


# Norepinephrine use in cardiogenic shock patients is associated with increased 30 day mortality

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## Abstract

**Aims** Norepinephrine is recommended as a first-line vasopressor agent in the haemodynamic stabilization of cardiogenic shock. The survival benefit of norepinephrine therapy has not been demonstrated in clinical practice, however. This study aimed to explore the relationship between norepinephrine use and outcomes in cardiogenic shock patients in real-world conditions.

**Methods and results** We conducted a retrospective cohort study based on the Medical Information Mart for Intensive Care III (MIMIC-III) database. Cardiogenic shock patients were enrolled and categorized into a norepinephrine group or a non-norepinephrine group. Propensity score matching (PSM) was used to control for confounders. Cox proportional-hazards models and multivariable logistic regression were used to investigate the relationship between norepinephrine treatment and mortality. A total of 927 eligible patients were included: 552 patients in the norepinephrine group and 375 patients in the non-norepinephrine group. After PSM, 222 cases from each group were matched using a 1:1 matching algorithm. Thirty day mortality for patients treated with norepinephrine was significantly higher than for those in the non-norepinephrine group (41% vs. 30%, OR 1.61, 95% CI 1.09–2.39,  $P = 0.017$ ; HR 1.50, 95% CI 1.09–2.06,  $P = 0.013$ ). In the multivariable analysis, there was no significant difference between norepinephrine therapy and long-term (90 day, 180 day, or 1 year) mortality (90 day (OR 1.19, 95% CI 0.82–1.74,  $P = 0.363$ ), 180 day (OR 1.17, 95% CI 0.80–1.70,  $P = 0.418$ ), 1 year (OR 1.14, 95% CI 0.79–1.66,  $P = 0.477$ ). Patients in the norepinephrine group required more mechanical ventilation (84% vs. 67%, OR 2.67, 95% CI 1.70–4.25,  $P < 0.001$ ) and experienced longer ICU stays (median 7 vs. 4 days, OR 7.92, 95% CI 1.40–44.83,  $P = 0.020$ ) than non-norepinephrine group.

**Conclusions** Cardiogenic shock patients treated with norepinephrine were associated with significantly increased short-term mortality, while no significant difference was found on long-term survival rates. Future trials are needed to validate and explore this association.

**Keywords** Cardiogenic shock; Norepinephrine; Large observational database; Cohort study; Propensity score-matching analysis

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## Introduction

Cardiogenic shock is defined as a low cardiac output state leading to life-threatening organ hypoperfusion and hypoxia.<sup>1,2</sup> Despite recent therapeutic advances, mortality of cardiogenic shock still remains high at up to 50%.<sup>3</sup> In current practice, vasopressors and inotropes are administered to approximately 90% of patients with cardiogenic shock for

haemodynamic stabilization.<sup>4</sup> Current United States and European guidelines have recommended the use of norepinephrine as the first-line vasoconstrictor for cardiogenic shock to maintain blood pressure and tissue perfusion (Class IIb, level of evidence B).<sup>3,5</sup>

Despite vasopressors frequent use, little evidence is available regarding their efficacy in improving clinical outcomes.<sup>6</sup> A randomized study found that norepinephrine

compared with epinephrine was associated with similar effects on arterial pressure and cardiac index but with less refractory shock, and favoured norepinephrine's use in patients with cardiogenic shock after myocardial infarction.<sup>7</sup> However, the study did not find a significant survival benefit when using norepinephrine. Nevertheless, a subgroup analysis of a large, randomized trial including 1679 patients showed that norepinephrine (compared with dopamine), was associated with a decreased 28 day mortality among the 280 patients with cardiogenic shock.<sup>8</sup>

Although these studies favoured norepinephrine as first-line therapy,<sup>3,5,6</sup> the survival benefit with using norepinephrine has not been demonstrated in real-life clinical practice. Therefore, we intended to perform an observational cohort study using the Medical Information Mart for Intensive Care III (MIMIC-III) database to evaluate the relationship between norepinephrine use and outcomes (mortality, efficacy and safety) in cardiogenic shock patients in real-world conditions.

## Methods

### Data source

Data for this study were collected from the Multiparameter Intelligent Monitoring in Intensive Care Database III (MIMIC-III). MIMIC-III is a large critical care database containing clinical data from the Beth Israel Deaconess Medical Centre in Boston, Massachusetts, USA between 2001 and 2012. MIMIC-III contains data associated with 38 597 distinct adult patients and 49 785 hospital admissions. The data covers adult patients in five critical care units (the proportion of distinct patients in total admissions), including Coronary Care Unit (CCU, 14.7%), Cardiac Surgery Recovery Unit (CSRU, 20.9%), Medical Intensive Care Unit (MICU, 35.4%), Surgical Intensive Care Unit (SICU, 16.5%), and Trauma Surgical Intensive Care Unit (TSICU, 12.5%).<sup>9</sup> This database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT), which controls and supports the dataset. We received approval to access the database the extract data needed for this project. This study was reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement<sup>10</sup> and the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.<sup>11</sup>

### Patient population

Patients with ICD-9 cardiogenic shock diagnosis codes (ICD-9-CM 785.51 or 998.01) were eligible if they fulfilled

the following criteria: (i) age  $\geq 18$  years at intensive care unit (ICU) admission; (ii) first hospitalization with no gaps in ICU stay; (iii)  $\geq 24$  h admitted in the ICU. Patients administered norepinephrine during their ICU stay were categorized as being in the norepinephrine group, while the remaining patients were placed in the non-norepinephrine group. The norepinephrine group included patients treated with norepinephrine alone or in combination with other vasoactive medication. Only those patients who did not receive norepinephrine were classified into the non-norepinephrine group.

### Variables and outcome

Structured query language scripts were retrieved from the GitHub website (<https://github.com/MIT-LCP/mimic-code>) and used to calculate patient demographic characteristics, vital signs, laboratory data, co-morbidities and disease severity scores from the database. Baseline data was calculated within the first 24 h after ICU admission. The values associated with the greatest severity of illness were used. For example, the lowest value of mean blood pressure and maximum value of lactate reported in the first 24 h were used. Data on the aetiologies of cardiogenic shock, use of vasopressors and inotropes, and specific procedures were also extracted from the database. Queried inotropic and vasopressor agents used during ICU admissions included norepinephrine, epinephrine, vasopressin, dopamine, dobutamine and milrinone.

The primary endpoint was 30 day mortality, which was defined as the survival status of patients on the 30th day after ICU admission. Mortality outcomes were also assessed at 90 days, 180 days and at 1 year. The secondary outcomes included 6 h urine output, 24 h urine output, vasopressor duration, use of mechanical ventilation, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO), and the length of hospital and ICU stays. Safety outcomes included arrhythmias (i.e. ventricular tachycardia, ventricular fibrillation, and ventricular flutter) and cardiac arrest during ICU stay, which were defined using ICD-9 diagnosis codes.

For variables with missing values  $< 13\%$  (Supporting Information, *Figure S1*), the missing values were replaced using multiple imputation.<sup>12</sup>

### Statistical analysis

The study population was categorized into norepinephrine and non-norepinephrine groups according to norepinephrine treatment status during their ICU stay. Continuous variables were expressed as means with standard deviations (SDs) under normal distribution and analysed

using Student's *t*-test or described as medians with interquartile ranges (P25, P75) using Wilcoxon non-parametric test. Categorical variables were represented as frequencies with percentages and compared using  $\chi^2$  tests.

Cox proportional-hazards regression model and logistic regression model were used to analyse the relationship between norepinephrine use and 30 day mortality in cardiogenic shock patients. We applied four association inference models: logistic regression-based univariate and multivariable analysis models,<sup>13</sup> a doubly robust model adjusting for all covariates, and a propensity score-based patient-matching model.

The linear regression model was utilized to analyse the association between norepinephrine and continuous outcomes. Hazards ratio (HR) or odds ratio (OR) and 95% confidence intervals (CIs) were reported in the Cox regression and linear regression analysis, respectively. We generated Kaplan–Meier curves to assess the probability of survival across the two groups.

A predefined subgroup analysis of the primary outcome was conducted according to two major aetiologies of shock, including acute myocardial infarction (AMI) and sepsis. Additionally, we excluded patients with sepsis in cardiogenic shock patients for further analysis in order to avoid heterogeneity and bias.

A sensitivity analysis was performed to compare complete cases versus imputed dataset.

## Propensity score matching

Propensity score matching was used to minimize the effect of confounding factors such as disease severity and adjunct treatment, which may lead to outcome bias. PSM calculations were based on variables associated with norepinephrine administration or death with a *P*-value <0.20 in the univariate analysis.<sup>14</sup> The following variables were matched: age, vital signs, laboratory data, co-morbidities (and disease severity score), aetiologies including AMI and sepsis, vasoactive agents including dobutamine, milrinone, epinephrine and vasopressin, procedures including percutaneous coronary intervention (PCI) and coronary bypass, medical history including hyperlipidaemia and old myocardial infarctions (OMI). A one-to-one nearest neighbour matching algorithm was applied using a calliper width of 0.1. Histograms were used to examine the PSM degree (Figure S2). Finally, 222 matched pairs were generated and applied to further analyses.

All statistical analyses were performed with R programming language (version 4.1.0). The R package 'MatchIt' was used for PSM. A *P* value <0.05 was considered to be statistically significant.

## Results

### Baseline characteristics

Of the 38 597 adult patients admitted to ICUs in the MIMIC-III database, 1137 patients met the definition of cardiogenic shock. After screening using this study's inclusion criteria, 927 eligible patients were enrolled. Finally, 552 patients were found to have been treated with norepinephrine during their ICU stay, while the remaining 375 patients did not receive norepinephrine (Figure 1). The baseline characteristics of enrolled patients are shown in Tables 1 and S1.

In the original cohort, patients in the norepinephrine group were more critically ill than in the non-norepinephrine group, with more severe haemodynamic impairment (mean MAP of 51 mmHg vs. 56 mmHg) and more severe organ failure (SOFA score of 8 vs. 5). The median duration of treatment with norepinephrine was 39 h (first and third quartiles: 15, 86) and the median dosage of norepinephrine was 23 mg (first and third quartiles: 6, 62). The median age was also significantly higher among the norepinephrine-treated patients than in the non-norepinephrine treated patients (74 vs. 71 years). In addition to norepinephrine, other vasopressors and inotropes were more common in the norepinephrine

**Figure 1** Flow chart of included patients. ICD, International Classification of Diseases; ICU, intensive care unit; MIMIC-III, Medical Information Mart for Intensive Care III.

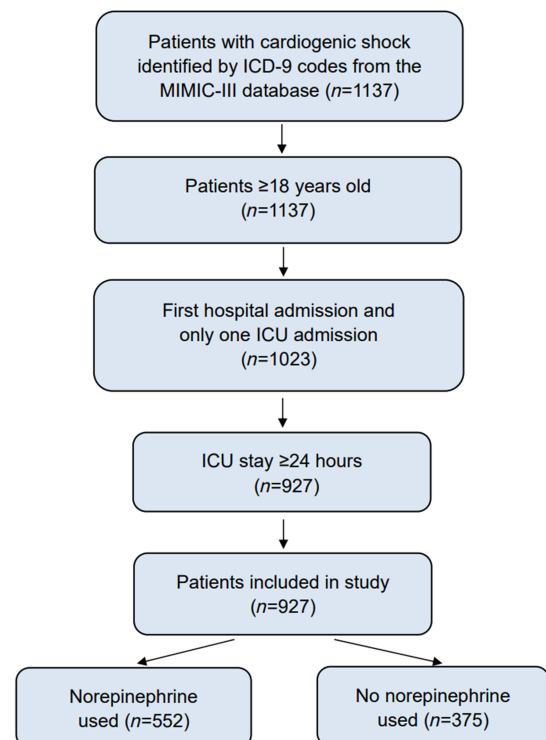


Table 1 Baseline characteristics between the original and matched cohorts for norepinephrine and non-norepinephrine sub-groups

Variables	Original cohort			Matched cohort			
	Non-NE group (n = 375)	NE group (n = 552)	P value	Non-NE group (n = 222)	NE group (n = 222)	P value	SMD
Age, median [IQR]	71 (61, 81)	74 (64, 82)	0.023	74 (64, 83)	75 (66, 82)	0.819	0.029
Gender, male (%)	206 (55)	334 (61)	0.105	120 (54)	136 (61)	0.15	0.146
BMI, median [IQR]	27.2 (23.5, 31.05)	27.39 (23.5, 31.32)	0.818	26.72 (23.07, 31.14)	26.95 (23.13, 31.22)	0.966	0.053
Vital signs and index, median [IQR]							
Maximum heart rate	104 (93, 119)	112 (96, 129)	<0.001	107 (93, 121)	107 (93, 122)	0.716	0.031
Minimum systolic pressure	81 (73, 89)	75 (65, 84)	<0.001	79 (70, 87)	77 (67, 87)	0.24	0.090
Minimum diastolic pressure	42 (35, 49)	38 (32, 45)	<0.001	41 (34, 47)	40 (34, 45)	0.261	0.052
Minimum mean arterial pressure	56 (48, 64)	51 (44, 58)	<0.001	55 (46, 62)	54 (46, 58)	0.346	0.016
Minimum SpO <sub>2</sub>	93 (89, 95)	91 (85, 94)	<0.001	93 (88, 95)	92.5 (88, 95)	0.973	0.038
Elixhauser co-morbidity index	7 (0, 15)	15 (6, 26)	<0.001	11 (1, 18)	11 (3, 19)	0.984	0.006
SOFA at admission	5 (3, 7)	8 (6, 11)	<0.001	7 (4, 8)	7 (4, 9)	0.505	0.069
SAPS II at admission (mean ± SD)	39 (31, 48)	51 (43, 60)	<0.001	45 ± 12	47 ± 14	0.091	0.161
Laboratory, median [IQR]							
Maximum lactate	2.7 (1.7, 4.5)	4.6 (2.5, 8.55)	<0.001	3.3 (2.1, 6)	3.1 (2.1, 5.95)	0.976	0.075
Minimum pH	7.29 (7.21, 7.36)	7.2 (7.12, 7.27)	<0.001	7.26 (7.18, 7.32)	7.25 (7.17, 7.31)	0.523	0.025
Minimum PO <sub>2</sub>	55 (34, 78.5)	39.5 (31, 62)	<0.001	45 (32, 64.75)	46 (33, 70)	0.404	0.068
Maximum PCO <sub>2</sub>	47 (41, 54)	53 (46, 63.25)	<0.001	51 (43, 57.75)	49 (43, 56)	0.545	0.079
Medical history, n (%)							
Old myocardial infarction	25 (7)	57 (10)	0.071	17 (8)	16 (7)	1	0.017
Hyperlipidaemia	126 (34)	151 (27)	0.049	60 (27)	59 (27)	1	0.010
Hypertension	204 (54)	291 (53)	0.662	119 (54)	111 (50)	0.506	0.072
Diabetes	131 (35)	171 (31)	0.234	78 (35)	82 (37)	0.767	0.038
Stroke	18 (5)	27 (5)	1	11 (5)	6 (3)	0.323	0.118
Aetiologies, n (%)							
Acute myocardial infarction	235 (63)	265 (48)	<0.001	126 (57)	126 (57)	1	<0.001
Sepsis	43 (11)	177 (32)	<0.001	36 (16)	33 (15)	0.793	0.037
Poisoning	1 (0)	4 (1)	0.654	0 (0)	3 (1)	0.248	0.166
Postoperative shock	2 (1)	8 (1)	0.331	1 (0)	1 (0)	1	<0.001
Myocarditis	1 (0)	2 (0)	1	0 (0)	0 (0)	1	<0.001
Vasopressors, n (%)							
Dopamine	170 (45)	274 (50)	0.222	124 (56)	107 (48)	0.129	0.154
Dobutamine	76 (20)	161 (29)	0.003	51 (23)	56 (25)	0.657	0.053
Milrinone	51 (14)	160 (29)	<0.001	28 (13)	30 (14)	0.723	0.045
Epinephrine	32 (9)	145 (26)	<0.001	28 (13)	30 (14)	0.888	0.027
Vasopressin	22 (6)	216 (39)	<0.001	22 (10)	25 (11)	0.758	0.044
Specific procedures, n (%)							
PCI	232 (62)	258 (47)	<0.001	116 (52)	123 (55)	0.568	0.063
Coronary artery bypass	39 (10)	84 (15)	0.043	30 (14)	30 (14)	1	<0.001
Heart assist system <sup>a</sup>	159 (42)	228 (41)	0.792	85 (38)	97 (44)	0.288	0.110
Thrombolysis	5 (1)	10 (2)	0.763	3 (1)	2 (1)	1	0.043

BMI, body mass index; IQR, interquartile range; NE, norepinephrine; PCI, percutaneous coronary intervention; SOFA, sequential organ failure assessment.

<sup>a</sup>Heart assist system includes pacemaker device, automatic cardioverter/defibrillator, intra-aortic balloon pump, ventricular external heart assist system, implantable heart assist system and temporary non-implantable extracorporeal circulatory assist device.

group (including dopamine, dobutamine, milrinone, epinephrine, and vasopressin). AMI was the most frequent cause of cardiogenic shock, present in approximately 50% of cases (48% vs. 63% in the norepinephrine vs. non-norepinephrine groups). Correspondingly, patients in the non-norepinephrine group had more PCI interventions.

After PSM, 222 cases from each group were matched using a 1:1 matching algorithm (Table 1). The overall quality of the matched sample was assessed by comparing the standardized difference of the means. There were no significant differences between the two matched groups with regards to all covariates.

### Mortality outcome and survival analysis

The initial univariate analysis demonstrated a significant association between norepinephrine use and increased 30 day mortality (OR 3.52, 95% CI 2.63–4.76,  $P < 0.001$ ; HR 2.79, 95% CI 2.18–3.58,  $P < 0.001$ ). In the extended multivariable logistic regression and Cox regression models, we observed that the OR and HR of norepinephrine use were consistently significant in all three models (OR range 1.49–1.61, HR range 1.50–1.64,  $P < 0.05$  for all) (Figure 2). After adjusting for the dosage and duration of norepinephrine, the norepinephrine use was also associated with increased 30 day mortality (OR 1.62, 95% CI 1.07–2.45,  $P = 0.023$ ; HR 1.80, 95% CI 1.35–2.41,  $P < 0.001$ ).

Kaplan–Meier survival curves for 30 days are shown in Figure 3. In the matched cohort, mortality at 30 days for patients treated with norepinephrine was significantly higher than for those not treated with norepinephrine (41% vs. 30%, HR 1.50, 95% CI 1.09–2.06,  $P = 0.013$ ). In the multivari-

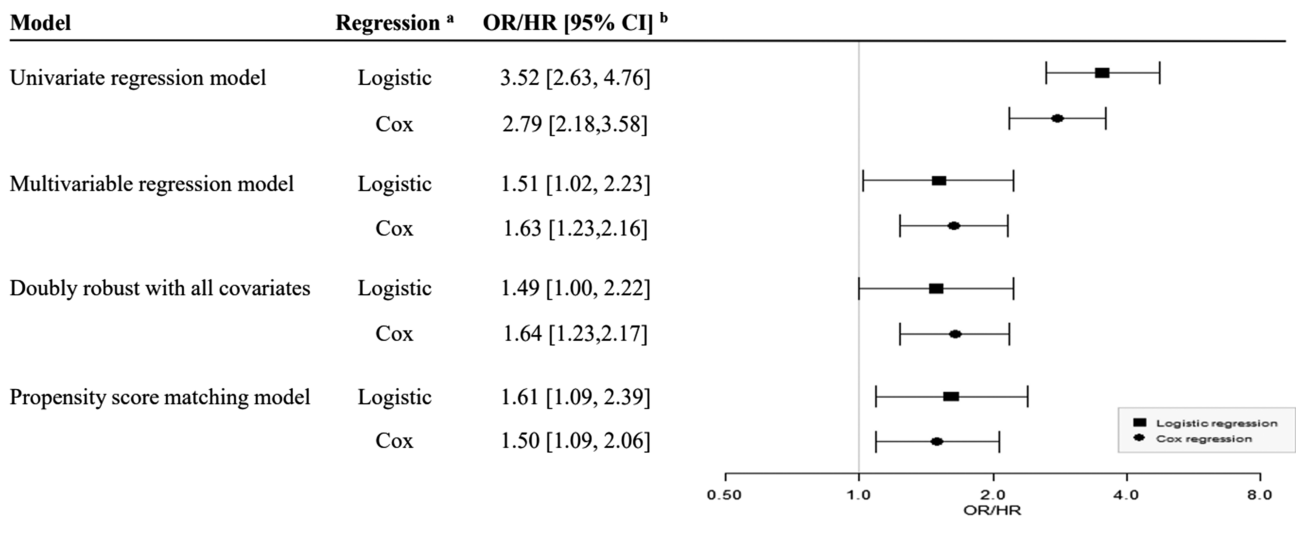
able analysis, there was no significant association between norepinephrine and long-term mortality (90 day OR 1.19, 95% CI 0.82–1.74,  $P = 0.363$ ; 180 day OR 1.17, 95% CI 0.80–1.70,  $P = 0.418$ ; 1 year OR 1.14, 95% CI 0.79–1.66,  $P = 0.477$ ). After adjusting for possible confounding factors, the results were similar in the matched cohort.

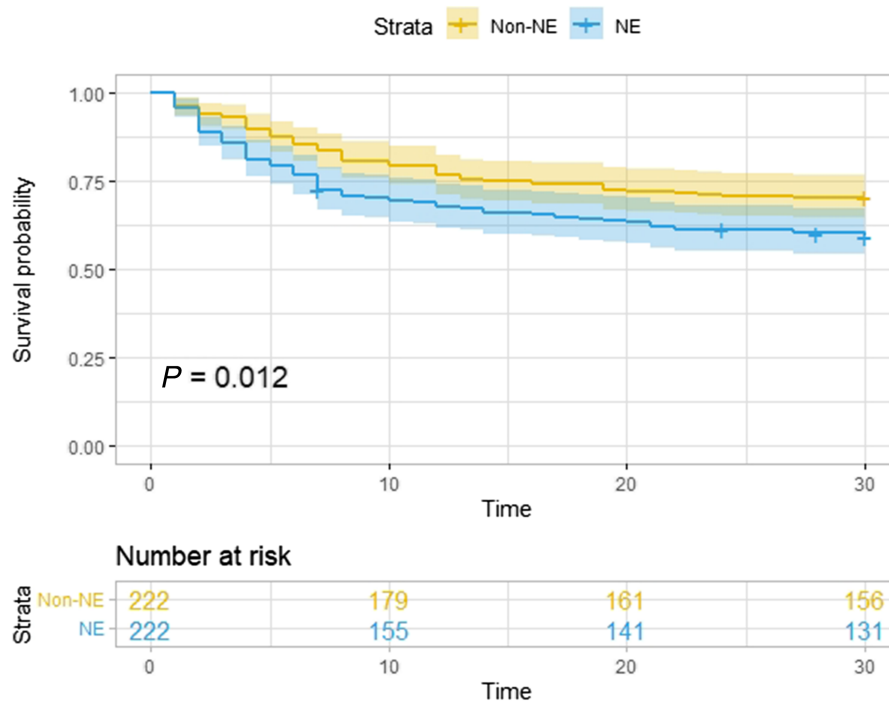
We have performed a sensitivity analysis to complete cases versus imputed dataset. The results were shown in Tables S1 and S2. The analysis results were similar between the complete cases and imputed dataset.

### Norepinephrine use and secondary efficacy/safety outcomes

The impact of norepinephrine use on the efficacy and safety outcomes was estimated in the original and matched cohort, respectively (Figure 4). The results showed that norepinephrine use was associated with less urine output during the first 24 h in ICU patients with cardiogenic shock (OR 0.75, 95% CI 0.58–0.97,  $P = 0.026$ ). Nevertheless, vasopressor duration was significantly longer in the norepinephrine group (OR 1.03, 95% CI 1.01–1.06,  $P = 0.005$ ). The length of ICU stay was also significantly longer in the norepinephrine group (median 7 vs. 4 days), while overall hospital stay duration was not significantly different between the two groups (median 11 vs. 8 days). With regard to specific organ support therapies, there was a significant difference in mechanical ventilation use between the norepinephrine and non-norepinephrine groups (matched cohort 84% vs. 67%, OR 2.67, 95% CI 1.70–4.25,  $P < 0.001$ ). There were no significant differences in terms of RRT or ECMO between the two groups. As for safety outcomes, cardiac arrest was more com-

**Figure 2** Primary outcome analysis with logistic and Cox regression modelling. CI, confidence interval; HR, hazards ratio; OR, odds ratio. <sup>a</sup>The regression analysis includes logistic regression analysis and Cox regression analysis. <sup>b</sup>OR is reported in logistic regression and HR in Cox regression analysis.



**Figure 3** Kaplan–Meier 30 day survival curves for patients with cardiogenic shock. NE, norepinephrine.

mon in cardiogenic shock patients with norepinephrine use (OR 2.14, 95% CI 1.25–3.73,  $P = 0.006$ ). Arrhythmias occurred at a similar rate between the two groups (matched cohort 27% vs. 22%).

### Subgroup analysis

The subgroup analysis also demonstrated a deleterious effect of norepinephrine on 30 day mortality in patients with post-AMI cardiogenic shock (crude HR 2.91, 95% CI 2.09–4.05,  $P < 0.001$ ; PSM cohort adjusted HR 1.59, 95% CI 1.02–2.5,  $P = 0.042$ ) (Table S3). Table S4 shows the baseline characteristics of this AMI subgroup. Kaplan–Meier survival curves demonstrate a significant difference between the norepinephrine and non-norepinephrine groups (Figure S3).

Among cardiogenic shock patients with sepsis, norepinephrine use was associated with increased 30 day mortality in the whole cohort (crude HR 1.70, 95% CI 1.03–2.80,  $P = 0.038$ ). In the matched cohort, there was no significant 30 day mortality difference between those treated with norepinephrine or not (PSM cohort adjusted HR 1.72, 95% CI 0.85–3.46,  $P = 0.130$ ) (Table S3). The baseline characteristics of the original cohort and the matched cohort in the sepsis subgroup are shown in Table S5. The Kaplan–Meier survival curves at 30 days are shown in Figure S4.

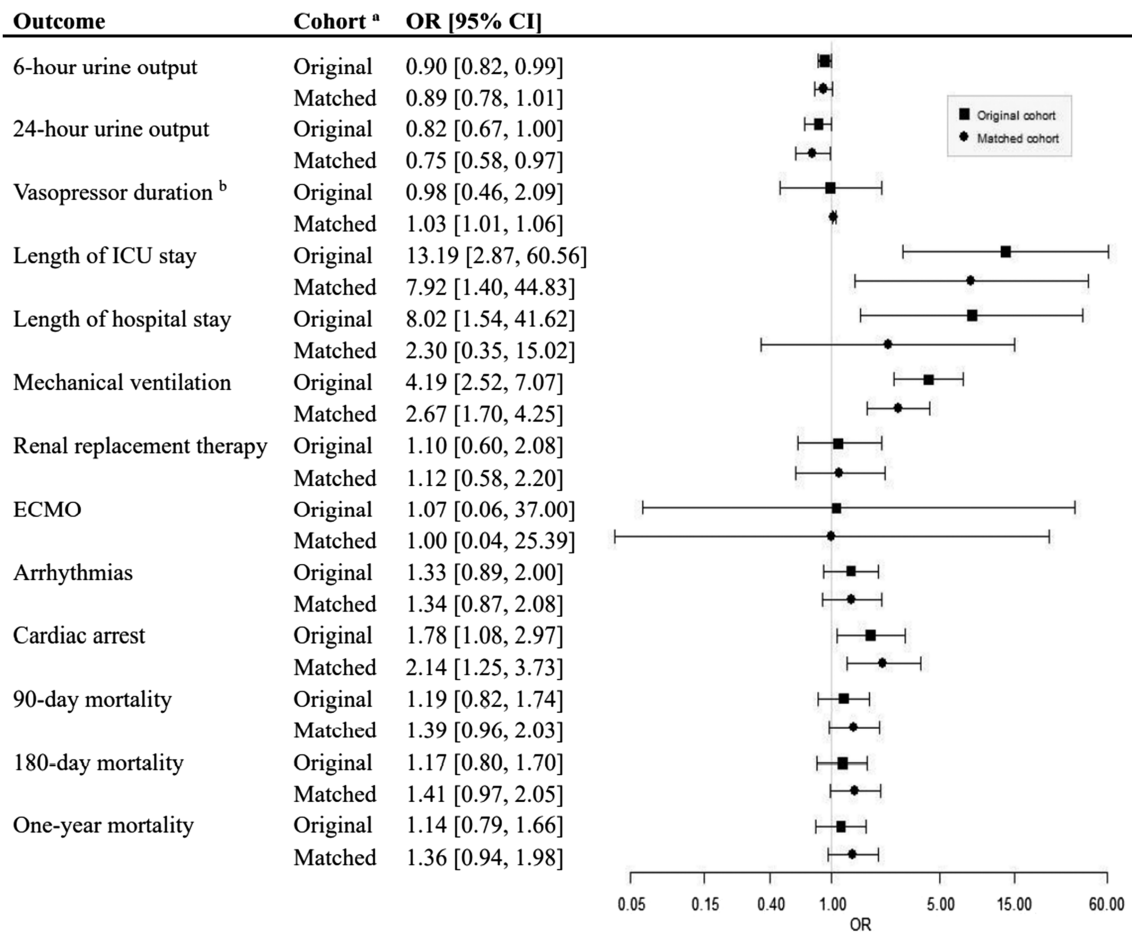
The Cox regression analysis of original cohort showed a deleterious effect of norepinephrine on 30 day mortality in cardiogenic shock patients without sepsis (crude HR 2.81, 95% CI 2.10–3.74,  $P < 0.001$ ). In the matched cohort, there was no significant 30 day mortality difference between those treated with norepinephrine or not (PSM cohort adjusted HR 1.43, 95% CI 0.98–2.09,  $P = 0.062$ ) (Table S3).

### Discussion

This study demonstrated that cardiogenic shock patients treated with norepinephrine are associated with a significantly increased 30 day mortality compared with PSM patients treated with other vasopressors. The norepinephrine group also had longer ICU stays and prolonged vasopressor use.

Vasoactive agents are administered for the initial improvement of hypotension or hypo-perfusion in approximately 90% of cardiogenic shock patients.<sup>3</sup> The European Society of Cardiology (ESC) recommended norepinephrine as the vasoconstrictor choice when tissue perfusion is insufficient. (Class IIb, level of evidence B).<sup>3</sup> The American College of Cardiology–American Heart Association (ACC/AHA) guidelines recommend norepinephrine as the first choice to maintain a MAP >65 mmHg acute myocardial infarction patients in cardiogenic shock.<sup>5</sup> However, our study did not find any survival

**Figure 4** Secondary outcome analysis between the original cohort and a propensity score-matched cohort. CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OR, odds ratio. <sup>a</sup>Multivariable regression analysis in original cohort. Univariate regression analysis in propensity score-matched cohort. <sup>b</sup>Vasopressor agents included: norepinephrine, epinephrine, vasopressin, and dopamine.



benefit to using norepinephrine for cardiogenic shock in clinical settings. Previous RCTs focused on comparing the impact of different vasopressor agents on patients in cardiogenic shock. In a randomized trial comparing norepinephrine to epinephrine in cardiogenic shock, the use of norepinephrine was associated with a lower incidence of refractory shock, but comparable mortality.<sup>7</sup> That RCT enrolled only 57 patients over a 4 year period, which may indicate a highly selected population.<sup>15</sup> Our study, based on a real-world electronic medical records, may provide more generalizability and validity for clinical practice. Comparing norepinephrine and dopamine use in diverse causes of shock, a large RCT including 1679 patients showed that norepinephrine was associated with decreased 28 day mortality in the subgroup of 280 patients in cardiogenic shock.<sup>8</sup> In our study containing data between 2001 to 2012, dopamine was used in 45 to 50% of the patients whereas a very low proportion of patients were on dobutamine or milrinone. The medication difference should be taken into consideration when interpreting the results.

Although norepinephrine may be preferred over other vasopressors, few studies investigated the outcomes of patients either receiving norepinephrine or not. A multinational CardShock study showed that the use of norepinephrine was associated with increased 90 day mortality, while there was no significant difference seen in that study’s multivariable logistic regression.<sup>16</sup> These results are consistent with our findings. However, no study to date evaluated the effect of norepinephrine use on short-term mortality in patients with cardiogenic shock. A post hoc analysis of the ALARM-HF dataset showed that norepinephrine use was associated with more than a 2.5-fold increase in the in-hospital mortality rate in acute heart failure patients.<sup>17</sup> But there was no further analysis of the cardiogenic shock subgroup.

In clinical practice, the deleterious impact of norepinephrine was also shown in the subgroup of patients with acute myocardial infarction. The CardShock study revealed that acute coronary syndrome is the most common cause of cardiogenic shock, including 68% of patients presenting with ST-elevation myocardial infarction.<sup>18</sup> In our study, AMI

accounted for 54% of all cardiogenic shock patients. In patients with post-AMI cardiogenic shock, the early haemodynamic profile included a depressed cardiac index and high systemic vascular resistance.<sup>19,20</sup> Norepinephrine as a vasoconstrictor may impair the microcirculation, increase afterload, and further increase myocardial oxygen consumption.<sup>21</sup> Among patients complicated by sepsis, there was no significant difference in mortality between the group treated with norepinephrine and the one that was not. In the subgroup of cardiogenic shock patients without sepsis, norepinephrine use showed a deleterious effect on 30 day mortality. These findings suggest that norepinephrine could be theoretically advantageous in vasodilatory cardiogenic shock but deleterious in normotensive cardiogenic shock.<sup>6</sup> A 'one-size-fits-all' approach to norepinephrine in this high-risk population may lead in unintended consequences for certain patients. Routine use of vasopressors in tailored cardiogenic shock populations may require differentiating the underlying aetiologies of cardiogenic shock including their haemodynamic phenotypes.<sup>22</sup>

As for global haemodynamic effects, patients in the norepinephrine group demonstrated higher lactate values and lower blood pressure than those in the non-norepinephrine group at baseline. These findings are consistent with the recommendations on norepinephrine use for insufficient tissue perfusion.<sup>3</sup> Nevertheless, norepinephrine infusion did not increase 24 h urine output, which may indicate inadequate kidney perfusion with norepinephrine. A randomized pilot study showed that norepinephrine-dobutamine use was associated with a decrease in lactate level compared to epinephrine.<sup>23</sup> However, such organ perfusion benefits were not demonstrated in those patients treated with norepinephrine alone in a clinical setting. A short-term trial was recently performed to evaluate the effect of norepinephrine infusion rates on obtaining a higher MAP value and a higher cardiac index (CI), but there is no data yet regarding this trial's outcomes.<sup>24,25</sup>

The use of vasopressors in cardiogenic shock is limited by their side-effects.<sup>4</sup> Arrhythmias may be of paramount concern. Our study found there was no significant difference between the two groups based on arrhythmia incidence. A large RCT including 1679 patients showed that, compared to dopamine, norepinephrine was associated with less arrhythmias and with a decreased mortality rate in the subgroup of patients with cardiogenic shock.<sup>8</sup> A pilot study also demonstrated that a norepinephrine group had lower arrhythmia rates than an epinephrine group.<sup>23</sup>

Meanwhile, our study also had several limitations. First, this was an observational study based on a single-centre electronic history record. The monocentric nature of the study limits the generalizability of the results. The diagnosis of cardiogenic shock is based on ICD-9 coding, and the results may be affected by selection bias. Second, MIMIC-III database contained data between 2001 and 2012. The medication and management algorithm ten years ago are somewhat dif-

ferent from now, which may limit the interpretation of our findings. Third, despite the careful propensity score matching analysis, residual unmeasured confounding variables cannot be fully excluded. The risk of confounding factors should be taken into consideration when interpreting our results. Fourth, some important cardiac functional parameters and haemodynamic variables were unavailable in this database. The association between MAP values and the norepinephrine use was unclear, which may potentially confound the results. Nevertheless, the association between norepinephrine use and poor outcomes does seem consistent. Future prospective studies are suggested to validate the associations we found in this study and further explore the best choice and optimal vasopressor dose for cardiogenic patients.

## Conclusions

Cardiogenic shock patients treated with norepinephrine were significantly associated with increased short-term mortality, while showing no significant difference in long-term survival. Future prospective trials are needed to validate this association in patients with cardiogenic shock.

## Conflict of interest

The authors declare that they have no competing interests.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Missing data profile of the original cohort.

**Figure S2.** Histograms of examining the propensity score matching degree.

**Table S1.** Baseline characteristics between norepinephrine and non-norepinephrine sub-groups for original complete data.

**Table S2.** Primary outcome analysis with logistic and Cox regression modelling for original complete data.

**Table S3.** Association between norepinephrine use and 30-day mortality by cox regression modelling in subgroups of cardiogenic shock patients.



**Table S4.** Baseline characteristics of the original cohort and the matched cohort in the subgroup of cardiogenic shock patients with acute myocardial infarction.

**Figure S3.** Kaplan–Meier 30-day survival curves for patients with cardiogenic shock and acute myocardial infarction in the propensity score matching cohort.

**Table S5.** Baseline characteristics of the original cohort and the matched cohort in the subgroup of cardiogenic shock patients with sepsis.

**Figure S4.** Kaplan–Meier 30-day survival curves for patients with cardiogenic shock and sepsis in the propensity score matching cohort.

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