Journal of Intensive Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Parenteral calcium administration and outcomes in critically ill patients with hypocalcemia: A retrospective cohort study

Max Melchers[1,2], Hanneke Pierre Franciscus Xaverius Moonen[1,2], Tessa Maria Breeman[1], Sjoerd Hendrika Willem van Bree[1], Arthur Raymond Hubert van Zanten[1,2,*]

[1] Department of Intensive Care Medicine, Gelderse Vallei Hospital, 6761 EP, Ede, The Netherlands
[2] Division of Human Nutrition and Health, Wageningen University & Research, HELIX (Building 124), 6708 WE, Wageningen, The Netherlands

ARTICLE INFO

Managing Editor: Jingling Bao/Zhiyu Wang

Keywords:
Intensive care
Sepsis
Septic shock
Calcium
Hemodynamics

ABSTRACT

Background: Hypocalcemia is common among patients admitted to the intensive care unit (ICU). The administration of calcium in critically ill patients with hypocalcemia remains debated, as previous data on outcomes are conflicting, and subgroup analyses are lacking. This study aimed to investigate the association between parenteral calcium administration and clinical outcomes in critically ill patients who had hypocalcemia with and without sepsis.

Methods: This retrospective cohort study included individuals who developed hypocalcemia during the first 7 days of admission to a mixed medical-surgical adult ICU at a University-affiliated teaching hospital. Patients who were not receiving renal replacement therapy, and were admitted to the ICU for at least 48 h between October 1, 2015 and September 1, 2020, were included. The primary outcomes included all-cause 180-day mortality and time-to-shock resolution. Subgroup analyses were conducted in sesis and nonsepsis patients with mild or moderate hypocalcemia, based on median splits. Proportional hazard regression analyses were performed to identify the association between parenteral calcium administration and outcome parameters.

Results: Among the 1100 patients who met the inclusion criteria, 427 (38.8 %) patients were admitted for sepsis and 576 (52.4 %) patients received parenteral calcium. Patients who received and did not receive parenteral calcium demonstrated no significant difference in 180-day mortality (adjusted hazard ratio [aHR]: 1.18, 95 % confidence interval [CI]: 0.90 to 1.56). Intravenous calcium administration reduced the probability of a shorter time to shock resolution (adjusted odds ratio: 0.81, 95 % CI: 0.70 to 0.94). Subgroup analyses in patients with and without sepsis indicated no significant association between calcium administration (aHR: 1.63, 95 % CI: 0.99 to 2.69) and 180-day mortality (aHR: 1.06, 95 % CI: 0.74 to 1.51). Notably, parenteral calcium was associated with an elevated risk of 90- and 180-day mortality in patients who had sepsis and mild hypocalcemia (aHR: 1.88, 95 % CI: 1.02 to 3.47 and aHR: 1.79, 95 % CI: 1.07 to 3.00, respectively).

Conclusions: Intravenous calcium administration did not provide survival or shock resolution benefits in ICU patients with hypocalcemia, and may even be harmful. Further research, including randomized controlled trials, are needed to confirm these findings.

Introduction

Calcium is an essential nutrient that fulfills many vital roles in the human body. These include regulation of hormone secretion, glycogen metabolism, nerve conduction, muscle contraction, blood homeostasis, and cell division.[1] Approximately half of the calcium in the serum is bound to proteins and anions, while the other half is available as ionized calcium (iCa).[1,2] Serum iCa is commonly measured in patients admitted to the intensive care unit (ICU), as calcium levels change with alterations in albumin levels and acid–base status.[1,2]

Hypocalcemia, a condition characterized by low blood calcium levels, is widely prevalent among patients admitted to the ICU.[1,2] Studies suggest that it is induced by

* Corresponding author: Arthur Raymond Hubert van Zanten, Department of Intensive Care Medicine, Gelderse Vallei Hospital, Division of Human Nutrition and Health, Wageningen University & Research, HELIX (Building 124), Stippenweg 4, 6708 WE Wageningen, The Netherlands.
E-mail addresses: zantena@zgv.nl, arthur.vanzanten@wur.nl (A.R.H. van Zanten).

https://doi.org/10.1016/j.jointm.2024.08.003
Received 19 June 2024; Received in revised form 12 August 2024; Accepted 13 August 2024
Available online xxx

Please cite this article as: M. Melchers, H.P.F.X. Moonen, T.M. Breeman et al., Parenteral calcium administration and outcomes in critically ill patients with hypocalcemia: A retrospective cohort study, Journal of Intensive Medicine, https://doi.org/10.1016/j.jointm.2024.08.003

catecholamines and systemic inflammation in patients with critical illness.[1,3–6] It is associated with poor outcomes, particularly in those in whom iCa levels fail to normalize during the early stages of critical illness.[7–13] However, several studies demonstrated no independent association between low iCa levels and mortality.[5,6,14,15] In addition, most patients admitted to the ICU do not experience health problems that are directly related to a hypocalcemic state (i.e., seizures, tetany, and cardiac arrhythmias).[1,2] Nevertheless, ICU physicians routinely administer calcium in an attempt to correct hypocalcemia.[2,3,16] This practice is driven by studies which suggest that correction of hypocalcemia may improve hemodynamics in critically ill patients by enhancing left ventricular function and vascular resistance.[3,17,18] Critical care guidelines also recommend the administration of intravenous calcium in cases of significant hemorrhage which is accompanied by hypocalcemia or hyperkalemia-related changes on the electrocardiogram (ECG).[19,20] However, the efficacy of this practice has never been confirmed in clinical trials. In addition, there is evidence to suggest that calcium supplementation may be harmful.[3] Calcium administration has been shown to worsen organ dysfunction and survival rates in murine models of sepsis. This may be attributed to a worsening of sepsis-induced calcium imbalance owing to a direct shift of additional calcium into the cells.[21–23] The imbalance over-activates calcium/calmodulin-dependent protein kinase pathways, increases mitochondrial dysfunction, and generates reactive oxygen species, leading to cell injury and vascular leakage.[21–26] In this context, increasing evidence shows that clinical outcomes may be better in patients with sepsis who receive calcium-channel antagonists before hospital admission; this may be attributed to the fact that these drugs prevent excessive shifting of extracellular calcium into the cells.[27–29]

Previous studies have focused on the association between calcium administration and short-term mortality.[15,24,30,31] However, the harmful effects that manifest in the longer term (i.e., oxidative stress, mitochondrial dysfunction, and cell damage) may have been overlooked;[21,25] this was evident from the findings of a recent clinical trial in cardiac arrest patients that had to be terminated prematurely.[32] Although calcium supplementation is common during ICU admission, only one retrospective cohort study has shown benefit;[30] several others have demonstrated either no effect or harm.[15,21,24,31] Notably, the pathophysiological mechanisms involved in calcium dysregulation may be more profound in patients with sepsis; however, calcium administration may improve hemodynamics in patients without sepsis. We therefore aimed to investigate the association between parenteral calcium administration (PCA) and clinical outcomes, including long-term mortality and time to shock resolution, in critically ill hypocalcemic patients with and without sepsis.

Methods

Study design and setting

This retrospective cohort study was conducted at the Gelderse Vallei Hospital, a university-affiliated teaching hospital located in Ede, The Netherlands. The hospital has two mixed medical-surgical adult ICUs with 12 and 5 beds, respectively. Both ICUs are managed by the same medical staff; this ensures the use of similar patient management protocols in both units. The study cohort included patients who were admitted to the ICU between October 1, 2015 and September 24, 2020. The Institutional Review Board of the Gelderse Vallei Hospital, Ede, approved the study titled “Hypophosphatemia and hypocalcemia: course, supplementations and associations with outcome in the general intensive care population” (approval number: 2101–012) on February 4, 2021. The study was conducted in compliance with the principles of the Helsinki Declaration of 1975 and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[33]

Inclusion and exclusion criteria

All patients who were aged at least 18 years, stayed in the ICU for at least 48 h, and had available data for at least one iCa measurement were included. As concurrent citrate infusions reduce iCa concentrations in patients receiving renal replacement therapy (RRT),[34] these patients were excluded to solely focus on endogenic hypocalcemia. In cases of readmission during the same episode of hospital stay, data from only the first instance of ICU admission were evaluated.

Data collection

Data pertaining to clinical parameters (age, sex, body mass index, and pre-existing comorbidities) were obtained from the local electronic patient data management systems, namely, MetaVision® (iMDsoft, Tel Aviv, Israel) and NeoZIS® (MI Consultancy, Katwijk, The Netherlands). The data regarding Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores, diagnosis at admission, and Barthel index were obtained from ICU admission records. Daily laboratory results and Sequential Organ Failure Assessment (SOFA) scores were recorded for the first 7 days of ICU admission. Data regarding the duration of vasopressor therapy and ventilator support throughout ICU admission were also collected. Dates of death were obtained from the electronic patient record system, Xcare® (Nexus, Vianen, the Netherlands), which is linked with the Dutch population register. All collected data were anonymized and stored on a secure computer system.

Subgroups

The study cohort was divided into sepsis and nonsepsis groups based on clinical assessment by the attending intensivist at the time of ICU admission. Assessment was typically performed based on the Sepsis-3 criteria, which pertain to new-onset organ dysfunction (increase in SOFA score by 2) in patients with known or suspected infection.[35] This was documented in the National Intensive Care Evaluation system, ensuring consistent recording across all cases. Patients were also divided into subgroups based on the presence of hyperkalemia (potassium ≥5.5 mmol/L) or clinically significant hemorrhage (excluding cerebral hemorrhage).

Hypocalcemia

Hypocalcemia was defined by serum iCa levels of <1.15 mmol/L, according to the local laboratory reference

values (iCa: 1.15–1.30 mmol/L). The measurements were obtained from arterial blood (ABL90 Flex Plus Analyser, Radiometer Medical ApS, København, Denmark) as part of routine daily measurements. The minimum value on the day of ICU admission was used to determine the presence of hypocalcemia on that day. As per a previous study, patients who developed hypocalcemia during the first 7 days of ICU admission were split into moderate and mild hypocalcemia groups based on quartiles of the minimum baseline iCa values in the entire cohort.[9] Patients with mild and moderate hypocalcemia during ICU admission were assigned to the moderate hypocalcemia group.

Calcium administration

Thresholds and (contra-)indications for calcium administration were not included in local protocols during the study period. Calcium was therefore not routinely administered in cases of hypocalcemia; it was administered at the discretion of the attending physician, usually via the intravenous route, as a 2000 mg bolus dose of calcium gluconate. If deemed safe, and if the patient was receiving it before hospital admission, 500 mg of calcium carbonate was administered once daily. For the analyses, patients who received intravenous calcium gluconate on the day of diagnosis of hypocalcemia were assigned to the PCA group; the others were assigned to the control group. The total dose of intravenous calcium (in grams) administered during the first 7 days of ICU admission was recorded.

Outcomes

The primary outcome was all-cause 180-day mortality. Secondary outcome parameters included the duration of mechanical ventilation and vasopressor therapy and length of stay in the ICU (ICULOS) and hospital (HLOS). The period from initiation until 24 h after cessation of vasopressor therapy was considered as the time to shock resolution. Data regarding ICU-, hospital-, 28-day, and 90-day all-cause mortality were recorded.

Statistical analysis

Categorical variables have been presented as counts and percentages, whereas continuous variables are presented as means±standard deviations or medians and interquartile ranges (IQRs) depending on normality. Normality was tested using the Kolmogorov–Smirnov test and visual inspection of plots. The Student's *t*-test was used for normally distributed data, and the Mann–Whitney *U* test was used in other cases; categorical variables were tested using the chi-squared test.

Cox regression analysis was performed to evaluate the association between PCA and the outcome parameters. Possible confounders were identified using a stepwise approach and the number of covariates were matched based on the one-in-ten rule. The same model was run by replacing PCA with combined enteral and parenteral administration. Covariates were excluded in the case of multicollinearity (as in the case of Spearman's correlation coefficient of 0.7) or violation of the proportional hazard assumption. In cases where multivariable analysis demonstrated a significant association between PCA and 180-day mortality, additional multivariable models were generated for 28- and 90-day mortality. Survival function plots were generated, and a two-sided *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 29.0 (IBM Corporation, Armonk, NY, USA; 2022) software.

Results

Study population

A total of 1468 patients were admitted to the ICU for the first time between October 1, 2015 and September 24, 2020. After excluding those who received RRT (n = 119) and did not have available data regarding iCa measurements (n = 29), 1320 patients were included for evaluation (Figure 1). A total of 12,599 individual iCa measurements were available from the included patients. The median baseline iCa value in the entire cohort was 1.10 (IQR: 1.06–1.15) mmol/L. Based on this range, iCa levels of <1.06 mmol/L and 1.06–1.14 mmol/L were considered as moderate and mild hypocalcemia, respectively. Hypocalcemia was observed during the first 7 days of ICU admission in 1100 (83.3 %) patients; these patients were included in the analysis. The patients with hypocalcemia had a median age of 70 (IQR: 59–77) years; 649 (59.0 %) were male, and 427 (38.8 %) were admitted to the ICU due to sepsis.

PCA

Among the 1100 patients with hypocalcemia, 576 (52.4 %) received PCA. Of these patients, 60.4 % (348/576) calcium was administered within 24 h of ICU admission; 45.8 % (264/576) and 24.7 % (142/574, as 3 patients in the PCA group were no longer in the ICU on day 3 of admission) of patients in the PCA group received calcium on days 2 and 3 (of ICU stay), respectively. The median dose of intravenous calcium received during the first 7 days of ICU admission was 2000 (IQR: 2000–6000) mg. Patients with mild hypocalcemia had a lower frequency of receiving PCA (36.0 % *vs.* 73.2 %, P <0.001), and the cumulative PCA dose within the first 7 days of ICU admission was lower than that in those with moderate hypocalcemia (median=2000 mg, [IQR: 2000–4000] *vs.* median=4000 mg, [IQR: 2000–6000], P<0.001). A total of 27 (4.7 %) patients received concurrent enteral calcium with PCA, whereas 24 (4.6 %) patients received only enteral calcium without PCA. Table 1 shows the patient characteristics at baseline and at ICU admission in those who received and did not receive PCA for hypocalcemia. Among 73 patients with hyperkalemia (potassium ≥5.5 mmol/L), 40 (54.8 %) patients received PCA.

Outcome data

Data regarding all-cause 180-day survival was available for all patients included in the primary analysis. A total of 255 (23.2 %) patients who developed hypocalcemia died within 180 days of ICU admission. Supplementary Table S1 shows a comparison of the baseline characteristics between survivors and nonsurvivors. In the group of patients who received PCA, 153 (26.6 %) patients died within 180 days after ICU admission; in contrast, 102 (19.5 %) patients died in the control group (hazard ratio [HR]=1.49, 95 % confidence interval [CI]: 1.16 to 1.92).

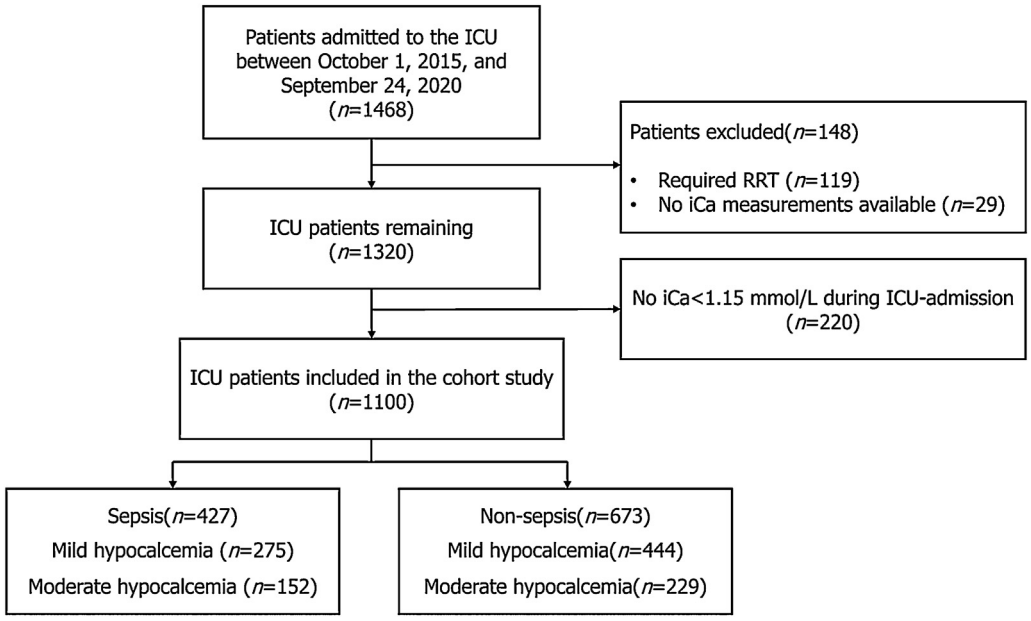

Figure 1. Flowchart of the study cohort after selection based on the inclusion and exclusion criteria and distribution into subgroups. Mild hypocalcemia = iCa 1.06–1.14 mmol/L; moderate hypocalcemia = iCa <1.06 mmol/L.
iCa: Ionized calcium; ICU: Intensive care unit; RRT: Renal replacement therapy.

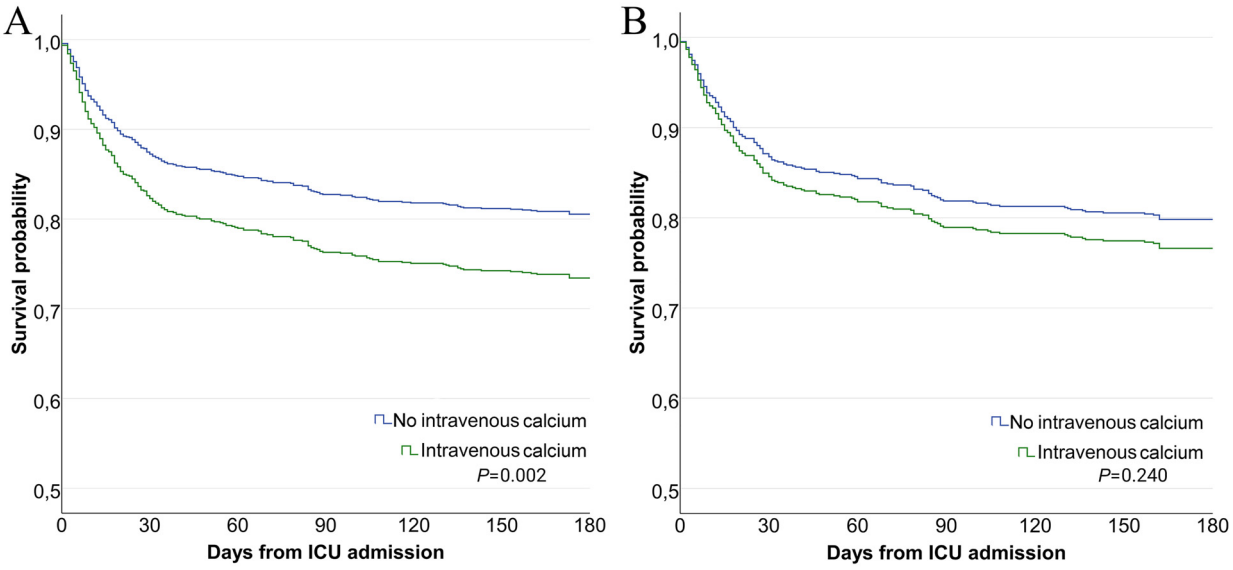

Figure 2. Survival curves of included patients with hypocalcemia who received and did not receive intravenous calcium. A: Univariate Cox regression analysis curve. B: Multivariable Cox regression analysis curve after correction for covariates age, APACHE IV score, BMI, Barthel index, COPD, serum albumin, arterial pH, serum creatinine, and duration of vasopressor therapy.
APACHE IV: Acute physiological and chronic health evaluation IV; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit.

On multivariable analysis, PCA was not found to be associated with 180-day mortality (adjusted HR [aHR]=1.18, 95 % CI: 0.90 to 1.56; Figure 2, Supplementary Table S2).

Sepsis and nonsepsis

Supplementary Tables S3–S6 show the differences in baseline characteristics between patients who received and did not receive PCA (in the four subgroups). PCA was associated with increased 180-day mortality in both groups of patients with and without sepsis (HR=1.63, 95 % CI: 1.09 to 2.43 and HR=1.28, 95 % CI: 0.93 to 1.77, respectively; Figures 3 and 4, Supplementary Tables S7 and S8). On multivariable analysis, the association between PCA and 180-day mortality reached near-significance (aHR=1.63, 95 % CI: 0.99 to 2.69) in patients with sepsis; however, no significant association was observed in those without sepsis (aHR=1.06, 95 % CI: 0.74 to 1.51).

The patient groups with and without sepsis were categorized as having mild or moderate hypocalcemia. In patients having sepsis with mild hypocalcemia, multivariable analyses revealed

Table 1
Baseline characteristics of study patients.

Baseline variables	Total (*n*=1100)	No intravenous administration (*n*=524)	Intravenous administration (*n*=576)	*P*-value
Age (years)	70 (59–77)	68 (56–76)	71 (61–78)	0.003
Sex, female	451 (41.0)	224 (42.7)	227 (39.4)	0.361
BMI on admission (kg/m^2)	26.5 (23–30)	26.8 (23.5–30.5)	26.3 (23.0–30.1)	0.167
APACHE IV-score	69 (48–84)	67 (52–84)	74 (61–91)	<0.001
SOFA-score	5 (3–7)	6 (3–8)	7 (5–9)	<0.001
Barthel-index	20 (16–20)	20 (18–20)	20 (18–20)	0.596
Comorbidities				
COPD	257 (23.3)	135 (25.7)	122 (21.2)	0.073
DM	275 (25.0)	123 (23.5)	152 (26.3)	0.265
Baseline blood tests				
CRP (mg/L)	96 (18–214)	80 (15–211)	108 (24–216)	0.075
Albumin (g/L)	26 (21–32)	28 (23–34)	25 (20–29)	<0.001
Creatinine (μmol/L)	82 (61–123)	83 (64–123)	100 (71–151)	<0.001
Arterial pH*	7.32 (7.24–7.40)	7.34 (7.25–7.41)	7.31 (7.23–7.39)	0.025
Arterial lactate†	2.2 (1.4–3.7)	1.8 (1.2)	2.6 (1.6–4.3)	<0.001
Glucose (mmol/L)‡	8.5 (7.3–10.3)	8.2 (7.2–10.0)	8.9 (7.36–10.5)	0.005
Baseline elektrolytes				
Minimum iCa (mmol/L)	1.09 (1.05–1.13)	1.12 (1.09–1.14)	1.03 (1.07–1.10)	<0.001
Maximum iCa (mmol/L)	1.16 (1.12–1.20)	1.17 (1.13–1.21)	1.15 (1.10–1.20)	<0.001
Sodium (mmol/L)‡	138 (135–141)	138 (135–141)	138 (135–141)	0.692
Magnesium (mmol/L)‡	0.72 (0.61–0.83)	0.75 (0.64–0.85)	0.70 (0.59–0.81)	<0.001
Potassium (mmol/L)‡	3.9 (3.6–4.4)	3.9 (3.6–4.3)	4.0 (3.6–4.4)	0.123
Phosphate (mmol/L)‡	1.05 (0.84–1.33)	1.05 (0.86–1.29)	1.05 (0.81–1.39)	0.528
ICU admission type				
Elective surgical	99 (9.0)	43 (8.2)	56 (9.7)	0.290
Emergency surgical	213 (19.4)	72 (13.7)	142 (24.6)	<0.001
Medical	782 (71.1)	407 (77.6)	375 (65.1)	<0.001
ICU admission reason				
Sepsis	427 (38.8)	185 (35.3)	242 (42.0)	0.023
Hemorrhage§	48 (4.4)	11 (2.1)	37 (6.4)	<0.001
Cardiac arrest	20 (1.8)	7 (1.3)	13 (2.3)	0.281

Categorical variables are presented as number (percentages) and continuous variables as median (interquartile range).
Missing data was observed in the following baseline characteristics (*n*): BMI (26), APACHE-IV (5), SOFA-score (4), Barthel-index (60), CRP (12), Albumin (28), Creatinine (12), Arterial pH (10), Arterial Lactate (12), Glucose (131), Sodium (12), Magnesium (51), Potassium (21) and Phosphate (49).
* Minimum value on admission day.
† Maximum value on admission day.
‡ Mean value on admission day.
§ Excluding cerebral hemorrhage.
APACHE IV: Acute Physiology and Chronic Health Evaluation IV; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-reactive Protein; DM: Diabetes mellitus; iCa: ionized calcium; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment score.

an association between PCA and increased 180- and 90-day mortality (aHR=1.79, 95 % CI: 1.07 to 3.00 and aHR=1.88, 95 % CI: 1.02 to 3.47, respectively; Supplementary Tables S9 and S10). However, no difference was observed in terms of 28-day mortality (aHR=1.19, 95 % CI: 0.64 to 2.23; Supplementary Table S11). In the remaining subgroups, multivariable analyses demonstrated no significant association between PCA and 180-day mortality (Supplementary Tables S12–S14).

Time to shock resolution

Patients who received PCA required a longer duration of vasopressor therapy (median=4, [IQR: 3–7] days *vs.* median=3, [IQR: 2–5] days, $P = 0.001$). On multivariable regression analysis, the group that received PCA showed a lower likelihood of experiencing a shorter time to shock resolution (adjusted odds ratio [aOR]=0.81, 95 % CI: 0.70 to 0.94; Supplementary Table S15); this was particularly relevant in patients without sepsis (aOR= 0.76, 95 % CI: 0.63 to 0.94; Supplementary Table S16) but not in sepsis patients (Supplementary Table S17). In addition, subgroup analyses showed that PCA in patients with mild hypocalcemia, both with and without sepsis, reduced the probability of a faster shock resolution (aOR=0.74, 95 % CI: 0.56 to 0.97 and aOR=0.71, 95 % CI: 0.54 to 0.92, respectively; Supplementary Tables S18 and S19), while this was not in patients with moderate hypocalcemia (Supplementary tables S20 and S21).

Additional analyses

The findings from univariate analysis of additional outcome parameters, in both PCA and control groups, are presented in Supplementary Tables S22–S28. The parameters included the HLOS, duration of mechanical ventilation; and ICU-, 28-day, and 90-day mortality in the subgroups. Multivariable analysis showed a non-significant association between ICULOS and PCA (aOR=0.89, 95 % CI: 0.88 to 1.01; Supplementary Table S29). In patients with hemorrhage or hyperkalemia, PCA was not associated with either 180-day mortality (HR=1.05, 95 % CI: 0.29 to 3.75 and HR=2.23, 95 % CI: 0.66 to 7.52, respectively; Supplementary Table S30) or shorter time to shock resolution (aOR=0.66, 95 % CI: 0.17 to 2.54 and aOR=1.34, 95 % CI: 0.61 to 2.95, respectively; Supplementary Tables S31 and S32).

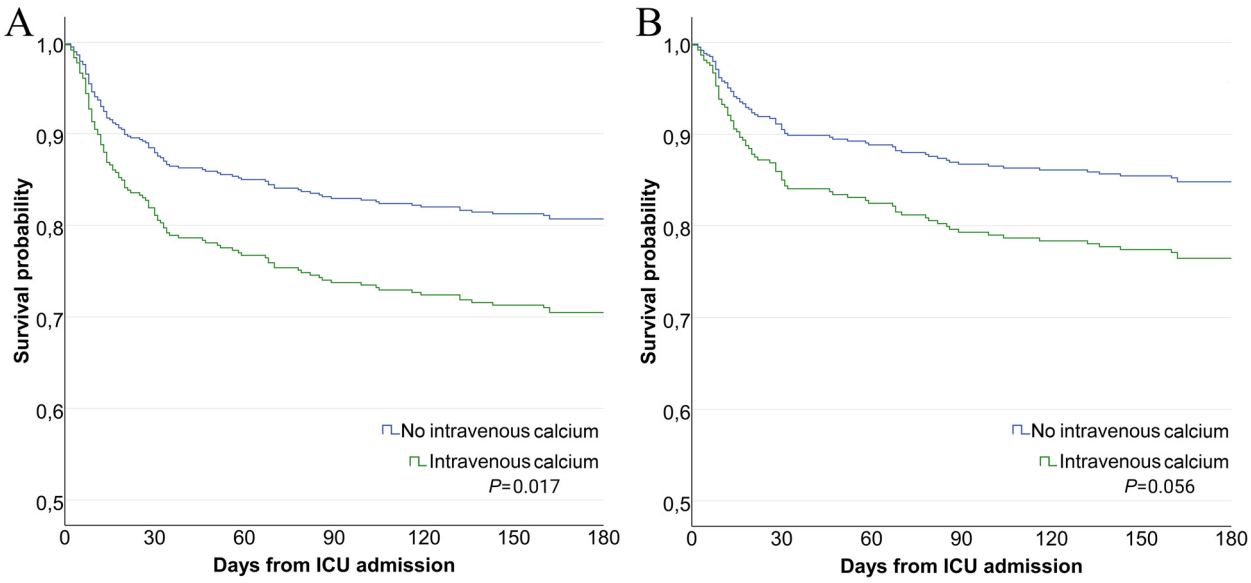

Figure 3. Survival curves of patients with sepsis and hypocalcemia who received and did not receive intravenous calcium. A: Univariate Cox regression analysis curve. B: Multivariable Cox regression analysis curve after correction for covariates age, APACHE IV score, BMI, Barthel index, DM, and vasopressor duration.
APACHE IV: Acute physiological and chronic health evaluation IV; BMI: Body mass index; DM: Diabetes mellitus; ICU: Intensive care unit.

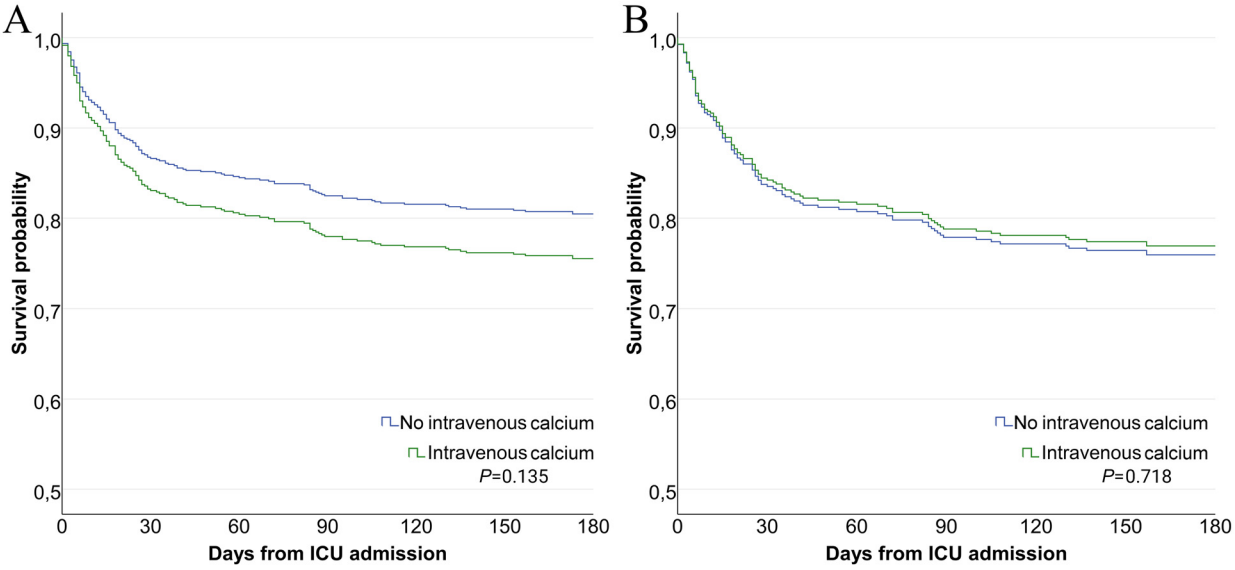

Figure 4. Survival curves of non-sepsis patients with hypocalcemia who received and did not receive intravenous calcium. A: Univariate Cox regression analysis curve. B: Multivariable Cox regression analysis curve after correction for the covariates age, APACHE IV score, Barthel index, COPD, serum albumin, and vasopressor duration.
APACHE IV: Acute physiological and chronic health evaluation IV; COPD: Chronic pulmonary obstructive disease; ICU: Intensive care unit.

Discussion

The findings from this retrospective cohort study, which included ICU patients with serum hypocalcemia, showed that intravenous calcium administration offered no benefits in terms of long-term mortality and time-to-shock resolution. Conversely, patients with hypocalcemia who were administered intravenous calcium demonstrated longer durations of ICULOS, mechanical ventilation, and vasopressor therapy; they also showed lower survival rates on univariate analysis. After adjusting for covariates, intravenous calcium administration was found to be independently associated with a reduced likelihood of shorter time to shock resolution. In addition, subgroup analyses showed that PCA was independently associated with increased all-cause 90- and 180-day mortality in patients with sepsis who had mild hypocalcemia (iCa 1.06 - 1.14 mmol/L).

Hypocalcemia is common in critically ill patients, and is especially seen in cases of excessive inflammation and catecholamine release.[3,5,13,14,21,22] Although the pathophysiological mechanisms are poorly understood, they may result from side effects of drugs and critical illness; both of these affect calcium homeostasis, leading to high levels of intracellular calcium and low levels of extracellular iCa.[1,3–6] The reported prevalence rates of hypocalcemia are found to vary among patients admitted to the ICU; this is most likely to be caused by differences among study populations and cutoff values used.[2] In our study, 83 %

of patients admitted to the ICU had developed hypocalcemia (defined by iCa levels of <1.15 mmol/L) during the first 7 days of admission; this finding is consistent with those of previous studies.[5,6]

Retrospective studies that evaluated the association between hypocalcemia and mortality in ICU patients, have reported mixed results.[7–14,31] Severe and persistent hypocalcemia during critical illness has shown the strongest association with mortality.[5,15,29,36] However, the causality between iCa levels and adverse outcomes remains unclear; in this context, hypocalcemia could represent an adaptive response to critical illness, and reflect disease severity.[2] Notably, iCa levels have often been found to spontaneously normalize during the course of a critical illness.[15,16,36] Nevertheless, patients admitted to the ICU are commonly administered intravenous calcium in an attempt to correct hypocalcemia;[2,16,36] this practice was also followed in more than half of the cases in our study cohort.

Current guidelines recommend calcium supplementation in patients with major bleeding and hypocalcemia, as calcium plays a vital role in coagulation;[19] studies show that low iCa levels may be predictive of poor clinical outcomes in these patients.[37] However, there is no available data to suggest that the achievement of normocalcemia offers any benefits in these patients.[38] In this context, it is common practice to administer calcium in cases of hyperkalemia-induced ECG abnormalities in order to stabilize the myocellular membrane; however, its effectiveness has not been demonstrated in any randomized controlled trials (RCTs).[20] In the current study, PCA was neither associated with rapid shock reversal nor improved survival in the subsets of patients with hyperkalemia and hemorrhage.

A recent RCT on patients with out-of-hospital cardiac arrest found calcium administration to offer no benefits in terms of return of spontaneous circulation; the trial was terminated prematurely, as fewer patients in the treatment arm reported favorable neurological outcomes and quality of life at 90 days.[32] The investigators hypothesized that calcium administration may result in cytosolic and mitochondrial calcium overload; this could stimulate oxidative stress and activate calcium-dependent proteolytic pathways. This hypothesis is similar to the proposed mechanism for calcium-induced toxicity in critical illness, particularly sepsis.[3] Several studies on animal models of sepsis have demonstrated increased morbidity and mortality following PCA; this may be attributed to activation of destructive enzymes and consequent mitochondrial dysfunction and cell injury.[21,23,25,26,39]

Previous studies have suggested that calcium supplementation may improve hemodynamics by increasing vascular resistance and left ventricular function owing to its positive inotropic effect.[17,18,40] However, a long-lasting clinically relevant benefit (in terms of hemodynamic parameters) has never been described in the critically ill.[3] In their study, Dotson et al.[24] found PCA to be associated with in-hospital mortality, acute respiratory failure, and new-onset shock in ICU patients who received parenteral nutrition. In the current study, patients receiving PCA showed a longer time to shock resolution, even after adjusting for confounders relevant to the hemodynamic status (such as duration of mechanical ventilation, albumin, and disease severity). Although causal inferences cannot be made from our data, it can be hypothesized that calcium administration may have increased vascular leak (as observed in animal models), and thereby extended the duration of vasopressor dependency.[21,24]

Only one study has shown calcium supplementation to offer potential benefits in ICU patients, indicating an independent association with lower mortality rates.[30] A sub-analysis of patients with sepsis, derived from the same database, demonstrated 28-day mortality after calcium supplementation to be higher in cases where iCa levels at admission were 1.01–1.20 mmol/L; however, those with iCa levels of <1.01 mmol/L possibly benefited from supplementation.[31] In the present cohort, PCA showed a trend toward a significant increase in 180-day mortality among patients with sepsis who had hypocalcemia. In those with mild hypocalcemia, PCA was associated with decreased 90- and 180-day survival; this concurs with the findings of He et al.[31] Nevertheless, the association between PCA and 28-day mortality was not significant. This observation is similar to the findings from the RCT performed by Vallentin et al.[32] that included patients with cardiac arrest; it may be explained by the long-term toxic effects of calcium overload, such as mitochondrial damage.[22] Notably, the duration of vasopressor therapy is known to contribute to ICULOS and ICU-acquired muscle weakness, which is associated with morbidity and poor long-term outcomes.[41–43] It is unclear whether this led to poor long-term outcomes in the present cohort; further investigation is needed via prospective trials that need to include follow-up evaluation after ICU and hospital discharge.

Certain limitations need to be considered while interpreting the results of this study. The findings from our single-center retrospective study may have limited generalizability due to specific ICU practices and patient demographics at our center. As in most ICUs, calcium was administered at the discretion of the attending ICU physician; this introduced potential selection bias, as patients receiving calcium were likely to be in a more serious condition. In addition, center-specific patterns may have hampered the applicability of our findings to other settings. Finally, the data were not sufficient to adjust for other potential covariates of vasopressor dependency, such as fluid balance and left ventricular function. Although it was possible to adjust for several strong predictors of mortality (including age, disease severity, and clinical frailty upon ICU admission[44–46]), residual confounding could have remained. Additionally, some factors may have acted as mediators rather than confounders, potentially obscuring the true effects of calcium administration.

Although our study provides valuable insights, its conclusions are not definitive and should be corroborated by further research. Multi-center prospective studies and comprehensive data collection should ideally be employed for further evaluation.

Conclusions

Hypocalcemia and consequent PCA were common in our large cohort of critically ill patients. However, PCA was not associated with improved outcomes. On the contrary, it was associated with prolongation of the time to shock resolution and reduced long-term survival in patients with sepsis. These findings underscore the need for caution during routine calcium administration in critically ill patients with hypocalcemia. An RCT is warranted to confirm our findings, elucidate the underly-

ing mechanisms, and establish evidence-based treatment guidelines.

CRediT authorship contribution statement

Max Melchers: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hanneke Pierre Franciscus Xaverius Moonen:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Tessa Maria Breeman:** Writing – review & editing, Methodology, Data curation. **Sjoerd Hendrika Willem van Bree:** Writing – review & editing, Methodology. **Arthur Raymond Hubert van Zanten:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization.

Acknowledgments

We would like to thank Dr. MJ Caldas Paulo (Wageningen University & Research, Wageningen, the Netherlands) for her guidance on the use of proportional hazard regression analyses.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

The study titled “Hypophosphatemia and hypocalcemia: course, supplementations and associations with outcome in the general intensive care population” was approved by the Institutional Review Board (approval number: 2101–012) of Gelderse Vallei Hospital, Ede, on February 4, 2021.

Conflict of Interest

Prof. Dr. ARH Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, AOP Pharma, Baxter, Danone-Nutricia, Dutch Medical Food, GE Healthcare, Medcaptain, Nestlé, PAION, and Rousselot. The other authors have nothing to declare.

Data Availability

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.08.003.

References

[1] Kelly A, Levine MA. Hypocalcemia in the critically ill patient. J Intensive Care Med 2013;28(3):166–77. doi:10.1177/0885066611411543.
[2] Aberegg SK. Ionized calcium in the ICU: should it be measured and corrected? Chest 2016;149(3):846–55. doi:10.1016/j.chest.2015.12.001.
[3] Melchers M, van Zanten ARH. Management of hypocalcaemia in the critically ill. Curr Opin Crit Care 2023;29(4):330–8. doi:10.1097/MCC.0000000000001059.
[4] Forsythe RM, Wessel CB, Billiar TR, Angus DC, Rosengart MR. Parenteral calcium for intensive care unit patients. Cochrane Database Syst Rev 2008(4):CD006163. doi:10.1002/14651858.CD006163.pub2.
[5] Egi M, Kim I, Nichol A, Stachowski E, French CJ, Hart GK, et al. Ionized calcium concentration and outcome in critical illness. Crit Care Med 2011;39(2):314–21. doi:10.1097/CCM.0b013e3181ffe23e.
[6] Hästbacka J, Pettilä V. Prevalence and predictive value of ionized hypocalcemia among critically ill patients. Acta Anaesthesiol Scand 2003;47(10):1264–9. doi:10.1046/j.1399-6576.2003.00236.x.
[7] Zhang Z, Xu X, Ni H, Deng H. Predictive value of ionized calcium in critically ill patients: an analysis of a large clinical database MIMIC II. PLoS One 2014;9(4):e95204. doi:10.1371/journal.pone.0095204.
[8] Anastasopoulos D, Kefaliakos A, Michalopoulos A. Is plasma calcium concentration implicated in the development of critical illness polyneuropathy and myopathy? Crit Care 2011;15(5):R247. doi:10.1186/cc10505.
[9] Yu Y, Yu J, Yao R, Wang P, Zhang Y, Xiao J, et al. Admission serum ionized and total calcium as new predictors of mortality in patients with cardiogenic shock. Biomed Res Int 2021;2021:6612276. doi:10.1155/2021/6612276.
[10] Wang B, Li D, Gong Y, Ying B, Cheng B. Association of serum total and ionized calcium with all-cause mortality incritically ill patients with acute kidney injury. Clin Chim Acta 2019;494:94–9. doi:10.1016/j.cca.2019.03.1616.
[11] Magnotti LJ, Bradburn EH, Webb DL, Berry SD, Fischer PE, Zarzaur BL, et al. Admission ionized calcium levels predict the need for multiple transfusions: a prospective study of 591 critically ill trauma patients. J Trauma 2011;70(2):391–5 discussion395–7. doi:10.1097/TA.0b013e31820b5d98.
[12] Müller B, Becker KL, Kränzlin M, Schächinger H, Huber PR, Nylèn ES, et al. Disordered calcium homeostasis of sepsis: association with calcitonin precursors. Eur J Clin Invest 2000;30(9):823–31. doi:10.1046/j.1365-2362.2000.00714.x.
[13] Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. Am J Med 1988;84(2):209–14. doi:10.1016/0002-9343(88)90415-9.
[14] Dias CR, Leite HP, Nogueira PC, Brunow de Carvalho W. Ionized hypocalcemia is an early event and is associated with organ dysfunction in children admitted to the intensive care unit. J Crit Care 2013;28(5):810–15. doi:10.1016/j.jcrc.2013.03.019.
[15] Steele T, Kolamunnage-Dona R, Downey C, Toh CH, Welters I. Assessment and clinical course of hypocalcemia in critical illness. Crit Care 2013;17(3):R106. doi:10.1186/cc12756.
[16] Baird GS, Rainey PM, Wener M, Chandler W. Reducing routine ionized calcium measurement. Clin Chem 2009;55(3):533–40. doi:10.1373/clinchem.2008.116707.
[17] Burchard KW, Simms HH, Robinson A, DiAmico R, Gann DS. Hypocalcemia during sepsis. Relationship to resuscitation and hemodynamics. Arch Surg 1992;127(3):265–72. doi:10.1001/archsurg.1992.01420030027005.
[18] Vincent JL, Bredas P, Jankowski S, Kahn RJ. Correction of hypocalcaemia in the critically ill: what is the haemodynamic benefit? Intensive Care Med 1995;21(10):838–41. doi:10.1007/BF01700968.
[19] Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care 2019;23(1):98. doi:10.1186/s13054-019-2347-3.
[20] Dépret F, Peacock WF, Liu KD, Rafique Z, Rossignol P, Legrand M. Management of hyperkalemia in the acutely ill patient. Ann Intensive Care 2019;9(1):32. doi:10.1186/s13613-019-0509-8.
[21] Collage RD, Howell GM, Zhang X, Stripay JL, Lee JS, Angus DC, et al. Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase signaling. Crit Care Med 2013;41(11):e352–60. doi:10.1097/CCM.0b013e31828cf436.
[22] Joseph LC, Barca E, Subramanyam P, Komrowski M, Pajvani U, Colecraft HM, et al. Inhibition of NAPDH oxidase 2 (NOX2) prevents oxidative stress and mitochondrial abnormalities caused by saturated fat in cardiomyocytes. PLoS One 2016;11(1):e0145750. doi:10.1371/journal.pone.0145750.
[23] Song SK, Karl IE, Ackerman JJ, Hotchkiss RS. Increased intracellular Ca2+: a critical link in the pathophysiology of sepsis? Proc Natl Acad Sci U S A 1993;90(9):3933–7. doi:10.1073/pnas.90.9.3933.
[24] Dotson B, Larabell P, Patel JU, Wong K, Qasem L, Arthur W, et al. Calcium administration is associated with adverse outcomes in critically Ill patients receiving parenteral nutrition: results from a natural experiment created by a calcium gluconate shortage. Pharmacotherapy 2016;36(11):1185–90. doi:10.1002/phar.1849.
[25] Malcolm DS, Zaloga GP, Holaday JW. Calcium administration increases the mortality of endotoxic shock in rats. Crit Care Med 1989;17(9):900–3. doi:10.1097/00003246-198909000-00012.
[26] Zaloga GP, Sager A, Black KW, Prielipp R. Low dose calcium administration increases mortality during septic peritonitis in rats. Circ Shock 1992;37(3):226–9.
[27] Lee CC, Lee MG, Lee WC, Lai CC, Chao CC, Hsu WH, et al. Preadmission use of calcium channel blocking agents is associated with improved outcomes in patients with sepsis: a population-based propensity score-matched cohort study. Crit Care Med 2017;45(9):1500–8. doi:10.1097/CCM.0000000000002550.
[28] Wiewel MA, van Vught LA, Scicluna BP, Hoogendijk AJ, Frencken JF, Zwinderman AH, et al. Prior use of calcium channel blockers is associated with decreased mortality in critically ill patients with sepsis: a prospective observational study. Crit Care Med 2017;45(3):454–63. doi:10.1097/CCM.0000000000002236.
[29] Ding X, Cui Y, Liang H, Wang D, Li L, Kan Q, et al. Association between prior calcium channel blocker use and mortality in septic patients: a meta-analysis of cohort studies. Front Pharmacol 2021;12:628825. doi:10.3389/fphar.2021.628825.
[30] Zhang Z, Chen K, Ni H. Calcium supplementation improves clinical outcome in intensive care unit patients: a propensity score matched analysis of a large clinical database MIMIC-II. Springerplus 2015;4:594. doi:10.1186/s40064-015-1387-7.

[31] He W, Huang L, Luo H, Chen J, Li W, Zhang Y, et al. The positive and negative effects of calcium supplementation on mortality in septic ICU patients depend on disease severity: a retrospective study from the MIMIC-III. Crit Care Res Pract 2022;2022:2520695. doi:10.1155/2022/2520695.
[32] Vallentin MF, Granfeldt A, Meilandt C, Povlsen AL, Sindberg B, Holmberg MJ, et al. Effect of intravenous or intraosseous calcium vs saline on return of spontaneous circulation in adults with out-of-hospital cardiac arrest: a randomized clinical trial. JAMA 2021;326(22):2268–76. doi:10.1001/jama.2021.20929.
[33] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7. doi:10.1016/S0140-6736(07)61602-X.
[34] Zheng Y, Xu Z, Fan Q, Zhu Q, Ma S, Lu J, et al. Calcium supplementation in CVVH using regional citrate anticoagulation. Hemodial Int 2019;23(1):33–41. doi:10.1111/hdi.12715.
[35] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10. doi:10.1001/jama.2016.0287.
[36] Ward RT, Colton DM, Meade PC, Henry JC, Contreras LM, Wilson OM, et al. Serum levels of calcium and albumin in survivors versus nonsurvivors after critical injury. J Crit Care 2004;19(1):54–64. doi:10.1016/j.jcrc.2004.02.011.
[37] Kronstedt S, Roberts N, Ditzel R, Elder J, Steen A, Thompson K, et al. Hypocalcemia as a predictor of mortality and transfusion. A scoping review of hypocalcemia in trauma and hemostatic resuscitation. Transfusion (Paris) 2022;62(Suppl 1):S158–66 Suppl 1. doi:10.1111/trf.16965.
[38] Chanthima P, Yuwapattanawong K, Thamjamrassri T, Nathwani R, Stansbury LG, Vavilala MS, et al. Association between ionized calcium concentrations during hemostatic transfusion and calcium treatment with mortality in major trauma. Anesth Analg 2021;132(6):1684–91. doi:10.1213/ANE.0000000000005431.
[39] Carlstedt F, Eriksson M, Kiiski R, Larsson A, Lind L. Hypocalcemia during porcine endotoxemic shock: effects of calcium administration. Crit Care Med 2000;28(8):2909–14. doi:10.1097/00003246-200008000-00037.
[40] Newman DB, Fidahussein SS, Kashiwagi DT, Kennel KA, Kashani KB, Wang Z, et al. Reversible cardiac dysfunction associated with hypocalcemia: a systematic review and meta-analysis of individual patient data. Heart Fail Rev 2014;19(2):199–205. doi:10.1007/s10741-013-9371-1.
[41] Boelens YFN, Melchers M, van Zanten ARH. Poor physical recovery after critical illness: incidence, features, risk factors, pathophysiology, and evidence-based therapies. Curr Opin Crit Care 2022;28(4):409–16. doi:10.1097/MCC.0000000000000955.
[42] Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2014;190(4):410–20. doi:10.1164/rccm.201312-2257OC.
[43] Brunello AG, Haenggi M, Wigger O, Porta F, Takala J, Jakob SM. Usefulness of a clinical diagnosis of ICU-acquired paresis to predict outcome in patients with SIRS and acute respiratory failure. Intensive Care Med 2010;36(1):66–74. doi:10.1007/s00134-009-1645-7.
[44] Kuzniewicz MW, Vasilevskis EE, Lane R, Dean ML, Trivedi NG, Rennie DJ, et al. Variation in ICU risk-adjusted mortality: impact of methods of assessment and potential confounders. Chest 2008;133(6):1319–27. doi:10.1378/chest.07-3061.
[45] Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, Bosman RJ, Peelen L, et al. External validation of Acute Physiology and Chronic Health Evaluation IV in Dutch intensive care units and comparison with Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II. J Crit Care 2011;26(1):e11–18. doi:10.1016/j.jcrc.2010.07.007.
[46] Ryrsø CK, Hegelund MH, Dungu AM, Faurholt-Jepsen D, Pedersen BK, Ritz C, et al. Association between Barthel Index, grip strength, and physical activity level at admission and prognosis in community-acquired pneumonia: a prospective cohort study. J Clin Med 2022;11(21):6326. doi:10.3390/jcm11216326.