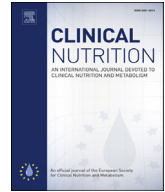




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## Short Communication

## Hypozincemia in the early stage of COVID-19 is associated with an increased risk of severe COVID-19

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## SUMMARY

**Background & aims:** Nutritional predisposition to severe coronavirus disease 2019 (COVID-19) remains unclear. Zinc deficiency could be critical since it is associated with a higher susceptibility to infections. We evaluated the prevalence of hypozincemia in the early stage of COVID-19, its association with risk factors for severe COVID-19 and its prognostic value for hospitalization for respiratory complications within 10 days.

**Methods:** For 152 COVID-19 patients and 88 non-COVID-19 patients admitted to COVID-19 screening centers, national early warning score for COVID-19 (NEWS) and laboratory analyses were performed to identify the risk for severe COVID-19. Multivariable logistic regression analysis assessed whether hypozincemia was an independent predictor of hospitalization for respiratory complications within 10 days (primary judgment criterion). The secondary judgment criteria were high NEWS score ( $\geq 7$ ), comorbidities and biomarkers associated with severe COVID-19.

**Results:** Hypozincemia was more frequent in COVID-19 patients compared to non-COVID-19 patients (27.6% vs 11.4%;  $p = 0.003$ ). Older patients ( $\geq 65$  years) and medically assisted nursing home residents were at higher risk of hypozincemia ( $p < 0.01$ ). Hypozincemia was associated with a worse NEWS score ( $p < 0.01$ ) and lymphopenia ( $p < 0.001$ ). Hypozincemia was independently associated with hospitalization for respiratory complications within 10 days (OR = 10.9, 95% CI = 2.3–51.6,  $p = 0.002$ ).

**Conclusions:** In the early stage of COVID-19, the prevalence of hypozincemia exceeded 20%. Hypozincemia was an independent predictor of hospitalization for respiratory complications within 10 days. This may suggest the importance of early detection and treatment of zinc deficiency in the nutritional management of COVID-19, especially in older people. Therefore, intervention and adjuvant treatment trials are strongly needed.

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## 1. Introduction

Nutritional predisposition to severe coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains unclear. Adequate zinc status could

be a key element because zinc deficiency is associated with a higher susceptibility to infections [1]. To our knowledge, no study has been conducted to explore zinc blood levels in the early stage of non-hospitalized COVID-19 patients. Our study aimed to evaluate the prevalence of hypozincemia in the early stage of COVID-19, its association with clinical or biological criteria of severity in subjects admitted to COVID-19 screening centers, and its prognostic value for hospitalization for respiratory complications within 10 days.

## 2. Methods

Approved by our institutional ethics committee (n°2020PI087), the study was conducted at University Hospitals of Nancy and Marseille on 240 consecutive patients with suspected COVID-19

**Abbreviations:** BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CV, coefficient of variation; ESPEN, European Society for Clinical Nutrition and Metabolism; NEWS, national early warning score for COVID-19; NRS, nutritional risk screening 2002; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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admitted to COVID-19 screening centers from April 24th to May 23rd, 2020. On admission, medical history assessment, clinical and biological evaluation were performed to identify risk factors for severe COVID-19. The risk of clinical deterioration was calculated by using national early warning score for COVID-19 (NEWS) [2] with three categories of risk: low (NEWS 0–4), medium (NEWS 5–6) and high (NEWS  $\geq 7$ ). Laboratory analysis included plasma zinc and selenium measurements, and biomarkers associated with severe COVID-19. COVID-19 patients were defined by two consecutive positive SARS-CoV-2 RT-PCR tests on nasopharyngeal swab specimens.

Plasma zinc and selenium concentrations were determined on a metal-free tube (BD Vacutainer® Trace Element Tubes) and measured by ICP–MS (Agilent® 7800 ICP–MS). Intra- and inter-assay coefficients of variation were below 5.5% for 25 µg/dL of zincemia and 6.0% for 25 µg/L of selenemia. Hyposelenemia was defined by selenemia <70 µg/L and hypozincemia according to specific cutoffs recommended by the World Health Organization (WHO) because zincemia is affected by sex, age, time of day, recent meals [3].

The prevalence of hypozincemia and hyposelenemia were determined in COVID-19 ( $n = 152$ ) and non-COVID-19 patients ( $n = 88$ ). The role of hypozincemia as a potential predisposing factor for COVID-19 was studied by comparing plasma zinc status, inflammation and lymphopenia in these two groups. Reliable clinical interpretation of trace element concentrations included inflammation assessment by applying C-Reactive Protein (CRP) level cutoffs (<10 mg/L for selenium and <20 mg/L for zinc) [4]. According to Guan et al. [5], lymphopenia was defined by lymphocyte count  $<1.5 \times 10^9/L$ .

Characteristics of COVID-19 patients according to hypozincemia permitted us to study the association of hypozincemia with risk factors for severe COVID-19 and with poor clinical outcomes. Clinical risk factors included underlying social and medical conditions associated with an increased risk for severe COVID-19 [5]. The primary judgment criterion was defined by hospitalization for respiratory complications within 10 days. The secondary judgment criteria were the risk factors for severe COVID-19 assessed on admission: high NEWS score ( $\geq 7$ ), comorbidities for severe COVID-19 (age  $\geq 65$  years, medically assisted nursing homes, smoker, obesity, arterial hypertension, chronic respiratory diseases, diabetes, cardiovascular diseases, cancer, chronic kidney diseases, immunosuppressive treatment), and biomarkers associated with severe COVID-19 (increases in white blood cell and neutrophil counts, higher neutrophil-to-lymphocyte ratio, increases in creatinine, CRP, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH) and D-dimer levels, decreases in platelet and lymphocyte counts, decreases in albumin and hemoglobin levels, and lower lymphocyte-to-CRP Ratio).

Statistical analyses were performed using Stata SE, version 12.2. In all analyses,  $p$ -value <0.05 was considered significant. Quantitative and qualitative variables were compared using Mann–Whitney U tests, Chi-square test or Fisher's exact test, as appropriate. Multivariable logistic regression analysis was performed to assess whether hypozincemia was an independent predictor of hospitalization for respiratory complications within 10 days.

### 3. Results

The prevalence of hypozincemia was significantly higher in COVID-19 patients compared to non-COVID-19 patients (27.6% vs 11.4%;  $p = 0.003$ ) whereas hyposelenemia was not (5.3% vs 11.4%;  $p = 0.08$ ). Compared to the French middle-aged population [6], the

prevalence of hypozincemia was significantly higher in COVID-19 middle-aged women (28.2% vs 10.0%;  $p < 0.001$ ) and men (25.0% vs 10.0%;  $p = 0.03$ ). In patients with low CRP levels, COVID-19 patients presented a higher prevalence of hypozincemia compared to non-COVID-19 patients (21.8% vs 11.1%;  $p < 0.05$ ). In COVID-19 patients, inflammation significantly increased this prevalence (73.3% vs 21.8%;  $p = 0.001$ ) (Fig. 1). Moreover, COVID-19 patients presented more hypozincemia alone than combined hyposelenemia and hypozincemia (23.7 vs 3.9;  $p < 0.001$ ), especially when CRP levels were low (20.3 vs 0.8;  $p < 0.001$ ).

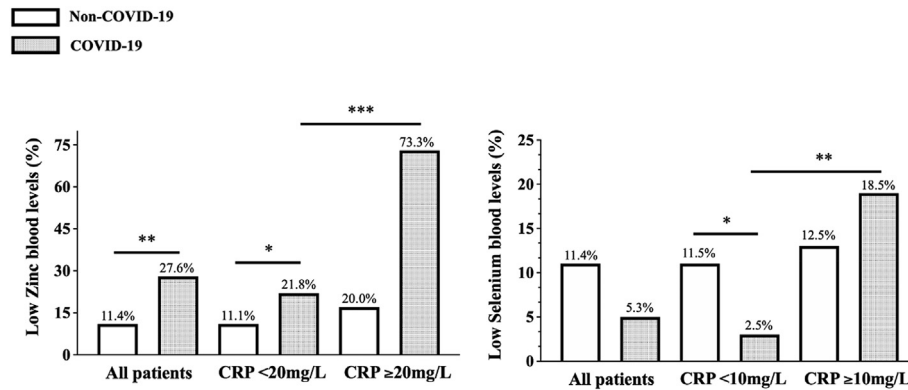
According to COVID-19 status (Table 1), hypozincemia in COVID-19 patients was mainly related to gender ( $p = 0.01$ ) and older age (65 and over) ( $p < 0.05$ ). It was not influenced by hypoalbuminemia, obesity, BMI <18.5 kg/m<sup>2</sup> or digestive manifestations. In patients with lymphopenia and low CRP levels, hypozincemia was significantly marked in COVID-19 patients compared to non-COVID-19 patients ( $p = 0.01$ ). Furthermore, in patients with hypozincemia and low CRP levels, lymphopenia was also more frequent in COVID-19 patients ( $p = 0.02$ ) (Table 1).

Characteristics of COVID-19 patients according to their plasma zinc status (Table 2) indicated that, among risk factors for severe COVID-19, the over-65s and patients living in medically assisted nursing homes were at higher risk of hypozincemia ( $p < 0.01$ ). On admission, a worse risk score of clinical deterioration (NEWS  $\geq 7$ ) was observed in the hypozincemia group ( $p < 0.01$ ). A higher frequency of hospitalization for respiratory complications within 10 days was reported in patients with hypozincemia compared to patients with normal zinc levels (16.7% vs 5.5%,  $p < 0.05$ ). Laboratory findings of COVID-19 patients showed that, compared to normal zinc levels, hypozincemia was associated with biomarkers for severe COVID-19 including increased CRP levels, higher neutrophil-to-lymphocyte ratio and lymphopenia ( $p < 0.001$ ). While high CRP levels were significantly associated with hypozincemia compared to normal zinc levels (27.5% vs 3.7%;  $p < 0.001$ ), hypozincemia was significantly marked in patients with low CRP levels compared to those with high CRP levels (72.5% vs 27.5%;  $p < 0.001$ ). Finally, in multivariate analysis (Table 3), hypozincemia was independently associated with hospitalization for respiratory complications within 10 days (OR = 10.9, 95% CI = 2.3–51.6;  $p = 0.002$ ).

### 4. Discussion

Our study reported a 2.4-fold higher prevalence of hypozincemia in the 152 COVID-19 patients compared to the 88 non-COVID-19 patients assessed in our COVID-19 screening centers. In COVID-19 patients, hypozincemia was not significantly combined with hyposelenemia or associated with BMI <18.5 kg/m<sup>2</sup>. In COVID-19 patients, while inflammation increased hypozincemia, hypozincemia was marked without a potential inflammation impact. We also showed that hypozincemia was associated with a worse risk score of clinical deterioration (NEWS  $\geq 7$ ). Finally, we showed that hypozincemia in the early stage of COVID-19 was an independent predictor of hospitalization for severe COVID-19 within 10 days.

In a smaller cohort of hospitalized patients, Heller et al. also showed that hypozincemia was higher in COVID-19 patients, and more particularly in non-survivors [7]. Consistently, Carlucci et al. showed that zinc supplementation increased the frequency of discharge and reduced mortality of COVID-19 [8]. Furthermore, Zhao et al. showed that NRS score (Nutritional Risk Screening 2002) over 5 was associated with a massive increase of mortality [9]. Consequently, because nutritional assessment is essential, further studies might be of interest in order to compare plasma zinc status according to the presence or absence of malnutrition.



**Fig. 1.** Distribution of hypozincemia and hyposelenemia (%) according to CRP levels and COVID-19 status. Qualitative variables were expressed as no. (%) or no./total no. (%) where total no. is the total number with available data, and compared using Chi-square test or Fisher's exact test, as appropriate. CRP cutoffs were determined to take count of potential inflammation impact in order to get reliable clinical interpretation of zinc and selenium levels. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

**Table 1**

Hypozincemia and lymphopenia distributions (%) in the 152 COVID-19 patients and the 88 non-COVID-19 patients.<sup>a</sup>

	Non-COVID-19		COVID-19		p-value
<b>Hypozincemia distribution, no/total no (%)</b>	10/88	(11.4%)	42/152	(27.6%)	<b>0.003</b>
<b>Characteristics of included patients</b>					
Age $\geq 65$ yr	2/12	(16.7%)	9/15	(60.0%)	<b>0.047</b>
Male gender	1/36	(2.8%)	16/71	(22.5%)	<b>0.01</b>
Medically assisted nursing homes	1/2	(50.0%)	7/9	(77.8%)	0.49
BMI <sup>b</sup> < 18.5 kg/m <sup>2</sup>	0/1	(0.0%)	3/6	(50.0%)	>0.99
Obesity (BMI $\geq 30$ kg/m <sup>2</sup> )	2/14	(14.3%)	3/21	(14.3%)	>0.99
Arterial hypertension	3/17	(17.6%)	7/20	(35.0%)	0.29
Chronic respiratory diseases	2/11	(18.2%)	6/13	(46.1%)	0.21
Diabetes (type 2)	1/2	(50.0%)	2/9	(22.2%)	0.49
Cardiovascular diseases	2/10	(20.0%)	7/15	(46.7%)	0.23
Cancer	2/6	(33.3%)	2/4	(50.0%)	>0.99
Chronic kidney diseases	0/0	/	1/2	(50.0%)	>0.99
Immunocompromised	0/2	(0.0%)	3/5	(50.0%)	0.43
Diarrhea	2/13	(15.4%)	7/27	(25.9%)	0.69
Albumin < 3.5 g/dL	1/1	(100.0%)	3/3	(100.0%)	>0.99
C-reactive protein (CRP) < 20 mg/L	9/81	(11.1%)	29/133	(21.8%)	<b>0.047</b>
C-reactive protein (CRP) $\geq 20$ mg/L	1/5	(20.0%)	11/15	(73.3%)	0.11
Lymphopenia <sup>c</sup>	1/16	(6.3%)	23/47	(48.9%)	<b>0.002</b>
and CRP < 20 mg/L	0/14	(0.0%)	13/34	(38.2%)	<b>0.01</b>
and CRP $\geq 20$ mg/L	1/2	(50.0%)	9/11	(81.8%)	0.42
<b>Lymphopenia distribution</b>	16/73	(21.9%)	47/108	(43.5%)	<b>0.003</b>
Hypozincemia	1/7	(14.3%)	23/31	(74.2%)	<b>0.006</b>
and CRP < 20 mg/L	0/6	(0.0%)	13/21	(61.9%)	<b>0.02</b>
and CRP $\geq 20$ mg/L	1/1	(100.0%)	9/9	(100.0%)	>0.99
Normal zinc blood level	15/66	(22.7%)	24/77	(31.1%)	0.26

Significant p-values are formatted in bold.

<sup>a</sup> Qualitative variables were expressed as no./total no. (%) where no. is the number of patients with hypozincemia or lymphopenia and total no. is the total number of patients with the characteristics, and compared using Chi-square test or Fisher's exact test, as appropriate.

<sup>b</sup> BMI: Body Mass Index, kg/m<sup>2</sup>.

<sup>c</sup> Lymphopenia was defined as lymphocyte count below  $1.5 \times 10^9/L$ .

We reported the first evidence linking hypozincemia with lymphopenia and inflammation in the early stage of COVID-19. Our results are consistent with the pleiotropic effects of zinc on the immune system and inflammation [1]. Zinc deficiency is known to increase interleukin IL-6 and to impair immunity by producing lymphopenia, especially in older people [1]. Conversely, inflammation reduces plasma zinc concentration during the acute phase of infection [1]. In the interrelationship between zinc and COVID-19, hypozincemia could reflect a primary zinc deficiency or a reversible status due to COVID-19-related inflammation which recovered in response to medical care [7]. Our results in non-hospitalized COVID-19 patients were

consistent with both hypotheses. Indeed, while inflammation increased hypozincemia, COVID-19 patients with hypozincemia were mainly associated with low CRP levels. Therefore, if our results are confirmed, and because nutrition status could be impaired during COVID-19, it would be cost-effective to detect early and correct zinc deficiency in the nutritional management of COVID-19.

We also found that the over-65s and residents in medically assisted nursing homes affected by COVID-19 were at higher risk of hypozincemia. These results add a novel piece to the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline [10], which recommended treatment of malnutrition in older

**Table 2**  
Characteristics of the 152 COVID-19 patients according to plasma zinc status.<sup>a</sup>

Characteristics	COVID-19 patients with hypozincemia				p-value
	Yes (N = 42)		No (N = 110)		
Time between symptoms onset and COVID-19 testing (days)	4	(3–7)	4	(3–6)	0.14
<b>Demographics</b>					
Median age (IQR) – yr	50	(32–58)	38	(26–52)	<b>0.01</b>
Male – no. (%)	16	(38.1)	55	(50.0)	0.19
Median BMI (IQR) – kg/m <sup>2</sup>	24.0	(22.6–26.3)	24.4	(22.3–28.7)	0.30
BMI < 18.5 kg/m <sup>2</sup> – no. (%)	3	(7.9)	3	(2.8)	0.18
<b>Presenting symptoms – no. (%)</b>					
Fever	25	(59.5)	31	(28.2)	<b>&lt;0.001</b>
Cough	22	(52.4)	53	(48.2)	0.64
Anosmia and/or ageusia	20	(47.6)	60	(54.5)	0.44
Headache	18	(42.9)	58	(52.7)	0.28
Myalgia	18	(42.9)	44	(40.0)	0.75
Rhinitis	17	(40.5)	44	(40.0)	0.96
Fatigue	11	(26.2)	36	(32.7)	0.44
Shortness of breath	10	(23.8)	28	(25.5)	0.83
Diarrhea	7	(16.7)	20	(18.2)	0.83
<b>Comorbidities for severe COVID-19 – no. (%)</b>					
Age ≥ 65 yr	9	(21.4)	6	(5.5)	<b>0.006</b>
Medically assisted nursing homes	7	(16.7)	2	(1.8)	<b>0.002</b>
Smoker	8	(19.0)	24	(21.8)	0.71
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	3	(7.9)	21	(19.3)	0.10
Arterial hypertension	7	(16.7)	13	(11.8)	0.43
Chronic respiratory diseases	6	(14.3)	7	(6.4)	0.19
Diabetes (type 2)	3	(7.1)	7	(6.4)	>0.99
Cardiovascular diseases	7	(16.7)	8	(5.5)	0.12
Cancer	2	(4.8)	2	(1.8)	0.31
Chronic kidney diseases	1	(2.4)	1	(0.9)	0.48
Immunosuppressive treatment	3	(7.1)	2	(1.8)	0.13
<b>Early warning score (NEWS<sup>b</sup>) – no. (%)</b>					
Median NEWS (IQR)	2	(1–4)	1	(0–2)	<b>&lt;0.001</b>
0–4 (low)	32	(76.2)	107	(97.3)	<b>&lt;0.001</b>
5–6 (medium)	6	(14.3)	3	(2.7)	<b>0.014</b>
≥7 (high)	4	(9.5)	0	(0.0)	<b>0.005</b>
<b>Laboratory findings<sup>c</sup> – median (IQR)</b>					
Plasma zinc concentration, µg/dL	59	(56–62)	74	(69–81)	<b>&lt;0.001</b>
White blood cell count, ×10 <sup>9</sup> /L	5.4	(4.2–7.0)	4.6	(3.6–6.0)	<b>0.03</b>
Hemoglobin, g/dL	13.5	(12.2–14.3)	14.3	(13.4–15.4)	<b>&lt;0.001</b>
Platelet count, ×10 <sup>9</sup> /L	230	(177–269)	220	(190–256)	0.92
Neutrophil cell count, ×10 <sup>9</sup> /L	3.1	(2.4–4.8)	2.3	(1.4–3.0)	<b>0.003</b>
Lymphocyte count, ×10 <sup>9</sup> /L	1.2	(0.9–1.5)	1.6	(1.4–2.1)	<b>&lt;0.001</b>
Neutrophil-lymphocyte ratio (NLR)	2.9	(1.6–5.4)	1.3	(0.9–1.8)	<b>&lt;0.001</b>
D-Dimer level, mg/L	0.33	(0.27–0.96)	0.28	(0.27–0.38)	<b>0.01</b>
C-reactive protein, mg/L	7	(2–20)	2	(1–5)	<b>&lt;0.001</b>
Lymphocyte-to-CRP ratio (LCR) (×10 <sup>9</sup> /L/mg/L)	0.15	(0.04–1.04)	0.76	(0.29–1.85)	<b>&lt;0.001</b>
Lactate dehydrogenase, UI/L	187	(169–237)	191	(169–216)	0.74
Ferritin, µg/L	252	(78–382)	182	(62–242)	<b>0.04</b>
Albumin, g/dL	4.4	(4.2–4.6)	4.7	(4.5–4.9)	<b>&lt;0.001</b>
Alanine aminotransferase (ALAT), UI/L	21	(16–31)	25	(19–41)	0.06
Aspartate aminotransferase (ASAT), UI/L	27	(20–33)	25	(23–32)	0.63
Total bilirubin, µmol/L	6	(4–8)	6	(4–7)	0.84
Creatine kinase, UI/L	65	(50–90)	84	(56–115)	0.09
Alkaline phosphatase, UI/L	63	(56–78)	63	(51–79)	0.53
Gamma-glutamyltransferase, UI/L	23	(15–32)	26	(16–45)	0.23
Creatinine, mg/dL	0.77	(0.67–0.93)	0.81	(0.70–0.97)	0.26
<b>Distribution<sup>d</sup> – no./total no (%)</b>					
Anemia	9/42	(21.4)	9/110	(8.2)	<b>0.045</b>
Albumin < 3.5 g/dL	3/39	(7.7)	0/106	(0.0)	<b>0.02</b>
D-dimer > 0.5 mg/L	15/41	(36.6)	19/109	(17.4)	<b>0.01</b>
C-reactive protein < 20 mg/L	<b>29/40</b>	<b>(72.5)</b>	<b>104/108</b>	<b>(96.3)</b>	<b>&lt;0.001</b>
C-reactive protein ≥20 mg/L	<b>11/40</b>	<b>(27.5)</b>	<b>4/108</b>	<b>(3.7)</b>	<b>&lt;0.001</b>
Lymphopenia	23/31	(74.2)	24/77	(31.2)	<b>&lt;0.001</b>
<b>Clinical course – no. (%)</b>					
Hospitalization for respiratory complications within 10 days	7	(16.7)	6	(5.5)	<b>0.046</b>

Significant p-values are formatted in bold.

<sup>a</sup> Quantitative continuous variables were expressed as medians with interquartile ranges (IQRs) compared using Mann–Whitney U tests. Qualitative variables were expressed as no. (%) or no./total no (%) where total no. is the total number with available data, and compared using Chi-square test or Fisher's exact test, as appropriate.

<sup>b</sup> NEWS: National Early Warning Score for COVID-19.

<sup>c</sup> To convert the values for zinc to µmol/L, divide by 6.54. To convert the values for creatinine to µmol/L, multiply by 88.4.

<sup>d</sup> Anemia was defined as hemoglobin values below 12 g/dL for women and 13 g/dL for men. Lymphopenia was defined as lymphocyte count below  $1.5 \times 10^9$ /L.

**Table 3**  
Multivariable analysis of determinants of hospitalization for acute respiratory complications within 10 days.<sup>a</sup>

Variable	n	Univariate analysis			Multivariate analysis		
		OR	95% C.I.	p-value	OR	95% C.I.	p-value
Hypertension	152	16.9	(4.8–59.9)	<0.001			
Diabetes	152	5.7	(1.3–25.3)	<0.001			
<b>Hypozincemia</b>	<b>152</b>	<b>3.4</b>	<b>(1.1–11.0)</b>	<b>0.035</b>	<b>10.9</b>	<b>(2.3–51.6)</b>	<b>0.002</b>
Age	152	1.1	(1.0–1.1)	0.001			
NEWS <sup>b</sup>	152	1.7	(1.3–2.2)	<0.001			
Neutrophil-lymphocyte ratio	108	1.3	(1.0–1.5)	0.014			
Creatinine	148	1.1	(0.9–1.0)	0.050	10.6	(1.4–85.5)	0.026
Body mass index (BMI)	147	1.1	(1.1–1.3)	0.027	1.2	(1.0–1.4)	0.035
C-reactive protein (CRP)	148	1.0	(0.9–1.0)	0.050			
Lactate dehydrogenase (LDH)	146	1.0	(1.0–1.0)	0.004			
Ferritin	107	1.0	(1.0–1.0)	0.001			
Alanine aminotransferase (ALAT)	146	1.0	(1.0–1.1)	0.008			
Aspartate aminotransferase (ASAT)	147	1.0	(1.0–1.1)	0.037	1.1	(1.0–1.2)	0.035
Gamma glutamyltransferase (GGT)	140	1.0	(1.0–1.0)	0.013			

Significant p-values are formatted in bold.

<sup>a</sup> All the categorical and continuous variables with p-values <0.05 in univariate analysis were retained as potential confounders in the multivariable analysis. Multivariable analysis was assessed by logistic regression using hospitalization for respiratory complications within 10 days as the primary outcome.

<sup>b</sup> NEWS: National Early Warning Score for COVID-19.

individuals infected with SARS-CoV-2. They highlight the need for early detection of zinc deficiency particularly in the more vulnerable COVID-19 patients. According to WHO and ESPEN recommendations [3,10], an early and adequate zinc supplementation should be part of a global nutritional strategy for preventing severe COVID-19.

## 5. Conclusions

The prevalence of hypozincemia defined by WHO criteria exceeded 20% in the early stage of COVID-19 even without a potential inflammation impact. Hypozincemia was associated with a worse risk score of clinical deterioration (NEWS  $\geq 7$ ) and was an independent predictor of hospitalization for respiratory complications within 10 days. This may suggest the importance of early detection and treatment of zinc deficiency in the nutritional management of COVID-19, especially in older people. Therefore, intervention and adjuvant treatment trials are strongly needed.

## Credit author statement

**Julien Fromonot:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing original Draft, Visualization. **Mickael Gette:** Visualization, Formal analysis, Investigation. **Amin Ben Lassoued:** Resources. **Jean-Louis Guéant:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing original Draft, Visualization, Supervision. **Rosa-Maria Guéant-Rodriguez:** Resources, Formal analysis, Investigation. **Régis Guieu:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing original Draft, Visualization, Supervision.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## References

- [1] Gammoh NZ, Rink L. Zinc in infection and inflammation. *Nutrients* 2017;9: 624. <https://doi.org/10.3390/nu9060624>.
- [2] Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019–2020 epidemic: preparing intensive care units—the experience in Sichuan Province, China. *Intensive Care Med* 2020;46:357–60. <https://doi.org/10.1007/s00134-020-05954-2>.
- [3] de Benoist B, Darnton-Hill I, Davidsson L, Fontaine O, Hotz C. Conclusions of the Joint WHO/UNICEF/IAEA/IZiNCG interagency meeting on zinc status indicators. *Food Nutr Bull* 2007;28:S480–4. <https://doi.org/10.1177/15648265070283s306>.
- [4] Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. *Am J Clin Nutr* 2012;95:64–71. <https://doi.org/10.3945/ajcn.111.023812>.
- [5] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20. <https://doi.org/10.1056/nejmoa2002032>.
- [6] Arnaud J, Touvier M, Galan P, Andriollo-Sanchez M, Ruffieux D, Roussel AM, et al. Determinants of serum zinc concentrations in a population of French middle-age subjects (SU.VI.MAX cohort). *Eur J Clin Nutr* 2010;64:1057–64. <https://doi.org/10.1038/ejcn.2010.118>.
- [7] Heller RA, Sun Q, Hackler J, Seelig J, Seibert L, Cherkezov A, et al. Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker. *Redox Biol* 2020;38:101764. <https://doi.org/10.1016/j.redox.2020.101764>.
- [8] Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol* 2020;69:1228–34. <https://doi.org/10.1099/jmm.0.001250>.
- [9] Zhao X, Li Y, Ge Y, Shi Y, Lv P, Zhang J, et al. Evaluation of nutrition risk and its association with mortality risk in severely and critically ill COVID-19 patients. *J Parenter Enteral Nutr* 2020. <https://doi.org/10.1002/jpen.1953>. e-pub 01 July.
- [10] Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al., Endorsed by the ESPEN council. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr* 2020;39:1631–8. <https://doi.org/10.1016/j.clnu.2020.03.022>.