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Association of noradrenaline dose with mortality in critically ill patients: a systematic review and dose-response meta-analysis

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Abstract

Background Noradrenaline is currently the first-line vasopressor in treatment of circulatory failure. Its dose reflects illness severity, and together with dopamine, dobutamine and adrenaline, it is used in the Sequential Organ Failure Assessment (SOFA) score to grade cardiovascular dysfunction. Over the years, noradrenaline use has increased and it has largely replaced dopamine. As part of the SOFA-2 update, we conducted a systematic review and dose-response meta-analysis to assess the association between noradrenaline dose and mortality.

Methods We searched MEDLINE, Embase, and Web of Science from 1 January 2013 to 30 October 2024 for studies reporting mortality by noradrenaline dose in critically ill adults. The primary outcome was mortality. We generated pooled relative risks (RR) and assessed linear and non-linear dose–response relationships. Mortality was also analysed by SOFA-2 noradrenaline categories. The study followed PRISMA guidelines and was registered with PROSPERO (CRD42024501533).

Results Nineteen studies, including totally 29,935 patients, were included in the systematic review, and six in the meta-analysis. We observed a consistent increase in mortality: the relative risk escalated by a factor of 1.5 for every 0.1 µg/kg/min increase in peak noradrenaline dose. We did not find inflection points in the dose-mortality curve. In SOFA-2 categories, hospital mortality was 16.5% in the dose category ≤ 0.2 µg/kg/min, 31.9% in the category > 0.2 to 0.4 µg/kg/min, and 40.3% in the category > 0.4 µg/kg/min ($p < 0.001$).

Conclusions In critically ill patients, escalating doses of noradrenaline correlate with an exponentially rising relative risk of mortality. This dose-dependent pattern reinforces the role of noradrenaline dose as a marker of cardiovascular failure severity.

Keywords Noradrenaline, Mortality, SOFA-2, Cardiovascular, Intensive care, Critical care

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Introduction

Circulatory failure is common in critical illness, and it may lead to multiple organ failure if not promptly addressed [1]. Noradrenaline (norepinephrine) is currently the most commonly used vasopressor to manage acute hypotension and circulatory failure [2–4]. Noradrenaline has multiple actions including immunomodulation [5] and cardiovascular effects [6, 7]. It is used to increase blood pressure through vasoconstriction [6]. Moreover, it may enhance cardiac output through venous constriction that leads to increased venous return [6], by improving critically low diastolic blood pressures to enhance coronary perfusion, and through possible inotropic effects [7].

The administration and the dose of vasopressor medication are indicative of the severity of circulatory failure [8, 9]. The most widely used organ dysfunction score, the Sequential Organ Failure Assessment (SOFA) score, includes dopamine, dobutamine, noradrenaline and adrenaline dose thresholds to quantify cardiovascular dysfunction [10]. However, clinical practice has changed since the introduction of SOFA in 1996: use of noradrenaline has become more common and it is initiated earlier, whereas dopamine use has decreased [11–13]. This has caused limitations in the cardiovascular component of the original SOFA: even a high score based on the dose of noradrenaline may not indicate a life-threatening circulatory failure [14, 15].

Recently, an international group of experts has proposed updating the SOFA score to align with current clinical practice [16], and the SOFA-2 score has been developed [17]. As part of this update, the SOFA-2 Task Force proposed two thresholds for noradrenaline dose, 0.2 and 0.4 μg/kg/min, to define severity categories of cardiovascular dysfunction. Our group pertaining to the cardiovascular organ system within the SOFA-2, conducted a systematic review and dose-response meta-analysis to investigate the relationship between noradrenaline dose and mortality. This analysis specifically sought to refine the cardiovascular component of the SOFA score by determining more accurate cutoff values for vasopressor doses, particularly noradrenaline, as a marker of circulatory dysfunction severity. While supporting the SOFA-2 revision, it also aimed to provide a clinically interpretable synthesis of available evidence for the broader intensive care community. Specifically, our objective was to determine whether a consistent dose–mortality association could be identified and quantified, in order to inform clinical decision-making and enhance risk awareness in patients receiving vasopressor therapy.

Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [18, 19] and was registered in the PROSPERO database prior to the study initiation (CRD 42024501533).

PICO question

In adult patients receiving noradrenaline (P), is there a specific threshold of noradrenaline dosage (I) above which mortality increases significantly, exhibiting an inflection point or linear rise (O)?

Search strategy

We systematically searched Medline (through PubMed), Embase and Web of Sciences (01-January-2013 to 30-October-2024) for papers reporting outcomes in adult (age 18 years or older) patients according to the dose of noradrenaline used. This time period of article publication was chosen to gather evidence from the last 12 years reflecting current clinical practice, particularly following the 2012 Surviving Sepsis Campaign Guidelines, which recommended the use of noradrenaline as the first-line vasopressor for septic shock management [20]. No language restriction was applied during the search. In brief, we used keywords as exact phrases and subject headings according to database syntaxes. The full search strategy is described in Additional file 1.

Eligibility and inclusion/exclusion criteria

We sought to include papers describing randomised controlled trials, nonrandomised clinical trials, observational cohort studies or case series of adult humans receiving noradrenaline and/or other vasopressors reported as noradrenaline-equivalent. Case reports, animal models and studies reporting children were excluded. To broaden the scope of existing evidence in the literature, we included all studies reporting mortality outcomes, regardless of the timepoints used. This inclusive approach was chosen to ensure a comprehensive collection of available data in the systematic review. For inclusion in the meta-analysis and dose-response meta-analysis, additional criteria were required. Specifically, studies had to report unadjusted mortality stratified across at least two noradrenaline dose levels for the overall meta-analysis, and at least three distinct dose categories for the dose–response meta-analysis, enabling modelling of the dose-mortality association. Studies that reported noradrenaline doses as noradrenaline-equivalents (NEE) were eligible provided the dose was expressed in μg/kg/min or convertible to this unit. Studies lacking sufficient stratification or reporting aggregate data across the entire cohort without dose stratification were excluded from the quantitative synthesis, even if otherwise eligible for the systematic review.

Paper selection

The titles and abstracts of all records were screened independently and in duplicate by two of the authors (IL, LD) using the Covidence software tool (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). The papers selected based on review of title and abstract were downloaded in full for further examination. Two authors (IL, LD) performed full paper screening. The papers selected after full paper screening were sent to the group for data extraction. Data extraction was performed by six authors (LD, MR, ARB, SH, ER, SL) with participation designed to ensure that each paper was evaluated independently by two reviewers. In cases of disagreement over data extraction, a third author (IL) resolved the conflict. Additionally, the reference lists of relevant articles were screened for additional potentially pertinent studies. Finally, we contacted the corresponding authors of the screened studies if questions arose regarding eligibility or data presentation.

Data extraction

Two authors independently extracted data from each study in duplicate using a standardized form. The extracted data were then consolidated and merged by one author (IL), who also resolved discrepancies as adjudicator. The data extracted included study characteristics (e.g. source country, study type, single/multicentre), patient demographics (age, sex), medical background, treatments, and outcomes. Data were also extracted to specify whether the noradrenaline dose referred to noradrenaline base or noradrenaline bitartrate.

Outcomes

For the systematic review, the main study outcome was unadjusted mortality at any time (intensive care unit (ICU), at 28 days, 30 days, in-hospital or at 90 days). For the meta-analysis, we selected the most frequently reported mortality timepoint, ensuring consistency and comparability across studies' data, for the overall and dose-response meta-analysis. The relationship between noradrenaline dose and mortality was computed through both relative risk and absolute risk.

Exposure

The independent variable explored was the dose of noradrenaline or noradrenaline-equivalent administered (μg/kg/min). For the overall and dose-response meta-analysis, we chose the most commonly reported estimator of noradrenaline dose (among peak, median, mean and starting dose).

Some studies reported dosing only in μg/min. These studies were included in the systematic review [21–23], and subsequently included in a sensitivity analysis of the dose-response meta-analysis.

Post-hoc analysis

This dose-response meta-analysis was initially conceived to obtain data for the SOFA score update. After the SOFA-2 Working group had determined the noradrenaline dose cutoffs for the new score [17, 24], we conducted post hoc analyses to evaluate the concordance between our findings and these thresholds. To this end, we stratified noradrenaline doses according to the SOFA-2 cutoffs (0.2 μg/kg/min and 0.4 μg/kg/min) and assessed mortality and patient distribution across these categories.

Assessment of risk of bias

For the primary outcome, we intended to assess risk of bias using the Cochrane Risk of Bias tool for randomised controlled trials and the Newcastle-Ottawa Scale for observational studies. As no randomised controlled trials were identified, two authors (IL, LD) independently and in duplicate assessed the risk of bias (RoB) of the included studies using only the Newcastle-Ottawa Scale [25]. Disagreements over RoB were resolved by consensus or, if necessary, adjudicated by a third author (MR).

The Newcastle-Ottawa Scale assesses studies based on three broad categories: selection, comparability, and outcome (for cohort studies) or exposure (for case-control studies). Each study is awarded up to nine points across these categories. We considered studies as of low risk of bias if they scored 7 to 9 points, intermediate risk of bias if they scored 4 to 6 points, and high risk of bias if they scored 3 points or fewer.

Certainty of the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence (i.e. the overall effect estimate) for the primary outcome [26].

Statistical analyses

The population characteristics were described as weighted means (and weighted standard deviation) or median and interquartile range for continuous variables, and weighted means of percentages and weighted standard deviation from percentages for categorical variables to gather a pooled description of the patients' profile. The results for the association between noradrenaline dose and mortality were reported as relative risks (RR) and their 95% confidence intervals (CI).

For the meta-analyses, we calculated the RR of mortality between the highest and lowest dose for each study. We then performed a random-effect meta-analysis using the Laird-DerSimonian method [27]. We examined statistical heterogeneity by visually inspecting forest plots

and using the nonparametric Cochran's Q test along with the I^2 statistic [28]. Heterogeneity was considered likely if Q exceeded the degrees of freedom (df) and confirmed if the p-value was 0.10 or less. A leave-one-out sensitivity analysis was performed to assess the individual influence of each study on the pooled effect size estimate and respective I^2. This method systematically excludes one study at a time and recalculates the overall effect, identifying whether any single study disproportionately influences the meta-analysis results.

An Egger test was performed to look for small size study effect.

Then, we examined the dose-response relationship between mortality and noradrenaline doses using a dose-response meta-analysis (DRMA) approach. Only the papers with two or more dose levels of noradrenaline dosage were considered for the DRMA. We created linear, quadratic and non-linear (restricted cubic splines) models. For the linear model, we calculated the linear trend (slope) and standard error linking the noradrenaline dose and the natural logarithm of the RR of mortality for each study, under the random effect method. The logarithmic transformation of the RR was performed to linearize the relationship between drug dosage and mortality risk, facilitating a more robust application of the linear regression model. The pooled effect was then calculated. For the quadratic and non-linear restricted cubic splines models, only studies providing three or more levels of noradrenaline dosages were considered, in contrast to the linear model which was conducted using studies with at least two reported dosage levels. The Wald test was used to test the hypothesis of non-linearity between the knots of the restricted cubic splines model. The performance of the models were compared using Akaike Information Coefficient (AIC) and adjusted R^2 [29, 30]. For the graphical representation of the model, we plotted the RR of in-hospital mortality against the noradrenaline dose after back-transforming from the logarithmic to the natural scale. We also plotted the expected absolute risk of mortality by applying the predicted relative risks to a baseline mortality risk of 6.5%, based on Pölkki et al. [15].

We implemented sensitivity analyses in the DRMA as follows: (1) studies examining only noradrenaline doses versus those using also noradrenaline-equivalent doses of other vasopressors, (2) studies published as abstracts versus studies published as peer-reviewed articles and (3) we added to the DRMA the studies reporting noradrenaline in µg/min. For this last analysis, we estimated the RR and its 95% CI based on the linear DRMA model by standardizing the NE dose of those articles on mean weights of 60, 65, 70, 75, 80, 85 kg.

In addition, we assessed the feasibility of conducting adjusted analyses by examining whether adjusted effect estimates could be aggregated and whether baseline severity covariates were available in a sufficient number of studies to support meta-regression.

As for post-hoc analysis, we compared the observed mortalities according to the noradrenaline dose cutoffs predefined by the SOFA-2 cardiovascular component score, using a Chi-square test, with Bonferroni correction for multiple comparisons.

All p-values were two-tailed, and those below 0.05 were considered statistically significant. All analyses were performed using R software (R Core Team 2013, R Foundation for Statistical Computing, Vienna, Austria, URL (http://www.R-project.org/) with the packages {meta} [31], {metafor} [32],{dosresmeta} [33] and {dmetar} [34].

Results

The literature search found 5,918 studies. After removing 3,703 duplicates, 2,215 studies were screened, out of which 2,099 were excluded and 116 were assessed for eligibility. We excluded 97 studies, mostly due to inadequate study design to answer our research question. Ultimately, 19 studies were included in this systematic review [21–23, 35–50], collectively covering 29,935 patients. Subsequently, six studies were included in the meta-analysis and dose-response meta-analysis [36, 41, 43, 44, 46, 47]. The authors of one study could not provide the data we required [51], and the study was therefore excluded from the analysis due to lack of detailed data for the meta-analysis. The details of the inclusion/exclusion process are shown in the PRISMA diagram (Fig. 1).

Included studies

All 19 studies were observational. Three of them were prospective [37, 45, 49]. Five studies were only published as poster presentations [40, 41, 44, 47, 48]. The data originated from three continents (Europe, Asia and America). Apart from four multi-centre studies [37, 39, 43, 49], all other studies were from single centres.

Most included studies ($n = 13$, 68%) focused on patients with septic shock, while six studies [21, 22, 36, 43, 45, 46] enrolled mixed ICU populations that included any patient receiving noradrenaline during their ICU stay. Eleven studies reported in-hospital mortality [21–23, 36, 41–44, 46, 47, 50], six studies reported 28-day or 30-day mortality [35, 37, 40, 45, 49, 50], two studies reported ICU mortality [21, 39], one study reported 90-day mortality only [38] and one abstract did not specify the mortality assessment timepoint [48].

The characteristics of the studies are presented in Table 1.

Baseline data

Fourteen studies reported the mean age of patients administered noradrenaline, yielding a weighted mean age of 66 ± 15 years for a total of 6,462 patients. In the

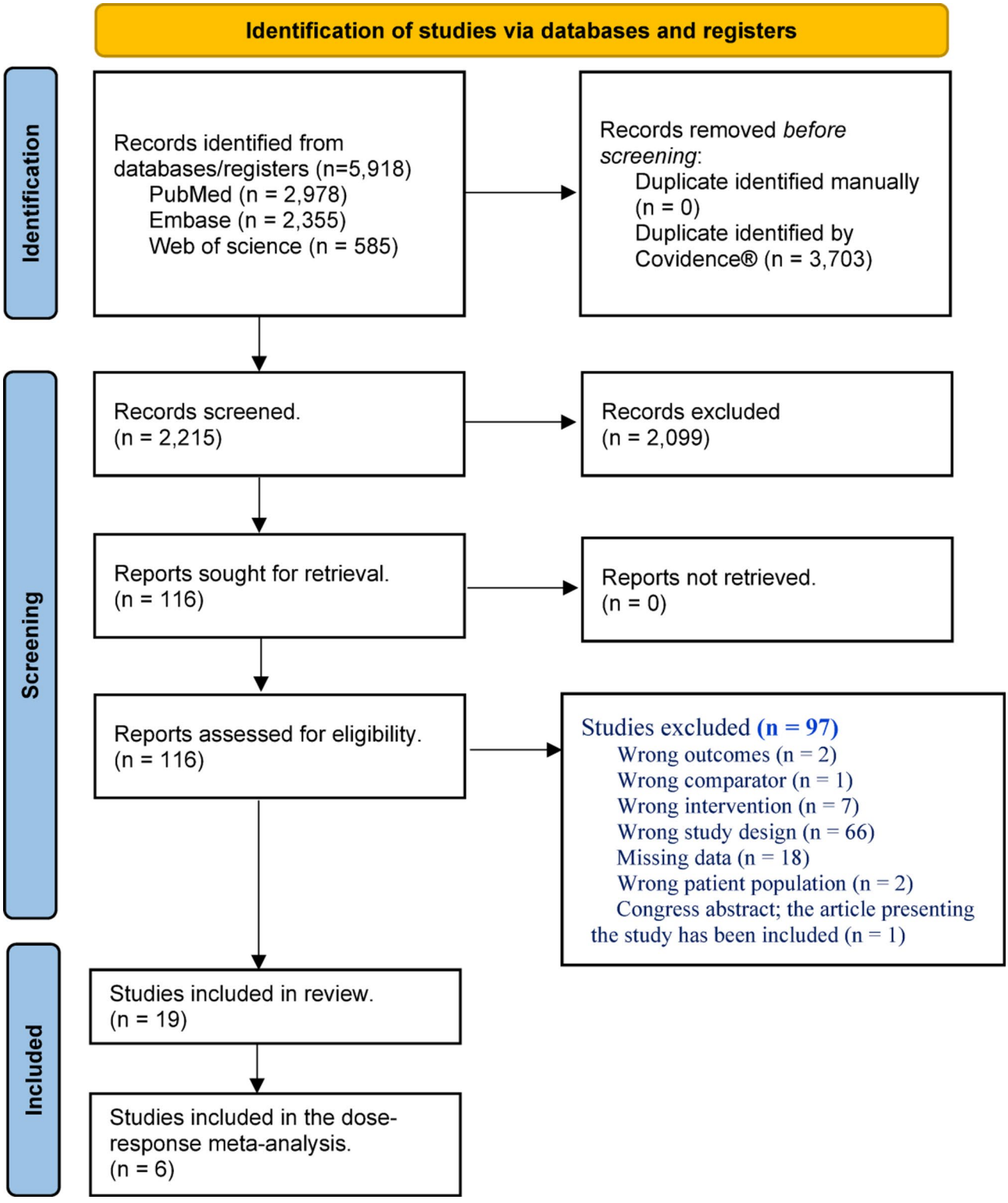

Fig. 1 Flow diagram of the systematic review including of databases

fifteen studies that reported the patients' sex, 60.4% ($n = 8{,}986$) of the patients were male [21, 23, 35–43, 45, 46, 49, 50]. Particular attention was given to patients' weight data, as noradrenaline dosage was expressed in µg/kg/min. However, only three studies provided patient weight (with a weighted mean weight of 84 ± 26 kg, $n = 720$ patients) [42, 46, 49]. The Charlson Comorbidity Index was provided in two studies ($n = 2{,}934$ patients) [36,

Table 1 Study characteristics

Author	Year	Country	Timepoint of outcome assessment	Total number of patients	Design	Number of centres	Years of inclusion	Type of patients	Noradrenaline formulation	Noradrenaline dose definition	Unit of noradrenaline	Time window for noradrenaline dose calculation	Type of publication	Newcastle-Ottawa scale overall assessment
Auchet	2017	France	28-day and 90-day	106	Retrospective	Single center	2008–2013	Septic shock	Bitartrate	Weight based mean dose	µg/kg/min	ICU stay	Article	6★
Brand	2017	USA	in-hospital	808	Retrospective	Single center	2009–2012	Septic shock	Bitartrate	Composite peak vasopressor dose load	µg/min	ICU stay	Article	6★
Burstein	2021	USA	in-hospital	2090	Retrospective	Single center	2007–2015	Mixed - Cardiologic	NR	Peak NEE	µg/kg/min	ICU stay	Article	6★
Cereuil	2022	France	28-day	119	Prospective	Multicentric	2016–2018	Septic shock	NR	Starting dose	µg/kg/min	T0	Article	6★
Chotalia	2021	UK	90-day	844	Retrospective	Single center	2016–2019	Septic shock	NR	4-day median daily dose of NEE	µg/kg/min	4 days	Article	6★
Domizi	2020	Europe	in-ICU	730	Retrospective	Multicentric	2011–2013	Septic shock	NR	1/T1 weight based mean dose, 2/Peak WB dose first 24 h, 3/Weight based mean dose first 24 h	µg/kg/min	1/first hour or 2/ first 24 h	Article	7★
Jurado	2022	USA	28-day	83	Retrospective	Single center	2019–2020	Septic shock	NR	Weight based mean dose of NE and E, with a threshold for each to define high-dose group	µg/kg/min	not reported	Abstract	6★
Meenach	2019	USA	in-hospital	694	Retrospective	Single center	2016–2017	Septic shock	NR	Max pressor dose expressed in NEE	µg/kg/min	ICU stay	Abstract	6★
Micheletto	2022	USA	in-hospital	58	Retrospective	Single center	2016–2018	Septic shock	NR	Weight based starting dose above or below the median	µg/kg/min	Starting dose	Article	7★
Pölkki	2024	Finland - USA	in-hospital	13,901	Retrospective	Multicentric	2013–2019	Mixed	Base	Max WB dosing during first 24 h	µg/kg/min	24 h	Article	7★
Sato	2022	USA	in-hospital	3375	Retrospective	Single center	2011–2020	Septic shock	NR	Maw WB NEE dose in first 24 h	µg/kg/min	24 h	Abstract	6★
Schupp	2023	Germany	30-day	339	Prospective	Single center	2019–2021	Sepsis or Septic shock	NR	Median WB NE dose in first 24 h	µg/kg/min	24 h	Article	6★

Table 1 (continued)

Author	Year	Country	Timepoint of outcome assessment	Total number of patients	Design	Number of centres	Years of inclusion	Type of patients	Noradrenaline formulation	Noradrenaline dose definition	Unit of noradrenaline	Time window for noradrenaline dose calculation	Type of publication	Newcastle-Ottawa scale overall assessment
Singer	2021	USA	in-hospital	550	Retrospective	Single center	2017–2018	Mixed	NR	1/Max infusion rate (µg/min and WB) and 2/total cumulative dose	µg/kg/min	ICU stay	Article	7★
Singer	2022	USA	in-hospital	351	Retrospective	Single center	2013–2021	Trauma	NR	Max NE dose, absolute µg/min	µg/min	ICU stay	Article	7★
Sviri	2014	Israel	in-ICU and in-hospital	166	Retrospective	Single center	2008–2010	Mixed	NR	Max NE dose, absolute µg/min, defining high and low dose around a threshold	µg/min	ICU stay	Article	6★
Vallabhajosyula	2018	USA	in-hospital and 1-year mortality	5353	Retrospective	Single center	2010–2015	Septic shock	NR	Peak NE > 1 µg/kg/min for >15 min define high dose	µg/kg/min	ICU stay	Abstract	7★
Wahby	2015	USA	NR*	150	Retrospective	Single center	NR	Septic shock	NR	Starting dose categorized in 3 groups (< 0.1, 0.1–0.5, >0.5)	µg/kg/min	Starting dose	Abstract	7★
Yamamura	2018	Japan	28-day	112	Prospective	Multicentric	2013–2016	Septic shock	NR	Weight based total dose over 7 first days	µg/kg/week	7 first days	Article	7★
Yu	2021	China	30-day in-hospital	106	Retrospective	Single center	2017–2019	Septic shock	NR	Weight based, poorly defined timepoints	µg/kg/min	6 first hours	Article	7★

NR: not reported, NEE: noradrenaline equivalent, ICU: intensive care unit

Table 2 Doses of noradrenaline or noradrenaline equivalent used in the included studies

Author	Year	Unit	Low/high dose
Burstein	2021	µg/kg/min	0.05/1.25
Meenach	2019	µg/kg/min	0.25/2.50
Pölkki	2024	µg/kg/min	0.10/0.50
Sato	2022	µg/kg/min	0.10/0.50
Singer	2021	µg/kg/min	0.03/0.55
Vallabhajosyula	2018	µg/kg/min	0.10/1.00

38]. Thirteen studies reported data on the SOFA score; however, due to the high heterogeneity in data reporting (median, variability of time points, cutoff reporting only), data aggregation was not possible [35–42, 45, 46, 48–50].

Six studies reported dosages in terms of noradrenaline equivalence rather than noradrenaline dose [23, 36, 38, 41, 42, 44]. In these studies, inotropes such as dopamine or dobutamine were generally included in the calculation using standard conversion formulas. We retained the noradrenaline-equivalent values as reported by the original study authors without recalculating individual components. Noradrenaline dosage measurement varied across studies: three studies reported dosages at the initiation of drug administration [37, 42, 48]; six studies documented the highest dose during the ICU stay [21–23, 36, 46, 47]; two studies noted the highest dose within the first 24 h of ICU admission [43, 44]; two studies recorded the median dose at the 24-hour mark [38, 45]; one study measured the mean infusion rate of noradrenaline at 24 h [39]; one study calculated the mean dose over the ICU stay [35]; and two studies provided unclear dosage reporting methods [40, 50]. Among the studies not included in the meta-analysis, two studies specified that the noradrenaline dosage was reported as noradrenaline bitartrate [23, 35]. Among the six studies included in the meta-analysis, one study explicitly stated that the dosage was expressed as noradrenaline base. In the remaining five studies, the dosage was presumed to be expressed as noradrenaline base based on the geographical location of the participating centers [36, 41, 44, 46, 47].

The final version of the database was validated by all the investigators and is provided in Additional file 2.

Risk of bias

The risk of bias was assessed using an adapted and modified Newcastle-Ottawa Scale, as detailed in Additional file 3. All studies received a rating of 6 to 9 stars out of 9. Studies reporting dosages in terms of noradrenaline-equivalent received a rating one star lower than those reporting dosages directly as noradrenaline.

Primary outcome

We first performed a high versus low dose random effect meta-analysis including studies that reported hospital mortality (the most frequently reported outcome) and peak dose of noradrenaline (the most frequently reported estimator), resulting in the inclusion of six studies [36, 41, 43, 44, 46, 47]. Definitions of high and low doses, as specified by each study, are detailed in Table 2. The random effect model found a pooled RR for mortality of 3.85 (95% CI, 3.24–4.57, $p < 0.01$) in high-dose versus low-dose patients, with significant heterogeneity ($I^2 = 87\%$, 95% CI [74–93], $\tau^2 = 0.03$, $p \leq 0.001$) and a prediction interval of [2.24–6.60] (Fig. 2). The Egger test found no significant signal for small size study effect ($p = 0.36$, Fig. 3). The leave-one-out analysis did not reveal any study contributing significantly to the effect size or the I^2 of the meta-analysis (Additional file 4). The GRADE assessment of the meta-analysis yielded a moderate certainty (Table 3).

Dose-response meta-analysis

For the dose-response meta-analysis, we included studies that reported hospital mortality (the most frequently reported outcome) and peak dose of noradrenaline (the most frequently reported estimator), while excluding

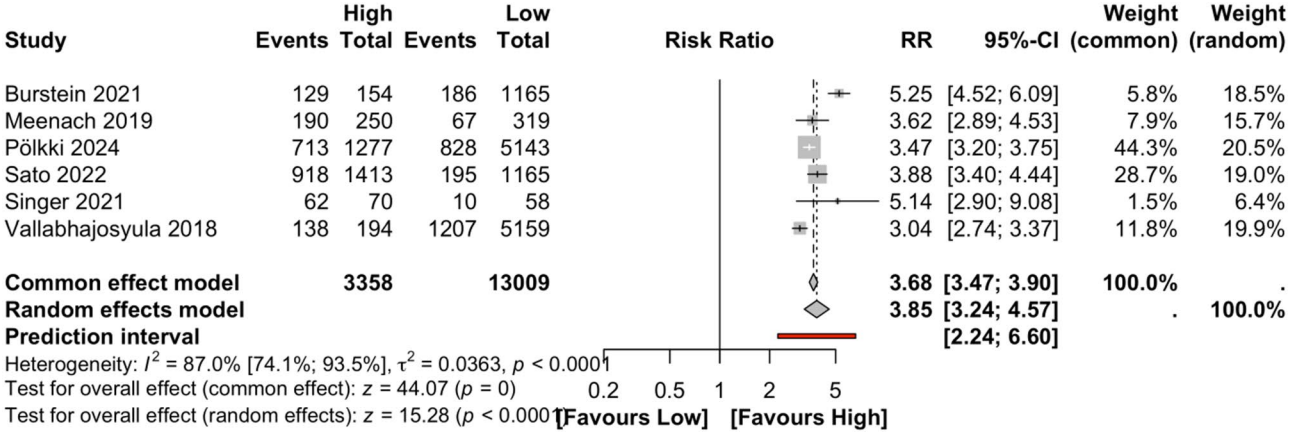

Fig. 2 Forest plot of the high vs. low dose meta-analysis examining mortality as a function of noradrenaline

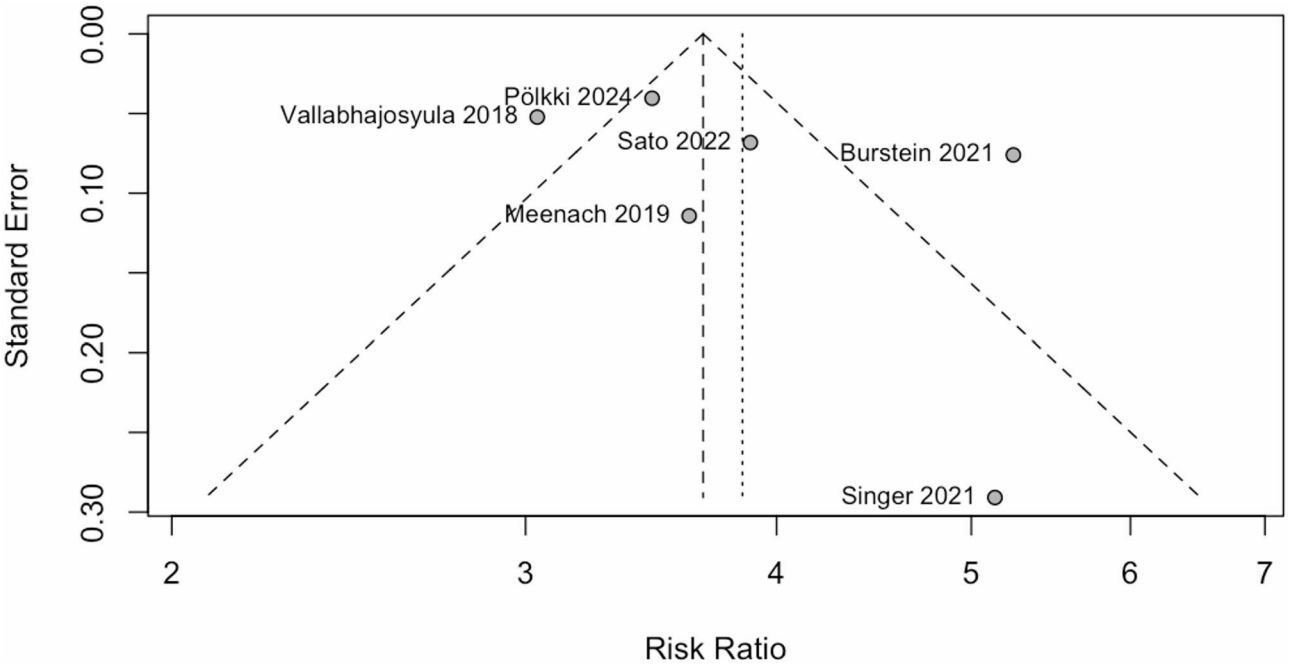

Fig. 3 Funnel plot examining the small-study effect

Table 3 GRADE assessment of the meta-analysis

Certainty assessment							Effect (relative risk 95% CI for every 0.1 µg/kg/min increase in noradrenaline)	Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Dose response meta-analysis								
6	Observational studies	Not serious	Not serious [a]	Not serious	Not serious	None	RR = 1.5 (1.3–1.8)	⨁⨁⨁◯ MODERATE

[a]: All the studies show consistent effect even though I^2 is high

studies that reported only one dose level, resulting in the inclusion of six studies [36, 41, 43, 44, 46, 47].

The linear (Chi2 = 28.1, df = 1, p-value < 0.001), the quadratic (Chi2 = 29.8, df = 2, p-value < 0.001) and the non-linear restricted cubic splines (Chi2 = 29.1, df = 2, p-value < 0.001) models showed a significant dose-response relationship between noradrenaline and hospital mortality. Under the linear model, the relative risk of death was multiplied by 1.5 (95% CI [1.3–1.8]) for each increment of 0.1 µg/kg/min in noradrenaline dose (Fig. 4). All the models showed a log-linear relationship (i.e. exponential) between noradrenaline and the relative risk of hospital mortality, with the linear model showing the best model performance (Additional file 5). The non-linear restricted cubic spline model failed to identify a clear inflection point. The expected absolute risk of mortality was plotted based on the linear model in Fig. 5.

Sensitivity analyses

We observed no significant subgroup differences between the studies reporting use of noradrenaline only (RR 3.4, 95% CI 2.8–4.2) and those reporting use of multiple vasopressors summarized as noradrenaline-equivalent (RR 4.2, 95% CI 3.4–5.1), $p_{interaction}$ = 0.15; and we observed comparable performance of the dose-response models in these subgroups (Additional file 6).

Likewise, we observed no significant subgroup differences between the studies published as full peer-reviewed articles (RR 4.3, 95% CI 3.3–5.5) and those published as abstracts (RR 3.4, 95% CI 2.7–4.3), $p_{interaction}$ = 0.20; and we observed comparable performance of the dose-response models in these subgroups Additional file 7).

We further examined the inclusion of studies reporting noradrenaline doses in µg/min in the analysis. After conversion based on assumed mean body weights ranging from 60 to 85 kg, did not modify the DRMA results substantially. The estimated effect sizes remained stable across all tested weight assumptions, with exponentiated coefficients ranging from 1.52 (95% CI 1.36–1.69) at 60 kg to 1.56 (95% CI 1.40–1.74) at 85 kg (Additional file 8).

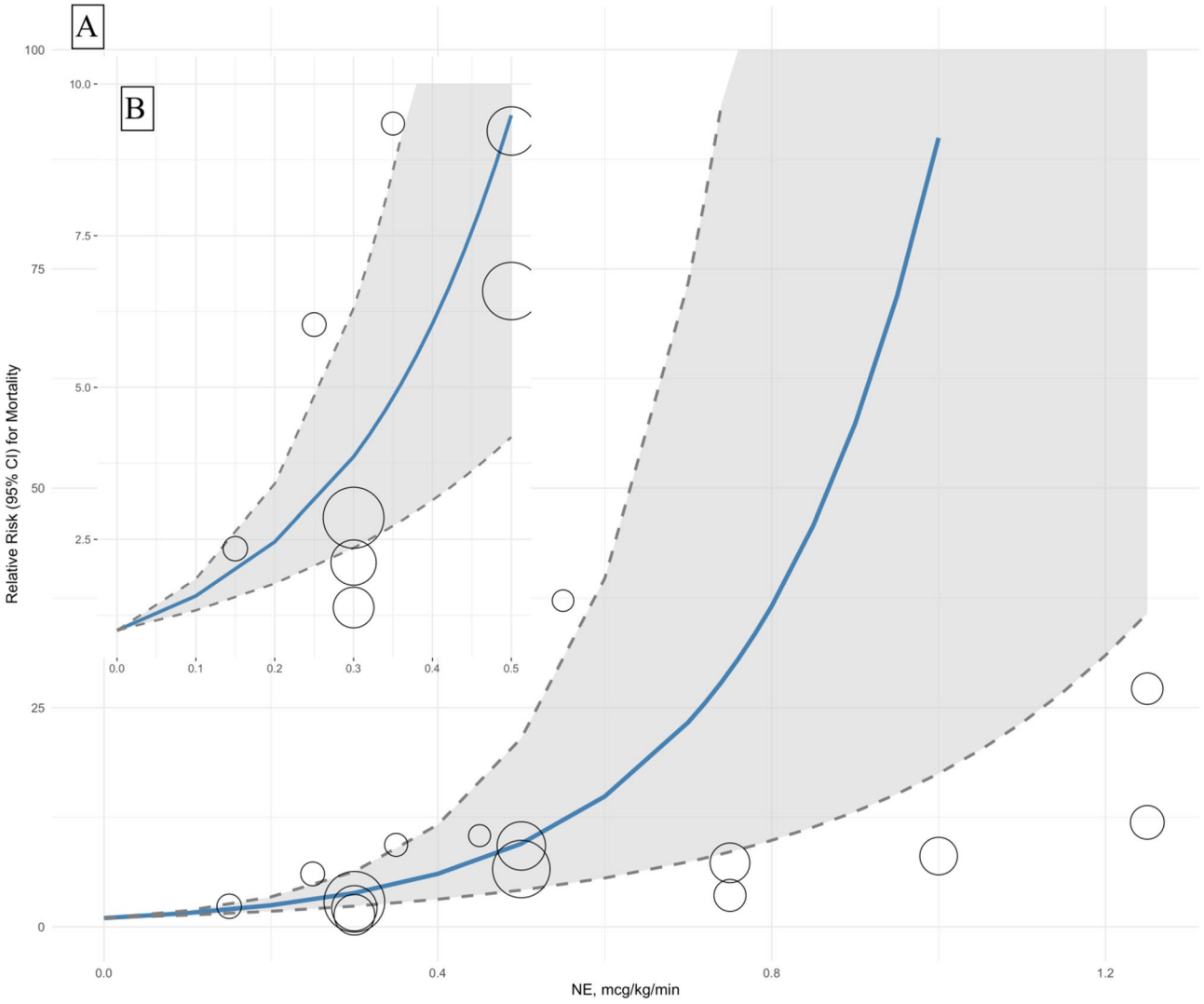

Fig. 4 Panel **A**: Dose-response relationship between noradrenaline dose and relative risk of hospital mortality. Panel **B**: Zoomed-in view of the lower-dose range (0–0.5 µg/kg/min) Confidence interval boundaries are shown in dash lines. The model showed that the risk is multiplied by an approximate factor of 1.5 for every 0.1 µg/kg/min increase in peak noradrenaline dose NE: noradrenaline

Among the included studies, only three reported multivariable analyses evaluating the association between noradrenaline dose and in-hospital mortality. However, these studies differed substantially in terms of statistical approach (Cox regression versus logistic regression), predictors of interest (categorical versus continuous noradrenaline dose), and adjustment variables. Due to this methodological heterogeneity, no quantitative synthesis of adjusted estimates was performed. A detailed summary of these adjusted analyses is provided in Additional file 9.

Finally, we also assessed the feasibility of conducting a meta-regression to account for illness severity, but this was not possible. Only a few studies reported stratified baseline severity variables (such as SOFA score or the Acute Physiology and Chronic Health Evaluation (APACHE) score or the presence of acute kidney injury or the use of renal replacement therapy) by noradrenaline dose group. No single variable was consistently available across a sufficient number of studies to allow robust modelling.

Post-hoc analysis

When categorising noradrenaline doses reported in the studies included in the dose-response meta-analysis into three predefined intervals based on the updated SOFA-2 score, ≤ 0.2, >0.2 to ≤0.4, and >0.4 µg/kg/min; a statistically significant difference in mortality was observed across dose categories, with mortality of 16.5% ($n = 1279/7773$), 31.9% ($n = 1175/3682$), and 40.3% ($n = 3609/8964$) in the ≤0.2, >0.2 to ≤0.4, and >0.4 µg/kg/min categories, respectively ($p < 0.001$). Pairwise

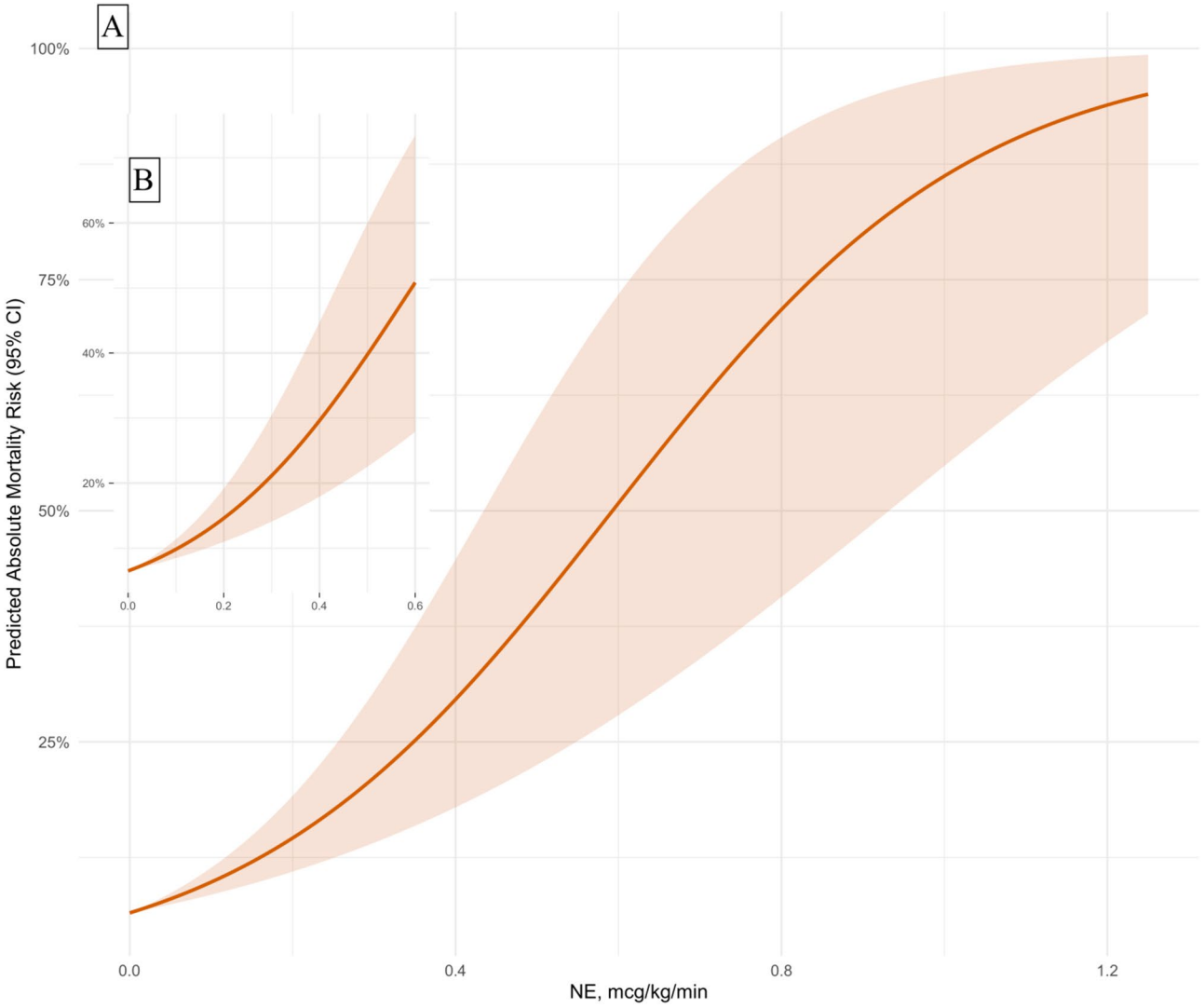

Fig. 5 Panel **A**: Dose-response relationship between noradrenaline dose and predicted absolute risk of hospital mortality, assuming a baseline risk of 6.5%. Panel **B**: Zoomed-in view of the lower-dose range (0–0.6 µg/kg/min) Confidence interval boundaries are shown in light orange NE: noradrenaline

comparisons confirmed significant differences between all groups ($p < 0.001$). The distribution of patients was as follows: 38% ($n = 7773$) in the ≤0.2 µg/kg/min category, 18% ($n = 3682$) in the >0.2 to ≤0.4 µg/kg/min category and 44% ($n = 8964$) in the >0.4 µg/kg/min category (Additional file 10).

Certainty of the evidence

The results of the GRADE assessment are reported in Table 3. The overall certainty was rated as moderate, based on consistent findings across observational studies and the magnitude of the association.

Discussion

This systematic review and unadjusted dose-response meta-analysis revealed that there may be an exponential association between increasing noradrenaline dose and relative risk of death among ICU patients, up to 1.25 µg/kg/min, up to 1.25 µg/kg/min. There were no clear inflection points or thresholds that would be logical choices as cutoffs to inform the SOFA score update. Instead, we observed a consistent increase in mortality risk, with the relative risk multiplied by an approximate factor of 1.5 for every 0.1 µg/kg/min increase in peak noradrenaline dose. This observation should raise awareness among clinicians managing patients with vasopressor-dependent shock. An increase as small as 0.1 µg/kg/min was consistently associated with higher mortality. Recognizing this may help identify patients whose cardiovascular failure is worsening, despite ongoing support. It may support earlier consideration of adjunctive vasopressors, re-evaluation of source control, volemia or cardiac function, or timely escalation of care. This dose–mortality relationship provides clinicians with a practical, interpretable

marker of severity that can inform bedside decisions in real time.

Our systematic review identified a wide variety of methods used to report noradrenaline dose and mortality in terms of units (weight-based or absolute), variable used (starting dose, mean dose, peak dose or cumulative dose) and time window of observation (from noradrenaline starting timepoint to the whole duration of ICU stay). This variety greatly impairs the possibility to draw firm conclusions from the existing literature. We focused on the peak noradrenaline dose for the statistical analysis, because it was most commonly reported and because of its clinical relevance [17]. However, we acknowledge that other estimators, such as time-weighted mean dose or cumulative exposure, may provide additional insight into vasopressor burden and severity trajectories. In particular, prior studies, including the study by Auchet et al. [35], have suggested that mean dose may outperform peak dose in predicting mortality in selected subgroups such as patients with refractory septic shock. Furthermore, the dose-response meta-analysis was based on publications that reported noradrenaline only or noradrenaline-equivalent to account for the use of other vasopressors.

As adjustment for other organ dysfunctions is achieved within the SOFA score, adjustment for potential confounders was not aimed for the purpose of score development. However, we considered adjustment for potential confounders to complete the analysis and reviewed the included studies for adjusted analyses. Three studies reported multivariable models, but their methodological heterogeneity, in terms of statistical approach, dose specification, and covariates, precluded any valid aggregation. Therefore, it was not possible to conduct a meaningful adjusted meta-analysis, and the dose-mortality association reported here should be interpreted descriptively.

The original SOFA score was developed as a descriptive tool for organ dysfunction rather than a predictive model. However, in the context of the SOFA-2 revision, outcome-anchored thresholds were introduced across organ systems to ensure that severity gradations remain clinically meaningful and reproducible. For the cardiovascular component in particular, the association between vasopressor dose and mortality was used as a guiding construct to inform threshold selection and improve the interpretability and bedside applicability of the score. Based on its predefined working methodology [17, 24], the SOFA-2 Working Group decided upon two cutoffs, 0.2 and 0.4 µg/kg/min. These are in accordance with the study by Pölkki et al. [43]. The statistical analysis used to define cutoffs in that study was based on the log-rank statistic test proposed by Contal and O'Quigley [52], which is an optimisation technique to maximise the separation between survival curves. From a statistical standpoint, discretising a continuous variable often leads to approximations and potential loss of information, as it imposes artificial boundaries on a naturally continuous distribution. Risk of death does not change abruptly between closely adjacent values, such as 0.19 and 0.21 or 0.39 and 0.41 µg/kg/min. This highlights the challenge of balancing clinical usability with statistical rigor. Nevertheless, the *post-hoc* analysis performed to test the updated SOFA-2 cutoffs showed clear differences in mortality between the categories defined by these cutoffs.

These findings align with prior research about the association of noradrenaline with patient outcomes in critical care settings [9]. However, our study has limitations. Primarily, our inclusion criteria encompassed all studies that reported mortality corresponding to varying dosages of noradrenaline. This approach inevitably led to diverse patient populations, including patients with septic shock, cardiogenic shock, and potentially even patients without shock who were receiving vasopressors to mitigate hypotension induced by other factors such as sedative drugs or renal replacement therapy. It also led to various definitions of noradrenaline dose, some using the maximal dose received, some the average, with various time frames. Therefore, a rigorous selection of studies was performed to include homogenous studies in the meta-analysis, leading to a smaller than anticipated sample of included studies.

Furthermore, inconsistencies in noradrenaline formulations may contribute to bias in meta-analyses. Noradrenaline products are marketed as injectable aqueous solutions with variable concentrations. To ensure stability, solubility, and safe intravenous administration, noradrenaline is dispensed as a salt formulation [53]. Different noradrenaline salts, including bitartrate monohydrate, tartrate (i.e. anhydrous bitartrate), and hydrochloride, are in use. This variability in formulation and dose reporting may introduce bias when pooling data from studies that did not specify the formulation used [54]. To mitigate this risk, we reviewed the origins of the included centres and standardised accordingly: most studies originated from U.S. centres, with one European study that explicitly stated converting data to noradrenaline base. Using standardised reporting practices is essential to achieve accuracy and comparability of future dose-response analyses. Noradrenaline dose should be expressed as the amount of noradrenaline base [55]. Lastly, our post hoc analyses revealed a higher-than-expected proportion of patients receiving very high doses of noradrenaline compared to previously published reports [17, 43]. Several factors may account for this discrepancy. The peak dose that we used in our analyses may reflect transient episodes of escalated vasopressor requirements. Additionally, the predominance of studies including septic shock patients, who often require the highest doses, may have influenced this observation. The

use of norepinephrine-equivalent doses in some studies may also have inflated total dose estimates. Finally, in several studies the formulation was not explicitly stated, and noradrenaline base was presumed, potentially leading to an overestimation of the actual dose administered.

At last, the inherent nature of a meta-analysis, and by extension a dose-response meta-analysis, is that its findings are only as robust as the studies it contains. In our case, all included studies were observational, carrying their inherent risk of bias. This was reflected in the substantial heterogeneity observed across studies, underscoring the need for prospective investigations with standardized definitions of vasopressor exposure and outcome reporting. Additionally, in the dose-response meta-analysis, we assumed that the modelled study-level association between noradrenaline dose and mortality reflects the patient-level dose-response, which is a strong assumption, but common in meta-analyses.

Conclusion

In this large meta-analysis, we identified a potentially exponential dose-response relationship between noradrenaline dose and relative risk of mortality in ICU patients. This work also informed development of SOFA 2.0 cardiovascular subscore.

Abbreviations

SOFA	Sequential organ failure assessment
RR	Relative risk
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PICO	Population intervention outcome comparison
ICU	Intensive care unit
ROB	Risk of bias
GRADE	Grading of recommendations assessment, development and evaluation
CI	Confidence intervals
DRMA	Dose-response meta-analysis
AIC	Akaike information coefficient

Supplementary Information

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Supplementary Material 1.

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Author contributions

M.R., I.L., L.D., A.R.B., S.H., S.L., E.R. ensured the data collection. I.L., L.D., A.R.B., M.R. defined the study design. The data analysis was performed by L.D., I.L., O.R.I.L., L.D., M.R., A.R.B. and O.R. were responsible for data interpretation. I.L., M.R., L.D., A.R.B., S.H., S.L., E.R. wrote the manuscript. All authors reviewed the manuscript and made critical revisions.

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Data availability

Availability of data and materials: Available in additional material.

Declarations

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181–247.
2. Annane D, Ouanes-Besbes L, de Backer D, Du B, Gordon AC, Hernández G, et al. A global perspective on vasoactive agents in shock. Intensive Care Med. 2018;44:833–46.
3. Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. Ann Intensive Care. 2019;9:20.
4. Bitton E, Zimmerman S, Azevedo LCP, Benhamou D, Cecconi M, De Waele JJ, et al. An international survey of adherence to surviving sepsis campaign guidelines 2016 regarding fluid resuscitation and vasopressors in the initial management of septic shock. J Crit Care. 2022;68:144–54.
5. Stolk RF, van der Poll T, Angus DC, van der Hoeven JG, Pickkers P, Kox M. Potentially inadvertent immunomodulation: norepinephrine use in sepsis. Am J Respir Crit Care Med. 2016;194:550–8.
6. Persichini R, Silva S, Teboul J-L, Jozwiak M, Chemla D, Richard C, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med. 2012;40:3146–53.
7. Hamzaoui O, Jozwiak M, Geffriaud T, Sztrymf B, Prat D, Jacobs F, et al. Norepinephrine exerts an inotropic effect during the early phase of human septic shock. Br J Anaesth. 2018;120:517–24.

8. Antonucci E, Polo T, Giovini M, Girardis M, Martin-Loeches I, Nielsen ND, et al. Refractory septic shock and alternative wordings: a systematic review of literature. J Crit Care. 2023;75:154258.
9. Ceausu D, Boulet N, Roger C, Alonso S, Lefrant J-Y, Boisson C, et al. Critical norepinephrine dose to predict early mortality during circulatory shock in intensive care: a retrospective study in 3423 ICU patients over 4-year period. Shock. 2024;62:682–7.
10. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-Related problems of the European society of intensive care medicine. Intensive Care Med. 1996;22:707–10.
11. Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. Ann Intensive Care. 2019;9:20.
12. Thongprayoon C, Cheungpasitporn W, Harrison AM, Carrera P, Srivali N, Kittamongkolchai W, et al. Temporal trends in the utilization of vasopressors in intensive care units: an epidemiologic study. BMC Pharmacol Toxicol. 2016;17:19.
13. Jentzer JC, Wiley B, Bennett C, Murphree DH, Keegan MT, Kashani KB, et al. Temporal trends and clinical outcomes associated with vasopressor and inotrope use in the cardiac intensive care unit. Shock. 2020;53:452–9.
14. Bachmann KF, Arabi YM, Regli A, Starkopf J, Reintam Blaser A. Cardiovascular SOFA score may not reflect current practice. Intensive Care Med. 2022;48:119–20.
15. Pölkki A, Pekkarinen PT, Takala J, Selander T, Reinikainen M. Association of sequential organ failure assessment (SOFA) components with mortality. Acta Anaesthesiol Scand. 2022;66:731–41.
16. Moreno R, Rhodes A, Piquilloud L, Hernandez G, Takala J, Gershengorn HB, et al. The sequential organ failure assessment (SOFA) score: has the time come for an update? Crit Care. 2023;27:15.
17. Ranzani OT, Singer M, Salluh JIF, Shankar-Hari M, Pilcher D, Berger-Estilita J. Development and Validation of the Sequential Organ Failure Assessment (SOFA)-2 Score. JAMA. 2025. https://doi.org/10.1001/jama.2025.2051618
18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
20. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580–637.
21. Sviri S, Hashoul J, Stav I, van Heerden PV. Does high-dose vasopressor therapy in medical intensive care patients indicate what we already suspect? J Crit Care. 2014;29:157–60.
22. Singer KE, Kodali RA, Wallen TE, Salvator A, Pritts TA, Droege CA, et al. The association of norepinephrine utilization with mortality risk in trauma patients. J Surg Res. 2022;280:234–40.
23. Brand DA, Patrick PA, Berger JT, Ibrahim M, Matela A, Upadhyay S, et al. Intensity of vasopressor therapy for septic shock and the risk of in-hospital death. J Pain Symptom Manage. 2017;53:938–43.
24. Moreno R, Rhodes A, Ranzani OT, Salluh J, Berger-Estilita J, Coopersmith CM. Rationale and methodological approach underlying the development of the SOFA (Sequential Organ Failure Assessment(SOFA)-2 Score: a consensus statement. JAMA Netw Open. 2025. https://doi.org/10.1001/jamanetworkopen.2025.45040
25. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
28. Deeks J, Higgins J, Altman D,Chapter 10: Analysing data and undertaking meta-analyses., Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions version 62 (updated February 2021) [Internet]. Cochrane; 2021. Available from: www.training.cochrane.org/handbook
29. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med. 2010;29:1037–57.
30. Liao W-C, Tu Y-K, Wu M-S, Lin J-T, Wang H-P, Chien K-L. Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. BMJ. 2015;349:g7371–7371.
31. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153–60.
32. Viechtbauer W. Conducting Meta-Analyses in *R* with the metafor Package. J Stat Soft [Internet]. 2010 [cited 2024 Mar 4];36. Available from: http://www.jstatsoft.org/v36/i03/
33. Crippa A, Orsini N. Multivariate dose-response meta-analysis: the Dosresmeta R package. J Stat Softw. 2016;72:1–15.
34. Harrer M, Cuijpers P, Furukawa T, Ebert DD. dmetar: Companion R Package For The Guide Doing Meta-Analysis in R. R package version 0.1.0. [Internet]. 2019. Available from: http://dmetar.protectlab.org/
35. Auchet T, Regnier M-A, Girerd N, Levy B. Outcome of patients with septic shock and high-dose vasopressor therapy. Ann Intensive Care. 2017;7:43.
36. Burstein B, Vallabhajosyula S, Ternus B, Murphree D, Barsness GW, Kashani K, et al. Outcomes associated with norepinephrine use among cardiac intensive care unit patients with severe shock. Shock. 2021;56:522–8.
37. Cereuil A, Ronflé R, Culver A, Boucekine M, Papazian L, Lefebvre L, et al. Septic shock: phenotypes and outcomes. Adv Ther. 2022;39:5058–71.
38. Chotalia M, Matthews T, Arunkumar S, Bangash MN, Parekh D, Patel JM. A time-sensitive analysis of the prognostic utility of vasopressor dose in septic shock. Anaesthesia. 2021;76:1358–66.
39. Domizi R, Calcinaro S, Harris S, Beilstein C, Boerma C, Chiche J-D, et al. Relationship between norepinephrine dose, tachycardia and outcome in septic shock: a multicentre evaluation. J Crit Care. 2020;57:185–90.
40. Jurado L, Carnino M. Adverse events associated with high-dose vasopressor use in septic shock patients. Crit Care Med. 2022;50:736.
41. Meenach C, Kelly A, Bensadoun E. Outcome of high dose vasopressor therapy in septic shock. American Journal of Respiratory and Critical Care Medicine [Internet]. 2019;199. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L630354990&from=export
42. Micheletto J, Belvitch P, Benken S. Vasopressor starting dose and association with hemodynamic goals, renal replacement therapy, and mortality. J Cri Int Care. 2022;13:90–6.
43. Pölkki A, Pekkarinen PT, Hess B, Blaser AR, Bachmann KF, Lakbar I, et al. Noradrenaline dose cutoffs to characterise the severity of cardiovascular failure: data-based development and external validation. Acta Anaesthesiol Scand. 2024;68:1400–8.
44. Sato R, Khanna A, Mucha S, Duggal A, Dugar S. Norepinephrine equivalent dose is strongly associated with in-hospital mortality in septic shock. Crit Care Med. 2022;50:713.
45. Schupp T, Weidner K, Rusnak J, Jawhar S, Forner J, Dulatahu F, et al. Norepinephrine dose, lactate or heart rate: what impacts prognosis in sepsis and septic shock? Results from a prospective, monocentric registry. Curr Med Res Opin. 2023;39:647–59.
46. Singer KE, Sussman JE, Kodali RA, Winer LK, Heh V, Hanseman D, et al. Hitting the vasopressor ceiling: finding norepinephrine associated mortality in the critically ill. J Surg Res. 2021;265:139–46.
47. Vallabhajosyula S, Kotecha A, Jentzer J, Ternus B, Frazee E, Iyer V. Clinical outcomes of high-dose norepinephrine in septic shock. Crit Care Med. 2018;46:682.
48. Wahby K, Zacholski K, Pangrazzi M. Do norepinephrine starting rates effect outcomes in septic shock? Crit Care Med. 2015;43:160.
49. Yamamura H, Kawazoe Y, Miyamoto K, Yamamoto T, Ohta Y, Morimoto T. Effect of norepinephrine dosage on mortality in patients with septic shock. J Intensive Care. 2018;6:12.
50. Yu C, Fan W, Shao M. Norepinephrine Dosage Is Associated With Lactate Clearance After Resuscitation in Patients With Septic Shock. Front Med [Internet]. 2021;8. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L636670421&from=export
51. Vincent, JL., Nielsen, N.D., Shapiro, N.I. et al. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. Ann. Intensive Care. 2018;8:107.
52. Contal C, O'Quigley J. An application of changepoint methods in studying the e ect of age on survival in breast cancer.
53. Goyer I, Lakbar I, Freund Y, Lévy B, Leone M. Norepinephrine dosing in France: time to move forward! Anaesth Crit Care Pain Med. 2024;43(4):101397. https://doi.org/10.1016/j.accpm.2024.101397
54. Morales S, Wendel-Garcia PD, Ibarra-Estrada M, Jung C, Castro R, Retamal J, et al. The impact of norepinephrine dose reporting heterogeneity on mortality prediction in septic shock patients. Crit Care. 2024;28:216.

55. Wieruszewski PM, Leone M, Kaas-Hansen BS, Dugar S, Legrand M, McKenzie CA, et al. Position paper on the reporting of norepinephrine formulations in critical care from the society of critical care medicine and European society of intensive care medicine joint task force. Crit Care Med. 2024. 52(4):p 521–530. https://doi.org/10.1097/CCM.0000000000006176

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