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PERSPECTIVE ARTICLE

Zinc, albumin, frailty, and drug safety in long-term care residents: A translational perspective

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Abstract

Older residents of long-term care facilities (LTCFs) are increasingly treated with complex pharmacotherapy while living with frailty, malnutrition, inflammation, recurrent infection, and reduced physiological reserve. Medication safety in this population cannot rely only on chronological age, diagnostic labels, renal function, or medication counts. This article proposes a translational framework in which serum zinc and albumin are interpreted with frailty and medication review to identify residents at increased risk of adverse drug reactions, infection-related prescribing, and prescribing cascades. Zinc links nutritional status with immune signaling, antioxidant defense, tissue repair, protein synthesis, and gene-regulatory pathways, whereas albumin links plasma zinc transport, inflammation, and pharmacokinetic vulnerability. Because both markers are routinely measurable, they may support individualized clinical management in LTCFs. The proposed approach is not a dosing algorithm, but a practical strategy for integrating biological vulnerability into safer prescribing, deprescribing, monitoring, and nutritional care.

Keywords: Zinc; Albumin; Frailty; Drug safety; Long-term care; Older adults; Pharmacokinetics; Biological markers

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1. Introduction

Older residents of long-term care facilities (LTCFs) represent an extreme phenotype of biological vulnerability. Many residents have multimorbidity, impaired mobility, cognitive decline, dysphagia or poor oral intake, recurrent infection, and exposure to multiple drugs. In this setting, drug safety cannot be understood only as avoidance of inappropriate prescriptions. The same drug and dose may have different consequences depending on inflammation, protein binding, micronutrient status, immune reserve, frailty, and the ability to report adverse symptoms.

A practical challenge is that medication review and nutritional assessment are often conducted in parallel rather than integrated. Prescribers review indications, doses, interactions, renal function, and potentially inappropriate medications. Nurses, dietitians, and care staff observe appetite, swallowing, wounds, infection, delirium, falls, and functional decline. Laboratory measurements such as serum zinc and albumin are available in many facilities, yet they are rarely used as part of a shared framework for medication safety.

Recent LTCF studies from Okinawa have described low and persistent serum zinc levels using routinely collected measurements, supporting the relevance of zinc status

as a real-world clinical marker in this population.[1,2] This article argues that serum zinc and serum albumin, although imperfect as isolated tests, can help connect molecular and protein biology with bedside medication management. When interpreted longitudinally alongside frailty, inflammation, nutritional intake, and medication exposure, these markers may help identify residents who require more cautious prescribing, closer monitoring, and coordinated nutritional care.

At the molecular level, zinc homeostasis is regulated by Zrt- and Irt-like proteins (SLC39), zinc transporters (SLC30), metallothioneins, and zinc-binding proteins that support gene regulation, protein synthesis, and immune signaling. Albumin is a major carrier of plasma zinc; inflammatory changes in albumin concentration and zinc distribution may therefore complicate the interpretation of circulating zinc as a direct measure of tissue stores. These mechanisms provide biological context for considering zinc and albumin together, without treating either measurement as a specific test of immune competence.

Recent clinical investigations in populations outside long-term care further illustrate the relevance—and limits—of this interpretation. In adults with cirrhosis, a prospective cohort study linked concurrent zinc deficiency and sarcopenia with hepatic encephalopathy and early mortality.[3] In a large surgical registry, serum albumin demonstrated prognostic discrimination for postoperative adverse outcomes when compared with frailty-based tools.[4] Although neither study directly validates adverse drug reaction prediction in LTCF residents, both support studying zinc, albumin, and functional vulnerability as complementary, context-dependent clinical signals.

These findings offer clinical analogies, not direct validation in LTCFs: the cirrhosis study examined hepatic outcomes, and the spine-surgery study examined perioperative outcomes; neither establishes that a zinc–albumin combination predicts medication-related harm in institutionalized older adults.

2. Zinc as more than a nutritional measurement

Zinc is often discussed as a micronutrient, but its biological role extends across immune signaling, antioxidant defense, tissue repair, protein synthesis, and regulation of gene expression. Zinc homeostasis involves transporters, metallothioneins, zinc-finger transcription factors, and zinc-binding proteins.[5,6] Therefore, low serum zinc in an older LTCF resident should not be interpreted merely as a dietary number; it may reflect a broader state of nutritional, inflammatory, and immune vulnerability.

The LTCF environment is particularly relevant because reduced food intake, dysphagia, wounds, recurrent infection, antibiotic exposure, and chronic inflammation often occur in the same resident. In nursing-home research, normal serum zinc concentrations were associated with lower incidence and duration of pneumonia, fewer new antibiotic prescriptions, and fewer pneumonia-related days.[7] These observations do not prove that zinc supplementation will prevent infection in every resident, but they support the clinical importance of zinc status in frail institutionalized older adults.

Serum zinc also requires cautious interpretation. It is influenced by acute-phase responses, sampling conditions, albumin concentration, and recent illness. A low value during acute inflammation may partly represent redistribution rather than total-body depletion, and a normal value does not exclude marginal deficiency in a frail resident with poor intake. For this reason, zinc should be interpreted as a longitudinal, contextual marker rather than a stand-alone trigger for supplementation.

3. Albumin as a protein-linked marker of pharmacological vulnerability

Albumin is central to this translational framework for two reasons. First, albumin is the major plasma protein involved in zinc transport, and changes in albumin concentration or binding properties can influence circulating zinc measurements.[8] Second, albumin binds many drugs, and hypoalbuminemia can alter the interpretation of total drug concentrations, free fractions, distribution, and toxicity risk.[9]

Clinically, low albumin should be viewed less as a simple malnutrition score and more as a vulnerability signal. Albumin reflects a mixture of nutritional intake, inflammation, catabolic illness, hepatic synthesis, renal or gastrointestinal loss, hydration, and disease burden. Composite indices such as the prognostic nutritional index, which integrates serum albumin and lymphocyte count, illustrate how albumin can function as part of a nutritional-immunological phenotype across clinical specialties.[10]

This distinction matters for medication safety. Hypoalbuminemia does not automatically mean that every highly protein-bound drug requires dose reduction. For many drugs, free concentration, clearance, distribution, and clinical response do not move in simple parallel. Nevertheless, hypoalbuminemia should prompt more careful clinical monitoring when drugs have narrow therapeutic windows, high toxicity potential, or concentration-dependent adverse effects. The key

intervention is not reflexive dose change but closer attention to sedation, delirium, falls, bleeding, gastrointestinal intolerance, anorexia, renal change, and infection-related prescribing.

Evidence linking albumin to drug disposition should not be conflated with proof that serum albumin independently predicts adverse drug reactions in LTCF populations. Acute illness, inflammation, hepatic and renal dysfunction, fluid shifts, and drug-specific clearance mechanisms may alter either biomarker or drug exposure, complicating causal interpretation. Accordingly, a low albumin value should prompt clinical contextualization rather than automatic drug dose adjustment.

4. Frailty, polypharmacy, and adverse drug reactions

Frailty and polypharmacy amplify each other. Frailty reduces the capacity to tolerate pharmacological stress, while polypharmacy increases the probability of drug–drug interactions, drug–disease interactions, prescribing cascades, and adverse drug reactions.[11-13] Medication count alone is therefore an incomplete marker. Five necessary medications may be safer than three poorly matched medications in a resident with delirium risk, anorexia, constipation, falls, and low albumin.

Existing prescribing tools remain essential. The Beers Criteria and STOPP/START criteria provide structured approaches to potentially inappropriate medications and prescribing omissions in older adults.[14,15] However, these tools do not fully incorporate biological reserve. A translational LTCF approach should therefore ask not only whether a drug is appropriate for the diagnosis, but whether the resident has the protein, immune, nutritional, and functional reserve to tolerate the drug at this time.

This approach may also help prevent prescribing cascades. Anorexia or taste disturbance may lead to appetite stimulants or supplements; sedation may be misinterpreted as behavioral change; constipation may be treated with additional laxatives while anticholinergic burden remains unaddressed; and infection-related deterioration may trigger repeated antibiotic courses without reassessment of nutrition, swallowing, wounds, and frailty. Zinc-albumin profiles cannot solve these problems alone, but they can make biological vulnerability visible during medication review.

5. A proposed translational framework

A practical LTCF framework should begin with the resident rather than the drug list. Table 1 summarizes a proposed approach. The purpose is not to create a rigid dosing algorithm, but to identify residents in whom medication decisions should be more conservative, more closely monitored, and more closely coordinated with nutritional and functional care.

Importantly, this is a conceptual adjunct to established medication review, not a validated algorithm for predicting adverse drug reactions. The associations of zinc with immune and nutritional biology, and of albumin with protein binding and illness severity, are established at different levels of evidence; however, their combined incremental prognostic value for drug harms in LTCFs has not been demonstrated. No uniform zinc or albumin cut-off should be used to classify residents as medication high-risk based on this framework alone.

Table 1. Translational framework linking zinc, albumin, frailty, and drug safety in long-term care

Clinical domain	What to assess	Translational interpretation	Potential clinical action
Frailty phenotype	Activities of daily living, falls, weight loss, mobility, cognition, appetite	Chronological age is replaced by biological vulnerability	Use frailty status to set treatment intensity, monitoring frequency, and deprescribing priorities
Zinc axis	Serum zinc, dietary intake, dysphagia, taste, wounds, recurrent infections	Marker of micronutrient, immune, and tissue-repair reserve	Repeat low values; evaluate inflammation and albumin; consider monitored supplementation when clinically appropriate
Albumin–inflammation axis	Albumin with CRP, renal/liver status, edema, catabolic illness	Protein-linked signal affecting zinc transport and drug exposure	Interpret total drug levels cautiously; consider TDM or closer toxicity monitoring for selected drugs
Medication safety	Medication count, potentially inappropriate medications, sedatives, anticholinergics, anticoagulants, antimicrobials	Drug risk is modified by biological reserve	Apply Beers and STOPP/START criteria; identify prescribing cascades and high-risk combinations
Follow-up outcomes	ADRs, infection days, antibiotic use, delirium, falls, wounds, function	Clinical endpoints for real-world translation	Track outcomes after medication and nutrition interventions

Abbreviations: ADR: Adverse drug reaction; CRP: C-reactive protein; PIM: Potentially inappropriate medication; TDM: Therapeutic drug monitoring.

6. Clinical implications

Implementation should be multidisciplinary. Nurses are often the first to recognize appetite change, somnolence, falls, wound deterioration, delirium, or functional decline. Pharmacists can identify protein-bound drugs, drug–mineral interactions, anticholinergic burden, and prescribing cascades. Dietitians can evaluate intake, swallowing, weight change, zinc intake, and supplementation safety. Physicians can integrate these observations with prognosis, goals of care, and medication priorities.

First, zinc and albumin should be interpreted longitudinally whenever possible. A single low zinc value during acute inflammation may be difficult to interpret, whereas repeated low values suggest persistent vulnerability.[1,2] Similarly, hypoalbuminemia should prompt assessment of inflammation, hydration, liver and kidney disease, edema, intake, and catabolic illness before it is used to guide medication decisions.

Second, abnormal zinc–albumin profiles should trigger focused medication review for drugs with high toxicity potential: sedatives, anticholinergics, anticoagulants, antiepileptics, certain antimicrobials, and drugs that worsen anorexia, constipation, falls, or delirium. For selected protein-bound or narrow therapeutic-window drugs, therapeutic drug monitoring or clinical toxicity monitoring may be more important than changing the dose solely because albumin is low.

Third, nutritional intervention should be targeted and monitored. Correcting zinc deficiency may be reasonable when deficiency is persistent and clinically plausible, but excessive zinc supplementation can cause harm and should not become an unmonitored routine intervention.[16] Copper status, gastrointestinal symptoms, interacting medications, and clinical endpoints such as wounds, infection frequency, appetite, and function should be considered.

Implementation must remain selective and proportionate to local resources. This article does not recommend universal serial zinc testing or a fixed testing interval. Albumin values already available from routine care may be reviewed alongside medication lists and functional changes; zinc assessment and repeat measurements should be individualized according to clinical indications, dietary concerns, persistent abnormalities, or changes after illness. Repeated testing can impose laboratory, transport, and staffing costs, and no cost-effectiveness analysis currently supports routine deployment of the proposed framework. In settings where tests are unavailable, conventional clinical assessment and evidence-based medication review remain the priority.

7. Research agenda

The proposed framework generates several testable hypotheses. First, a combined phenotype of low zinc, hypoalbuminemia, and frailty may predict adverse drug reactions, infections, antibiotic exposure, falls, hospitalization, or mortality more accurately than medication count alone. Second, zinc–albumin trajectories may identify windows of vulnerability after infection, hospitalization, or nutritional decline. Third, medication review triggered by biological vulnerability markers may reduce prescribing cascades or prevent functional deterioration.

Future studies should avoid overmedicalizing nutrition. Zinc status is not a stand-alone therapeutic target; it is one component of a broader biological system. Research should therefore combine routine laboratory markers, frailty instruments, medication exposure, and real-world outcomes. LTCFs are especially appropriate settings for this work because residents are often excluded from randomized trials despite representing the population in whom drug harms and nutritional vulnerability are most consequential.

Future validation should first determine whether serum zinc, albumin, and frailty add predictive information for adjudicated adverse drug reactions beyond established medication-review tools and standard clinical covariates. Multicenter prospective cohorts should prespecify outcomes, evaluate discrimination and calibration, account for acute infection, inflammation, hepatic and renal disease, hydration, and medication exposure, and test whether repeated measures offer incremental value. No validated joint cut-off values currently identify high-risk LTCF residents; candidate thresholds would require derivation and external validation. Subsequent pragmatic or cluster-randomized trials could examine whether integrating these markers with Beers and STOPP/START reviews reduces preventable drug harms while collecting data on testing costs, staff time, downstream utilization, and cost-effectiveness.

8. Conclusion

Zinc status and serum albumin provide a practical translational bridge between molecular biology, protein transport, immune vulnerability, frailty, and drug safety. In older LTCF residents, concurrent low zinc and hypoalbuminemia should be interpreted as possible signals of reduced biological reserve rather than isolated laboratory abnormalities. Integrating these markers with frailty assessment and structured medication review may support safer prescribing, more appropriate deprescribing, targeted nutritional care, and individualized monitoring.

This approach requires validation, but it offers a clinically feasible way to bring biological context into medication safety for frail older adults.

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