

# Effect of Early versus Delayed Use of Norepinephrine on Short-Term Outcomes in Patients with Traumatic Hemorrhagic Shock: A Propensity Score Matching Analysis

Bing Zhang<sup>1,\*</sup>, Xue Dong<sup>2,\*</sup>, Jia Wang<sup>2</sup>, Gong-Ke Li<sup>1</sup>, Yong Li<sup>3</sup>, Xian-Yao Wan<sup>2</sup>

<sup>1</sup>Department of Emergency Intensive Care Medicine, Affiliated Hospital of Yangzhou University, Yangzhou, 225000, People's Republic of China;

<sup>2</sup>Department of Critical Care Medicine, The First Affiliated Hospital of Dalian Medical University, Dalian, 116000, People's Republic of China;

<sup>3</sup>Department of Critical Care Medicine, Affiliated Hospital of Yangzhou University, Yangzhou, 225000, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Xian-Yao Wan, Department of Critical Care Medicine, The First Affiliated Hospital of Dalian Medical University, No. 193 Joint Road, Sha He Kou District, Dalian, 116000, People's Republic of China, Tel +86 41183635963, Fax +86 41183635025, Email Wan\_xianyao23@126.com; Yong Li, Department of Critical Care Medicine, Affiliated Hospital of Yangzhou University, No. 368 Hanjiang Middle Road, Hanjiang District, Yangzhou, 225000, People's Republic of China, Tel/Fax +86 51482981199, Email yzliyong0304@163.com

**Background:** Guidelines recommend norepinephrine (NE) for the treatment of fatal hypotension caused by trauma. However, the optimal timing of treatment remains unclear.

**Objective:** We aimed to investigate the effect of early versus delayed use of NE on survival in patients with traumatic haemorrhagic shock (HS).

**Materials and Methods:** From March 2017 to April 2021, 356 patients with HS in the Department of Emergency Intensive Care Medicine of the Affiliated Hospital of Yangzhou University were identified using the emergency information system and inpatient electronic medical records for inclusion in the study. Our study endpoint was 24 h mortality. We used a propensity score matching (PSM) analysis to reduce bias between groups. Survival models were used to evaluate the relationship between early NE and 24 h survival.

**Results:** After PSM, 308 patients were divided equally into an early NE (eNE) group and a delayed NE (dNE) group. Patients in the eNE group had lower 24 h mortality rates than those in the dNE group (29.9% versus 44.8%, respectively). A receiver operating characteristic analysis demonstrated that a cut-off point for NE use of 4.4 h yielded optimal predictive value for 24 h mortality, with a sensitivity of 95.52%, a specificity of 81.33% and an area under the curve value of 0.9272. Univariate and multivariate survival analyses showed that the survival rate of patients in the eNE group was higher ( $p < 0.01$ ) than those in the dNE group.

**Conclusion:** The use of NE within the first 3 h was associated with a higher 24 h survival rate. The use of eNE appears to be a safe intervention that benefits patients with traumatic HS.

**Keywords:** norepinephrine, traumatic haemorrhagic shock, propensity score matching

## Introduction

Severe trauma is a global public health problem, causing approximately 5.8 million deaths annually, with a mortality rate of more than 10%.<sup>1</sup> Haemorrhagic shock (HS) is a severe complication of trauma and is the primary cause of early death in patients with trauma.<sup>2,3</sup> Guidelines recommend restrictive fluid resuscitation<sup>4</sup> and permissive hypotension strategies<sup>5-7</sup> for HS until bleeding is controlled. The 2019 European guideline on the management of major bleeding and coagulopathy following trauma recommends the use of norepinephrine (NE) for maintaining target arterial blood pressure in

patients with life-threatening hypotension.<sup>8</sup> However, this guideline does not clearly state the optimal timing for the use of NE. Therefore, the timing of NE use remains unclear.

Rigorous data regarding the efficacy and safety of NE in patients with HS are currently lacking. One multicenter prospective cohort study showed that early use of vasopressors might be hemodynamically detrimental compared with using fluid resuscitation alone and should be used with caution.<sup>9</sup> However, we found a significantly higher proportion of patients undergoing thoracotomy in the early cohort of this study, which may have influenced patient hemodynamic outcomes. In another prospective study of 518 patients with HS, after propensity score matching (PSM), the early use of NE (eNE) use had no adverse effect on 24 h mortality compared with no NE use.<sup>10</sup> In a recent study of 4253 patients with septic shock, patients with HS in an eNE group had longer survival, shorter durations of NE use and possibly delayed or reversed organ failure.<sup>11</sup> This suggests that eNE may benefit patients. However, whether eNE benefits patients with HS is unclear. Therefore, the optimal timing of NE use in patients with traumatic HS requires further investigation.

To date, uniform criteria for the timing of NE initiation in the management of HS have not been established. In this study, we extrapolated previous research results<sup>11–13</sup> and defined eNE as an interval between NE treatment and HS of  $\leq 3$  h; delayed NE (dNE) was defined as an NE duration of  $> 3$  h. We aimed to investigate the impact of eNE versus dNE on the survival of patients with traumatic HS.

## Materials and Methods

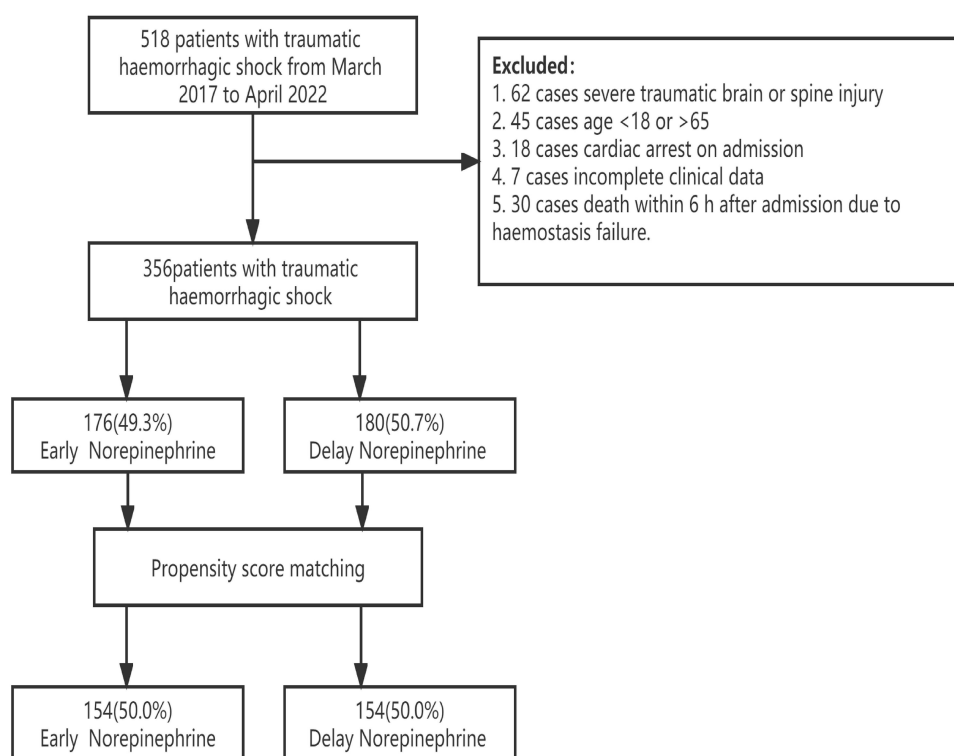
### Study Population

This was an observational study in which we retrospectively analysed the medical history data of 518 patients with traumatic HS admitted to the emergency intensive care unit (ICU) of the Affiliated Hospital of Yangzhou University with a diagnosis of traumatic HS between March 2017 and April 2021. Traumatic HS was defined as a severely traumatised patient with mean arterial pressure (MAP) of  $< 65$  mmHg on admission, requiring surgical control of active bleeding, the transfusion of more than four units of red blood cells (RBCs) within 6 h of admission and the use of NE within 24 h of admission. The exclusion criteria included age  $< 18$  years or  $> 65$  years, cardiac arrest at admission, severe brain or spinal injury (because of different target blood pressures), death due to haemostatic failure within 6 h of admission and incomplete clinical data. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Yangzhou University, and informed consent was obtained from all participants (2021-YKL3-01-001).

The vasoactive drug NE was used for preliminary treatment, and the start time of traumatic HS was defined as the first recorded MAP of  $< 65$  mmHg. Based on the time of traumatic HS onset and the timing of NE treatment, patients were divided into two groups: an eNE group and a dNE group. Patients were allocated to the eNE group if the timespan was  $\leq 3$  h. Patients with an interval of  $> 3$  h between NE treatment and HS were allocated to the dNE group. The detailed flowchart of the enrolled patients is shown in Figure 1.

### Data Collection

The clinical data of all enrolled patients were extracted from the emergency information system and inpatient electronic medical records. Baseline characteristics were collected within 24 h after admission and included age, sex, Charlson Comorbidity Index (CCI), body mass index (BMI), complications (hypertension, myocardial infarction, congestive heart failure, chronic pulmonary disease, diabetes mellitus, kidney disease, cancer, leukaemia, lymphoma and metastatic cancer), mechanism of injury (blunt), cause of injury (motor vehicles, bikes, pedestrians, falls and other reasons), pre-hospital status (MAP, heart rate [HR], fluid amount, intubation and initial Glasgow Coma Scale [GCS] score), on-admission status (MAP, HR), intubation, initial GCS score, haemoglobin, blood glucose, blood lactate and serum creatinine), severity scores (sequential organ failure assessment [SOFA] score on the first day, injury severity score [ISS] score on the first day and acute physiology, age, chronic health evaluation [APACHE III] score on the first day), NE use (timing, maximum NE dose within 24 h, total dose within 24 h, and target MAP need time), fluid resuscitation within 24 h (RBCs, lyophilised plasma, fibrinogen, platelets, total of non-blood fluid infusion, total of all fluid infusion), damage control surgery, 24 h mortality, in-hospital mortality, acute kidney injury (AKI) within 24 h, continuous renal replacement



**Figure 1** Flowchart of study design and patient selection.

therapy (CRRT)-free days, invasive mechanical ventilation (IMV)-free days, hospital length of stay (HLOS) and ICU length of stay (ICU LOS).

## Study Endpoint

The primary endpoint was 24 h mortality, and the secondary endpoints were in-hospital mortality, incidence of AKI, duration of non-CRRT, duration of non-IMV therapy, HLOS and ICU LOS. The duration of non-IMV therapy and non-CRRT was expressed as 28 d after admission, ie the number of days the patient survived without IMV therapy or CRRT. If the patient died within 24 h, the time of death was used as the endpoint. According to the European guideline on the management of major bleeding and coagulopathy following trauma,<sup>8</sup> the target MAP for fluid resuscitation was set at 50–60 mmHg. The diagnosis of AKI was based on the Improving the Global Prognosis Guidelines for kidney disease,<sup>14</sup> and AKI was not assessed in patients with end-stage renal disease.

## Statistical Methods

Stata 16.0 statistical software was used. The normality of the data was tested using the Shapiro–Wilk method. Normally distributed data were expressed as mean ( $\pm$ SD), and non-normally distributed data were expressed as M (Q1, Q3). Categorical variables were indicated as numbers and percentages. The results were depicted as boxplot diagrams. To reduce bias, PSM was used to obtain a control cohort of patients in the eNE group and the dNE group, with a matching ratio of 1:1 and a calliper value of 0.2, with age, male, CCI, BMI, complications, mechanism of injury, cause of injury, pre-hospital status, on-admission status, severity scores, NE use, fluid resuscitation within 24 h and damage control surgery as covariates without substitution. A Kaplan–Meier survival analysis and a Streg regression model were used to evaluate the relationship between eNE and the 24 h survival rate of patients. The area under the receiver operating characteristic (ROC) curve was calculated to determine the predictive abilities of the timing of NE use for 24 h mortality. A value of  $P < 0.05$  was considered statistically significant.

## Results

### General Characteristics of the Patients

A total of 518 patients were diagnosed with traumatic HS. Of these, 162 were excluded, including 45 patients aged <18 years or >65 years, 18 patients with cardiac arrest on admission, 62 patients with a severe brain or spinal injury caused by different target blood pressures, 30 patients who died of haemostatic failure within 6 h of admission and 7 patients with incomplete clinical data. Finally, 356 patients met the inclusion criteria. The mean age of the patients was  $49.8 \pm 14.4$  years, and 189 were male (53.1%). The most common injuries were bicycle injuries (143, 40.2%), followed by motor vehicle injuries (82, 23.0%), falls (74, 20.8%), pedestrian injuries (47, 13.2%) and other injuries (10, 2.8%). Ultimately, 176 patients (49.3%) were subordinated to the eNE group, and 180 patients (50.7%) were subordinated to the dNE group. After PSM, the eNE and dNE groups each had 154 patients. Therefore, 308 patients participated in the final analysis (Figure 1).

Before PSM, there were significant differences in age, complications (hypertension), mechanism of injury, pre-hospital status (MAP and initial GCS score), on-admission status (MAP and haemoglobin), first-day ISS score, first-day SOFA score, first-day APACHE III score, timing of NE use, target MAP need time, 24 h total of non-blood fluid infusion and 24 h total of all fluid infusion between the groups ( $P < 0.05$ ). After PSM, there were significant differences in the timing of NE use, target MAP need time, total of non-blood fluid infusion and total of all fluid infusion between the eNE and dNE groups ( $P < 0.05$ ) (Table 1, Figure 2).

**Table 1** Comparison of Baseline Data of Patients Between Early Norepinephrine and Delayed Norepinephrine Before and After Propensity Score Matching

Variables	Before PSM			After PSM		
	EN (n=176)	DN (n =180)	P-value	EN (n =154)	DN (n =154)	P-value
Age, years, (mean $\pm$ SD)	48.5 $\pm$ 15.8	50.0 $\pm$ 13.1	0.006	50.2 $\pm$ 12.4	51.0 $\pm$ 11.5	0.512
Male sex, n (%)	93(52.8)	96(53.3)	0.926	78(50.6)	79(51.3)	0.744
CCI, point, median (IQR)	7(6–9)	7(6–9)	0.882	7(5–9)	8(6–9)	0.082
BMI, kg m <sup>-2</sup> , median (IQR)	23.5(22.0–26.9)	23.5(22.0–26.9)	0.819	22.5(21.1–25.4)	22.5(21.4–25.9)	0.800
Complication, n (%)						
Hypertension	58(32.9)	69(38.3)	0.001	54(35.1)	52(33.8)	0.709
Myocardial infarction	53(30.1)	48(26.7)	0.471	46(30.1)	45(26.7)	0.334
Congestive heart failure	51(29.0)	53(29.4)	0.932	43(30.0)	44(28.6)	0.632
Chronic pulmonary disease	43(24.4)	48(26.7)	0.629	38(24.6)	39(25.3)	0.504
Diabetes mellitus	41(23.3)	44(24.4)	0.799	36(23.4)	37(24.0)	0.321
Kidney disease	33(18.8)	37(20.6)	0.668	28(18.2)	29(18.8)	0.409
Cancer	6(3.4)	7(3.9)	0.809	4(2.6)	5(3.2)	0.422
Leukemia	9(5.1)	9(5.0)	0.961	6(3.9)	8(5.2)	0.221
Lymphoma	17(9.7)	23(12.8)	0.352	12(7.8)	14(9.1)	0.074
Metastatic cancer	21(11.9)	18(10.0)	0.560	16(10.4)	15(9.7)	0.177
Mechanism of injury, blunt, n (%)	144(81.8)	162(90.0)	0.008	134(87.0)	136(88.3)	0.428
Cause of injury, n (%)						
Motor vehicles	40(22.7)	42(23.3)	0.892	35(22.7)	36(22.3)	0.118
Bikes	70(39.8)	73(40.6)	0.880	65(42.2)	64(41.6)	0.647
Pedestrian	25(14.2)	22(12.2)	0.380	21(13.6)	18(11.7)	0.209
Fall	36(20.5)	38(21.1)	0.879	31(20.1)	29(18.8)	0.355
Other	5(2.8)	5(2.8)	0.971	3(1.9)	4(2.6)	0.090
Pre-hospital status, median (IQR)						
MAP (mmHg)	55(54.3–56.8)	59(56.2–59.7)	0.002	56(55.1–58.2)	55(54.1–56.3)	0.425
HR (beats min <sup>-1</sup> )	105(104–110)	106(105–111)	0.551	102(100–109)	104(102–107)	0.633
Fluid amount (mL)	500(250–1000)	500(350–1000)	0.652	550(350–1000)	550(450–1000)	0.704
Intubation, n (%)	19(10.8)	21(11.7)	0.436	12(7.8)	13(8.4)	0.092
Initial GCS score, point	8(6–11)	13(10–15)	0.003	13(10–15)	14(11–15)	0.087

(Continued)

Table 1 (Continued).

Variables	Before PSM			After PSM		
	EN (n=176)	DN (n=180)	P-value	EN (n=154)	DN (n=154)	P-value
On-admission status, median (IQR)						
MAP (mmHg)	58(55.8–61.2)	62(57.2–63.5)	0.001	62(59.2–64.5)	63(60.2–65.8)	0.644
HR (beats min <sup>-1</sup> )	99(98–106)	98(96–105)	0.604	97(95–102)	98(96–103)	0.544
Intubation, n (%)	14(8.0)	16(8.9)	0.280	12(7.8)	10(6.5)	0.406
Initial GCS score, point	14(11–15)	14(10–15)	0.654	13(10–14)	12(11–15)	0.864
Hemoglobin, g dL <sup>-1</sup>	6(4.9–9.4)	7(5.1–9.6)	0.001	7(6.8–11.6)	9(8.9–11.8)	0.325
Blood glucose, mg dL <sup>-1</sup>	167(138.0–182.0)	167(141.5–182.0)	0.305	166(139.0–190.0)	168(148.5–192.0)	0.505
Blood lactate, mmol L <sup>-1</sup>	3.7(3.2–4.1)	3.7(3.2–4.1)	0.705	3.9(3.4–4.5)	3.8(3.5–4.8)	0.542
Serum creatinine, mg dL <sup>-1</sup>	1.5(1.3–1.8)	1.5(1.3–1.8)	0.847	1.4(1.2–1.7)	1.5(1.2–1.9)	0.759
Severity scores, point, median (IQR)						
SOFA score I <sub>st</sub> day	7(5–8)	9(7–9)	0.042	7(5–8)	8(7–9)	0.468
ISS score I <sub>st</sub> day	23(16–38)	26(16–36)	0.021	30(19–42)	29(18–38)	0.074
APACHE III score I <sub>st</sub> day	74(61.0–79.5)	78(63.0–81.0)	0.015	74(61.0–82.0)	75(62.0–81.0)	0.080
NE use, median (IQR)						
Timing, hour	2.2(1.7–2.5)	4.3(3.7–6.5)	<0.001	2.3(1.7–2.5)	4.4(3.8–6.5)	<0.001
Maximum NE rate within 24h, ug kg <sup>-1</sup> min <sup>-1</sup>	0.6(0.2–1.1)	0.6(0.3–1.0)	0.705	0.5(0.3–1.0)	0.6(0.2–1.1)	0.420
Total dose within 24h, mg	31(24–72)	30(20–72)	0.940	30(23–70)	31(24–73)	0.722
Target MAP need time, hour	8.2(6.4–10.4)	16.0(13.9–24.0)	<0.001	8.2(6.3–9.9)	15.0(12.6–17.0)	<0.001
Fluid resuscitation within 24h, median (IQR)						
RBC, mL	1050(750–1650)	1350(750–1650)	0.629	1100(850–1800)	1250(765–1950)	0.084
Lyophilized plasma, mL	900(500–1100)	950(650–1150)	0.080	910(580–1150)	965(750–1020)	0.064
Fibrinogen, g	3(0–3)	3(0–3)	0.901	3(0–3)	3(0–3)	0.804
Platelet, units	2(0–2)	2(0–2)	0.899	1(0–2)	2(0–2)	0.083
Total of non-blood fluid infusion, mL	3027(1991–4492)	3760(2691–4637)	0.004	2930(1807–4451)	3770(2691–4637)	<0.001
Total of all fluid infusion, mL	5150(4041–7152)	6672(4700–7430)	<0.001	5155(4150–7200)	6500(4850–7690)	<0.001
Damage control surgery, n (%)	58(33.0)	60(33.3)	0.843	54(35.1)	59(38.3)	0.116

**Abbreviations:** PSM, propensity score matching; EN, early norepinephrine; DN, delay norepinephrine; SD, standard deviation; CCI, Charlson comorbidity index; BMI, body mass index; MAP, mean arterial pressure; HR, heart rate; GCS, Glasgow Coma Scale; SOFA, sequential organ failure assessment; ISS, injury severity score; APACHE, acute physiology, age, chronic health evaluation; RBC, red blood cell; NE, norepinephrine.

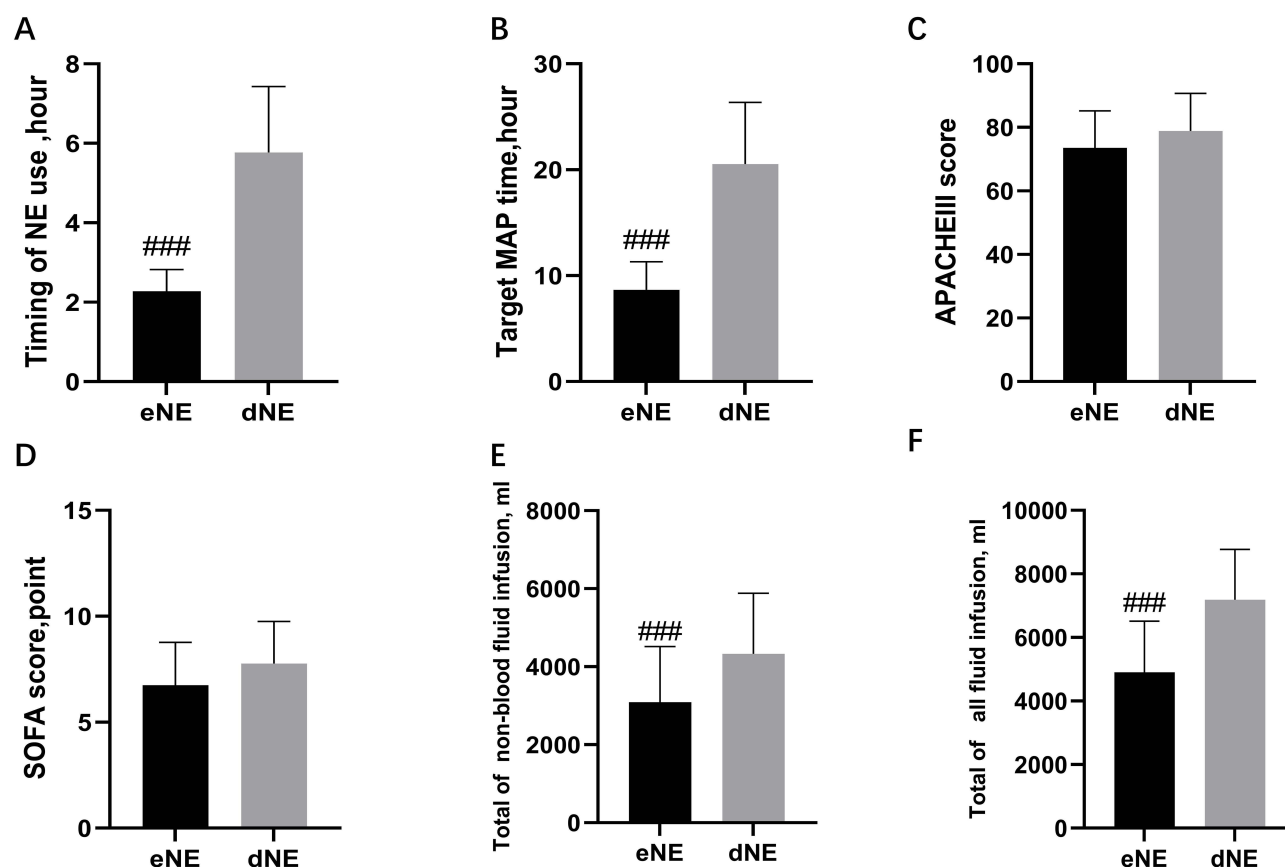
## Primary Study Endpoint

Before PSM, the 24 h mortality rate in the eNE group was lower than that in the dNE group (54, 30.7% versus 45.0%;  $P < 0.001$ ). After PSM, the 24 h mortality rate in the eNE group was still lower than that in the dNE group (46, 29.9% versus 69, 44.8%,  $P < 0.001$ ) (Table 2). The ROC analysis demonstrated that a 4.4 h cut-off point for the timing of NE use gave the optimal predictive value for 24 h mortality, with a sensitivity of 95.52%, a specificity of 81.33% and an AUC of 0.9272; these were better than other potential risk factors, such as the ISS score (0.6859), APACHE III score (0.7232), SOFA score (0.7961), total of non-blood fluid infusion (0.8103) and total of all fluid infusion (0.8045) (Figure 3).

The Kaplan–Meier survival analysis of 24 h mortality showed that the survival rate of the eNE group was higher than that of the dNE group ( $P < 0.001$ ) (Figure 4). The Streg regression model showed that the scores for ISS, APACHE III and SOFA; initial blood lactate, 24 h total of non-blood fluid infusion and dNE were significantly associated with 24 h survival ( $P < 0.05$ ) (Table 3).

## Secondary Study Endpoint

Regardless of PSM, compared with the dNE group, there was no significant difference in AKI incidence, HLOS, ICU LOS, duration of non-CRRT and non-IMV therapy and in-hospital mortality in the eNE group ( $P > 0.05$ ) (Table 2).



**Figure 2** Comparison of the characteristics of patients in the early group and the delayed group. The timing of norepinephrine use (A); Target mean arterial pressure need time (B); APACHE III score 1st day (C); SOFA score 1st day (D); The total of non-blood fluid infusion (E); Total of all fluid infusion (F). ### Compared with dNE,  $P < 0.001$ . **Abbreviations:** MAP, mean arterial pressure, APACHE, acute physiology, age, chronic health evaluation. SOFA, sequential organ failure assessment. eNE, early norepinephrine; dNE, delay norepinephrine.

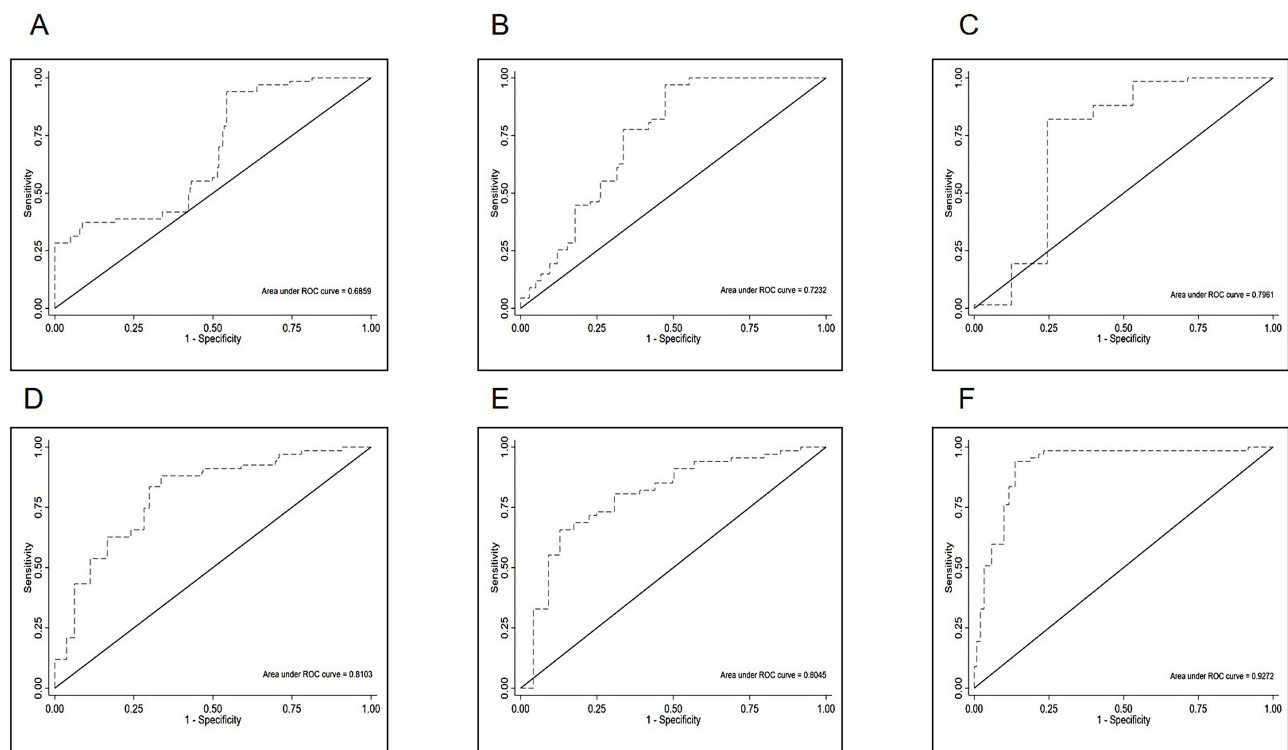
## Discussion

Early NE may be beneficial for the prognosis of patients with HS. However, the optimal timing of NE administration remains unclear. Our study showed that dNE was associated with a significant increase in 24 h mortality ( $OR = 1.30$ ,  $P < 0.001$ ). In addition, the Kaplan–Meier survival analysis of the pre-PSM and post-PSM cohorts showed that the patients in

**Table 2** Comparison of Clinical Outcomes of Patients Between Early Norepinephrine and Delayed Norepinephrine Before and After Propensity Score Matching

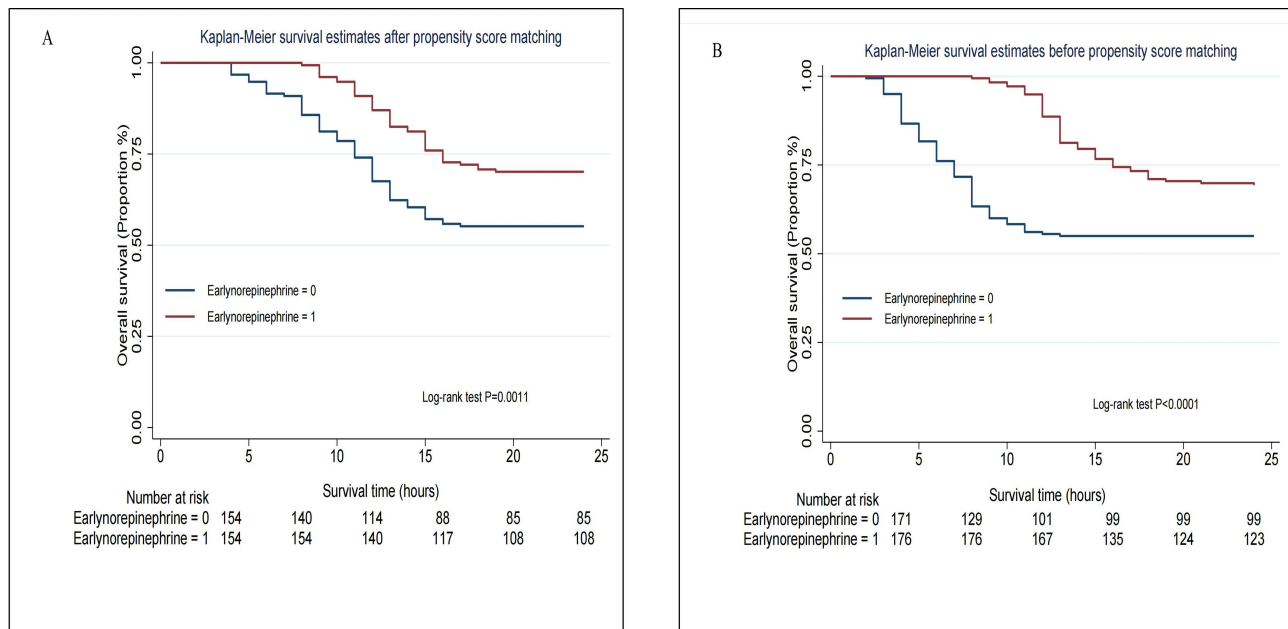
Outcomes	Before PSM			After PSM		
	EN (n=176)	DN (n=180)	P-value	EN (n=154)	DN (n=154)	P-value
Primary endpoints						
24-hour mortality, n (%)	54(30.7)	81(45.0)	<0.001	46(29.9)	69(44.8)	<0.001
Secondary endpoints						
In-hospital mortality, n (%)	38(21.6)	43(23.8)	0.072	32(18.2)	39(25.3)	0.065
Acute kidney injury within 24h, n (%)	40(22.7)	45(25.0)	0.053	36(23.4)	40(26.0)	0.054
Continuous renal replacement therapy-free day, median (IQR)	15(12–21)	12(10–18)	0.062	16(13–22)	13(11–19)	0.074
Invasive mechanical ventilation-free day, median (IQR)	20(16–24)	18(14–21)	0.112	21(18–25)	19(16–22)	0.114
Hospital length of stay, day, median (IQR)	14(9–16)	15(12–23)	0.125	14(10–15)	14(12–21)	0.216
ICU length of stay, day, median (IQR)	5(3–7)	6(4–10)	0.420	5(2–7)	6(6–9)	0.337

**Abbreviations:** PSM, propensity score matching; EN, early norepinephrine; DN, delay norepinephrine; ICU, intensive care unit; IQR, interquartiles (25–75).



**Figure 3** Receiver operating characteristic (ROC) curves of ISS score (A), APACHE III (B), SOFA score (C), Total of non-blood fluid infusion (D), Total of all fluid infusion (E), and Timing of NE use (F) for 24h mortality in patients with THS.

**Abbreviations:** ISS, injury severity score; APACHE, acute physiology, age, chronic health evaluation; SOFA, sequential organ failure assessment; NE, norepinephrine.



**Figure 4** Kaplan-Meier survival estimates based on 24h mortality. After propensity score matching (A); Before propensity score matching (B).

the eNE group had a higher survival rate after admission than those in the dNE group. The multivariate Streg regression analysis also showed that dNE was associated with a lower 24 h survival rate.

It has been found that trauma-induced haemorrhage and hypovolemia can trigger an intricate neurohormonal response.<sup>15</sup> Thus, trauma-induced hypotension is associated not only with hypovolemia but also with sympathetic



**Table 3** The Streg Regression Model Analysis Based on Traumatic Hemorrhagic Shock Patients with 24 Hour-Mortality

Variables	HR	95% CI	Z-value	P-value
ISS score 1st day	1.04	1.02–1.06	4.39	<0.001
APACHE III score 1st day	1.03	1.01 –1.04	3.24	0.002
Sofa score 1st day	1.18	1.02–1.36	2.11	0.023
Initial blood lactate	1.22	1.09–1.36	3.97	<0.001
Total of non-blood fluid infusion	1.00	0.92–1.11	2.88	0.008
Delay norepinephrine	1.24	1.13–1.36	3.04	0.004

**Abbreviations:** HR, hazard ratio; CI, confidence interval; ISS, injury severity score; SOFA, sequential organ failure assessment; APACHE, acute physiology, age, chronic health evaluation.

suppression-induced vasodilation.<sup>16</sup> Vasopressor administration plays an important role in treating vascular paralysis and sustaining adequate perfusion pressure among patients with trauma and hypotension. Recent research has supported the biological plausibility of using NE for patients with trauma and HS.<sup>10</sup> Haemorrhage is a time-dependent process, and its early recognition and management are critical. Our findings showed that eNE was associated with decreased mortality, which was consistent with previous studies. Poloujadoff et al<sup>17</sup> found that NE infusion at a rate of 50 µg·100 g<sup>-1</sup>·h<sup>-1</sup> within 75 minutes of traumatic HS significantly improved the survival rate of rats at 210 minutes. A recent study also showed that eNE was associated with increased short-term survival rates in patients with sepsis.<sup>18</sup> Another retrospective study demonstrated that if the time from the onset of shock to the use of NE was more than 2 h, the 28 d mortality rate was significantly increased, and for each additional hour, mortality increased by 5.3%.<sup>19</sup> Preliminary animal studies have shown that NE mainly acts as a vasoconstrictor, which can constrict arterial vessels and activate venous  $\alpha$ -adrenergic receptors.<sup>20</sup> This induces venous vasoconstriction, diverting splanchnic blood volume to the systemic circulation, while the activation of  $\beta_2$ -adrenergic receptors reduces venous resistance and increases venous return.<sup>21</sup> Recent data from an animal model showed improved survival after NE infusion, irrespective of a lower or higher blood pressure target.<sup>22</sup>

Therefore, we hypothesised that using eNE to improve hemodynamic status might have a positive effect on survival time. However, a few clinical trials have shown that eNE has no positive effect on the survival time of patients with traumatic HS<sup>10</sup> or is even harmful.<sup>9</sup> We believe that there might be selection bias, as the increased proportion of thoracotomies performed affects the hemodynamic status of patients and negatively impacts survival time. Additionally, other studies examined the combined exposure to any vasopressor, including phenylephrine, dopamine, vasopressin and NE. Furthermore, the grouping of the study population or the concentration of vasoactive drugs might have influenced the trial results. Singer et al<sup>23</sup> found that higher maximum doses of NE were associated with increased mortality and that patients with trauma who commenced NE more than 24 h after injury may have a dire prognosis. Therefore, our study used a PSM analysis to reduce bias as much as possible and borrowed from the grouping method used by most studies.<sup>11–13</sup>

Our study found that eNE was not associated with a shorter ICU LOS, a shorter HLOS and a longer duration of non-IMV therapy. Animal studies have shown that the early administration of NE reduced blood loss and fluid requirements during MAP-directed fluid resuscitation in rats with HS.<sup>24</sup> Other studies have also demonstrated eNE to be associated with less fluid infusion and improved outcomes.<sup>25,26</sup> This is because, in critically ill patients, the higher the positive fluid balance, the worse the possible prognosis.<sup>17,27–30</sup> Although there may be several reasons for the lower mortality in patients receiving eNE, the rapid restoration of blood flow in combination with lower fluid accumulation could restore tissue perfusion rapidly and avoid the harm caused by fluid overload.<sup>31</sup> Our study found that eNE could reduce the time of target MAP need and reduce the 24 h total of all fluid infusion, especially that of 24 h total of non-blood fluid infusion. However, eNE was not beneficial in terms of lowering the risk of pulmonary oedema and congestive heart failure, improving respiratory function, shortening HLOS and reducing the duration of IMV therapy.

Our study also found that eNE did not reduce the incidence of AKI or shorten the duration of CRRT. Domizi et al<sup>32</sup> found that high doses or a high frequency of NE could lead to serious complications, such as AKI or arrhythmia. A recent double-blind prospective study found that eNE neither caused AKI or serious cardiovascular events nor increased the duration of renal replacement therapy, although it might be beneficial for early fluid resuscitation in patients with shock.<sup>33</sup>



This interpretation was basically consistent with our findings. In addition, we also found that blood lactate levels were significantly reduced with eNE. Bai et al<sup>19</sup> and Hernandez et al<sup>34</sup> also found that after HS, blood lactate levels were significantly reduced at each time point of eNE.

Our results showed that higher SOFA and APACHE III scores, initial blood lactate levels, total non-blood fluid infusion and dNE were independent risk factors for 24 h mortality in patients with traumatic HS. This conclusion was basically consistent with those of recent studies.<sup>31,35,36</sup>

The highlights of our study are as follows: First, our research was the first to compare the effects of eNE versus dNE on the short-term outcomes of patients with traumatic HS. Second, we applied PSM to minimise selection bias and make the data from the early and delayed groups more comparable. Third, because the proportional hazards assumption of the Cox model did not hold, we used a Streg regression analysis to assess the association between eNE and 24 h survival.

## Limitations

Our study has some limitations. First, the sample size of the study population was small, which might have led to selection bias. Second, although this study controlled for confounding factors by using PSM and a regression analysis, there might still be confounders. Finally, this was a retrospective study, although it was based on synthetic and abundant clinical data from high-level research university hospitals.

## Conclusions

The use of NE within the first 3 h was associated with higher 24 h survival rates. The use of eNE appears to be a safe intervention that benefits patients with traumatic HS. Considering the conflicting evidence in the literature, there is a need for large-scale randomised controlled trials to investigate and clarify the potential clinical association of eNE use with survival among patients with traumatic HS.

## Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Affiliated Hospital of Yangzhou University (2021-YKL3-01-001). Written informed consent was obtained from all participants.

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## Disclosure

The authors report no conflicts of interest in this work.

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