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Sex differences in electrolyte imbalances caused by SARS-CoV-2: A cross-sectional study

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Abstract

Background: Since SARS-CoV-2 spread, evidence regarding sex differences in progression and prognosis of COVID-19 have emerged. Besides this, studies on patients' clinical characteristics have described electrolyte imbalances as one of the recurrent features of COVID-19.

Methods: We performed a cross-sectional study on all patients admitted to the emergency department (ED) from 1 March to 31 May 2020 who had undergone a blood gas analysis and a nasopharyngeal swab test for SARS-CoV-2 by rtPCR. We defined positive patients as cases (n = 710) and negatives as controls (n = 619), for a total number of patients of 1.329. The study was approved by the local ethics committee Area 3 Milan. Data were automatically extracted from the hospital laboratory SQL-based repository in anonymised form. We considered as outcomes potassium (K^+), sodium (Na^+), chlorine (Cl^-) and calcium (Ca^{++}) as continuous and as categorical variables, in their relation with age, sex and SARS-CoV-2 infection status.

Results: We observed a higher prevalence of hypokalaemia among patients positive for SARS-CoV-2 (13.7% vs 6% of negative subjects). Positive patients had a higher probability to be admitted to the ED with hypokalaemia (OR 2.75, 95% CI 1.8-4.1, $P < .0001$) and women were twice as likely to be affected than men (OR 2.43, 95% CI 1.67-3.54, $P < .001$). Odds ratios for positive patients to manifest with an alteration in serum Na^+ was (OR 1.6, 95% CI 1.17-2.35, $P < .001$) and serum chlorine (OR 1.6, 95% CI 1.03-2.69, $P < .001$). Notably, OR for positive patients to be hypocalcaemic was 7.2 (95% CI 4.8-10.6, $P < .0001$) with a low probability for women to be hypocalcaemic (OR 0.63, 95% CI 0.4-0.8, $P = .005$).

Conclusions: SARS-CoV-2 infection is associated with a higher prevalence of hypokalaemia, hypocalcaemia, hypochloraemia and sodium alterations. Hypokalaemia is more frequent among women and hypocalcaemia among men.

Arianna Pani and Elvira Inglese are contributed equally to this work.

1 | INTRODUCTION

Since December 2019 the world has been struggling to fight the novel coronavirus SARS-CoV-2. As soon as the virus spread in China, researchers noticed the higher predisposition of men to contract COVID-19.[1,2] Evidence that emerged subsequently also revealed an association between male sex and more severe disease and death.[3,4] Some authors have attributed the reasons for these differences to sex differences in immune response,[5] to differences in the prevalence of smoking subjects among men and women[6] and to genetics.[7] Few studies have investigated the impact of sex differences in clinical manifestations of the disease other than disease severity and mortality.[8]

Early studies on COVID-19 have highlighted the association between the disease and sodium (Na^+), potassium (K^+), calcium (Ca^{++}) and chloride (Cl^-) abnormalities.[1,9,10] Chen et al[11] described a high prevalence of hypokalaemic subjects among patients hospitalised with COVID-19. Furthermore, the severity of the disease was associated with a higher degree of hypokalaemia. Authors have also shown, in a small sample of patients, that hypokalaemic subjects had a higher mean urinary K^+ output than non-hypokalaemic patients, suggesting a possible implication for increased K^+ urine loss.

This mechanism could be explained by the disruption caused by the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) with a possible impact on the renin-angiotensin system (RAS). Despite the aforementioned evidence, little is still known regarding electrolyte disturbances in COVID-19 and in SARS-CoV-2 infection.

The aim of this study was to examine the prevalence of electrolyte imbalances among patients with SARS-CoV-2 infection in a large cohort and its distribution according to age and sex.

What's known

- Since SARS-CoV-2 spread, evidence regarding sex differences in progression and prognosis of COVID-19 have emerged.
- Besides, studies on patients' clinical characteristics have described electrolyte imbalances as one of the recurrent features of COVID-19.

What's new

- We observed a higher prevalence of hypokalaemia in patients positive for SARS-CoV-2, and women were twice as likely to be affected than men.
- Positive patients also had a higher prevalence of hypocalcaemia, hypochloraemia and sodium alteration. Hypokalaemia appears to be more frequent among women and hypocalcaemia among men.
- Sex differences in electrolyte imbalances in COVID-19 patients were for the first time observed and detailed.

2 | METHODS

The study protocol was approved by the Ethics Committee Area 3 Milano (prot. 92-15032020). Signed informed content was obtained for each participant. This study was conducted in accordance with the principles of the 1964 Declaration of Helsinki. Strengthening the Reporting of Observational *Studies* in Epidemiology (STROBE) reporting guidelines.

This cross-sectional study has been performed at the ASST GOM Niguarda Hospital in Italy, in which there are all medical specialties both for adult and children. It is a regional reference for Lombardy and national for Italy for transplants, some rare diseases, heart diseases, for time-dependent diseases, major traumas and emergencies.

During the pandemic, it was chosen as a hub to face the hospitalisation needs of COVID-19 positive patients and to manage the regional vaccination plan. The Lombardy Region has modified the hospital network by creating sixteen hubs that respond to specific non-COVID-19 emergencies. Thanks to this, we can distinguish and exclude patients with previous diseases that could influence evaluated study outcomes.

In fact, in this study, the transferred patients to other hubs for the management of trauma, cardiological and/or vascular surgery emergencies, were excluded from the controls, as well as patients with chronical liver disease or eating disorders that was managed by outpatient departments outside the hospital.

2.1 | Data sources

At the ASST GOM Niguarda hospital, we store all analytical results of the tests performed in the laboratory in an SQL-based repository. With the purpose to conduct this study, a query was created to extract data with no personal information other than gender and date of birth. This query extracted laboratory results based on the date of execution, the requesting department and the type of service performed. Derived data supporting the findings of this study are available from the corresponding author on request.

The fields extracted were: patient's ID (a numeric string that uniquely identifies the patient without personal data), sex, birth date day of lab tests execution (with a truncation for the extracted data referred to the period 1 March to 31 May), tests ID, tests results and hospital ward.

In this way we, were able to collect the biochemical and microbiological profile of patients at admittance to the emergency department (ED) and categorise patients based on their positivity (or negativity) to SARS-CoV-2, sex and age.

2.2 | Study patients and covariates

We considered a cohort of patients admitted to the ED from 1 March to 31 May 2020 and screened for SARS-CoV-2 infection with fever, desaturation, or symptoms attributable to infection. As

TABLE 1 Characteristics of study population

	SARS-CoV-2− (619)	SARS-CoV-2+ (710)	*P* value
Female (%, n)	48.2 (297)	39.0 (274)	.001
Age (mean, SD)	61.9 (21.15)	63.7 (16.2)	<.001
Class of age (%, n)			
<65 years	50.0 (308)	50.3 (353)	.002
65-75	13.8 (85)	20.6 (145)	
>75	36.7 (226)	30.2 (212)	
pH (mean, SD)	7.31 (0.19)	7.23 (0.37)	<.001
Lactate, mEq/L (mean, SD)	2.17 (1.58)	1.72 (1.45)	.001
Leucocytes	10.30 (9.38)	8.08 (6.01)	.627
Neutrophils	7.10 (4.00)	5.98 (4.02)	.431
Haemoglobin	14.03 (2.23)	13.93 (1.92)	.010
Calcium, mEqL (mean, SD)	1.20 (0.10)	1.12 (0.07)	<.001
Chloride, mEq/L (mean, SD)	102.86 (4.28)	101.62 (4.17)	.321
Potassium, mEq (mean, SD)	4.11 (0.62)	3.80 (0.49)	<.001
Sodium, mEq/L (mean, SD)	137.43 (4.36)	135.84 (4.50)	.319
Blood glucose, mg/dL (mean, SD)	131.78 (60.60)	143.06 (63.29)	.275
Creatinine, mg/dL (mean, SD)	1.11 (0.63)	1.15 (0.96)	.116
eGFR, mL/min/1.73 mq (mean, SD)	74.06 (44.10)	74.36 (44.41)	.907
Renal disease (%, n)			
eGFR < 90	24.7 (138)	23.7 (156)	.227
60 < eGFR < 89	4.5 (243)	49.0 (323)	
30 < eGFR < 59	25.8 (144)	20.8 (137)	
15 < eGFR < 29	4.7 (26)	4.7 (31)	
eGFR < 15	1.4 (8)	1.8 (12)	

Niguarda is a COVID-19-hub, a good percentage of patients with COVID-19 symptoms were diverted to our hospital. This allowed us to have access to a good population useful for our study and to exclude patients with other chronical interfering pathologies managed by other institutes. Inclusion criteria were: age over 18 years and the performance, during the permanence in the Emergency Department, of at least one blood gas analysis (both arterial and venous) performed using POC Siemens RAPIDPoint 500 Blood Gas System. Compared with central Laboratory analyzers, results obtained from POC Siemens RAPIDPoint 500 blood gas system are stackable for all tested parameters taken into consideration in this study. These results are warranted for our own procedures and devices.[12] We collected data regarding electrolyte profile, pH, blood glucose, white blood cell counts, lymphocyte counts, neutrophils and creatinine.

Exclusion criteria were: patients who were admitted to specialist wards (ie, for diagnosis of cardiological diseases, liver disease or major trauma). Therefore, only those patients who have been kept for non-specialist observation are considered controls.

We defined cases and controls according to the positivity or negativity to the nasopharyngeal swab test for SARS-CoV-2 by rtPCR (GeneFinder TMCOVID-19 Plus RealAmp Kit, ELITech; Allplex TM2019-nCoV Assay, Seegene) performed according to the World Health Organization (WHO) guidance. Positive patients were defined as cases and negatives as controls.

Patients were then categorised into three classes according to age (under 65 years, between 65 and 75 years and over 75 years) and according to sex and age range combined into six groups: (a) females aged below 65 years; (b) females aged between 65 and 75 years; (c) females aged over 75 years; (d) males aged below 65 years; (e) males aged between 65 and 75 years and (f) males aged over 75 years.

2.3 | Outcomes

As outcomes, we considered potassium (K^+), sodium (Na^+), chloride (Cl^-) and calcium (Ca^{++}) both as continuous and as categorical variables, in their relationship with age, sex and SARS-CoV-2 infection status. We defined imbalances of K^+, Na^+, Cl^- and Ca^{++}, according to ranges presented in Table S1.

Leveraging the fact that a blood gas analysis was performed on the majority of patients accepted to the ED, we decided to consider the electrolyte values deriving from this analysis, to avoid potential bias because of the comparison of different methods.

We analysed potential effect modifiers such as renal disease, by calculating the estimated Glomerular Filtration Rate (eGFR) using

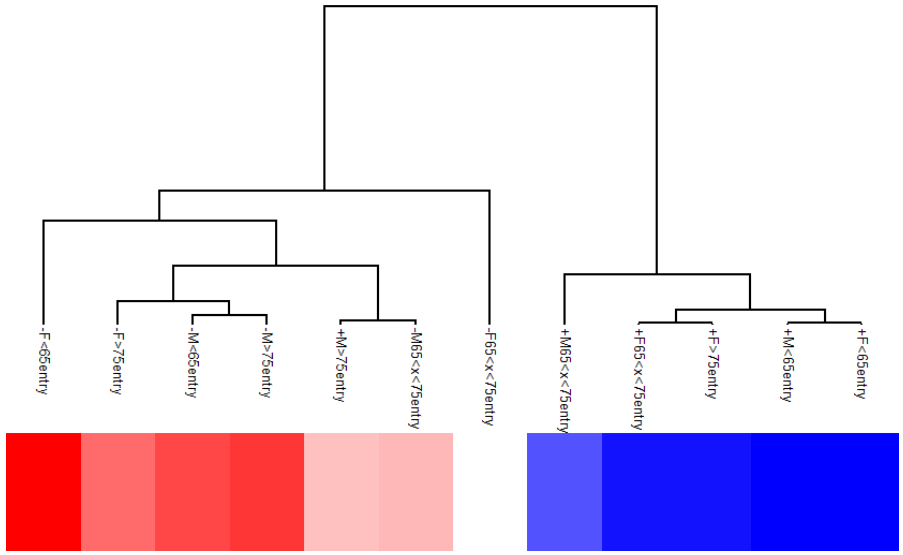

FIGURE 1 Heatmap of Post hoc Tukey's HDS test results. A Tukey's multiple comparisons test was performed to compare potassium between all groups. Euclidean distance and average linkage were used for the clustering process. The test results were pre-processed using k-means before applying clustering and generating the heatmap and the dendrogram. All test results were transformed for the analysis in Z-score intensity signal. Z-score is constructed by taking the ratio of weighted mean difference and combined standard deviation according to Box and Tiao (1992).[15] The application of a classical method of data normalisation, z-score transformation, provides a way of standardising data across a wide range of experiments

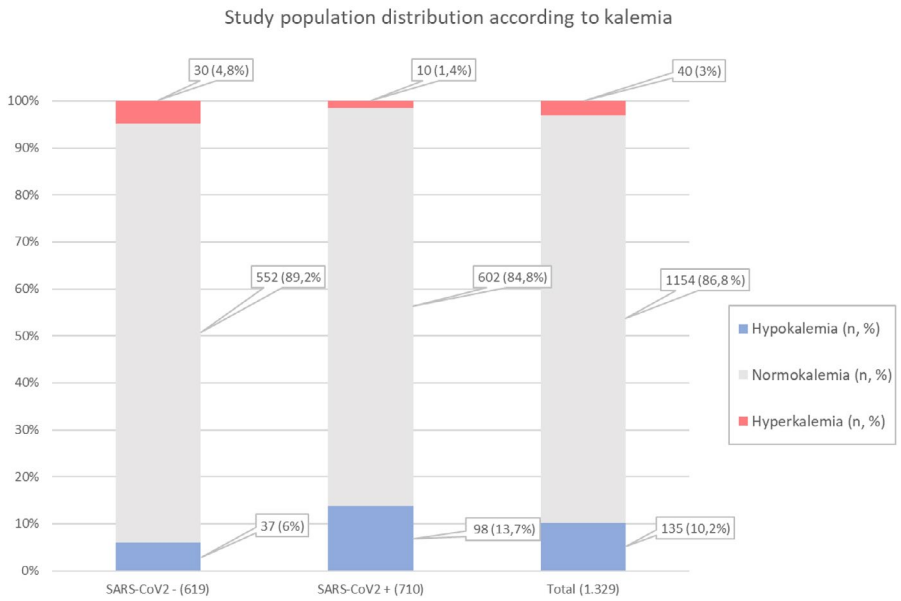

FIGURE 2 Study population distribution according to kalaemia

the formula developed by the Modification of Diet in Renal Disease Study Group (MDRD).[13]

To get closer to precision medicine, it would be preferable to have all the information available in electronic form and the Human Phenotype Ontologies (HPO) is a useful tool for this purpose, making information available at different levels of granularity. The power of HPO has been demonstrated to enrich clinical data, including infectious diseases[14] and for this, to describe outcomes we use the terms of the "Human Phenotype Ontology" (HPO) to better promote the link between SARS-CoV2 to their phenotypes in support of infectious disease research.

2.4 | Statistical analysis

Patients characteristics were summarised with mean and standard deviation for continuous variables and with number and percentages for categorical ones. Differences between the two cohorts have been tested with t-test and chi-square test, or Fisher exact test, respectively.

Assumption of normality distribution was evaluated by Shapiro-Wilk test. A three-way ANOVA test was performed to evaluate differences among sex, class of age and presence of SARS-CoV-2

TABLE 2 Comparison between kalaemia and SARS-CoV-2 infection according to age and sex

		Hyperkalaemia				Hypokalaemia				Not abnormal kalaemia			
		SARS-CoV-2−		SARS-Cov-2+		SARS-CoV-2−		SARS-Cov-2+		SARS-CoV-2−		SARS-Cov2+	
		N	%	N	%	N	%	N	%	N	%	N	%
<65	M	2	1.40	4	1.80	2	1.40	18	8.00	140,	97.20	202	90.20
65 < x < 75	M	1	1.70	1	1.20	5	8.60	7	8.10	52	89.70	78	90.70
>75	M	2	1.70	2	1.70	8	6.80	12	10.30	107	91.50	103	88.80
<65	F	19	11.80	1	0.80	8	5.00	28	21.90	134	83.20	99	77.30
65 < x < 75	F	1	3.70	0	0.00	2	7.40	12	21.80	24	88.90	43	78.20
>75	F	5	4.60	1	1.10	12	11.00	19	20.90	92	84.40	71	78.00

The intensity of the red color highlights the classes of patients in which the prevalence of subjects with potassium imbalances is higher.

TABLE 3 Univariable logistic regression of probability to develop hypokalaemia for patients with SARS-CoV-2 infection

	Non-hypokalaemia		Hypokalaemia				
	n	%	n	%	OR	95% CI	*P* value
SARS-CoV-2 positive	612	86.2	98	13.0	2.52	1.7-3.7	<.001
SARS-CoV-2 negative	582	94.0	37	6.0	1		

infection on potassium values. Tukey's multiple comparisons test was performed for post hoc comparison. Several logistic regression analyses were performed to evaluate the relationship between SARS-CoV-2 infection and electrolyte imbalances separately. Odds ratios (ORs) and 95% confidence intervals (95% CI) were reported. Multivariable logistic regression considering SARS-CoV-2 positivity, age group and sex on hypokalaemia, hypochloraemia, hypocalcaemia and abnormal natraemia were performed. Odds ratios and 95% CI were reported. *P* values <.05 were considered statistically significant.

3 | RESULTS

For the retrospective cohort study of consecutive patients admitted to the ED from 1 March 2020 to 31 May 2020 who had undergone blood gas analysis, 1329 patients were included. Seven hundred and ten (53%) patients resulted positive to the nasopharyngeal swabs rtPCR test for SARS-CoV-2 and 619 resulted negative.

Patients baseline characteristics between the two groups are summarised in Table 1. The case-cohort was characterised by a lower prevalence of female subjects (39%, 274/710), lower mean pH and lactate values (7.23 ± 0.37 and 1.72 ± 1.45 mEq/L) and an electrolyte panel significantly different from controls for K^+ and Ca (3.80 ± 0.49 vs 4.11 ± 0.62 mEq/L and 1.20 ± 0.10 vs 1.12 ± 0.07 mEq/L, respectively). Both cohorts were homogeneous for age, eGFR and renal disease prevalence. The prevalence of patients aged between 65 and 75 years was significantly higher in the SARS-CoV-2 positive cohort (20.6%, 145), while there was a lower prevalence of patients aged under 75 years (30.2%, 212).

3.1 | Potassium

We analysed the distribution of serum K^+ values as a continuous parameter with a three-way ANOVA on the basis of SARS-CoV-2 positivity or negativity, three classes of ages (years >65; 65 to 75; >75) and sex. Results showed a clusterisation (Figure 1) of serum K^+ values according to those parameters, and in particular to SARS-CoV-2 status.

We then divided cases and controls cohorts according to their kalaemic state (Figure 2) and observed a higher prevalence of patients with hypokalaemia in the group with SARS-CoV-2 infection.

Further analyses of the population according to sex and class of age (Table 2) allowed us to observe a higher prevalence of hypokalaemic patients among women positive for SARS-CoV2. The prevalence was similar for all classes of age. The difference between positive and negative patients was statistically significant for men below 65 years ($P = .013$), women below 65 years ($P < .001$). In women, over 75 years it was possible to note a difference that did not reach statistical significance ($P = .069$).

At binary logistic regression, the OR for patients with SARS-CoV-2 to present with hypokalaemia at admission to the ED is twice than the one for non-infected patients (Table 3). At multivariable logistic regression, adjusting for age and sex, the probability to be admitted to the ED with hypokalaemia was nearly three times higher for patients with SARS-CoV-2 infection (OR 2.75, 95% CI 1.8-4.1, $P < .001$) (Figure 3).

For women, the probability to be admitted to the ED with hypokalaemia, adjusting for SARS-CoV-2 positivity and age, is more than twice than the one for men (OR 2.43, 95% CI 1.67-3.54, $P < .001$) (Figure 3).

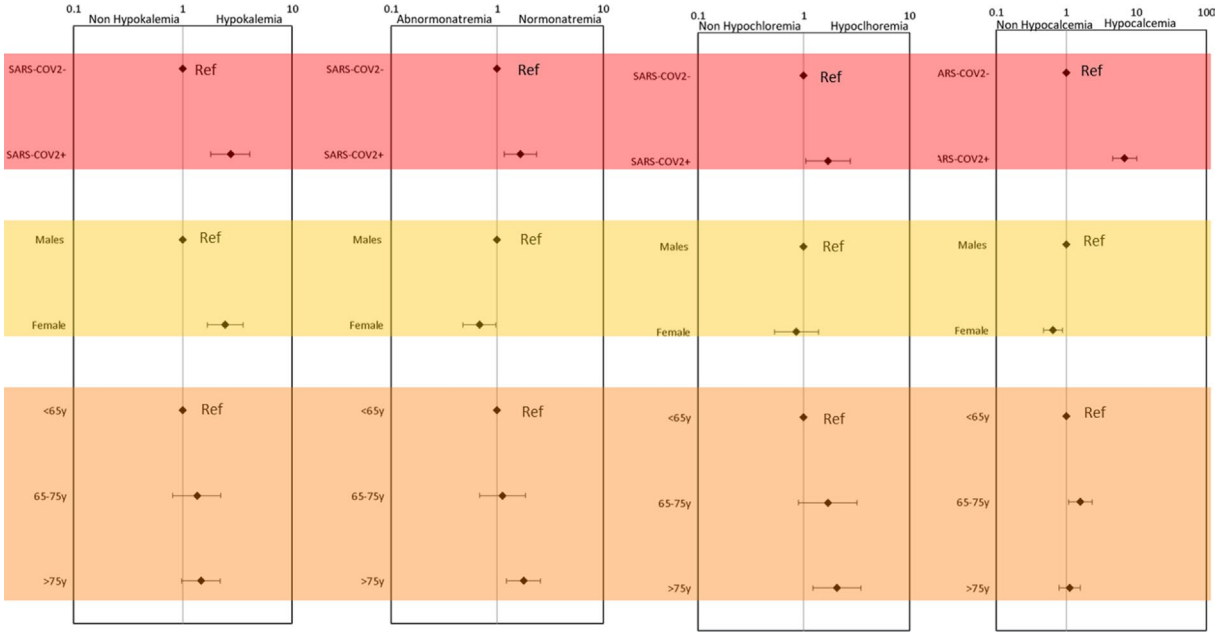

FIGURE 3 Multivariable logistic regression of kaleamia, natraemia, chloraemia and calcaemia according to SARS-Cov2 infection, class of age

3.2 | Other electrolytes

Regarding natraemia, we observed a higher prevalence of both patients with hyperrnatraemia and hyponatraemia among positive subjects (Table A in Supporting Information). Women tended to be more hypernatraemic while men were more hyponatraemic. However, these differences among groups were not statistically significant (Table B in Supporting Information). At logistic regression, patients with SARS-CoV-2 infection had a slightly higher probability to present to the ER with an alteration in natraemia (OR 1.6, 95% CI 1.17-2.35, $P < .001$).

We detected also a mild tendency of infected patients to present with hypochloraemia (Table C Supporting Information) with no differences for sex and age groups (Table D Supporting Information).

Lastly, nearly 30% of patients with SARS-CoV-2 infection presented to the ED with hypocalcaemia vs 5.3% of negative subjects and only 0.4% were hypercalcaemic among cases, compared with 7.4% of controls (Table E Supporting Information). Differences among sex and age groups were visible with a lower prevalence of hypocalcaemia among women compared with men, independently from infection status, and very significant differences between cases and controls for each of the six subgroups based on age group and sex. Prevalence of hypocalcaemia among male patients with SARS-CoV-2 infection ranged from 28% to 34%, compared with 16% to 32% of females (Table F in Supporting Information). At binary logistic regression, the OR for being hypocalcaemic if positive to SARS-CoV-2 was 7.2 (95% CI 4.8-10.6, $P < .0001$) and at multivariable logistic regression women had a lower probability to have hypocalcaemia (OR 0.63, 95% CI 0.4-0.8 $P = .005$) (Figure 3).

4 | DISCUSSION

In this cohort study, we evaluated the association between electrolyte imbalances and SARS-CoV-2 infection, deepening its distribution

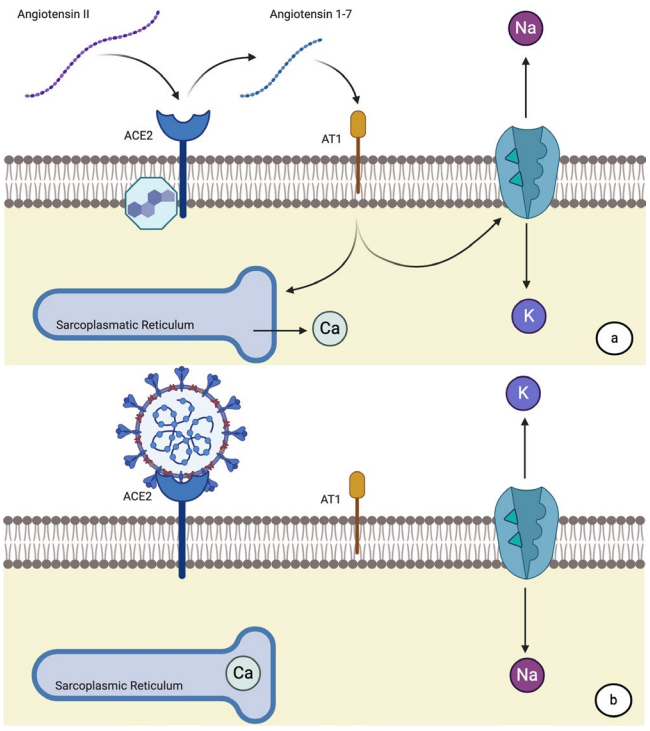

FIGURE 4 Actions of ACE2 on potassium, sodium and calcium imbalance and impact of SARS-CoV-2 infection. Created with BioRender.com

according to age and sex.

To our knowledge, this is the first study conducted on a very large sample describing electrolytes alterations in patients infected with SARS-CoV-2 at admission to the ED and compared with a similar cohort of non-infected patients. Differently from the results reported by Chen et al,[11] we observed a lower prevalence of hypokalaemic patients and a lower severity of hypokalaemia. This is because we considered not only patients hospitalised for COVID-19, but a population of subjects positive to SARS-CoV-2 with a highly heterogeneous grade of the disease.

Moreover, the novelty of this study lies in the description of the important and significant differences observed among female and male patients. Among women, the difference in the prevalence of hypokalaemic patients between cases and controls tended to decrease with increasing age. This could be an expression of a different hormonal influence between pre- and postmenopausal women. This is supported by the influence of female sex hormones, mainly oestrogens, on ACE2 which are able to impact the ACE/ACE2 activity ratio and the expression of angiotensin 1-7,[16,17] also according to age.[18] Regarding calcium we observed a reverse trend, with a higher prevalence of hypocalcaemia among male patients; a trend is also observed in the non-positive population but exacerbated by SARS-CoV-2 infection. As reported elsewhere,[19] sex differences in hypocalcaemia could be correlated to the more frequent use of vitamin D and/or calcium among women for osteoporosis prevention.[20]

From a pathophysiological perspective, SARS-CoV-2 is able to penetrate human cells by binding to ACE2 through a receptor-binding domain present on the spike glycoprotein.[21] ACE2 is a receptor implied in the RAS system, in particular in the modulation of renal sodium transporters,[22,23] especially the Na^+/K^+ ATPase on the baso-lateral membrane of epithelial tubular cells.[24,25] As explained in Figure 4, ACE2 cleaves angiotensin II in angiotensin 1-7, which is able to exert a natriuretic function by acting on the AT1 receptor. Furthermore, the action of ACE2 is also important to the vasodilation triggered by Ca^{++} release from the endoplasmic reticulum induced by angiotensin 1-7. The disruption of this pathway caused by the binding of SARS-CoV-2 on ACE2 could underlie the electrolytes alterations observed in this study and others as well.[1,9,10,11] Indeed, recent studies reported evidence of kidney damage manifesting as tubular dysfunction and necrosis, endothelial alterations and deposition of complement complex on tubules.[26,27]

Electrolyte imbalances, especially of potassium and calcium, associated with SARS-CoV-2 infection could also help explain the numerous reports of QT prolongations, arrhythmias and cardiac deaths reported in patients with COVID-19[28-30] and ascribed to treatments with macrolides and hydroxychloroquine.[31,32] This highlights the importance to continuously monitor and manage hypokalaemia and electrolytes imbalances[33,34]

The limitations of this study lie in its retrospective nature and in the non-correlation of lab values with disease severity and clinical outcomes. Besides this, we believe that our findings are important to better understand the pathophysiology of COVID-19 disease, and especially sex differences in the manifestation of the disease which certainly impact on better prognosis for women.

Clinical implications of this study are relevant from different perspectives. Monitoring kalaemia, calcaemia and electrolytes in general, is important in patients with COVID-19 and immediate supplementation should be suggested. The role of electrolytes imbalances should be further investigated also to understand the association with cardiovascular events reported in other studies.

AUTHOR CONTRIBUTIONS

Arianna Pani, Elvira Inglese and Francesco Scaglione contributed to study conception and design, data acquisition, analysis and interpretation, and paper drafting. Valeria Cento, Claudia Alteri and Andrea Bellone, contributed to data acquisition and analysis. Michele Senatore contributed to study design and data acquisition. Massimo Puoti, Chiara Vismara, Federica Di Ruscio, Oscar Massimiliano Epis, Fabrizio Colombo and Paolo Tarsia, gave critical revision for intellectual content and contributed with patient enrolment and management. Valentina Panetta and Alessandra Romandini, contributed to data analysis and interpretation, paper drafting, and gave critical revision. Mauro Moreno contributed to data interpretation, paper drafting, and gave critical revision for intellectual content. Francesco Scaglione gave critical revision for intellectual content.

TRANSPARENCY DECLARATION

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DISCLOSURES

All authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material. The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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