Clinical Kidney Journal, 2021, vol. 14, no. 10, 2227–2233

doi: 10.1093/ckj/sfab122
Advance Access Publication Date: 6 July 2021
Original Article

ORIGINAL ARTICLE

Hypernatraemia and low eGFR at hospitalization in COVID-19 patients: a deadly combination

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ABSTRACT

Background. The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on the general population and the burden of pre-existing comorbidities has heavily affected the outcome of the infection. Hyponatraemia has been frequently described. Conversely, hypernatraemia has rarely been described in COVID-19.

Methods. The studied cohort encompasses all COVID-19 patients consecutively admitted to the Messina Hospital, Italy, during the first wave of the epidemic. Since healthcare structures were not overwhelmed at that time, indications for hospitalization were homogeneous throughout the study period. Serum sodium levels, kidney function [estimated glomerular filtration rate (eGFR)], demographic and clinical characteristics were recorded at admission. Correlation between mortality, sodium and eGFR was evaluated by survival curves and univariate and multivariate regression models.

Results. Baseline biochemical and clinical data at the time of admission were available for 115 COVID-19-confirmed patients. The median age at admission was 73 years (48% men), with a median Charlson Comorbidity Index of 4. A total of 23.5% of patients presented with a sodium level $\geq$146 mmol/L, while 7.8% had sodium $<$135 mmol/L. Hypernatraemic patients were older, with higher comorbidity. Age, hypernatraemia and reduced eGFR were associated with increased mortality in both univariate and multivariate regression models ($P < 0.001$). The combination of hypernatraemia and reduced renal function at admission had an odds ratio of 47.67 (95% confidence interval 10.08–225.43) of dying compared with patients with an eGFR $\geq$60 mL/min and sodium $<$145 mmol/L.

Received: 21.4.2021; Editorial decision: 21.6.2021

Conclusions. Our study suggests that the association between hypernatraemia and reduced eGFR at referral is a highly relevant prognostic marker for death during hospitalization. The role of this association should be further tested in larger, multicentre cohorts.

Keywords: COVID-19, electrolytes, hypernatraemia, kidney function, mortality, SARS-CoV-2, sodium

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a major impact on fragile patients and, among them, patients with chronic kidney disease (CKD), whether or not on dialysis [1–3]. Furthermore, COVID-19 is associated with different kidney function alterations, often characterized by tubular involvement and electrolyte derangements.

Hyponatraemia has frequently been reported in COVID-19 patients and has been associated with poor outcomes [4–7]. In a large series from New York, up to 30% of hospitalized COVID-19 patients developed hyponatraemia, which was associated with mortality [7]. In a French multicentric study, hyponatraemia was almost twice as prevalent in COVID-19 patients admitted to the emergency department as in matched controls (20.4% versus 12.3%, respectively) and was associated with mortality [8]. Furthermore, hyponatraemia has been found to correlate with the degree of pulmonary involvement in COVID-19 patients [9].

The pathogenesis of electrolyte unbalance is only partially understood and several factors may contribute, thus explaining the differences observed in various settings. For instance, there have been reports associating hyponatraemia to the development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with inappropriate secretion of antidiuretic hormones [10, 11]. Proximal tubular necrosis or an incomplete Fanconi syndrome could also contribute to electrolyte alterations as a reflex of direct kidney injury by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), as viral particles have been demonstrated in renal tubular cells [12, 13].

Conversely, hypernatraemia has less frequently been reported in COVID-19 patients. In two large and recently published series, the prevalence of hypernatraemia ranged between 3.7% and 7%, while hyponatraemia was reported in 20.5–44.6% of patients [14, 15].

Both hypo- and hypernatraemia have been associated with in-hospital mortality in COVID-19 patients [14]. Different hospitalization criteria, at least partly limited to the shortage of healthcare resources, may account for some of the reported epidemiological differences.

In this context, we report on our experience in the city of Messina, in Sicily, where the peak of the epidemic occurred later and at a lesser degree than in the north of Italy and the lower number of infections did not lead to a rapid saturation of hospital beds. This particular context allowed us to analyse data gathered in a cohort of patients affected by COVID-19 severe enough to warrant hospitalization and selected in a relatively homogeneous way.

While the onset of new variants, the use of vaccines and increased medical expertise may have changed the natural history of the infection, the outbreak is not yet at its end, and reflecting on some peculiar experiences may be of interest for the future. With this aim, we report on the strong association found in our setting between hypernatraemia, reduction of kidney function and risk of death in patients hospitalized for COVID-19.

MATERIALS AND METHODS

Setting of the study

This observational study was performed in the A.O.U. Policlinico 'G. Martino' Hospital in Messina, a city of ~300 000 inhabitants. Inclusion criteria were being admitted to the COVID Unit (105 patients) or to the intensive care unit (ICU) (18 patients) because of SARS-CoV-2 infection between 8 March and 27 April 2020 and availability of plasma sodium levels at admission (115 patients). COVID-19 diagnosis was confirmed according to the World Health Organization recommendations by means of a nasopharyngeal swab positive for SARS-CoV-2, detected by reverse transcription polymerase chain reaction (RT-PCR) [16].

Data collection

The following data were gathered. Clinical data included sex, age, Charlson Comorbidity Index (CCI) and comorbidities at admission [arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), CKD, cardiovascular disease and neoplasia], development of acute kidney injury [AKI, defined as per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines] [17], need for invasive ventilation and death during hospitalization. Biochemical data at admission included serum white blood cell (WBC) count, serum haemoglobin, serum platelet, serum D-dimer, serum creatinine, serum urea, serum lactate dehydrogenase (LDH), serum creatinine, estimated glomerular filtration rate (eGFR) calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation [18], creatinine phosphokinase (CPK), serum myoglobin, serum sodium, serum potassium and serum C-reactive protein (CRP).

Statistical analysis

We stratified patients according to their serum sodium levels at admission into three groups: hyponatraemia (<135 mmol/L, 9 patients), normal (135–145 mmol/L, 79 patients) and hypernatraemia (≥146 mmol/L, 27 patients) (the baseline sodium level was not available for 8 patients).

Statistical analysis was performed with SPSS version14 (SPSS, Chicago, IL, USA) and JASP version 0.11.1 (JASP Team, Amsterdam, The Netherlands).

Descriptive analysis. The Shapiro–Wilk test was used to verify the normal distribution of the data and the Leven test was used to verify homoscedasticity. Discrete variables are presented as percentages while continuous variables are reported as median (minimum–maximum). Differences were compared with the chi-squared test or Fisher's exact test, as appropriate, and the Mann–Whitney test. The analysis of variance test was used to compare the three groups (hyponatraemia, normal sodium and hypernatraemia).

Kaplan–Maier curves were used to evaluate and compare mortality.

The area under the curve (AUC) of the receiver operator characteristics (ROC) curve was computed to determine the optimal cut-off points of sodium and eGFR to predict mortality by means of Youden's index.

All previously mentioned biochemical variables were tested for correlation with death in univariate analysis. All the significant variables in the univariate analysis were considered for the multivariate analysis. Since WBC count, CRP, LDH, CPK, myoglobin and D-dimer were mutually correlated and all were also correlated with eGFR (as assessed by the Pearson correlation test; Supplementary data, Table S1), we chose to include only CRP in the multivariable model as a marker of disease severity, because of its lower correlation with eGFR (Supplementary data, Table S1).

Multivariate logistic regression was used to determine the association of hypernatraemia and eGFR with death adjusted for sex, age and CRP. Due to collinearity between serum sodium and eGFR and the collinearity of eGFR and age, we designed two different models: one considering age, sex, serum sodium and CRP and the second one considering sex, eGFR and CRP as continuous variables (Table 2). The choice of the covariates was clinical, after exclusion for collinearity. The absence of significant collinearity was further tested *a posteriori* with the variance inflation factor (VIF). Focused principal component analysis [19] was used to determine the association of both serum sodium and eGFR and the other variables with death (Figure 3).

A two-tailed α risk at 5% was considered statistically significant.

Ethical issues

The study was conducted in accordance with the Declaration of Helsinki.

At admission to A.O.U. Policlinico 'G. Martino' Hospital, all patients had the opportunity to decide whether or not to give consent to use their clinical data, in anonymous form, for scientific purposes. Due to the non-interventional, observational and retrospective nature of this study, according to Italian regulations, approval by an ethics committee was not needed.

RESULTS

Overall data

From the start of the epidemic, >500 patients with suspected COVID-19 were evaluated in the hospital emergency room; between 8 March and 27 April 2020, 123 COVID-19 patients were hospitalized, 105 in the COVID Unit and 18 in the ICU. The median age of hospitalized patients was 73 years (range 18–100) with a median CCI of 4 (range 0–11). Of these, 18 patients (15.65%) had a history of CKD, 55 (47.83%) of hypertension, 30 (26.09%) of diabetes and 29 (25.22%) of ischaemic heart disease. During hospitalization, 44 patients (38.26%) developed AKI (defined by the KDIGO guidelines), 17 patients (14.78%) needed invasive ventilation and 28 patients (24.35%) died (Table 1).

Distribution of sodium levels

Table 1 reports the characteristics of the hospitalized COVID-19 patients divided according to sodium level at admission: hyponatraemia (<135 mmol/L, 9 patients), normal (135–145 mmol/L, 79 patients) and hypernatraemia (≥146 mmol/L, 27 patients). The sodium level at admission was not available for eight patients.

Patients with hypernatraemia had a higher CCI ($P = 0.01$), higher creatinine and lower eGFR at admission and were more frequently affected by CKD ($P = 0.01$). They also had a greater need for invasive ventilation ($P = 0.004$) and displayed a higher incidence of AKI during hospitalization ($P < 0.001$). D-Dimer, myoglobin, WBC count and CRP were also higher in patients with hypernatraemia (Table 1). Conversely, no significant difference was found in chronic therapy recorded at admission (Supplementary data, Table S2).

Analysis of survival

Overall mortality was 24.35%. Mortality was the highest in patients with hypernatraemia (62.96%); no deaths were recorded in the hyponatraemia group, while 13.93% of patients with a normal sodium level at hospitalization died. Kaplan–Meier analysis confirms the increased mortality in the hypernatraemia group ($P < 0.001$) (Figure 1) and, within the limits of a small series, the severity of hypernatraemia was further correlated with mortality (Supplementary data, Figure S1).

Based on the correlation between sodium levels and eGFR at admission and of both with survival, we used ROC curves to identify the best cut-points of eGFR and sodium level. Youden's index was at 59.6 mL/min for eGFR (AUC 0.749; Supplementary data, Figure S2) and at 143.5 mmol/L for sodium (AUC 0.782; Supplementary data, Figure S3). Figure 2 illustrates the combined effect of these two variables on mortality. Death risk was significantly increased in cases in which there was both a low eGFR and a high sodium level. Patients with hypernatraemia had an odds of death 10.25-fold [95% confidence interval (CI) 3.88–27.09] higher than patients with serum sodium <143.5 mmol/L; patients with reduced eGFR had an odds of death 6.56-fold (95% CI 2.55–16.89) higher than patients with normal renal function. Hypernatraemic patients with an eGFR <59.6 mL/min had a 47.67-fold (95% CI 10.08–225.43) higher odds of death during hospitalization than patients with normal renal function and serum sodium <143.5 mmol/L ($P < 0.001$).

Multivariate analysis

In Model 1, sodium was an independent mortality risk factor, as well as eGFR in Model 2 (Table 2). The residual analysis confirmed the validity of the two models (Supplementary data, Figures S4 and S5) while the VIF values suggest that the model is not affected by collinearity between the variables chosen. To better highlight the relative weight of each variable on the risk of death, we performed a focused principal component analysis (Figure 3) that suggested sodium and eGFR have a similar weight on mortality (Figure 3).

DISCUSSION

Derangements in electrolyte levels have been extensively described in acute and chronic diseases, have an overall negative weight on prognosis and are particularly common in COVID-19. Attention to the importance of sodium derangements in COVID-19 has been drawn by several studies [8, 20, 21]. The relationship between electrolyte derangements and AKI in COVID-19 has also been underlined [22–24].

The reported prevalence of hyper- and hypernatraemia in patients affected by COVID-19 is very variable and ranges from <5% to 9% and <10% to >30%, respectively. Differences in genetic background, food habits, indications for tests (outpatients, at referral, during hospitalization in the ICU and in hospitalization wards), definitions of hypo- and hypernatraemia and the

Table 1. Baseline characteristics of the population

Characteristics	All cases	Groups according to sodium value at hospitalization			
		Hyponatraemia	Normonatraemia	Hypernatraemia	P-value
Sodium (mmol/L), median (min–max)	141 (128–173)	<135	≥135–≤145	>145	
Patients, *n*	115	9	79	27	
Sex (male), *n* (%)	55 (47.83)	4 (44.44)	37 (46.84)	14 (51.85)	0.884
Age (years), median (min–max)	73 (18–100)	71 (41–86)	70 (18–100)	81 (39–92)	0.062
CKD, *n* (%)	18 (15.65)	0	9 (11.39)	9 (33.33)	**0.010**
Hypertension, *n* (%)	55 (47.83)	5 (55.56)	33 (41.77)	17 (62.96)	0.146
Diabetes, *n* (%)	30 (26.09)	3 (33.33)	17 (21.52)	10 (37.04)	0.249
Chronic obstructive lung disease, *n* (%)	10 (8.70)	1 (11.11)	6 (7.59)	3 (11.11)	0.825
Cardiopathy, *n* (%)	29 (25.22)	3 (33.33)	18 (22.78)	8 (29.63)	0.657
Neoplasia, *n* (%)	6 (5.22)	1 (11.11)	3 (3.80)	2 (7.41)	0.544
CCI, median (min–max)	4 (0–11)	3 (0–6)	3 (0–11)	5 (0–10)	**0.010**
AKI, *n* (%)	44 (38.26)	2 (22.22)	23 (29.11)	19 (70.37)	**<0.001**
Invasive ventilation, *n* (%)	17 (14.78)	2 (22.22)	6 (7.59)	9 (33.33)	**0.004**
Death, *n* (%)	28 (24.35)	0	11 (13.92)	17 (62.96)	**<0.001**
Haemoglobin (g%), median (min–max)	12.7 (7.4–16.9)	11.75 (9.4–14.5)	13.00 (8.8–16.6)	11.50 (7.4–16.9)	**0.022**
White blood cell count ($\times 10^3/mm^3$), median (min–max)	6.3 (1.9–21.2)	6.9 (2.7–15.2)	5.7 (2.6–21.2)	8.9 (1.9–20.6)	**0.002**
Lymphocytes (cells/mm^3) median (min–max)	1289 (274–5200)	1092 (690–2107)	1306 (274–5200)	1261 (418–2060)	0.238
Lymphocytes (%), median (min–max)	23.0 (2.0–60.0)	17.0 (10.0–43.0)	27.0 (2.0–60.0)	11.0 (4.0–38.0)	**<0.001**
Platelet ($\times 10^4/mm^3$), median (min–max)	18.5 (3.0–44.3)	23.5 (11.8–36.0)	18.1 (3–44.3)	18.7 (3.8–40.5)	0.386
D-Dimer (μg/mL), median (min–max)	1.08 (0.27–4.01)	1.65 (0.320–4.01)	0.72 (0.270–4.01)	2.02 (0.34–4.01)	**<0.001**
Creatinine (mg/dL), median (min–max)	0.9 (0.3–10.9)	0.9 (0.3–1.9)	0.9 (0.3–2.9)	1.5 (0.4–10.9)	**<0.001**
eGFR (mL/min), median (min–max)	72.1 (2.8–152.1)	80.9 (50–130.7)	74.1 (18–152)	40.1 (2.8–137)	**0.009**
Urea (mg/dL), median (min–max)	40 (10–341)	29 (10–112)	38 (11–178)	76 (15–341)	**<0.001**
LDH (U/L), median (min–max)	430 (222–3317)	630 (224–1109)	357 (222–1209)	623 (226–3317)	**<0.001**
CPK (U/L), median (min–max)	67.5 (10–5450)	228 (10–863)	54 (13–5450)	149 (24–4296)	0.136
Potassium (mmol/L), median (min–max)	4.3 (2.7–6.7)	3.9 (3–4.3)	4.3 (3–5.3)	4.2 (2.7–6.7)	0.109
Myoglobin (ng/mL), median (min–max)	60 (21–15 000)	123.0 (21–865)	43.0 (21–1604)	273.5 (30–15 000)	**0.001**
CRP (mg/dL), median (min–max)	2.86 (0.05–49.6)	7.20 (0.13–23.65)	1.60 (0.05–49.6)	7.88 (0.10–34.7)	**<0.001**

min: minimum; max: maximum.
P-values refer to the comparison of the three groups, i.e. hypo-, normo- and hypernatraemia. Statistically significant values are in bold.

Table 2. Multivariable logistic regression

Variables	OR	CI 95%		P-value	VIF
		Lower	Higher		
Model 1 for death risk					
Age	1.056	1.014	1.100	0.009	1.11
Sex (male versus female)	0.745	0.247	2.250	0.602	1.14
Serum sodium concentration	1.143	1.054	1.240	0.001	1.04
CRP	1.062	1.001	1.126	0.048	1.16
Model 2 for death risk					
Sex (male versus female)	0.766	0.293	2.002	0.587	1.05
eGFR	0.972	0.956	0.988	0.001	1.00
CRP	1.052	0.996	1.111	0.070	1.06

prevalence of comorbidities may explain these differences, but the picture is not yet fully elucidated.

In this context, the main finding of our study is to describe a particularly ominous association, the simultaneous presence of reduced eGFR and hypernatraemia at hospitalization (Figure 2).

In the context of an overall mortality rate of 24% during hospitalization, comparable to what is reported in several European settings [25–27] and in the USA [28], the presence of reduced eGFR at admission was associated with significantly higher odds of death during hospitalization (6.56 times higher than patients with an eGFR ≥59.6 mL/min) and with the presence of hypernatraemia (10.25 times higher than patients with serum sodium <143.5 mmol/L). However, it was the combination of the two (hypernatraemia and low eGFR) that bore the highest odds of death during hospitalization (47.67 times higher than patients with eGFR ≥59.6 mL/min and serum sodium <143.5 mmol/L; $P < 0.001$) (Figure 2). The prognostic value of this association has, to our knowledge, not been reported and its high statistical significance warrants attention.

Hypernatraemia is a well-known prognostic marker in critically ill patients in ICUs [29, 30]. It is therefore not surprising that this association was also found in our cohort, composed of

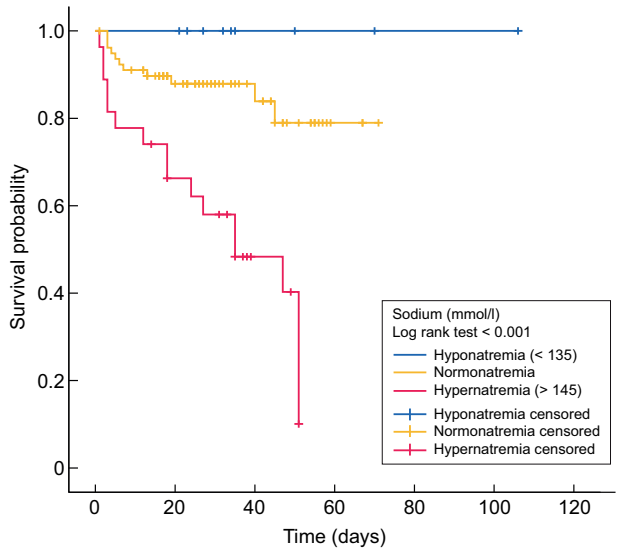

FIGURE 1: Kaplan–Meier curve according to sodium level stratification (hyponatraemia, normonatraemia and hypernatraemia).

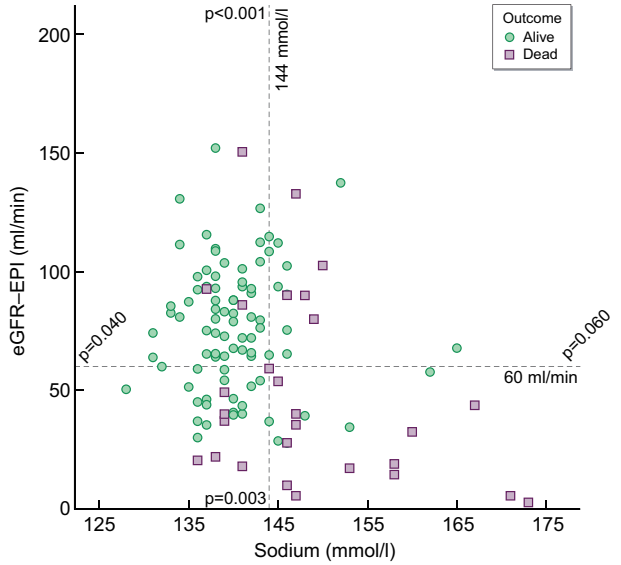

FIGURE 2: Relationship between sodium and eGFR at admission and patient survival. P-values in the figure indicate the results of the chi-squared test between two adjacent sections of the figure. P-value of comparison between patients with sodium <143.5 mmol/L and eGFR ≥59.6 mL/min and patients with sodium ≥143.5 mmo/L and eGFR <59.6 mL/min was <0.001. Youden's index was used to define thresholds on the basis of ROC curves to identify the best cut-points of eGFR and sodium level.

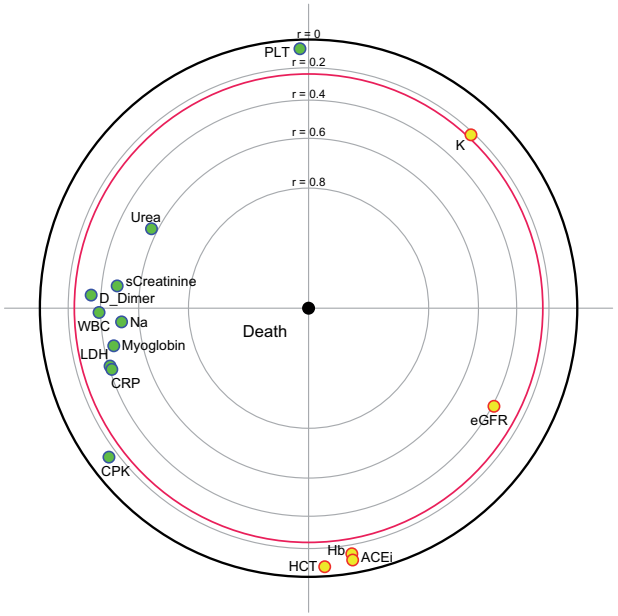

FIGURE 3: Focused principal component analysis for death risk. The red circle corresponds to the limit of statistical significance: everything inside the circle is significantly associated to death. Yellow circles correspond to a negative correlation and green circles correspond to a positive correlation. Variables diametrically opposite had an inverse correlation between themselves, while the 'cloud' of variables on the middle left part of the graph shows the variable interrelationship, without a preponderance of one over another in regard to mortality. ACEi, angiotensin-converting enzyme inhibitor; Hb, haemoglobin; HCT, haematocrit; K, serum potassium; Na, serum sodium; PLT, platelet and sCreatinine, serum creatinine.

hospitalized patients [14, 31, 32]. However, it is difficult to interpret the role hypernatraemia and low eGFR play in our context, as our study presents some peculiarities.

First, hypernatraemia was more frequent in our cohort than in previously published reports and its prevalence was higher than the prevalence of hyponatraemia, which, in contrast, is usually reported as more common. The reasons for this difference in the prevalence of sodium derangements are not clear. Sicily is an island, and thus the genetic background may be different when compared with mainland Italy and Europe. Also, the local cuisine is spicy and salty. Both issues may have played a role in this finding. However, probably most importantly, the population hospitalized was relatively old (median age 73 years), older overall than the population described in most of the previous large reports, and hypernatraemia was more frequent in our older patients (median age 81 years), in keeping with a higher risk of dehydration in older individuals, in particular in the presence of an underlying CKD. Interestingly, further in keeping with our data, in the recent reports from the USA and Spain, which overall have younger populations (median age 65–69 years), the median age of patients with hypernatraemia was ≥80 years [14, 15].

While the studies mentioned above reported on an association between high sodium levels and mortality, ours is the first to highlight how mortality was higher in patients with hypernatraemia and low eGFR at referral.

As expected in a real-life observational study, we found multiple correlations between the different factors (age and lower eGFR; age, lower eGFR and hypernatraemia; age and mortality), and in such a setting, disentangling the effects of each element is difficult if not impossible, as visually depicted in the principal component analysis (Figure 3). Within these limits, we built two different multivariate models, entering alternatively sodium and eGFR (Table 2). The models, whose validity is supported by the residual analysis (Supplementary data, Figures S4 and S5) and VIF values, suggest that each factor is similarly affecting the outcomes, and in this context, we preferred simply describing their combination in Figure 2.

A lack of data on urinary osmolarity at hospitalization does not allow us to go beyond a simple description of this association. Different non-specific mechanisms, including dehydration, which is relatively frequent in elderly patients, in particular with fever, or multifactorial tubular damage, could be

responsible for hypernatraemia and an increased incidence of AKI [33], but the role of SARS-CoV-2, possibly via the down-regulation of angiotensin-converting enzyme 2 receptors, cannot be ruled out [34].

The relatively small sample size and the multiple strict correlations among variables of interest are major limits of this work. However, within all the limits of a relatively small series and the lack of urinary data and specific information on dehydration at hospitalization, our study has the strength of being gathered in a setting in which, due to the lack of saturation of hospital resources, the indications for hospitalization can be considered homogeneous and a systematic analysis of eGFR and sodium levels was possible in the majority of the cases at a fixed and consistent moment, i.e. hospitalization. This point may be important, as the results may be clinically useful for an initial prognostic evaluation and this may be a strength with respect to other large series gathering sodium levels at variable intervals during hospitalization [21, 29, 31].

Furthermore, the retrospective study design does not allow establishing a clear cause–effect relationship between sodium, eGFR and mortality. This limitation, shared by most observational studies, mainly regards the interpretation of the data from a physiopathology point of view, but does not affect the clinical interest of tagging patients with high sodium levels associated with reduced kidney function as a subset deserving particular attention during hospitalization.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

Thanks to Susan Finnel for her careful language editing.

FUNDING

No funding was received for this study. The Centre Hospitalier Le Mans covered editing and publishing expenses.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

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