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SYSTEMATIC REVIEW

Hypotension during intensive care stay and mortality and morbidity: a systematic review and meta-analysis

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Abstract

Purpose: The aim of this study is to provide a summary of the existing literature on the association between hypotension during intensive care unit (ICU) stay and mortality and morbidity, and to assess whether there is an exposure-severity relationship between hypotension exposure and patient outcomes.

Methods: CENTRAL, Embase, and PubMed were searched up to October 2022 for articles that reported an association between hypotension during ICU stay and at least one of the 11 predefined outcomes. Two independent reviewers extracted the data and assessed the risk of bias. Results were gathered in a summary table and studies designed to investigate the hypotension-outcome relationship were included in the meta-analyses.

Results: A total of 122 studies (176,329 patients) were included, with the number of studies varying per outcome between 0 and 82. The majority of articles reported associations in favor of 'no hypotension' for the outcomes mortality and acute kidney injury (AKI), and the strength of the association was related to the severity of hypotension in the majority of studies. Using meta-analysis, a significant association was found between hypotension and mortality (odds ratio: 1.45; 95% confidence interval (CI) 1.12–1.88; based on 13 studies and 34,829 patients), but not for AKI.

Conclusion: Exposure to hypotension during ICU stay was associated with increased mortality and AKI in the majority of included studies, and associations for both outcomes increased with increasing hypotension severity. The meta-analysis reinforced the descriptive findings regarding mortality but did not yield similar support for AKI.

Keywords: Hypotension, Mortality, Morbidity, Meta-analysis, Intensive care unit

Introduction

Maintaining adequate perfusion pressure in vital organs is a pivotal aspect of critical care management. Since bedside tissue perfusion monitoring remains difficult, blood pressure is often used as a surrogate measure. Although continuous blood pressure monitoring is widely used in the intensive care unit (ICU) [1], maintaining normotensive thresholds in the critically ill remains challenging. The reported incidences of hypotension vary widely due to heterogeneity in studied patient populations and hypotension definitions used, thereby complicating study comparison [2–4]. Reported definitions differ in the parameter(s) used (e.g., systolic blood pressure [SBP] and mean arterial pressure [MAP]), the type of threshold used (absolute or relative), and the required duration of the pressure drop. Consequently, 140 distinct definitions of hypotension are reported in the literature [5]. However, in the ICU a MAP below 65 mmHg is most frequently used [6].

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The relationship between hypotension during the ICU stay and organ damage has been described in numerous, primarily (retrospective) observational, studies [3, 4, 7, 8]. Smischney et al. additionally demonstrated that the strength of this association increased with incremental depth of hypotension, suggesting an exposure–severity relationship between hypotension and patient outcomes [4]. The effect of hypotension during ICU stay on the incidence of hypoperfusion-related complications has not been studied in a randomized clinical trial (RCT) to date. Several RCTs, all with neutral findings, have tested the effect of assigning patients to higher or lower blood pressure targets on mortality or vegetative state [9–11]. Notably, in these trials the average blood pressure in the lower blood pressure target groups was above 65 mmHg, and therefore, higher than the commonly used thresholds to define hypotension [6].

Although hypotension has been extensively studied in ICU patients, a summary of available literature outlining patient outcomes affected by hypotension exposure during ICU stay does not exist. Understanding how different definitions of hypotension influence the strength of the associations between hypotension and these outcomes could aid ICU physicians in selecting appropriate blood pressure targets. In this systematic review with meta-analyses, we aim to assess existing literature on the associations between exposure to hypotension during ICU stay and mortality and morbidity. We hypothesize that exposure to hypotension is associated with patient mortality and morbidity, regardless of the studied patient population, and that the strength of this association increases with both decreasing blood pressure thresholds and prolonged exposure to hypotension.

Take-Home Message

In this systematic review containing 122 articles (176,329 patients), exposure to hypotension during intensive care unit stay correlated with elevated mortality rates. Furthermore, the majority of the included studies reported associations between hypotension and increased acute kidney injury (AKI) rates, with the strength of the associations intensifying for both outcomes as hypotension severity increased. The associations between hypotension and patient outcomes were especially pronounced when mean arterial pressure fell below 60 mmHg and systolic blood pressure dropped below 90 mmHg for mortality, and when mean arterial pressure dropped below 55 mmHg for AKI.

Methods

Systematic review

This systematic review followed the methodology outlined in the Cochrane Handbook for systematic review and PRISMA guidelines. The PRISMA checklist is provided in supplementary Table 1. The study protocol was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42020213244. A clinical librarian helped search PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant articles up to October 17th 2022. Search terms included medical subject headings (MeSH), free terms, and synonyms for 'intensive care unit,' 'hypotension,' and the outcomes of interest. The complete search strategy is available in supplementary Text 1.

Two independent reviewers screened titles, abstracts, and full texts using the review program Rayyan [12]. Any discrepancies were resolved through discussion with a third reviewer. We included studies in adult patients (> 16 years old) that reported an association between hypotension (as defined by the authors) during ICU stay, and mortality and morbidity, and excluded case reports, literature studies, articles not written in English, and those without full texts or lacking a definition of hypotension. Articles were additionally excluded if the full text or the definition of hypotension could not be obtained despite contacting the authors, if hypotension exposure during procedures (e.g., renal replacement therapy) was studied, or if the sample size was inadequate, defined as less than one event of the outcome of interest in the hypotension or no hypotension group. To avoid overlapping data, we included only the article with the least potential for bias when multiple articles presented findings from the same patient cohort. When the potential for bias was equal, the study with the most frequently used hypotension definition was selected.

Data extraction

Blinded data extraction was performed in duplicate using a predefined template. Subsequently, the data extraction sheets were merged, and in the event of any discrepancies, the original article was re-evaluated. The following data were collected: study design, patient characteristics, hypotension definition, outcome definition, type of blood pressure measurement, and outcome data.

Quality assessment

Prior to conducting the analyses, we critically appraised included articles in duplicate (JaS and BR, SR, or VK) using the Cochrane risk of bias tool for randomized controlled trials [13] and the Newcastle–Ottawa Scale (NOS) for non-randomized studies [14]. The NOS is a grading system with a scale of 0–9 based on four selection criteria, two comparability criteria, and three outcome criteria, with higher scores suggesting a smaller potential for bias. Quality assessors were blinded to each other's quality assessment.

Objectives

The pre-specified patient outcomes included mortality, acute kidney injury (AKI), myocardial infarction, ischemic cerebrovascular accident (iCVA), delirium, poor cognitive functioning, ICU length of stay, duration of mechanical ventilation, quality of life, post intensive care syndrome (PICS), and World Health Organisation Disability Assessment Schedule (WHODAS) score. We included articles reporting an association between hypotension during ICU stay and at least one of the outcomes mentioned above, regardless of the reported definition of the outcome (e.g., ICU mortality or in-hospital mortality). The primary objective of this systematic review was to provide a descriptive overview of reported associations between exposure to hypotension and the predefined outcomes. Only studies specifically designed to study this relationship, including RCTs and observational studies that conducted a confounder-adjusted analysis to determine an unbiased estimate of the hypotension-outcome association, were used for the primary objective. Secondary objectives were to determine the aggregated direction of the association per patient outcome by pooling the (adjusted) results of individual studies in a meta-analysis, to assess whether there is an exposure-severity relationship between hypotension exposure and patient outcomes within studies that compared multiple levels of hypotension exposure, and to identify harm thresholds for hypotension when applicable.

Meta-analyses

Studies were eligible for inclusion in the meta-analyses if they were designed to study the relationship between hypotension and one of the predefined patient outcomes. Observational studies additionally had to report a confounder-adjusted outcome measure (e.g., adjusted odds ratio [OR]) and the list of confounders included in the analysis. Meta-analysis was conducted if at least three studies per predefined outcome reported the same outcome measure (OR, relative risk [RR], or hazard ratio [HR]). When studies reported multiple confounder-adjusted outcome measures, the outcome measure most frequently reported by other studies was selected for meta-analyses (e.g., adjusted OR for mortality and HR for myocardial injury). If a study reported outcome data for multiple definitions for hypotension (e.g., MAP < 65 mmHg and SBP < 90 mmHg) or for multiple outcome definitions (e.g., in-hospital mortality and ICU mortality), the data corresponding to the definition that was most frequently reported in other included articles were used in the meta-analyses. Studies reporting an association for multiple outcomes (e.g., mortality and AKI) were included in each corresponding meta-analysis. We used the inverse variance method to conduct random-effect meta-analyses, thereby incorporating the assumption that different studies estimate distinct, yet related, study effects [15]. However, fixed-effect meta-analysis was used when fewer than six articles were available per outcome, as an accurate estimation of the between-study variance could not be obtained. The percentage of variance due to between-study variation was estimated by the I^2 statistic. Funnel plots were used to examine potential publication bias. We opted for Peter's test, a modified version of Macaskill's test [16], to assess for funnel plot asymmetry since we expected considerable between-study variation, as indicated by previous systematic reviews on intraoperative hypotension [17–19]. Subgroup meta-analysis per pre-defined ICU patient population was conducted if at least three studies reported data on the same patient population.

Sensitivity meta-analyses

Two sensitivity analyses were conducted to assess the influence of decisions made during the design of this systematic review and meta-analysis on the associations found. In our first sensitivity analysis, we added studies that were not specifically designed to study the relationship between hypotension and patient outcomes, but nonetheless reported a hypotension-related outcome measure obtained from multivariable analysis. The second sensitivity analysis included all studies from which an OR (adjusted or unadjusted) could be extracted or calculated and was conducted to minimize the exclusion of studies caused by heterogeneity in reported outcome measures.

Effect of perceived hypotension severity on mortality and acute kidney injury

We conducted exploratory meta-analyses by stratifying studies based on the severity of hypotension studied. The large variation in hypotension definitions reported in literature complicates the ranking of hypotension definitions. Currently, there is no consensus on the definition of hypotension, and the difference in the potential harmfulness of using MAP versus SBP-based definitions is unknown. We, therefore, asked an expert panel of nine intensivists to rank the reported definitions of hypotension in terms of perceived severity by clinical experts. The expert panel ranked the definitions on a scale from 1 to 9, with 9 being the most severe definition of hypotension (see supplementary Table 2). Multiple definitions could receive the same rank if thought to be equally severe. The median ranking score per definition was used to stratify studies into three groups of perceived severity of hypotension: mild (rank 1–3), moderate (rank 4–6), and severe hypotension (rank 7–9). However, the limited variety in hypotension definitions reported by studies

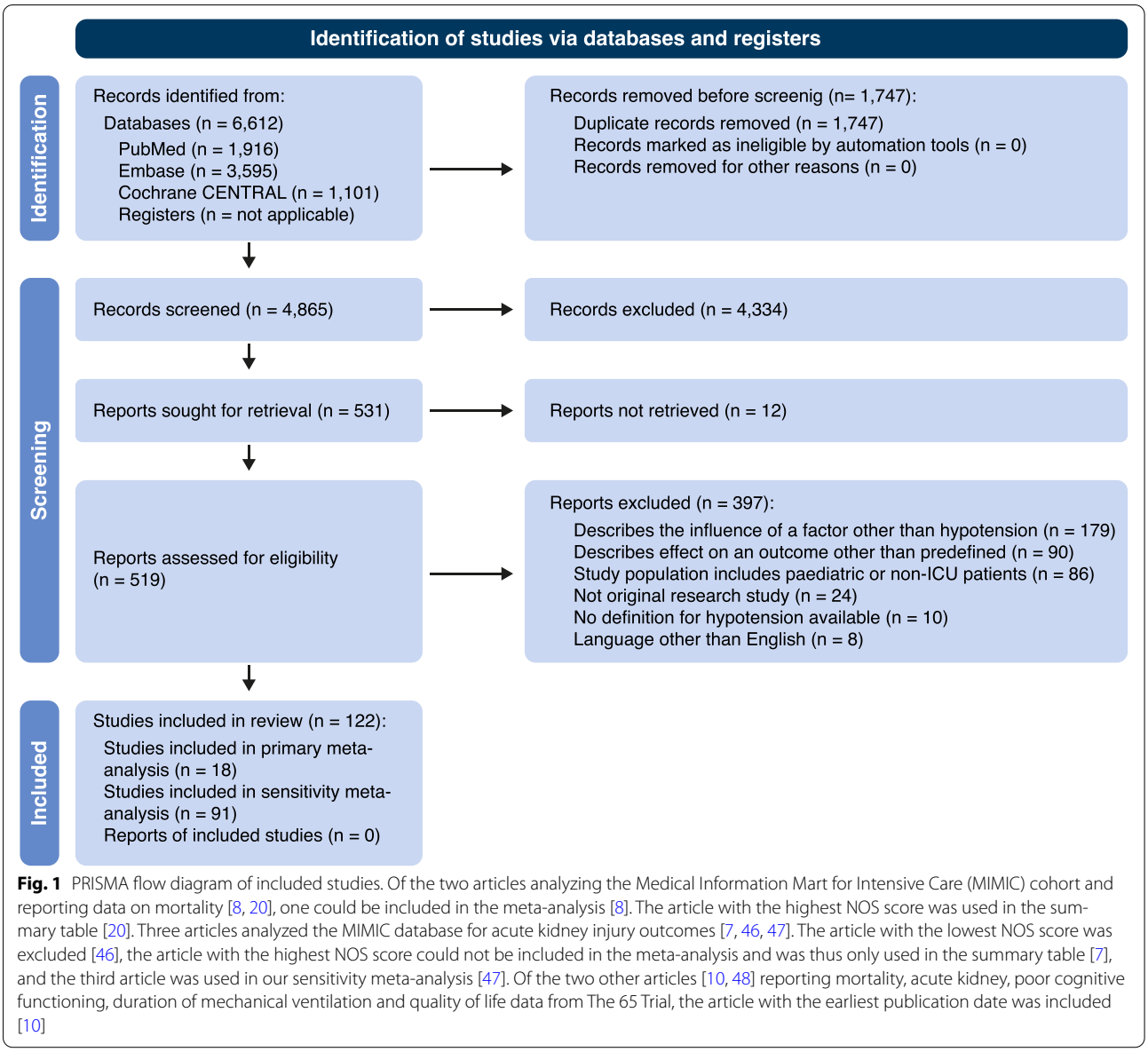

Fig. 1 PRISMA flow diagram of included studies. Of the two articles analyzing the Medical Information Mart for Intensive Care (MIMIC) cohort and reporting data on mortality [8, 20], one could be included in the meta-analysis [8]. The article with the highest NOS score was used in the summary table [20]. Three articles analyzed the MIMIC database for acute kidney injury outcomes [7, 46, 47]. The article with the lowest NOS score was excluded [46], the article with the highest NOS score could not be included in the meta-analysis and was thus only used in the summary table [7], and the third article was used in our sensitivity meta-analysis [47]. Of the two other articles [10, 48] reporting mortality, acute kidney, poor cognitive functioning, duration of mechanical ventilation and quality of life data from The 65 Trial, the article with the earliest publication date was included [10]

designed to study the hypotension-outcome relationship did not allow for this exploratory analysis. We, therefore, opted to include all studies that reported a hypotension-related outcome measure obtained from multivariable analysis (similar to the studies included in our first sensitivity analysis) in this exploratory meta-analysis.

Results

Study characteristics

A total of 4865 unique articles were identified in PubMed, Embase, and CENTRAL. We excluded 4334 articles based on title and abstract, 397 based on full text, and 12 because no full text was obtained after contacting the corresponding authors. The PRISMA flow diagram for this systematic review is available in Fig. 1. In total, 122 articles (176,329 patients) were included in this systematic review, of which 18 were included in the primary meta-analyses, and 91 were included in sensitivity analyses. The majority of articles were cohort studies, eight were (quasi) RCTs, three case-controls, and one was propensity score matched. There was a large heterogeneity in the studied patient populations, and women were underrepresented in the majority of studies. The number of studies per outcome ranged from 82 for mortality and zero for PICS and WHODAS scores. A summarized overview of all included articles with relevant outcome data is available in the supplementary Table 3. All non-randomized studies had a NOS score of four or

higher, and the potential for bias in the included RCTs ranged from "low" to "some concern" (supplementary Table 4). Over 40 different definitions for hypotension were reported. These definitions varied in terms of the type of parameter reported (e.g., SBP or patients requiring vasopressor therapy) and the threshold used (e.g., SBP < 100 mmHg or > 30% decrease from baseline).

Mortality

Out of the 82 included articles (144,623 patients) that reported outcome data for this parameter, 18 (62,804 patients) were specifically designed to study the hypotension-mortality relationship [2–4, 9–11, 20–31]. Twelve (67%) of these studies, conducted in eight distinct patient populations, reported an association in favor of 'no hypotension', and none in favor of hypotension. Five articles reported associations for increasing severity of hypotension [3, 4, 20, 21, 26], four of which reported increasing associations with mortality for incremental depth or duration of hypotension [3, 4, 20, 21]. A MAP below 60 mmHg was associated with mortality in all six studies reporting outcome data for this definition of hypotension [3, 4, 21, 22, 26, 30] and a SBP below 90 mmHg in three of the four studies [2, 22, 25]. A total of 13 articles (34,829 patients) were included in the meta-analysis (Fig. 2), where an association between hypotension and mortality was found with an OR of 1.45 (95% confidence interval [CI] 1.12–1.88; $I^2 = 94\%$) [2, 9–11, 21–25, 28–31]. There was no sign of publication bias based on the funnel plot (supplementary Fig. 1) and Peter's test ($t = -1.05$, $df = 11$, p-value 0.317). Sensitivity meta-analysis including RCTs and all observational studies that reported an adjusted odds ratio for hypotension (30 studies, 48,086 patients), regardless of the studies' objectives, or including studies from which an OR (adjusted or unadjusted) could be extracted or calculated (65 studies, 67,909 patients), increased the strength of the association (see supplementary Fig. 2A, B).

Acute kidney injury

We included 36 articles (76,614 patients) on AKI, of which 14 (24,714 patients) were dedicated to studying the hypotension-AKI relationship [3, 4, 7, 9–11, 26, 32–38]. Of the 14 studies, eight (57%) reported an association in favor of 'no hypotension' and none in favor of 'hypotension'. Studies with an association in favor of 'no hypotension' were conduct in four distinct patient populations. Six articles investigated the effect of incremental depth or duration of hypotension on AKI, with five of them finding stronger associations as the severity of hypotension increased [3, 4, 7, 32, 33]. A MAP below 55 mmHg was associated with AKI in three of the four articles studying this definition [3, 4, 7]. Meta-analysis including six articles (13,765 patients) did not demonstrate an association between hypotension and AKI (OR 1.17; 95% CI 0.97–1.41; $I^2 = 54\%$; see Fig. 3) [3, 9–11, 33, 38]. No funnel plot asymmetry was noted (supplementary Fig. 1) and Peter's test was not statistically significant ($t = 1.49$, $df = 4$, p-value 0.210), indicating absence of potential publication bias. No associations were found using subgroup meta-analysis stratified per patient population (supplementary Fig. 3A). Sensitivity analyses including all studies reporting an adjusted odds ratio (13 studies, 15,269 patients) or including all studies from which an OR (adjusted or unadjusted) could be obtained (27 studies, 28,852 patients), resulted in an association in favor of 'no hypotension' (see supplementary Fig. 3B, C).

Myocardial injury

The association between myocardial injury and ICU hypotension was reported in seven articles (15,414 patients), three of which (14,717 patients) reported outcome data from an analysis dedicated to study the hypotension-myocardial injury relationship [3, 4, 35]. Two of the hypotension-specific studies reported an association in favor of 'no hypotension', and none in favor of hypotension. Duration and depth of hypotension did not impact the association with myocardial injury [3, 4]. The heterogeneity in reported outcome measures resulted in an insufficient number of studies to conduct the main meta-analysis. Sensitivity meta-analysis based on studies reporting an adjusted HR for hypotension (three studies, 6158 patients), regardless of the studies' objectives, resulted in an association in favor of 'no hypotension' (supplementary Fig. 4).

Ischemic cerebrovascular accident

A total of two articles (3637 patients) reported on the association with iCVA, one of which (3169 patients) conducted a confounder-adjusted analysis to isolate the hypotension-iCVA relationship [4]. In this study, no association between hypotension and iCVA was found.

Delirium

Three (1932 patients) out of six (3119 patients) included studies were designed to study the hypotension-delirium relationship [39–41]. One reported an association in favor of 'no hypotension,' while none favored hypotension.

Poor cognitive functioning

Eleven articles (9490 patients) reported on cognitive functioning, of which three studies (2144 patients) conducted an analysis to determine the confounder-adjusted association with hypotension [10, 11, 42]. The lowest MAP measured in the first six hours of ICU stay was

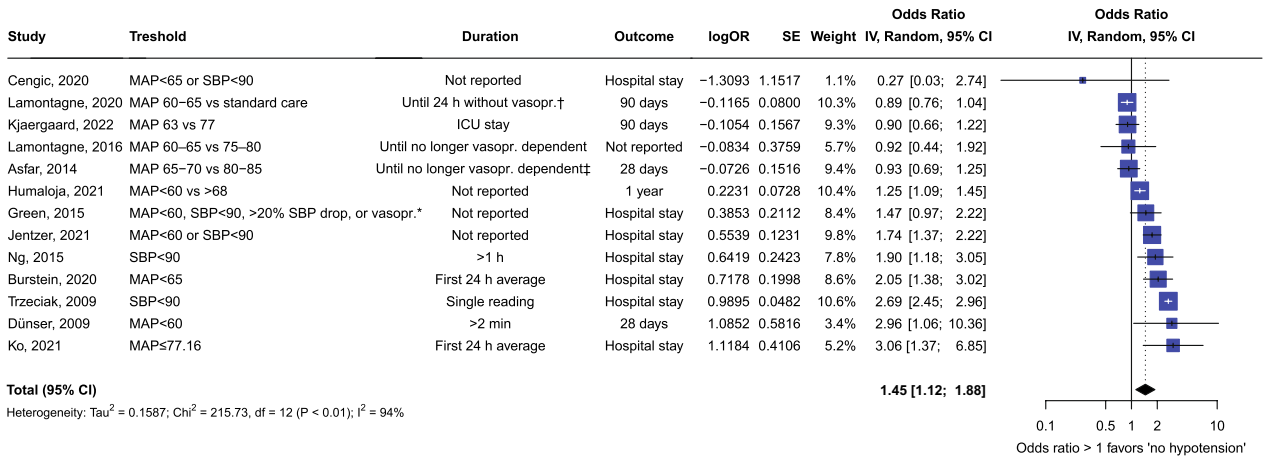

Fig. 2 Forest plot for mortality. The forest plot is based on 13 articles (34,829 patients) designed to study the hypotension-mortality relationship. This includes randomized controlled trials and observational studies that conducted a confounder-adjusted analysis specifically to study this relationship [2, 9–11, 21–25, 28–31]. A random-effects meta-analysis based on the inverse variance method was conducted. All blood pressure thresholds are displayed in mmHg. *CI* confidence interval, *h* hour, *ICU* intensive care unit, *MAP* mean arterial pressure, *min* minute, *SBP* systolic blood pressure, *vasopr.* vasopressor. *Within 30 min post endotracheal intubation. †Or transfer or death. ‡Or until 5 days after randomization

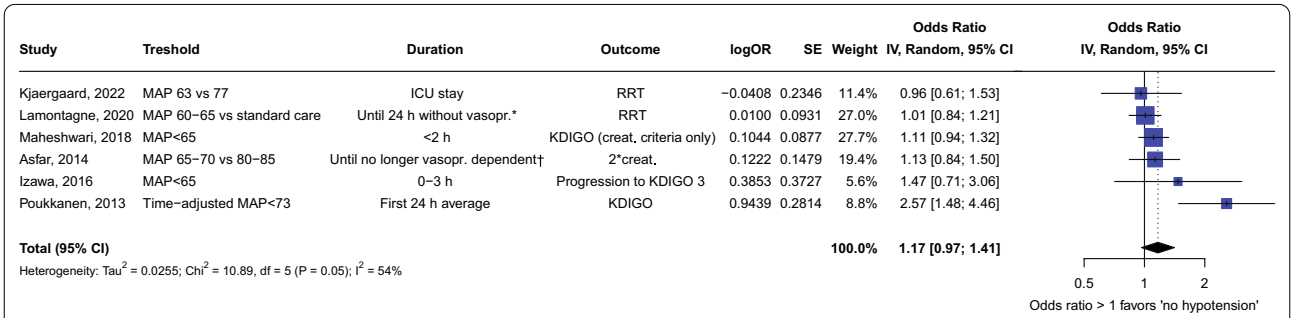

Fig. 3 Forest plot for acute kidney injury. The forest plot is based on articles designed to study the hypotension-acute kidney injury relationship. This includes randomized controlled trials and observational studies that conducted a confounder-adjusted analysis specifically to study this relationship [3, 9–11, 33, 37, 38]. A random-effects meta-analysis based on the inverse variance method was conducted. All blood pressure thresholds are displayed in mmHg. *AKI* acute kidney injury, *CI* confidence interval, *creat.* serum creatinine, *h* hour, *ICU* intensive care unit, *KDIGO* Kidney Disease Improving Global Outcomes criteria, *MAP* mean arterial pressure, *RRT* renal replacement therapy, *vasopr.* vasopressor. *Or transfer or death. †Or until 5 days after randomization

associated with poor cognitive functioning in one study and none of the articles reported an outcome in favor of hypotension [42]. No main meta-analysis was conducted as all studies reported a different outcome measure, but a sensitivity meta-analysis including four studies (1293 patients) reporting an adjusted RR for hypotension, regardless of the study's objectives, resulted in an association in favor of 'no hypotension' (supplementary Fig. 5).

Length of ICU stay

We included nine articles (7580 patients) on the association between hypotension and length of ICU stay, two of which (3206 patients) were specifically designed to study this relationship [10, 31]. No significant associations were found.

Duration of mechanical ventilation

Two articles (748 patients) on hypotension and duration of mechanical ventilation were included, one of which

(479 patients) conducted a hypotension specific analysis but no significant associations were reported.

Quality of life

Two articles (1858 patients) studied the association with quality of life, one of which (1462 patients) was designed to study this association. No association with hypotension was reported by this study.

Effect of severity of hypotension exposure on mortality and morbidity

Our exploratory subgroup analysis did not demonstrate a relation between the perceived hypotension severity as ranked by intensivists and the strength of association with mortality and AKI (supplementary Fig. 6A, B).

Discussion

Exposure to hypotension during ICU stay was associated with increased mortality and morbidity in the majority of articles included in this systematic review. The descriptive findings for mortality were underscored by our meta-analysis and sensitivity analyses but conflicting results were found for the association with AKI. The number of studies for other outcomes was insufficient to conduct our main meta-analysis. Incremental depth or duration of hypotension resulted in a stronger association with poor patient outcomes in the majority of studies reporting outcome data for multiple gradations of hypotension exposure, suggesting an exposure-severity relationship. Hypotension definitions most consistently associated with mortality and AKI were a MAP below 60 mmHg or SBP below 90 mmHg and MAP below 55 mmHg, respectively.

Our results are in line with three systematic reviews on the relationship between intraoperative hypotension and postoperative mortality and AKI [17–19]. Among these reviews, two conducted meta-analyses that, much like our own review, relied on cohort and case–control studies [18, 19]. Wijnberge et al.'s review additionally reported a stronger association between hypotension and morbidity for severe hypotension compared to mild and moderate hypotension [18]. This observation found support in the work of Wesselink et al., who, instead of conducting a meta-analysis, created a synthesis table by organizing studies based on the severity of hypotension studied and presenting their associations with postoperative adverse outcomes [17]. The strength of the association progressively correlated with the depth of the hypotensive event in their systematic review. We found similar results within studies comparing multiple definitions for hypotension, but our exploratory meta-analyses based on the perceived severity of hypotension as ranked by intensivists did not support this exposure-severity relationship. However, the number of studies ranked as mild and severe hypotension was, with three or less, limited. In addition, we could not fully assess the impact of potential confounding factors on the association between hypotension severity and patient outcomes, primarily due to the heterogeneity in the reporting of these potential confounders (e.g., ICU patient population and disease severity score).

Randomized trials studying the effect of hypotension on mortality and morbidity are limited due to challenges in maintaining predefined blood pressure targets and the absence of consensus on the definition for hypotension. This systematic review included four RCTs that assigned patients to different blood pressure targets [9–11, 24]. Although these trials showed a clear distinction in average blood pressure values in both study arms, the average MAP in the lower target group of all RCTs exceeded the commonly used hypotension definitions of MAP < 65 mmHg and SBP < 90 mmHg. Consequently, exposure to hypotension in the lower target groups might have been limited compared to the observational studies included in this systematic review. Furthermore, assigning patients to a higher blood pressure threshold does not necessarily prevent hypotensive events. Patients in both the higher and lower blood pressure target group may have had similar exposure to critically low blood pressure, even if the average blood pressure of one group was substantially higher. Moreover, maintaining higher blood pressure thresholds required higher vasopressor dosages [9, 11], which is independently associated with poor patient outcomes [43, 44]. This may have contributed to the neutral findings of blood pressure target RCTs, and the absence of an association between hypotension and AKI in our main meta-analysis, as halve of the included studies were RCTs.

Our systematic review has limitations that affect the interpretation and clinical applicability of the findings. Most studies included did not primarily aim to study the relationship between hypotension and patient outcomes, but rather sought predictors of patient outcomes. As a result, reported adjusted ORs, RRs, and HRs were often not adjusted for biases specifically relevant to the hypotension-patient outcomes relationship, resulting in a relatively small number of studies included in the assessment of our primary objective. Moreover, differing patient populations, outcome definitions, and reported outcome data among studies hindered interpretation of the results. We aimed to address some differences by limiting our sensitivity meta-analyses to articles from which an OR could be extracted or calculated and by stratifying studies per ICU patient population but the number of studies reporting on the same patient population was insufficient for subgroup meta-analysis in all outcomes

except AKI. Adding to the complexity was the wide range of reported hypotension definitions. While most studies mentioned the threshold for hypotension, the minimally required event duration or time spent below a certain threshold was often not specified. This hinders data synthesis and the ranking of hypotension severity, as hypotensive events with a MAP of 55 mmHg for one minute might be less harmful compared to a MAP of 60 mmHg for 1 h. Therefore, we only assessed the exposure-severity relation within studies and based the hypotension ranking of our exploratory meta-analysis on expert opinion. Employing this hypotension ranking method was deemed the best available approach to conduct an exposure-effect meta-analysis, but this method has not been validated. Consequently, the results of the exploratory analysis should be interpreted with caution. Furthermore, clinical context information of hypotensive events was limited. This means that both a patient with a temporary SBP < 90 mmHg due to an anesthetic drug bolus and a patient with a persistent SBP < 90 mmHg due to distributive shock were labeled as hypotensive, despite differences in disease severity, event etiology, duration, and potential damage caused. These factors collectively contributed to extensive heterogeneity. Additionally, most articles did not provide information on patient exposure to hypotension prior to ICU admission. Thus, the associations described in this review are not exclusively attributable to hypotension during ICU stay. Lastly, exposure to hypotension may have a causal effect on mortality, but it is essential to recognize that hypotension severity also serves as a marker of illness severity. As a result, the prognosis differs among patients with varying degrees of hypotension exposure. Therefore, a precise estimate of the causal effect of hypotension on outcomes cannot be obtained through meta-analysis due to the inability to meet the consistency or Stable Unit Treatment Value Assumption required for causal effect estimation [45]. Nonetheless, the observed relationship between exposure and severity within studies highlights that sustained interventions to modify hypotension can substantially change patient outcomes. Future intervention trials should concentrate on causally treating each hypotensive event or even preventing hypotension, instead of merely comparing blood pressure targets. Observational studies should distinctly define both the threshold and duration of hypotensive events, should assess the relationship between hypotension and outcome for multiple hypotension definitions, and should explore hypotension exposure as a continuous variable rather than binary before we can fully comprehend the causality between hypotension during ICU stay and patient outcomes.

Conclusion

In conclusion, exposure to hypotension during ICU stay was associated with an increase in mortality. The majority of included studies additionally reported associations between hypotension exposure and acute kidney injury. Furthermore, the associations for both outcomes increased with increasing hypotension severity in studies comparing multiple levels of hypotension exposure. The direction of the associations found between hypotension and patient outcomes was particularly consistent for a mean arterial pressure below 60 mmHg and systolic blood pressure below 90 mmHg for mortality and mean arterial pressure below 55 mmHg for acute kidney injury. Interventional studies targeting specific patient populations and outcomes are essential to fully comprehend the causality between hypotension during ICU stay and patient outcomes.

Supplementary Information
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Author contributions
JaS, NM, WV, JiS, DPV, and APJV contributed to the conception and design of the study. The data acquisition was conducted by JaS, BTBR, SRR, JTMT, and VCK. The analysis and interpretation of the data were performed by JaS, JiS, DPV, and APJV. The first draft of the article was written by JaS, and all authors provided critical revisions. All authors approved the submitted version of the article.

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Data availability
The data that support the findings of this study are available from the authors upon reasonable request.

Declarations

Conflicts of interest
JS, DPV and APJV report receipt of consulting fees from Edwards Lifesciences paid to the institution. DPV additionally reports receipt of research grants from Philips and Edwards Lifesciences and APJV reports receipt of unrestricted research grants from Edwards Lifesciences.

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