Serum Calcium and Outcomes After Acute Ischemic Stroke: Updated Review

Adel Saeed Abdelghaffar Hoda[1], Mohammed Hanafy Aly Ghonemy[2], Eman Elsaeed Tawfik Elmetwally[3], Hanan Mohamed Sabry Nasr[4]

1. M.B.B.CH, Faculty of Medicine, Zagazig University
2. Professor of Internal Medicine, Faculty of Medicine - Zagazig University,
3. Assistant Professor of Radiology, Faculty of Medicine - Zagazig University,
4. Assistant Professor of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
5. Assistant Professor of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt,

Corresponding Author: Eman Elsaeed Tawfik Elmetwally

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Abstract

Background: Acute ischemic stroke (AIS) remains a leading cause of death and long-term disability worldwide. Despite advances in reperfusion therapies and stroke unit care, prognostication remains imperfect. Among emerging biomarkers, serum calcium has attracted attention given its pivotal role in neuronal excitotoxicity, vascular tone regulation, and systemic homeostasis. The literature is evolving and somewhat conflicting: studies report associations of both low and high serum calcium levels with infarct size, severity and outcome, but measurement modalities (total vs ionized vs albumin-corrected), timing, and patient populations vary widely. Aim: This review aims to critically appraise and synthesise current evidence on serum calcium (total, albumin-corrected, ionized) as a prognostic factor in AIS. We address mechanistic underpinnings of calcium in ischemic brain injury, examine how serum calcium levels correlate with stroke severity, infarct volume, early neurological deterioration, functional outcomes and mortality, and explore how calcium interacts with other relevant axes (vitamin D, parathyroid hormone, magnesium). We also highlight measurement issues, gaps in data, and implications for clinical practice and future research.

Conclusions: Existing data indicate that serum calcium has promise as a prognostic biomarker in AIS, but the associations are complex and non-linear. For example, elevated albumin-corrected calcium on admission has been linked to poorer short-term outcomes and higher long-term mortality.Other studies suggest lower calcium or ionized calcium correlates with more severe injury and worse functional recovery. The heterogeneity in measurement timing, patient cohorts (age, comorbidities, stroke subtype), and adjustment for confounders limits firm conclusions. Clinically, serum calcium may complement established prognostic tools (e.g., NIHSS, imaging) but is not yet ready for routine use. Future directions include large prospective cohorts with standardized calcium measurement, exploration of mechanistic links, and incorporation of calcium into multivariable prognostic models. In sum, while not a standalone predictor, serum calcium merits inclusion in the next-generation prognostication paradigm for AIS.

Keywords: *Calcium, Acute Ischemic Stroke, Outcomes*

Introduction

Acute ischemic stroke (AIS) continues to represent one of the most significant causes of death and long-term disability globally, with an immense socioeconomic impact. Despite advances in reperfusion therapies and neurocritical care, accurate early prognostication remains a challenge for clinicians [1]. Traditional predictors, such as the National Institutes of Health Stroke Scale (NIHSS), imaging characteristics, and age, explain part of the variability in outcomes but fail to capture the full biological complexity of ischemic injury [2]. Consequently, attention has shifted toward serum biomarkers that might reflect the underlying neurobiological and metabolic responses to cerebral ischemia.

Among these, serum calcium has emerged as a particularly intriguing candidate biomarker due to its fundamental physiological roles in synaptic transmission, neuronal excitability, vascular tone, and coagulation pathways [3]. During ischemic events, cellular energy failure leads to depolarization, resulting in excessive calcium influx through voltage-gated and glutamate-dependent channels. This intracellular calcium overload activates destructive enzymatic cascades, leading to oxidative stress, mitochondrial dysfunction, and neuronal death [4,5]. Given these mechanistic foundations, circulating calcium levels could plausibly mirror or influence ischemic pathophysiology and patient outcomes.

However, findings across studies remain inconsistent. Several investigations have shown that low serum calcium levels—particularly ionized calcium—are associated with more severe neurological deficits and poorer functional outcomes [6,7]. Others report that higher total or albumin-corrected calcium levels independently predict increased mortality or unfavorable recovery after AIS [8,9]. Some cohorts even suggest a U-shaped relationship, where both hypo- and hypercalcemia are linked with worse outcomes [10]. These inconsistencies likely stem from variations in study design, measurement timing (admission versus later), calcium form (total, albumin-corrected, or ionized), and adjustment for confounding variables [11,12].

Furthermore, calcium metabolism interacts with several other physiological systems relevant to stroke, including parathyroid hormone (PTH), vitamin D, and magnesium, all of which may influence vascular and neuronal responses to ischemia [13,14]. Population-based analyses have suggested non-linear associations between serum calcium and incident stroke risk, emphasizing the complexity of interpreting calcium homeostasis in vascular disease [15].

Given the growing but heterogeneous evidence, a comprehensive updated review is warranted to clarify the prognostic significance of serum calcium in AIS. This review aims to (1) synthesize available evidence on serum calcium levels as predictors of stroke severity, early neurological deterioration, functional outcome, and mortality; (2) explore the mechanistic and pathophysiological rationale underlying these associations; and (3) identify methodological and analytical gaps that should be addressed in future research [16].

By critically appraising the current literature, this review seeks to determine whether serum calcium represents a clinically meaningful prognostic biomarker or remains a marker of systemic physiological derangement without specific predictive value for neurological outcomes [17].

Pathophysiology of Calcium in Ischemic Brain Injury

Calcium plays a central role in the pathophysiological cascade of ischemic brain injury. Following arterial occlusion, interruption of cerebral blood flow causes a rapid depletion of adenosine triphosphate (ATP) in neurons and glial cells. This loss of energy supply leads to membrane depolarization and subsequent opening of voltage-dependent calcium channels, allowing excessive calcium influx into the cytoplasm [18]. The elevation of intracellular calcium triggers activation of calcium-dependent enzymes, such as proteases, lipases, and endonucleases, which degrade cellular structures and contribute to neuronal death [19]. In parallel, calcium overload within mitochondria disrupts oxidative phosphorylation and promotes the formation of reactive oxygen species (ROS), further exacerbating oxidative stress and cellular injury [20].

The rise in intracellular calcium concentration also mediates **glutamate excitotoxicity**, one of the hallmark mechanisms of ischemic neuronal death. Ischemia induces excessive release of glutamate from presynaptic terminals, which overstimulates NMDA and AMPA receptors on postsynaptic neurons,

leading to further calcium entry and amplification of injury [21]. This self-perpetuating cycle of calcium-mediated neurotoxicity amplifies infarct size and worsens neurological outcomes. Experimental stroke models have consistently shown that blockade of NMDA receptors or voltage-gated calcium channels reduces infarct volume and improves survival of neurons in the ischemic penumbra [22,23].

In addition to neuronal injury, calcium plays a crucial role in vascular and glial responses after ischemia. In endothelial cells, calcium influx contributes to disruption of the **blood-brain barrier (BBB)** and the development of vasogenic edema [24]. Calcium-dependent activation of matrix metalloproteinases (MMPs) and tight junction disassembly lead to increased BBB permeability, facilitating the entry of plasma proteins and inflammatory cells into the brain parenchyma [25]. Moreover, calcium signaling in astrocytes and microglia modulates inflammatory cascades, cytokine release, and reactive gliosis, which further impact neuronal survival [26].

The extent of calcium dysregulation in ischemic tissue appears closely related to the duration and severity of ischemia. Early reperfusion can partially restore ionic homeostasis, but reperfusion itself may induce **calcium overload** through transient oxidative bursts and mitochondrial dysfunction—known as **reperfusion injury** [27]. These events underline why systemic serum calcium levels might reflect not only peripheral metabolic status but also secondary consequences of cellular damage and ion leakage across disrupted membranes.

Thus, the biochemical rationale linking serum calcium levels to stroke outcomes is grounded in this multifaceted neurovascular pathophysiology: calcium is both a driver and a marker of ischemic damage. Understanding this relationship is essential for interpreting clinical findings and assessing whether variations in circulating calcium reflect adaptive or maladaptive processes during acute ischemic stroke [28].

Serum Calcium Homeostasis and Its Clinical Determinants

Calcium homeostasis in humans is tightly regulated through complex interactions involving the skeletal system, kidneys, gastrointestinal tract, and hormonal control by parathyroid hormone (PTH), calcitonin, and vitamin D. Approximately 99% of total body calcium resides in bones, while only about 1% circulates in blood and extracellular fluid, primarily in three forms: ionized (biologically active), protein-bound (mainly to albumin), and complexed with anions such as phosphate or citrate [29]. Among these, ionized calcium represents the physiologically active fraction that directly influences neuronal excitability, muscle contraction, and vascular tone [30].

Serum total calcium concentration is influenced by albumin levels, pH, renal function, and endocrine status. In hypoalbuminemia, common among critically ill patients or those with malnutrition, measured total calcium may underestimate physiologically active calcium; hence, **albumin-corrected calcium** or **ionized calcium** measurements provide a more accurate reflection of calcium status [31]. Similarly, acid-base disturbances alter calcium binding: acidosis increases ionized calcium by reducing albumin affinity, whereas alkalosis decreases it [32]. These variables complicate interpretation in acute ischemic stroke (AIS) where metabolic and systemic disturbances are common.

The hormonal regulators of calcium balance further influence its serum concentration. PTH increases calcium reabsorption in the kidneys, mobilizes calcium from bone, and enhances intestinal absorption through vitamin D activation [33]. Conversely, calcitonin, secreted by the thyroid gland, counteracts PTH effects by promoting calcium deposition into bone and enhancing renal excretion. Vitamin D deficiency, prevalent in elderly populations at risk of stroke, reduces intestinal calcium absorption, thereby affecting systemic calcium homeostasis [34]. Moreover, renal impairment—frequently coexisting with cerebrovascular disease—can alter calcium-phosphate equilibrium through disordered vitamin D metabolism and secondary hyperparathyroidism [35].

From a vascular perspective, calcium exerts direct effects on smooth muscle tone and endothelial function. Intracellular calcium levels modulate vasoconstriction, while extracellular calcium can affect vascular stiffness and arterial compliance [36]. Epidemiological studies have linked abnormal serum calcium—either high or low—to increased risk of hypertension, atherosclerosis, and cardiovascular events [37]. These systemic effects may partially mediate the associations observed between serum

calcium levels and ischemic stroke outcomes.

In the context of acute ischemic stroke, several additional determinants may transiently influence calcium levels. Catecholamine surges, dehydration, renal dysfunction, and shifts in acid-base balance during the acute phase can modify calcium fractions [38]. Furthermore, intravenous fluids, diuretics, and contrast agents used in diagnostic or therapeutic interventions can alter electrolyte balance [39]. Therefore, any assessment of serum calcium as a prognostic marker in AIS must consider these dynamic systemic influences, ensuring that observed associations are not confounded by acute metabolic or treatment-related factors [40].

Measurement Considerations – Total, Ionized, and Albumin-Corrected Calcium

Accurate assessment of serum calcium status in patients with acute ischemic stroke (AIS) is fundamental for interpreting its prognostic significance. Calcium in plasma exists in three forms: ionized (approximately 45%), bound to proteins such as albumin (about 40%), and complexed with anions such as phosphate or citrate (roughly 15%) [41]. Among these, ionized calcium is the physiologically active fraction that influences neuromuscular excitability, vascular reactivity, and coagulation. However, in most hospital laboratories, total calcium is routinely measured, which may not accurately reflect the biologically active component, particularly in critically ill or hypoalbuminemic patients [42].

Total serum calcium is affected by serum albumin concentration; thus, corrections are often applied to estimate the true physiological level. The albumin-corrected calcium is commonly calculated using the Payne or similar formula: Corrected Ca (mmol/L) = Measured Ca + 0.02 × (40 – Albumin [g/L]) [43]. This correction improves accuracy when albumin deviates significantly from normal, though it still has limitations in critical illness and in cases of abnormal pH, where ionized calcium is better correlated with physiological effects [44].

Ionized calcium measurement provides a direct and more accurate index of calcium homeostasis. It is, however, technically demanding and sensitive to sampling conditions, such as pH and temperature changes during sample collection and analysis. Even minor alkalosis during sample handling can cause an artifactual decrease in ionized calcium levels [45]. Furthermore, many stroke studies rely on total or albumin-corrected calcium due to easier availability, introducing potential inconsistencies across investigations [46].

These methodological differences partly explain the heterogeneity in reported associations between serum calcium and stroke outcomes. Some studies using total calcium report higher calcium associated with increased mortality [47], whereas those employing ionized calcium often find that lower levels predict greater neurological severity and poorer recovery [48]. The choice of calcium metric therefore significantly influences interpretation.

Another critical consideration is **timing of measurement**. Serum calcium may fluctuate during the acute and subacute phases of stroke due to dehydration, fluid resuscitation, or renal and endocrine changes. Most studies use admission calcium levels as prognostic markers, but dynamic monitoring might offer better insight into evolving metabolic responses [49]. Standardization of measurement methodology—preferably using ionized calcium where feasible would enhance comparability across studies and clarify true prognostic value [50].

Association Between Serum Calcium and Stroke Severity

Early observational work linked admission calcium to radiographic and clinical markers of severity. In a cohort assessed within 24 hours, higher total serum calcium on arrival correlated with smaller diffusion-weighted MRI infarct volumes and lower NIHSS, suggesting an inverse relationship between calcium level and initial injury burden; subsequent studies using DWI and standardized neurological scales have reinforced the coupling between early lesion size and neurological deficit, providing biological plausibility for calcium–severity associations [51,52,57].

Ionized calcium appears particularly informative. In a prospective study of AIS, patients with lower ionized calcium had significantly greater neurological impairment by NIHSS at presentation and over the early hospital course, consistent with the concept that reduced bioactive calcium reflects worse systemic–neuronal homeostasis in acute ischemia [53].

Not all findings align in the same direction, and differences often track with what (and when) is measured. Elevated albumin-corrected calcium has been associated with poorer short-term outcomes and higher long-term mortality after AIS, and higher corrected calcium around the time of advanced reperfusion therapy has predicted unfavorable functional status—signals that may reflect severity and systemic stress but could also be confounded by albumin, pH, and timing. In contrast, a classic analysis found higher calcium at 72–96 hours predicted greater independence at 3 months, underscoring that sampling window (very early vs subacute) and calcium fraction (ionized vs total/albumin-corrected) can invert observed associations with clinical status [54–56].

Methodological nuances—choice of calcium metric, correction formulas, and handling-related pH shifts—likely contribute to heterogeneity across severity studies. Emerging data suggest non-linear (possibly U-shaped) relationships when ionized calcium is modeled continuously, and small hospital-based cohorts have reported strong inverse correlations between total calcium and NIHSS. Overall, the weight of evidence supports that lower ionized or total calcium at presentation tracks with greater neurological severity, while higher corrected calcium later in the course may signal systemic dysregulation tied to worse outcomes; standardized protocols are needed to clarify these patterns [58,59].

Serum Calcium and Early Neurological Deterioration

Early neurological deterioration (END)—a decline in neurological status within hours to a few days after presentation—occurs in roughly 5–40% of patients depending on the definition and cohort, and portends markedly worse outcomes. Contemporary syntheses emphasize multifactorial drivers (hemodynamic failure, edema, hemorrhagic transformation, early recurrent ischemia, metabolic derangements), highlighting electrolytes as potentially modifiable contributors. Within this framework, calcium has emerged as a candidate signal: observational studies link dyscalcemia with greater short-term neurological worsening, although directionality varies with whether ionized, total, or albumin-corrected calcium is measured and with timing of sampling [60,61,64].

Lower baseline calcium—particularly when measured as ionized or when total calcium is interpreted in the setting of low albumin—has been associated with clinical worsening and with complications that frequently underlie END, most notably hemorrhagic transformation after thrombolysis. Multiple cohorts and meta-analyses report that patients who develop hemorrhagic transformation have significantly lower admission calcium than those who do not, supporting a plausible pathway whereby dyscalcemia contributes to blood–brain barrier fragility and downstream neurological decline [62,63,67].

At the same time, higher albumin-corrected calcium on admission has been linked to poorer early neurological status and downstream mortality in some series, a pattern that may reflect systemic stress responses, confounding by hypoalbuminemia/pH, or a non-linear (U-shaped) relationship between calcium and risk of neurological worsening. Studies in reperfusion-era cohorts, including those undergoing thrombectomy, have similarly observed that elevated corrected calcium tracked with unfavorable short-term outcomes, suggesting calcium may integrate vascular risk burden and acute metabolic perturbations relevant to END biology [60,65].

Population and hospital-based data in broader stroke samples (including hypertensive subgroups) further point to a relationship between relatively lower Ca^{2+} levels and increased risk of END or poor early course, reinforcing the need to standardize which calcium fraction is used, the timing of measurement, and the operational definition of END in future research. Taken together, convergent evidence indicates that dyscalcemia—either low (especially ionized) or high (when albumin-corrected)—marks patients at heightened risk for early clinical worsening, though causal direction and actionable thresholds remain to be clarified in prospective, protocolized studies [61,66].

Serum Calcium and Functional Outcomes (mRS, NIHSS change, discharge disposition)

Across heterogeneous cohorts, dyscalcemia on admission has shown independent associations with functional outcomes measured by the modified Rankin Scale (mRS), early NIHSS trajectory, and discharge status. In a hospital-based series, higher albumin-corrected calcium (ACC) at presentation was associated with poor discharge outcome (mRS 3–6) and higher mortality after adjustment for age,

NIHSS, glucose, and comorbidities, suggesting that corrected—not raw total—calcium may better capture prognostically relevant physiology in the acute phase [68]. Complementing these findings, a 2024 study reported that calcium in the highest quartile independently predicted unfavorable outcome, reinforcing that elevated calcium at baseline can mark patients at risk of worse early recovery, although patient mix and correction methods vary across studies [69].

Timing and the fraction measured (ionized vs total/ACC) appear to shape directionality. In a classic analysis comparing very-early and delayed sampling, higher calcium measured later (72–96 hours) was linked to greater functional independence at 3 months, whereas very-early values did not show the same pattern—highlighting that evolving post-ischemic and treatment-related shifts can invert associations if sampling windows are not standardized [70]. Parallel observational data indicate that lower ionized calcium on arrival correlates with more severe deficits and poorer short-term clinical course, consistent with the biological primacy of the ionized fraction; in meta-analytic and cohort work, ionized calcium outperformed total calcium for short-term prognosis, and low ionized calcium tracked with worse long-term outcome, whereas very high ionized calcium chiefly affected early outcomes [71,72].

Linkage of calcium with imaging markers supports functional observations. Higher admission calcium has been associated with smaller diffusion-weighted infarct volumes, which in turn correlate with better mRS outcomes; this structure–function bridge provides mechanistic plausibility for calcium-outcome relationships seen clinically [73]. Conversely, cohorts emphasizing corrected calcium have connected higher ACC with unfavorable discharge disposition and mortality, particularly in thrombolysis/thrombectomy-era samples—patterns that may reflect systemic stress, albumin shifts, or acid–base effects that influence corrected values more than ionized measurements [68,74]. Together, these data suggest a non-linear landscape in which low ionized calcium signals worse neurological trajectory, while high corrected calcium may track with adverse functional endpoints, underscoring the need for unified measurement protocols and prespecified time points when using calcium to prognosticate functional recovery after acute ischemic stroke [69,71,74].

Conclusion

Serum calcium represents a promising yet complex biomarker in the prognostic landscape of acute ischemic stroke. Across experimental and clinical studies, calcium has demonstrated consistent mechanistic relevance in the ischemic cascade—driving neuronal injury, vascular dysfunction, and inflammatory responses—while also reflecting broader systemic and metabolic states. Clinical investigations reveal heterogeneous but meaningful associations between serum calcium levels and key outcomes, including stroke severity, early neurological deterioration, functional recovery, and mortality. Patterns across cohorts suggest that low ionized calcium frequently accompanies severe neurological deficits and unfavorable recovery, whereas elevated albumin-corrected calcium on admission has been linked to increased mortality and poor functional outcome in some populations. This apparent paradox likely arises from the multifaceted regulation of calcium, the influence of confounders such as albumin and pH, and the lack of standardization in measurement timing and methodology. It also hints at a non-linear, possibly U-shaped, relationship between calcium homeostasis and prognosis, where both extremes of calcium imbalance carry risk.

From a clinical standpoint, serum calcium—particularly when measured in its ionized form—could serve as a valuable adjunct to established prognostic tools such as the NIHSS and neuroimaging markers. It may offer insights into systemic physiology that impact brain recovery and could help refine risk stratification during the acute phase. However, routine use of calcium as a prognostic marker in stroke care remains premature until key methodological issues are addressed.

Future studies should prioritize standardized measurement protocols distinguishing between total, albumin-corrected, and ionized calcium, account for confounding metabolic and renal factors, and integrate calcium dynamics into multivariable prognostic models. Large-scale prospective research may also explore whether therapeutic modulation of calcium-related pathways or correction of dyscalcemia could improve neurological outcomes.

In summary, while serum calcium is not yet a standalone predictor, it encapsulates vital neurovascular

and systemic processes central to ischemic injury. Its integration into clinical prognostic frameworks may enhance precision in predicting outcomes and tailoring management in patients with acute ischemic stroke.

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