This article has been accepted for publication in ARCHDISCHILD following peer review.
The definitive copyedited, typeset version is available online at
10.1136/archdischild-2023-326576

Paediatric Trauma and hypocalcaemia: a systematic review

Mary-Beth Toner, Michael Coffey, Ulugbek Nurmatov, Stephen Mullen

Abstract:

Background: Trauma is a leading cause of mortality and morbidity in children worldwide. While adult studies have demonstrated hypocalcaemia's association with adverse outcomes, its impact on paediatric trauma patients remains understudied. This systematic review aims to investigate current evidence into the prevalence, clinical implications, and associations of hypocalcaemia in paediatric trauma.

Methods: A comprehensive literature search was conducted searching four databases, grey literature and additional sources for original studies looking at outcomes for paediatric trauma patients with ionised calcium measurements before blood product administration. Exclusion criteria comprised studies which included patients with blood products administration prior to calcium measurement, case reports, case series, reviews, and papers not available in English. The review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42023432473. Data extraction was performed on included papers and quality assessment performed using Newcastle-Ottawa scale.

Results: Of 779 initial studies, two studies met inclusion criteria for detailed analysis. Both retrospective-cohort studies, originating in Israel, and collectively included 568 patients. Hypocalcaemia incidence ranged from 5.3% to 19.8%. Although trends towards increased

mortality, blood transfusion requirements, and prolonged hospital stays were observed in hypocalcaemic patients, statistical significance was not consistently achieved.

Conclusion: Hypocalcaemia in paediatric trauma appears reduced in incidence compared to adult populations. Limited available studies suggest potential associations with adverse outcomes, although most were not statistically significant. Studies had small patient numbers, necessitating further prospective research to facilitate a clearer understanding. Insights from such studies can guide patient management and improve outcomes in this vulnerable population.

What is already known on this topic – ***summarise the state of scientific knowledge on this subject before you did your study and why this study needed to be done***

Hypocalcaemia in trauma is of emerging interest as we understand more about the complex interplay of factors such as acidosis, hypothermia and coagulopathy leading to a proposed 'diamond of death'. There have been multiple studies examining this relationship in adult populations but to date we do not know the prevalence of hypocalcaemia in paediatric trauma patients.

What this study adds – ***summarise what we now know as a result of this study that we did not know before***

Our review identified two studies, both retrospective. Within these studies the prevalence of hypocalcaemia in paediatric trauma patients was between 5.3 and19.8%. This is significantly lower than what has been previously studied in similar adult populations which has documented incidence as high as 74%.

How this study might affect research, practice or policy – ***summarise the implications of this study***

Our findings underscore a notable difference in the incidence of hypocalcaemia in paediatric trauma compared to the prevalence in adult populations, there were general trends toward mortality, increased length of hospital / PICU stay or need for blood transfusion but further studies with greater patient numbers are required to fully assess the impact of hypocalcaemia in this vulnerable patient group.

Introduction

Trauma is the leading cause of mortality and morbidity for children globally.[1] Haemorrhagic shock in children has a 30-day mortality of up to 50%, contrasting with 20-25% in adult patients.[2] There is no scientific consensus to explain this discrepancy, but theories include reduced absolute blood volume in children, variation in mechanism and pattern of injury, and physiological differences in response to trauma. Effective trauma management of haemorrhagic shock relies on timely resuscitation strategies, including blood product administration and haemostatic interventions.[2, 3] Recent evidence has emerged on the role hypocalcaemia in adult trauma patients. [3, 4, 5, 6] The potential significance has led to suggestion of an amendment to the lethal trauma triad to give hypocalcaemia a recognised place alongside, hypothermia, acidosis, and coagulopathy, proposing the 'lethal diamond'.[7, 8]

In trauma, calcium reduction can occur through a variety of mechanisms including haemorrhage, impaired calcium homeostasis, intracellular shifts, lactate chelation and iatrogenic haemodilution.[3, 9] Calcium has a role in coagulation cascades, influencing the ability of blood to clot effectively.[10, 11] As calcium is utilised for coagulation cascades ionised calcium levels decline which precipitates acidosis and worsens coagulopathy.[8]

Administration of citrated blood products to counteract coagulopathy and haemorrhage worsens hypocalcaemia as citrate chelates calcium, reducing ionised calcium levels.[11,12] Hypothermia and hypoperfusion in trauma can worsen this phenomenon due to a reduction in citrate metabolism by the liver. Additionally, hypocalcaemia impairs cardiac contractility therefore reduced calcium levels can lead to compromised cardiac function, which in turn contributes to hypotension, underscoring the pervasive influence of hypocalcaemia in trauma.[10]

Whilst it is well established that hypocalcaemia can be driven by large volumes of citrate containing blood products, adult studies have suggested that there is a high incidence of hypocalcaemia present prior to any resuscitation.[13] The importance of addressing hypocalcaemia in this context becomes apparent when we consider that adult studies have shown its association with pre-hospital hypotension, the need for blood transfusion, and increased mortality. [5,6,7,14] Studies also suggests that the degree of initial hypocalcaemia may correlate with mortality and need for blood transfusion. [15,16, 17, 18]

Despite evidence for the critical role of calcium in trauma, the rate and impact of hypocalcaemia in the paediatric population has not been subjected to thorough investigation. Existing research primarily focuses on adults, leaving a substantial gap in our understanding of the significance in paediatric patients. Considering this knowledge gap, this systematic review aims to address the question: In paediatric trauma patients, what is the incidence of hypocalcaemia and how does hypocalcaemia impact outcomes compared to those with normocalcaemia especially with regard to requirement of bloods products, length of stay and mortality? By synthesising existing evidence, we aim to provide a comprehensive overview

of the current state of knowledge in this field and identify areas where further research is needed.

Methods

Search strategy and selection criteria

We searched four databases including Embase, Medline, Scopus, and Web of Science for studies published from inception until 31st May 2023. The search was conducted on 1st June 2023. In August 2023, we conducted a grey literature search, manually reviewed reference lists, and contacted international experts in this field for additional papers or research.

A Medline search strategy was initially developed (see Appendix A). Studies were eligible for inclusion if they included paediatric (below 18 years of age) trauma patients with an ionised calcium measurement prior to any blood product transfusion. Studies were excluded if they included patients who had received blood products before initial calcium measurement or were case reports, case series, reviews or not available in English.

Study selection

Study titles and abstracts were independently checked by two reviewers MBT and MC according to previously detailed selection criteria. Duplicates were removed. Discrepancies were resolved through discussion. A third reviewer SM was available if needed. Full text articles were obtained for potentially eligible studies, which were independently reviewed, and studies which did not meet the described criteria were removed.

Data extraction and quality assessment.

Relevant data was manually extracted from each paper with customised data extraction forms created using Microsoft Excel. These were tested and approved by the group prior to data extraction. For non-controlled/retrospective studies, we assessed quality using the Newcastle-Ottawa Score. [19]

Registration and reporting

The systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) CRD42023432473: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023432473

Within this protocol we had anticipated assessing risk of bias using the Cochrane ROB tool. However, this approach was amended during the review as both eligible studies were retrospective cohort studies, and the Newcastle-Ottawa score provided a better-quality assessment.

Results

Our initial database searches of Embase, Medline, Scopus, and Web of Science yielded 779 studies (Figure 1).[20] After removing duplicates (172), 607 unique articles were identified and reviewed by title and abstract. 603 articles were excluded following initial review, these articles did not meet inclusion criteria or were not relevant, i.e., were not related to a paediatric population, or hypocalcaemia in the setting of trauma. We identified 4 articles that met initial inclusion criteria. These 4 articles underwent full-text evaluation. 2 were excluded as they included patients who had received blood products prior to first calcium measurement. No new articles were identified from grey literature search, reference review or

following contact with experts. Our analysis therefore focused on 2 studies - Epstein 2022 and Gimelraikh 2022 (Table 1). [21, 22]

Table 1 showing study characteristics.

First Author, y	Country	Study Design	Sample Size	Median Age, y (IQR)	Male, %	Definition Hypocalcaemia
Epstein et al, 2022 [16]	Israel	Retrospective cohort Single trauma centre Adult and paediatric	N = 457	11 (6-15)	78.3	Severe hypocalcaemia iCa <1mmol/L Mild Hypcalcaemia iCa 1mmol/L - 1.1mmol/L Normal Ca^{2++} ≥1.1mmol/L
Gimelraikh et al, 2022 [17]	Israel	Retrospective cohort Single trauma centre Paediatric Hospital	N= 111	11 (4-15)	78	Severe hypocalcaemia iCa <1mmol/L Hypcalcaemia iCa 1mmol/L - 1.16mmol/L Normal Ca^{2++} 1.16mmol/L - 1.31mmol/L

Epstein et al. 2022, a retrospective cohort study, conducted in a level 1 trauma centre in Israel. There were 457 participants, with median age of 11 years, 78.3% male. Classification of hypocalcaemia was based on ionised calcium (iCa) levels: defining severe hypocalcaemia (iCa < 1 mmol/L), mild hypocalcaemia (iCa 1 mmol/L - 1.1 mmol/L), and normal calcium (iCa≥ 1.1 mmol/L).[21]

Gimelraikh et al. 2022, a retrospective cohort study in a level 1 paediatric trauma centre in Israel. There were 111 participants, with median age of 11 years, 78% male. Classification of hypocalcaemia was based on iCa levels: defining severe hypocalcaemia (iCa < 1 mmol/L), hypocalcaemia (iCa 1 mmol/L - 1.16 mmol/L), and normal calcium (iCa 1.16 mmol/L - 1.31 mmol/L).[22]

Study quality

Quality assessment was accomplished using the Newcastle-Ottawa-Score (NOS) as summarised in Table 2.[19] Studies were evaluated on three domains, selection of the study groups; comparability of the groups; and ascertainment of the outcome of interest, with a

maximum score of nine. We assessed both studies to be of good quality based on this evaluation.

Table 2. Quality assessment of included studies using Newcastle-Ottawa Score

Study	Selection			Comparability			Outcome		
	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for age and gender	Study controls for injury characteristics	Assessment of outcome	Follow up long enough	Adequacy of follow up
Epstein	*	*	*		*	*	*	*	
Gimelraikh	*	*	*		*	*	*	*	

Frequency of hypocalcaemia

In Epstein et al. 24 individuals (5.2%) presented with hypocalcaemia, including three (0.7%) cases of severe hypocalcaemia. Gimelraikh et al. reported 22 (19.8%) hypocalcaemic cases including three (2.7%) cases of severe hypocalcaemia. Epstein et al. reported that the hypocalcaemic group was statistically older and exhibited higher Injury Severity Score (ISS) compared to their normocalcaemic counterparts.

Both studies shared a common set of outcome measures, encompassing in-hospital mortality, length of hospital stay, length of Paediatric Intensive Care Unit (PICU) stay, and requirement for blood products. We will discuss these outcome measures below.

Blood transfusion

Both studies included blood transfusion as an outcome measurement, though differed in how this was defined. Epstein et al. as need for blood transfusion in ED and Gimelraikh et al. as blood transfusion within first 48 hours of hospital admission.

Hypocalcaemia was associated with increased incidence of blood transfusion (29.2% vs. 6.5%, $p < .001$) by Epstein et al. On performance of logistic regression model taking account ISS, paediatric shock index, lactate, and calcium as independent variables, patients with hypocalcaemia had a five-fold increase in blood transfusion [odds ratio 5.44 (95% CI: 1.44–20.58, $p = .01$)].

Gimelraikh et al reported an increase in hypocalcaemic patients requiring blood transfusion (27.3% vs 20.6%, p=0.67) compared with normocalcaemic patients but did not attain statistical significance.

Mortality

Both studies reported a trend towards increased mortality in hypocalcaemic participants compared to normocalcaemic participants, although neither demonstrated statistical significance. Epstein et al. showed more than a two-and-a-half-fold increase in in-hospital mortality between the hypocalcaemic and normocalcaemic groups (8.3% vs. 3.0%, $p = 0.4$). Likewise, in the Gimelraikh et al. study, the mortality rate for the hypocalcaemia group was 9-fold higher than the normocalcaemic group (9.9% vs. 1.1% p=0.18).

Length of Hospital and PICU Stay

Epstein et al. showed higher length of hospital stay which was not statistically significant. There was no difference in length of PICU stay in the hypocalcaemic group (Table 3). Gimelraikh et al, showed both increased length of hospital and length of PICU stay in the hypocalcaemic group, although these results were not statistically significant.

Table 3 Summary of key outcomes for included studies.

First Author, y	Hypocalcaemia, % (no of patients/total)	Mortality, % (no of patients/total) Hypocalcaemia vs. normocalcaemia	Need for Transfusion, % (no of patients/total) Hypocalcaemia vs. normocalcaemia	Length of hospital stay, d Hypocalcaemia vs. normocalcaemia	Length of PICU stay, d Hypocalcaemia vs. normocalcaemia

Epstein et al, 2022 [21]	Severe: 0.7% (3/457) Mild: 4.6% (21/457) Total: 5.3% (24/457)	8.3% (2/24) vs 3% (13/433) P = 0.4	29.2% (7/24) vs 6.5% (28/433) ***P <0.001***	7.5 vs 6 P = 0.43	2 vs 2 P = 0.67
Gimelraikh et al, 2022 [22]	Severe: 2.7% (3/111) Total: 19.8% (22/111)	9.1% (2/22) vs 1.1% (1/89) P = 0.18	27.3% (6/22) vs 20.2% (18/89) P = 0.67	8 vs 6 P = 0.36	3 vs 2 P = 0.43

Other factors

Both Epstein et al. and Gimelraikh et al. found a statistically insignificant higher Prothrombin Time (PT), ISS and reduced Glasgow Coma Scale in their hypocalcaemic cohort.

Discussion

Our systematic review aimed to critically assess and synthesise existing literature on the topic of hypocalcaemia in paediatric trauma patients. Despite a wide literature search for research in this area, there was a paucity of papers available. Through comprehensive analysis of two distinct retrospective studies conducted by Epstein et al. (2022) and Gimelraikh et al. (2022), insights into prevalence, clinical implications, and potential associations of hypocalcaemia in this specific population were elicited.

The prevalence of hypocalcaemia ranged from 5.3-19.8%. Hypocalcaemia in paediatric trauma patients was associated with adverse outcomes, including an increased need for blood transfusion with a trend towards increased mortality and length of stay. However, statistical significance was not consistently achieved. This is different than what has been documented in adult studies, which have reported incidence of hypocalcaemia between 23-74% in adult trauma patients. Adult studies have also shown statistically significant associations between hypocalcaemia and mortality. [3,6,14]

No specific age adjustment for calcium measurements is available for paediatric patients, however, there is an acceptance that calcium levels are lower at birth and peak between the ages of 15 to 25.[23] No extensive literature is available on the prevalence of hypocalcaemia in the general healthy paediatric populations however there is evidence showing that hypocalcaemia is prevalent in critically unwell children and close monitoring with correction beneficial.[24, 25, 26] Interestingly, parallel to our findings in this review that the incidence of hypocalcaemia in paediatric trauma patients is lower than that reported in adult patients the same is mirrored in the incidence of hypocalcaemia in critically unwell patients. Evidence shows that 50-88% of critically unwell adult patients have a low ionised calcium [27] whereas literature focusing on critically unwell children shows a lower incidence of 14-17.9%. [25, 26]

In one study of critically ill non-trauma children, there was a statistically significant association between hypocalcaemia and mortality, although, it was noted that the hypocalcaemia cohort, had higher severity of illness, often secondary to sepsis and no causation between hypocalcaemia and mortality was suggested by the authors.[24] Similarly, a recent study published in August 2023 looking at hypocalcaemia in the critically ill adult, remarked on a statistically significant association between hypocalcaemia and mortality. The authors proposed that hypocalcaemia was a response to clinical illness and reflected the extent of cell death and disease severity as opposed to the causative factor of clinical deterioration.[27]

In our review we aimed to ascertain the prevalence of transfusion-independent hypocalcaemia on admission to hospital in paediatric trauma. A study assessing transfusion practices in paediatric trauma reported the incidence of hypocalcaemia in adolescents between 41-46%. This study was excluded from our review as it assessed hypocalcaemia as a

secondary outcome or complication of transfusion.[28] We excluded two studies which included patients who had blood products transfused prior to first calcium measurement. Prevalence of hypocalcaemia in these studies were 46.5% and 47.9%.[23, 29] These results may have been confounded by the effect of citrate containing blood products on calcium.

Limitations

This systematic review was limited by paucity of eligible studies. Only two studies were identified, both had relatively low numbers of patients with hypocalcaemia and raises the question whether the studies were of sufficient power to detect relevant outcomes. Due to several key inherent difference between the two studies, relatively small sample sizes and limitations in terms of bias performing a meaningful meta-analysis was not possible.

Although retrospective studies contribute valuable insights to research, they inherently possess limitations that warrant consideration. Both studies relied on trauma registries for data collection, patients inadvertently not included in these registries may have been a potential source for selection bias. Additionally, excluding patients transferred from other facilities may have skewed analysis, the 111 patients included in Gimelraikh et al. are considerably outnumbered by the 1136 excluded due to being transferred from other facilities. Excluding these critically injured children might have affected overall understanding of outcomes. Retrospective studies are more vulnerable to confounding variables that can distort measured outcomes. The extended duration of data collection in these studies raises the possibility that changes in patient management over time may have influenced outcomes. Both studies identified originated from Israel potentially limiting the application of their findings to other paediatric populations.

Our review is subject to potential publication bias, studies which did not find association between hypocalcaemia and outcomes, such as need for blood transfusion, mortality, or prolonged length of stay in paediatric trauma patients, may not have been published. Interestingly, it appears that this area of interest is emerging, all four papers in our full-text review were published between 2021 and 2023.

Future Research

We would recommend further studies on the role of hypocalcaemia in paediatric trauma patients, initially with a large multi-centre prospective or retrospective study reporting incidence and outcomes. Consideration should be given assessing the importance of hypocalcaemia pre and post transfusion and impact on outcomes. Finally, we would recommend a controlled trial to ascertain whether treatment of hypocalcaemia in paediatric trauma patients impacts outcome. Such a trial may prove difficult due to ethical approval and the large number of patients required given the low incidence of hypocalcaemia reported in our review.

Conclusion

In conclusion, our findings underscore a notable difference in the incidence of hypocalcaemia in paediatric trauma compared to the prevalence in adult populations. We cannot make definitive statements regarding the association between hypocalcaemia and critical outcomes such as increased mortality, blood transfusion requirements, coagulopathy, or the length of hospital or PICU stay. We acknowledge that hypocalcaemia has been identified as an independent predictor of mortality in adult populations and in critically ill paediatric patients, in addition to the role it plays in the intricate interplay of coagulopathy, acidosis, hypothermia, and cardiac contractility.

As such it is important to remain mindful of the potential impact of hypocalcaemia in paediatric trauma patients. We advocate for further prospective studies, encompassing larger and more diverse patient populations, to provide clearer understanding of the relationship between hypocalcaemia and critical outcomes. Such insights will guide the optimisation of patient management and ultimately improve patient outcomes.

We believe that, to date, this is the most detailed and comprehensive systematic review undertaken to assess the subject of hypocalcaemia in trauma in a paediatric population. We have aimed to present a high-quality review to the highest international standards, using transparent methodology, exhaustive literature search, including grey literature and up-to-date insights to deliver an authoritative stance on the current knowledge in this area.

Acknowledgement

The authors would like to thank Richard Fallis for his advice and support as Subject Librarian for Medicine, Dentistry and Biochemical Sciences Medical Library, Queen's University Belfast. His contribution to our literature searches was invaluable.

The authors would also like to acknowledge successful submission of a poster presentation based upon this work entitled Calcium Conundrum: Unravelling the role of hypocalcaemia in paediatric trauma to the Irish Paediatric Emergency Medicine conference 20-21st March 2024.

Competing Interests

None declared.

Funding Statement

This systematic review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributorship Statement

SM initially conceptualised and designed the review protocol. MBT and MC conducted literature search, performed data extraction and risk of bias assessments. UN had significant input into data analysis. MBT and MC had a primary responsibility for drafting the initial manuscript. SM and UN supervised the review process, critically reviewing and revising the article. All authors contributed to (and agreed on) the final version. SM is the guarantor of the work.

References

1) GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10;385(9963):117-71. doi: 10.1016/S0140-6736(14)61682-2. Epub 2014 Dec 18. PMID: 25530442; PMCID: PMC4340604.
2) Russell RT, Bembea MM, Borgman MA, Burd RS, Gaines BA, Jafri M, Josephson CD, Leeper CM, Leonard JC, Muszynski JA, Nicol KK, Nishijima DK, Stricker PA, Vogel AM, Wong TE, Spinella PC. Pediatric traumatic hemorrhagic shock consensus conference research priorities. J Trauma Acute Care Surg. 2023 Jan 1;94(1S Suppl 1):S11-S18. doi: 10.1097/TA.0000000000003802. Epub 2022 Oct 7. PMID: 36203242; PMCID: PMC9805504.
3) Vasudeva, Mayank MBBS; Mathew, Joseph K. MBBS, FACEM; Groombridge, Christopher MBBS, FACEM; Tee, Jin W. MD, FRACS; Johnny, Cecil S. MBBS, FACEM; Maini, Amit MBBS, FACEM; Fitzgerald, Mark C. MD, FACEM. Hypocalcemia in trauma patients: A systematic review. Journal of Trauma and Acute Care Surgery 90(2):p 396-402, February 2021. | DOI: 10.1097/TA.0000000000003027
4) Choi, Y. C., & Hwang, S. Y. (2008). The Value of Initial Ionized Calcium as a Predictor of Mortality and Triage Tool in Adult Trauma Patients. *Journal of Korean Medical Science*, *23*(4), 700-705. https://doi.org/10.3346/jkms.2008.23.4.700
5) Imamoto T, Sawano M Effect of ionized calcium level on short-term prognosis in severe multiple trauma patients: a clinical study Trauma Surgery & Acute Care Open 2023;8:e001083. doi: 10.1136/tsaco-2022-001083
6) Magnotti, Louis J. MD; Bradburn, Eric H. DO; Webb, David L. MD; Berry, Stepheny D. MD; Fischer, Peter E. MD, MS; Zarzaur, Ben L. MD, MPH; Schroeppel, Thomas J. MD; Fabian, Timothy C. MD;

Croce, Martin A. MD. Admission Ionized Calcium Levels Predict the Need for Multiple Transfusions: A Prospective Study of 591 Critically Ill Trauma Patients. The Journal of Trauma: Injury, Infection, and Critical Care 70(2):p 391-397, February 2011. | DOI: 10.1097/TA.0b013e31820b5d98

7) Wray, J. P., Bridwell, R. E., Schauer, S. G., Shackelford, S. A., Bebarta, V. S., Wright, F. L., Bynum, J., & Long, B. (2021). The diamond of death: Hypocalcemia in trauma and resuscitation. *The American Journal of Emergency Medicine*, *41*, 104-109. https://doi.org/10.1016/j.ajem.2020.12.065
8) Ditzel RM Jr, Anderson JL, Eisenhart WJ, Rankin CJ, DeFeo DR, Oak S, Siegler J. A review of transfusion- and trauma-induced hypocalcemia: Is it time to change the lethal triad to the lethal diamond? J Trauma Acute Care Surg. 2020 Mar;88(3):434-439. doi: 10.1097/TA.0000000000002570. PMID: 31876689.
9) DeBot M, Sauaia A, Schaid T, Moore EE. Trauma-induced hypocalcemia. Transfusion. 2022 Aug;62 Suppl 1:S274-S280. doi: 10.1111/trf.16959. Epub 2022 Jun 24. PMID: 35748689
10) Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, Schöchl H, Hunt BJ, Sauaia A. Trauma-induced coagulopathy. Nat Rev Dis Primers. 2021 Apr 29;7(1):30. doi: 10.1038/s41572-021-00264-3. Erratum in: Nat Rev Dis Primers. 2022 Apr 22;8(1):25. PMID: 33927200; PMCID: PMC9107773.
11) https://criticalcarenow.com/dont-forget-the-calcium-in-trauma/
12) Giancarelli A, Birrer KL, Alban RF, Hobbs BP, Liu-DeRyke X. Hypocalcemia in trauma patients receiving massive transfusion. J Surg Res. 2016 May 1;202(1):182-7. doi: 10.1016/j.jss.2015.12.036. Epub 2015 Dec 30. PMID: 27083965.
13) Byerly S, Inaba K, Biswas S, Wang E, Wong MD, Shulman I, Benjamin E, Lam L, Demetriades D. Transfusion-Related Hypocalcemia After Trauma. World J Surg. 2020 Nov;44(11):3743-3750. doi: 10.1007/s00268-020-05712-x. Epub 2020 Jul 30. PMID: 32734451; PMCID: PMC7391918.
14) Vivien, Benoît, et al. "Early hypocalcemia in severe trauma." *Critical care medicine* 33.9 (2005): 1946-1952.
15) Imamoto, Toshiro, and Makoto Sawano. "Effect of ionized calcium level on short-term prognosis in severe multiple trauma patients: a clinical study." *Trauma Surgery & Acute Care Open* 8.1 (2023): e001083.
16) Helsloot D, Fitzgerald M, Lefering R, Verelst S, Missant C; TraumaRegister DGU. Trauma-induced disturbances in ionized calcium levels correlate parabolically with coagulopathy, transfusion, and mortality: a multicentre cohort analysis from the TraumaRegister DGU®. Crit Care. 2023 Jul 6;27(1):267. doi: 10.1186/s13054-023-04541-3. PMID: 37415194; PMCID: PMC10324195.
17) Vettorello, M.; Altomare, M.; Spota, A.; Cioffi, S.P.B.; Rossmann, M.; Mingoli, A.; Chiara, O.; Cimbanassi, S. Early Hypocalcemia in Severe Trauma: An Independent Risk Factor for Coagulopathy and Massive Transfusion. *J. Pers. Med.* 2023, *13*, 63. https://doi.org/10.3390/jpm13010063
18) Cherry RA, Bradburn E, Carney DE, Shaffer ML, Gabbay RA, Cooney RN. Do early ionized calcium levels really matter in trauma patients? J Trauma. 2006 Oct;61(4):774-9. doi: 10.1097/01.ta.0000239516.49799.63. PMID: 17033540.
19) Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp,
20) Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230
21) Epstein D, Ben Lulu H, Raz A, Bahouth H. Admission hypocalcemia in pediatric major trauma patients-An uncommon phenomenon associated with an increased need for urgent blood transfusion. Transfusion. 2022 Jul;62(7):1341-1346. doi: 10.1111/trf.16936. Epub 2022 May 31. PMID: 35638746.
22) Gimelraikh Y, Berant R, Stein M, Berzon B, Epstein D, Samuel N. Early Hypocalcemia in Pediatric Major Trauma: A Retrospective Cohort Study. Pediatr Emerg Care. 2022 Oct 1;38(10):e1637-e1640. doi: 10.1097/PEC.0000000000002719. Epub 2022 Apr 12. PMID: 35413033
23) Cornelius BG, Clark D, Williams B, Rogers A, Popa A, Kilgore P, Cvek U, Trutschl M, Boykin K, Cornelius A. A retrospective analysis of calcium levels in pediatric trauma patients. Int J Burns Trauma. 2021 Jun 15;11(3):267-274. PMID: 34336394; PMCID: PMC8310872.
24) Cardenas-Rivero N, Chernow B, Stoiko MA, Nussbaum SR, Todres ID. Hypocalcemia in critically ill children. J Pediatr. 1989 Jun;114(6):946-51. doi: 10.1016/s0022-3476(89)80435-4. PMID: 2786063.
25) Broner, CYNTHIA W., et al. "Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients." *Critical care medicine* 18.9 (1990): 921-928.
26) Gauthier, Bernard, et al. "Hypocalcemia and hypercalcitoninemia in critically ill children." *Critical care medicine* 18.11 (1990): 1215-1219.

27) Melchers, Max, and Arthur Raymond Hubert van Zanten. "Management of hypocalcaemia in the critically ill." *Current Opinion in Critical Care* 29.4 (2023): 330-338.
28) Livingston MH, Singh S, Merritt NH. Massive transfusion in paediatric and adolescent trauma patients: incidence, patient profile, and outcomes prior to a massive transfusion protocol. Injury. 2014 Sep;45(9):1301-6. doi: 10.1016/j.injury.2014.05.033. Epub 2014 Jun 5. PMID: 24950797.
29) Ciaraglia A, Lumbard D, Deschner B, Barry L, Braverman M, Eastridge B, Stewart R, Liao L, Jenkins D, Nicholson S. The effects of hypocalcemia in severely injured pediatric trauma patients. J Trauma Acute Care Surg. 2023 Sep 1;95(3):313-318. doi: 10.1097/TA.0000000000003902. Epub 2023 Feb 13. PMID: 36787433.

Figures

Figure 1 showing PRISMA 2020 flow diagram.