Critical Care Medicine
November 2025 • Volume 53 • Number 11 • Pages e2380–e2381

LETTER TO THE EDITOR

Ionized Hypocalcemia and ICU Mortality: Marker of Severity or Modifiable Risk Factor?

Gauthier Nendumba, MD[1]
Thibault Gennart, MD[1]
Nathan De Lissnyder, MD[2]
Sydney Blackman, MD[3]
Thalie Al Haddad[4]
Patrick M. Honore, MD, PhD, FCCM[1]

To the Editor:

The article by Li et al (1), published in a recent issue of *Critical Care Medicine*, offers a valuable contribution to the understanding of electrolyte disturbances in critically ill patients. However, several aspects warrant further consideration.

The authors report that the mean ionized calcium (iCa) levels during the first 24 hours following ICU admission were independently associated with ICU mortality in their large retrospective cohort of nonhypercalcemic patients (1).

This association has been examined in numerous retrospective studies, although findings have varied (2, 3). While univariable analyses often show a link between hypocalcemia and increased mortality (4), this relationship frequently weakens after adjustment for confounders. Notably, only severe hypocalcemia (commonly defined as iCa < 0.90–1.00 mmol/L) tends to remain significantly associated with mortality in multivariable models (5).

The largest of these studies, involving 15,409 ICU patients in China, did report a modest association between mild hypocalcemia and mortality (2). However, their definition of mild hypocalcemia (iCa 0.90–1.15 mmol/L) was lower than thresholds used in many other studies (M. Melchers et al, unpublished observations, 2023).

Taken together, the current body of evidence does not support a direct causal link between low iCa levels and adverse outcomes in ICU patients. Instead, hypocalcemia may serve as a surrogate marker of illness severity. It has been hypothesized that this state reflects an adaptive response to critical illness and tissue injury, rather than a direct contributor to organ dysfunction—a hypothesis deserving of further study in prospective, randomized controlled trials (2).

1 *CHU UCL Godinne Namur, UCLouvain Medical School, Yvoir, Belgium.*
2 *Vrije Universiteit Brussel, UZ Brussel, Brussels, Belgium.*
3 *CHIREC, ULB University, Brussels, Belgium.*
4 *ULB University, Brussels, Belgium.*

Drs. Nendumba and Honore designed the article. All authors participated in drafting and reviewing. All authors read and approved the final version of the article.

The authors have disclosed that they do not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000006836

REFERENCES

1. Li FY, Chen Y, Zhou X, et al; China National Critical Care Quality Control Center Group and China Critical Care Clinical Trials Group (CCCCTG): Association of hypocalcemia and mean arterial pressure with patient outcome in ICU. *Crit Care Med* 2025; 53:e839–e849
2. Melchers M, van Zanten ARH: Management of hypocalcaemia in the critically ill. *Curr Opin Crit Care* 2023; 29:330–338
3. Muller B, Becker KL, €anzlin M, et al: Disordered calcium homeostasis of sepsis: Association with calcitonin precursors. *Eur J Clin Invest* 2000; 30:823–831
4. Egi M, Kim I, Nichol A, et al: Ionized calcium concentration and outcome in critical illness. *Crit Care Med* 2011; 39:314–321
5. Steele T, Kolamunnage-Dona R, Downey C, et al: Assessment and clinical course of hypocalcemia in critical illness. *Crit Care* 2013; 17:R106