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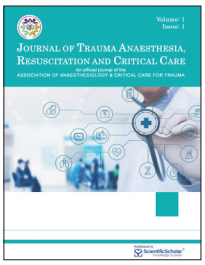

Review Article

Hypocalcemia as a Predictor of Mortality in Trauma Patients: A Systematic Review and Meta-analysis

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ABSTRACT

Hypocalcemia is commonly observed in trauma patients and has been linked to adverse clinical outcomes. However, its role as a predictor of mortality remains unclear. This systematic review and meta-analysis aim to evaluate the association between hypocalcemia and in-hospital mortality in trauma patients. A comprehensive literature search was conducted across multiple databases, including Medline (PubMed), Ovid (Embase), Scopus, Cochrane Central Register of Controlled Trials, and the US Clinical Trial Registry, up to September 2024. Additional manual searches were performed using Google Scholar and ResearchGate. Observational studies reporting mortality and other clinical outcomes in trauma patients with and without hypocalcemia were included. The risk of bias was assessed using the Cochrane Collaboration Risk of Bias 2.0 tool. Data were pooled using a random-effects model, and results were expressed as risk ratio (RR) or mean difference with 95% confidence intervals (CIs). A total of 11 observational studies involving 35,029 patients were included. Hypocalcemia was associated with a significantly increased risk of in-hospital mortality (RR = 1.82, 95% CI: 1.52–2.17, $P < 0.00001$) with moderate heterogeneity ($I^2 = 40\%$). Severe hypocalcemia further elevated mortality risk (RR = 2.74, 95% CI: 1.92–3.90, $P < 0.00001$, $I^2 = 22\%$). In addition, hypocalcemia was linked to an increased incidence of massive transfusion (RR = 2.40, 95% CI: 1.79–3.23, $P < 0.00001$, $I^2 = 65\%$). However, no significant differences were found in duration of hospital stay, intensive care unit stay, or ventilator days between patients with hypocalcemia and normocalcemia. Hypocalcemia is a significant predictor of in-hospital mortality and an increased need for massive transfusion in trauma patients. These findings highlight the importance of monitoring and managing calcium levels in trauma care. Further prospective studies are needed to establish causal relationships and optimize clinical interventions.

Keywords: Hypocalcemia, Massive transfusion, Meta-analysis, Mortality, Systematic review, Trauma

INTRODUCTION

Calcium plays a vital role in several physiological processes, including vasomotor tone regulation, platelet activation, and the proper functioning of both intrinsic and extrinsic coagulation pathways. Hypocalcemia has been identified as a critical factor linked to poor outcomes in trauma patients. It is frequently observed in severe trauma cases and is further aggravated by hemorrhagic shock and blood transfusions. These conditions contribute to the development of coagulopathy, hypothermia, and acidosis – collectively known as the "lethal triad" – which can trigger a vicious cycle of worsening shock. The inclusion of hypocalcemia to this triad has led to the concept of the "Lethal Diamond," which was first described by Ditzel *et al.*[1,2]

Hypocalcemia in trauma patients results from several interconnected mechanisms. Hemorrhage contributes to the depletion of the body's calcium reserves, while hemorrhage-induced hypotension and subsequent acidosis diminish albumin's affinity for calcium, thereby reducing serum ionized calcium (iCa) levels.[3,4] In addition, lactic acidosis further exacerbates hypocalcemia by directly binding iCa. Before transfusion, several factors may contribute to complications, including the dilutional effects of crystalloid resuscitation, intracellular calcium shifts following ischemia-reperfusion injury, and alcohol consumption. Subsequently, massive transfusion can result in an excessive citrate load which is exacerbated by impaired citrate metabolism due to hypothermia, hypoperfusion, and hepatic dysfunction.[5] Hypocalcemia exacerbates the lethal triad, further complicating trauma outcomes. Calcium functions as an essential cofactor in various stages of the coagulation cascade; consequently, its deficiency markedly impairs hemostasis and exacerbates acute trauma-induced coagulopathy. Furthermore, decreased calcium levels adversely affect myocardial contractility and reduce vascular tone, thereby compromising perfusion.[6] In light of these pathophysiological effects, the correlation between hypocalcemia and increased mortality is not surprising. While the association between ionized hypocalcemia and adverse outcomes in trauma has been previously observed, the existing evidence is predominantly in patients receiving massive transfusion. Studies[7,8] have reported that hypocalcemia is associated with increased mortality, coagulopathy, and transfusion requirements in trauma patients, and these studies included total serum calcium rather than iCa, which is the physiologically active component and more relevant in the acute trauma setting. This has spurred interest in optimizing calcium resuscitation strategies, and its role as an independent driver of adverse outcomes and a marker of trauma severity remains unclear. The current resuscitation guidelines advocate calcium supplementation during transfusion.[9] However, the variability in protocols and limited prospective data on the impact of calcium correction on survival have hindered the establishment of standardized treatment approaches.

This systematic review consolidates current evidence on the association between hypocalcemia and trauma-related outcomes. By examining the link between serum calcium levels and patient mortality, the review aims to guide future research and clinical practice while addressing key gaps in our understanding of hypocalcemia's role in trauma care.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[10] [Supplementary file: PRISMA 2020 checklist]. The review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024605186).

Literature search

We systematically searched for articles in Medline (PubMed), Ovid (Embase), Scopus, Cochrane Central Registry of Trials, and the US Clinical Trial Registry. Additional manual searches were conducted using Google Scholar and ResearchGate to examine the effect of hypocalcemia on mortality in patients with trauma. We utilized a combination of controlled vocabulary terms and free keywords: "Hypocalcemia," "mortality," and "trauma." No limitations were applied to publication year or language. The search was conducted until September 2024. Furthermore, we examined references from relevant studies and review articles to identify potential additions to the analysis.

Eligibility criteria

Randomized controlled trials (RCTs), non-RCTs, and observational/retrospective studies assessing the impact of hypocalcemia on mortality in patients with trauma were included. Both English and non-English trials were eligible, and the non-English studies were translated using a Google online translator. The exclusion criteria included case reports, editor letters, and expert opinions.

Study selection

Two reviewers (BY and VN) independently screened the titles and abstracts identified through the literature search. Full-text articles of studies that potentially met the inclusion criteria were then retrieved and assessed**.** Any disagreements regarding study inclusion were resolved through discussion with a third reviewer (AS).

Data extraction

A standardized data extraction form was created using Microsoft Excel. Data extraction was performed by BY and independently verified by VN. The form captured key variables, including year of publication, incidence of in-hospital mortality, length of hospital and intensive care unit (ICU) stay, duration of mechanical ventilation, and the need for massive blood transfusion.

Two independent reviewers (BY and SJ) evaluated the trial bias using the Cochrane Collaboration Risk of Bias 2.0 tool. Risk was categorized as low, moderate, or high across domains, such as intervention deviations, missing outcome data, outcome measurement, result selection, and overall bias. Disagreements were resolved by the third author (VN).

Primary and secondary outcomes

The primary outcome was in-hospital mortality in trauma patients with and without hypocalcemia. The secondary outcomes included length of hospital stay, length of ICU stay, duration of mechanical ventilation, and the need for massive blood transfusion.

Heterogeneity was assessed using the I^2 statistic. All results were quantitatively analyzed using a random-effects model. For dichotomous variables, such as the incidence of in-hospital mortality and massive blood transfusion, the risk ratio (RR) with a 95% confidence interval (CI) was used. Continuous variables, such as length of hospital stay, length of ICU stay, and duration of mechanical ventilation, were presented as mean difference (MD) with the corresponding 95% CI. The median and interquartile range data were transformed into the estimated mean and standard deviation using the techniques described by Wan *et al*.[11] and Luo *et al*.[12] Statistical significance was set at $P < 0.05$. The results were assessed using forest plots and presented as RR or MD for the main and secondary outcomes.A funnel plot for meta-analysis assessed publication bias, and statistical analysis was conducted using Review Manager 5.4.

RESULTS

This review comprised 11 observational studies[13-23] of 647 screened publications involving 35,029 patients [Figure 1 and Table 1]. Among them, three[13,16,23] were prospective studies, one study[15] was ambispective, and seven[14,17-22] were retrospective observational studies. All studies defined hypocalcemia as a serum calcium level of <1 mmol/L. Five studies[13,15,17,20,22] further examined severe hypocalcemia, using <0.9 mmol/L[13,15,20,22] and <0.8 mmol/L[17] as cutoff values.

Risk of bias assessment

The risk of bias across individual studies is summarized in Figure 2. Three studies[15,21,23] demonstrated concerns related

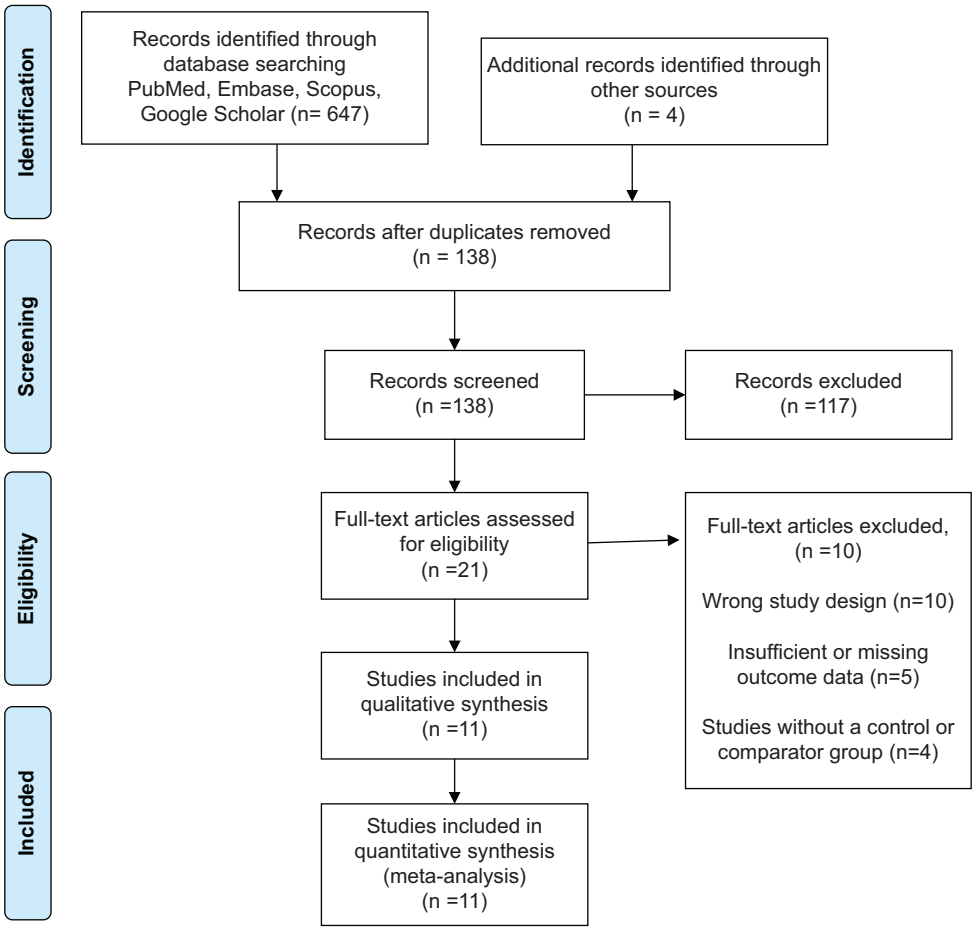

Figure 1: Preferred reporting items for systematic reviews and meta-analysis flow diagram. Green + low risk of bias, yellow: moderate risk of bias.

Table 1: Characteristics of the included studies.

Author (Year)	Country	Type	Sample (*n*)	Hypocalcemia cutoff (mmol/L)	Outcomes	Mortality	Patient characteristics
Vivien *et al* (2005)[13]	France	Prospective	212	<1.1 (severe <0.9)	Mortality	Increased	Consecutive severe trauma patients
Cherry *et al* (2006)[14]	USA	Retrospective	396	<1	Mortality, LOHS, LOICU, LOMV	Increased	Level I trauma patients
Choi and Hwang (2008)[15]	Korea	Ambispective	255	<1.1 (severe <0.88)	Mortality	Increased	Consecutive trauma patients
Magnotti *et al* (2011)[16]	USA	Prospective	591	<1	Mortality, MT	Increased	Trauma patients
Vasudeva *et al* (2020)[17]	Australia	Retrospective	226	<1.1 (severe <0.8)	Mortality, MT	Increased	Trauma patients with ISS >12
Vettorello *et al* (2022)[18]	Italy	Retrospective	798	<1.1	Mortality, MT, LOHS	Increased	Trauma patients with ISS ≥16
Helsloot *et al* (2023)[19]	Germany	Retrospective	30,183	<1.1	Mortality, LOHS, LOICU, MT	Increased	Major trauma with AIS ≥3
Davis *et al* (2022)[20]	USA	Retrospective	190	<1.1 (severe <0.9)	Mortality, LOHS, MT	No difference	Polytrauma with traumatic brain injury
Ciaraglia *et al* (2024)[21]	USA	Retrospective	1981	<1	Mortality, LOHS, MT	Increased	Traumatic injury with Level 1, 1α trauma activation
Liaud-Laval *et al* (2024)[22]	France	Retrospective	137	<1.2 (severe <0.9)	Mortality, LOICU, LOMV, MT	No difference	Major trauma
Mahanna Ahmed *et al* (2024)[23]	Egypt	Prospective	60	<1.1	Mortality, LOICU	Increased	Traumatic brain injury

LOHS: Length of hospital stay, LOICU: Length of intensive care unit stay, LOMV: Length of mechanical ventilation, MT: Massive transfusion, ISS: Injury severity score, AIS: Abbreviated injury scale

to confounding, participant selection bias, and measurement of outcomes.

Meta-analysis

In-hospital mortality

A total of 10 studies[13-21,23] with 33,818 patients in both groups found that patients in the hypocalcemia group had a significantly higher incidence of in-hospital mortality than those in the normocalcemia group (RR = 1.82, 95% CI: 1.52–2.17, $P < 0.00001$), with moderate heterogeneity between the studies ($I^2 = 40\%$, $P = 0.09$) [Figure 3a]. Four studies[13,15,20,22] presented data on severe hypocalcemia and showed a significantly higher incidence of mortality in the severe hypocalcemia group than in the hypocalcemic group (RR = 2.74, 95% CI: 1.92–3.90, $P < 0.00001$), with low heterogeneity between the studies ($I^2 = 22\%$) [Figure 3b]. A funnel plot of the studies included for the primary outcome, incidence of in-hospital mortality, to assess publication bias is shown in Supplementary Figure 1.

Length of hospital stay

Three studies[14,19,21] assessing the length of hospital stay showed no significant differences between the normocalcemia and hypocalcemia (RR = −0.37, 95% CI: −2.15, 1.41, $P = 0.68$), with considerable heterogeneity between studies ($I^2 = 91\%$) [Figure 3c].

Length of ICU stay

Five studies[14,19,21-23] assessed the length of ICU stay and found no significant difference between normocalcemia and hypocalcemia (RR = 0.49, 95% CI: −0.99–1.97, $P = 0.51$) with considerable heterogeneity between the studies ($I^2 = 93\%$) [Figure 4a].

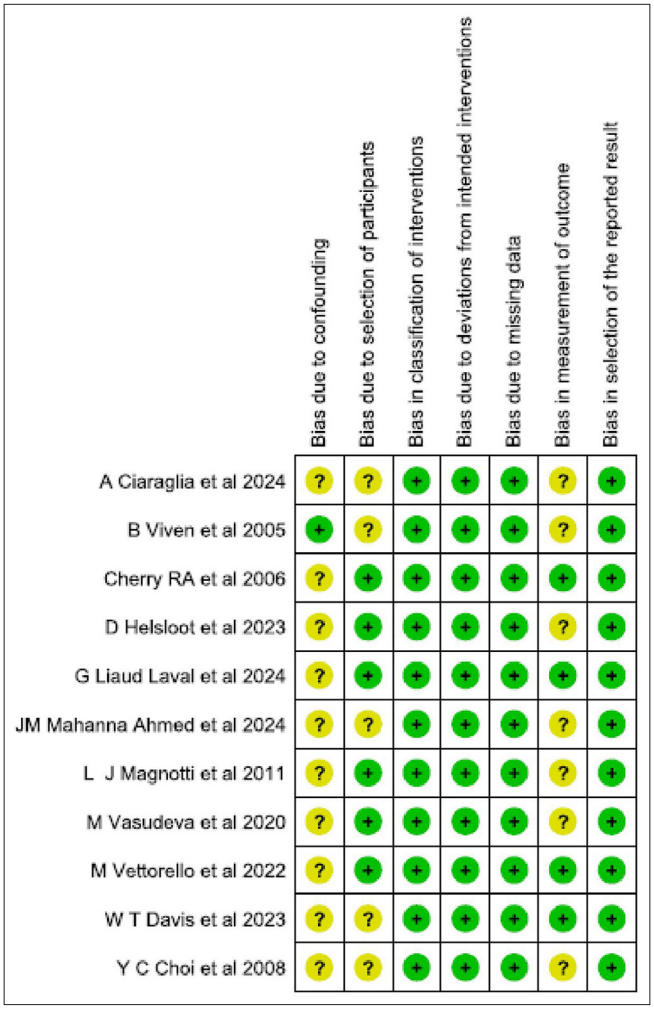

Figure 2: Risk Of Bias In Non-randomized Studies - of Interventions. (ROBINS-I) assessment for the included non-randomized cohort studies. Green + low risk of bias, yellow: Moderate risk of bias.

Massive transfusion

Five studies[16,17,19,21,22] presented data on massive transfusion that showed a significantly higher incidence of massive transfusion in the hypocalcemia group than in the normocalcemic group (RR = 2.40, 95% CI: 1.79–3.23, $P < 0.00001$), with substantial heterogeneity between the studies ($I^2 = 65\%$) [Figure 4b].

Duration of mechanical ventilation

There was no significant difference in the duration of ventilator days in two studies[14,21] between normocalcemia and hypocalcemia (RR = 0.00, 95% CI: −0.35–0.35, $P = 1.00$), with no heterogeneity between the studies ($I^2 = 0\%$) [Figure 4c].

DISCUSSION

In this study, we identified a significant association between hypocalcemia and increased mortality in trauma patients. The substantial increase in mortality observed among hypocalcemic patients suggests that calcium disturbances may exacerbate the physiologic stress of trauma, leading to worse outcomes. Our findings align with previous research demonstrating that calcium plays a critical role in coagulation, cardiovascular function, and cellular signaling, all of which are vital in the acute trauma setting.[24] Hypocalcemia induces both electrical and mechanical dysfunction in the heart. It prolongs the QT interval and precipitates dysrhythmias. Moreover, hypocalcemia can result in acute cardiovascular decompensation.[25] Calcium plays a crucial role in maintaining vascular tone; its deficiency may lead to hypotension. Desai *et al*.[26] observed a direct correlation between iCa levels and blood pressure, wherein hypocalcemic patients necessitated higher vasopressor support compared to normocalcemic ICU patients (41% vs. 14%).[26-28]

The severity of hypocalcemia (mild, moderate, or severe) correlates with increasing mortality with the highest in severe hypocalcemia. Hypocalcemia, especially severe hypocalcemia, appears to be a valuable prognostic indicator for mortality in trauma patients. This could help in risk stratification and resource allocation in trauma care. Hypocalcemia's impact is most pronounced in the early resuscitation phase, affecting acute survival rather than prolonged recovery. The strong association between hypocalcemia and mortality suggests that calcium levels could be an important therapeutic target. However, further research is needed to determine if calcium supplementation improves outcomes.

Our results also indicate that hypocalcemia is associated with an increased need for massive transfusion. This finding is consistent with the pathophysiology of trauma-induced coagulopathy, wherein citrate anticoagulants in transfused blood products chelate calcium, potentially exacerbating hypocalcemia. Calcium is a key cofactor in the coagulation cascade, and hypocalcemia can worsen trauma-induced coagulopathy, increasing the risk of uncontrolled bleeding. Hypocalcemia contributes to coagulopathy, hypotension, and cardiac dysfunction, exacerbating hemorrhagic shock and increasing mortality. Since the role of calcium is important in coagulation cascade activation, hypocalcemia may contribute to continued bleeding and increase transfusion requirements, creating a cycle that further depletes calcium levels. These findings highlight the potential benefit of routine calcium monitoring and early supplementation in trauma patients requiring large-volume

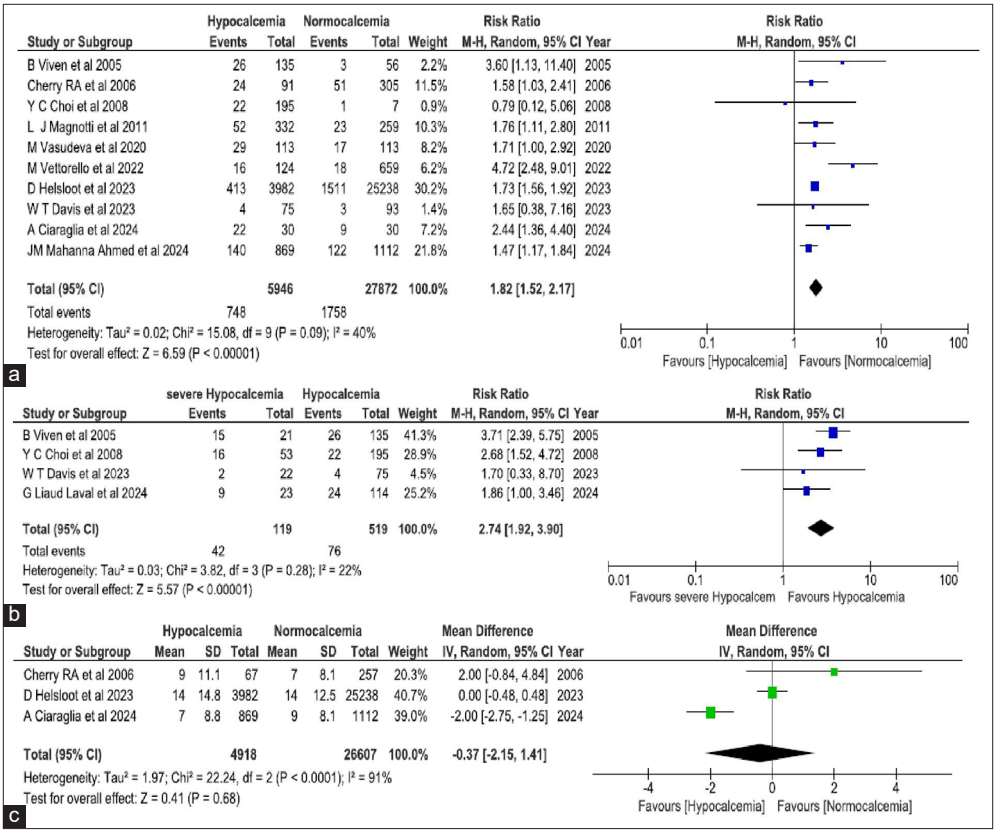

Figure 3: Forest plot for incidence of mortality, (a) hypocalcemia versus normocalcemia, (b) severe hypocalcemia versus hypocalcemia, (c) length of hospital stay. CI: confidence interval, M-H: Mantel-Haenszel, IV: Inverse variance, SD: Standard deviation.

resuscitation. Patients who received pre-hospital blood transfusions exhibited marginally lower initial iCa levels compared to those who did not undergo transfusion.[29] The link between hypocalcemia and massive transfusion highlights the complex interplay between calcium homeostasis and coagulation in trauma. This relationship warrants further investigation to optimize transfusion protocols.

Despite the significant differences in mortality and transfusion requirements, we did not observe significant differences in ICU stay, hospital stay, or ventilator days between hypocalcemic and normocalcemic patients. This finding suggests that while hypocalcemia is a critical early predictor of mortality, surviving patients may achieve similar recovery trajectories irrespective of initial calcium levels. The lack of difference in these secondary outcomes could be due to aggressive correction of hypocalcemia during ICU admission or the influence of other factors, such as the severity of associated injuries and overall resuscitation strategies. Future studies should explore whether early calcium supplementation can mitigate these adverse outcomes in trauma patients. It is necessary to create and develop standardized protocols for calcium monitoring and supplementation in trauma patients in light of the observations in our study.

Our study has several limitations. First, the observational and retrospective nature of the included studies limits our ability to infer causation and the heterogeneity observed in some outcomes. In addition, factors such as the lack of consistency in the definition of hypocalcemia, timing of calcium measurement, pre-existing conditions, and concurrent treatments were not consistently accounted for across studies. Further prospective studies are needed to establish standardized calcium monitoring and supplementation protocols to improve trauma outcomes.

Future research should focus on prospective studies to establish causality, investigate the optimal timing and dosing of calcium supplementation, and explore the mechanisms linking hypocalcemia to adverse outcomes in trauma. In addition, studies examining the impact of calcium correction on survival and other clinical outcomes are needed to guide evidence-based management strategies.

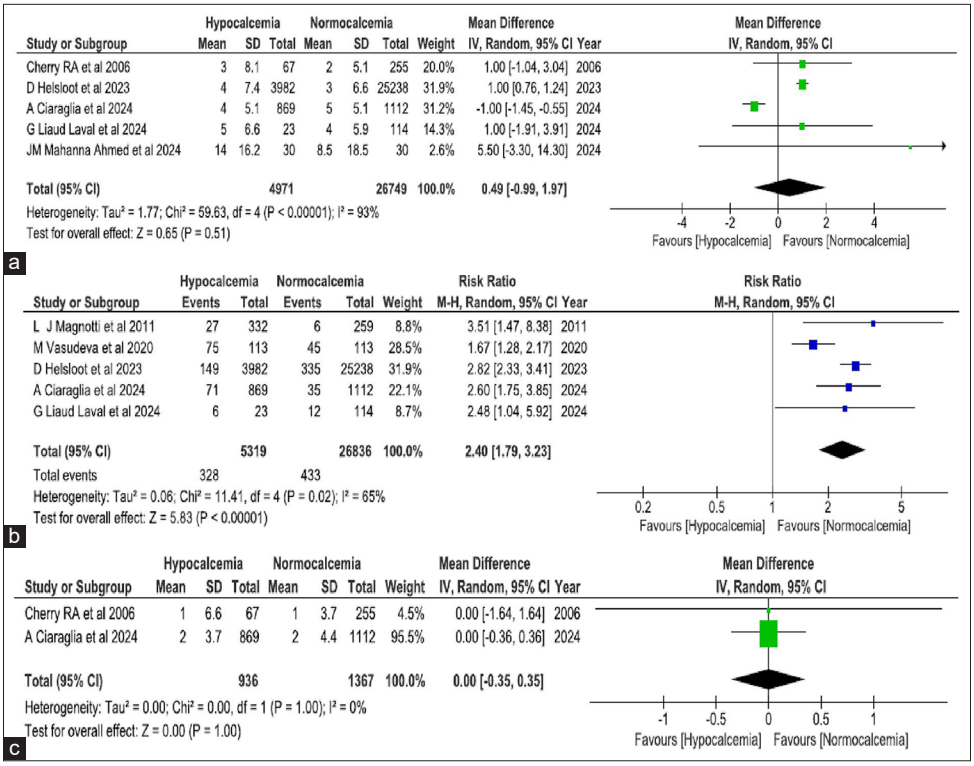

Figure 4: Forest plot for (a) length of ICU stay, (b) massive transfusion, (c) length of ventilator days. CI: confidence interval, M-H: Mantel-Haenszel, IV: Inverse variance, SD: Standard deviation.

CONCLUSION

This meta-analysis provides strong evidence that hypocalcemia is associated with increased mortality and massive transfusion requirements in trauma patients. These findings highlight the potential of hypocalcemia as both a prognostic indicator and therapeutic target in trauma care. However, further research is needed to establish causality and develop evidence-based management strategies for hypocalcemia in trauma patients.

Authors' contributions: BY: Conceptualization, search strategy, study selection, data extraction and analysis, manuscript drafting and editing. SJ: Search strategy, study selection, risk of bias assessment, and editing. VN: Search strategy, study selection, data extraction and analysis, risk of bias assessment, AS: Conceptualization, study selection, risk of bias assessment, and manuscript drafting and editing.

Ethical approval: Institutional review board approval is not required.

Declaration of patient consent: Patient's consent is not required as there are no patients in this study.

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