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Hypermagnesemia and hyperphosphatemia are highly prevalent in patients with COVID-19 and increase the risk of death

Justyna Malinowska[a,b,*], Milena Małecka-Giełdowska[a,c], Diana Bańkowska[d], Kinga Borecka[d], Olga Ciepiela[a,c]

[a] Department of Laboratory Medicine, Medical University of Warsaw, Warsaw, Poland
[b] Doctoral School at Medical University of Warsaw, Warsaw, Poland
[c] Central Laboratory, Central Teaching Hospital of University Clinical Center of Medical University of Warsaw, Warsaw, Poland
[d] Students Scientific Group of Laboratory Medicine, Medical University of Warsaw, Warsaw, Poland

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ABSTRACT

Objectives: Nonrespiratory manifestations of COVID-19 include endocrine disorders, among which are calcium-magnesium-phosphate homeostasis abnormalities, which seem to influence the disease severity and patient outcome. The aim of this study was to evaluate the prevalence and impact of calcium-magnesium-phosphate and vitamin D3 disorders on survival in patients hospitalized for COVID-19 depending on the severity of the disease and kidney function.

Design or methods: The study was conducted between April 2020 and May 2021 at Central Clinical Hospital in Warsaw, Poland. A total of 146 patients who had tested concentration of at least one of the studied elements, estimated glomerular filtration ratio, creatinine levels, and blood saturation, and were diagnosed with COVID-19 disease were included in the analysis.

Results: We found that hypermagnesemia was common and associated with a 1.5-fold increased risk of death in the whole cohort. Hyperphosphatemia also increased the risk of death, exactly 2.4-fold. Furthermore, we found a statistically significant association between increased mortality in the whole cohort and hypovitaminosis D3 ($P < 0.05$). Serum creatinine concentration and estimated glomerular filtration ratio significantly correlated with serum magnesium and phosphate levels.

Conclusion: Hypermagnesemia, hyperphosphatemia, and hypovitaminosis D but not hypocalcemia influence the mortality of patients with COVID-19. These parameters should be monitored routinely in this group of patients, especially in those with decreased kidney function.

Introduction

COVID-19 is characterized by several symptoms such as fever, cough, fatigue, and lymphocytopenia (Guan *et al.*, 2020). However, the longer this pandemic lasts, the more diverse the disease picture becomes. Nonrespiratory manifestations include endocrine disorders, among which are calcium-magnesium-phosphate homeostasis abnormalities, which appear to be of clinical significance in patients with severe disease.

Over the last 2 years, most reports on the calcium-magnesium-phosphate metabolism in COVID-19 concerned hypocalcemia; consequently, it was considered that reduced serum calcium concentration is a recurrent feature of this disease (Bossoni *et al.*, 2020; Cappellini *et al.*, 2020; Di Filippo *et al.*, 2020). There have also been reports of the high prevalence of vitamin D deficiency in patients with severe COVID-19, which may be one of the causes of hypocalcemia in this group (Bennouar *et al.*, 2021). As for magnesium and phosphate, although studies are reporting common hypomagnesemia and hypophosphatemia in patients with COVID-19 and even an association with disease severity, they are limited in number (van Kempen and Deixler, 2021). Hypomagnesemia has been described as a factor that may worsen the course and prognosis of patients with COVID-19, and magnesium supplementation seemed to be one possible therapeutic intervention (Tan *et al.*, 2020; Tang *et al.*, 2020; van Kempen and Deixler, 2021; Wallace, 2020). Moreover, hypermagnesemia found on admission may be a new marker

* Corresponding author: Justyna Malinowska, Banacha 1a, 02-097 Warsaw, Poland, Tel.: +48-22-599-24-05.
E-mail address: justyna.malinowska@wum.edu.pl (J. Malinowska).

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of the severity of the disease and adverse outcome because it seems to be significantly associated with the increased mortality of patients infected with SARS-CoV-2 (Sharma *et al.*, 2022).

Abnormal levels of electrolytes, especially hypermagnesemia, are usually associated with decreased renal function because the kidneys are involved in the maintenance of calcium-magnesium-phosphate homeostasis (Blaine *et al.*, 2015). Moreover, COVID-19 impacts kidney function and is associated with an increased risk and the occurrence of acute kidney injury (AKI) (Fisher *et al.*, 2020; Kant *et al.*, 2020). The disease has also a particular effect on patients with pre-existing chronic kidney disease (CKD) (Kant *et al.*, 2020). One of the reasons why COVID-19 so often impacts kidney function is that the binding site for SARS-CoV-2, which is angiotensin-converting enzyme 2, is abundantly present in the proximal tubule cells (Fisher *et al.*, 2020)

The aim of this study was to evaluate the prevalence and impact on survival of calcium-magnesium-phosphate and vitamin D3 disorders in patients hospitalized for COVID-19 depending on the severity of the disease and kidney function.

Materials and Methods

A retrospective analysis of serum total and ionized calcium, magnesium, phosphate, vitamin D3, albumin, and creatinine concentrations, blood pH, saturation, estimated glomerular filtration ratio (eGFR), age, sex, disease severity, comorbidities, and the outcome was performed among patients hospitalized in the Central Clinical Hospital of the Medical University of Warsaw between April 2020 and May 2021 because of COVID-19 infection. A total of 146 patients who (i) had tested concentration of at least one of the studied elements and (ii) were diagnosed with COVID-19 using real-time polymerase chain reaction assay of nasal and pharyngeal swab with clinical signs of infection were included in the study. Patients were divided into two groups: severe COVID-19 (N = 111) and nonsevere COVID-19 (N = 35) based on the saturation of hemoglobin with oxygen upon admission and using cut-off points proposed by the Polish Society of Epidemiologists and Doctors of Infectious Diseases (Flisiak *et al.*, 2020); severe COVID-19 was diagnosed when saturation was <90% and nonsevere COVID-19 when saturation was ≥90%. The exclusion criteria were data gaps that made it impossible to determine the age or concentration of any of the parameters tested. The older patients were defined as patients over 60 years of age.

Data were collected from the hospital's database. Calcium, ionized calcium (assessed at a standard pH of 7.4), magnesium, phosphate, vitamin D3, albumin, and creatinine concentrations, blood pH, and saturation were tested upon admission or during the first 24 hours of hospitalization.

Adapted reference values: for magnesium, 0.75-1.0 mmol/l; for total calcium, 2.15-2.5 mmol/l; for ionized calcium, 1.05-1.3 mmol/l; for phosphate, 0.8-1.5 mmol/l; for vitamin D, 30-50 ng/ml; for blood pH, 7.32-7.42 pH. The reference limit used for hypoalbuminemia diagnosis was <3.5 g/ml. For those subjects who had decreased albumin concentration (n = 35), we calculated a corrected calcium concentration using the equation: Ca corrected = Ca + 0.02 (40−Alb), where Ca is total calcium in mmol/l and Alb is albumin (g/l). Reference values for creatinine for females are in the range of 0.48-0.93 mg/dl and for males, in the range of 0.63-1.16 mg/dl (Delanaye *et al.*, 2017). The eGFR value was used to determine the stage of CKD, respectively stages 1-2, eGFR ≥60 ml/min/1.73 m^2; stage 3, eGFR = 30-59 ml/min/1.73 m^2; stage 4, eGFR = 15-29 ml/min/1.73 m^2; and stage 5, eGFR ≤15 ml/min/1.73 m^2 (Hill *et al.*, 2016).

The research was conducted according to the rules of the bioethical committee of the Medical University of Warsaw and all data were anonymized.

Statistical Analysis was performed using Microsoft Office Excel 2019, Statsoft Statistica, and GraphPad Prism. Shapiro-Wilk test was used to assess the normality of the distribution of the results. For data with a normal distribution, we used *t*-test (effect of sex and age on serum ionized calcium and magnesium concentration, the difference in mean magnesium concentration between patients with creatinine level >1.5 mg/dl and ≤1.5 mg/dl) and analysis of variance (comparison of mean serum magnesium concentrations between groups of patients at different CKD stages). For data with non-Gaussian distribution, we used Mann-Whitney U test (effect of sex and age on phosphate, corrected calcium, vitamin D, and creatinine concentration, an association with fatal outcome, the difference in median phosphate concentration between patients with creatinine level >1.5 mg/dl and ≤1.5 mg/dl, difference in median age between severe and nonsevere groups), Kruskal-Wallis test (comparison of median serum phosphate concentrations between groups of patients at different CKD stages), chi-square test with the appropriate corrections (comparison of the frequency of hypo-, normo-, and hyperconcentrations of the parameters studied between the groups with severe and nonsevere COVID-19, the difference in the incidence of creatinine concentration >1.5 mg/dl between sexes, and comparison of patients based on the outcome in terms of disease severity and the occurrence of biochemical abnormalities) and Spearman's rank correlation coefficient (correlation of glomerular filtration rate and creatinine levels with studied electrolytes). We also performed logistic regression analysis of the impact of changes in the studied parameters on the chance of death in total patients. We considered P <0.05 as statistically significant and marked it in the text in bold.

Results

A total of 146 patients hospitalized at the University Clinical Center of the Medical University of Warsaw with severe or nonsevere COVID-19 were included in the study. Older patients predominated in the group (63.7%, 93/146), with the median of 64.5 years. Males made up the majority of the group (62%, 90/146). However, there was no statistical association between disease severity and age or sex. For basic information on patients, see Table 1.

Biochemical evaluation

Simple statistical analysis was performed to evaluate the prevalence of calcium-magnesium-phosphate and vitamin D3 disorders and the dependence of their occurrence on sex and disease severity. In our study group, the most common disturbances were hypovitaminosis D3 with a prevalence of 51%, hypercalcemia with an incidence of 46.6%, and increased creatinine levels, which was diagnosed in 45% of our study group. Serum creatinine concentration above 1.5 mg/dl, traditionally used as a cut-off point to diagnose AKI, was found in 35 patients (24%). On the other hand, the least common disturbances were hypophosphatemia (6%) and decreased creatinine level, which were found in 3.4% of all patients. There was a significant difference between the sexes only in serum creatinine level (P <0.00001). Most of the female patients had normal creatinine levels (64%, n = 36), whereas half of the male patients had an increased serum creatinine concentration (53%, n = 47). An analysis of differences in serum concentration of the evaluated parameters between severe and nonsevere patients provided statistically significant results only in the case of phosphate and creatinine. Moreover, hyperphosphatemia was significantly more frequent in the nonsevere COVID-19 group (P = 0.0038). All of the obtained results are set out in Table 2.

Table 1
Baseline patient characteristics by COVID-19 severity.

Variables	Total (N = 146)	Severe COVID-19 (N = 111)	Nonsevere COVID-19 (N = 35)	*P*-value
Age (y)	64.5	64	70	0.25
Sex				
Male	90 (62%)	68 (61%)	22 (63%)	0.89
Female	56 (38%)	43 (39%)	13 (37%)	
Comorbidities				0.98
Diabetes	21 (14%)	17 (15%)	4 (11%)	
Hypertension	18 (12%)	13 (12%)	5 (14%)	
Cancer	1 (0.7%)	-	1 (3%)	
Median SpO_2 (%)	70.35	57.5	95.4	<**0.0000001**

Table 2
Summary of the prevalence of calcium-magnesium-phosphate and vitamin D3 disorders, and the dependence of their occurrence on sex and disease severity.

Variables		Total calcium	Total magnesium	Phosphate	Ionized calcium	Vitamin D3	Creatinine
N		58	66	85	24	43	146
Female (%)		38	29	34	54	33	38
Mean, SD		2.62 ± 0.64	0.88 ± 0.15	1.34 ± 0.63	1.18 ± 0.13	29.17 ± 14.9	1.38 ± 1.05
Hypo (%)	Total	12	17	6	8	51	3.4
	Severe	12	18	7	12	53	3
	Nonsevere	12	12	4	0	43	6
Normo (%)	Total	41	65	75	92	40	51.6
	Severe	40	66	81	88	36	53
	Nonsevere	44	63	62	100	57	46
Hyper (%)	Total	47	18	19	-	9	45
	Severe	48	16	12	-	11	44
	Nonsevere	44	25	34	-	0	48
Female vs male mean serum level		$P = 0.97$	$P = 0.1$	$P = 0.48$	$P = 0.19$	$P = 0.19$	***P*** <**0.00001**
Severe and nonsevere patients mean serum level		$P = 0.96$	$P = 0.665$	***P* = 0.034**	$P = 0.814$	$P = 0.811$	***P* = 0.0023**
The incidence of hypo-, normo- and hypercon-centration in severe vs nonsevere patients	Hypo	$P = 0.63$	$P = 0.47$	$P = 0.51$	$P = 0.49$	$P = 0.47$	$P = 0.35$
	Normo	$P = 0.943$	$P = 0.964$	$P = 0.051$	$P = 0.493$	$P = 0.265$	$P = 0.47$
	Hyper	$P = 0.976$	$P = 0.319$	***P* = 0.004**	-	$P = 0.477$	$P = 0.68$

An assessment of kidney function's influence on evaluated parameters

Serum creatinine concentration significantly correlated with serum magnesium (R = 0.36, *P* **<0.001**) and phosphate concentrations (R = 0.23, *P* = **0.031**) but not with serum total calcium (R = 0.12, *P* = 0.38), ionized calcium (R = -0.07, *P* = 0.7), nor vitamin D concentration (R = 0.08, *P* = 0.63). Moreover, mean serum magnesium and median phosphate concentrations in patients with serum creatinine concentration ≤1.5 mg/dl were significantly lower than in patients with serum creatinine levels >1.5 mg/dl (Figure 1).

More than half of the group (82/146) had normal kidney function, and 86% (122/146) were in CKD stages 1-3. The eGFR significantly correlated with serum magnesium concentration (R = -0.44, ***P*** **<0.0001**) and serum phosphate concentration (R = 0.23, *P* = **0.029**) but not with serum total calcium (R = 0.08, *P* = 0.54), ionized calcium (R = -0.126, *P* = 0.52), nor vitamin D concentration (R = 0.16, *P* = 0.3). Furthermore, mean magnesium concentration was significantly lower in CKD stages 1-2 group compared with stages 3 and 4 (*P* = **0.006**). Similarly, median phosphate concentration in CKD stages 1-2 was also significantly lower than in stages 3 and 5 (*P* = **0.015**).

An association between serum concentration of the studied parameters and fatal outcome

Of the 146 patients enrolled in the study, 41 died. These patients were older, with a median of 71 years versus 63 years in the group of patients who survived (*P* = 0.0041). Table 3 shows that they were significantly more often in the nonsevere COVID-19 group and had hypocalcemia (total and ionized), hypermagnesemia, hyperphosphatemia, and increased creatinine levels.

Table 3
Comparison of patients based on the outcome in terms of disease severity, and the occurrence of biochemical abnormalities.

Variables \ Outcome		Death	Survival	*P*-value
Disease severity	Severe COVID-19	25	86	
	Nonsevere COVID-19	16	19	**0.0078**
Hypocalcemia		4	3	**0.0424**
Hypercalcemia		9	18	0.1945
Hypomagnesemia		2	9	0.5520
Hypermagnesemia		7	5	**0.0053**
Hypophosphatemia		1	4	0.6982
Hyperphosphatemia		12	4	**0.00001**
Hypocalcemia (ionized calcium)		2	0	**0.0472**
Hypovitaminosis D3		5	17	0.8591
Hypervitaminosis D3		0	4	0.3682
Decreased creatinine levels		2	3	0.2994
Increased creatinine levels		30	36	**0.00001**

We also compared patients' results based on their outcomes using the Mann-Whitney test. To check the influence of the disease severity on the effect of abnormal electrolyte concentrations on the mortality of patients, we performed this analysis in all patients, severe, and nonsevere groups. We found a statistically sig-

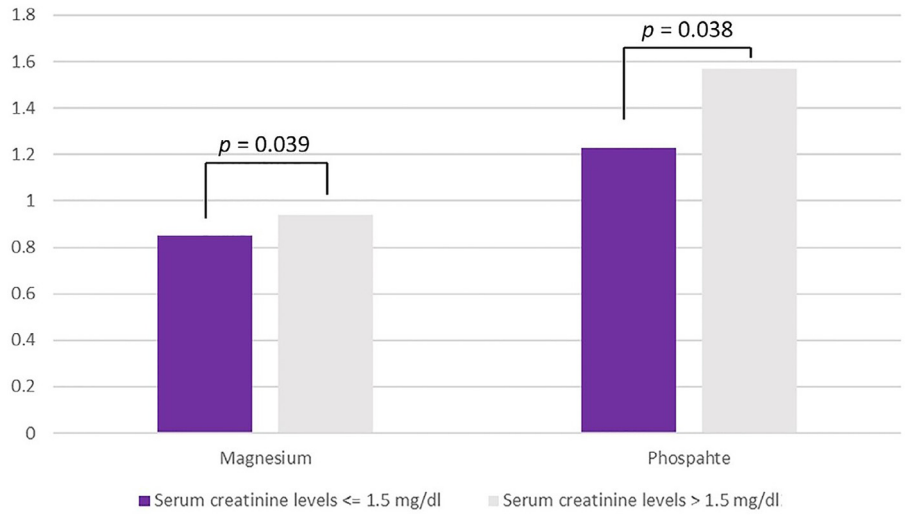

Figure 1. Comparison of mean magnesium and median phosphate concentration between patients with serum creatinine concentration ≤ 1.5 mg/dl and > 1.5 mg/dl.

Table 4
An association between serum concentration of studied parameters and fatal outcome in total patients, nonsevere, and severe COVID-19 groups.

Variables	Total patients	Nonsevere	Severe
	P-value		
Hypercalcemia	0.7	0.525	0.31
Hypomagnesemia	0.06	0.29	0.17
Hyperphosphatemia	0.14	0.62	0.256
Hypocalcemia (ionized calcium)	1	1	0.39
Hypovitaminosis D3	**0.05**	0.846	0.059
Increased creatinine levels	<**0.00001**	0.19	<**0.0001**
Decreased eGFR	<**0.00001**	0.071	<**0.0001**

Table 5
The odds ratio for death in total patients related to changes in the studied parameters.

Variables	OR	95% CI
Hypocalcemia	0.714	0.6832-2.0130
Hypermagnesemia	**1.500**	1.4830-3.100
Hyperphosphatemia	**2.400**	1.4311-4.033
Hypovitaminosis D3	0.7642	0.8565-1.053
Hypocalcemia (ionized calcium)	1.002	0.8544-2.0131
Increased creatinine levels	0.7351	0.2176-1.799
Decreased eGFR	0.9616	0.8905-1.028

nificant association between an increased mortality in total patients and hypovitaminosis D3 ($P = 0.05$), increased creatinine levels ($P < 0.00001$), and decreased eGFR ($P < 0.00001$). Similarly, in the severe COVID-19 group, there was also a significant association between fatal outcome and increased creatinine levels ($P < 0.0001$) and decreased eGFR ($P < 0.0001$) (Table 4).

However, we also performed a logistic regression analysis of the impact of changes in the studied parameters on the chance of death in the whole cohort, including data on age, sex, serum creatinine concentration, eGFR, and comorbidities (Table 5). The only statistically significant results that we have found concerned magnesium and phosphate. The odds ratio (OR) for magnesium was 1.500, indicating a 1.5-fold increase in the odds of fatal hospitalization for patients with hypermagnesemia. Above normal phosphate levels were also associated with an increased, exactly 2.4-fold, chance of death (OR = 2.400).

Discussion

In our study group, males made up 62% of total patients. It is in line with observations of other researchers that a severe course of COVID-19 is more common among males, resulting in hospitalization. The probable causes are weakened immune response to infection in men and an increase in angiotensin-converting enzyme 2 expression, which is a receptor that SARS-CoV-2 binds to (Mohamed *et al.*, 2021; Viveiros *et al.*, 2021).

The older patients predominated in our study group (63.7%). This observation is similar to those made in other studies and justified because age is one of the major risk factors, maybe even the most significant one, for COVID-19 (Chen *et al.*, 2021; Tian *et al.*, 2020; Wu *et al.*, 2020).

The SARS-CoV-2 infection has a particular impact on kidney function in patients with AKI and also on patients with pre-existing CKD (Kant *et al.*, 2020). The assessment of kidney function is vital when analyzing the influence of a given disease on the calcium-magnesium-phosphate balance because the kidneys, gut, and bones are regulating their homeostasis (Blaine *et al.*, 2015). CKD influences these minerals' serum concentration in the most profound way, especially magnesium (van de Wal-Visscher *et al.*, 2018). CKD is usually diagnosed when eGFR is below 60 ml/min/1.73 m^2 (Pasala and Carmody, 2017). However, even with lower eGFR values, and thus worse kidney function, compensatory mechanisms, such as an increase in fraction excretion of magnesium, prevent serum minerals concentration changes. This state continues through CKD stages 1 to 3 but becomes insufficient in more advanced stages 4 to 5 (van de Wal-Visscher *et al.*, 2018). In our study, the majority of patients (86%) were in the CKD stage 1-3, in which calcium, magnesium, and phosphate levels should not be influenced by improper kidney function.

Another marker of kidney function is creatinine, although not an ideal one, because an increased serum creatinine can be caused by larger muscle mass, a high-protein diet, and drugs (Pasala and Carmody, 2017). In our study group, increased creatinine concentration was common and occurred in 34% of female patients and 53% of male patients, and there was a statistically significant association between serum creatinine level and sex ($P < 0.00001$). This is in line with the observations of other researchers (O'Leary *et al.*, 2017).

Serum creatinine level is a parameter used to diagnose AKI (Ronco *et al.*, 2019). Traditionally, the cut-off point used for that

purpose was 1.5 mg/dl but currently, it is recommended to access changes in serum creatinine concentration during hospitalization, and only an established increase in its concentration indicates AKI (O'Leary *et al*., 2017). However, we analyzed only test results taken upon admission or during the first 24 hours of hospitalization. This is why we have only evaluated the association of serum creatinine levels with serum concentration of studied minerals as well as the incidence of serum creatinine levels of more than 1.5 mg/dl, without referring to the occurrence of AKI. We found that serum creatinine concentration and eGFR significantly correlated with serum magnesium and phosphate levels. Our results are in line with the observations of other researchers (Felsenfeld *et al*., 2015). Although the incidence of advanced CKD (14% of the patients) and serum creatinine levels >1.5 mg/dl (24% of the patients) was moderately low in our study group, these abnormalities were significantly associated with fatal outcome in the whole cohort and the severe group; hence, we have included data on eGFR and creatinine concentration in the logistic regression analysis to avoid any interference.

In our study group, hypocalcemia was not as prevalent as in other studies, 12% versus 62.6% (Liu *et al*., 2020) in patients with severe COVID-19, 12.5% versus 67% (Pal *et al*., 2020) in patients with nonsevere COVID-19, and 12% versus 80% in total patients (di Filippo *et al*., 2021b). It is not probable that the cause of this difference lies in the selected method of assessment of calcium concentration, as in the study, in which the incidence of hypocalcemia reached 80%, researchers tested plasma ionized calcium concentration (di Filippo *et al*., 2021b). So did we, and only 12% of the patients with severe COVID-19 had hypocalcemia. However, we found that hypocalcemia was still significantly more prevalent in patients who did not survive (**0.0424**). However, we did not find any association between hypocalcemia and fatal outcome, which is contrary to the results of other researchers (di Filippo *et al*., 2021b; Liu *et al*., 2020).

The incidence of hypercalcemia in our study group was unexpectedly high, 48% (severe COVID-19) and 43.75% (nonsevere COVID-19). This could be another calcium-magnesium-phosphate imbalance observed in the COVID-19 pandemic, as it had been in other viral diseases (Prager *et al*., 1994). However, although so common, hypercalcemia does not appear to affect the mortality of patients with COVID-19. Normally, hypercalcemia can be caused by hyperparathyroidism, malignancies, drugs, or hypervitaminosis D (Turner, 2017). The latter is not probable in this study because we assessed vitamin D3 concentrations in our study group and found that hypervitaminosis was not that common. On the other hand, hyperparathyroidism may be a probable cause of such a high incidence of hypercalcemia in our study group, as its treatment has become difficult during the pandemic (Lisco *et al*., 2021). Another possible explanation for abnormal calcium concentrations in patients with COVID-19 is impaired compensatory parathyroid hormone response, caused by parathyroid gland disfunction due to critical illness and inflammation (di Filippo *et al*., 2021a). However, we did not include serum parathyroid hormone concentration in our analysis; hence, those remain the only possible circumstances.

In our study group, hypomagnesemia (Mg <0.75 mmol/l) was found in 18% of patients severe with COVID-19 and 12.5% of the nonsevere COVID-19 group. Interestingly, this prevalence is in line with some (12.5-18% vs 12.2%) (Haraj *et al*., 2021) or lower than other reports (12.5-18% vs 32-48%) (Quilliot *et al*., 2020; Sarvazad *et al*., 2020). Magnesium deficiency is discussed as a risk factor for severe COVID-19 infection but also, to some extent, a result of it (Iotti *et al*., 2020). Although hypomagnesemia causes an increase in the production of cytokines and systemic inflammation, we did not observe any significant association between hypomagnesemia and increased mortality ($P = 0.06$) (Sarvazad *et al*., 2020). Moreover, the prevalence of hypermagnesemia (Mg >1.0 mmol/l) was higher and occurred in 16% of subjects with severe COVID-19 and 25% of patients with nonsevere COVID-19. Although it is a much higher prevalence than is usually found in the hospital population (16-25% vs 5.7-13.5%) (Jahnen-Dechent and Ketteler, 2012), it is lower than that reported by Sharma *et al* (54%) (Sharma *et al*., 2022). Hypermagnesemia may be more frequent in this group of patients because people infected with SARS-CoV-2 experience complex cellular damage that can result in the release of magnesium ions from the intracellular compartment, where 99% is stored under physiologic conditions, into the extracellular compartment (Sharma *et al*., 2022). An increased risk of death in intensive care units due to hypermagnesemia has already been reported but only once in association with severe COVID-19 (Broman *et al*., 2018; Sharma *et al*., 2022). However, in our study, OR for hypermagnesemia also indicates an increased chance of death. It seems that the concentration of magnesium is a parameter that should be carefully monitored in this group of patients.

Hypophosphatemia in our study group was found only in 7% (severe COVID-19) and 3.8% (nonsevere COVID-19) of patients. Phosphate deficiency is recognized as one of the risk factors for a severe COVID-19, but the difference in the incidence of this disorder between the groups in our study group was not statistically significant ($P = 0.51$) (van Kempen and Deixler, 2021). Furthermore, we found a statistically significant difference in the incidence of hyperphosphatemia between severe and nonsevere COVID-19 groups, 12% versus 34.2% ($P =$ **0.004**). There are no scientific data on the incidence of hyperphosphatemia in the course of COVID-19, but there are reports of cases in which the infection is the cause of this abnormality (Elkattawy *et al*., 2020; Tchidjou *et al*., 2020). As important as phosphate is for energy metabolism, its high concentrations are life-threatening, irrespective of kidney function, which was also indicated by our OR analysis in which above normal phosphate levels were associated with an increased, exactly 2.4-fold, chance of death (Broman *et al*., 2018). Viral infection may also be a cause of transient hyperphosphatemia, but we cannot comment on this because included only measurements made upon admission (Tchidjou *et al*., 2020).

Hypovitaminosis D3 was found in 51% of total patients and was associated with increased mortality ($P = 0.05$). Similar results were obtained by other researchers, 39-55.7% (Baktash *et al*., 2021; Pereira *et al*., 2020). It may be caused by a high prevalence of vitamin D deficiency worldwide (Lips *et al*., 2019).

Interestingly, we found hypervitaminosis D only in the severe COVID-19 group (11%). Because researchers studying COVID-19 cases focus on hypovitaminosis D, there is very limited data on hypervitaminosis D incidence in this group of patients; compared with the results of studies on the hospital population, the prevalence is higher, 11% vs 4.1% (Sharma *et al*., 2017). The probable cause of it is the misuse of dietary supplements, which could be taken by the patients in too high doses (Rahesh *et al*., 2020).

We did not find any sex or age dependence regarding almost all of the studied elements. It is in line with some but not all studies. For example, hypomagnesemia was found to be more prevalent in female patients with COVID-19 in one study (Quilliot *et al*., 2020), but there was no sex or age dependence in others (Haraj *et al*., 2021). In the case of serum calcium concentration, sex and age also appear to be unrelated to the obtained results (di Filippo *et al*., 2021b; Liu *et al*., 2020), as well as in hypovitaminosis D (Baktash *et al*., 2021).

Conclusions

Calcium-magnesium-phosphate homeostasis disturbances are very common among patients with COVID-19, with hypermagne-

semia and hyperphosphatemia increasing the risk of death. These parameters should be regularly monitored.

Conflicts of interest

The authors have no competing interests to declare.

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Author contributions

Conceptualization, O.C.; methodology, O.C., J.M.; software, M.M., J.M., validation, M.M., O.C.; formal analysis, J.M.; investigation, J.M., M.M., D.B., K.B.; resources, O.C., M.M.; data curation, O.C.; writing—original draft preparation, J.M.; writing—review and editing, M.M., D.B., K.B, O.C.; visualization, J.M., O.C; supervision, O.C.; project administration, J.M., O.C., M.M. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement

The bioethics committee at the Medical University of Warsaw stated that this study was not a medical experiment and did not require the committee's opinion (AKBE / 135/2021).

Informed consent statement

Not applicable due to the study's retrospective nature.

Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical reasons.

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