

Research Article

Moving Towards Reliable Assessment of Zinc Depletion in Acutely Admitted Geriatric Patients

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Abstract

Background: Many admitted geriatric patients are malnourished with insufficient intake of trace elements. Zinc status is crucial to maintaining normal immune function and is assessed using plasma zinc concentration. However, plasma zinc drops with increased systemic inflammation (high CRP and hypoalbuminemia), challenging interpretation in older infected patients. Currently, guidelines are unclear for assessing zinc status and prescribing zinc supplements.

Methods: A cross-sectional study investigating the prevalence of low plasma zinc and low albumin-corrected zinc among older patients admitted to the geriatric ward at Copenhagen University Hospital, Herlev and Gentofte. Prescription of zinc supplements and the association between low levels of zinc and infections, readmissions, and mortality were analyzed.

Results: Of the included 143 patients (median age 84 years), 93 (65%) had low plasma zinc (<10 µmol/L). After adjusting for albumin level, only 56 patients (39%) had low levels of zinc, and thereby possible zinc deficiency. Out of the 93 patients with low plasma zinc, only 36 (39%) received zinc supplements at discharge (22-44 mg/daily). Plasma zinc was found to be negatively correlated with CRP

($p < 0.001$) and positively correlated with albumin ($p > 0.001$). Low plasma zinc was associated with poorer 1-year mortality (2.17, 95% CI 1.01-4.76). However, after adjustment of albumin level, low zinc levels were not associated with poorer outcomes.

Conclusion: Plasma zinc cannot be used to evaluate zinc status in hospitalized, often infected, geriatric patients. Our study suggests that albumin-corrected zinc is a more reliable assessment of zinc status in hospitalized geriatric patients and should guide zinc supplementation.

Keywords: Albumin-corrected zinc; Infection; Malnutrition; Older

Keypoints

- Zinc is crucial to maintain normal immune function, but zinc status is challenging to determine in hospitalized older patients
- Current guidelines are unclear for assessing zinc status and prescribing zinc supplements
- This cross-sectional study supports that plasma zinc alone cannot be used to evaluate zinc status in hospitalized geriatric patients and that albumin-corrected zinc is likely to be a more correct assessment to diagnose zinc depletion

Introduction

Frail older patients are typically admitted to geriatric wards due to acute illness, common infections, or exacerbation of chronic illness and loss of function. Many older patients are at nutritional risk after long-lasting insufficient nutritional intake or one sided “Tea and toast diet” [1], leading to malnutrition as part of their geriatric syndrome [1]. The risk of malnutrition increases with age and is related to comorbidity [2] and frailty [3], but it is largely underdiagnosed and consequently also undertreated [2,4]. In acutely admitted geriatric patients the majority have nutritional impairments [4] which can lead to increased morbidity, prolonged hospital stays and rehabilitation, loss of function, and decreased quality of life [1,2,5]. Decreased food intake is often accompanied by an insufficient intake of several vitamins and trace elements such as zinc [6].

Zinc deficiency is defined as a state of low intake of zinc, or increased loss of zinc, and simultaneous low plasma zinc, or symptoms [7]. Typical deficiency related symptoms include skin irritation, reduced appetite and decreased healing of wounds [8]. Additionally, even mild zinc deficiency can lead to an impaired immune function, which is associated with increased risk of infectious diseases [6]. Moderate zinc deficiency includes cell-mediated immune dysfunctions and impaired wound healing [9]. Zinc also plays a role in several aspects of the antioxidant defense system [9,10].

Zinc supplements act by improving the reaction of the immune system, instead of suppressing the immune reaction like other anti-inflammatory drugs (e.g., glucocorticoids). It has been shown that zinc supplementation in older adults reduces unspecific preactivated T cells and improves T cell response [11]. Furthermore, the state of

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zinc deficiency and the aging immune system has been shown to have several similarities [12], which is why it has been suggested that even healthy older adults could benefit from zinc supplementation [13]. Low levels of plasma zinc have also been reported in a number of malignancies [14,15], but the potential beneficial effect of zinc supplements in preventing cancers remains unclear [16]. Additionally, there is a lack of consensus of treatment of deficiency conditions among older patients, including optimal doses of zinc and duration of treatment. In clinical practice today, there is a risk of both under- and overtreatment with zinc supplements, decreasing compliance to the patient's other medications if overtreated [17]. There is also a risk for recurrent deficiency after substitution if the nutritional intake remains insufficient.

Prevalence of low plasma zinc seems higher in older people compared to younger populations [18], and especially in hospitalized subjects [19,20]. However, prevalence of zinc deficiency in geriatric inpatients in general is unknown. Plasma zinc concentration is the most common method of assessment of zinc status because it is cost-effective and easy to analyze [7]. However, zinc is bound to albumin and plasma zinc concentration drops with increased systemic inflammatory response, mediated by lower hepatic production of many zinc carrier proteins, an increased capillary permeability, and an increased deposition of zinc into the liver cells [13,21]. Additionally, clinical laboratory reference values used in clinical practice are based on younger persons and it is known that plasma zinc concentrations fluctuate by as much as 20% during a 24-hour period due to food ingestion [7]. Thus, it is challenging to interpret zinc status from plasma zinc in admitted older patients, since they are likely to possess both an acute inflammatory response, and a more chronic inflammatory level due to comorbidities. A recent study from Jørgensen et al., [22] including patients with short bowel syndrome or cirrhosis, suggested that zinc should be adjusted in relation to hypoalbuminemia to achieve a better interpretation of zinc levels and true zinc deficiency.

There are, to our knowledge, no studies who have investigated the prevalence of low albumin-corrected zinc among geriatric patients. The present study, therefore, aimed to evaluate the prevalence of low plasma zinc and low albumin-corrected zinc among older acutely admitted patients, to investigate occurrence of supplements given, and the association between low levels of albumin-corrected zinc and infections, readmissions, and mortality.

Methods

Study design and participants

The study is a cross-sectional design investigating plasma zinc and albumin-corrected zinc among older patients admitted to the geriatric ward at Copenhagen Hospital University of Herlev and Gentofte during May 2021. All patients admitted to the geriatric ward during the study had extended nutritional blood samples drawn at least one time during their admission, independently of nutritional status.

Data collection and variables

Data were retrospectively collected from the electronic medical record. Baseline characteristics included age, sex, Body mass index (BMI, kg/m²), any weight loss reported at admission, use of walking aids, living condition, domestic help, comorbidity, polypharmacy and nutritional supplements. Comorbidity was evaluated by using CIRS-G (Cumulative Illness Rating Scale- Geriatric). Readmission within 3 months, and mortality within 3 months and 1 year after discharge was noted.

Plasma zinc and albumin-corrected zinc

Plasma zinc was considered normal between 10-19 µmol/l according to local reference values. Thus, plasma zinc values below 10 µmol/l was considered "low". According to Jørgensen et al., [22], plasma zinc values can be adjusted for hypoalbuminemia, to prevent overestimation of efficiencies. Based on a cohort of healthy blood donors, the correlation between albumin and zinc (β) was found with a linear regression. Reference for albumin was based on Macdonnell et al., [23] using the highest value of the lowest decile of albumin in their healthy cohort, which was set to 45. Jørgensen et al., used the following equation to adjust for hypoalbuminemia:

$$Zn_{corrected} = Zn_{measured} - (\beta * (Albumin_{measured} - Albumin_{ref}))$$

The albumin reference used for the present analysis was set to the mean of the normal reference value for persons over 70 years, i.e., 39.5 g/L. The correlation coefficient (β) from the linear regression was calculated for the present cohort, as the correlation between albumin and zinc could be different in older patients compared with healthy blood donors. In the present cohort β was found to be 0.212, establishing the following model:

$$Zn_{corrected} = Zn_{measured} - (0.212 * (Albumin_{measured} - 39.5))$$

Statistics

Baseline characteristics were presented as descriptive data for all patients and for patients depending on normal or low plasma zinc levels. Categorical variables were compared using a Chi-squared test, otherwise Fisher's exact test was used. Differences in distribution of continuous baseline variables were performed with the Wilcoxon rank sum test. Correlation analysis was performed using Pearson's correlation coefficient.

Frequencies of readmissions and mortality at 3 months and 1 year for patients with low albumin-corrected zinc compared with patients with normal values were analyzed with the chi square test. Binary outcomes were also analyzed by binary logistic regression and presented as Odds Ratios (ORs) and 95% Confidence Intervals (CIs), and validated in a multivariate analysis including age, sex, and BMI.

The correlation coefficient (β) for the albumin corrected model was found in the linear regression. The statistical software IBM SPSS Statistical Viewer version 25 was used for all analyses with a 5% significance level.

Results

In total, 168 patients were admitted to the geriatric ward during May month in 2021. Three of the participants were duplicates as they were readmitted during the period and 22 did not have extended blood samples drawn (missing data). The current study population consisted of 143 participants (Figure 1). The baseline characteristics are displayed in table 1 for all patients and for patients with normal or low plasma zinc levels, with and without adjustments for albumin level. Median age was 84 years (ranged from 65-100) and 89 patients (62%) were women. Most patients lived in their own homes (82%) and 18% were admitted patients from intermediate care or nursing homes. No significant differences in baseline characteristics were seen between patients with low or normal plasma zinc. However, fewer nursing home residents than patients living in their own homes had low albumin-corrected zinc.

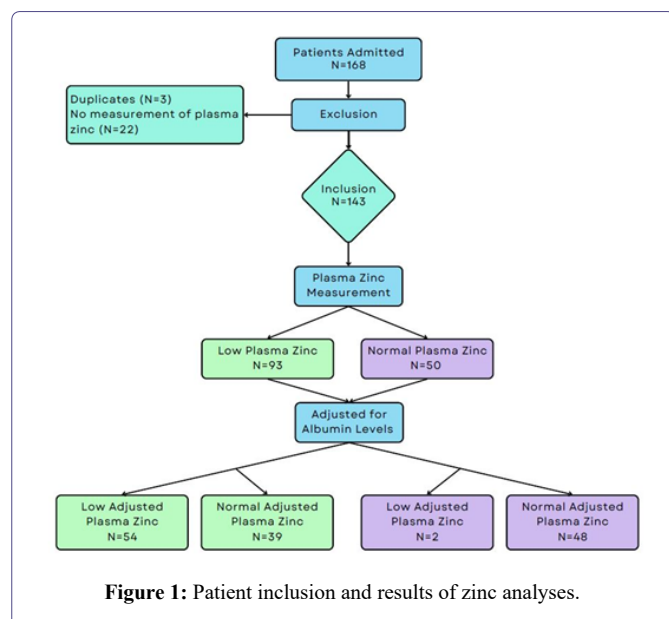


Figure 1: Patient inclusion and results of zinc analyses.

Zinc levels and adjustments for hypoalbuminemia

Overall, 93 patients (65%) had low plasma zinc (<10 µmol/l). After adjusting for albumin based on equation suggested by Jørgensen et al., [22], 56 patients (39%) had low levels of zinc, and thereby possible zinc deficiency. The majority of patients had elevated C-Reactive Protein (CRP) levels >5mg/L 110 (77%), 87 patients (61%) had CRP >20 mg/L, and 49 patients (34%) had hypoalbuminemia. All patients with plasma zinc < 6 µmol/l had albumin-corrected zinc below <10 µmol/l, and thereby possible zinc deficiency. Plasma zinc was found to be negatively correlated with CRP ($r = -0.465$, $p < 0.001$) and positively correlated with albumin ($r = 0.525$, $p > 0.001$).

Multivitamin and zinc supplements at admission

A portion of the patients were treated with multivitamin or zinc supplements at admission (15% vs. 7.0%). There was a tendency towards higher frequencies of multivitamins and zinc supplements prescribed among patients admitted from nursing homes compared with patients admitted from own homes (24% vs. 13%, $p = 0.147$ and 16% vs. 5.1%, $p = 0.052$).

In total, 9 patients (18%) of the 50 patients with normal plasma zinc received multivitamins compared with 12 (13%) of the 93 patients with low plasma zinc (Table 1). Additionally, 4 (8.0%) of 50 patients with normal plasma zinc and 6 (7%) of the 93 patients with low plasma zinc, had zinc supplements. When adjusting for hypoalbuminemia, 7 (13%) of the 56 patients with low albumin-corrected zinc and 14 (16%) of the 87 patients with normal albumin-corrected zinc were treated with multivitamins. Furthermore, 3 (5.4%) of the 56 patients with low albumin-corrected zinc and 7 (8.0%) of the 87 patients with normal albumin-corrected zinc, were already in treatment with zinc supplements.

Zinc supplements at discharge

Totally 36 (39%) of patients with low plasma zinc, received zinc supplements (22-44 mg/daily). Of the 56 patients with low albumin-corrected zinc, 28 (50%) received zinc supplements at

discharge. At discharge, a total of 38 (27%) out of the entire population had zinc supplements added to their medication list compared with at admission.

Prognosis

Overall, 51 (37%) patients were readmitted at least once within three months, and 31 (22%) patients died within three months. One year mortality was 35%. In addition, five patients died during hospitalization, and all of them had low plasma zinc. Furthermore, 41% of patients with low plasma zinc died within the 1st year of follow up, compared with only 24% among patients with normal plasma zinc ($P = 0.044$) (Table 2). However, when using albumin-corrected zinc no difference was seen in 1-year mortality.

No difference in 3-months readmission rates and 3-months mortality was seen between patients with low vs. normal levels of plasma zinc or albumin-corrected zinc. More patients with elevated CRP (>5 mg/L) died within the 1st year, compared with patients with normal CRP (40% vs. 18%, $p = 0.021$). No difference in outcomes was seen at 3 months. Patients with hypoalbuminemia, had higher 3-months' and 1-year mortality compared with patients with normal albumin levels (43% vs. 11%, $p < 0.001$) and (51% vs. 27%, $p = 0.004$, respectively). Low plasma zinc was associated with increased 1-year mortality (2.17, 95% CI 1.01-4.76), but could not be validated in the multivariate model. After adjustment of albumin level, low zinc level was not associated with poorer outcomes (Table 3).

Hypoalbuminemia was found to be associated with higher mortality at 3 months and 1 year in the univariate analysis and confirmed in the multivariate analysis (2.86, 95% CI 1.39-5.88 and 4.00, 95% CI 1.69-9.09 respectively). Elevated CRP (>5 mg/L) was also found to be associated with increased 1-year mortality (3.03, 95% CI 1.15-7.87), but could not be confirmed in the multivariate analysis.

Discussion

In this cross-sectional study of 143 acutely admitted geriatric patients, we found that more than half of the patients had low plasma zinc based on plasma zinc concentration. When adjusting zinc measurements for albumin levels, the prevalence of zinc depletion decreased from 65% to 39% of patients. The high prevalence of low plasma zinc is in line with Girodon et al., [24] who found low plasma zinc in 61% of older admitted patients. In addition, it has long been known that zinc concentration is lower among older adults compared to younger adults [18,25] and in hospitalized patients compared to healthy adults [26]. However, we found the prevalence of patients with low plasma zinc to be lower in patients admitted from care homes than in patients admitted from their own home. This could be due to the tendency found towards more frequent use of supplements but also more sufficient nutritional intake.

Low albumin can be caused by a low intake of protein. Furthermore, a prevalent reason for low albumin in hospitalized patients is high levels of CRP. A major reason for admission in the present study was infection with most patients' CRP levels over 20 mg/L, indicating an active systemic immune response. We found a significant association between plasma zinc and CRP, in line with Duncan et al., [21] who found that plasma zinc concentration decreased when CRP increased. Systemic inflammatory response is known to decrease plasma zinc concentrations independently of the actual zinc status [21]. However, plasma zinc is usually normalized after clinical improvement [27,28].

Characteristics		All patients N (%)	Normal plasma zinc N = 50 n (%)	Low plasma zinc N = 93 n (%)	P	Normal albumin-corrected zinc N = 87 n (%)	Low albumin-corrected zinc N = 56 n (%)	P
Sex	Female	89 (62%)	33 (66)	56 (60%)	0.496	56 (64)	33 (59)	0.513
	Male	54 (38%)	17 (34)	37 (40%)		31 (36)	23 (41)	
Age	Years median (range)	84 (65 - 100)	82 (65 - 100)	85 (65 - 97)	0.424	83 (65 - 100)	85.5 (69 - 97)	0.325
BMI	Median (range)	24.7 (15.5 - 42)	29 (24.7 - 33.5)	25 (15.5 - 42)	0.570	24.2 (16.5 - 40.8)	23.7 (16.2 - 36.6)	0.595
Living condition	Own Home	118 (82)	39 (78)	79 (85)	0.297	67 (77)	51 (91)	0.031
	Intermediate or nursing home	25 (18)	11 (22)	14 (15)		20 (23)	5 (8.9)	
Walking aid	No walking aid	38 (27)	17 (34)	21 (23)	0.350	22 (25)	16 (29)	0.646
	Walking aid	78 (55)	24 (48)	54 (58)		46 (53)	32 (57)	
	Wheelchair bound	25 (17)	9 (18)	16 (17)		18 (21)	7 (13)	
	NA	2 (1.4)	2 (2.2)	2 (2.2)		1 (1.1)	1 (1.8)	
CIRS - G	Score (range)	8 (1 - 16)	8 (1 - 16)	8 (1 - 14)	0.357	8 (1 - 16)	8 (1 - 14)	0.994
Daily medication	No. (range)	8 (0 - 25)	9.5 (1 - 25)	7 (0 - 17)	0.120	8 (0 - 25)	7 (0 - 16)	0.420
Daily intake of pills	No. (range)	12 (0 - 38)	13 (1 - 38)	11 (0 - 28)	0.466	12 (0 - 38)	10.5 (0 - 27)	0.551
Multivitamin at admission	Yes	21 (15)	9 (18)	12 (13)	0.412	14 (16)	7 (13)	0.554
Zinc supplement at admission	Yes	10 (7.0)	4 (8.0)	6 (7.0)	0.740	7 (8.0)	3 (5.4)	0.538
Weight loss N=136	No	96 (71%)	37 (79%)	59 (66%)	0.130	61 (70)	35 (67)	0.635
	Yes	40 (29%)	10 (21%)	30 (34%)		22 (25)	18 (32)	

Table 1: Baseline characteristics.

	Readmission < 3 months N = 138*			3-months mortality N = 143			1-year mortality N = 143		
	Readmission N = 56	No readmission N = 82		Dead N = 31	Alive N = 112		Dead N = 50	Alive N = 88	
	n (%)	n (%)	P	n (%)	n (%)	P	n (%)	n (%)	P
Normal plasma zinc	20 (40)	30 (60)	0.917	8 (25)	42 (38)	0.227	12 (24)	38 (76)	0.044
Low plasma zinc	36 (41)	52 (59)		23 (75)	70 (63)		38 (41)	55 (59)	
Normal albumin-corrected zinc	35 (41)	50 (59)	0.857	21 (24)	66 (76)	0.374	31 (35)	56 (64)	0.835
Low albumin-corrected zinc	21 (19)	32 (81)		10 (18)	46 (82)		19 (34)	37 (66)	
Normal albumin	38 (41)	54 (59)	0.806	10 (11)	84 (89)	<0.001	25 (27)	69 (73)	0.004
Low albumin	18 (39)	28 (61)		21 (43)	28 (57)		25 (51)	24 (49)	
Normal CRP	13 (39)	20 (61)	0.874	3 (9.7)	30 (91)	0.054	6 (18)	27 (82)	0.021
> CRP 5 mg/L	43 (41)	62 (59)		28 (25)	82 (75)		44 (40)	66 (60)	
Normal CRP	22 (39)	34 (61)	0.789	10 (18)	46 (82)	0.374	15 (27)	41 (73)	0.100
> CRP 20 mg/L	34 (41)	48 (59)		21 (24)	66 (76)		35 (40)	52 (60)	

Table 2: Outcomes depending on baseline blood results.

* 5 patients died during hospitalization

	Readmission < 3 months N = 138*			3-months mortality N = 143			1-year mortality N = 143		
	Readmission N = 56	No readmission N = 82		Dead N = 31	Alive N = 112		Dead N = 50	Alive N = 88	
	n (%)	n (%)	P	n (%)	n (%)	P	n (%)	n (%)	P
Normal p-zinc	20 (35)	30 (37)	0.917	8 (26)	42 (38)	0.227	12 (24)	38 (43)	0.044
Low p-zinc	36 (65)	52 (63)		23 (74)	70 (63)		38 (76)	55 (57)	
Zinc sufficient	35 (63)	50 (61)	0.857	21 (68)	66 (59)	0.374	31 (62)	56 (64)	0.835
Zink deficiency**	21 (37)	32 (39)		10 (32)	46 (41)		19 (38)	37 (36)	
Normal albumin	38 (68)	54 (67)	0.806	10 (32)	84 (75)	<0.001	25 (50)	69 (78)	0.004
Low albumin	18 (32)	28 (33)		21 (68)	28 (25)		25 (50)	24 (22)	

Normal > CRP 5 mg/L	13 (23) 43 (77)	20 (24) 62 (76)	0.874	3 (9.7) 28 (90)	30 (27) 82 (73)	0.054	6 (12) 44 (88)	27 (31) 66 (69)	0.021
Normal CRP > CRP 20 mg/L	22 (39) 34 (61)	34 (41) 48 (59)	0.789	10 (32) 21 (68)	46 (41) 66 (59)	0.374	15 (30) 35 (70)	41 (47) 52 (53)	0.100

Table 3: Outcomes depending on blood results.

* 5 patients died during hospitalization ** adjusted for albumin level

Measurement of zinc-dependent cell-mediated immune function, has demonstrated mild zinc deficiency despite normal plasma zinc [29]. Therefore, laboratory characterization of mild zinc deficiency, and the interpretation of plasma zinc concentration is difficult. Duncan et al., [21] stated that plasma zinc concentrations could not be interpreted clinically when CRP levels were above 20 mg/L. Accordingly, the ESPEN micronutrient guideline [7] recommends that plasma zinc should be used to confirm suspicion of clinical zinc deficiency and monitoring provision, and that measurement of CRP and albumin is necessary for interpretation.

We found that patients with low plasma zinc concentration had significantly higher occurrence of hypoalbuminemia. Jørgensen et al., [22] also found a strong association between hypoalbuminemia and low levels of zinc and suggested that zinc levels should be adjusted for level of albumin before interpreted and used for diagnosis of zinc deficiency. In a following study, Hedegaard et al., [28] found that albumin-corrected zinc values in acutely admitted patients with infections were comparable to the patients' plasma zinc at 14 days follow up after admission. The authors suggest that the assay could be a proper way to assess zinc depletion during infection. When adjusting zinc measurements for albumin levels in the present study, prevalence of zinc depletion decreased from 65% to 39% of patients. Thus, the prevalence matches well with insufficient zinc intake in half of older adults [30], thus supporting that albumin-corrected zinc may be a more accurate method to evaluate zinc status in older admitted patients with elevated CRP. However, the former study only evaluated zinc intake through nutrition, not including zinc-containing supplements.

In the present study few patients were already receiving multivitamin or zinc supplementation at admission and only zinc supplementation seemed to reduce the number of patients with low albumin-corrected zinc. The total number of patients receiving multivitamins at admission or at discharge were small, considering that all older adults >70 years in Denmark with reduced appetite are recommended to receive daily multivitamin supplementation [31]. At discharge, 25% of the patients received zinc supplements. Although this must be considered an overtreatment for those who did not have low albumin-corrected zinc, there might have been a beneficial effect with improved immune function. Prasad et al., [32] found significantly fewer signs of infections among older, but healthy, participants recruited from a senior center, after intake of 45 mg zinc daily. Furthermore, zinc supplements have been found to have a positive impact on survival in the COVID pandemic independent of their plasma zinc status [33].

Low plasma zinc and low albumin-corrected zinc in the present study were not associated with readmissions or mortality within 3-months. However, there was an observed link between low levels of zinc and one-year mortality. This association, however, could not be verified through the multivariate analysis. Therefore, the inclination toward an adverse outcome is likely influenced by other factors,

such as hypoalbuminemia. Additionally, it has been shown that patients with COVID-19 and low serum zinc concentration had worse outcomes [34]. The authors did not take plasma albumin into account, and poorer outcome could again be driven by hypoalbuminemia. This highlights the need for correct laboratory methods of assessment of zinc status such as albumin-corrected zinc. Due to the multifactorial reasons for low zinc levels, plasma zinc might be considered a biomarker for frailty as it also may contribute to immune senescence [6].

A strength of the study is the discussion of different methods to assess whether an acutely infected geriatric patient needs zinc supplementation. Limitations include a small sample size. Additionally, there was no data on nutritional status including nutritional and sufficient zinc intake. Furthermore, potential symptoms of zinc deficiency were not described, and could not be collected retrospectively. Furthermore, it is challenging to assess symptoms of mild zinc deficiency especially among older patients who often present with infections and malnutrition at admission [4]. Thus, making the ESPEN guidelines [7] of diagnosing clinical zinc deficiency difficult to use when treating older hospitalized adults due to lack of reliable methods in the general clinical practice for measuring zinc deficiency. We believe that a strength of this study is its contribution to the discussion of how to use the available methods in geriatric patients.

Ultimately, the prevalence of low levels of plasma zinc was 65% among acutely admitted geriatric patients in the present study. After adjusting for albumin level, the prevalence was only 39%, although still a significant number. Plasma zinc alone cannot be used to evaluate zinc status in hospitalized geriatric patients, who often have high CRP and low albumin. Our study supports the suggestion that albumin-corrected zinc is likely to be a more correct assessment to diagnose "true" zinc depletion in hospitalized patients with high CRP. Further trials investigating the association between albumin-corrected zinc, zinc intake and symptoms of zinc deficiency in older medical patients are needed.

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