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ORIGINAL ARTICLE

Relationship between kalemia and intensive care unit admission or death in hospitalized COVID-19 patients: A cohort study

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Summary
Background. — SARS-CoV-2 uses Angiotensin-Converting Enzyme 2 as a viral gateway to the cell and could interact with the renin-angiotensin-aldosterone system. Other studies have shown kalemia abnormalities in patients with severe forms of coronavirus disease 2019. Our goal was to assess the prognosis value of kalemia within ten days of symptom offset in the COVID-19 hospitalized population.
Methods. — We analyzed data from a prospective cohort that included 65 patients with COVID-19, admitted between March 15, 2020, and March 21, 2020. The study aimed at determining the relationship between baseline kalemia and the admission to an intensive care unit (ICU) or death.

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Results. — The median age of the patients was 65 [54—79] years old, and 66.2% of the patients were men. Baseline kalemia under 3.8 mmol/l occurred in 31 patients (48%), including 11 patients (35.5%) who were admitted to an ICU and one patient (3.2%) who died before ICU admission. In the primary end-point analysis, the adjusted hazard ratios for admission to an ICU or death were 3.52 [95% confidence interval (CI), 1.12 to 11.04] among patients with low baseline kalemia.

Conclusion. — Our study suggests that low kalemia levels within ten days of the first symptom onset might be associated with an increased risk of intensive care unit admission or death. The future perspective should be to better understand this relationship.

Background

A major coronavirus disease 2019 (COVID-19) outbreak hit Wuhan in December 2019 before rapidly spreading around the world, infecting more than 126 million people [1—3]. The first case in Europe was diagnosed in France on January 24, 2020 [4], followed by a massive outbreak. Studies have shown that the virus was using the Angiotensin-Converting Enzyme 2 (ACE-2) as a viral gateway to penetrate host cells and could have interactions with the renin-angiotensin system (RAS) [5—12]. However, a recent study showed a high prevalence of hypokalemia in COVID patients might be due to RAS dysregulation. Moreover, an association was found between the intensity of the low potassium level and some clinical and biological signs of COVID-19 disease severity [13,14]. Therefore, kalemia disorders could be an indirect sign of the clinical severity of the disease, without any knowledge of whether they impact more robust prognostic criteria such as admission to an intensive care unit (ICU) or death. To confirm those findings, we assessed the prognosis value of kalemia (lower level within ten days of symptom offset) in the COVID-19 population hospitalized in our institution.

Methods

Study population

In this single-center prospective cohort, 65 patients were consecutively enrolled between March 15, 2020, and March 21, 2020, in Georges Pompidou European Hospital in Paris (France) with SARS-CoV-2 infection as previously described [15].

Patients over 18 years who had criteria for hospitalization according to local guidelines and who received a diagnosis of SARS-CoV-2 infection confirmed by a nasopharyngeal swab test were included. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [16]. The institutional ethical committee approved the study (SARCODO study; CPP2020-04-048/2020-A01048-31/20.04.21.49318), and patients gave standard written consent to the use of their data.

Study design

We classified patients into two groups according to the median baseline kalemia—low kalemia ($\leq$ 3.8 mmol/L) and no low kalemia (> 3.8 mmol/L). A kalemia result was considered baseline if recorded within ten days of the first symptom onset. Patients were considered to have a low kalemia occurrence if they had at least one baseline kalemia less than or equal to 3.8 mmol/L within ten days of the first symptoms onset. This period corresponds approximately to the median time to acute respiratory distress syndrome (ARDS) or ICU admission found in the literature [1,17—19]. We aimed to compare clinical characteristics and laboratory findings between those groups and analyze the prognostic value of baseline kalemia.

Data Collection

Baseline characteristics, including demographic, clinical, biological, radiological, and outcome data were extracted from electronic medical records using a standardized data collection. Laboratory findings included serum kalemia level, serum creatinine level, hemogram, C-reactive protein (CRP) level, D-dimer level, and troponin level. We used a score based on the percentage of lung involvement assessed by chest computed tomography (CT) as a CT severity score ranging from 0 to 4—0 as normal, 1 as < 25% abnormality, 2 as 25—50% abnormality, 3 as 50—75% abnormality, and 4 as > 75% abnormality [20]. Recorded treatments included beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blockers (ARB-2), diuretics, centrally acting antihypertensive, and non-steroidal anti-inflammatory drugs (NSAIDs).

Outcome

The primary composite outcome was defined as admission to an ICU or in-hospital death. Secondary outcomes included maximum CRP serum level—defined as the highest CRP value recorded during the patient's stay, the maximum oxygen flow rate—defined as the highest oxygen flow rate administration during the patient's stay and the minimum hemoglobin level, defined as the lowest hemoglobin level presented by the patients during the hospital stay.

Statistical analysis

Continuous variables were expressed as median (interquartile range [IQR]), and qualitative variables were expressed as number (proportion). The primary outcome evaluation

was done by considering the time calculated from symptom onset, defined as the date on which symptoms first began, to in-hospital death or ICU admission, or the last follow-up contact. We presented kalemia, CRP, and oxygen administration trends as a time plot showing the respective medians according to the time from symptom onset. Creatinine serum level variable has been log-transformed to achieve normality. Serum potassium levels were dichotomized based on the median value to create two groups: patients who had a low kalemia occurrence (≤ 3.8 mmol/L) and those who had no low kalemia occurrence (> 3.8 mmol/L). We used a bootstrap method with 10 000 replications to calculate 95% confidence intervals (CIs) for median and proportion differences between both groups [21]. Those CIs have not been adjusted for multiple testing and should not allow inference interpretation. Multiple imputations were used to handle missing data [22]. No variable had more than 5% missing data except for the CT scan severity score, which is shown in baseline characteristics but not included in the analysis. No previous hypothesis was chosen, and no sample size was calculated as this was an exploratory study. Kaplan-Meier and adjusted Cox proportional hazards models were used to evaluate the association between low kalemia and the primary outcome. Proportional-hazards assumptions were tested graphically using scaled Schoenfeld residuals. Adjusted logistic regressions were used to analyze the association between low kalemia occurrence and secondary outcomes. All logistic regression model assumptions were met adequately. No interaction was found between variables. Adjusted variables were chosen a priori according to their potential impact on kalemia or prognosis—serum creatinine level, the presence of an ACE inhibitor or ARB-2, the presence of a diuretic, the maximum oxygen flow rate, age, and the D-dimer levels [23,24]. Final variables included in models assessing primary and secondary outcomes were chosen according to the best model fit based on the lowest Akaike information criterion. We considered a two-sided p-value< 0.05 as significant. Tests were only performed on primary and secondary outcomes to limit inflation of the type I error. These exploratory analyses were performed using R software 3.6.0 version for Mac (Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Sixty-five patients were included with a median age of 63.00 [IQR: 54.00, 79.00] years, including 43 males (66.2%). The main baseline clinical and demographic characteristics are summarized in Table 1. Concerning cardiovascular risk factors, almost half of the patients had hypertension at baseline (43.8%), one-third of the patients were current or former smoker (current smoker: 6.8%, former smoker: 20.5), approximately one-sixth of the patients were diabetic (16.9%) and one-third of the patients had dyslipidemia (29.2%). The most frequent symptoms were fever (93.8%), cough (73.4%), and dyspnea (46.9%). Very few presented with diarrhea (10·9%). Abnormal laboratory findings were increased CRP level (median: 74.00 mg/L, IQR: 21.55—126.50 mg/L), decreased lymphocytes (median: 0.90 G/L, IQR: 0.69—1.18 G/L), and increased D-dimer levels (median: 999.00 μg/L, IQR: 692.00—1778.00 mg/L). Median [IQR] kalemia values at baseline were 3.90 [3.60—4.20] mmol/L. One-third of patients took an ACE inhibitor or ARB-2 at the inclusion (ACE inhibitor: 15·4%, ARB-2: 13.8), and only four patients received NSAIDs (6.2%). From available scannographic data, most patients had a CT scan severity

Table 1 Baseline characteristics.

Characteristic	Patients ($n = 65$)
Median age [IQR]—year	63.00 [54.00, 79.00]
Median weight [IQR]—kilogram	75 [65.80, 86.25]
Median height [IQR]—meter	1.71 [1.65, 1.77]
Median Body Mass-Index [IQR]—kg/m2	25.03 [23.59, 28.00]
Male sex—no. (%)	43 (66.2)
Diabetes—no. (%)	11 (16.9)
Smoking status—no./total no. (%)	
Current smoker	3/44 (6.8)
Former smoker	9/44 (20.5)
Never smoked	32/44 (72.7)
Hypertension—no./total no. (%)	28/64 (43.8)
Dyslipidemia—no. (%)	19 (29.2)
Asthenia—no. (%)	28 (43.1)
Fever—no. (%)	61 (93.8)
Headache—no./total no. (%)	13/64 (20.3)
Dyspnea—no./total no. (%)	30/64 (46.9)
Cough—no./total no. (%)	47/64 (73.4)
Diarrhea—no./total no. (%)	7/64 (10.9)
Median serum creatinine [IQR]—μmol/L	79.00 [61.50, 106.50]
Median CRP [IQR]—mg/L	74.00 [21.55, 126.50]
Median haemoglobin [IQR]—g/dL	13.00 [11.20, 14.40]
Median lymphocytes [IQR]—G/L	0.90 [0.69, 1.18]
Median neutrophils [IQR]—G/L	3.95 [2.99, 5.90]
Median kalemia [IQR]—mmol/L	3.90 [3.60, 4.20]
Median D-dimer [IQR]—μg/L	999.00 [692.00, 1778.00]
Median troponin [IQR]—ng/L	8.50 [5.05, 20.55]
Beta-blockers—no. (%)	8 (12.3)
Calcium channel blockers—no. (%)	11 (16.9)
ACE inhibitor or ARB-2—no. (%)	
None	46 (70.8)
ACE inhibitor	10 (15.4)
ARB-2	9 (13.8)
Diuretics—no. (%)	6 (9.2)
Centrally acting antihypertensive—no. (%)	1 (1.5)
NSAIDs—no. (%)	4 (6.2)
CT scan severity score—no./total no. (%)	
0	5/39 (12.8)
1	12/39 (30.8)
2	15/39 (38.5)
3	5/39 (12.8)
4	2/39 (5.3)

Table 2 Clinical characteristics of patients according to the presence of a baseline low kalemia.

Characteristic	Patients with a kalemia > 3.8 mmol/L (n = 34)	Patients with a kalemia ≤ 3.8 mmol/L (n = 31)	Difference [95% CI][a]
Median age [IQR]—year	63.50 [52.25, 82.25]	63.00 [55.00, 77.00]	0.50 [−15.00; 17.00]
Median weight [IQR]—kilogram	75.00 [69.75, 83.15]	77.00 [64.00, 90.00]	−2.00 [−14.80; 7.00]
Median height [IQR]—meter	1.72 [1.68, 1.80]	1.70 [1.63, 1.75]	0.02 [−0.04; 0.07]
Median Body Mass-Index [IQR]—kg/m2	24.84 [23.85, 27.62]	26.35 [23.46, 28,73]	−1.51 [−3.87, 1.17]
Male sex—no. (%)	23 (67.6)	20 (64.5)	3.1 [−21.0; 25.2]
Diabetes—no. (%)	7 (20.6)	4 (12.9)	7.7 [−11.1; 25.0]
Smoking status—no./total no. (%)			
Current smoker	1/22 (4.5)	2/22 (9.1)	−4.6 [21.1; 9.0]
Former smoker	5/22 (22.7)	4/22 (18.2)	4.5 [−19.8; 29.0]
Never smoked	16/22 (72.7)	16/22 (72.7)	0.0 [−26.7; 25.4]
Hypertension—no./total no. (%)	14/33 (42.4)	14/31 (45.2)	−2.8 [−26.8; 22.0]
Dyslipidemia—no. (%)	10 (29.4)	9 (29.0)	0.4 [−21.9; 21.8]
Asthenia—no. (%)	15 (44.1)	13 (41.9)	2.2 [−22.5; 26.0]
Fever—no. (%)	33 (97.1)	28 (90.3)	6.8 [−2.9;19.6]
Headache—no./total no. (%)	6/33 (18.2)	7/31 (22.6)	−4.4 [−24.2; 14.8]
Dyspnea—no./total no. (%)	13/33 (39.4)	17/31 (54.8)	−15.4 [−38.3; 10.0]
Cough—no./total no. (%)	24/33 (72.7)	23/31 (74.2)	−1.5 [−23.1; 20.0]
Diarrhea—no./total no. (%)	3/34 (8.8)	4/30 (13.3)	−4.5 [−22.6; 8.5]
Median serum creatinine [IQR]—μmol/L	83.50 [65.75, 130.50]	71.00 [59.00, 86.00]	12.50 [−9.00; 39.00]
Median CRP [IQR]—mg/L	74.50 [20.38, 114.50]	66.80 [34.60, 140.00]	7.70 [−43.00; 46.07]
Median haemoglobin [IQR]—g/dL	13.00 [11.22, 14.80]	13.00 [11.10, 14.15]	0.00 [−1.80; 1.70]
Median Lymphocytes [IQR]—G/L	0.94 [0.63, 1.16]	0.87 [0.72, 1.35]	0.07 [−0.20; 0.23]
Median neutrophils [IQR]—G/L	4.26 [3.07, 5.87]	3.89 [2.66, 5.75]	0.37 [−0.83; 1.87]
Median D-dimer [IQR]—μg/L	1292.00 [761.50, 2517.50]	978.00 [683.75, 1525.50]	314.00 [−226.50; 1519.80]
Median Troponin [IQR]—ng/L	12.35 [5.30, 20.85]	7.10 [4.95, 18.50]	5.25 [−6.50; 14.90]
Beta-blockers—no. (%)	4 (11.8)	4 (12.9)	−1.1 [−17.3; 14.1]
Calcium channel blockers—no. (%)	4 (11.8)	7 (22.6)	−10.8 [−30.2; 5.0]
ACE inhibitor or ARB-2—no. (%)			
None	22 (64.7)	24 (77.4)	−12.7 [−34.2; 9.0]
ACE inhibitor	7 (20.6)	3 (9.7)	10.9 [−7.3; 26.5]
ARB-2	5 (14.7)	4 (12.9)	1.8 [−16.4,;17.4]
Diuretics—no. (%)	3 (8.8)	3 (9.7)	−0.9 [−16.4; 11.5]
Centrally acting antihypertensive—no. (%)	0 (0.0)	1 (3.2)	−3.2 [−22.6; 0.0]
NSAIDs—no. (%)	1 (2.9)	3 (9.7)	−6.8 [−22.6; 2.4]
CT scan severity score—no./total no. (%)			
0	3/17 (17.6)	2/21 (9.5)	8.1 [−11.5; 33.3]
1	4/17 (23.5)	7/21 (33.3)	−9.8 [−37.0; 21.2]
2	8/17 (47.1)	7/21 (33.3)	13.7 [−18.7; 44.6]
3	2/17 (11.8)	3/21 (14.3)	−2.5 [−22.2; 21.1]
4	0/17 (0.0)	2/21 (9.5)	−9.5 [−31.3; 0.0]

[a] The 95% confidence intervals (CIs) of the differences have not been adjusted for multiple testing and should not allow inference interpretation

score of 1 (30.8%) or 2 (38.5%), and only 5.3% of patients had a score of 4.

Outcome results

The baseline characteristics of those groups were well balanced according to the 95% confidence interval differences available in Table 2.

Patients were split according to the median kalemia level (3.9 mmol/L) into two groups—low kalemia occurrence (≤ 3.8 mmol/L) and no low kalemia occurrence (> 3.8 mmol/L).

Fig. 1 shows trends in median kalemia, CRP levels, and oxygen administration since the first day of symptoms. In Table 3, the unadjusted analysis did not find any significant difference between both groups concerning the median difference of the highest oxygen flow rate administration, the highest CRP level, or the lowest hemoglobin level presented by patients during the hospital stay. Fig. 2 shows the Kaplan—Meier curves for the primary outcome (admission to an ICU or death) during the hospital stay. Twelve patients

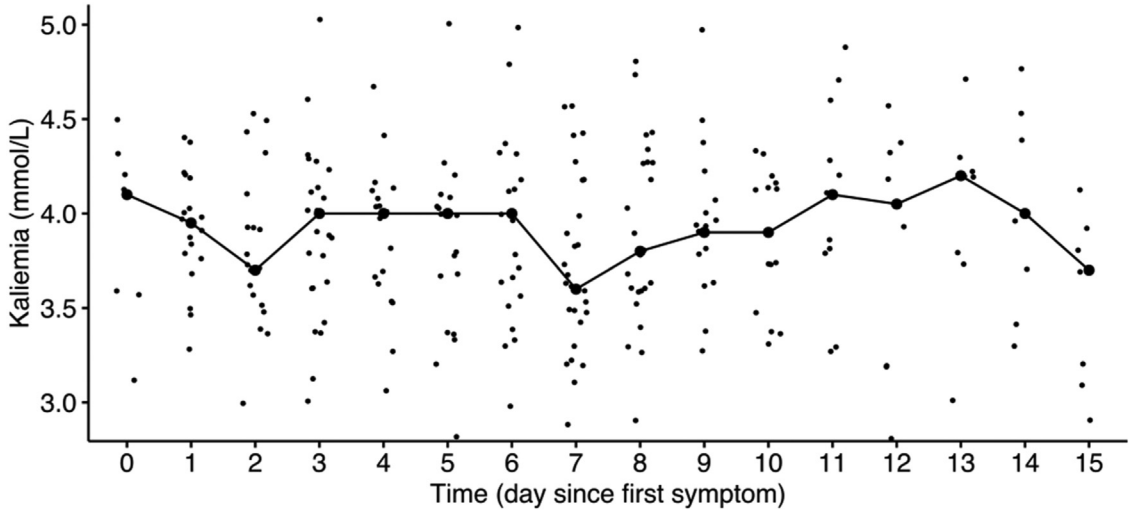

Figure 1 Evolution of the median kalemia level since the first day of symptom onset.

Table 3 Primary and secondary outcomes.

Characteristic	Patients with a kalemia > 3.8 mmol/L ($n = 34$)	Patients with a kalemia ≤ 3.8 mmol/L ($n = 31$)	Difference [95% CI][a]	Adjusted HR [95% CI][b]	*P*-value
ICU admission or death—no. (%)	9 (26.5)	12 (38.7)	−12.24 [−36.34; 9.68]	3.52 [1.12; 11.04]	0.0309
ICU admission—no. (%)	9 (26.5)	11 (35.5)	−9.0 [−33.1; 12.7]	3.59 [1.03; 12.52]	0.0445
Death—no. (%)	4 (11.8)	2 (6.5)	5.3 [−10.0; 17.6]		

Characteristic	Patients with a kalemia > 3.8 mmol/L ($n = 34$)	Patients with a kalemia ≤ 3.8 mmol/L ($n = 31$)	Difference [95% CI][a]	Adjusted OR [95% CI][c]	*P*-value
Median highest O2 administration [IQR]—L/min	2.00 [0.25, 3.75]	2.00 [1.25, 3.75]	0 [−2.00; 0.25]	1.05 [0.90; 1.23]	0.52
Median highest CRP [IQR]—mg/L	95.75 [27.35, 135.97]	129.30 [78.70, 180.30]	−33.55 [−83.20; 16.55]	1.00 [1.00; 1.01]	0.16
Median lowest haemoglobin [IQR]—g/dL	11.20 [8.95, 12.95]	10.30 [8.15, 12.10]	0.9 [− 0.9; 2.8]	0.800 [0.642; 0.997]	0.047

[a] The 95% confidence intervals (CIs) of the differences have not been adjusted for multiple testing and should not allow inference interpretation.
[b] Adjusted variables were serum creatinine level, the presence of an ACE inhibitor or ARB-2, the maximum oxygen flow rate, and the D-dimer level.
[c] Adjusted variables were serum creatinine level, the presence of an ACE inhibitor or ARB-2, the presence of a diuretic and the age.

(38.7%) were admitted to an intensive care unit or died in the low kalemia group against nine patients (26.5) in the other group (adjusted hazard ratio, 3.52; 95% CI, 1.12 to 11.04; $P = 0{\cdot}0309$). No association was found between patients with a baseline kalemia ≤ 3.8 mmol/L and maximum oxygen flow rate required by the patients (odds ratio, 1.05; 95% CI, 0.90 to 1.23), or between baseline kalemia and the maximum CRP value (odds ratio, 1.00; 95% CI, 1.00 to 1.01). However, a significant adjusted association was found between baseline kalemia and the minimum hemoglobin level presented by the patients during the hospital stay (odds ratio, 0.80; 95% CI, 0.64 to 0.99).

Discussion

This prospective monocentric observational study investigates the prognosis value of kalemia in hospitalized COVID-19 patients and its association with laboratory findings. The results suggest that low levels of kalemia within ten days of the first symptom onset are associated with admission in ICU or death and with the minimum hemoglobin level presented by the patients during the hospital stay. However, we did not find any association between kalemia and CRP levels or the oxygen administration, but our study might be underpowered to detect any of them.

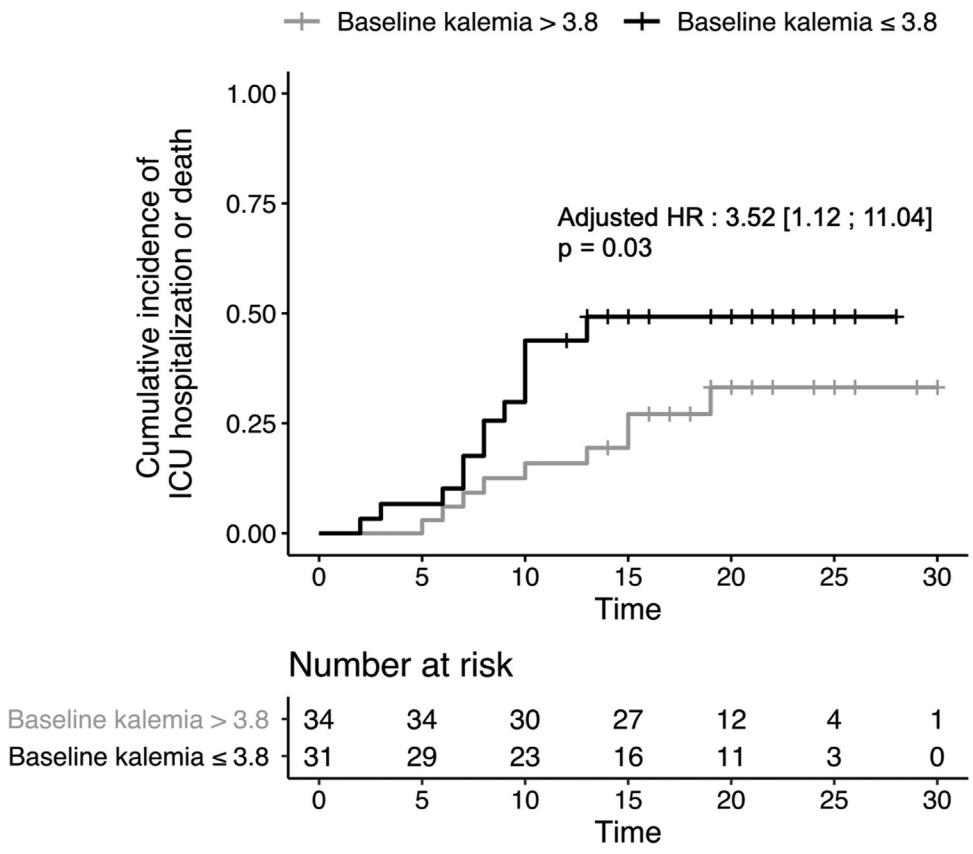

Figure 2 Cumulative incidence of ICU admission or death among COVID-19 patients.

A recent study showed that patients with COVID-19 had a higher incidence of hypokalemia and that the intensity of hypokalemia was associated with disease severity in terms of clinical symptoms and biomarkers [13]. To our knowledge, our study is the only one that showed a prognostic impact of kalemia on ICU admission or death.

However, these findings have some limitations. The frequency of kalemia sampling depended on the clinician's appreciation and the patient's need for monitoring. Besides, we do not know any kalemia value before hospitalization since blood samples were performed at the hospital or any potential potassium supplementation from medical records. Thus, the potassium measurement is not optimal, and it could be interesting to perform a new study with regular and standardized potassium monitoring. Otherwise, a significant amount of missing data prevented us from analyzing the CT-scan severity scores. It would have been interesting to explore the relationship between kalemia and scannographic severity. Our study is exploratory and cannot give rise to inference interpretations since it only concerns one center and patients who required hospitalization. A significant limitation is the lack of data on kaliuresis, which could have informed us of the origin of the potassium loss. However, a recent study [13] showed an increased urinary K+ output in patients with hypokalemia compared with patients with normokalemia and suggested it is caused by a dysfunction of the renin-angiotensin system (RAS). Indeed, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE-2), a metallopeptidase involved in the renin-angiotensin system[6], to gain entry into the host cell[8,9]. The binding between ACE-2 and the SARS-CoV2 Spike protein downregulates ACE-2 [10], which mechanically increases the concentrations of angiotensin I and angiotensin II [11,12] and explains the urinary loss of potassium due to a secondary increase of aldosterone[5]. Moreover, some authors suggest that reduced ACE-2 activity could be associated with poor prognosis in patients with acute respiratory distress syndrome [25]. In our study, a low kalemia value could be an early sign of a more significant ACE-2 reduction, and therefore a sign of vulnerability to the infection. Kalemia could constitute another critical element to assess for the COVID-19 prognostic along with D-dimer, troponin levels [26,27], or markers of endothelial activation [28,29], and it might be interesting to investigate the clinical relevance of a gravity score combining them.

Conclusion

Our study shows that low levels of kalemia within ten days of the first symptom onset is a prognostic factor for ICU admission or death in COVID-19 hospitalized patients. Further studies should be conducted on a larger scale to confirm our results to understand better the pathophysiological links between RAS, kalemia disorders, and prognosis in patients with COVID-19.

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Disclosure of interest

The authors declare that they have no competing interest.

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Online Supplement. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jdmv.2021.10.006.

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