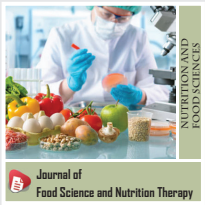
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Review Article

The Limitations of Albumin-Adjusted Calcium in Neonates and Children: Developmental Physiology, Analytical Bias and Diagnostic Reliability

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Abstract

Background: Direct ionised calcium represents the biologically active calcium fraction, whereas automated laboratory systems commonly report albumin-adjusted ("corrected") calcium using the adult-derived Payne equation anchored at an adult albumin target of 40–45 g/L. Because neonates and young infants exhibit physiologically lower and dynamically changing serum albumin concentrations, applying adult adjustment parameters introduces systematic positive mathematical bias and frequent false-positive hypercalcaemia flags.

Methods: In this expert peer-reviewed clinical evaluation and quality improvement initiative at East Sussex Healthcare NHS Trust (United Kingdom), we retrospectively reviewed paired neonatal and paediatric serum total calcium and albumin reports, quantified mathematical bias across gestational and postnatal age strata, and recalculated adjusted calcium using locally established, age-stratified serum albumin reference interval midpoints (27.0 g/L at 27 weeks' gestation; 29.0 g/L at 28–35 weeks; 32.0 g/L in term neonates ≤28 days; 37.0 g/L at 1–12 months; and 41.5 g/L at >12 months), alongside establishing a prospective Bland–Altman validation protocol against direct ionised calcium.

Results: Adult-anchored equations inflated neonatal adjusted calcium by up to +0.38 mmol/L at lower neonatal albumin limits, aligning with published UK multicentre neonatal bias of 6.8%–9.0%. Age-specific midpoint recalculation successfully reclassified spurious hypercalcaemia episodes into expected neonatal intervals, preventing unnecessary venepuncture and secondary endocrine testing.

Conclusion: Adult-derived adjustment equations systematically overestimate neonatal calcium and compromise diagnostic stewardship. Direct ionised calcium remains the clinical gold standard; when unavailable, age-specific albumin midpoint recalculation integrated within a structured clinical pathway provides a safer interim safeguard pending prospective ionised calcium validation.

Introduction

Calcium homeostasis is essential for neonatal and paediatric neuromuscular excitability, myocardial contractility, blood coagulation, bone mineralisation, and intracellular signalling [1,2]. In human plasma, total serum calcium circulates in three distinct physicochemical fractions: free ionised calcium (approximately 50%), protein-bound calcium predominantly complexed to serum albumin (approximately 40%), and calcium bound to small diffusible anions such as citrate, phosphate, and bicarbonate (approximately 10%) [2,3]. Total serum calcium denotes the combined concentration of all three circulating fractions; ionised calcium refers to the unbound, physiologically active divalent cation fraction regulated tightly by parathyroid hormone (PTH), vitamin D metabolites, and calcitonin; and albumin-adjusted ("corrected") calcium represents a mathematically derived estimate intended to normalise total serum calcium for variations in circulating

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albumin concentration when direct ionised calcium measurement is unavailable [1–3].

Because direct measurement of ionised calcium requires strict anaerobic specimen handling and rapid point-of-care or blood-gas analysis, clinical biochemistry laboratories have relied for over five decades on linear regression equations to estimate albumin-adjusted calcium [1,2]. The most widely implemented formula was derived by Payne et al. in 1973 from 200 consecutive adult clinical chemistry specimens with abnormal serum protein concentrations [1]:

Adjusted Calcium (mmol/L) = Total Calcium (mmol/L) + 0.02 × [40 - Measured Albumin (g/L)]

Crucially, the original Payne equation was derived exclusively from an adult cohort and was never validated against direct ionised calcium measurements [1,3]. Applying an adult albumin anchor (typically 40 g/L, or 45 g/L on certain automated laboratory middleware platforms) to neonatal and paediatric populations creates a fundamental developmental mismatch. Physiological serum albumin concentrations rise progressively from early preterm gestation (21–33 g/L) through term birth (24–40 g/L) and infancy (25–49 g/L) before reaching adult concentrations after 12 months of age, while unadjusted total calcium reference intervals simultaneously undergo substantial postnatal shifts [5–7].

Diagnostic reliability, automation bias, and clinical stewardship

Contemporary clinical pathology and diagnostic stewardship literature increasingly recognises how automated laboratory information management system (LIMS) reporting defaults shape clinical decision-making and patient safety [3,8–11]. Automation bias and cognitive heuristics predispose clinicians to act upon asterisked "abnormal" flags generated by automated middleware, even when the underlying physiological equations are invalid for neonates [10,11]. In hospitalised neonates, spurious biochemical hypercalcaemia flags trigger tangible iatrogenic harm, including repeated painful heel-prick or venous sampling, cumulative iatrogenic blood loss, unwarranted interruption of routine nutritional calcium or vitamin D supplementation, prolonged hospital stay, parental anxiety, and cascading secondary endocrine investigations [10,12].

Recent large-scale empirical studies between 2021 and 2026 have questioned the routine diagnostic reliability of albumin-adjusted calcium across diverse clinical populations. Kenny et al. emphasised that direct ionised calcium should be prioritised whenever calcium status is clinically consequential, whereas unadjusted total calcium suffices as an initial screen in low-risk patients [3]. In a 2025 population-based cohort study of 22,658 patients, Desgagnés et al. demonstrated that albumin-adjusted calcium correlated poorly with ionised calcium, performed no better than unadjusted total calcium, and systematically overestimated true hypercalcaemia while underestimating true hypocalcaemia [8]. Similarly, a 2026 prospective intensive care study by Özdemir et al. confirmed poor diagnostic concordance between multiple albumin-correction formulas and direct ionised calcium in physiologically unstable patients [9]. Within paediatrics, Jassam et al. evaluated adult versus age-specific calcium adjustment equations across three UK teaching hospitals and reported a 6.8% to 9.0% relative difference in neonates under one month of age [2].

Methods

This initiative was designed as a two-phase observational quality improvement (QI) project and clinical practice evaluation conducted within the Special Care Baby Unit (SCBU) and general paediatric inpatient wards at East Sussex Healthcare NHS Trust (ESHT), United Kingdom. Phase 1 comprised a retrospective clinical practice review of routine neonatal and paediatric bone profile biochemistry reports to examine the mathematical mechanism and clinical consequences of automated hypercalcaemia flagging. Phase 2 established a standardised bedside interpretive pathway alongside a formal prospective validation protocol. In accordance with UK National Health Service (NHS) Health Research Authority (HRA) governance criteria, Phase 1 constituted an internal clinical service evaluation using anonymised routine clinical biochemistry data; formal Research Ethics Committee approval and individual parental consent were not required.

Routine inpatient and neonatal unit biochemical bone profiles containing paired serum total calcium and serum albumin measurements were reviewed. Specimens were excluded if they lacked a paired serum albumin measurement or were obtained during documented severe acid–base disturbance (blood pH <7.25 or >7.50). Routine central laboratory biochemistry profiles were analysed on automated platforms using standard colorimetric assays, with automated LIMS middleware calculating adjusted calcium via an adult SI Payne equation. To mitigate systematic upward bias when direct ionised calcium was unavailable, we applied a pragmatic recalculation substituting the mathematical midpoint of locally established, age-stratified serum albumin reference intervals [13,14]:

Age-Specific Adjusted Calcium (mmol/L) = Total Calcium (mmol/L) + 0.02 × [Age-Specific Albumin Midpoint (g/L) - Measured Albumin (g/L)] (Table 1).

Table 1: Age-stratified serum albumin reference intervals and target midpoints used in local pragmatic adjustment [13,14].

Paediatric Group	Age / Gestational Stratification	Local Albumin Interval (g/L)	Target Midpoint Used (g/L)
Preterm neonate	27 weeks' gestation	21–33	27.0
Preterm neonate	28–35 weeks' gestation	22–36	29.0
Term neonate	Birth to 28 days	24–40	32.0
Infant	1–12 months	25–49	37.0
Child	>12 months	35–48	41.5*

***Note:** The mathematical midpoint of the 35–48 g/L reference interval for children >12 months is 41.5 g/L.

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Results and clinical evaluation

In our retrospective clinical practice review, automated LIMS reporting repeatedly flagged apparently elevated corrected calcium concentrations in clinically asymptomatic neonates whose unadjusted total calcium values were unremarkable for age. Joint evaluation with clinical biochemistry confirmed two compounding sources of error: first, applying an adult albumin target of 40 g/L (or 45 g/L in local middleware) to neonates whose physiological albumin typically spans 21–36 g/L added an artificial upward adjustment of +0.08 to +0.38 mmol/L; second, automated LIMS alerts compared the resulting value against an adult reference interval (2.17–2.44 mmol/L) rather than neonatal reference intervals, which physiologically extend up to approximately 2.80 mmol/L during the first weeks of life [6,7].

In our unit's observational practice review, recalculating flagged results using the age-specific albumin midpoint reclassified the majority of apparent hypercalcaemia episodes into expected neonatal ranges mirroring the 6.8% to 9.0% neonatal relative bias quantified across three UK centres by Jassam et al. [2] and prevented clinicians from initiating unnecessary secondary endocrine investigations (such as serum PTH, 25-hydroxyvitamin D, and urinary calcium-to-creatinine ratios).

Quantitative worked examples

Comparison of routine neonatal cases highlights a critical operational discrepancy across UK clinical laboratories: whereas the standard textbook SI Payne formula applies a reference albumin target of 40 g/L, certain UK laboratory middleware systems apply a locally derived adult reference target of 45 g/L. For example, in a preterm neonate (33+3 weeks' gestation) with a total calcium of 2.75 mmol/L and serum albumin of 37 g/L:

- Adult-Adjusted Calcium (45 g/L middleware target): 2.75 + 0.02 × (45 - 37) = 2.91 mmol/L (flagged abnormal against adult upper limit of 2.44 mmol/L).
- Adult-Adjusted Calcium (40 g/L textbook target): 2.75 + 0.02 × (40 - 37) = 2.81 mmol/L.
- Age-Specific Adjusted Calcium (29.0 g/L preterm midpoint): 2.75 + 0.02 × (29 - 37) = 2.59 mmol/L (bringing the value securely within normal neonatal limits) (Table 2).

Discussion

The central laboratory medicine challenge illustrated by our clinical evaluation is the interaction between a mathematical adjustment formula and the reference population embedded within it. By anchoring adjustment to an adult albumin concentration of 40 g/L (or 45 g/L on certain analytical platforms), the conventional Payne equation answers a clinically irrelevant hypothetical question for a neonate: what the infant's calcium concentration would be if they possessed adult serum albumin levels [1,2]. In daily clinical practice, this mathematical bias directly undermines diagnostic stewardship and patient safety [10–12]. When automated LIMS middleware flags an adjusted calcium of 2.87–3.08 mmol/L with an abnormal asterisk against an adult reference interval, clinicians experience strong automation bias to pursue artefact [10,11].

Furthermore, a critical biochemical question is whether the conventional slope coefficient of 0.02 mmol/g (0.8 mg/dL per g/dL) remains valid across neonatal and paediatric age groups. In the original Payne regression, 0.02 represented the average change in total calcium per 1 g/L change in albumin across 200 adult specimens [1]. However, subsequent clinical biochemistry investigations have demonstrated that calcium–albumin binding stoichiometry varies substantially depending on the analytical assay used for albumin—specifically bromocresol green (BCG) versus bromocresol purple (BCP) dye-binding methods—as well as across patient populations [2,3,5]. BCG methods tend to overestimate serum albumin in neonates due to non-specific binding to alpha- and beta-globulins, whereas BCP methods yield lower, more specific albumin measurements, thereby altering the apparent regression slope [2,5,16].

Our evaluation addresses four primary methodological limitations: (1) retrospective design and selection/verification bias; (2) retention of the adult-derived 0.02 slope coefficient and assay-specific BCG/BCP binding bias; (3) non-parametric midpoint approximation and reference-interval transferability bias; and (4) physiological confounding by unmeasured anions,

Table 2: Risk-stratified seven-step clinical pathway for interpreting serum calcium in neonates and children.

Step	Clinical Action	Diagnostic Reliability & Patient Safety Rationale
1	Assess clinical context and pre-test probability	Evaluate symptoms, signs, and risk factors for calcium disturbance (e.g., extreme prematurity, parenteral nutrition, vitamin D therapy).
2	Review unadjusted total serum calcium	Interpret measured total calcium directly against validated, age-specific paediatric laboratory reference intervals before reviewing automated adjusted values [3,6,7].
3	Obtain direct ionised calcium when indicated	Whenever calcium homeostasis is clinically in question or results will alter management, measure direct ionised calcium (the biological gold standard) [2–4,8,9].
4	Interpret ionised calcium alongside blood pH	Account for acid–base status when reviewing blood-gas ionised calcium, as acidaemia and alkalaemia directly shift protein-bound calcium equilibrium [4,15].
5	Apply age-specific adjustment (only if iCa unavailable)	When ionised calcium cannot be obtained and protein adjustment is warranted, recalculate using the locally verified age-specific albumin midpoint rather than adult targets [2,5].
6	Do not diagnose hypercalcaemia on adjusted values alone	Prevent overdiagnosis and iatrogenic harm: never initiate invasive endocrine workups or treatment based solely on an albumin-adjusted calculation [3,8–11].
7	Investigate confirmed true hypercalcaemia	Once hypercalcaemia is confirmed on direct ionised calcium, execute targeted diagnostic investigation (PTH, phosphate, vitamin D metabolites, and renal function).

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lipaemia, or acid–base shifts [2,4,8,9,16]. These limitations reinforce that while age-specific midpoint recalculation provides a vital interim bedside safeguard, prospective validation via Bland–Altman analysis against direct ionised calcium remains essential [8,9].

Conclusion

Automated adult-derived calcium adjustment formulas systematically overestimate neonatal calcium and compromise diagnostic stewardship by generating false-positive hypercalcaemia flags. Direct ionised calcium remains the clinical gold standard; when unavailable, age-specific albumin midpoint recalculation integrated within a structured clinical pathway provides a safer interim safeguard pending prospective ionised calcium validation.

Author statements and declarations

Authors' Contributions: AO conceived the clinical evaluation, performed the retrospective clinical review, drafted the manuscript, and led revisions. AR contributed to clinical biochemistry data review, assay evaluation, and methodological oversight. MK contributed to clinical protocol development and departmental governance review. SG contributed to manuscript revision and clinical data interpretation. SM and GSC provided senior clinical oversight, structural editing, and final supervision. All authors approved the final manuscript.

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Ethics Approval and Patient Consent: In accordance with UK NHS Health Research Authority (HRA) guidance, this project was conducted as an internal clinical quality improvement and service evaluation review using anonymised routine clinical biochemistry data; formal Research Ethics Committee approval and individual patient consent were not required.

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References

1. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J. 1973;4(5893):643-646. Available from: 10.1136/bmj.4.5893.643.

2. Jassam N, Gopaul S, McShane P, McHugh A, Coleman R, Thompson D, et al. Calcium adjustment equations in neonates and children. Ann Clin Biochem. 2012;49(4):352-358. Available from: 10.1258/acb.2011.011060.

3. Kenny CM, Murphy CE, Boyce DS, Ashley DM, Jahanmir J. Things we do for no reason™: calculating a "corrected calcium" level. J Hosp Med. 2021;16(8):499-501. Available from: 10.12788/jhm.3619.

4. Wang S, Toffaletti JG. pH effects on measurements of ionized calcium and ionized magnesium in blood. Arch Pathol Lab Med. 2002;126(8):947-950. Available from: 10.5858/2002-126-0947-PEOMOI.

5. Weaving G, Batstone GF, Jones RG. Age and sex variation in serum albumin concentration: an observational study. Ann Clin Biochem. 2016;53(1):106-111. Available from: 10.1177/0004563215593561.

6. Roizen JD, Shah V, Levine MA, Carlow DC. Determination of reference intervals for serum total calcium in the vitamin D-replete pediatric population. J Clin Endocrinol Metab. 2013;98(12):E1946-E1950. Available from: 10.1210/jc.2013-3105.

7. Levaillant L, Linglart A, Letamendia E, Bouvattier C, Rothenbuhler A, Adamsbaum C, et al. Serum calcium normal range in 1,000 term newborns. Horm Res Paediatr. 2025;98(2):136-147. Available from: 10.1159/000534042.

8. Desgagnés N, King JA, Kline GA, Seiden-Long I, Leung AA. Use of albumin-adjusted calcium measurements in clinical practice. JAMA Netw Open. 2025;8(1):e2455251. Available from: 10.1001/jamanetworkopen.2024.55251.

9. Özdemir E, Yılmaz T, Düzenci D. Limited diagnostic utility of albumin-corrected calcium in the intensive care unit: a prospective comparison with ionised calcium. PLoS One. 2026;21(3):e0354233. Available from: 10.1371/journal.pone.0354233.

10. Lyell D, Coiera E. Automation bias and verification complexity: a systematic review. J Am Med Inform Assoc. 2017;24(2):423-431. Available from: 10.1093/jamia/ocw105.

11. Korenstein D, Chimonas S, Barrow B, Keyhani S, Troy A, Lipitz-Snyderman A. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. JAMA Intern Med. 2018;178(10):1401-1407. Available from: 10.1001/jamanetworkopen.2018.3573.

12. Coon ER, Quinonez RA, Moyer VA, Schroeder AR. Overdiagnosis: how our compulsion for diagnosis may be harming children. Pediatrics. 2014;134(5):1013-1023. Available from: 10.1542/peds.2014-1778.

13. Sheffield Children's NHS Foundation Trust. Clinical chemistry reference ranges. Version 3. Sheffield: Sheffield Children's NHS Foundation Trust; 2022.

14. Safer Care Victoria. Normal laboratory values for neonates: clinical guidance. Melbourne: Victorian Department of Health; 2023.

15. Mirzazadeh M, Morovat A, James T, Smith I, Kirby J, Shine B. Point-of-care testing of electrolytes and calcium using blood gas analysers: it is time we trusted the results. Emerg Med J. 2016;33(3):181-186. Available from: 10.1136/emermed-2015-204669.

16. Labriola L, Wallemacq P, Gulbis B, Jadoul M. The impact of the assay for measuring albumin on corrected ('adjusted') calcium concentrations: a persistent clinical pitfall in the era of standardized assays. Nephrol Dial Transplant. 2023;38(5):1089-1095. Available from: 10.1093/ndt/gfac285.

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