



Negative prognostic impact of electrolyte disorders in patients hospitalized for Covid-19 in a large multicenter study

Simonetta Genovesi^{1,2} · Giuseppe Regolisti^{3,4} · Paola Reborà⁵ · Giuseppe Occhino⁵ · Michele Belli¹ · Giulio Molon⁶ · Giuseppe Citerio^{7,8} · Anna Beltrame⁹ · Alessandro Maloberti^{7,10} · Elena Generali^{11,12} · Cristina Giannattasio^{7,10} · Oscar Massimiliano Epis¹³ · Claudio Rossetti¹⁴ · Giuseppe Bellelli^{7,15} · Ana Lleo De Nalda^{11,12} · Ilaria Capua¹⁶ · Maria Grazia Valsecchi⁵

Received: 23 May 2022 / Accepted: 31 July 2022
© The Author(s) under exclusive licence to Italian Society of Nephrology 2022

Abstract

Background The prognostic impact of electrolyte disorders in hospitalized COVID-19 patients is unclear.

Methods The study included all adult patients hospitalized for COVID-19 in four hospitals in Northern Italy between January 2020 and May 2021 with at least one serum potassium and sodium measurement performed within 3 days since admission. Primary outcome was in-hospital death; secondary outcome was Intensive Care Unit (ICU) admission. A cause-specific Cox proportional-hazards regression model was used for investigating the association between potassium and sodium (as either categorical or continuous variables) and mortality or admission to ICU.

Results Analyses included 3,418 adult hospitalized COVID-19 patients. At multivariable analysis, both hyperkalemia (Hazard Ratio, [HR] 1.833, 95% Confidence Interval [CI] 1.371–2.450) and sK above the median (K 5.1 vs 4.1 mmol/L: HR 1.523, 95% CI 1.295–1.798), and hyponatremia (HR 2.313, 95%CI 1.772–3.018) and sNa above the median (Na 149 vs 139 mmol/L: HR 1.442, 95% CI 1.234–1.686), were associated with in-hospital death, whereas hypokalemia and hyponatremia were not. Hyponatremia was associated with increased hazard of ICU admission (HR 1.884, 95%CI 1.389–2.556).

Conclusions Electrolyte disorders detected at hospital admission may allow early identification of COVID-19 patients at increased risk of adverse outcomes.

Keywords Electrolytes · Sodium · Potassium · COVID-19 · Mortality · Intensive care units

✉ Simonetta Genovesi
simonetta.genovesi@unimib.it

¹ School of Medicine and Surgery, Nephrology Clinic, Milano-Bicocca University, Milan, Italy

² Istituto Auxologico Italiano, IRCCS, Milan, Italy

³ Clinica e Immunologia Medica, Azienda Ospedaliero-Universitaria, Parma, Italy

⁴ Department of Medicine and Surgery, University of Parma, Parma, Italy

⁵ Bicocca Bioinformatics Biostatistics and Bioimaging Centre, School of Medicine and Surgery Milano-Bicocca University, Milan, Italy

⁶ Cardiology Department, IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Verona, Italy

⁷ School of Medicine and Surgery, Milano-Bicocca University, Milan, Italy

⁸ NeuroIntensive Care Unit, ASST-Monza, Monza, Italy

⁹ Department of Infectious/Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Verona, Italy

¹⁰ Cardiology 4, Cardio Center, ASST GOM Niguarda Hospital, Milan, Italy

¹¹ Department of Biomedical Sciences, Humanitas University, Emanuele, Italy

¹² Internal Medicine and Hepatology Unit, IRCCS Humanitas Research Hospital, via Manzoni 56, 20089 Rozzano, Milan, Italy

¹³ Division of Rheumatology, Multispecialist Medical Department, Niguarda Hospital, Milan, Italy

¹⁴ Department of Training and Research, Niguarda Hospital, Milan, Italy

¹⁵ Acute Geriatric Unit, ASST San Gerardo Hospital, Monza, Italy

¹⁶ One Health Center of Excellence, University of Florida, Gainesville, FL 32611, USA

Electrolyte derangements are common in severe diseases and also occur in patients with coronavirus disease 2019 (COVID-19). Hypokalemia is a clinically relevant electrolyte derangement in this setting [1]. Conversely, critically ill patients are prone to developing hyperkalemia and hypernatremia [2]. A U-shaped relationship between both serum potassium (sK) and serum sodium (sNa) with mortality was found in hospitalized patients with heart failure, chronic kidney disease (CKD), or diabetes [2, 3]. Because of the low sample size and the heterogeneity of the studies, it is unclear if and to what extent electrolyte disorders affect outcomes in COVID-19 patients.

In a large population of patients hospitalized for COVID-19, we therefore evaluated whether potassium and sodium disorders were independently associated with mortality or admission to the intensive care unit (ICU).

This retrospective cohort study included all adult patients hospitalized for COVID-19 in four hospitals in Northern Italy between January 2020 and May 2021 with at least one serum potassium and sodium measurement performed within 3 days since admission. Primary outcome was in-hospital death; secondary outcome was ICU admission. The patients were followed-up until the first occurrence of either hospital discharge, transfer to another unit, or death. A cause-specific Cox proportional-hazards regression model was used to investigate the association between potassium and sodium (as either categorical or continuous variables) and mortality or admission to ICU. (See Supplementary Material for an extended version of the methods).

The study was approved by the Ethics Committee of the coordinating center (San Gerardo Hospital, Monza) and by the IRB of each center and registered at ClinicalTrials.gov (Identifier: NCT04670094, Dec 15, 2020).

We analysed a total of 4,555 patients, of whom 1,137 were excluded, leaving 3,418 patients for final analyses (eFigure 1). The main clinical characteristics and blood chemistry parameters at admission of included patients according to potassium and sodium categories are shown in eTable 1. Comparisons between included and excluded patients are shown in eTable 2.

Serum potassium values were within the normal range in 2,893 (84.6%) patients, low in 306 (9.0%) and high in 219 (6.4%).

Serum sodium values were within the normal range in 2917 (85.3%) patients, low in 352 (10.3%) and high in 149 (4.4%).

Female gender [odds ratio (OR) 0.417, 95% confidence interval (CI) 0.317–0.549, male vs female], older age (OR 1.015, 95% CI 1.006–1.024), lower platelet count (OR 0.997, 95% CI 0.995–0.998) and higher C-reactive protein (CRP) values (OR 1.003, 95% CI 1.002–1.005) were associated with hypokalemia at multivariable analysis (eTable 3, Model A). Male gender (OR 1.490, 95% CI 1.020–2.178)

and higher platelet count (OR 1.005, 95% CI 1.004–1.006) were positively associated with hyperkalemia, while older age (OR 0.985, 95% CI 0.973–0.998), eGFR (OR 0.959, 95% CI 0.952–0.966), and sNa values (OR 0.950, 95% CI 0.917–0.985) were negatively associated with this disorder (eTable 3, Model B).

Ischemic heart disease (OR 1.948, 95% CI 1.313–2.891), diabetes mellitus (OR 1.990, 95% CI 1.499–2.642), and higher CRP values (OR 1.003, 95% CI 1.001–1.004) were associated with hyponatremia (eTable 3, Model C), whereas older age (OR 1.026, 95% CI 1.007–1.044), diagnosis of dementia (OR 4.522, 95% CI 2.828–7.231), lower eGFR (OR 0.986, 95% CI 0.978–0.994) and hemoglobin (OR 0.900, 95% CI 0.814–0.995) values were associated with hypernatremia (eTable 3, Model D).

There were 609 (17.8%) in-hospital deaths. We observed a significant trend towards increasing mortality in patients with electrolyte disorders [467 (16.1%), 62 (20.3%) and 80 (36.5%) for patients with normal, low, or high sK values, respectively ($p < 0.001$); 455 (15.6%), 74 (21.0%) and 80 (53.7%) for patients with normal, low, or high sNa values, respectively ($p < 0.001$)]. Figure 1 depicts crude cumulative incidence of death according to sK (panel A) and sNa (panel B) values over the first 60 days of hospitalization. For both electrolytes, the relationship between serum concentrations and the crude probability of death was described by a J-shaped curve (eFigure 2). After adjusting for potential confounders, older age (HR 1.051, 95% CI 1.042–1.060), hyperkalemia (HR 1.833, 95% CI 1.371–2.450) and hypernatremia (HR 2.313, 95% CI 1.772–3.018) at the time of hospital admission, previous stroke (HR 1.372, 95% CI 1.058–1.778), lower eGFR levels (HR 0.993, 95% CI 0.989–0.997) and indices of greater severity of infection [lower platelet count (HR 0.998, 95% CI 0.997–0.999), higher lymphocyte count (HR 1.022, 95% CI 1.004–1.040), and higher CRP values (HR 1.004, 95% CI 1.003–1.005)] were associated with a higher hazard of death, whereas hypokalemia and hyponatremia were not. Multiple imputations for missing values confirmed the results (Table 1). The HR of in-hospital mortality as a function of sK and sNa levels are depicted in Fig. 1, panels C and D, respectively. Potassium or sodium levels above the median values (4.1 mmol/L for sK and 139 mmol/L for sNa) were associated with a significantly higher hazard of death, while electrolyte concentrations below the median values were not. HRs for in-hospital mortality are also shown per 1 mmol/L sK changes below and above the median value (Fig. 1E) and per 10 mmol/L sNa changes below and above the median value (Fig. 1F). An additional analysis was done to assess whether, among hyponatremic patients, those with a plasma urea value greater than 5 mmol/L and therefore presumably hypovolemic [4] had a higher mortality rate. The analysis showed that the

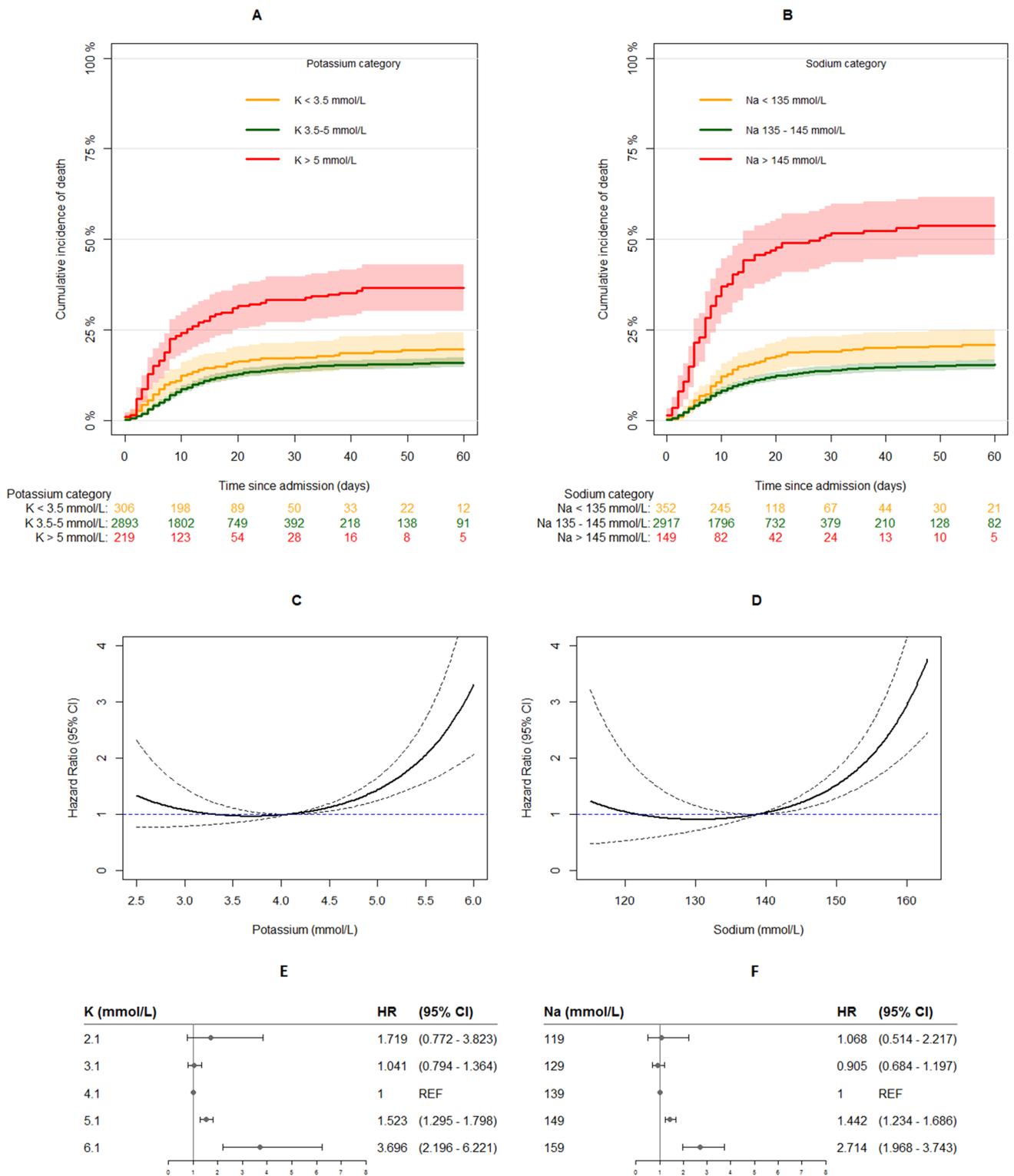


Fig. 1 Cumulative incidence of death by potassium (A) and sodium (B) categories. In-hospital mortality Hazard Ratio (HR) as a function of potassium (C) and sodium (D). HR of in-hospital mortality

per 1 mmol/L or per 10 mmol/L below and above the median value of potassium (4.1 mmol/L, E) and sodium (139 mmol/L, F). Estimates based on Cox model shown in eTable 4

Table 1 Multivariable Cox regression model on mortality by potassium and sodium categories

	Complete cases ($n = 2824$, deaths $n = 506$)			Multiple imputation ($n = 3418$, deaths $n = 609$)		
	HR	95% CI	p value	HR	95% CI	p value
Male (yes vs no)	1.133	(0.929–1.381)	0.2192	1.131	(0.944–1.355)	0.1822
Age (years)	1.051	(1.042–1.060)	<0.0001	1.051	(1.043–1.059)	<0.0001
Hypokalemia ($K < 3.5$ vs 3.5 – 5 mmol/L)	0.878	(0.652–1.182)	0.3907	0.871	(0.664–1.142)	0.3176
Hyperkalemia ($K > 5$ vs 3.5 – 5 mmol/L)	1.833	(1.371–2.450)	<0.0001	1.961	(1.521–2.528)	<0.0001
Hyponatremia ($Na < 135$ vs 135 – 145 mmol/L)	1.079	(0.819–1.421)	0.5912	1.122	(0.876–1.437)	0.3617
Hypernatremia ($Na > 145$ vs 135 – 145 mmol/L)	2.313	(1.772–3.018)	<0.0001	2.238	(1.746–2.870)	<0.0001
History of stroke (yes vs no)	1.372	(1.058–1.778)	0.0170	1.365	(1.083–1.721)	0.0085
Platelets ($10^3/\mu\text{L}$)	0.998	(0.997–0.999)	<0.0001	0.998	(0.997–0.999)	<0.0001
Lymphocytes ($10^3/\mu\text{L}$)	1.022	(1.004–1.040)	0.0151	1.002	(0.987–1.017)	0.8156
eGFR ($\text{ml}/\text{min}/1.73 \text{ m}^2$)	0.993	(0.989–0.997)	0.0005	0.993	(0.990–0.997)	0.0003
C-Reactive protein (mg/L)	1.004	(1.003–1.005)	<0.0001	1.004	(1.003–1.005)	<0.0001

Complete cases excluded patients with at least one missing datum among history of stroke, platelets, lymphocytes, eGFR and C-Reactive protein
HR hazard ratio, *CI* confidence interval, *K* Potassium, *Na* Sodium, *eGFR* estimated glomerular filtration rate

cumulative incidence of death was higher in patients with urea > 5 mmol/L (log-rank test $p < 0.001$, eFigure 3).

In 2384 patients it was possible to collect information on acute kidney injury (AKI) onset during hospitalization ($n = 318$, 13.3%). When incident AKI was added to the final survival models, the main results did not change, but AKI was independently associated with mortality both in the model in which *K* and *Na* were included as categorical variables (HR 2.448, 95% CI 1.901–3.153) and in the model in which they were included as continuous variables (HR 2.496, 95% CI 1.937–3.215) (eTable 5 and eTable 6).

Three hundred forty-five (10.1%) patients were admitted to the ICU during their hospitalization. The patients with hyponatremia were more likely to experience ICU admission than those with normal *sNa* values [58/352 (16.5%) vs 271/2917 (9.3%), $p < 0.001$]. Hypokalemia was negatively (HR 0.454 95% CI 0.266–0.773), whereas hyponatremia was positively (HR 1.884, 95% CI 1.389–2.556) associated with the hazard of ICU admission (eTable 7, Model A). Markers of greater severity of COVID-19 [lower platelet count (HR 0.999, 95% CI 0.997–1.000), higher lymphocyte count (HR 1.023, 95% CI 1.011–1.034), and higher CRP values (HR 1.008, 95% CI 1.007–1.010)] were positively, while older age (HR 0.977, 95% CI 0.969–0.985) and cancer (HR 0.574, 95% CI 0.333–0.987) were negatively associated with ICU admission (eTable 7, Model A). When *sK* and *sNa* values were entered into the model as continuous variables, a negative association was confirmed between *sNa* concentration and the hazard of ICU admission (HR 0.953, 95% CI 0.925–0.983), and a direct association emerged between *sK* level and ICU admission (HR 1.275, 95% CI 1.031–1.578) (eTable 7, Model B).

In 1,633 patients it was possible to collect information on AKI onset prior to ICU admission ($n = 169$, 10.4%). When incident AKI was added to the cause-specific Cox regression models on admission to ICU, main results were unchanged and AKI was not independently associated with this outcome (eTable 8).

The main finding of this study is that hyperkalemia and hypernatremia were strongly associated with an increased risk of death in a large population of patients hospitalized for COVID-19. This association remained significant even after adjusting for new-onset AKI during hospital stay, a factor independently associated with mortality both in the general hospitalized population and in patients admitted for COVID-19 [5].

The negative prognostic impact of hyperkalemia is well known in non-COVID-19 populations [3], particularly because of the high risk of ventricular arrhythmias and cardiovascular mortality. A direct pathogenetic role of hyperkalemia in increasing the risk of death can be hypothesized also in COVID-19 patients; however, it should be underscored that, compared to patients with normal *sK* values, hyperkalemic patients in our population were significantly older and had a higher prevalence of comorbidities. Therefore, because of the retrospective design of this study, we cannot exclude that hyperkalemia may rather represent a marker of increased cardiovascular risk in our population.

A significant association between hypernatremia and mortality has been reported in both non-COVID-19 and COVID-19 patients [6, 7]. Hypernatremia may increase the risk of death through different mechanisms, including decreased brain volume, vascular rupture, cerebral demyelination and permanent neurologic deficits. In our

population, hypernatremia at admission more than doubled the hazard of death compared with the presence of normal sNa levels. However, due to the retrospective design of our study, hypernatremia at admission may have been rather a marker of the severity of clinical conditions or patient frailty than a causal factor for the risk of death.

In our cohort hyponatremia was associated with a greater burden of comorbidities, as well as with a lower lymphocyte count and higher CRP values and with the hazard of ICU admission, reinforcing the hypothesis that in the COVID-19 population hyponatremia may be regarded as a marker of the severity of clinical conditions in surviving patients. In addition, plasma urea values greater than 5 mmol/L were associated with a higher cumulative incidence of death, suggesting that patients with hypovolemic hyponatremia might have a worse prognosis, as previously suggested [4].

Because electrolyte measurements were performed only at hospital admission, we cannot exclude that derangements in plasma potassium and/or sodium levels may have preceded the development of COVID-19 severe enough to require hospitalization, and may have affected the severity or lethality of the disease. Indeed, in a large retrospective study on electronic health records of patients with COVID-19, non-survivors were significantly more likely to have high plasma potassium or sodium levels in the thirty days following COVID-19 onset than survivors [8]. Alternatively, the viral infection per se may have induced the development of dysnatremia and/or dyskalemia. Interestingly renal damage and hyperkalemia were found in fatal cases of critically ill patients affected by another zoonotic Coronavirus, MERS-CoV [9].

Our study has some limitations. Thrombocytosis can be associated with pseudo-hyperkalemia. However, given the observed baseline platelet counts, virtually no cases of thrombocytosis were observed in our population. Moreover, in the study by Hirsch et al. [7] the association between hyponatremia and mortality was no longer significant after correction for serum glucose values. This may imply that hyponatremia in patients with severe hyperglycemia may have been rather a proxy for more severe clinical conditions. Unfortunately, plasma glucose values were not collected in our database, and thus we could not correct serum sodium for glucose values.

In conclusion, our data support the hypothesis that hyperkalemia and hypernatremia at hospital admission may be associated with a higher risk of death in non-critically ill COVID-19 patients. Conversely, hyponatremia may be associated with a higher risk of ICU admission. Attention to detect electrolyte disorders at the time of admission in COVID-19 patients may help in the early identification of those at higher risk of adverse outcomes.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40620-022-01429-3>.

Acknowledgements We would like to thank the Covid-19 Niguarda Working Group, the STORM Steering Committee and data management, the Humanitas COVID team and the Sacro Cuore Don Calabria Hospital COVID team for sharing data. COVID-STORM Clinicians: Paolo Bonfanti, Andrea Biondi, Giuseppe Foti, Giacomo Bellani, Giuseppe Citerio, Ernesto Contro, Alberto Pesci, Maria Grazia Valsocchi, Marina Cazzaniga. COVID-STORM data management: Davide Gaudesi, Emanuela Rossi, Nicoletta Cordani.

Author contributions Conceptualization, SG and GR; methodology, SG, PR and MG; software, PR and GO; formal analysis, PR and GO; data curation, GM, GC, AB, AM, EG, CG, OE, CR, GB, AL; writing—original draft preparation, SG, GR and PR; writing—review and editing, SG, GR, MG and MB; supervision, IC and MG. All authors have read and agreed to the published version of the manuscript.

Funding The research was partially supported by the Italian Ministry of Education, University and Research (MGV, 2017-NAZ-446/PRIN 0178S4EK9). The research was partially supported by the Italian Ministry of Health.

Data availability Please contact the corresponding author regarding data requests. STROBE statements are provided as supplemental material.

Declarations

Conflict of interest The results presented in this paper have not been published previously in whole or in part. All authors declare no conflict of interest.

Ethics approval and consent to participate The study (COMORBIDITIES) was approved by the Ethics Committee of the coordinating center (San Gerardo Hospital, Monza) and by the IRB of each center and registered at ClinicalTrials.gov (Identifier: NCT04670094, Dec 15, 2020). When possible informed consent was obtained from all subjects involved in the study. Otherwise the study was conducted under authorizations guaranteed by Article 89 of the GDPR EU Regulation 2016/679, which guarantees the processing for purposes of public interest, scientific or historical or statistical purposes of health data. In addition, this is a retrospective study.

References

- Noori M, Nejadghaderi SA, Sullman MJM, Carson-Chahhoud K, Kolahi AA, Safiri S (2021) Epidemiology, prognosis and management of potassium disorders in Covid-19. *Rev Med Virol*. <https://doi.org/10.1002/rmv.2262> (Epub ahead of print)
- Gao XP, Zheng CF, Liao MQ, He H, Liu YH, Jing CX, Zeng FF, Chen QS (2019) Admission serum sodium and potassium levels predict survival among critically ill patients with acute kidney injury: a cohort study. *BMC Nephrol* 20(1):311. <https://doi.org/10.1186/s12882-019-1505-9>
- Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA (2017) Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 46(3):213–221. <https://doi.org/10.1159/000479802> (Epub 2017 Sep 2)

4. Tzoulis P, Waung JA, Bagkeris E, Hussein Z, Biddanda A, Cousins J, Dewsnip A, Falayi K, McCaughran W, Mullins C, Naeem A, Nwokolo M, Quah H, Bitat S, Deyab E, Ponnampalam S, Bouloux PM, Montgomery H, Baldeweg SE (2021) Dysnatremia is a predictor for morbidity and mortality in hospitalized patients with COVID-19. *J Clin Endocrinol Metab* 106(6):1637–1648. <https://doi.org/10.1210/clinem/dgab107>
5. Hansrivijit P, Qian C, Boonpheng B, Thongprayoon C, Vallabhajosyula S, Cheungpasitporn W, Ghahramani N (2020) Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis. *J Investig Med* 68(7):1261–1270. <https://doi.org/10.1136/jim-2020-001407> (Epub 2020 Jul 12)
6. Kovesdy CP, Lott EH, Lu JL, Malakauskas SM, Ma JZ, Molnar MZ, Kalantar-Zadeh K (2012) Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation* 125(5):677–684. <https://doi.org/10.1161/CIRCULATIONAHA.111.065391> (Epub 2012 Jan 5)
7. Hirsch JS, Uppal NN, Sharma P, Khanin Y, Shah HH, Malieckal DA, Bellucci A, Sachdeva M, Rondon-Berrios H, Jhaveri KD, Fishbane S, Ng JH; Northwell Nephrology COVID-19 Research Consortium. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. *Nephrol Dial Transpl.* 2021;36(6):1135–1138. <https://doi.org/10.1093/ndt/gfab067>.
8. Nahkuri S, Becker T, Schueller V, Massberg S, Bauer-Mehren A (2021) Prior fluid and electrolyte imbalance is associated with COVID-19 mortality. *Commun Med (Lond)* 1:51. <https://doi.org/10.1038/s43856-021-00051-x>
9. Singh SK (2016) Middle east respiratory syndrome virus pathogenesis. *Semin Respir Crit Care Med* 37(4):572–577. [https://doi.org/10.1055/s-0036-1584796\(Epub2016Aug3\)](https://doi.org/10.1055/s-0036-1584796(Epub2016Aug3))

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.