EGYPTIAN JOURNAL OF ANAESTHESIA
2023, VOL. 39, NO. 1, 266–276
https://doi.org/10.1080/11101849.2023.2192096

Longitudinal analysis of electrolyte prolife in intensive care COVID-19 patients

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ABSTRACT

Introduction: According to a substantial body of research, electrolyte abnormalities are a common manifestation in coronavirus disease 2019 (COVID-19) patients and are associated with adverse outcomes. This study aimed to investigate electrolyte imbalances in COVID-19 patients and assess their relation to mortality.

Methods: Adult COVID-19 patients hospitalized in the Security Forces Hospital in Saudi Arabia from June 8th till August 18th, 2020 were enrolled in this retrospective observational study. We examined baseline characteristics, comorbidities, acute organ injuries, medications, and electrolyte levels including sodium, potassium, chloride, calcium, bicarbonate, phosphate, and magnesium on ICU admission, as well as every following day of ICU stay, until death or discharge. Patients were stratified according to survival, and differences in variables between groups were compared using Mann-Whitney's U test or Fisher's exact test. Longitudinal electrolyte profiles were modeled using random intercept linear regression models.

Results: A total of 60 COVID-19 patients were enrolled. Compared to survivors, non-survivors had significantly higher sodium and phosphate on admission and death, higher potassium and magnesium at death, and significantly lower calcium at death. Abnormalities in admission levels of chloride and bicarbonate were also more frequently observed in non-survivors. Furthermore, in the deceased group, we observed a daily increase in potassium and phosphate levels, and a daily decrease in sodium and chloride. Finally, calcium increased in non-survivors over time, however, not as significantly as in the survivor group.

Conclusion: Admission levels of electrolytes and changes over the course of ICU stay appear to be associated with mortality in COVID-19 patients.

ARTICLE HISTORY
Received 14 December 2022
Accepted 13 March 2023

KEYWORDS
Electrolytes; COVID-19; mortality; ICU; longitudinal analysis

1. Introduction

Since its inception in December 2019, the severe acute respiratory disease coronavirus 2 (SARS-CoV-2), responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic, has been a focus of a vast amount of research on the prognostic value of various clinical and laboratory parameters in infected patients [1–5]. In this regard, electrolyte disturbances have shown promising potential in aiding risk stratification of COVID-19 patients and guiding treatment [4,6], in addition to providing clues for the underlying mechanisms leading to adverse outcomes.

Physiologically, electrolytes serve a number of critical roles. For example, potassium levels determine stability of cardiomyocyte membrane potentials, and disturbances may lead to cardiac arrhythmia [7], whilst calcium and magnesium are essential in immune function and protection against oxidative stress [8]. A number of recent studies have reported findings of electrolyte deficiency or excess in COVID-19 patients on admission [5,6,9–12]. Electrolyte disturbances might be related to underlying patient characteristics, comorbidities, nutrition, vitamin D status, and medication use. On the other hand, the many pathological processes occurring in COVID-19 even before hospital presentation, such as cytokine storm and acute kidney injury (AKI), may also explain electrolyte imbalances on admission and further along the disease course [13,14]. Notably, several electrolyte disturbances appear to be linked to viropathic effects of SARS-CoV-2 on the renin-

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/11101849.2023.2192096.

aldosterone-angiotensin system (RAAS), a primary regulator of electrolyte homeostasis, through binding of human angiotensin converting enzyme-2 (ACE2) receptor [6,15–17]. Whether they present at baseline or develop over the course of illness, one may suspect that any disturbance in electrolyte balance may worsen outcome of COVID-19 illness, given their many important physiologic roles. Indeed, electrolyte deficiency or excess has been associated with adverse outcomes such as need for mechanical ventilation, intensive care unit (ICU) admission, and mortality in many recent studies [5,6,8–12]. Certain authors have gone on to suggest that correction of these abnormalities may improve outcomes [6,18–20], while some have found evidence in support of these recommendations [21]. Accordingly, investigating disruption of electrolyte homeostasis in COVID-19 may not only offer insight into the pathophysiology of SARS-CoV-2 infection, but also suggests potential therapeutic options for minimizing disease severity. As a result, in this retrospective observational study, we aimed to examine alterations in a panel of electrolytes in COVID-19 patients over the course of their stay in the ICU, measuring levels from admission to discharge/death, and explore the association with survival.

2. Methods

2.1. Study design and cohort

In this retrospective observational study, adult patients presenting to the ICU with reverse transcriptase polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection, during the period 8th of June 2020 till 18th of August 2020 were enrolled. Besides routine maintenance intravenous fluids, patients with electrolytes deficiency were supplemented with specific electrolyte solutions (e.g., KCl) per physician discretion. The fluid of choice for most patients was normal saline (NS). Patients with NPO (Nil Per Os) status were administered 5% dextrose in normal saline (D5NS), while those with hypernatremia were administered ½NS or D5½NS. Total parenteral nutrition (TPN) was not administered to any patient. Renal patients received Osmolyte or Nepro as enteral nutrition, while diabetic patients were fed Glucerna. An antiviral medication, Favipiravir, was given routinely to all patients, and no impact on electrolytes was observed.

This study was approved by the Institutional Review Board (IRB) of the Security Forces Hospital in accordance with the National Committee of Bio Ethics (NCBE) in Saudi Arabia and received a waiver of informed consent due to no greater than minimal risk to participants. This study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local and national legislation.

2.2. Measurements and endpoints

Serum levels of electrolytes, including total serum sodium, potassium, chloride, albumin-corrected calcium, bicarbonate, phosphate, and magnesium, were recorded on ICU admission, as well as every following day of ICU stay, until death or discharge. The levels were quantified using an Ion-Selective Electrode (ISE) (Roche Cobas 8000; Roche Diagnostics, Basel, Switzerland). We also extracted data on patients' baseline characteristics, comorbidities, acute organ injuries, and medication use from their medical records. Acute cardiac injury (ACI) was defined as serum level of high-sensitivity cardiac troponin T (cTnT) above the upper limit of normal (>100 ng/L) at any point during hospital stay [22]. AKI was defined as increase in serum creatinine by ≥26.5 µmol/L within 48 hours after ICU admission [23]. Acute liver injury (ALI) was defined as over 3× the upper normal limit of serum alanine transaminase (ALT > 123 U/L) and/or aspartate transaminase (AST > 120 U/L), and/or over 2× the upper normal limit of alkaline phosphatase (ALP >260 U/L), γ-glutamyl transpeptidase (GGTP > 122 U/L), and/or total bilirubin (TBIL > 34.2 µmol/L) at any point during hospital stay [24].

The primary endpoint studied was death. Longitudinal measures of electrolytes were modeled for survivors and non-survivors as continuous response variables.

2.3. Statistical analysis

Continuous data were reported as median and interquartile range (IQR), and differences between groups were analyzed by Mann-Whitney's U test. Categorical data were presented as frequency (%), and differences between groups were calculated using Fisher's exact test. Different longitudinal electrolyte profiles for survivors and non-survivors were modeled using random intercept linear regression models, to account for within-subject correlation of daily measures, as well as for intrinsic variability between patients at admission. Statistical analysis was performed using R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria), and $p < 0.05$ was chosen as the threshold of significance.

3. Results

Out of a total of 60 COVID-19 patients enrolled, 35 (58.3%) survived, while 25 (41.7%) died over the course of hospitalization. The median period spent in the ICU was 11.5 days, with no significant difference between survival groups (p = 0.417). Baseline characteristics, comorbidities, medications used, and acute organ injuries of this cohort are presented in Table 1.

The median age was 57 years, and males accounted for 73.3% ($n = 44$) of the total sample. While those that died were significantly older (67

Table 1. Baseline characteristics and comorbidities for COVID-19 patients in total and by survival.

Variable		Total (*n*=60)	Died (*n*=25)	Survived (*n*=35)	p-value
Baseline demographics					
Age, years		57 (48.7–67.2)	67 (56–72)	50 (41.5–62)	**0.002**
Sex	Male	44	19 (76%)	25 (71.4%)	0.921
	Female	16	6 (24%)	10 (28.6%)	
BMI, m/kg2		31 (27.7–36.5)	30.8 (27.7–41.3)	31.1 (29.0–35.3)	1
Obesity		17	8 (32%)	9 (25.7%)	0.46
Hypertension		31	16 (64%)	15 (42.9%)	0.124
Coronary Artery Disease		3	2 (8%)	1 (2.9%)	0.565
Heart Failure		4	4 (16%)	0	**0.026**
Hyperlipidemia		18	9 (36%)	9 (25.7%)	0.395
Diabetes		34	15 (60%)	19 (54.3%)	0.793
COPD		1	1 (4%)	0	0.417
Chronic Kidney Disease		8	5 (20%)	3 (8.6%)	0.259
History of stroke		4	2 (8%)	2 (5.7%)	1
Days in ICU		11.5 (6–21.2)	10 (4–24)	12 (7–21)	0.417
Medications					
Antihypertensive (Beta Blocker)		8	5 (20.0%)	3 (8.6%)	0.244
Antihypertensive (Calcium Channel Blocker)		21	7 (28.0%)	14 (40.0%)	0.579
Antihypertensive (Alpha Agonist)		1	1 (4.0%)	0 (0.0%)	0.397
(Lipid Lowering) Statins		18	10 (40.0%)	8 (22.9%)	0.147
ACE inhibitor		12	5 (20.0%)	7 (20.0%)	1
(Renin-Angiotensin System) Angiotensin Receptor Blocker		8	3 (12.0%)	5 (14.3%)	1
Diuretic (Loop Diuretic)		6	4 (16.0%)	2 (5.7%)	0.202
Diuretic (Thiazide Diuretic)		3	1 (4.0%)	2 (5.7%)	1
Other diuretic		1	1 (4.0%)	0 (0.0%)	0.397
Antiplatelet (Aspirin)		12	8 (32.0%)	4 (11.4%)	**0.047**
Anticoagulant		6	3 (12.0%)	3 (8.6%)	0.673
Acute organ injury					
Acute Kidney Injury		22	13 (52.0%)	9 (25.7%)	0.054
Acute Cardiac Injury		9	7 (28.0%)	2 (5.7%)	**0.026**
Acute Liver Injury		31	16 (64.0%)	15 (42.9%)	0.113
Need for Dialysis*		7	5 (25%)	2 (6.5%)	0.096

All continuous data presented as median (IQR), with P-values calculated using Mann-Whitney's U test. All categorical data presented as frequency (%), with P-values calculated using Fisher's exact test. Statistical significance denoted with bold text. BMI – body mass index; COPD – chronic obstructive pulmonary disease. ICU – intensive care unit. *Patients on dialysis for chronic kidney disease were excluded.

vs. 50 years; $p = 0.002$), there were no significant differences with regard to gender between survival groups ($p = 0.921$). BMI was elevated overall (31 m/kg [2], and comparable between survival groups ($p = 1$). Regarding comorbidities, hypertension (51.7%; $n = 31$) and diabetes (56.7%; $n = 34$) were the most prevalent overall, but only heart failure (HF) was observed more frequently in non-survivors (16% vs. 0%; $p = 0.026$). ACI was significantly more prevalent in patients who died (28% vs. 5.7%, $p = 0.026$), while the frequencies of AKI and ALI were comparable between the groups. Seven patients required dialysis after AKI (31.8%), but there was no difference in this requirement between survival groups. Finally, of the administered medications, only antiplatelet agents were taken significantly more often by non-survivors (32% vs. 11.4%, $p = 0.047$). There were no significant differences in the use of any antihypertensive, diuretic, or anticoagulant agents between survival groups ($p > 0.05$).

3.1. Electrolytes

The median levels of all electrolytes measured on admission were within the physiologically normal range, with no significant difference between groups (Table 2A). On the contrary, electrolyte levels at discharge/death displayed significant differences (Table 2B). Although median electrolyte levels were also all within normal range, non-survivors had significantly higher sodium ($p = 0.002$), potassium ($p = 0.002$), phosphate ($p = 0.028$), and magnesium levels ($p = 0.034$), and significantly lower calcium levels ($p < 0.001$). No differences were observed for chloride ($p = 0.532$) and bicarbonate ($p = 0.130$).

Frequency of COVID-19 patients with electrolyte levels below, within, or above their respective reference range on admission, stratified by survival, is represented in Supplemental Table 1. Of all electrolytes analyzed, the difference between these frequencies were statistically significant for chloride and bicarbonate. On admission, a significantly greater proportion of patients that died had hypo- or hyperchloremia than those that survived (36% vs. 20%, and 24% vs. 5.7%, respectively) [$p = 0.023$], and significantly fewer of those that died had normal chloride levels on admission, compared to survivors (40% vs. 74.3%, $p = 0.023$). Likewise, a significantly greater proportion of patients that died had hypo- or hyperbicarbonatemia than those that survived (48% vs. 22.9%, and 4% vs. 0%,

Table 2. Electrolyte levels on ICU admission and at discharge/death, in total and by survival.

Variable	Reference range	Total	Died	Survived	p-value
A. Electrolytes on ICU Admission					
Sodium	135–147 mmol/L	138 (135.5–141)	137.5 (135.8–142.2)	138 (135.5–139.5)	0.621
Potassium	3.5–5.0 mmol/L	4.3 (3.8–4.7)	4.4 (4.0–4.7)	4.2 (3.7–4.5)	0.227
Chloride	98–106 mmol/L	100 (97–102.2)	99 (96–105)	101 (98–102)	0.754
Calcium	2–2.5 mmol/L	2.11 (2.03–2.21)	2.09 (2.03–2.16)	2.14 (2.04–2.24)	0.329
Bicarbonate	21–28 mmol/L	22 (19–24)	21 (18–24)	23 (21–24)	0.087
Phosphate	0.97–1.45 mmol/L	1.01 (0.87–1.29)	1.17 (0.91–1.36)	0.96 (0.81–1.22)	0.094
Magnesium	0.65–1.05 mmol/L	0.87 (0.77–0.98)	0.86 (0.76–0.98)	0.88 (0.80–0.99)	0.400
B. Electrolytes at Discharge/Death					
Sodium	135–147 mmol/L	140 (137–145.8)	146 (139.5–149)	139 (136.5–141)	**0.002**
Potassium	3.5–5.0 mmol/L	4.3 (3.9–7.7)	4.9 (4.2–5.6)	4.1 (3.9–4.5)	**0.002**
Chloride	98–106 mmol/L	102 (97–105)	103 (96–107)	100 (97.7–104.2)	0.532
Calcium	2–2.5 mmol/L	2.16 (2.01–2.28)	2.00 (1.83–2.16)	2.22 (2.14–2.35)	**<0.001**
Bicarbonate	21–28 mmol/L	23 (20–25)	21 (16.2–25.5)	23 (22–24.5)	0.130
Phosphate	0.97–1.45 mmol/L	1.22 (1.03–2.11)	1.38 (1.06–2.86)	1.12 (0.94–1.54)	**0.028**
Magnesium	0.65–1.05 mmol/L	0.92 (0.84–1.02)	0.96 (0.88–1.14)	0.90 (0.81–0.94)	**0.034**

All continuous data presented as median (IQR), with P-values calculated using Mann-Whitney's U test. Statistical significance denoted with bold text.

respectively) [$p = 0.035$], and significantly fewer of those that died had normal chloride levels on admission, compared to survivors (48% vs. 77.1%, $p = 0.035$).

Linear mixed effects regression models were used to estimate the trajectory of electrolyte measures over time. Given that different measures of the same patient are known to be correlated, and to account for inter-individual variation at ICU admission, a different intercept was used for each patient by including a random intercept term in each model. The number of days in ICU and the final status of death or survival were included as explanatory variables, as well as the interaction between them. A significant interaction term indicates that the effect of time passing is different for each group (deceased and survivors) [Table 3]. When not significant, the interaction term is ignored, and the effect of time is the same for both deceased and survivors. When the interaction is significant, but the main effect of time is not, this indicates the survivor group did not experience significant change over time, while the deceased group did, and the effect is given by the interaction parameter. When both the main effect of time and the interaction effect are statistically significant, changes over time exist but are different in each group. Changes over time in the survivor group are given by the main effect of time, while changes in the deceased group are given by the sum of the main effect and the interaction effect.

Table 3. Random intercept models (longitudinal trajectory) for electrolytes.

Variable	Coefficient	Std. Error	p-value
A. Sodium			
Days in ICU	0.029	0.023	0.215
Death	3.843	1 017	**<0.001**
Days in ICU*Death	−0.181	0.031	**<0.001**
B. Potassium			
Days in ICU	−0.007	0.003	**0.015**
Death	0.109	0.123	0.378
Days in ICU*Death	0.018	0.004	**<0.001**
C. Chloride			
Days in ICU	−0.016	0.024	0.506
Death	1.371	1.123	0.227
Days in ICU*Death	−0.196	0.032	**<0.001**
D. Calcium			
Days in ICU	0.007	0.001	**<0.001**
Death	−0.052	0.036	0.158
Days in ICU*Death	−0.005	0.001	**<0.001**
E. Bicarbonate			
Days in ICU	−0.006	0.017	0.720
Death	−0.576	0.862	0.507
Days in ICU*Death	0.040	0.023	0.087
F. Phosphate			
Days in ICU	0.012	0.003	**<0.001**
Death	0.484	0.126	**<0.001**
Days in ICU*Death	−0.001	0.003	0.766
G. Magnesium			
Days in ICU	−0.009	0.001	0.157
Death	0.031	0.033	0.357
Days in ICU*Death	0.001	0.001	0.074

Statistical significance denoted with bold text.

All results of longitudinal analysis are presented in Table 3, and estimated trajectories can be observed in Supplemental Figure 1. The model for sodium showed patients who died had an average of 3.8 mmol/L higher sodium at admission than those who survived, but that sodium decreased at a rate of 0.18 mmol/L every day for non-survivors, while for survivors the change over time was not significant. On average, sodium was still higher in non-survivors at the time of death, as it would take over 21 days for the decrease to invalidate the initial difference. The model for potassium showed that although there were no significant differences between non-survivors and survivors at admission, patients who survived had daily decrease of 0.007 mmol/L of potassium, patients who died had daily increase of 0.011 mmol/L. The model for chloride also showed a significant interaction term, indicating that while there was no significant change over time in chloride levels for survivors, patients who died had an average daily decrease of 0.196 mmol/L. All patients showed increase in calcium levels over time, but the size of daily increase differed between survivors and non-survivors. While survivors' calcium levels rose by 0.007 mmol/L daily, the increase for non-survivors was of 0.002 mmol/L. Patients who died had an average of 0.484 mmol/L more phosphate than survivors on admission, and both groups showed significant increase of 0.012 mmol/L a day. Bicarbonate and magnesium did not show any significant change over time or difference between groups.

4. Discussion

Overall, based on our results it appears that electrolyte levels measured on admission as well as subsequent daily changes may be indicative of survival in COVID-19 patients. The exact mechanisms of electrolyte imbalance are uncertain, however, among the comorbid conditions and medications analyzed, only ACI, HF, and antiplatelet use might explain some of the observed differences as these were more prevalent in non-survivors.

4.1. Sodium

Measured at discharge/death, sodium was significantly higher in patients who died. On longitudinal analysis, the admission levels were higher in non-survivors, while a gradual decrease thereon was associated with death. These observations are in concordance with prior research. Redant et al. found that although sodium levels were normal in COVID-19 patients on admission, hypernatremia developed in 52% once they were transferred to the ICU [25]. Research shows that critically ill patients, in general, are at increased mortality risk if hypernatremia is present [26,27]. The same appears to be true in COVID-19. In one study, the finding of hypernatremia at any point during hospitalization for COVID-19 was associated with 3.05-fold increased mortality risk [20]. Hypernatremia may be attributed to cutaneous fluid loss secondary to fevers, reduced fluid intake, anorexia, and diarrhea [25], stressing the importance of adequate fluid therapy in this patient population, which on the other hand must be carefully balanced against the risk of pulmonary edema [28]. In COVID-19, tropism for the ACE2 receptor and transmembrane protease, serine 2 (TMPRSS2) in the renal proximal collecting tubules, responsible for resorbing 60% of filtered water, may result in tubulopathy with water loss and concomitant hypernatremia [29]. Although HF was found more frequently among the deceased group, it cannot explain why this group had a higher level of sodium than survivors, given that this condition is most frequently associated with hyponatremia secondary to release of anti-diuretic hormone [30]. Use of aspirin, as an antiplatelet agent, was also more frequent among non-survivors. However, through its inhibitory effect on renal COX-2 enzyme, prostaglandin secretion, and in turn the RAAS, hyponatremia and hyperkalemia would be the expected electrolyte imbalance [31].

According to some research, admission hyponatremia appears to be a more common finding than hypernatremia (24.6% vs. 5.3% in one study, and 30% vs 4% in another), and also associated with increased risk of death [11,20]. In a pooled analysis of five studies involving a sample of 1415 COVID-19 patients, Lippi et al. identified that more severely ill patients had significantly lower sodium levels [6]. Moreover, in one small retrospective cohort study, correction of hyponatremia was associated with lower odds of mortality (odds ratio = 0.185) [32]. Hyponatremia in critically ill patients may result from an exaggerated inflammatory response to infection involving cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6), which stimulate release of anti-diuretic hormone [33,34]. Despite our finding of higher sodium levels in non-survivors on admission to the ICU compared to survivors, this mechanism may in part explain the gradual decrease in sodium observed in the non-survivor group over time. One recent study demonstrated an association between IL-6 and hyponatremia in SARS-CoV-2 infected patients, providing support for cytokine storm induced ADH release potentially being responsible for hyponatremia in these patients [35]. The association between hyponatremia and severity, however, might not be a causal one, but simply parallel to severe outcomes caused by cytokine storm [36]. Though, Post et al. suggested that hyponatremia may be linked to disease severity by upregulating renal ACE2 receptors, inadvertently facilitating increased entry of SARS-CoV-2 into host cells; however, this has not been verified in humans [37].

4.2. Potassium

Potassium was higher in non-survivors when measured at death, near the upper bound of the reference range.

In longitudinal analysis, we observed a gradual increase of potassium levels in patients who died, while those that survived had a gradual decrease until discharge. In contrast to hypokalemia, hyperkalemia seems to be a less frequently reported manifestation of SARS-CoV-2 infection. In one study, hyperkalemia was 5-fold more prevalent in COVID-19 patients admitted to the ICU than in non-ICU admitted patients (9.0 vs. 1.2%) [5]. Liu et al. found that COVID-19 patients with average potassium level ≥5.0 mmol/L had a significantly increased risk of 30-day mortality [12]. Possible mechanisms of elevated potassium in this patient population include COVID-19-related AKI, end-stage renal disease, hemodynamic instability, high cell turnover, and even acute limb ischemia due to thrombosis [14,38–41]. However, AKI may be ruled out as a contributing factor in our cohort, given the comparable incidence of AKI and need for dialysis in survivors and non-survivors. Although, the sample size may have precluded statistical significance with respect to difference in these factors. It has also been hypothesized that hyperkalemia in COVID-19 might be a consequence of decreased availability of furin, a protease used by SARS-CoV-2 to facilitate binding to ACE2, but also necessary to activate the potassium wasting epithelial sodium channels (ENaC) [42]. Interestingly, ENaC dysfunction has also been implicated in severe pulmonary edema in COVID-19, given its important role in fluid clearance [15,43]. RAAS inhibitors, used to address chronic HF and hypertension, may be a culprit of hyperkalemia [44]. However, in our cohort, ACE inhibitors and ARBs (angiotensin receptor blockers) were not use more frequently by non-survivors, who were hyperkalemic. Aspirin may also cause hyperkalemia via its inhibitory action on RAAS in the kidneys [31]. Although it was used more frequently in the deceased group, it was a part of patients' chronic medication regimen, and hence cannot explain acute changes observed throughout the course of ICU stay. The difference in potassium between groups was not present on admission and developed over the course of ICU stay. Such an acute change is more likely a consequence of COVID-19 illness or medication used to treat it, rather than any underlying comorbid condition (i.e., HF) and chronic medications used (i.e., aspirin therapy, antihypertensives targeting RAAS). Heparin, which was used for thromboprophylaxis in critically ill COVID-19 patients with elevated D-dimer levels, may in rare cases cause hyperkalemia via suppression of aldosterone synthesis [45]. However, this anticoagulant was only used by three patients, and potassium level was high only in one of them, on the upper bound of the normal range.

Conversely, there seems to be much more abundant data on the prevalence of hypokalemia among COVID-19 patients [9,46–48]. In one recent study, for instance, severe hypokalemia (<3.0 mmol/L) was reported in 18% of hospitalized COVID-19 patients, while mild hypokalemia (>3.0 and <3.5 mmol/L) was found in 37%, with the rest being normokalemic [47]. Alfano et al. detected hypokalemia in 41% of 290 non-ICU admitted COVID-19 patients, although the majority were only mildly hypokalemic [46]. Unlike our observations, prior studies also suggest that COVID-19 patients requiring intensive care have an even higher degree of potassium depletion, with one study estimating the prevalence of hypokalemia at 60.4% in ICU admitted patients, increasing further in those requiring invasive mechanical ventilation [9]. In their pooled analysis, Lippi and colleagues established that the degree of hypokalemia is associated with COVID-19 severity [6]. It is now well accepted that through binding the ACE2 receptor, SARS-CoV-2 down-regulates breakdown of angiotensin II, resulting in over-activity of the RAAS [6,15]. Subsequently, aldosterone activates ENaC facilitating potassium wasting from the kidneys, and ultimately resulting in reduced serum potassium levels [16]. Moreover, potassium loss may be exacerbated in patients with gastrointestinal symptoms such as diarrhea, reported in up to 49.5% of COVID-19 patients [49]. Hypokalemia in COVID-19 is particularly dangerous as it may trigger cardiac arrhythmias, heart injury, dysfunction of respiratory muscles, and may even aggravate acute respiratory distress syndrome (ARDS) [6].

4.3. Calcium

We found evidence of hypocalcemia in non-survivors at death, bordering on the lower bound of the reference range. In the survivor group, the levels of calcium were significantly higher at discharge. Longitudinally, we observed that although calcium levels increased in all patients over time, survivors had greater magnitude of daily increase. Observational studies show that, although variable, the incidence of hypocalcemia is relatively high among COVID-19 patients, and the degree correlated with severity. Sun et al. reported hypocalcemia in nearly 75% of COVID-19 patients on admission [50]. In non-severe COVID-19 patients the prevalence of hypocalcemia was observed to be 67% [51], while it was 35.8% in severely ill patients [18]. Variability in incidence between studies may be attributed to various intrinsic patient characteristics such as renal, pancreatic, or hepatic dysfunction along with vitamin D status, which may differ depending on geographic location [18,52,53]. Nonetheless, a large body of research supports the fact that the degree of hypocalcemia is correlated with disease severity [6,50,54]. Hypocalcemia in severe COVID-19 is not surprising as it can often be observed in the critical care setting, with proposed mechanisms ranging from vitamin D deficiency/resistance, acquired hypoparathyroidism, and 1α-hydroxylase deficiency to hypoalbuminemia, acute renal failure, and respiratory alkalosis

[51,52,55,56]. Interestingly though, findings of hypocalcemia in non-severe patients suggest a mechanism unique to SARS-CoV-2 infection [51]. Based on previously elucidated mechanisms involving calcium homeostasis of the original SARS-CoV (−1) coronavirus [57], and its homology to SARS-CoV -2, Cappellini et al. proposed that depletion of circulating calcium in COVID-19 patients may be a direct consequence of increased calcium utilization by SARS-CoV-2 for the viral life cycle as well as for activation of inflammatory pathways [58,59]. Furthermore, SARS-CoV-2 may directly impair calcitriol production given that the receptor used for viral attachment, ACE2, is co-expressed with renal 1α-hydroxylase on proximal renal tubule cells [51]. Several prior studies have found associations between low calcium (≤2.0 mmol/L in one study, and≤2.05 mmol/L in another) and mortality [18,50], which is in line with our observations (median serum calcium 2.00 mmol/L in non-survivors at death), and supports the proposition that poor outcome may be in part explained by COVID-19-induced hypocalcemia. It should be noted that we did not assess vitamin D levels in our cohort, hence it cannot be ruled out as a confounding factor on baseline calcium levels and subsequent changes. Singh et al. argued that this state is more likely to be caused by the binging of ionized calcium with unsaturated fatty acids generated following adipose lipolysis in COVID-19, rather than any imbalance in the calcium-parathyroid hormone-vitamin D axis [60]. The main reason being that chronic hypovitaminosis D would not present with acute calcium changes seen in COVID-19 [60]. Unfortunately, our findings cannot provide support for this hypothesis as fatty acids only bind calcium in an ionized state, whereas we measured total calcium which in part comprises complexed calcium. All comorbidities that may influence calcium are comparable between groups and are thus unlikely to account for our observations. Although HF and ACI were more frequently observed in patients that died, these conditions would not result in hypocalcemia, but may instead be a consequence of low calcium and explain the association between hypocalcemia and mortality in COVID-19 [61–63]. Aspirin use, on the other hand, has been reported to produce hypocalcemia, through a mechanism independent of prostaglandin inhibition [64]. Although calcium levels were comparable in all patients at admission, greater use of aspirin by those in the deceased group may in part explain why calcium did not normalize over time as it did in survivors. It should be also noted, in hypoalbuminemic states such as COVID-19, the extent of hypocalcemia can be underestimated producing in false negatives when total calcium measurements are corrected for albumin, as was done in our study [19].

4.4. Magnesium

Magnesium was elevated in non-survivors when measured at death, however no significant changes were observed over time for either group. Research shows that magnesium abnormalities are associated with adverse outcomes in COVID-19. Quilliot and colleagues measured magnesium levels in 300 hospitalized COVID-19 patients soon after admission, and discovered that hypomagnesemia (<0.75 mmol/L) was present in up to 48%, and most strongly associated with moderate disease severity [65]. Patients with hypermagnesemia (≥0.95 mmol/L) were more likely to have critical disease in this study, although, hypomagnesemia was still more prevalent in the critically ill, leading the authors to conclude that dysmagnesemia may be associated with poor outcomes [65]. In contrast, Alamdari et al. found that deceased COVID-19 patients had significantly lower magnesium levels on admission compared to the recovered group [66]. According to a comprehensive meta-analysis, magnesium deficiency on admission is frequently reported in critically ill patients and associated with an increased mortality risk (pooled risk ratio, RR = 1.76) [67]. Hypomagnesemia is associated with abnormalities in other electrolytes as well as with cardiac arrhythmias, in part explaining increased mortality [67]. Moreover, magnesium serves an important role in modulating immune function and protecting against oxidative stress, coagulopathy, and endothelial dysfunction [8]. Deficiency favors proinflammatory cytokine production, and may lead to sepsis and septic shock in critically ill patients [10]. Moreover, magnesium has a crucial role in natural killer (NK) and CD8+ T cell function. In SARS-CoV-2 infection, deficiency would result in reduced CD8+ T cell cytotoxicity, exacerbating COVID-19-related cytokine storm as more burden is put on the more proinflammatory innate immune cells to combat the virus [8,68]. In contrast, we failed to observe any difference in admission levels of magnesium. Rather, hypermagnesemia was detected in non-survivors when measured at death, which may point towards it being an outcome of more severe illness, likely a consequence of rapid mobilization from tissues in aggressive disease [65].

4.5. Phosphate

Interestingly, increased levels of phosphate were found in deceased patients when compared to the levels in those that were discharged. Furthermore, on longitudinal analysis, admission phosphate levels were higher in non-survivors, although levels increased by the same magnitude in both groups over time. Evidence suggests that those with more severe disease course should have depleted phosphate and magnesium levels, as these minerals are necessary to

replenish ATP depleted during cytokine storm [13]. The finding of increased phosphate as well as magnesium in non-survivors may be explained by excessive release of intracellular stores of these electrolytes following muscle breakdown in a hypercatabolic state [13]. Although AKI, a common complication of COVID-19, may further exacerbate hyperphosphatemia [69], there was no significant difference in incidence of AKI between survival groups in our cohort. This finding is consistent with the observation of hypocalcemia in non-survivors, as excess phosphate binds circulating free calcium.

4.6. Chloride and bicarbonate

When measured categorically, based on frequency of patients with electrolyte levels below, within, or above reference range, below and above normal admission levels of both chloride and bicarbonate were observed more frequently among non-survivors than survivors. No differences were observed for chloride and bicarbonate when measured at death/discharge. Chloride, however, was observed to decrease over time of ICU stay in patients that died. In a pooled analysis by Lippi et al., no association was observed between chloride and COVID-19 severity [6]. In contrast, another study found that among several other electrolytes, low baseline chloride was associated with greater mortality risk, need for ICU admission, need for mechanical ventilation, and longer duration of hospitalization [4]. Likewise, Duan et al. observed that patients progressing to more severe COVID-19 had lower chloride levels [70]. This is in line with our longitudinal analysis where chloride levels gradually declined in non-survivors. These changes have been attributed to renal injury in COVID-19 [4,71], although the non-significant difference in AKI between survivors and non-survivors may suggest that there are additional factors at play. As for bicarbonate, one retrospective study found elevated levels in 45.9% of severely ill COVID-19 patients [72], while another study reported this finding in 33.6% of COVID-19 patients [73], which may be a compensatory response to respiratory acidosis when lung involvement in COVID-19 impairs the ability to expel CO_2. Conversely, metabolic acidosis, with low bicarbonate, appears to be a less prevalent finding (reported in 2.8% of a sample of COVID-19 patients) [73]. Lower levels may be expected in patients with diarrhea as a symptom of COVID-19, or as a result of reduced renal tubular resorbing capacity in patients with renal impairment [73].

There were some limitations in this study. First, single center design and small sample size limits the external validity of our findings. Nonetheless, many of our findings are corroborated by prior research. Second, there was no control group of non-SARS-CoV -2 infected patients, hence we cannot ascertain to what extent these findings are unique to COVID-19. Magnesium and calcium status was based on total serum levels rather than the physiologically active ionized fractions, which would be more useful for understanding the relationship between observed changes in electrolytes and patients' outcomes. A strength of employing random intercept models was in that it accounted for baseline variation between patients, such that electrolyte supplementation before COVID-19 would not be a confounding factor.

5. Conclusion

In the present study, admission levels of electrolytes and changes over the course of ICU stay appear to be associated with mortality in patients with SARS-CoV-2 infection. Compared to survivors, non-survivors had significantly higher sodium and phosphate levels on admission and death, higher potassium and magnesium levels at death, and significantly lower calcium levels at death. Abnormalities in admission levels of chloride and bicarbonate were also more frequently observed in non-survivors. Furthermore, in the deceased group, we observed a daily increase in potassium and phosphate levels, and a daily decrease in sodium and chloride. Finally, calcium increased in non-survivors over time, however, not as significantly as it did in the survivor group.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of the Security Forces Hospital in accordance with the National Committee of Bio Ethics (NCBE) in Saudi Arabia (Reference number: H-01-R-069) and received a waiver of informed consent due to no greater than minimal risk to participants.

References

[1] Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med. 2020;76:97–99.
[2] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med CCLM. 2020;58(7):1131–1134.
[3] Henry BM, de Oliveira MHS, Benoit S, et al. Hematologic, biochemical and immune biomarker

abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med CCLM. 2020;58 (7):1021–1028. DOI:10.1515/cclm-2020-0369

[4] Tezcan ME, Dogan Gokce G, Sen N, et al. Baseline electrolyte abnormalities would be related to poor prognosis in hospitalized coronavirus disease 2019 patients. New Microbes New Infect. 2020;37:100753.

[5] Rostami Z, Shafei S, Nemati E, et al. POS-109 COMMON ELECTROLYTE ABNORMALITIES in HOSPITALIZED COVID-19 PATIENTS. Kidney Int Rep. 2021;6(4):S45. DOI:10.1016/j.ekir.2021.03.117

[6] Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem Int J Lab Med. 2020;57 (3):262–265.

[7] Ravens U, Cerbai E. Role of potassium currents in cardiac arrhythmias. Europace. 2008;10 (10):1133–1137.

[8] DiNicolantonio JJ, O'keefe JH. Magnesium and Vitamin D deficiency as a potential cause of immune dysfunction, cytokine storm and disseminated intravascular coagulation in COVID-19 patients. Mo Med. 2021;118 (1):68–73.

[9] Moreno-Pérez O, Leon-Ramirez J-M, Fuertes-Kenneally L, et al. Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: a case series of 306 Mediterranean patients. Int J Infect Dis. 2020;100:449–454.

[10] Limaye CS, Londhey VA, Nadkart MY, et al. Hypomagnesemia in critically ill medical patients. J Assoc Physicians India. 2011;59:19–22.

[11] Atila C, Sailer CO, Bassetti S, et al. Prevalence and outcome of dysnatremia in patients with COVID-19 compared to controls. Eur J Endocrinol. 2021;184 (3):413–422. DOI:10.1530/EJE-20-1374

[12] Liu S, Zhang L, Weng H, et al. Association between average plasma potassium levels and 30-day mortality during hospitalization in patients with COVID-19 in Wuhan, China. Int J Med Sci. 2021;18(3):736–743. DOI:10.7150/ijms.50965

[13] van Kempen Tatg, Deixler E, van Kempen TATG. SARS-CoV-2: influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19. Am J Physiol Endocrinol Metab. 2021;320(1):E2–6.

[14] Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. Ann Med. 2020;52(7):345–353.

[15] Noori M, Nejadghaderi SA, Sullman MJM, et al. How SARS-CoV-2 might affect potassium balance via impairing epithelial sodium channels? Mol Biol Rep. 2021;48(9):6655–6661. DOI:10.1007/s11033-021-06642-0

[16] Zaika O, Mamenko M, Staruschenko A, et al. Direct activation of ENaC by angiotensin II: recent advances and new insights. Curr Hypertens Rep. 2013;15 (1):17–24. DOI:10.1007/s11906-012-0316-1

[17] Zimmer MA, Zink AK, Weißer CW, et al. Hypernatremia—a manifestation of COVID-19: a case series. A&A Practice. 2020;14(9):e01295. DOI:10.1213/XAA.0000000000001295

[18] Bennouar S, Cherif AB, Kessira A, et al. Vitamin D deficiency and low serum calcium as predictors of poor prognosis in patients with severe COVID-19. J Am Coll Nutr. 2021;40(2):104–110. DOI:10.1080/07315724.2020.1856013

[19] El-Kurdi B, Khatua B, Rood C, et al. Mortality from coronavirus disease 2019 increases with unsaturated fat and may be reduced by early calcium and albumin supplementation. Gastroenterology. 2020;159 (3):1015–1018.e4. DOI:10.1053/j.gastro.2020.05.057

[20] Tzoulis P, Waung JA, Bagkeris E, et al. Dysnatremia is a predictor for morbidity and mortality in hospitalized patients with COVID-19. J Clin Endocrinol Metab. 2021;107(6):1637–1648. dgab.

[21] Tan CW, Ho LP, Kalimuddin S, et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition. 2020;79–80:111017.

[22] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. DOI:10.1016/S0140-6736(20)30183-5

[23] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–184.

[24] Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol. 2020;73(3):566–574. DOI:10.1016/j.jhep.2020.04.006

[25] Redant S, Vanderhulst J, Maillart E, et al. Significance of hypernatremia due to SARS-CoV-2 associated ARDS in critically ill patients. J Transl Intern Med. 2020;8 (4):255–260. DOI:10.2478/jtim-2020-0038

[26] Lindner G, Funk G-C, Schwarz C, et al. Hypernatremia in the critically Ill is an independent risk factor for mortality. Am J Kidney Dis. 2007;50(6):952–957. DOI:10.1053/j.ajkd.2007.08.016

[27] Darmon M, Timsit J-F, Francais A, et al. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. Nephrol Dial Transplant. 2010;25 (8):2510–2515. DOI:10.1093/ndt/gfq067

[28] Casey J, Semler M, Rice T. Fluid management in acute respiratory distress syndrome. Semin Respir Crit Care Med. 2019;40(01):057–065.

[29] Pan X, Xu D, Zhang H, et al. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive care Med. 2020;46 (6):1114–1116. DOI:10.1007/s00134-020-06026-1

[30] Oren RM. Hyponatremia in congestive heart failure. Am J Cardiol. 2005;95(9):2–7.

[31] Schlondorff D. Renal complications of nonsteroidal anti-inflammatory drugs. Kidney Int. 1993;44 (3):643–653.

[32] de La Flor Jc, Gomez-Berrocal A, Marschall A, et al. Impacto de la corrección temprana de la hiponatremia en el pronóstico de la infección del síndrome respiratorio agudo grave del coronavirus 2 (SARS-CoV-2). Medicina Clínica. 2021;159(1):S0025775321004619. DOI:10.1016/j.medcli.2021.07.006

[33] Ohta M, Ito S. [Hyponatremia and inflammation]. Rinsho Byori. 1999;47(5):408–416.

[34] Swart RM, Hoorn EJ, Betjes MG, et al. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol. 2011;118(2):45–p51. DOI:10.1159/000322238

[35] Berni A, Malandrino D, Parenti G, et al. Hyponatremia, IL-6, and SARS-CoV-2 (COVID-19) infection: may all fit together? J Endocrinol Invest. 2020;43(8):1137–1139. DOI:10.1007/s40618-020-01301-w

[36] Melo AKG, Milby KM, Caparroz ALMA, et al. Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: a living systematic review and meta-analysis. PLoS ONE. 2021;16(6):e0253894. DOI:10.1371/journal.pone.0253894
[37] Post A, Dullaart RPF, Bakker SJL. Sodium status and kidney involvement during COVID-19 infection. Virus Res. 2020;286:198034.
[38] Benedetti C, Waldman M, Zaza G, et al. COVID-19 and the kidneys: an update. Front Med. 2020;7:423.
[39] Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol. 2020;16(6):308–310.
[40] Demirci T, Deshwal H, Goldenberg R. THE 'CLOT' THICKENS: hYPERKALEMIA DUE to ACUTE LIMB ISCHEMIA in COVID-19. Chest. 2021;160(4):A613.
[41] Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26 (7):1017–1032. DOI:10.1038/s41591-020-0968-3
[42] Szabó GT, Kiss A, Csanádi Z, et al. Hypothetical dysfunction of the epithelial sodium channel may justify neurohumoral blockade in coronavirus disease 2019. ESC Heart Fail. 2021;8(1):171–174. DOI:10.1002/ehf2.13078
[43] Matalon S, Bartoszewski R, Collawn JF. Role of epithelial sodium channels in the regulation of lung fluid homeostasis. Am J Physiol Lung Cell Mol Physiol. 2015;309(11):L1229–1238.
[44] Sidhu K, Sanjanwala R, Zieroth S. Hyperkalemia in heart failure. Curr Opin Cardiol. 2020;35(2):150–155.
[45] Aull L, Chao H, Coy K. Heparin-induced hyperkalemia. DICP Ann Pharmacother. 1990;24(3):244–246.
[46] Alfano G, Ferrari A, Fontana F, et al. Hypokalemia in patients with COVID-19. Clin Exp Nephrol. 2021;25 (4):401–409. DOI:10.1007/s10157-020-01996-4
[47] Chen D, Li X, Song Q, et al. Assessment of hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in Wenzhou, China. JAMA Netw Open. 2020;3(6):e2011122. DOI:10.1001/jamanetworkopen.2020.11122
[48] Nasomsong W, Ungthammakhun C, Phiboonbanakit D, et al. Low serum potassium among patients with COVID-19 in Bangkok, Thailand: coincidence or clinically relevant? Trop Doct. 2020;51 (2):004947552097817. DOI:10.1177/0049475520978174
[49] Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020;51 (9):843–851. DOI:10.1111/apt.15731
[50] Sun J-K, Zhang W-H, Zou L, et al. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. Aging. 2020;12 (12):11287–11295. DOI:10.18632/aging.103526
[51] Pal R, Ram S, Zohmangaihi D, et al. High prevalence of hypocalcemia in non-severe COVID-19 patients: a retrospective case-control study. Front Med. 2021;7:590805.
[52] Kelly A, Levine MA. Hypocalcemia in the Critically Ill patient. J Intensive Care Med. 2013;28(3):166–177.
[53] Pranata R, Supriyadi R, Huang I, et al. The association between chronic kidney disease and new onset renal replacement therapy on the outcome of COVID-19 Patients: a meta-analysis. Clin Med Insights: Circ Respir Pulm Med. 2020;14:117954842095916.
[54] Di Filippo L, Formenti AM, Rovere-Querini P, et al. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. Endocrine. 2020;68(3):475–478. DOI:10.1007/s12020-020-02383-5
[55] Lind L, Carlstedt F, Rastad J, et al. Hypocalcemia and parathyroid hormone secretion in critically ill patients. Crit Care Med. 2000;28(1):93–99. DOI:10.1097/00003246-200001000-00015
[56] Zaloga GP. The multifactorial basis for hypocalcemia during sepsis: studies of the parathyroid hormone-Vitamin D axis. Ann Intern Med. 1987;107 (1):36.
[57] Nieto-Torres JL, DeDiego ML, Verdiá-Báguena C, et al. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLOS Pathog. 2014;10(5):e1004077. DOI:10.1371/journal.ppat.1004077
[58] Cappellini F, Brivio R, Casati M, et al. Low levels of total and ionized calcium in blood of COVID-19 patients. Clin Chem Lab Med CCLM. 2020;58(9):e171–173. DOI:10.1515/cclm-2020-0611
[59] Zhou Y, Frey TK, Yang JJ. Viral calciomics: interplays between Ca2+ and virus. Cell Calcium. 2009;46 (1):1–17.
[60] Singh VP, Khatua B, El-Kurdi B, et al. Mechanistic basis and therapeutic relevance of hypocalcemia during severe COVID-19 infection. Endocrine. 2020;70 (3):461–462. DOI:10.1007/s12020-020-02530-y
[61] Jafari Fesharaki M, Ahmadi N, Karimi Taheri K. Reversible heart failure in a patient with hypocalcemic cardiomyopathy. J Geriatr Cardiol JGC. 2021;18 (12):1063–1067.
[62] Hurley K, Baggs D. Hypocalcemic cardiac failure in the emergency department. J Emerg Med. 2005;28 (2):155–159.
[63] Solzbach U, Kitterer H-R, Haas H. Reversible Herzinsuffizienz bei schwerer Hypokalzämie. Herz. 2010;35(7):507–511.
[64] Gomaa AA, Hassan HA, Ghaneimah SA. Effect of aspirin and indomethacin on the serum and urinary calcium, magnesium and phosphate. Pharmacol Res. 1990;22 (1):59–70.
[65] Quilliot D, Bonsack O, Jaussaud R, et al. Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors. Magnes Res. 2020;33 (4):114–122. DOI:10.1684/mrh.2021.0476
[66] Alamdari NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. Tohoku J Exp Med. 2020;252(1):73–84. DOI:10.1620/tjem.252.73
[67] Jiang P, Lv Q, Lai T, et al. Does hypomagnesemia impact on the outcome of patients admitted to the intensive care unit? a systematic review and meta-analysis. Shock. 2017;47(3):288–295. DOI:10.1097/SHK.0000000000000769
[68] Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020;17(5):533–535. DOI:10.1038/s41423-020-0402-2
[69] Jung S-Y, Kwon J, Park S, et al. Phosphate is a potential biomarker of disease severity and predicts adverse outcomes in acute kidney injury patients undergoing continuous renal replacement therapy. PLoS ONE. 2018;13 (2):e0191290. DOI:10.1371/journal.pone.0191290
[70] Duan J, Wang X, Chi J, et al. Correlation between the variables collected at admission and progression to severe cases during hospitalization among patients with COVID-19 in Chongqing. J Med Virol. 2020;92 (11):2616–2622. DOI:10.1002/jmv.26082

[71] Yousaf Z, Al-Shokri SD, Al-Soub H, et al. COVID-19-associated SIADH: a clue in the times of pandemic! Am J Physiol Endocrinol Metab. 2020;318(6):E882–885. DOI:10.1152/ajpendo.00178.2020

[72] Mondal S, Das TK, Bhattacharya S, et al. Blood gas analysis among COVID-19 patients: a single centre retrospective observational study. J Clin Diagn Res. Epub ahead of print 2021. DOI:10.7860/JCDR/2021/49835.15185.

[73] Alfano G, Fontana F, Mori G, et al. Acid base disorders in patients with COVID-19. Int Urol Nephrol. Epub ahead of print 11 June 2021;54(2):405–410. DOI:10.1007/s11255-021-02855-1