

Phenylephrine versus Norepinephrine for Hemodynamic Support in Tachycardic Septic Shock: A Propensity-Weighted Retrospective Cohort Study

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Abstract

Background

Norepinephrine (NE) is the universally recommended first-line vasopressor for the resuscitation of septic shock. However, in the setting of tachyarrhythmia, phenylephrine (PE) to augment mean arterial pressure (MAP) while theoretically avoiding beta-1 mediated chronotropy is occasionally used. The clinical efficacy and safety of this phenotype-specific approach remain poorly defined. We evaluated whether PE, compared with NE, improves rate control and clinical outcomes in septic shock patients presenting with tachycardia.

Methods

We conducted a retrospective observational cohort study utilizing the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Adult patients with septic shock and a baseline heart rate > 100 bpm were included. Causal inference was achieved using Inverse Probability of Treatment Weighting (IPTW) to emulate a target trial. The primary outcome was the cumulative incidence of persistent tachycardia (> 100 bpm) evaluated via a Fine-Gray competing risk model. Secondary outcomes included 28-day mortality, bradycardia, new renal replacement therapy (RRT), ventilator- or vasopressor-free days, and lactate clearance. We also conducted subgroup analysis by dividing groups into those with baseline atrial fibrillation and with sinus tachycardia.

Results

A total of 2,281 patients were included (NE 1,554; PE 727). Following IPTW, baseline covariates were well-balanced. PE was not associated with improved heart rate control. Secondary outcomes showed no significant difference, except for new RRT (OR 1.19, 95% CI 1.02–1.38, $p = 0.026$) and ventilator-free days (MD -1.00 days, 95% CI -1.97 to -0.02, $p = 0.046$). Subgroup analyses indicated that these findings were not consistent regardless of whether the patient had a history of atrial fibrillation or sinus tachycardia, except those with sinus tachycardia treated with phenylephrine experienced a significant reduction in ventilator-free days (MD -1.67 days; 95% CI -2.87 to -0.47, $p = 0.006$).

Conclusions

In septic shock patients with tachycardia, the initial use of phenylephrine did not improve heart rate control compared to norepinephrine and was associated with significant renal and respiratory harm, which implies against the routine substitution of phenylephrine even in septic shock with tachycardia.

Introduction

Septic shock is a life-threatening form of circulatory failure characterized by profound vasodilation, altered microcirculation, and systemic hypotension, which is associated with a mortality rate frequently exceeding 30%.[1] The cornerstone of hemodynamic resuscitation in septic shock relies on fluid administration and the prompt initiation of vasopressors. The Surviving Sepsis Campaign (SSC) recommends norepinephrine as the first-line vasopressor to restore mean arterial pressure (MAP) and ensure adequate organ perfusion.[2] Norepinephrine achieves this primarily through potent alpha-1 adrenergic agonism, which induces arterial and venous vasoconstriction, and concurrent beta-1 adrenergic activity providing inotropic and chronotropic support.[3, 4]

While compensatory tachycardia is a physiological necessity to maintain cardiac output in the setting of distributive shock and hypovolemia, persistent and severe tachycardia poses a significant clinical challenge. Heart rates exceeding 100 to 110 beats per minute (bpm) limit diastolic filling time, impair coronary perfusion, and exponentially increase myocardial oxygen demand.[5] In critically ill patients—many of whom suffer from concurrent ischemic heart disease or sepsis-induced cardiomyopathy—this supply-demand mismatch can precipitate myocardial injury, type 2 myocardial infarction, and progressive hemodynamic collapse.[6, 7] Furthermore, the development of tachyarrhythmias, particularly atrial fibrillation with rapid ventricular response (AF RVR), is an independent predictor of mortality in the intensive care unit (ICU).[8]

In patients with septic shock and tachyarrhythmia (e.g., sinus tachycardia or AF RVR), clinicians are faced with a therapeutic dilemma. The administration of norepinephrine may exacerbate tachycardia via its beta-1 chronotropic effects. Consequently, a phenotype-directed strategy in which norepinephrine is substituted with phenylephrine can be employed.[9] Phenylephrine is a synthetic, pure alpha-1 adrenergic receptor agonist completely devoid of beta-1 or beta-2 activity, which augments MAP without directly stimulating the sinoatrial node. However, phenylephrine may induce a baroreceptor-mediated reflex bradycardia in response to increased systemic vascular resistance (SVR).[10, 11]

However, the clinical utility and safety of phenylephrine in patients with septic shock and tachyarrhythmia remains controversial. Pure alpha-1 agonism significantly increases left ventricular afterload. In the setting of no cardiovascular disease, this can be tolerated without deleterious hemodynamic effects. However, in patients with septic shock who may also have depressed cardiac contractility, increasing afterload without providing concomitant beta-1 inotropic support could lead to a precipitous drop in stroke volume and cardiac output.[9, 11] Furthermore, unopposed alpha-1 systemic vasoconstriction can compromise microcirculatory blood flow, particularly in the splanchnic and renal beds, which potentially exacerbates sepsis-induced organ dysfunction.[12, 13]

Previous literature comparing these two agents is notably sparse. Small randomized controlled trials from the early 2000s, alongside subsequent meta-analyses, demonstrated that phenylephrine could achieve similar MAP targets as norepinephrine without overt differences in mortality.[10, 14] However, these studies were insufficiently powered to detect differences in organ failure rates and did not specifically evaluate potential complications associated with tachycardia, or the tachycardia phenotype.

Consequently, the routine use of phenylephrine is relegated to a "salvage" or "alternative" therapy in current guidelines.[2] Given the absence of large-scale randomized trials targeting this specific clinical scenario, we aimed to evaluate whether the initial use of phenylephrine, compared to norepinephrine, improves the rate of persistent tachycardia resolution in septic shock patients presenting with a heart rate > 100 bpm, and to assess the impact of this drug selection on subsequent organ dysfunction (specifically renal and respiratory failure), and overall 28-day mortality.

Methods

Design and Population

We conducted a retrospective cohort study utilizing the MIMIC-IV (version 3.1) database, which comprises publicly available, de-identified data from ICU patients at Beth Israel Deaconess Medical Center (2008–2022). [15–17] The establishment of this database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). Because the database is fully de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provision, the requirement for individual patient consent was waived. We included adult patients (age ≥ 18 years) meeting Sepsis-3 criteria for septic shock.[1] To ensure the capture of a sustained tachycardic phenotype, inclusion required a baseline mean heart rate > 100 beats per minute (bpm) calculated across all recorded vital signs during the 4 hours preceding vasopressor initiation. Patients were excluded if they received both vasopressors simultaneously, received epinephrine or vasopressin as a first-line agent, had missing baseline vital signs, or had missing survival data. The cohort was stratified by the initial vasopressor received—norepinephrine (control) or phenylephrine (intervention)—and patients were analyzed according to this initial treatment assignment regardless of subsequent vasopressor switching or addition, mimicking an intention-to-treat framework.

Target Trial Emulation and Outcomes

To minimize immortal time and time-zero bias inherent to the acute resuscitation phase, we employed a target trial emulation framework incorporating a pre-specified 4-hour grace period immediately following vasopressor initiation.[18, 19] The primary outcome was the cumulative incidence of persistent tachycardia, defined as the failure to achieve or maintain a heart rate ≤ 100 bpm evaluated exclusively between 4 hours and 7 days post-initiation of vasopressor. Secondary outcomes included 28-day all-cause mortality, bradycardia, new requirement for renal replacement therapy (RRT) excluding patients with baseline end-stage renal disease, ventilator-free days (VFD) at day 28, vasopressor-free days at day 28, and time to lactate clearance (< 2.0 mmol/L). Patients dying before 28 days were assigned zero VFDs and vasopressor-free days.

Missing Data and Causal Inference

To address non-random missing baseline data and prevent case-deletion bias, we utilized Multiple Imputation by Chained Equations (MICE, $m = 5$) with Predictive Mean Matching (PMM), pooling the results of the multiple imputed datasets for final analysis.[20–22] To estimate the unconfounded marginal effect of phenylephrine, we applied Inverse Probability of Treatment Weighting (IPTW). Propensity scores were estimated using multivariable logistic regression incorporating age, gender, Sequential Organ Failure Assessment (SOFA) score, Charlson Comorbidity Index [23], baseline lactate, creatinine, initial MAP, initial mean heart rate, and history of congestive heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, diabetes, hypertension, and atrial fibrillation. Weights were stabilized and truncated at 10 to prevent mathematical instability. Covariate balance was confirmed using standardized mean differences ($SMD < 0.10$).

Statistical Modeling and Subgroup Analysis

The primary outcome was analyzed using a Fine-Gray subdistribution hazard model to account for the competing risk of death prior to tachycardia resolution.[24] Binary secondary outcomes (bradycardia, new RRT) were evaluated using IPTW-weighted logistic regression (yielding Odds Ratios), and continuous outcomes (VFD, vasopressor-free days, lactate clearance) via IPTW-weighted linear regression (yielding Mean Differences). Overall 28-day survival was assessed with an IPTW-weighted Cox proportional hazards model. Finally, the entire analytical pipeline was stratified to evaluate pre-specified subgroups based on baseline rhythm: history of atrial fibrillation versus no other indicated etiology for tachyarrhythmia. Analyses were performed in R (version 4.5.1) with statistical significance set at a two-sided $p < 0.05$.

Results

Baseline Characteristics

From the MIMIC-IV database, a total of 2,281 adult patients meeting Sepsis-3 criteria with a baseline mean heart rate > 100 bpm were included in the final analysis. Of these, 1,554 (68.1%) received norepinephrine as their initial vasopressor, while 727 (31.9%) received phenylephrine. **(Additional file 1)** Prior to IPTW adjustments, several baseline differences were apparent between the cohorts. Patients receiving phenylephrine were older (mean age 63.4 vs. 61.4 years, $p = 0.007$) and showed increased tachycardia (mean heart rate [HR] 118.18 vs. 114.80, $p < 0.001$). A higher percentage of patients with a history of congestive heart failure (CHF) received norepinephrine compared with phenylephrine (34.0% vs. 29.4%, $p = 0.035$), whereas a higher percentage of patients with a history of atrial fibrillation received phenylephrine compared with norepinephrine (32.7% vs. 39.9%, $p = 0.001$). Patients receiving phenylephrine presented with lower overall organ dysfunction as evidenced by a lower mean SOFA score (3.58 vs. 4.70, $p < 0.001$), lower baseline lactate (3.64 vs. 3.93 mmol/L, $p = 0.039$), and lower baseline creatinine (1.63 vs. 1.84 mg/dL, $p = 0.004$). (Table 1) Following MICE-PMM imputation and the application of Inverse Probability of Treatment Weighting, the cohorts were adequately matched across

all physiological, demographic, and historical covariates (all SMDs < 0.10). (Additional file 2 and Additional file 3)

Table 1
Baseline characteristics

	Norepinephrine (n = 1,554)	Phenylephrine (n = 727)	p-value	SMD
Demographics				
Age, mean (SD)	61.46 (16.12)	63.40 (15.93)	0.007	0.121
Male gender, n (%)	836 (53.8)	414 (56.9)	0.173	0.063
Hemodynamics				
MAP, mean (SD)	80.24 (43.40)	81.84 (41.36)	0.406	0.038
Mean HR, mean (SD)	114.80 (11.62)	118.18 (14.14)	< 0.001	0.262
Underlying diseases				
Charlson Comorbidity Index, mean (SD)	5.32 (3.05)	5.35 (3.02)	0.845	0.009
History of CHF, n (%)	528 (34.0)	214 (29.4)	0.035	0.098
History of COPD, n (%)	439 (28.2)	228 (31.4)	0.141	0.068
History of CKD, n (%)	340 (21.9)	163 (22.4)	0.813	0.013
History of Diabetes, n (%)	466 (30.0)	206 (28.3)	0.449	0.036
History of HTN, n (%)	543 (34.9)	287 (39.5)	0.04	0.094
History of AF, n (%)	508 (32.7)	290 (39.9)	0.001	0.15
Test results				
Baseline lactate, mean (SD)	3.93 (3.30)	3.64 (2.89)	0.039	0.095
Baseline creatinine, mean (SD)	1.84 (1.58)	1.63 (1.56)	0.004	0.13
SOFA score, mean (SD)	4.70 (2.26)	3.58 (1.82)	< 0.001	0.546

SMD standardized mean difference; SD standard deviation; MAP mean arterial pressure; CHF congestive heart failure; COPD chronic obstructive pulmonary disease; CKD chronic kidney disease; HTN hypertension; AF atrial fibrillation; SOFA sequential organ failure assessment

Primary Outcome

Following the 4-hour grace period, the primary outcome assessed the presence of persistent tachycardia, which is the failure of the vasopressor to maintain heart rate stability. The cumulative incidence curves for norepinephrine and phenylephrine tracked closely together throughout the 7-day observation period. In the fully weighted Fine-Gray competing risk model, the use of phenylephrine did not improve heart rate control, compared to norepinephrine (subdistribution hazard ratio [sHR] 1.26, 95% CI 0.96–1.66, $p = 0.099$; Fig. 1a). We also evaluated the dynamic chronotropic response during the acute resuscitation phase, which showed continuous heart rate trajectories over the first 24 hours. While the phenylephrine group exhibited a visually lower mean heart rate trajectory during this initial period compared to the norepinephrine group, this modest trend did not translate into a statistically significant or clinically meaningful benefit (Fig. 1b).

Secondary Outcomes

Among secondary outcomes, there was no statistically significant difference in 28-day all-cause mortality (HR 0.97, 95% CI 0.83–1.15, $p = 0.750$; Fig. 2), rate of bradycardia, and the number of vasopressor-free days (all P s > 0.05). However, the phenylephrine group had 19% higher odds of requiring new RRT (Table 2 **and** Fig. 3a; OR 1.19, 95% CI 1.02–1.38, $p = 0.026$), which indicates that phenylephrine was associated with a statistically significant increase in renal injury. In addition, phenylephrine use was associated with significantly fewer ventilator-free days over the 28-day period (Table 2 **and** Fig. 3b; MD -0.99 days, 95% CI -1.96 to -0.02, $p = 0.045$), which indicates prolonged dependency on invasive mechanical ventilation.

Table 2
Primary and Secondary Outcomes

Outcome	Estimate	95% CI	P-value
Persistent Tachycardia (sHR)	1.259	0.958, 1.657	0.099
28-day mortality (HR)	0.974	0.828, 1.146	0.750
Bradycardia (OR)	0.893	0.752, 1.059	0.193
New RRT (OR)	1.188	1.021, 1.384	0.026
Ventilator-free days (MD)	-0.995	-1.970, -0.020	0.046
Vasopressor-free days (MD)	-0.059	-1.101, 0.984	0.912
Lactate clearance (MD)	-0.158	-3.796, 3.479	0.932

sHR subdistribution hazard ratio; OR odds ratio; RRT renal replacement therapy; MD mean difference

Subgroup Analysis: Atrial Fibrillation vs. No other indicated etiology for tachyarrhythmia

To investigate the hypothesis that phenylephrine provides a chronotropic benefit, the cohort was stratified into patients with a history of atrial fibrillation (n = 798) and those with no other indicated etiology for tachyarrhythmia (n = 1,483).

Interaction testing revealed that the lack of primary benefit was consistent across both cohorts. Specifically, phenylephrine did not significantly alter the subdistribution hazard for persistent tachycardia in either the atrial fibrillation (Fig. 4a; sHR 1.15; 95% CI 0.87–1.53, p = 0.326) or no other indicated etiology for tachyarrhythmia subgroups (Fig. 4a; sHR 1.19; 95% CI 0.72–1.96, p = 0.501). Regarding secondary outcomes, the significant risk of new RRT observed in the overall cohort was attenuated within the stratified analysis, which resulted in lack of statistical significance in both subgroups. While all other secondary outcomes mirrored the overall cohort, patients with no other indicated etiology for tachyarrhythmia treated with phenylephrine experienced a significant reduction in ventilator-free days (Fig. 4b; MD -1.67 days; 95% CI -2.87 to -0.47, p = 0.006), which was absent in the atrial fibrillation group.

Discussion

In this large, balanced, retrospective cohort study of patients with septic shock who presented with clinically significant tachycardia, the initial use of phenylephrine as a primary vasopressor failed to improve heart rate control compared to norepinephrine. In addition, in the primary cohort, the use of phenylephrine was associated with a significant increase in the incidence of acute kidney injury that required new renal replacement therapy, as well as a reduction in ventilator-free days. However, our subgroup analyses revealed that these safety signals did not persist across all baseline rhythms. Only patients with no other indicated etiology for tachyarrhythmia as their baseline rhythm showed a significant reduction in ventilator-free days.

Phenylephrine is often used in septic shock with the rationale that it will increase vagal tone to avoid significant tachycardia.[25] Our findings challenge the paradigm that substituting a pure alpha-1 agonist as initial vasopressor therapy mitigates tachycardia in patients with septic shock. Septic shock is associated with excessive sympathetic outflow and high plasma catecholamine levels, and adrenergic receptor blockade has been shown to be beneficial in patients with septic shock.[26–28] Despite increased vagal tone associated with phenylephrine administration, our study found no significant differences in sHR in patients with tachycardia treated with phenylephrine vs. norepinephrine as the initial vasopressor in septic shock.

One potential mechanism which might explain our findings relates to the pharmacologic mechanism of phenylephrine vs. norepinephrine. The absence of beta-1-mediated chronotropy provides a rationale for the use of phenylephrine in patients with septic shock and tachyarrhythmias. However, the hemodynamics of distributive shock is complex and integrated. In septic shock, up to 60% of patients experience sepsis-induced cardiomyopathy, characterized by biventricular systolic and diastolic dysfunction.[7] In this compromised state, the heart is highly sensitive to acute increases in afterload. [29] Phenylephrine induces unopposed systemic vasoconstriction, which can markedly increase left

ventricular afterload.[11] This increase in SVR without compensatory inotropic support is a potential mechanism whereby phenylephrine administration might lead to decreased stroke volume. Therefore, it is notable that the phenylephrine group in our study demonstrated a trend toward higher sHR for persistent tachycardia, though this observation did not reach statistical significance in the adjusted model. Thus, we speculate that in some patients with septic shock and tachyarrhythmia, phenylephrine-induced reduction in cardiac output leads to sustained or even exacerbated tachycardia. In addition, decreased cardiac output can lead to a compensatory endogenous sympathetic surge in patients with septic shock.[5, 26] Autologous catecholamine release might override the baroreceptor-mediated reflex bradycardia that may be expected in the setting of phenylephrine and further worsen tachycardia.[5]

Of note, we found a significant (19%) increase in the odds of new RRT requirement associated with phenylephrine compared with norepinephrine. The renal microcirculation is exquisitely sensitive to exogenous catecholamines.[30] Norepinephrine, through both alpha and beta effects, may preserve or even improve renal blood flow in vasodilatory shock by increasing the perfusion pressure gradient without completely occluding the afferent arterioles.[12, 31] In contrast, the pure, potent alpha-1 agonism of phenylephrine may lead to excessive constriction of the renal vasculature, thus reducing renal blood flow and glomerular filtration rate.[13] The disparate pharmacologic effects of phenylephrine vs. norepinephrine on the renal system is one possible explanation of the increased incidence of RRT observed in the phenylephrine group compared with the norepinephrine group. Catecholamine-mediated kidney damage induced by deleterious hemodynamic effects of phenylephrine is another potential mechanism that might explain our findings.[13, 32]

We further speculate that the increased incidence of RRT in the phenylephrine group may be directly related to the reduction in ventilator-free days also found in this group. Here, acute kidney injury and subsequent oliguria might lead to volume overload, exacerbating pulmonary edema and prolonging the requirement for mechanical ventilation.[33, 34] Our findings in these secondary outcomes raise potential crucial differences in the clinical effects of norepinephrine vs. phenylephrine which necessitate further investigation.

Our application of a 4-hour grace period aligns with modern Target Trial Emulation frameworks and represents a significant methodological strength.[18] In observational critical care data, treatments are continuously titrated against dynamic variables. By ignoring the chaotic "salvage phase" of the first four hours where fluid boluses and vasopressor dosing fluctuate wildly, our analysis was designed so that our primary outcome evaluated the true, steady-state pharmacological efficacy of the drug, minimizing immortal time bias. Furthermore, the use of MICE-PMM helped ensure that vital laboratory markers used for propensity balancing accurately reflected the complex biology of critically ill patients.[20–22]

This study has several limitations. First, this is a retrospective, observational study. Thus, while our analyses identified differences between phenylephrine and norepinephrine groups, randomized controlled trials and prospective studies are required to further identify clinical effects of these vasopressor agents in patients with septic shock with tachyarrhythmias. Also, while IPTW successfully

balanced all measured covariates, residual unmeasured confounding remains a possibility. Specifically, the database lacks granular, continuous echocardiographic data. We were unable to stratify patients by their baseline ejection fraction or left ventricular outflow tract (LVOT) velocities, which dictate individual tolerance to afterload effects from vasopressors. Furthermore, while the presence of a history of atrial fibrillation was balanced, we could not definitively confirm via electrocardiography (ECG) and/or continuous ECG strips that every patient in the AF subgroup was experiencing AF RVR at the time of vasopressor initiation, which leads to potential misclassification bias. In addition, the study period extended from 2008–2022, which is a 14 year time span that cannot account for changes in critical care practice over this time period that may have affected the results. Despite these limitations, our study used Target Trial Emulation methodology to minimize potential bias and deployed propensity score matching to achieve that the groups were adequately matched across all covariates.

Conclusions

In conclusion, our data indicates no differences between an initial vasopressor strategy of phenylephrine vs. norepinephrine to manage heart rate in tachycardic septic shock. In addition, results of key secondary outcomes indicate that initial use of phenylephrine may be harmful despite the theorized pharmacologic mechanisms of this agent. Because the use of phenylephrine did not provide a chronotropic benefit, coupled with the significant increase in the risk of severe acute kidney injury seen in this study, we speculate that the therapeutic strategy of isolated manipulation of systemic vascular resistance may produce untoward hemodynamic effects in patients with septic shock with tachyarrhythmia. Further studies are critically needed to determine the optimal initial vasopressor choice in patients with septic shock and tachyarrhythmia.

Abbreviations

- **AF:** Atrial fibrillation
- **CHF:** Congestive heart failure
- **CI:** Confidence interval
- **CKD:** Chronic kidney disease
- **COPD:** Chronic obstructive pulmonary disease
- **HR:** Hazard ratio / Heart rate
- **HTN:** Hypertension
- **IPTW:** Inverse probability of treatment weighting
- **LVOT:** Left ventricular outflow tract
- **MAP:** Mean arterial pressure
- **MD:** Mean difference
- **MICE:** Multiple Imputation by Chained Equations

- **NE:** Norepinephrine
- **OR:** Odds ratio
- **PE:** Phenylephrine
- **PMM:** Predictive Mean Matching
- **RRT:** Renal replacement therapy
- **SD:** Standard deviation
- **sHR:** Subdistribution hazard ratio
- **SMD:** Standardized mean difference
- **SOFA:** Sequential Organ Failure Assessment
- **SVR:** Systemic vascular resistance
- **VFD:** Ventilator-free days

Declarations

Ethics approval and consent to participate

The MIMIC-IV database is a publicly available, de-identified database approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). Requirement for individual patient consent was waived due to the retrospective and de-identified nature of the data.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is available in the PhysioNet repository, [<https://doi.org/10.13026/6zh1-qc69>].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YS and YL conceptualized the study. YS and GM performed the data curation and formal statistical analysis. ZH, JK, DM, BB, and KC provided critical methodological review and clinical interpretation of the data. YS drafted the primary manuscript. All authors read and approved the final manuscript.

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Figures

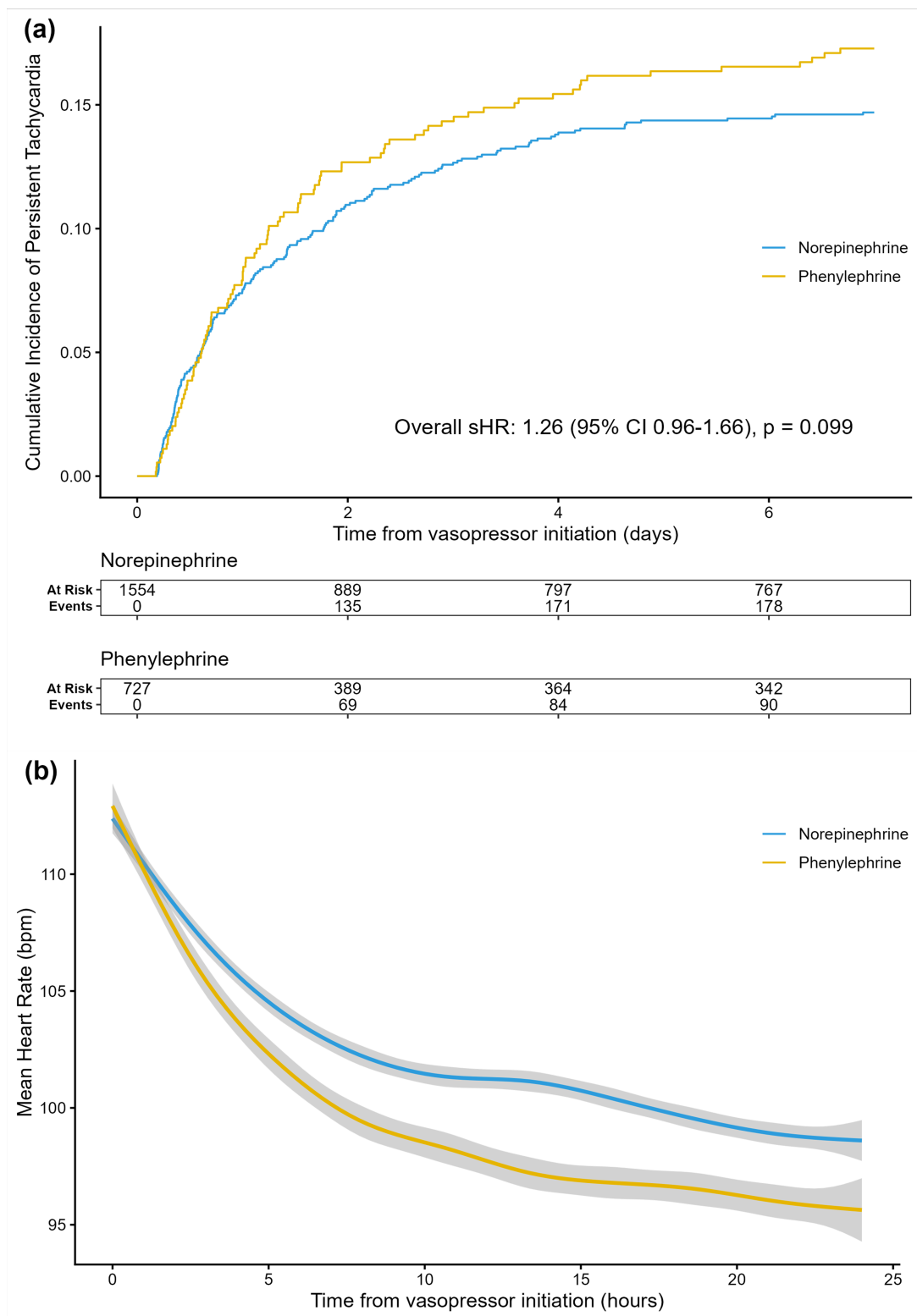


Figure 1

Primary Outcome and Hemodynamic Trajectory

(a) Cumulative Incidence of Persistent Tachycardia. Cumulative incidence function (CIF) for heart rate resolution (≤ 100 bpm) with death as a competing risk. Phenylephrine did not significantly increase the probability of rate control compared to norepinephrine (sHR 1.26; 95% CI 0.96–1.66; $p=0.099$). **(b) 24-**

Hour Heart Rate Trajectory. Mean heart rate trends over the first 24 hours of therapy modeled via generalized additive models (GAM). Both cohorts demonstrated similar chronotropic reduction during acute resuscitation.

*sHR*subdistribution hazard ratio; *CI* confidence interval; *bpm* beats per minute

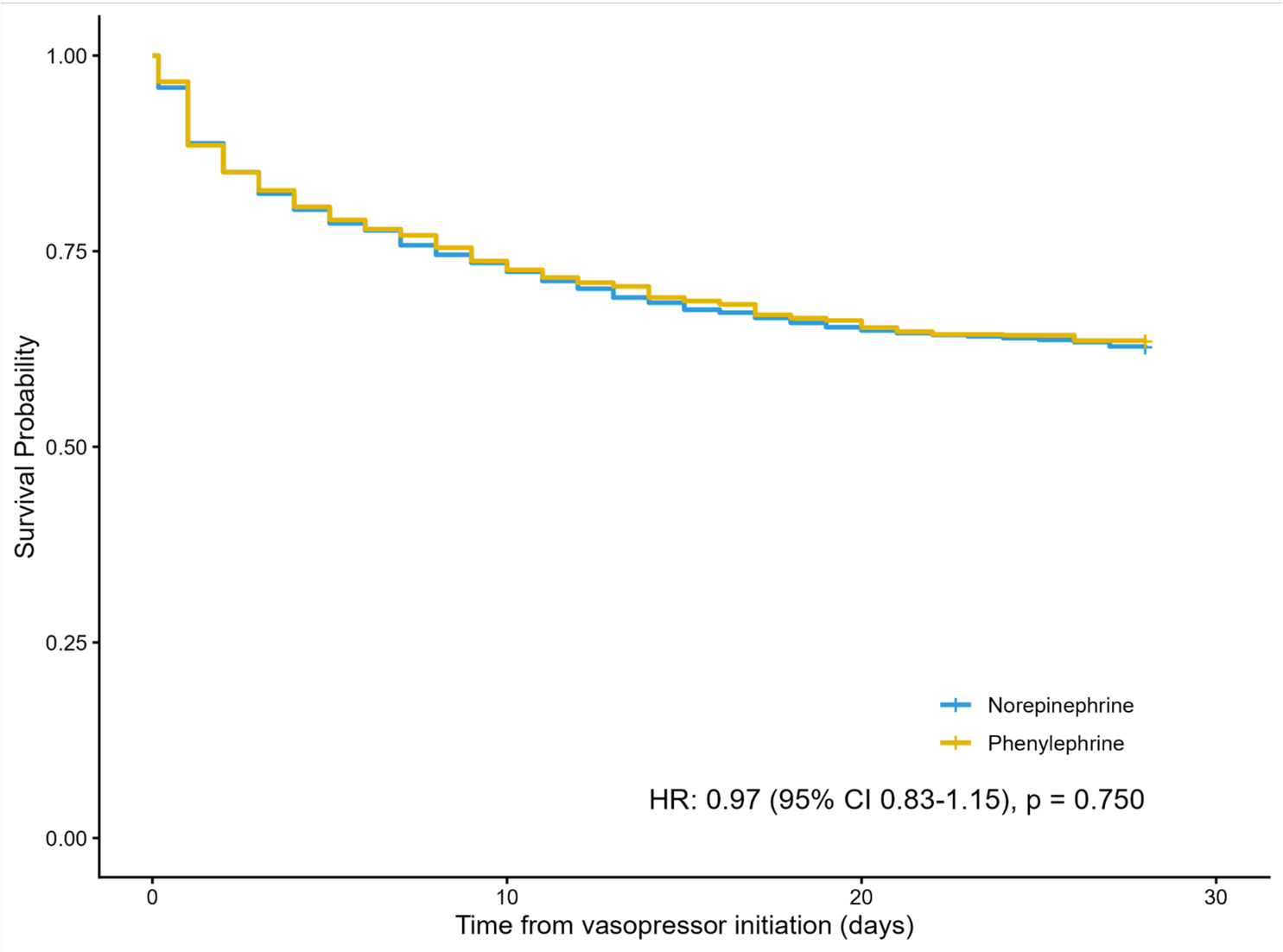


Figure 2

28-Day Adjusted Survival.

Kaplan-Meier curves illustrating survival probability over 28 days, adjusted using inverse probability of treatment weighting (IPTW). Comparison between the norepinephrine and phenylephrine cohorts revealed no statistically significant difference in all-cause mortality (HR 0.97; 95% CI 0.83–1.15; p=0.750).

*HR*hazard ratio; *CI* confidence interval

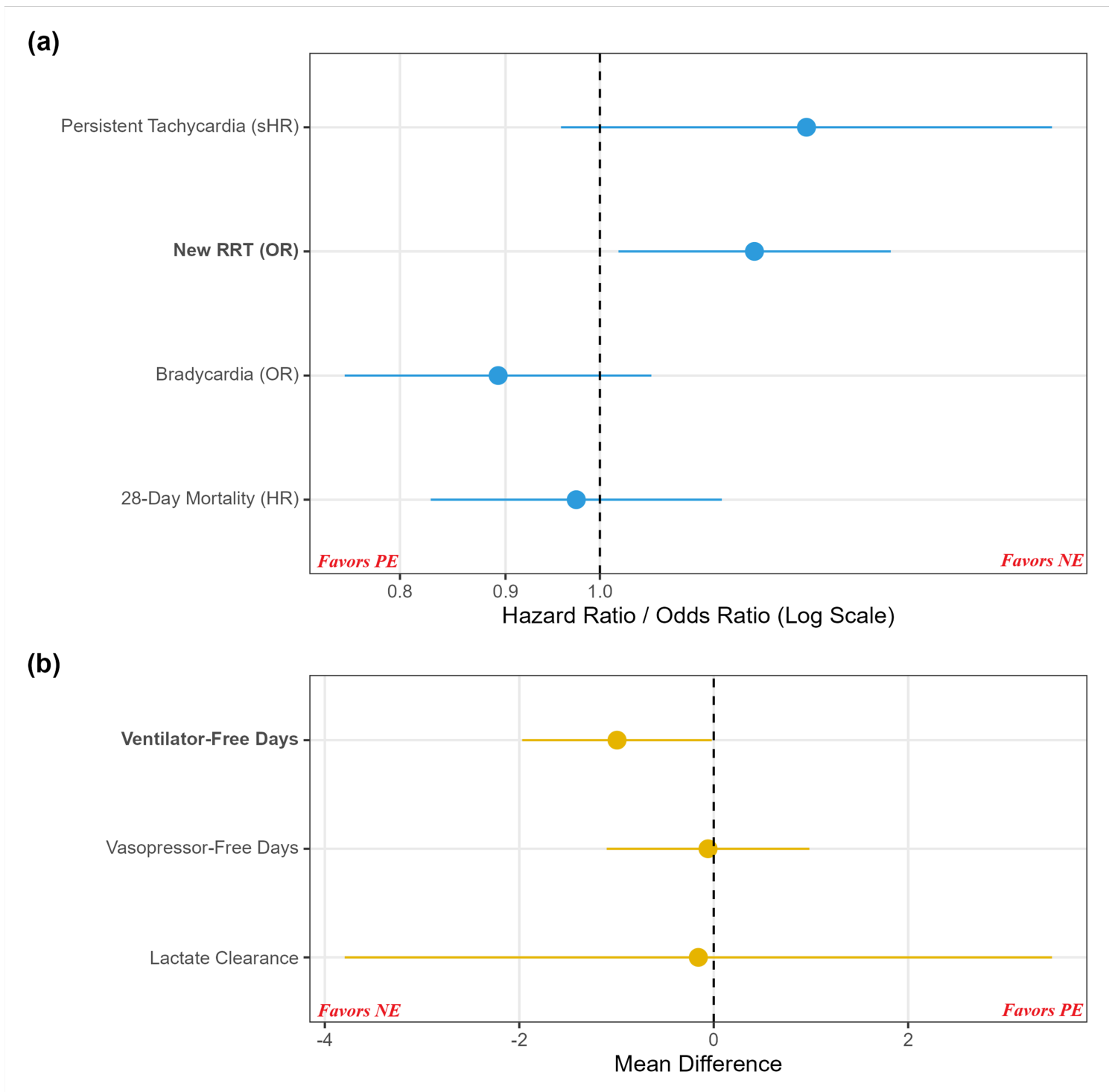


Figure 3

Overall Treatment Effects of Phenylephrine versus Norepinephrine.

Forest plots illustrating the adjusted treatment effects in the primary cohort. (a) Ratio-based outcomes including the subdistribution hazard ratio (sHR) for persistent tachycardia, odds ratios (OR) for new renal replacement therapy (RRT) and bradycardia, and the hazard ratio (HR) for 28-day mortality. (b) Continuous outcomes expressed as mean differences (MD), including ventilator-free days, vasopressor-free days, and time to lactate clearance. Error bars represent 95% confidence intervals.

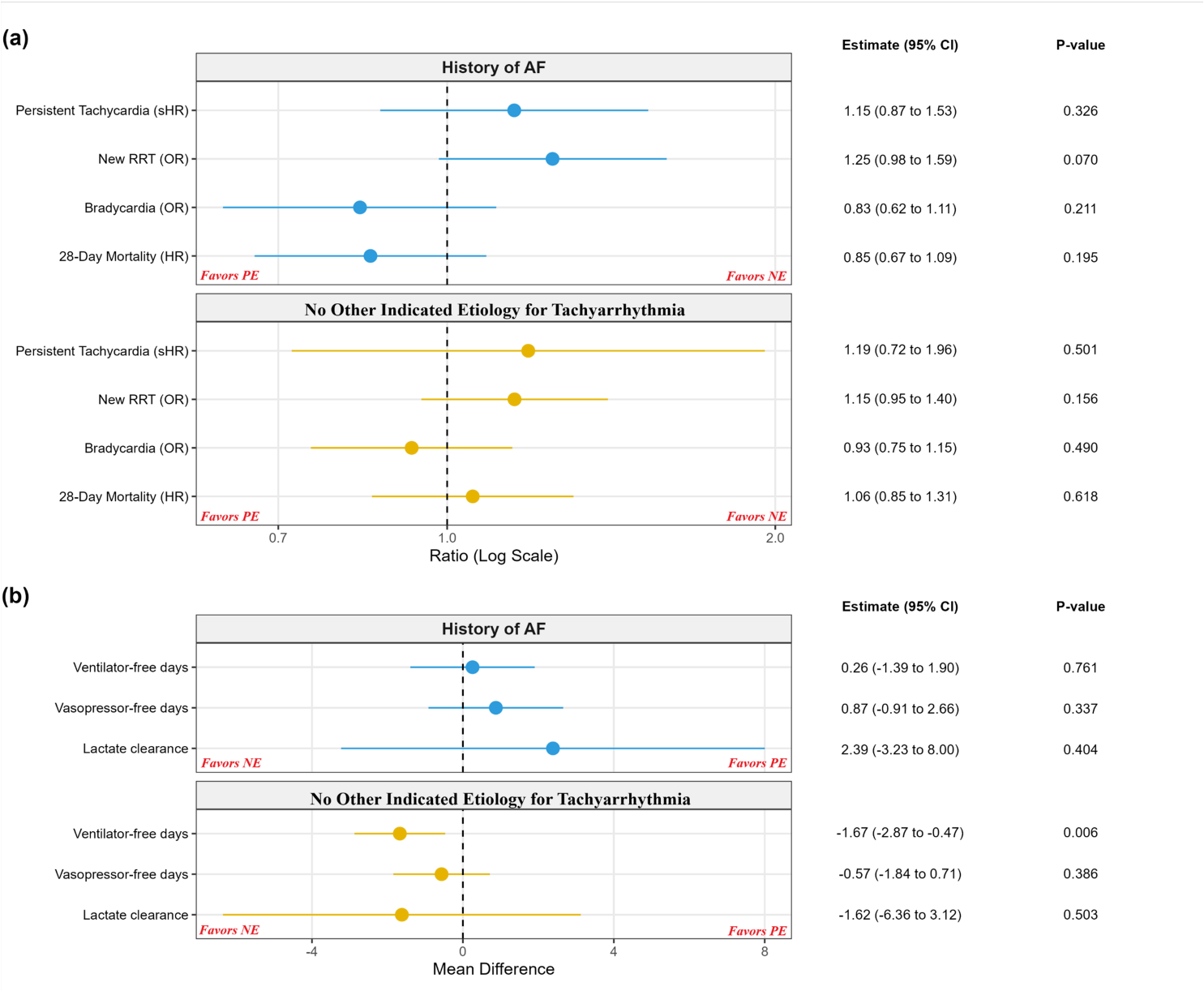


Figure 4

Subgroup Analysis of Treatment Effects.

Forest plots and integrated numerical summaries are provided for patients with a history of atrial fibrillation (top section of each panel) and those with no other indicated etiology for tachyarrhythmia at baseline (bottom section of each panel).

CIconfidence interval; sHR subdistribution hazard ratio; OR odds ratio; HR hazard ratio; RRT renal replacement therapy; AFatrial fibrillation; PE Phenylephrine; NE Norepinephrine

Supplementary Files

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