Association between serum Calcium and 28-day mortality in Pediatric Pneumonia: Insights from a PICU Retrospective Cohort

Jinling Zhao
Affiliated Hospital of Jiangnan University
Meihong Liu
Shaanxi Provincial People's Hospital
Dan Yu
Affiliated Wuxi Fifth Hospital of Jiangnan University
Ying-ying Zhang (zyy926926@126.com)
Affiliated Wuxi Fifth Hospital of Jiangnan University

Article

Keywords: Calcium, Mortality, Pediatric, Pneumonia

Posted Date: February 1st, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3888074/v1

Additional Declarations: No competing interests reported.

Abstract

This study investigates the impact of serum calcium levels on the 28-day hospital mortality rate in children with pneumonia, a topic not extensively explored previously. Analyzing data from 414 patients at Zhejiang University Medical College's Children's Hospital (2010–2019), the study categorized patients by serum calcium levels for 28-day mortality monitoring. Results show that each 1mmol/dL increase in serum calcium reduced 28-day mortality risk by 26% (HR: 0.74, 95% CI: 0.65–0.85). Patients with higher serum calcium levels had a 63% lower mortality rate compared to those with lower levels (HR: 0.37, 95% CI: 0.16–0.85). These findings, consistent across various subgroups, highlight serum calcium as a significant prognostic marker for pediatric pneumonia, influencing clinical decisions and pointing to the need for further research in this area.

Introduction

Pneumonia, an acute lower respiratory tract inflammation, continues to be a leading cause of child mortality worldwide. Annually, it claims the lives of over 2 million individuals, with nearly 30% of these cases occurring in children under the age of 5[1–3]. While the period from 2000 to 2015 witnessed a decline in pneumonia-related child fatalities, attributed to advancements in vaccination and public health measures, it continues to pose a significant health threat, especially to children with underlying conditions such as immunodeficiency, airway hyperreactivity, or cardiovascular issues.[3–5]

Calcium, a multifaceted intracellular messenger, plays a vital role in various biological processes including gene expression, cell proliferation, and cell death.[6] It is crucial in both healthy cellular functions and in the pathology of diseases like pneumonia. The role of calcium in the mechanisms of pneumonia is particularly complex. During cellular infection, calcium facilitates the apoptotic elimination of pathogens as part of the host defense mechanism.[7] Concurrently, it can be exploited by viruses to enhance their replication and invasion capabilities, notably in coronavirus infections, where alterations in calcium homeostasis are closely linked to viral spread and activation of inflammatory responses in the host.[7–9]

Calcium's regulation of the immune system's response to infection is crucial, and its dysregulation can exacerbate illness. Recent studies indicate that calcium disturbances are prevalent in various clinical contexts, including pediatric sepsis[10], traumatic injury[11], childhood diarrhea[12], adult cardiovascular disease[13, 14], acute kidney injury[15], and all-cause mortality among inpatients[16], particularly with hypocalcemia,as observed in COVID-19 pneumonia patients[17]. However, the specific role and mechanisms of calcium in pediatric pneumonia, especially its association with the in-hospital mortality rate of pediatric pneumonia patients, remain under-explored.

Thus, this study aims to delve into whether there is an association between serum calcium levels at admission and the 28-day mortality of pediatric pneumonia patients. By comprehensively understanding this relationship, we aspire to offer new perspectives on the disease progression and prognosis of pneumonia patients. We anticipate that this research will not only enrich our understanding of the relationship between calcium and pneumonia but also provide substantial support for future clinical practices and treatment decisions, thereby contributing to the improvement of treatment outcomes and survival rates for pneumonia patients.

Results

Baseline characteristics of study subjects

We enrolled a total of 414 patients, with an average age of 22.9 ± 33.6 months. Male patients constituted 42.0% of the total study cohort. The overall prevalence of 28-day hospital mortality in this group was 11.1%. Table 1 presents the baseline characteristics of patients grouped according to serum calcium levels. The group with higher serum calcium exhibited higher levels of hemoglobin, albumin, cholesterol, serum sodium, serum potassium, and monocytes, and these differences were statistically significant ($P < 0.05$). Conversely, this group showed lower levels of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST), as well as a lower 28-day mortality rate. However, there were no statistically significant differences in terms of gender, oxygen saturation, blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT), and length of stay in the ICU (Table 1).

Association between serum Calcium and 28-day hospital Mortality

Smooth curve fitting revealed a significant linear relationship between serum calcium levels and the risk of 28-day mortality (non-linearity $P = 0.75$, Supplementary Figure S1). This analysis employed a restricted cubic spline model adjusted for multiple variables. The curve demonstrates that as the level of serum calcium increases, the risk of 28-day mortality shows a downward trend, indicating that higher serum calcium levels are associated with a reduced risk of mortality within 28 days.

Univariate analysis indicated a significant correlation between serum calcium and 28-day hospital mortality (HR 0.79, 95% CI: 0.72–0.88, $P < 0.001$, Supplementary Table 1). In the multivariate model, higher serum calcium levels were associated with a decreased risk of adverse outcomes in pneumonia patients. For every 1 mmol/dL increase in serum calcium, the risk of adverse outcomes significantly decreased by 26% (HR: 0.74, 95% CI: 0.65–0.85). Analysis of serum calcium as a categorical variable showed a consistent trend across four adjusted models, indicating that higher serum calcium is associated with a lower hazard ratio for mortality. In the fully adjusted model, compared to the lowest quartile group (Q1), the middle quartile group (Q2) had a 49% reduced risk of 28-day mortality (HR: 0.51, 95% CI: 0.25–1.08), while the highest quartile group (Q3) had a hazard ratio of 0.37 (95% CI: 0.16–0.85) (Table 2). Furthermore, cumulative mortality risks for both Q2 and Q3 groups were higher, as confirmed by the log-rank test (Fig. 2).

The results of sensitivity analyses

The correlation between serum calcium and 28-day hospital mortality remained consistent across different subgroups and was not influenced by factors such as age, gender, length of ICU stay, participants' serum albumin levels, oxygen saturation, or the occurrence of bacteremia ($p > 0.05$, Fig. 3). This robust association underscores the independence of serum calcium as a predictive factor for 28-day hospital mortality. These findings affirm the robustness and reliability of our research results, highlighting serum calcium as a potential biomarker for monitoring the prognosis of pediatric pneumonia patients. This translation into American English is crafted to ensure academic rigor, logical structure, and accuracy, fitting for a scholarly medical research paper.

After excluding records with incomplete variables, our study focused on 278 patients. Cox regression analysis confirmed our initial findings: higher serum calcium levels significantly reduce the risk of 28-day in-hospital mortality in pediatric pneumonia patients. Specifically, each 1 mmol/mL increase in serum calcium was

associated with a 30% decrease in mortality risk (HR: 0.7, 95% CI: 0.6–0.81). The risk reduction was more pronounced in the higher quartiles of serum calcium levels, with the middle and highest quartiles showing a 41%(HR: 0.59, 95% CI: 0.24–1.45) and 72%(HR: 0.28, 95% CI: 0.09–0.9) decreased mortality risk, respectively, compared to the lowest quartile (Supplementary Table 2). These results emphasize the predictive value of serum calcium in short-term outcomes for pediatric pneumonia.

Discussion

In two pediatric intensive care unit studies, 84% of patients exhibited electrolyte imbalances, with hypocalcemia being the most common at 57.6%. The mortality rate for hypocalcemic patients was significantly higher at 28.3%, compared to 7.5% for those with normal calcium levels, indicating that hypocalcemia is common in critically ill pediatric patients and is associated with a higher mortality rate.[18, 19] The research conducted explored the significant relationship between serum calcium levels and 28-day mortality in pediatric pneumonia patients. Findings indicated that patients with higher serum calcium levels (22.0 to 23.5 mmol/dL) had a significantly reduced 28-day mortality risk by 49% compared to those with lower levels (below 21.9 mmol/dL), and this risk reduction was even greater, at 63%, for levels above 23.6 mmol/dL. Subgroup analysis confirmed the consistency of this association across different clinical subgroups, emphasizing the importance of monitoring and managing serum calcium levels in pediatric pneumonia.

In our study involving pediatric pneumonia patients in the PICU, serum calcium levels emerged as an independent prognostic factor for in-hospital mortality, aligning with findings from other studies.[10, 20–24] Notably, research by Yan et al. on sepsis and multiple myeloma, along with Yang et al.'s comprehensive cohort analysis, identified non-linear relationships.[21, 22] Specifically, in sepsis patients, a decline in serum calcium below 9.0 mg/dL significantly increased mortality risk.[20] In contrast, for multiple myeloma patients, optimal survival correlated with serum calcium levels around 8.40 mg/dL, with both higher and lower levels indicating increased mortality[22]. Yang's extensive cohort studies in UK Biobank and NHANES also discovered a U-shaped correlation between albumin-adjusted calcium levels and all-cause or cardiovascular mortality, with linear association observed in cancer mortality.[21] Our findings, consistent with these studies, establish a direct relationship between serum calcium and mortality, underscoring the clinical importance of monitoring and managing serum calcium levels.

Under physiological conditions, unbound calcium inversely correlates with serum pH as calcium ions compete with hydrogen ions for binding sites on proteins such as albumin.[25] In trauma patients, lower blood calcium levels are associated with worsened acidosis, a condition prevalent in trauma and critically ill patients needing extensive blood transfusions.[26, 27] Studies indicate a significant direct relationship between ionized calcium levels and arterial pH in trauma patients.[27, 28] Our research underscores the independent association between serum calcium levels and 28-day mortality in pediatric pneumonia, even after adjusting for pH. Furthermore, research shows hypocalcemia is common in neonatal sepsis and significantly linked to higher mortality.[10] While our study did not specifically identify sepsis patients, we adjusted for blood culture results in our model. These findings emphasize the importance of serum calcium in assessing the prognosis of severe pediatric diseases, confirming its stable relationship with mortality across different clinical contexts in pediatric pneumonia. In a study conducted within an intensive care unit, the relationship between serum calcium levels and arterial blood pressure was analyzed. It was found that ionized calcium levels were directly associated with

arterial blood pressure, and patients with hypocalcemia were more likely to require vasopressor support compared to those with normal calcium levels.[29] In our study, due to a significant number of missing blood pressure values, we could not analyze the impact of blood pressure on the relationship between serum calcium levels and 28-day mortality in pediatric pneumonia patients. This limitation highlights an area for improvement in future research, where we aim to incorporate blood pressure data to provide a more comprehensive understanding of the factors influencing mortality in pediatric pneumonia cases.

In critical care settings, serum calcium is an essential screening tool, and ionized calcium levels more sensitively reflect the severity of illness.[30] Hypocalcemia in critically ill patients is an independent risk factor for mortality, particularly in those requiring extensive blood transfusions. While the need to treat hypocalcemia is recognized, specific thresholds and parameters for its supplementation are still under research.[31] Overcorrection and the risks of hypercalcemia must also be considered. Moreover, studies indicate that intravenous calcium salts can significantly impact blood pressure and cardiac function in critically ill patients, especially in septic shock.[32] These findings emphasize the importance of monitoring and adjusting serum calcium levels in critical care management.

Based on data from a large teaching hospital, this retrospective cohort study delves into the relationship between serum calcium levels and 28-day mortality rates among pediatric pneumonia patients. With strict inclusion and exclusion criteria and adjustments for key confounding factors like age, gender, ICU stay length, bacteremia presence, arterial blood gas pH, blood lactate, oxygen saturation, serum creatinine, and potassium, the study's reliability and practicality are enhanced. Despite the study's authenticity and innovative therapeutic value, its small sample size and single-center nature require cautious interpretation. Unmeasured confounders may also influence the results. Nonetheless, this research lays the groundwork for future extensive, multicenter, prospective studies to validate and extend these findings.

Conclusion

This research emphasizes the crucial role of serum calcium as a predictor of 28-day mortality in pediatric pneumonia cases. The study confirms that higher serum calcium correlates with reduced mortality risk, underscoring its potential as a key biomarker for severity assessment and prognosis in pediatric pneumonia. This insight is pivotal for clinical decision-making. Ongoing investigations are essential to understand the mechanisms better and validate these findings in diverse clinical settings.

Materials and Methods

PIC database:

The PIC (Paediatric Intensive Care) database is a large, freely accessible resource containing de-identified health-related data of 12881 pediatric patients hospitalized in the intensive care unit (ICU) of the Children's Hospital affiliated with Zhejiang University School of Medicine from 2010 to 2019. [33]This project was authorized by the Institutional Review Board/Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine (2019_IRB_052).

Clinical Data Collection:

After completing registration with the Collaborative Institutional Training Initiative (CITI), access was granted to use the PIC database. All laboratory variables were obtained from the first blood sample drawn post-admission to the PICU. The clinical data collected included patient characteristics, vital signs, laboratory findings, and mortality outcomes.

Patient Selection:

For this study, individuals aged between 28 days and 18 years, who were definitively diagnosed with pneumonia, were included. The inclusion criteria were as follows: patients diagnosed with pneumonia during their ICU stay, defined by ICD-9 codes JB.900 and JB.901. Of the 828 patients initially identified from the PIC database (considering only their first ICU admission), 31 neonates under 28 days old, 105 patients who died within 2 days of admission to the ICU, and 278 patients with missing serum calcium data were excluded, leaving a total of 414 patients for this study (Fig. 1).

Survival information was extracted from the 'Patients' table within the PIC database. Data related to hospitalization duration and time of death were obtained from the 'Admissions' table. Laboratory tests and microbiological cultures were gathered from the 'LabEvents' and 'MicrobiologyEvents' tables, respectively.

Outcome Measurement:

In the PIC database, within the 'Patients' section, 28-day mortality was identified as the primary outcome measure. To ensure accurate inclusion of pneumonia patients, the study team confirmed pneumonia as the main diagnosis based on detailed symptoms and diagnoses recorded at admission and discharge. Consequently, pneumonia was established as the cause of death in the discharge diagnoses. The key outcome variable assessed in this research was the rate of 28-day mortality, calculated from the date of admission to the date of death. This approach enabled a precise measurement of short-term mortality in pediatric pneumonia patients, offering valuable insights for clinical practice and future research.

Covariates:

The selection of confounders inclusion were based on a combination of the results from univariate Cox regression analysis, previous literature reports,[12, 34] and covariate impact on the exposure-outcome association greater than 10%. The final model included the following covariates: age, gender, length of stay in the ICU, presence of bacteremia, arterial blood gas pH, blood lactate, blood oxygen saturation, serum creatinine, and serum potassium.

Statistical Analysis

Serum calcium levels, due to their minimal numerical variation, were amplified tenfold from their original values for analysis, with measurements presented in mmol/dL. Patients were stratified into three categories based on serum calcium levels (21.9 mmol/dL, 22.0-23.5 mmol/dL, and > 23.6 mmol/dL).

Categorical data were expressed as percentages. Continuous data following a normal distribution were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were described using

the median and interquartile range (IQR). To evaluate baseline characteristics, we employed one-way analysis of variance (ANOVA) to determine statistical differences among the serum calcium tertiles for continuous variables. The chi-square test was used to examine differences in categorical variables. The relationship between serum calcium levels and the risk of 28-day mortality was analyzed using restricted cubic splines. We applied a Cox proportional hazards model to calculate the hazard ratio (HR). Kaplan-Meier curves were plotted to illustrate outcomes across different groups, and the log-rank test was utilized for comparing cumulative mortality rates. The presence of potential multicollinearity was evaluated using the variance inflation factor (VIF), with a threshold of VIF ≥ 5 indicating significant multicollinearity. Five models were constructed for the analysis: Model 1 adjusted for age and sex; Model 2 further adjusted for length of stay in the ICU and blood culture outcomes; Model 3 additionally included adjustments for arterial blood gas (ABG) pH, lactate levels, oxygen saturation; Model 4 additionally adjusted for serum potassium and serum creatinine.

A series of sensitivity analyses were conducted to ascertain the robustness of our research findings. Initially, baseline serum calcium was categorized into three groups (low to high), and the stability of the hazard ratio (HR) estimates was evaluated by calculating the trend p-value. Further, our dataset presented missing values as follows: serum creatinine had a 6.5% missing rate (27 cases), lactate (LAC) 10.6% (44 cases), pH 9.7% (40 cases), potassium 10.1% (42 cases), and oxygen saturation 9.9% (41 cases), all other variables involved in the analysis were complete without any missing data. To address these missing values, we implemented a robust statistical method, employing multiple imputation with 5 replications and the chained equations method within the R mice procedure. This approach was selected to bolster the statistical strength of our analysis and reduce potential biases stemming from the missing data. Thirdly, due to a high rate of missing data for albumin, which made it unsuitable for inclusion as a confounder in the modelyet acknowledging albumin's importance as a prognostic indicator, we conducted sensitivity analyses to explore the potential impact of albumin alterations. This included an interaction analysis, despite its absence from the main model adjustments.

Subgroup analyses were carried out using a stratified Cox proportional hazards model, stratifying by age (≤ 2 months, 3–11 months, ≥ 12 months), gender, length of stay in the ICU (≤ 5 days, 6–11 days, > 12 days), albumin levels (≤ 36.2g/L, 36.3-40.7g/L, ≥ 40.8g/L), oxygen saturation (< 95%, ≥ 95%), and the blood culture outcomes. The likelihood ratio test was utilized to evaluate interactions between subgroups.

In addressing the challenge posed by missing data in our analysis, we implemented a strict data inclusion criterion, whereby only those patient records with complete datasets, including all covariates, were retained. This approach ultimately resulted in a final sample size of 278 patients for our analysis. On this refined dataset, we conducted a Cox regression analysis. The findings and detailed results of this analysis are presented in the supplementary tables of our study. This approach was taken to mitigate any potential biases that could arise from incomplete data, ensuring the robustness and reliability of our findings (Supplementary Table S2).

Our study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure the rigor and comprehensiveness of our observational research.

Statistical analyses were conducted using R version 3.3.2 (http://www.R-project.org, R Foundation) and Free Statistics software version 1.7. A two-tailed p-value < 0.05 was considered statistically significant.

Abbreviations

ALT
glutamic pyruvic transaminase
AST
glutamic oxaloacetic transaminase
LDH
lactate dehydrogenase
RDW
red cell distribution width. CRP,C-reactive protein,PH,arterial blood gas pH,γ-GT,Gamma-glutamyl transpeptidase
BUN
blood urine nitrogen,Glu,Blood glucose

Declarations

Acknowledgments

The authors would like to extend their heartfelt appreciation to the individuals responsible for developing and maintaining this database. Additionally, the authors would like to express their gratitude to the clinical scientist team and Dr. Jinbao Ma for their continuous support and valuable advice.

Author contributions

J.L.Z. played a pivotal role in the conception and design of the study, data acquisition, data analysis, interpretation of results, drafting the manuscript, and revising it critically for important intellectual content. M.H.L. significantly contributed to the study's design, data acquisition, analysis and interpretation, and was involved in drafting and revising the manuscript. D.Y. was involved in the study's design, data analysis, and interpretation of results. Y.Y.Zwas instrumental in the study's conception, design, data acquisition and analysis, interpretation of results, drafting the manuscript, and its revision. All authors have reviewed and approved the final version of the manuscript.

Funding

This study was supported by the Medical Key Laboratory Construction Project (No. ZDXK2021006).

Data Availability Statement

The data used in this study are sourced from the publicly accessible Pediatric Intensive Care (PIC) database. This database contains de-identified health-related data of pediatric patients admitted to the ICU of Children's Hospital affiliated with Zhejiang University School of Medicine from 2010 to 2019. The database, comprising 12881 pediatric patients' records, is available at http://pic.nbscn.org//. Details on the specific dataset used, analytical methods, and results can be found within this paper and its supplementary materials. For further inquiries about data access and details, please contact the corresponding author.

Declaration of No Conflicts of Interest

The authors affirm that there are no conflicts of interest, including any commercial or financial relationships that could potentially bias the research findings.

References

1. Orimadegun AE, Adepoju AA, Myer L. A Systematic Review and Meta-analysis of Sex Differences in Morbidity and Mortality of Acute Lower Respiratory Tract Infections Among African Children. *Journal of pediatrics review* 2020; 8(2):65–78.
2. McAllister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *The Lancet Global health* 2019; 7(1):e47-e57.
3. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet (London, England)* 2016; 388(10063):3027–3035.
4. Jesenak M, Banovcin P, Jesenakova B, Babusikova E. Pulmonary manifestations of primary immunodeficiency disorders in children. *Frontiers in pediatrics* 2014; 2:77.
5. Nguyen TK, Tran TH, Roberts CL, Fox GJ, Graham SM, Marais BJ. Risk factors for child pneumonia - focus on the Western Pacific Region. *Paediatric respiratory reviews* 2017; 21:95–101.
6. Clapham DE. Calcium signaling. *Cell* 2007; 131(6):1047–1058.
7. Chen X, Cao R, Zhong W. Host Calcium Channels and Pumps in Viral Infections. *Cells* 2019; 9(1).
8. Saurav S, Tanwar J, Ahuja K, Motiani RK. Dysregulation of host cell calcium signaling during viral infections: Emerging paradigm with high clinical relevance. *Molecular aspects of medicine* 2021; 81:101004.
9. Straus MR, Tang T, Lai AL, Flegel A, Bidon M, Freed JH, et al. Ca(2+) Ions Promote Fusion of Middle East Respiratory Syndrome Coronavirus with Host Cells and Increase Infectivity. *Journal of virology* 2020; 94(13).
10. Liu Y, Chai Y, Rong Z, Chen Y. Prognostic Value of Ionized Calcium Levels in Neonatal Sepsis. *Annals of nutrition & metabolism* 2020; 76(3):193–200.
11. Gimelraikh Y, Berant R, Stein M, Berzon B, Epstein D, Samuel N. Early Hypocalcemia in Pediatric Major Trauma: A Retrospective Cohort Study. *Pediatric emergency care* 2022; 38(10):e1637-e1640.
12. Sharifuzzaman, Ahmed T, Afroze F, Sarmin M, Shaly NJ, Chisti MJ. Hypocalcaemia in children hospitalised for diarrhoea was associated with a higher death rate than those without hypocalcaemia. *Acta paediatrica (Oslo, Norway : 1992)* 2020; 109(7):1487–1488.
13. Miura S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, et al. Association of Hypocalcemia With Mortality in Hospitalized Patients With Heart Failure and Chronic Kidney Disease. *Journal of cardiac failure* 2015; 21(8):621–627.
14. Shiyovich A, Plakht Y, Gilutz H. Serum calcium levels independently predict in-hospital mortality in patients with acute myocardial infarction. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2018; 28(5):510–516.

15. 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. *Clinica chimica acta; international journal of clinical chemistry* 2019; 494:94–99.
16. Thongprayoon C, Cheungpasitporn W, Chewcharat A, Mao MA, Thirunavukkarasu S, Kashani KB. Hospital mortality and long-term mortality among hospitalized patients with various admission serum ionized calcium levels. *Postgraduate medicine* 2020; 132(4):385–390.
17. Mehta M, Ghani H, Chua F, Draper A, Calmonson S, Prabhakar M, et al. Retrospective case-control study to evaluate hypocalcaemia as a distinguishing feature of COVID-19 compared with other infective pneumonias and its association with disease severity. *BMJ open* 2021; 11(12):e053810.
18. Naseem F, Saleem A, Mahar IA, Arif F. Electrolyte imbalance in critically ill paediatric patients. *Pakistan journal of medical sciences* 2019; 35(4):1093–1098.
19. Singhi SC, Singh J, Prasad R. Hypocalcaemia in a paediatric intensive care unit. *Journal of tropical pediatrics* 2003; 49(5):298–302.
20. Yan D, Xie X, Fu X, Pei S, Wang Y, Deng Y, et al. U-SHAPED ASSOCIATION BETWEEN SERUM CALCIUM LEVELS AND 28-DAY MORTALITY IN PATIENTS WITH SEPSIS: A RETROSPECTIVE ANALYSIS OF THE MIMIC-III DATABASE. *Shock (Augusta, Ga)* 2023; 60(4):525–533.
21. Yang M, Miao J, Du L, Wang J, Yang J, Lu J, et al. Serum Calcium Concentrations and Risk of All-Cause and Cause-Specific Mortality: Results From 2 Prospective Cohorts. *The Journal of clinical endocrinology and metabolism* 2023; 108(8):e527-e535.
22. Mao Y, Zhu S, Geng Y. Association between serum calcium and in-hospital mortality in critical patients with multiple myeloma: a cohort study. *Hematology (Amsterdam, Netherlands)* 2022; 27(1):795–801.
23. Schmitz T, Thilo C, Linseisen J, Heier M, Peters A, Kuch B, et al. Low serum calcium is associated with higher long-term mortality in myocardial infarction patients from a population-based registry. *Sci Rep* 2021; 11(1):2476.
24. Thongprayoon C, Cheungpasitporn W, Hansrivijit P, Medaura J, Chewcharat A, Mao MA, et al. Impact of Changes in Serum Calcium Levels on In-Hospital Mortality. *Medicina (Kaunas, Lithuania)* 2020; 56(3).
25. Wang S, McDonnell EH, Sedor FA, Toffaletti JG. pH effects on measurements of ionized calcium and ionized magnesium in blood. *Archives of pathology & laboratory medicine* 2002; 126(8):947–950.
26. De Robertis E, Kozek-Langenecker SA, Tufano R, Romano GM, Piazza O, Zito Marinosci G. Coagulopathy induced by acidosis, hypothermia and hypocalcaemia in severe bleeding. *Minerva anestesiologica* 2015; 81(1):65–75.
27. Ho KM, Leonard AD. Concentration-dependent effect of hypocalcaemia on mortality of patients with critical bleeding requiring massive transfusion: a cohort study. *Anaesthesia and intensive care* 2011; 39(1):46–54.
28. Vivien B, Langeron O, Morell E, Devilliers C, Carli PA, Coriat P, et al. Early hypocalcemia in severe trauma. *Critical care medicine* 2005; 33(9):1946–1952.
29. Desai TK, Carlson RW, Thill-Baharozian M, Geheb MA. A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. *Critical care medicine* 1988; 16(6):578–582.
30. Tee MC, Holmes DT, Wiseman SM. Ionized vs serum calcium in the diagnosis and management of primary hyperparathyroidism: which is superior? *American journal of surgery* 2013; 205(5):591–596; discussion 596.

31. Kelly A, Levine MA. Hypocalcemia in the critically ill patient. *Journal of intensive care medicine* 2013; 28(3):166–177.
32. Whelan AJ, Ricci M, Harthan AA, Deshpande G. Calcium Responsive Pediatric Septic Shock Refractory to Isotonic Crystalloids and Inotropic Agents. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG* 2022; 27(8):765–769.
33. Zeng X, Yu G, Lu Y, Tan L, Wu X, Shi S, et al. PIC, a paediatric-specific intensive care database. *Scientific data* 2020; 7(1):14.
34. Lu Y, Song L. Clinical Significance of Procalcitonin, Lactic Acid, and Endotoxin Testing for Children With Severe Pneumonia and Sepsis. *Alternative therapies in health and medicine* 2023; 29(3):218–223.

Tables

Table 1. Baseline Clinical and Demographic Characteristics of Pediatric Pneumonia Patients

Variables	Total	Q1≤21.9	22.0≤Q2≤23.5	Q3≥23.6	P-value
	(n = 414)	(n = 137)	(n = 136)	(n = 141)	
Serum Calcium(mmol/dL)	22.6 ± 2.1	20.3 ± 1.7	22.7 ± 0.5	24.7 ± 0.8	< 0.001
Gender, n (%)					0.081
Male	174 (42.0)	47 (34.3)	63 (46.3)	64 (45.4)	
Female	240 (58.0)	90 (65.7)	73 (53.7)	77 (54.6)	
Age(month)	7.0 (2.0, 22.0)	16.0 (4.0, 48.0)	6.0 (3.0, 21.2)	4.0 (2.0, 10.0)	< 0.001
Hemoglobin(g/L)	107.1 ± 19.7	101.9 ± 21.7	107.6 ± 18.7	112.0 ± 17.1	< 0.001
RDW(CV%)	14.7 ± 2.3	14.8 ± 2.4	14.4 ± 1.8	14.7 ± 2.6	0.422
White blood cell(10^9/L)	10.1 (6.8, 14.5)	10.0 (6.0, 16.4)	8.4 (6.4, 12.4)	11.0 (8.7, 14.9)	0.004
Lymphocyte (10^9/L)	2.7 (1.6, 5.3)	2.1 (1.3, 3.9)	2.6 (1.5, 4.2)	4.4 (2.3, 6.8)	< 0.001
Neutrophil(10^9/L)	5.1 (2.9, 9.0)	6.8 (4.0, 10.7)	4.6 (2.4, 7.2)	4.6 (2.8, 7.8)	0.003
Monocyte (10^9/L)	0.6 (0.3, 1.0)	0.5 (0.2, 0.9)	0.5 (0.3, 0.8)	0.7 (0.4, 1.1)	0.008
Platelet(10^9/L)	316.0 (218.5, 404.5)	261.5 (166.8, 340.8)	297.0 (223.0, 378.0)	372.5 (291.2, 490.2)	< 0.001
CRP(g/L)	21.5 ± 30.7	32.1 ± 40.8	19.0 ± 26.2	12.2 ± 14.1	< 0.001
PH	7.3 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	0.868
Oxygen saturation(%)	89.4 ± 15.3	88.5 ± 14.0	90.2 ± 16.6	89.5 ± 15.3	0.674
Lactic acid(mmol/L)	1.9 (1.3, 2.9)	1.6 (1.2, 2.6)	1.9 (1.3, 2.6)	2.3 (1.6, 3.2)	< 0.001
ALT(U/L)	23.0 (16.0, 41.0)	27.0 (16.0, 54.0)	22.0 (16.0, 37.0)	22.0 (16.0, 35.5)	0.183
AST(U/L)	45.0 (33.0, 73.0)	56.5 (34.0, 99.5)	45.0 (32.0, 70.0)	41.0 (33.0, 53.0)	0.006
Albumin (g/L)	38.2 ± 6.0	33.1 ± 5.4	39.2 ± 4.3	42.1 ± 4.5	< 0.001
Cholesterol(mmol/l)	3.3 ± 1.1	2.9 ± 1.3	3.2 ± 0.9	3.7 ± 1.0	< 0.001
Sodium(mmol/l)	137.4 ± 4.9	136.3 ± 5.9	137.6 ± 4.9	138.4 ± 3.5	0.003
Potassium(mmol/l)	4.1 ± 0.7	3.8 ± 0.8	4.1 ± 0.6	4.3 ± 0.6	< 0.001
Chloride(mmol/l)	105.2 ± 5.6	105.8 ± 5.9	104.5 ± 5.0	105.3 ± 5.7	0.2

Triglycerides(mmol/l)	1.0 (0.7, 1.3)	1.1 (0.8, 1.4)	1.0 (0.7, 1.2)	1.0 (0.7, 1.3)	0.069
γ-GT(U/L)	26.0 (14.0, 53.0)	23.0 (13.0, 47.5)	27.0 (13.0, 62.2)	28.0 (14.0, 56.0)	0.511
LDH(U/L)	386.0 (302.5, 574.5)	527.5 (371.0, 898.2)	373.0 (288.0, 517.0)	335.5 (286.2, 397.8)	< 0.001
BUN(mmol/l)	3.3 (2.4, 4.9)	3.4 (2.2, 5.6)	3.3 (2.7, 4.3)	3.1 (2.3, 4.6)	0.465
Creatinine(umol/l)	42.1 ± 17.3	47.1 ± 25.8	40.0 ± 10.1	39.1 ± 9.6	< 0.001
Glu(mmol/L)	7.0 ± 3.2	7.3 ± 3.4	7.3 ± 3.8	6.3 ± 2.4	0.038
Length of stay in the ICU(days)	12.4 ± 16.2	15.0 ± 19.8	11.2 ± 14.7	11.1 ± 13.3	0.072
Positive blood cultures (%)					0.069
NO	233 (56.3)	88 (64.2)	70 (51.5)	75 (53.2)	
YES	181 (43.7)	49 (35.8)	66 (48.5)	66 (46.8)	
28 days mortality,n (%)					0.029
NO	368 (88.9)	114 (83.2)	123 (90.4)	131 (92.9)	
YES	46 (11.1)	23 (16.8)	13 (9.6)	10 (7.1)	

Abbreviations: ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; LDH, lactate dehydrogenase; RDW, red cell distribution width. CRP, C-reactive protein, PH, arterial blood gas pH,γ-GT,Gamma-glutamyl transpeptidase;BUN, blood urine nitrogen,Glu, Blood glucose

P-values were obtained through one-way ANOVA analysis for continuous variables and chi-square test for categorical variables.

Table 2. The relationship between serum calciumand and 28 days Mortality in Pediatric Pneumonia Patients.

Exposure	n.event%	Crude	Adjusted HR(95% CI)			
		HR(95% CI)	Model 1	Model 2	Model 3	Model 4
Serum calcium(mmol/dL)	46 (11.1)	0.79 (0.72~0.88)	0.78 (0.71~0.87)	0.78 (0.71~0.87)	0.78 (0.7~0.87)	0.74 (0.65~0.85)
Serum calcium quartiles						
Q1 (≤21.9mmol/dL)	23 (16.8)	1(Ref)	1(Ref)	1(Ref)	1(Ref)	1(Ref)
Q2 (22.0-23.5mmol/dL)	13 (9.6)	0.55 (0.28~1.09)	0.5 (0.25~1.01)	0.52 (0.26~1.05)	0.48 (0.23~0.99)	0.51 (0.25~1.08)
Q3 (≥23.6mmol/dL)	10 (7.1)	0.4 (0.19~0.84)	0.35 (0.16~0.76)	0.37 (0.17~0.8)	0.48 (0.23~0.99)	0.37 (0.16~0.85)

HR, Hazard Ratio.

Model 1 adjusted for age and sex;

Model 2 further adjusted for length of stay in the ICU and blood culture outcomes;

Model 3 additionally included adjustments for arterial blood gas (ABG) pH, lactate levels, oxygen saturation;

Model 4 additionally adjusted for serum potassium and serum creatinine.

Figures

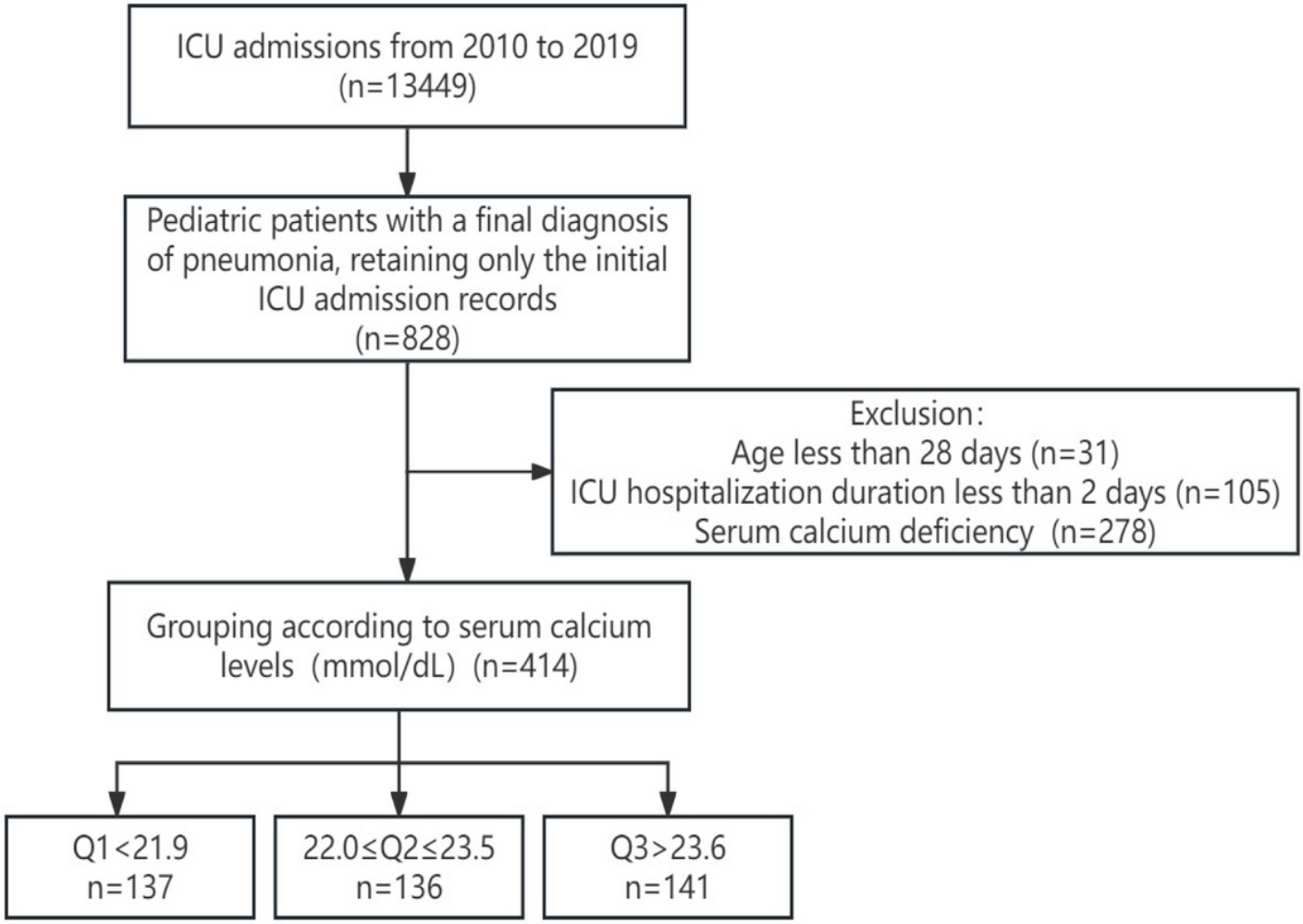
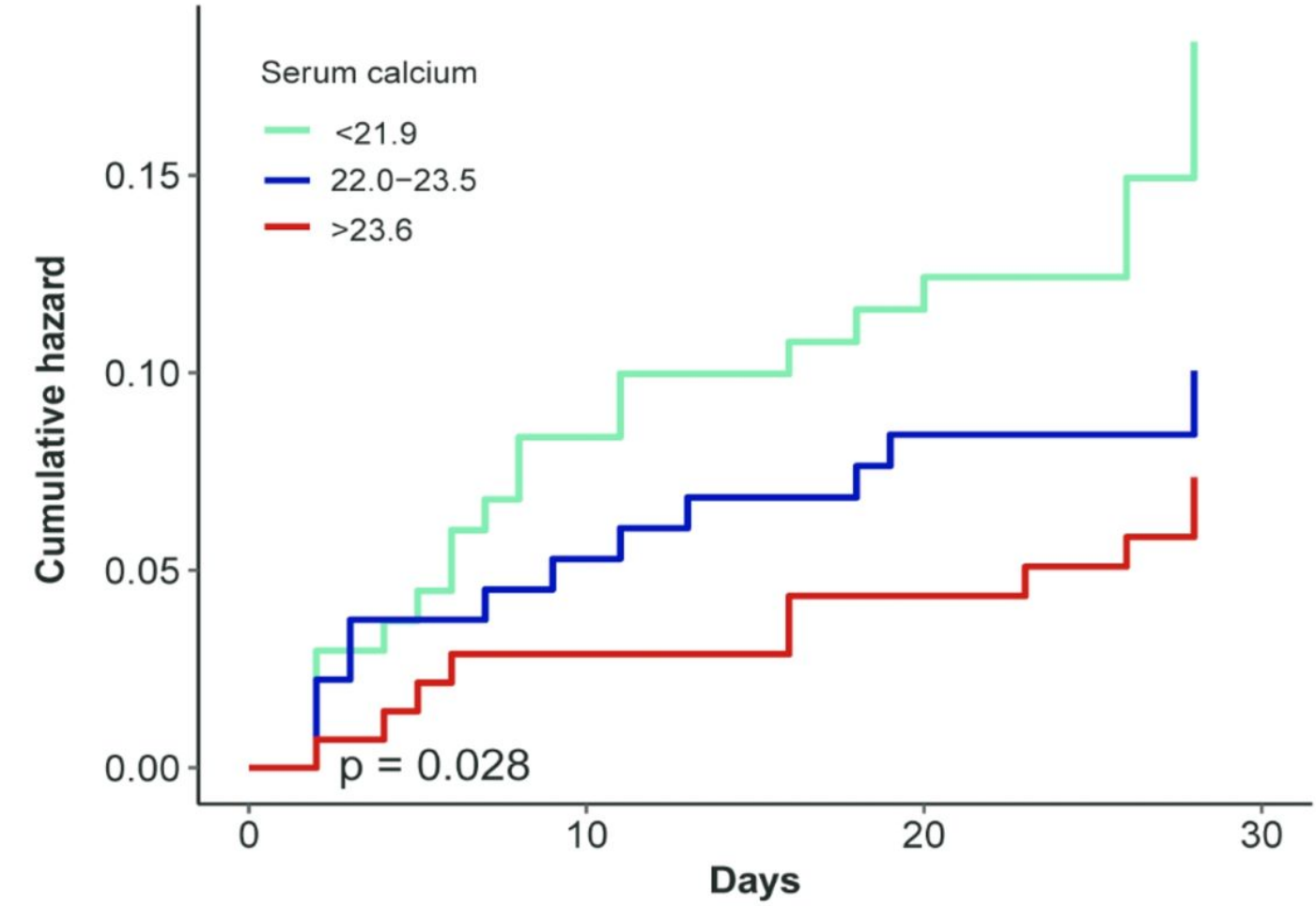


Figure 1

Patient Selection Flowchart for the Pediatric Pneumonia Study.



Number at risk

<21.9	137	126	122	0
22.0–23.5	136	129	125	0
>23.6	141	137	135	0

Figure 2

Cumulative Mortality Hazard Over 28 Days by Serum Calcium Levels in Pediatric Pneumonia Patients

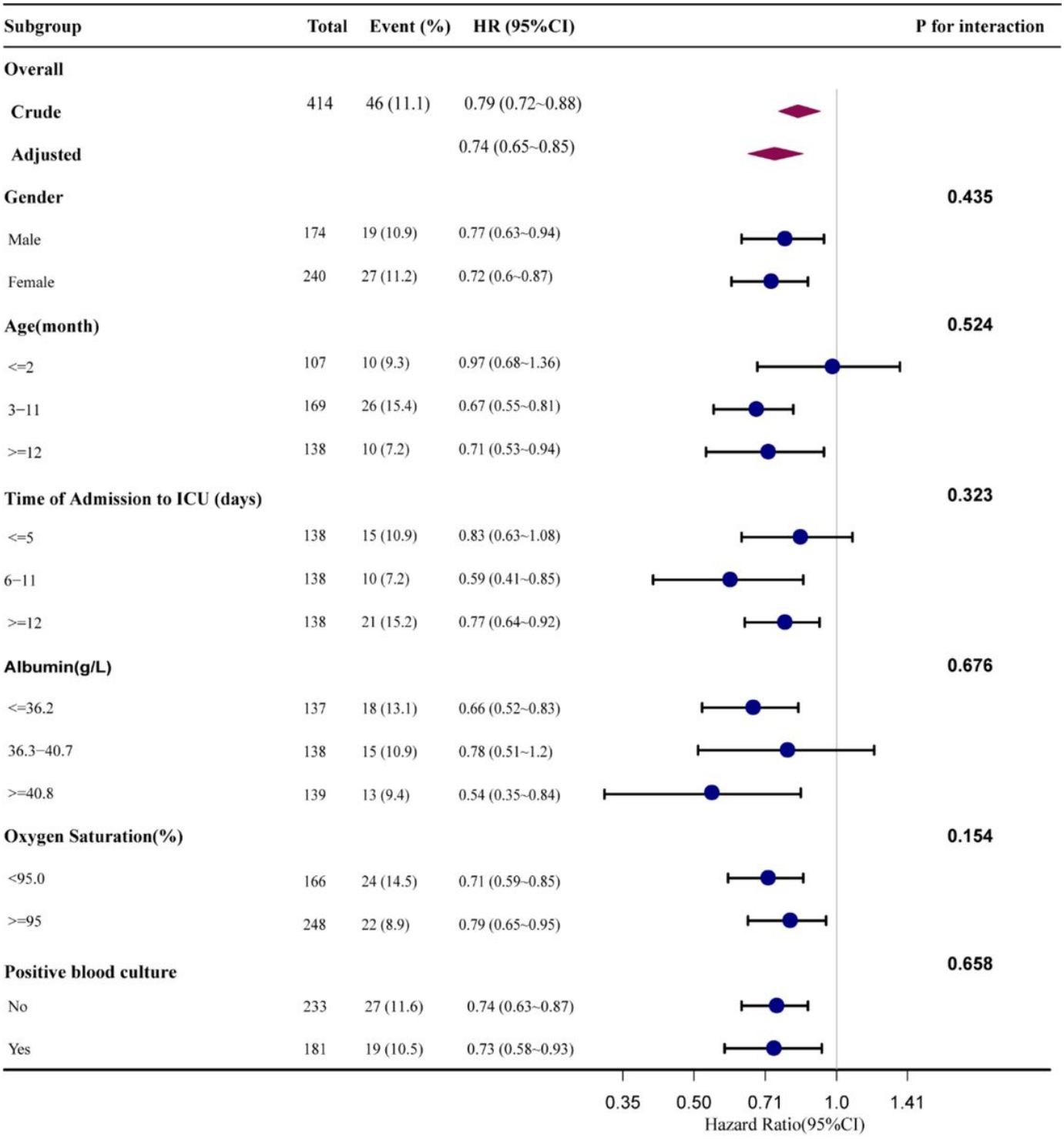


Figure 3

The correlation between serum calcium and 28-day hospital mortality remained consistent across different subgroups and was not influenced by factors such as age, gender, length of ICU stay, participants' serum albumin levels, oxygen saturation, or the occurrence of bacteremia ($P > 0.05$)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.doc