–0.09~0.241	0.370			
Platelets(k/μL)	–0.004	–0.008~0.001	0.133			
sCr (μmol/L)	–0.023	–0.391~0.346	0.904			
BUN	–0.013	–0.036~0.010	0.253			
Hemoglobin	–0.082	–0.396~0.233	0.611			
Heart rate (bpm)	–0.002	–0.032~0.029	0.910			
CHF	2.415	1.118~3.712	<0.001	2.015	0.689~3.340	0.003
Preexisting HF	–4.496	–8.322~–0.660	0.022	–3.764	–7.486~–0.041	0.048
Temperature	0.683	0.279~1.088	0.001			
Dobutamine	–0.434	–2.493~1.625	0.679			

APS-III – Acute Physiology Score III; BUN – blood urea nitrogen; CHF – congestive heart failure; HF – heart failure; NE – norepinephrine; NE – norepinephrine; sCR – serum creatinine; SOFA – Sequential Organ Failure Assessment; VAS –vasopressin.

patients with septic shock [14]. In addition, NE has replaced epinephrine as the first-line booster for patients in cardiogenic shock [16]. The guidelines are based on some randomized controlled trials (RCTs) that recommended NE instead of dopamine for cardiogenic shock, but the role of the 2 drugs in septic shock with HF remains controversial [17]. VAS is a non-catecholamine booster drug, and in some recent studies, use of it rather than epinephrine has been shown to significantly decrease mortality in patients with cardiovascular disease and sepsis [18]. VAS was recommended as the second-line vasopressor for sepsis in the SSC guidelines [14]. However, in animal studies, it has been demonstrated to have a negative impact on coronary perfusion [19]. VAS can also induce profound vasoconstriction in the fluid reservoir of the splanchnic vasculature. However, given the lack of human data on the drug's adverse effects and its efficacy when used in combination with NE, VAS should be the first choice when added to NE for sepsis in patients with preexisting HF [20]. Dopamine, which is recommended as a last-line vasopressor for septic shock, can increase arrhythmias [14]. However, some trials have not demonstrated that dopamine increases cardiac adverse effects in patients with acute HF [21,22]. Because of the lack of evidence for vasopressors in patients with sepsis who already have HF, the data on which the SSC guidelines were based are primarily from subgroups within studies on sepsis, septic shock, and other shock presentations [20].

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Table 8. Demographic characteristics and clinical basis data for patients in the low-, moderate-, and high-dose dopamine groups.

Variables	Dopamine dose group			*P* value
	Low (<5 μg/kg/min)	Moderate (5–15 μg/kg/min)	High (>15 μg/kg/min)	
	(n=93)	(n=293)	(n=52)	
Demographics				
Age (years, mean±SD)	74.93±12.29	74.88±12.28	72.27±12.29	0.982
Sex (% Male)	50 (53.8%)	133 (45.4%)	25 (48.1%)	0.379
Weight (kg)	82.61±29.27	81.11±25.30	79.08±22.17	0.487
Temperature	36 (35.58, 36.49)	36 (35.56, 37.3)	35.8 (35.3, 37.4)	0.397
Heart rate (bpm)	82.33±18.91	82.44±18.16	83.69±17.92	0.688
CHF	40 (43%)	145 (49.5%)	27 (51.9%)	0.480
Preexisting HF	92 (98.9%)	289 (98.6%)	51 (98.1%)	0.829*
Dobutamine	10 (10.8%)	29 (9.9%)	8 (15.4%)	0.500
Laboratory tests				
Lactate (mmol/L)	2.42±1.86	2.14±1.76	1.99±1.36	0.333
Bilirubin (mg/dL)	0.86±1.57	0.94±2.24	1.05±2.03	0.776
sCR (μmol/L)	1.78±1.23	2.11±1.63	2.08±1.58	0.156
BUN (mmol/L)	37.45±24.07	43.55±27.77	43.86±24.72	0.334
Platelets (k/μL)	240.33±123.95	239.49±105.28	252.46±110.86	0.290
Hemoglobin (g/dL)	10.32±1.76	10.61±1.95	10.69±1.88	0.287
Scores				
SOFA	5 (4,7)	6 (5,8)	7 (6,9)	<0.001
APS-III	49 (39.5, 58.5)	54 (43, 65.5)	55.5 (49, 69.5)	0.001
SAPS II	40 (32, 48)	45 (37, 52)	48 (39.25, 58.75)	<0.001
GCS	14 (10, 15)	13 (9, 15)	11 (7.25, 14)	0.012
PaO_2/FiO_2	231 (166.8, 329.5)	193.7 (130.7, 289.4)	192.5 (134, 302)	0.046

APS-III – Acute Physiology Score III; BUN – blood urea nitrogen; CHF – congestive heartfFailure; HR – heart rate; sCR – serum creatinine; SAPS II – Simplified Acute Physiology Score II; SD – standard deviation, SOFA – Sequential Organ Failure Assessment.
* Using Fisher's exact test.

In the present retrospective study based on real-world data, we have found that for patients with sepsis and HF who need vasopressors, NE+VAS may be harmful (7-, 28-, and 90-day mortality, and other endpoints). A 5-year cumulative survival analysis indicated that the rate of mortality was higher in patients treated with NE+VAS ($P<0.001$). Analyses using the adjusted Cox retrospective model showed that use of a combination of NE and VAS was an independent risk factor for long-term survival in these patients. This is consistent with a recent network meta-analysis suggesting that NE+VAS increases mortality rates in patients with sepsis [23]. We may need to avoid this combination in patients with sepsis and HF who require vasopressors.

In terms of arrhythmia, we compared our results those from published RCTs and found some similarities and differences [16,24]. One of the studies included patients with cardiogenic and septic shock. The double-blind and randomized Comparison of Dopamine and Norepinephrine in the Treatment of Shock [24] trial enrolled 1679 patients, of whom 858 were

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Table 9. Outcomes of patients in the low-, moderate-, and high-dose dopamine groups.

Variable	Dopamine dose group			*P* value
	Low (<5 μg/kg/min)	Moderate (5–15 μg/kg/min)	High (>15 μg/kg/min)	
	(n=93)	(n=293)	(n=52)	
Mortality rates (%)				
7-day	8 (8.6%)	28 (9.6%)	9 (17.3%)	0.195
28-day	19 (20.4%)	71 (24.2%)	17 (32.7%)	0.245
90-day	31 (33.3%)	109 (37.2%)	21 (40.4%)	0.698
Mechanical ventilation (%)	50 (53.8%)	172 (58.7%)	37 (71.2%)	0.119
Vent durations (h)	56 (2.25, 206)	140 (38.67, 285.5)	32.32 (0, 143.8)	<0.001
New RRT (%)	1 (1.1%)	3 (1%)	0 (0%)	1*
AKI (%)	26 (28%)	57 (19.5%)	8 (10.8%)	0.123
Increased heart rate (bpm)	33.45±25.93	32.53±22.15	35.04±23.42	0.356
Emerging arrhythmias (%)	47 (50.5%)	146 (49.8%)	23 (44.2%)	0.733
Emerging malignant arrhythmias (%)	3 (3.2%)	15 (5.1%)	4 (7.7%)	0.534
Reduced hemoglobin (g/dL)	1.36±1.28	1.73±1.55	1.78±1.41	0.259
Platelet decline (k/μL)	64.06±65.2	70.14±69.1	81.65±71.54	0.986

* Using Fisher's exact test. AKI – acute kidney injury; RRT – renal replacement therapy.

assigned to dopamine and 821 to NE, in 8 centers in Belgium, Austria, and Spain. No significant difference was shown in the mortality rates for patients with shock who were treated with dopamine and those who were treated with NE. This result was congruent with our study. However, dopamine was associated with more arrhythmias compared with NE. This is inconsistent with our results after PSM. The types of shock included the Comparison of Dopamine and Norepinephrine in the Treatment of Shock trial were septic (62.2%), cardiogenic (16.7%), and hypovolemic (15.7%). Patients with serious arrhythmias, such as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia, were excluded. NE can be used on an open-label basis, so the dopamine group may have received it in combination with NE. These variations in what was included and excluded may explain why our findings differ from those of the De Backer et al. Eventually, those authors concluded that the greater advantage seen in the NE group over the dopamine group came from cardiac rather than septic shock in the subgroup hazard ratio analysis.

Dopamine binds α1- and β1-adrenergic and dopaminergic DA1 and DA2 receptors, the latter causing splanchnic and renal vasodilation at low doses in preclinical studies and small clinical trials ("low-dose dopamine") [13]. Therefore, we also performed a subgroup analysis of the dopamine group. There were no differences between the low- and high-dose dopamine groups in AKI or other secondary outcome indicators. Compared with high-dose dopamine, low doses may not be nephroprotective in critically ill patients [25].

The present study has several limitations. First, retrospective comparisons were performed with PSM to minimize selection bias, but unobserved confounders may remain. For example, different treatment periods could lead to changes in treatment concepts, which may bias the results. Treatment with inotropic drugs may be necessary in patients with severe sepsis. If the retrospective analysis is interpreted hastily without limiting for that, the protective effective of the drugs may not be taken into consideration. Therefore, the results of the present study should be considered in the context of the target population and the limited comparison of the drugs. Subsequent validation of the data in prospective RCTs is needed. In addition, given the limitations of the information in the database, we did not classify preadmission cardiac function and exercise tolerance per patient. These conditions may have affected the duration of treatment, especially for MV. In addition, both pathogens and antibiotics could cause alterations in blood composition. Last but not least, the present study was done in a single center. A prospective, multicenter study with a larger sample size would be more convincing.

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Conclusions

In patients with sepsis and HF who need vasopressors, NE+VAS can reduce survival compared with NE or dopamine alone. Compared with the other 2 options, dopamine can shorten ICU and hospital stays in these patients.

Supplementary Data

Supplementary Table 1. Microbiology data for the patients.

Variables	NE group (n=1055)		NE+VAS group (n=371)		Dopamine group (n=438)		*P* value
Bacterium (%)							
Non-fermenter	56	(5.3%)	24	(6.5%)	14	(3.2%)	0.089
Tubercle bacillus	3	(0.3%)	1	(0.3%)	2	(0.5%)	0.856*
Anaerobic bacteria	5	(0.5%)	4	(1.1%)	3	(0.7%)	0.377*
Clostridium	24	(2.3%)	11	(3.0%)	10	(2.3%)	0.742
Corynebacterium	10	(0.9%)	6	(1.6%)	5	(1.1%)	0.550*
Enterobacter	106	(10.0%)	49	(13.2%)	46	(10.5%)	0.235
Enterococcus	60	(5.7%)	25	(6.7%)	28	(6.4%)	0.725
Gram-negative bacteria	41	(3.9%)	10	(2.7%)	28	(6.4%)	0.023
Gram-positive bacteria	19	(1.8%)	10	(2.7%)	8	(8.7%)	0.548
Klebsiella	60	(5.7%)	13	(3.5%)	21	(4.8%)	0.246
Proteus vulgaris	25	(2.4%)	6	(1.6%)	9	(2.1%)	0.683
Staphylococcus species	256	(24.3%)	86	(23.2%)	109	(24.9%)	0.850
Streptococci	39	(3.7%)	9	(2.4%)	16	(3.7%)	0.492
Fungi (%)	192	(18.2%)	70	(18.9%)	61	(13.9%)	0.095
Virus (%)	10	(0.9%)	0	(0.0%)	2	(0.5%)	0.147*

There were 1592 patients (85.4%) who had the microbiological results in this study. Gram-negative bacteria: other gram-negative bacteria not classified. Gram-positive bacteria: other gram-positive bacteria not classified. Non-fermenter included *Acinetobacter*, *Burkholderia*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. * Using Fisher's exact test.

Conflicts of interest

None.

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Supplementary Table 2. Multiple linear regression analysis of MV duration in the NE, NE+VAS, VAS, and dopamine groups.

Parameter	Univariate (n=1909)			Multivariate (n=1909, stepwise elimination)		
	Unstandardized B	95% CI	*P* value	Unstandardized B	95% CI	*P* value
Sex (Male)	6.717	−12.781~26.214	0.499			
Age	−2.458	−3.167~−1.748	<0.001	−1.907	−2.590~−1.224	<0.001
Weight (kg)	0.725	0.354~1.096	<0.001			
Race (White)	−16.6	−38.426~5.227	0.136			
Group (NE reference)			0.000			
Vasopressin	−23.847	−88~40.305	0.466			
NE+VAS	120.66	96.66~144.65	<0.001	94.415	70.010~118.821	<0.001
Dopamine	−80.036	−102.9~−57.17	<0.001	−37.898	−60.548~−15.247	0.001
SOFA	2.950	−0.03~5.93	0.052	−6.316	−9.362~−3.270	<0.001
APS-III	0.707	0.255~1.159	0.002			
GCS	−13.483	−15.81~−11.156	<0.001	−13.090	−15.509~−10.671	<0.001
Lactate (mmol/L)	2.815	−2.181~7.811	0.269			
PaO_2/FiO_2	−0.061	−0.134~0.013	0.106			
Bilirubin (mg/dL)	1.754	−0.959~4.467	0.205			
Platelets (k/μL)	0.005	−0.074~0.083	0.909			
sCr (μmol/L)	−7.817	−13.984~−1.650	0.013			
BUN	−0.229	−0.610~0.152	0.238			
Hemoglobin	−0.107	−5.339~5.125	0.968			
Heart rate (bpm)	0.526	0.019~1.034	0.042			
CHF	82.67	61.312~104.02	<0.001			
Preexisting HF	−30.491	−94.637~33.656	0.351			
Temperature	16.482	9.733~23.231	<0.001	10.928	4.498~17.358	0.001

APS-III – Acute Physiology Score III; BUN – blood urea nitrogen; CHF – congestive heart failure; GCS – Glasgow Coma Score; HF – heart failure; MV – mechanical ventilation; NE – norepinephrine; sCR – serum creatinine; SOFA – Sequential Organ Failure Assessment; VAS – vasopressin.

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