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Title: Clinical Outcomes of Norepinephrine-Phenylephrine vs. Norepinephrine-Vasopressin in Septic Shock: A Retrospective Cohort Study

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Clinical Outcomes of Norepinephrine-Phenylephrine vs. Norepinephrine-Vasopressin in Septic Shock: A Retrospective Cohort Study

Abstract

Purpose: This study aims to compare the clinical outcomes of norepinephrine combined with phenylephrine (NE-PE) versus norepinephrine combined with vasopressin (NE-VP) in patients with septic shock.

Materials and Methods: This retrospective cohort study included septic shock patients identified from the Medical Information Mart for Intensive Care (MIMIC-IV; 2008-2019) and the eICU Collaborative Research Database (eICU-CRD). Within the MIMIC-IV cohort, propensity score matching (PSM) and stabilized inverse probability of treatment weighting (IPTW) were carried out to balance baseline characteristics between groups, with outcomes compared across the crude, PSM, and IPTW cohorts. Multivariable logistic regression was further employed for subgroup analyses to assess the association between NE-VP versus NE-PE and in-hospital mortality. The observed association was subsequently validated using the external eICU-CRD cohort. Interaction and marginal effects were evaluated within the MIMIC-IV cohort to determine whether Shock Index modified the treatment effect of NE-VP versus NE-PE on in-hospital mortality.

Results: The MIMIC-IV cohort comprised 753 patients (NE-PE: 238; NE-VP: 515), with an eICU-CRD validation cohort of 313 (NE-PE: 67; NE-VP: 246). After 1:1 PSM (336 patients; 168 pairs) and stabilized IPTW (weighted n=724.7), both methods effectively reduced selection bias. Consistently across PSM/IPTW cohorts, the NE-PE group exhibited a shorter duration of dual vasopressor therapy and a lower in-hospital mortality rate. Multivariable regression analysis within the MIMIC-IV cohort confirmed reduced in-hospital mortality for NE-PE versus NE-VP, a finding further validated in the eICU-CRD cohort. Subgroup analyses with interaction testing within the MIMIC-IV cohort revealed that the mortality reduction associated with NE-PE was particularly pronounced in patients aged < 65 years and in those without hypertension. Marginal effect analysis further indicated that higher Shock Index values amplified the mortality risk associated with NE-VP versus NE-PE.

Conclusion: In septic shock patients, NE-PE may be associated with reduced in-hospital mortality compared to NE-VP, especially among patients aged <65 years or those without hypertension. The Shock Index may serve as a valuable indicator for selecting a secondary vasopressor during vasopressor escalation.

Keywords: septic shock; norepinephrine; phenylephrine; vasopressin; MIMIC-IV

Introduction

Septic shock, characterized by refractory hypotension and tissue hypoperfusion, is a severe manifestation of sepsis and a leading cause of mortality in intensive care units (ICU) [1]. Despite significant advancements in critical care, the management of septic shock remains a formidable challenge, with mortality rates exceeding 30% [2,3]. Fluid resuscitation and vasopressor therapy are fundamental strategies for reversing hemodynamic instability. Current guidelines recommend norepinephrine (NE) as the first-line vasopressor due to its combined α-adrenergic and β-adrenergic effects, which effectively increase mean arterial pressure (MAP) and cardiac output [4]. However, given that excessive NE infusion has been shown to adversely affect patient outcomes and a single vasopressor may be insufficient to achieve hemodynamic stability in refractory shock, strategic vasopressor escalation is generally required [5,6]. Although vasopressin (VP) addition has been shown to reduce mortality in patients with less severe shock receiving NE < 15 μg/min, recommendations for combination therapy still lack high-quality evidence [7].

Phenylephrine (PE)—a selective α-1 adrenergic receptor agonist that primarily causes vasoconstriction, often accompanied by increased systemic vascular resistance and reflex bradycardia—can also be considered as an alternative in vasopressor escalation [8,9]. Nevertheless, the benefit of adding PE in improving outcomes in patients with septic shock receiving NE infusion remains controversial. Although PE has been

proposed as a potentially beneficial agent for achieving heart rate control, increased cardiac output, and correction of metabolic abnormalities, studies have shown mixed outcomes [10]. For instance, PE boluses before NE infusion were found to be associated with early hemodynamic stability but higher ICU mortality [11]. Additionally, the combination of NE and PE could lead to higher hospital mortality compared to NE alone [12]. Nevertheless, PE can serve as an alternative secondary vasopressor in clinical practice when VP is unavailable or contraindicated [13]. Given the heterogeneity of pathological vasodilation and impaired vasopressor response observed in patients with septic shock—such as internal vasopressin deficiency or α_1-adrenergic desensitization—we hypothesize that the efficacy of the NE-PE combination will vary across clinically identifiable subgroups relative to the NE-VP combination [14,15]. However, direct head-to-head comparisons of these dual vasopressor regimens remain particularly limited [16].

The present study aims to compare the clinical outcomes of NE-PE versus NE-VP in patients with septic shock. By employing propensity score matching (PSM) and stabilized inverse probability of treatment weighting (IPTW), we aim to provide a more balanced comparison of these two treatment regimens. Furthermore, we examined the effects of NE-PE versus NE-VP across diverse patient characteristics to identify factors that could guide the selection of the optimal vasopressor combination in clinical practice. This retrospective cohort study has been reported in line with the STROCSS guidelines [17].

Material and Methods

Database

The data of discovery cohort in this present study was obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV 2.2) database, a contemporary dataset constructed by the Massachusetts Institute of Technology (MIT), comprising over 50,000 unique patients admitted to ICU with comprehensive and precise digital information from Beth Israel Deaconess Medical Center between 2008 and 2019 [18,19]. The data used for validation was obtained from the eICU Collaborative Research Database (version 2.0), which comprised deidentified health data associated with over 200,000 admissions to ICUs across the United States between 2014 and 2015 [20,21]. Informed consent was waived due to the deidentification of the two publicly accessible datasets according to the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor method, which protects private information. Author Dong secured access to the two datasets by completing the Collaborative Institutional Training Initiative (CITI) program and relevant examinations on PhysioNet (Record ID: 51348270) [22].

Study population

This retrospective study, adhering to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), included patients with septic shock who exhibited a Sequential Organ Failure Assessment (SOFA) score of ≥2 points, hyperlactatemia (>2 mmol/L), and required

volume resuscitation and vasopressors to reverse hypotension [23]. Specifically, we included septic shock patients aged over 18 years who received vasopressor therapy with NE, PE or VP, and those who were treated exclusively with the combination of NE-PE or NE-VP.

The exclusion criteria were as follows:1) patients who experienced multiple admissions to the ICU and required vasopressor administration during a single hospitalization. 2) septic shock patients treated with the combination of NE-PE or NE-VP for less than 1 hour during the initial phase, or those who initiated the combination regimen more than 24 hours after ICU admission. 3) patients who diagnosed with other types of shock (cardiogenic shock, traumatic shock, and postoperative shock) according to the International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10) codes. 4) Patients without identifiable vasoactive medication dosing records or absent volume resuscitation documentation.

Data collection and Variable Definitions

The collected data included demographics (age, sex, height, weight, body mass index [BMI], and ethnicity), type of hospital and ICU admission, underlying diseases (diabetes, hypertension, myocardial infarction, congestive heart failure, renal disease, and malignant cancer), laboratory examinations (white blood cell, neutrophils, lymphocytes, platelets, hemoglobin, creatinine, blood urea nitrogen [BUN], lactate and pH), vital signs (heart rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP], and atrial fibrillation),

and interventions (use of vasopressor, corticosteroids, intravenous fluid administration, mechanical ventilation support, and continuous renal replacement therapy [CRRT]). To measure the severity of illness, the Charlson Comorbidity Index score was calculated based on the recorded ICD-9 and ICD-10 codes from each patient's diagnoses. The Acute Physiology and Chronic Health Evaluation III (APACHE III) scores were also calculated on the first day of each ICU patient's stay. SOFA scores and each of its components were extracted as well. This study defined the initiation of dual vasopressor therapy as the starting point. To best capture patients' disease status at the time of vasopressor escalation, the most recent data recorded within 4 hours before and after this start point, including vital signs, laboratory examinations, SOFA scores, and interventions, were incorporated into the analysis.

Information on vasopressor and corticosteroid drugs was also collected, including drug names, doses, routes of administration, and administration period. Subsequently, the norepinephrine-equivalent dose was generated based on the dosage of dual vasopressor therapy in the first hour, calculated according to the formula: norepinephrine (μg/kg/min) + 1/10 × phenylephrine (μg/kg/min) + 2.5 × vasopressin dose (U/min) [24]. Furthermore, in light of the evidence supporting low-dose corticosteroids as an effective adjunct therapy, corticosteroid use at a dose of ≤500 mg hydrocortisone (or equivalent) per day was identified a key variable [25].

Outcomes

In-hospital mortality was considered as the primary outcome. Secondary endpoints included ICU mortality, duration of dual vasopressor therapy, total duration of vasopressor use, length of ICU stay, length of hospital stay, ischemia of intestine, and failure of hemodynamic maintenance (defined as death within 6 hours after discontinuation of vasopressor therapy).

Statistical analysis

In this study, the normality of continuous data was assessed using skewness and kurtosis analysis, and visual inspection of frequency distribution curves. Continuous variables are presented as median (interquartile range) for non-normally distributed data, or mean ± standard deviation (SD) for normally distributed data. Comparisons between groups for continuous variables were performed using the two-sided t-test or the Mann-Whitney U test, depending on the distribution. Categorical variables were presented as frequencies and percentages, and were compared using the chi-square ($\chi 2$) test. Extreme values were Winsorized using the winsor2 command in STATA, with cut-off points at the 1st and 99th percentiles. Missing values were then imputed using the R package missForest if the missingness was less than 30% for a variable; else, the variable was excluded [26].

To balance baseline characteristics between groups within the MIMIC-IV cohort, both propensity score matching (PSM) and stabilized inverse probability of treatment weighting (IPTW) were employed. The propensity score (PS) was estimated using a multivariable logistic

regression model, adjusted for all potential confounders, including age, gender, BMI, ethnicity, hospital and ICU admission type, Charlson Comorbidity Index, underlying diseases, APSIII score, SOFA score (with its components), heart rate, atrial fibrillation, MAP, norepinephrine-equivalent dose, corticosteroid use, intravenous fluid input, CRRT, invasive ventilation support, and laboratory variables. A 1:1 nearest-neighbor propensity score matching (PSM) procedure without replacement was performed, with a standardized difference in propensity scores (PS) exceeding 0.02 deemed unmatched [27]. Stabilized weights (SW) were calculated as follows: for the NE-VP group, weight = pt/PS; for the NE-PE group, weight = (1-pt)/(1-PS), where pt denotes the unadjusted probability of being in the NE-VP group [28]. The standardized mean differences (SMDs) was computed to assess the efficiency of PSM and IPTW in reducing the differences of baseline characteristics between groups, with an SMD $\leq$ 0.1 indicating satisfactory balance. Due to the non-normal distribution of outcomes such as length of hospital or ICU stay, and duration of vasopressor use, a general linear model (GLM) with SW was employed to assess differences between groups after IPTW.

Multivariable logistic regression was employed to explore the association between vasopressor regimens (NE-PE *vs.* NE-VP) and in-hospital mortality in the MIMIC-IV cohort, adjusting for specified covariates. This primary analysis was then validated externally using independent multivariable logistic regression models in the eICU-CRD cohort. To further investigate whether the effect of NE-VP versus NE-PE on in-hospital mortality varied across subgroups stratified by age, gender, comorbidities (including diabetes, hypertension, myocardial infarction, congestive heart failure), and corticosteroid use, multivariable logistic regression models were employed with interaction terms to assess

heterogeneity across subgroups.

To assess whether the Shock Index modified the treatment effect of NE-VP versus NE-PE on in-hospital mortality, we performed multivariable logistic regression adjusted for potential confounders, with an interaction term between Shock Index and treatment group. We then computed the marginal effects of Shock Index on in-hospital mortality within each treatment group using STATA's margins command and visualized the inter-group risk differences with 95% confidence intervals (CIs). Variance inflation factor (VIF) was calculated to identify and exclude variables with multicollinearity (VIF >5). Statistical analyses were conducted using Stata/MP (version 17.0) and R (version 4.1.2). Statistical significance was defined as a P-value<0.05.

Results

Comparison of patients baseline characteristics and outcomes

After excluding 57 patients diagnosed as other types of shock, 753 critically ill patients with septic shock from the MIMIC-IV database were included in the analysis (Figure.1). Among them, 238 septic shock patients received NE-PE therapy, while 515 patients were exposed to NE-VP. Additionally, an independent validation cohort of 313 septic shock patients from the eICU-CRD was identified, comprising 67 patients in the NE-PE group and 246 in the NE-VP group. The missing data and VIF for the variables are presented in Supplementary Table S1 and S2.

As demonstrated in the MIMIC-IV cohort (Table 1), significant differences were observed in ICU admission type, platelet count, creatinine, BUN, APSIII score, SOFA score, and continuous renal replacement therapy (CRRT) receipt. Compared to the NE-PE group, the NE-VP group exhibited a higher proportion of medical ICU admissions, elevated APSIII and SOFA scores (notably in hepatic, cardiovascular, and renal components), higher creatinine and BUN levels but lower platelet counts, a greater proportion receiving CRRT and low-dose corticosteroid. In addition, the NE-PE group had a higher norepinephrine-equivalent dose than the NE-VP group, but the difference was not statistically significant (P = 0.087). This pattern of greater multiorgan dysfunction severity in the NE-VP group was corroborated in the eICU-CRD validation cohort (Supplementary Table S3), indicating that patients receiving NE-VP had more complex baseline disease profiles..

PSM and stabilized IPTW analysis

After PSM and stabilized IPTW, differences in covariates were found to be well balanced between patients in the NE-PE and NE-VP groups, as shown in Supplementary Table S4. and Figure 2. The PSM generated 168 patient pairs treated with NE-PE and NE-VP therapies. In the pseudo-population created by stabilized IPTW, 226.9 standardized patients received NE-PE therapy, while 497.8 received NE-VP therapy (Supplementary Table S4). The distribution of stabilized weights was illustrated in Supplementary Figure 1, with no extreme values were observed. Clinical outcomes between individuals in the NE-PE and NE-VP groups were further compared in the crude cohort, PSM and IPTW

cohorts, as shown in Table 2. Compared with the NE-VP group, the NE-PE group demonstrated no significant differences in the following endpoints: length of hospital stay [PSM cohort: 12.1 (6.7, 22.3) *vs.* 11.2 (4.6, 24.1) days, $P = 0.356$; IPTW cohort: 11.7 (6.4, 23.0) *vs.* 11.6 (5.3, 21.9) days, $P = 0.808$], length of ICU stay [PSM cohort: 4.9 (2.7, 10.1) *vs.* 4.1 (2.1, 7.7) days, $P = 0.106$; IPTW cohort: 4.9 (2.6, 9.1) *vs.* 4.4 (2.3, 7.9) days, $P = 0.241$], total duration of vasopressor use [PSM cohort: 41.3 (19.8, 75.1) *vs.* 41.7 (23.5, 71.7) hours, $P = 0.771$; IPTW cohort: 40.4 (22.0, 76.6) *vs.* 46.5 (25.6, 83.9) hours, $P = 0.100$], proportion of patients diagnosed with ischemia of intestine (PSM cohort: 2.4 *vs.* 2.9 %, $P = 0.735$; IPTW cohort: 1.4 *vs.* 2.8 %, $P = 0.198$), and proportion of patients failure of hemodynamic maintenance (PSM cohort: 17.3 *vs.* 25.0 %, $P = 0.083$; IPTW cohort: 16.7 *vs.* 22.7 %, $P = 0.120$). Additionally, the NE-PE group exhibited a lower ICU mortality rate compared to the NE-VP group in the PSM cohort (21.4 *vs.* 30.4%, $P = 0.062$), with statistical significance only observed in the IPTW cohort (19.9 *vs.* 30.7%, $P = 0.011$). Notably, in both the PSM and IPTW cohorts, individuals in the NE-PE group had significantly shorter median duration of dual vasopressor therapy [PSM cohort: 3.5 (1.8, 8.2) *vs.* 19.9 (7.8, 37.4) hours, $P < 0.001$; IPTW cohort: 3.5 (1.8, 9.3) *vs.* 19.8 (9.5, 39.7) hours, $P < 0.001$], as well as lower in-hospital mortality rate (PSM cohort: 26.8 *vs.* 38.1 %, $P = 0.027$, IPTW cohort: 27.0 *vs.* 37.6 %, $P = 0.022$).

External Validation, subgroups analysis and marginal effect analysis

As displayed in Figure 3, multivariate logistic regression analysis revealed the association between the effect of NE-VP versus NE-PE and

in-hospital mortality in each specified group. In the MIMIC-IV cohort, multivariable regression adjusted for key covariates demonstrated significantly elevated in-hospital mortality with NE-VP versus NE-PE (adjusted OR 1.73, 95% CI: 1.15–2.62; *P* = 0.009). This association was robustly validated in the eICU-CRD cohort through four independently constructed models: Model 1 (OR 1.94, 95% CI: 1.04–3.59; *P* = 0.036), Model 2 (OR 2.60, 95% CI: 1.35–5.02; *P* = 0.004), Model 3 (OR 2.30, 95% CI: 1.05–5.04; *P* = 0.038), and MODEL 4 (OR 2.44, 95% CI: 1.09–5.47; *P* = 0.030), with consistently elevated mortality risks across all validation models collectively confirming the detrimental association of NE-VP therapy. Interestingly, significant heterogeneity was observed across age (*P* for interaction =0.030) and hypertension status (*P* for interaction =0.036). Compared to NE-PE, NE-VP was associated with significantly higher in-hospital mortality in septic shock patients aged <65 years (OR 3.56, 95%CI: 1.61-7.51; *P*=0.001) and those without hypertension (OR 2.94, 95%CI: 1.57-5.49; *P*=0.020), suggesting NE-PE may be the preferred regimen in these subgroups.

Moreover, a significant interaction was observed between vasopressor strategy (NE-PE *vs.* NE-VP) and Shock Index regarding in-hospital mortality (*P* for interaction=0.036). As depicted in Figure 4, higher Shock Index significantly increased mortality risk in the NE-VP group (average marginal effect=0.177, 95% CI: 0.040-0.313, *P* = 0.011), but not in the NE-PE group (average marginal effect= -0.075, 95% CI : -0.259 - 0.109, *P* = 0.426). At higher levels of Shock Index, the 95% CI of the marginal effects for NE-PE and NE-VP diverge without overlap, indicating that NE-PE is associated with a potential survival advantage compared to NE-VP.

Discussion

Septic shock, which typically manifests as distributive shock, is characterized by low systemic vascular resistance and an initial increase in cardiac output that may subsequently decline. Moreover, it is marked by inadequate tissue perfusion and microcirculatory disturbances, often accompanied by abnormal vasomotor function and catecholamine resistance [29]. Excessive NE dosing has been shown to potentially cause tachycardia or ventricular arrhythmias, increase myocardial oxygen consumption, worsen tissue hypoperfusion, elevate lactate levels, and exacerbate immune dysregulation in septic shock patients by enhancing inflammatory responses through catecholamine pathways [30–32]. Previous research indicates that the addition of VP is effective in reducing the required dosage of NE, mitigating catecholamine-associated toxicity, and decreasing mortality in patients presenting with low NE doses and low lactate levels [33–35]. However, comparative studies on vasopressor combinations remain limited. While existing research has shown no significant difference in mortality between the combination of NE and PE and that of NE and VP, these findings are constrained by small sample sizes and suboptimal data quality [36]. For refractory shock, the optimal vasopressor treatment strategy remains to be elucidated.

This study leveraged the strengths of the MIMIC-IV and eICU-CRD database and obtained detailed and comprehensive data for analysis. The results showed no notable differences between the NE-VP and NE-PE groups regarding total vasopressor duration or hemodynamic

maintenance failure within the MIMIC-IV cohort. However, the NE-VP group experienced a significantly longer duration of dual vasopressor therapy. Despite PSM and IPTW produced cohorts with different baseline characteristics, such as a lower norepinephrine-equivalent dose in the IPTW cohort than in the PSM cohort, these findings were consistent across both PSM and IPTW cohorts. This suggests that both strategies can achieve hemodynamic stability, but the combination of NE-VP may require a longer time to reach a stable hemodynamic state [37]. This could also be due to the longer half-life of VP and its potential to suppress endogenous vasopressin secretion. A slower tapering process is required upon discontinuation to avoid rebound hypotension, thereby prolonging the duration of dual vasopressor therapy. In contrast, PE can be used in septic shock to manage norepinephrine-induced arrhythmias. PE does not directly affect myocardial contractility, allowing for more rapid hemodynamic stabilization and earlier discontinuation. The result were consistent across both PSM and IPTW cohorts from the MIMIC-IV database, demonstrating that in-hospital mortality was lower in the NE-PE group than in the NE-VP group. This survival disadvantage was further supported by multivariable regression analyses in both the MIMIC-IV cohort and the eICU-CRD validation cohort, collectively confirming significantly increased mortality risk with NE-VP therapy. The observed mortality elevation may be attributable to the longer duration of dual vasopressor therapy in the NE-VP group. Vasopressin is associated with several adverse effects, including arrhythmias, reduced mesenteric blood flow, and heightened risks of intestinal complications and acute kidney injury [38–40]. Subgroup analysis indicated that the disparity in in-hospital mortality was predominantly observed among patients younger than 65 years and those without hypertension. This

suggests that vasopressin's adverse effects may be less tolerable in these subgroups, potentially increasing mortality. These patients may have more sensitive cardiovascular systems, higher baseline organ perfusion, and unique inflammatory and metabolic responses, making them more susceptible to vasopressin's adverse effects. In contrast, PE, with its shorter half-life, may be more beneficial for these patients.

Additionally, this study further revealed that among patients with higher shock indices, the NE-PE group exhibited lower in-hospital mortality compared to the NE-VP group. The shock index serves as a straightforward metric for evaluating the severity of septic shock and hemodynamic instability. Patients with elevated Shock Index typically manifest severe hypotension and tachycardia. The selective activation of the α-1 receptor by PE can effectively augment systemic vascular resistance and mitigate the risk of arrhythmias associated with high-dose NE.

While this study indicates that PE may confer advantages over VP in specific patient populations, it is important to acknowledge that PE is also associated with side effects, such as reflex bradycardia and excessive peripheral vasoconstriction. In patients with refractory shock requiring high doses of NE to maintain blood pressure, the sensitivity of alpha-adrenergic receptors may be diminished due to receptor downregulation or desensitization [41]. This can render the therapeutic efficacy of PE less predictable. Consequently, the selection and administration of vasoactive agents in septic shock must be tailored to the individual patient. Urgently required are larger-scale randomized controlled trials to offer clearer directives regarding vasopressor escalation protocols.

Despite these promising findings, several limitations of our study should be acknowledged. Although we employed PSM and IPTW to balance groups, the potential influence of unknown confounding factors cannot be entirely ruled out. Additionally, our study focused on patients treated with either NE-PE or NE-VP, excluding those requiring more aggressive vasoactive strategies. Although this approach facilitated a direct comparison of these two vasopressor combinations, the relatively low mortality rate observed in our study suggests that our findings may not be generalizable to patients with more severe septic shock [36,42].

Conclusions

In conclusion, this study suggests that while NE-VP and NE-PE achieve comparable hemodynamic stability, NE-PE may offer mortality benefits, particularly in younger patients, those without hypertension, and those with higher shock indices. However, the prolonged dual therapy and adverse effects of VP, contrasted with PE's selective action and potential limitations, underscore the complexity of vasopressor management in septic shock. Individualized treatment strategies and robust clinical trials remain critical to optimizing outcomes in this challenging condition.

Conflicts of Interest

The authors declare no conflicts of interests.

Sources of Funding

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Ethical Approval

Given the public characteristics of the MIMIC-IV and eICU-CRD data, ethical approval was deemed unnecessary.

Consent

Informed consent was not required for this study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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Figure legends:

Figure 1. Flow diagram of participant selection in MIMIC-IV database and eICU-CRD database.

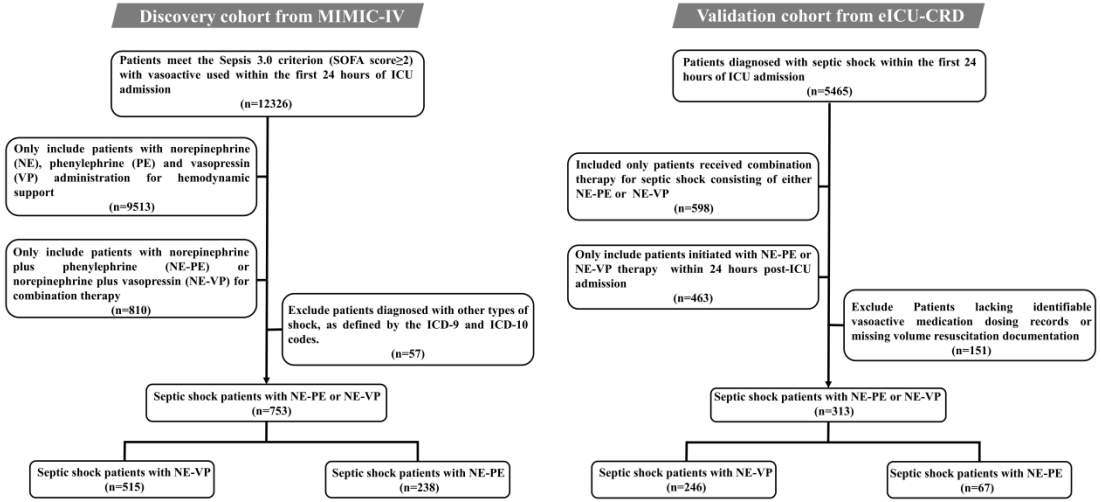


Figure 2. Balance in clinical characteristics before and after PSM and stabilized IPTW within the MIMIC-IV cohort, standardized differences of clinical characteristics were well-balanced between groups.

PSM: Propensity Score Matching; IPTW: Inverse Probability of Treatment Weighting; BMI: Body mass index; MAP, Mean Arterial Pressure; APSIII: Acute Physiology Score-III. SOFA: the Sequential Organ Failure Assessment Scores. BUN: blood urea nitrogen. CNS: Central Nervous System. Grey shading indicates pre-adjustment imbalance; colored bars show post-PSM/post-IPTW balance.

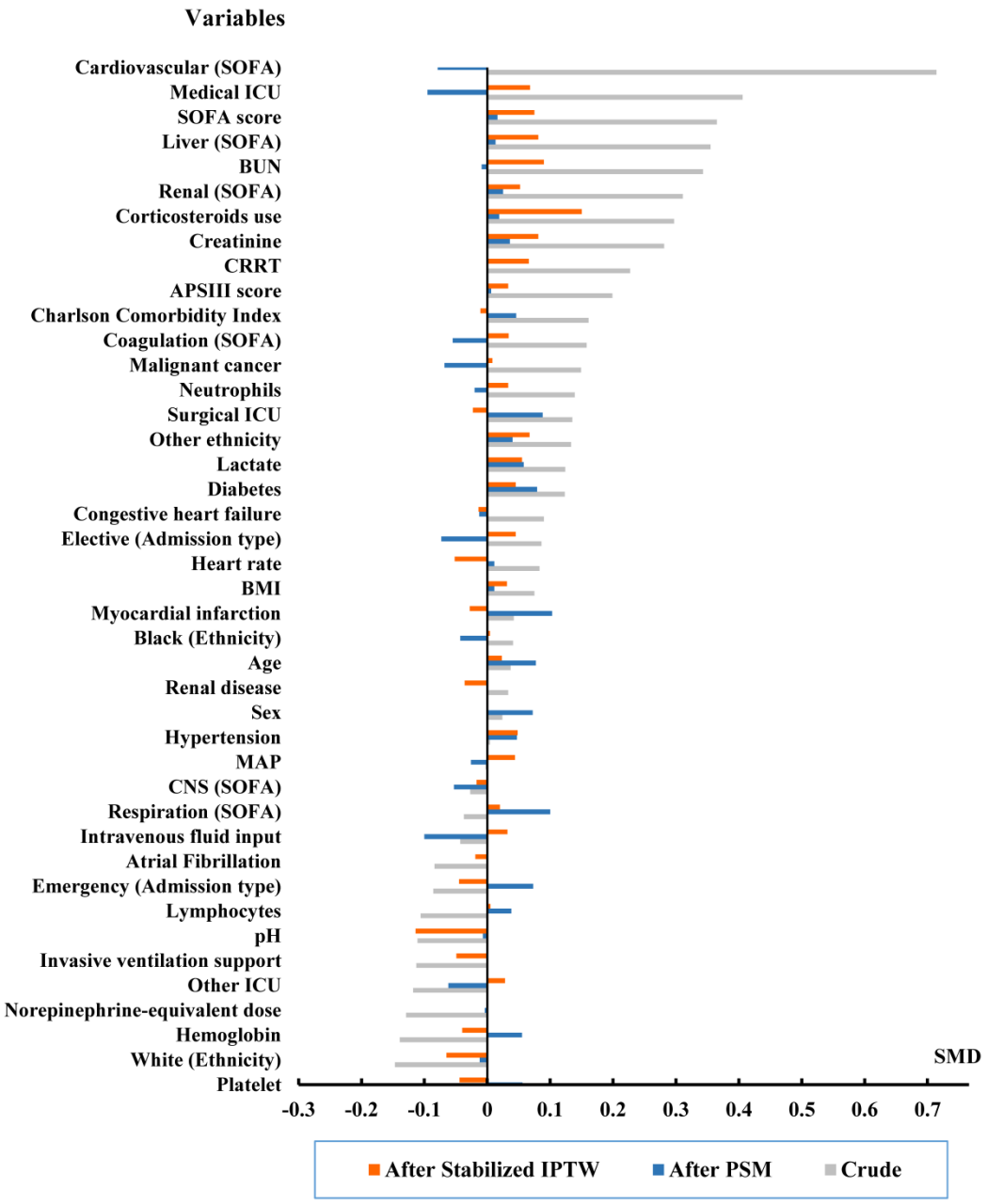
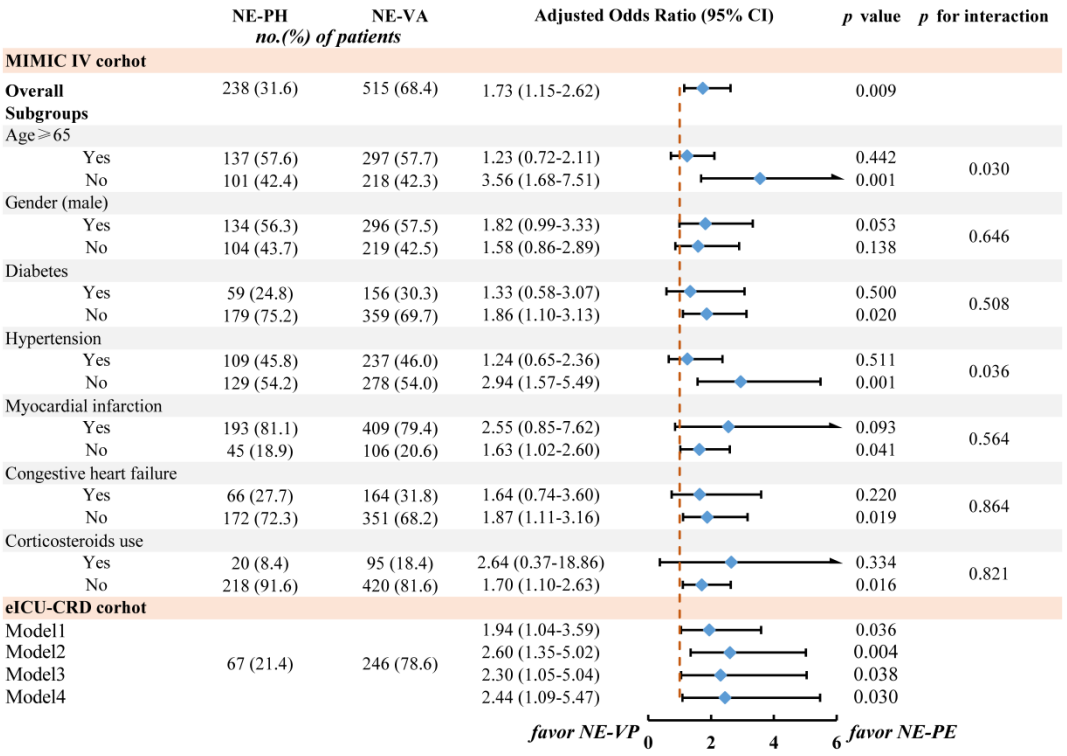

Variables
Cardiovascular (SOFA)
Medical ICU
SOFA score
Liver (SOFA)
BUN
Renal (SOFA)
Corticosteroids use
Creatinine
CRRT
APSIII score
Charlson Comorbidity Index
Coagulation (SOFA)
Malignant cancer
Neutrophils
Surgical ICU
Other ethnicity
Lactate
Diabetes
Congestive heart failure
Elective (Admission type)
Heart rate
BMI
Myocardial infarction
Black (Ethnicity)
Age
Renal disease
Sex
Hypertension
MAP
CNS (SOFA)
Respiration (SOFA)
Intravenous fluid input
Atrial Fibrillation
Emergency (Admission type)
Lymphocytes
pH
Invasive ventilation support
Other ICU
Norepinephrine-equivalent dose
Hemoglobin
White (Ethnicity)
Platelet
SMD
-0.3
-0.2
-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
After Stabilized IPTW
After PSM
Crude

Figure 3. Results of external validation, subgroup analysis and interaction analysis.

In the MIMIC-IV cohort, covariates were adjusted for age, sex, admission type, BMI, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, diabetes, hypertension, renal disease, malignant cancer, APSIII score, SOFA score, heart rate, atrial fibrillation, MAP, norepinephrine-equivalent dose, corticosteroids use, intravenous fluid input, CRRT, invasive ventilation support, neutrophils, lymphocytes, creatinine, bun, hemoglobin, platelet, lactate.

In the eICU-CRD validation cohort, Model 1: unadjusted; Model 2: adjusted for Demographics (age ≥65 years, male gender, BMI), Comorbidities (myocardial infarction, congestive heart failure, diabetes, hypertension, renal disease, malignant cancer), ICU type (medical ICU); Model 3: Model 2 + Laboratory values (WBC, lymphocytes, hemoglobin, platelets, creatinine, BUN, lactate, log-transformed ALT, log-transformed total bilirubin),Vital signs (heart rate, MAP), Severity score (SOFA); Model 4: Model 3 + Interventions (norepinephrine-equivalent dose, corticosteroids, 6-hour fluid infusio

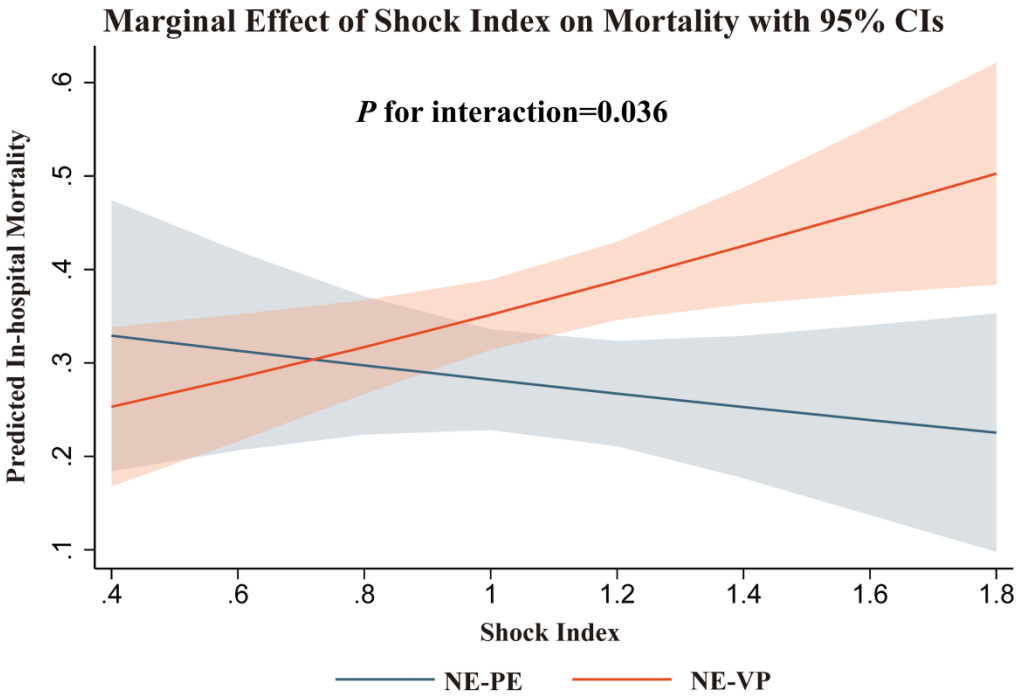


n, CRRT, invasive mechanical ventilation).

Figure 4. Marginal effect analysis of the MIMIC-IV cohort based on multi-variates logistic regression.

Covariates were adjusted for age, sex, admission type, BMI, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, diabetes, hypertension, renal disease, malignant cancer, APSIII score, SOFA score, heart rate, atrial fibrillation, norepinephrine-equivalent dose, corticosteroids use, intravenous fluid input, CRRT,

invasive ventilation support, neutrophils, lymphocytes, creatinine, bun, hemoglobin, platelet, lactate. AME, average marginal effect.



Group	AME (95%CI)	*P* value
NE-PE	-0.075 (-0.259, 0.109)	0.426
NE-VP	0.177 (0.040, 0.313)	0.011

Table 1. Baseline Characteristics between Septic Shock Patients Treated with norepinephrine combined with phenylephrine and norepinephrine combined with

vasopressin in the MIMIC-IV cohort.

Characteristics	Overall n=753	NE-PE n=238	NE-VP n=515	SMD	*p* value
Age, year	66.5±15.7	66.1±15.8	66.7±15.7	0.037	0.633
Sex (male), n (%)	430 (57.1)	134 (56.3)	296 (57.5)	0.024	0.763
BMI, kg/m²	28.2±7.3	27.8±7.2	28.4±7.3	0.075	0.338
Ethnicity, n (%)					
White	473 (62.8)	161 (67.6)	312 (60.6)	0.147	0.062
Black	66 (8.8)	19 (8.0)	47 (9.1)	0.041	0.607
Other ethnicity	214 (28.4)	58 (24.4)	156 (30.3)	0.133	0.094
Admission type, n (%)					
Emergency	636 (84.5)	206 (86.6)	430 (83.5)	0.086	0.282
Elective	117 (15.5)	32 (13.4)	85 (16.5)	0.086	
ICU type, n (%)					
Surgical	212 (28.2)	77 (32.4)	135 (26.2)	0.135	0.082
Medical	422 (56.0)	101 (42.4)	321 (62.3)	0.406	<0.001
Other ICU	293 (38.9)	102 (42.9)	191 (37.1)	0.118	0.131
Co-morbidities, n (%)					
Myocardial infarction	151 (20.1)	45 (18.9)	106 (20.6)	0.042	0.594
Congestive heart failure	230 (30.5)	66 (27.7)	164 (31.8)	0.09	0.255
Diabetes	215 (28.6)	59 (24.8)	156 (30.3)	0.123	0.121
Hypertension	346 (45.9)	109 (45.8)	237 (46.0)	0.004	0.955
Renal disease	194 (25.8)	59 (24.8)	135 (26.2)	0.033	0.678
Malignant cancer	133 (17.6)	33 (13.8)	100 (19.4)	0.149	0.063
Charlson Comorbidity Index	5.7±3.1	5.3±3.1	5.8±3.1	0.161	0.039
Laboratory examinations					
Neutrophils, 10^9/L	14.1±9.4	13.2±8.4	14.5±9.8	0.139	0.084
Lymphocytes, 10^9/L	1.1±0.8	1.2±0.8	1.1±0.8	0.106	0.180
Hemoglobin, g/L	10±2.1	10.2±2.1	9.9±2.1	0.139	0.077
Platelet, 10^9/L	204.7±132.7	220.0±129.8	197.6±133.5	0.171	0.031

Creatinine, mg/dL	2.1±1.7	1.8±1.3	2.2±1.8	0.281	0.001
BUN, mg/dL	37.4±26.3	31.5±21.5	40.1±27.8	0.343	<0.001
Lactate, mmol/L	3.7±2.9	3.4±2.4	3.8±3.1	0.124	0.131
pH	7.29±0.11	7.28±0.10	7.30±0.11	0.111	0.154
Vital signs					
Heart rate, bmp	96.8±19.1	95.7±19.4	97.3±19.0	0.083	0.290
Atrial Fibrillation, n(%)	96 (12.7)	35 (14.7)	61 (11.8)	0.084	0.274
SBP, mmHg	93.7±15.9	93.0±17.3	93.8±15.2	0.047	0.541
DBP, mmHg	50.6±10.8	50.8±12.5	50.4±10.0	0.033	0.659
MAP, mmHg	64.9±11.1	64.9±13	64.9±10.1	0.003	0.971
APSIII score	69.8±25	66.3±26.1	71.4±24.4	0.199	0.010
SOFA score	7.9±3.1	7.1±2.9	8.2±3.1	0.365	<0.001
Respiration	1.2±1.4	1.2±1.4	1.2±1.4	0.037	0.641
Coagulation	0.7±1	0.6±0.9	0.7±1	0.158	0.048
Liver	0.6±1.1	0.3±0.9	0.7±1.2	0.355	<0.001
Cardiovascular	3.8±0.4	3.6±0.5	3.9±0.3	0.714	<0.001
CNS	0.4±1	0.5±1	0.4±0.9	0.027	0.726
Renal	1.2±1.2	0.9±1.1	1.3±1.3	0.311	<0.001
Interventions					
Norepinephrine-equivalent dose (μg/Kg/min)	0.35±0.16	0.37±0.18	0.35±0.14	0.129	0.087
Corticosteroids use, n(%)	115 (15.3)	20 (8.4)	95 (18.4)	0.297	<0.001
CRRT, n(%)	25 (3.3)	2 (0.8)	23 (4.5)	0.227	0.010
Invasive ventilation support, n(%)	472 (62.7)	158 (66.4)	314 (61.0)	0.113	0.154
Intravenous fluid input (ml)	1076.3±989.5	1106.1±1067.7	1062.5±951.9	0.043	0.574

MIMIC-IV, Medical Information Mart for Intensive Care IV; BMI, Body Mass Index; ICU, Intensive Care Unit; BUN, Blood Urea Nitrogen; pH, potential of Hydrogen; MAP, Mean Arterial Pressure; APSIII, Acute Physiology Score-III; SOFA, the Sequential Organ Failure Assessment Scores; CNS, Central Nervous System; CRRT, Continuous Renal Replacement Therapy.

Table 2. Clinical outcomes between patients in the MIMIC-IV cohort receiving norepinephrine combined with phenylephrine versus norepinephrine combined with vasopressin for Septic Shock after propensity score matching and stabilized inverse probability of treatment weighting.

Clinical outcomes	The crude cohort			The PSM cohort			The stabilized IPTW cohort		
	NE-PE n=238	NE-VP n=515	*p* value	NE-PE n=168	NE-VP n=168	*p* value	NE-PE n=226.9	NE-VP n=497.8	*p* value
Length of hospital stay (days)	11.9 (6.4, 22.3)	11.8 (5.6, 21.9)	0.644	12.1 (6.7, 22.3)	11.2 (4.6, 24.1)	0.356	11.7 (6.4, 23.0)	11.6 (5.3, 21.9)	0.808
Length of ICU stay (days)	4.6 (2.5, 9.2)	4.6 (2.3, 8.1)	0.769	4.9 (2.7, 10.1)	4.1 (2.1, 7.7)	0.106	4.9 (2.6, 9.1)	4.4 (2.3, 7.9)	0.241
Duration of dual vasopressor therapy (hours)	3.7 (1.9, 9.7)	20.5 (9.8, 40.4)	<0.001	3.5 (1.8, 8.2)	19.9 (7.8, 37.4)	<0.001	3.5 (1.8, 9.3)	19.8 (9.5, 39.7)	<0.001
Total duration of vasopressor use (hours)	40.4 (20.1, 71.3)	47.2 (26.3, 88.9)	0.004	41.3 (19.8, 75.1)	41.7 (23.5, 71.7)	0.771	40.4 (22.0, 76.6)	46.5 (25.6, 83.9)	0.100
Ischemia of intestine, n(%)	6 (2.5)	13 (2.5)	0.998	4 (2.4)	5 (2.9)	0.735	3.2 (1.4)	13.7 (2.8)	0.198
Failure of hemodynamic maintenance, n(%)	39 (16.4)	117 (22.7)	0.046	29 (17.3)	42 (25.0)	0.083	38.0 (16.7)	112.8 (22.7)	0.120
ICU mortality, n(%)	46 (19.3)	157 (30.5)	0.001	36 (21.4)	51 (30.4)	0.062	45.2 (19.9)	153.0 (30.7)	0.011
Hospital mortality, n(%)	60 (25.2)	194 (37.7)	0.001	45 (26.8)	64 (38.1)	0.027	61.2 (27.0)	187.2 (37.6)	0.022

PSM, Propensity Score Matching; IPTW, Inverse Probability of Treatment Weighting; Failure of hemodynamic maintenance was defined as death within 6 hours after discontinuation of vasopressor therapy.

SDC link:

Supplementary Figure/Table - http://links.lww.com/JS9/F343

Highlights

- Optimal vasopressor combination strategy in septic shock remains unclear.
- This is the largest retrospective cohort study on vasopressor combinations and patient outcomes.
- Propensity score matching and stabilized inverse probability of treatment weighting were used to balance patient baseline characteristics.
- Age, hypertension status, and shock index may guide the selection of norepinephrine combined with phenylephrine.