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ORIGINAL ARTICLE

Electrolyte imbalances as poor prognostic markers in COVID-19: a systemic review and meta-analysis

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Abstract

Purpose Serum electrolyte imbalances are highly prevalent in COVID-19 patients. However, their associations with COVID-19 outcomes are inconsistent, and of unknown prognostic value. We aim to systematically clarify the associations and prognostic accuracy of electrolyte imbalances (sodium, calcium, potassium, magnesium, chloride and phosphate) in predicting poor COVID-19 clinical outcome.

Methods PubMed, Embase and Cochrane Library were searched. Odds of poor clinical outcome (a composite of mortality, intensive-care unit (ICU) admission, need for respiratory support and acute respiratory distress syndrome) were pooled using mixed-effects models. The associated prognostic sensitivity, positive and negative likelihood ratios (LR + , LR-) and predictive values (PPV, NPV; assuming 25% pre-test probability), and area under the curve (AUC) were computed.

Results We included 28 observational studies from 953 records with low to moderate risk-of-bias. Hyponatremia (OR = 2.08, 95% CI = 1.48–2.94, $I^2 = 93\%$, $N = 8$), hypernatremia (OR = 4.32, 95% CI = 3.17–5.88, $I^2 = 45\%$, $N = 7$) and hypocalcemia (OR = 3.31, 95% CI = 2.24–4.88, $I^2 = 25\%$, $N = 6$) were associated with poor COVID-19 outcome. These associations remained significant on adjustment for covariates such as demographics and comorbidities. Hypernatremia was 97% specific in predicting poor outcome (LR + 4.0, PPV = 55%, AUC = 0.80) despite no differences in CRP and IL-6 levels between hypernatremic and normonatremic patients. Hypocalcemia was 76% sensitive in predicting poor outcome (LR- 0.44, NPV = 87%, AUC = 0.71). Overall quality of evidence ranged from very low to moderate.

Conclusion Hyponatremia, hypernatremia and hypocalcemia are associated with poor COVID-19 clinical outcome. Hypernatremia is 97% specific for a poor outcome, and the association is independent of inflammatory marker levels. Further studies should evaluate if correcting these imbalances help improve clinical outcome.

Keywords Electrolytes · Severe acute respiratory syndrome · Hypernatremia · Death risk · Intensive care · Respiratory medicine

Introduction

Since the first case of the coronavirus disease 2019 (COVID-19) in December 2019 [1], more than 400 million people have been diagnosed and cumulative deaths have exceeded 6 million as of 11th February [2]. Biochemical markers associated with risk of deterioration and poor outcome (such as C-reactive protein, ferritin, lactate dehydrogenase) were used to triage patients and allocate hospital resources as healthcare systems became overwhelmed. [3–9] Recent studies have reported high prevalence of electrolyte imbalances in COVID-19 patients and associated these imbalances with more severe infection. [10, 11] Tzoulis et al. reported that dysnatremia was associated with a higher risk for mechanical ventilation and mortality [12]. Several hypotheses exist

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that explain this prevalence, such as the involvement of cell entry receptor angiotensin-converting enzyme 2 (ACE2), a key enzyme in the renin-angiotensin system (RAS) [13, 14]. As serum electrolytes tests are readily available in laboratories, they are useful as prognostic markers in COVID-19 to help risk stratify patients.

While previous meta-analyses have reported associations of hypocalcemia and hyponatremia with COVID-19 severity [15, 16], recent published studies have also suggested associations of other electrolyte imbalances such as dysnatremia, dyskalemia, dysmagnesemia and dyschloremia with COVID-19 severity [12, 17–21]. However, these associations are varied and no pooled prognostic value was reported. Furthermore acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS), which are common complications in severe COVID-19 infections, were not included as outcomes when evaluating these associations [22, 23]. Hence, we sought to conduct a systematic review and meta-analysis to investigate the association of electrolyte imbalances with COVID-19 outcomes. Given the disruption this pandemic has brought to daily lives [24, 25], coupled with the immense toll on some healthcare systems [26], this review is both timely and clinically relevant to help improve risk stratification and resource allocation.

Methods

This review is registered on PROSPERO (CRD42021257711) and reported according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Supplementary Table S1, Online Resource) [27].

Search strategy

We searched three databases (PubMed, Embase and Cochrane Library) from inception till 22nd May 2021 using search terms related to COVID-19 and electrolyte imbalances concerning the electrolytes sodium, calcium, potassium, magnesium, chloride and phosphate (Supplemental Methods, Online Resource). We also hand-searched the bibliography of included articles and relevant reviews but included no additional studies.

Study selection, data extraction, risk of bias assessment and quality of evidence

Two authors independently selected relevant studies, extracted key data and assessed risk of bias in a blinded manner using the online platform Rayyan [28]. We accepted observational studies published as full-length articles in peer-reviewed journals that reported the associations of electrolyte imbalances in patients diagnosed with COVID-19 that were either higher (e.g. hypernatremia) or lower (e.g. hyponatremia) than the normal physiological range. Outcomes of interest included mortality, intensive care unit (ICU) admissions, respiratory support, acute respiratory distress syndrome (ARDS) and/or acute kidney injury (AKI). We also included articles that reported the laboratory parameters of serum creatinine (SCr), C-reactive protein (CRP) and interleukin-6 (IL-6) at admission. We excluded case reports, reviews and letters, as well as articles published in languages other than English. We extracted key data and assessed the risk of bias using the Newcastle–Ottawa Scale (Supplemental Methods, Online Resource). Overall quality of evidence was assessed using the GRADE framework [29].

Statistical analyses

We did separate meta-analyses for each type of electrolyte imbalance to compute a summary estimate of the association of the electrolyte imbalance with the above specified clinical outcomes using an inverse variance-weighted mixed-effects model (Supplemental Methods, Online Resource). We pooled odds ratios for dichotomous outcomes and mean differences for continuous outcomes including laboratory parameters and hospitalization time (Supplemental Methods, Online Resource). We defined poor outcome as a composite of mortality, ICU admission, respiratory support (oxygen supplementation, invasive and/or non-invasive ventilation) and ARDS due to their resource-intensive nature, in line with previous landmark studies on severe COVID [30, 31]. If available, we also pooled odds ratios that adjusted for potential confounders such as sex, age and comorbidities such as diabetes, cardiovascular diseases and chronic liver disease. We generated a summary receiver operator characteristic curve (SROC), Fagan's nomogram, coupled funnel plots and calculated the area under the curves (AUC), sensitivity, specificity, positive (LR +) and negative likelihood ratios (LR-), and positive (PPV) and negative predictive values (NPV) to evaluate the performance and prognostic value of each type of electrolyte imbalance in predicting the unadjusted odds of poor outcome. We assessed and considered between-study heterogeneity as significant if the I^2 statistic was $\geq 50\%$ and the p-value for the Q-test was < 0.10 [32]. To investigate potential sources of heterogeneity, we prespecified various study-level characteristics (Supplemental Methods, Online Resource) to perform subgroup or sensitivity analyses. We conducted all analyses using RevMan (version 5.4), Stata (version 17) and RStudio (version 1.4) using the *meta* package (version 4.18).

Results

We screened 953 records after removing duplicates and subsequently identified 28 studies for inclusion after

screening based on the title and abstract, followed by screening based on full-text (Fig. 1) [12, 17–21, 33–54]. Twenty-four studies were included in our various meta-analyses [12, 17–20, 33–40, 42, 44–53].

Study characteristics

Of the 28 included studies (Table 1), 21 were retrospective cohorts [12, 17, 18, 20, 21, 36–44, 46, 48, 50–54], four were prospective cohorts [19, 33–35], two were cross-sectional[45, 49] and one was a case–control study [47].

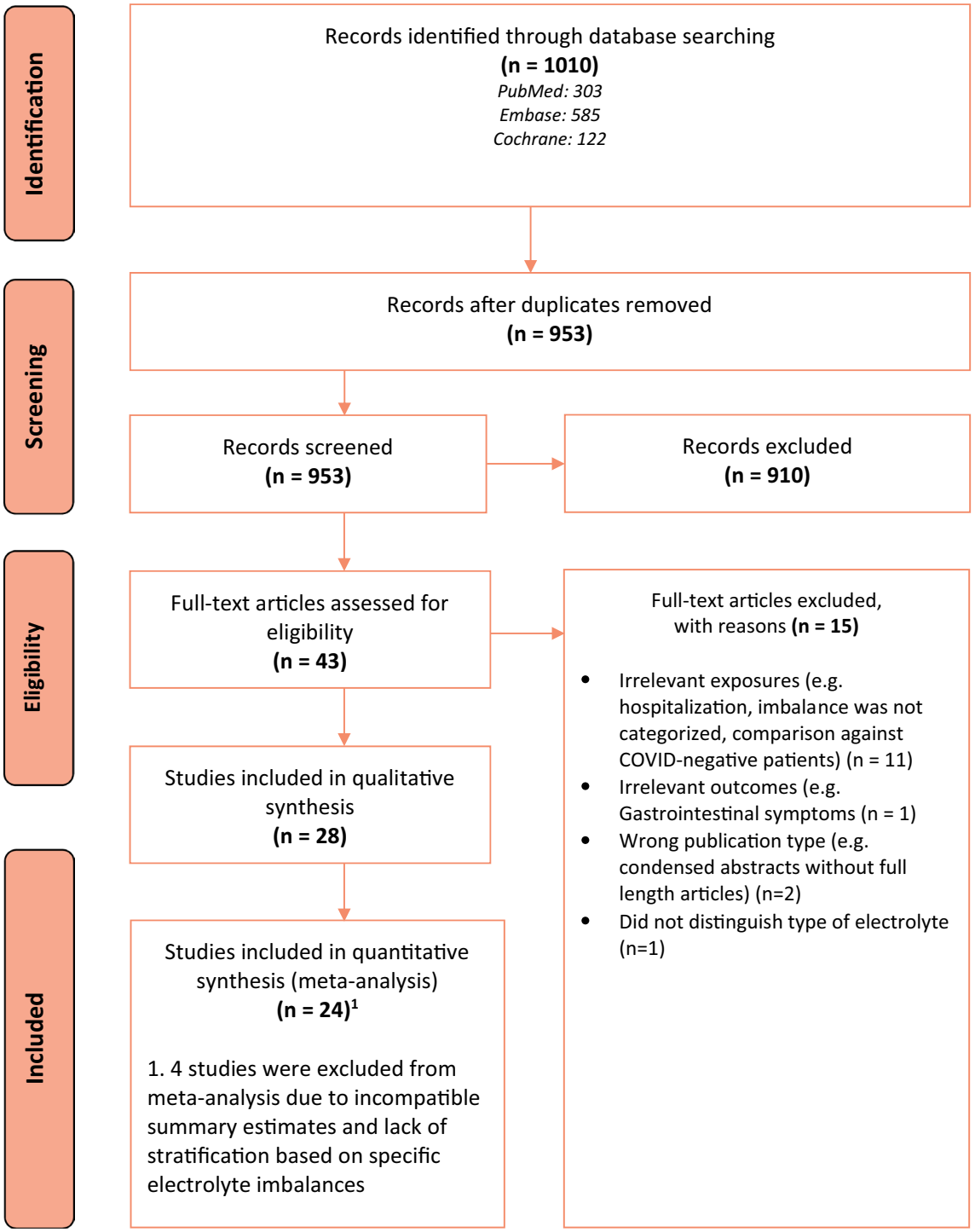


Fig. 1 PRISMA flow diagram of the study selection process

Table 1 Summary of included studies

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Alfano, 2020 Italy	Retrospective cohort	320 65.9 64.8 (Mean)	WHO interim guidelines	N.S	Hypokalemia	< 3.5 mmol/L	At any time during hospitalization	1, 2, 5, 6, 7	Sex, age and SOFA score	7
Asghar, 2020 Pakistan	Prospective cohort	373 67.0 52.9 (Mean)	RT-qPCR	N.S	Hypernatremia	> 145 mmol/L	At admission	1, 3	N.A	7
Atila, 2021 Switzerland	Prospective cohort	172 55.8 60.0 (Mean)	RT-qPCR	N.S	Hyponatremia, Hypernatremia	Hyponatremia: < 135 mmol/L Hypernatremia: > 145 mmol/L	At admission	1, 2, 3, 4, 7, 8	Sex, age, no. of comorbidities (presence of coronary heart disease, heart failure, arterial hypertension, pneumopathy, renal failure, hepatopathy, obesity, rheumatological disease, immunosuppression inclusive HIV infection, cerebrovascular disease, active neoplastic disease and diabetes mellitus)	9

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Bennouar, 2020 Algeria	Prospective cohort	120 69.2 62.3 (Mean)	According to WHO criteria	100% Severe according to WHO guidelines	Hypocalcemia	< 2.20 mmol/L	At admission	1	Sex, age, acute kidney injury, cardiac injury, blood glucose, C-reactive protein levels, neutrophil–lymphocyte-ratio, lactate dehydrogenase, albumin and total cholesterol	7
Berni, 2021 Italy	Retrospective cohort	380 61.6 67.5 (Median)	Laboratory confirmed (details N.S.)	N.S	Hyponatremia, Hypernatremia	Hyponatremia: < 135 mmol/L Hypernatremia: > 145 mmol/L	At admission	1, 2, 3, 6, 8	Sex and age	8
De Carvalho, 2021 France	Retrospective cohort	296 53.7 68.4 (Mean)	RT-qPCR	N.S	Hyponatremia	< 135 mmol/L	Within 24 h of COVID-19 suspicion	1, 2, 3, 6, 7	Sex, age, tympanic temperature, diabetes, serum creatinine, ALT, lymphocyte count and oxygen flow rate at admission	7
Chen, 2020 China	Retrospective cohort	179 50.3 45 (Mean)	According to the criteria by National Health Commission of China	21% severe, 2% critical according to WHO guidelines	Hypokalemia	Mild hypokalemia: 3—3.5 mmol/L Severe hypokalemia: < 3 mmol/L	N.S	6, 7	N.A	6

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Frontera, 2020 USA	Retrospective cohort	4645 62.9 62.5	RT-qPCR	N.S	Hyponatremia	Mild hyponatremia: 130 – 134 mmol/L moderate hyponatremia: 121 – 129 mmol/L Severe hyponatremia: < 120 mmol/L	At admission	1, 3, 5, 6, 8	Sex, age, race, BMI, past medical history, admission laboratory abnormalities, admission SOFA score, renal failure, encephalopathy and mechanical ventilation	8

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Hirsch, 2021 USA	Retrospective cohort	9946 59.4 66.4 (Mean)	RT-qPCR	N.S	Hyponatremia, Hypernatremia	Mild hyponatremia: 130 – 135 mmol/L Severe hyponatremia: < 130 mmol/L Mild hypernatremia: 145 – 149 mmol/L Severe hypernatremia: ≥ 150 mmol/L	At admission	1, 6, 7	Sex, age, race, BMI, diabetes, hypertension, cardiovascular diseases, respiratory diseases, chronic kidney disease, chronic liver disease, cancer, oxygen saturation, systolic blood pressure, hemoglobin, lymphocyte, red cell distribution width, platelet, serum creatinine, bilirubin and albumin, CRP, serum ferritin	8
Hu, 2020 China	Retrospective cohort	1254 51.1 56 (Median)	According to the criteria by National Health Commission of China	15.9% severe, 6.7% critical, according to National Health Commission of China guidelines	Hyponatremia, Hypernatremia	Hyponatremia: < 135 mmol/L Hypernatremia: > 145 mmol/L	N.S	1, 3, 5, 6	N.A	5

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Hu, 2021* China	Retrospective cohort	206 48.1 53.7 (Mean)	RT-qPCR	4.9% severe, 2.4% critical, according to National Health Commission of China guidelines	Hyponatremia, Hypokalemia	Hyponatremia: < 135 mmol/L Hypokalemia: < 3.5 mmmol/L	At admission	Prolonged hospitalization	N.A	6
Liu, 2020 China	Retrospective cohort	107 48.6 68 (Median)	According to WHO interim guidance criteria	100% severe according to National Health Commission of China guidelines	Hypocalcemia	< 2.15 mmol/L	Within 24 h of admission	A composite of 1, 2 and 3, as well as 6 and 7	Sex, age, hypertension, diabetes, C-reactive protein, procalcitonin, interleukin-6 and D-dimer	7
Ma, 2020* China	Retrospective cohort	1160 52.2 46 (Median)	Laboratory confirmed (details N.S.)	N.S	Hyponatremia, Hypokalemia	N.S	N.S	Unfavourable outcome defined as mortality or disease progression from moderate to severe illness	Sex, age, BMI and first onset COVID-19 symptoms	8
Moreno, 2020 Spain	Retrospective cohort	306 57.8 65 (Median)	RT-qPCR	N.S	Hypokalemia	Mild hypokalemia: 3–3.5 mmol/L Severe hypokalemia: < 3 mmol/L	Within 72 h of hospital admission	1, 2, 3, 8	Age, sex, dyspnea, PaO2, lactate dehydrogenase, procalcitonin, CRP, BNP, lymphocyte count, opacity of lung x ray	9
Nasomsong, 2021 Thailand	Cross-sectional	36 63.9 42.6 (Mean)	RT-qPCR	N.S	Hypokalemia	< 3.5 mmol/L	At COVID-19 diagnosis	3, 6, 8	N.A	5

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Osman, 2021 Oman	Retrospective cohort	445 62 50.8 (Mean)	N.S	33.6% had an admission score of 5–8 based on the WHO Ordinal Scale for Clinical Improvement	Hypocalcemia	< 2.1 mmol/L	At admission	1, 2, 3, 4, 7, 8	N.A	5
Quilliot, 2020 France	Prospective cohort	300 60.7 68 (Median)	RT-qPCR and/or chest CT scans	36% were severe, 49.7% were critical according to WHO guidelines	Hypomagnesemia	< 0.75 mmol/L	5.29 ± 5.02 days after admission	2, 3	N.A	5
Raesi, 2021 Iran	Case–control	91 60.4 55.4 (Mean)	RT-qPCR	55.9% were severe according to WHO guidelines	Hypocalcemia	< 2.15 mmol/L	Within 24 h of admission	1, 2, 8	N.A	5

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Ruiz-Sánchez, 2020 Canada, Germany, China, Ecuador, Cuba, Italy, Spain	Retrospective cohort	4464 58 66 (Median)	RT-qPCR	All had pneumonia	Hyponatremia, Hypernatremia	Hyponatremia: < 135 mmol/L Hypernatremia: > 145 mmol/L	At admission	1, 8	Sex, age, hypertension, dyslipidemia, diabetes, obesity, smoking, chronic kidney disease, chronic liver disease, cardiovascular disease, cerebrovascular disease, chronic lung disease, cancer, immunosuppression, use of angiotensin-converting enzyme inhibitors/angiotensin-2-receptor antagonists, oxygen saturation, serum creatinine and type of pneumonia	9

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Sarvazad, 2020 Iran	Cross-sectional	58 56.9 62 (Median)	RT-qPCR and/or chest CT scans	N.S	Hyponatremia, Hypernatremia, Hypokalemia, Hyperkalemia, Hypomagnesemia, Hypermagnesemia	Hyponatremia: 121—134 mmol/L Hypernatremia: > 146 mmol/L Mild hypokalemia: 3—3.4 mmol/L Severe hypokalemia: < 3 mmol/L Hyperkalemia: > 5.5 mmol/L Mild hypomagnesemia: 0.52—0.7 mmol/L Severe hypomagnesemia: < 0.51 mmol/L Hypermagnesemia: > 1.07 mmol/L	At admission	2		5
Sun, 2020 China	Retrospective cohort	241 46.5 65 (Median)	RT-qPCR	69.3% severe, 10.5% critical, according to National Health Commission of China guidelines	Hypocalcemia	Mild hypocalcemia: 2.0—2.2 mmol/L Severe hypocalcemia: < 2.0 mmol/L	At admission	1, 3, 4, 5, 6, 7	N.A	6
Tezcan, 2020 Turkey	Retrospective cohort	408 46.1 54.3 (Mean)	RT-qPCR or according to Turkey's national guidelines	N.S	Hypocalcemia, Hyponatremia, Hypokalemia, Hypochloremia	N.S	At admission	1	Sex, age, disease severity, time between disease onset and hospitalization, comorbidities, pulmonary infiltrations, fever and hypoxemia during hospitalization	8

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Torres, 2021 Spain	Retrospective cohort	316 65 65 (Median)	RT-qPCR or clinical, radiologic and lab findings that are consistent with other COVID-19 patients	N.S	Hypocalcemia	< 2.12 mmol/L	Within 72 h of hospital admission	1, 2, 3, 6, 7	Sex, advanced life support, SpO_2/FiO_2, lymphocyte count, C-reactive protein, D dimer and potassium levels	7
Trecarichi, 2020 Italy	Retrospective cohort	50 57.1 80 (Mean)	Positive SARS-CoV-2 molecular test conducted on nasopharyngeal swab	52% severe, according to Italy National Institute of Health criteria	Hypernatremia	> 145 mmol/L	At admission	1	Lymphocyte count, cardiovascular disease excluding hypertension, interleukin-6 levels	6
Tzoulis, 2021 UK	Retrospective cohort	488 56.8 68 (Median)	RT-qPCR	N.S	Hyponatremia, Hypernatremia	Hyponatremia: < 135 mmol/L Hypernatremia: > 145 mmol/L	First 5 days of admission	1, 3	Sex, age, ethnicity, smoking status, number of co-morbidities, urea and C-reactive protein levels	8
Wu, 2020* China	Retrospective cohort	125 52.8 55 (Median)	Detection of SARS-CoV-2 RNA	1.6% were severe, defined as dyspnea, hypoxemia and/or lung infiltrates > 50%	Hyponatremia, Hypernatremia, Hypocalcemia, Hypokalemia, Hyperkalemia, Hypochloremia	Hyponatremia: < 136 mmol/L Hypernatremia: > 145 mmol/L Hypocalcemia: < 2.2 mmol/L Hypokalemia: < 3.5 mmol/L Hyperkalemia: > 5.1 mmol/L Hypochloremia: < 99 mmol/L	At admission	Prolonged hospitalization	Age and comorbidities	7
Zheng, 2021 China	Retrospective cohort	161 62.8 64 (Median)	RT-qPCR	All were ICU patients	Hypocalcemia	< 1.8 mmol/L	At admission	1	N.A	5

Table 1 (continued)

First author, year country	Study design	Total sample size % male average age	COVID-19 diagnosis method	COVID-19 baseline severity	Electrolyte imbalances studied	Definition of electrolyte imbalance	Timepoint of electrolyte measurement	Outcomes studied	Covariates	NOS score (out of 9)
Zhou, 2020* China	Retrospective cohort	127 N.S N.S	RT-qPCR	All had pneumonia	Hypocalcemia	< 2.2 mmol/L	Within 24 h of admission	Progression from mild/moderate infection to severe/critical infection	N.A	5

*Not included in meta-analyses; *NS* not stated; *NA* not applicable; 1, Mortality; 2, ICU admission; 3, Respiratory support; 4, Acute respiratory distress syndrome; 5, Acute kidney injury; 6, Serum creatinine; 7, C-reactive protein; 8, Hospitalization time

Sensitivity analyses excluding non-cohort studies did not change our findings substantially. A total of 14, 10, two studies and one study were conducted in Asia [21, 33, 37, 40–43, 45–47, 49, 50, 53, 54], Europe [12, 17, 19, 20, 34, 36, 38, 44, 51, 52], America [18, 39] and Africa[35], respectively. One study spanned across America, Asia and Europe [48]. When assessed using the Newcastle–Ottawa Scale, twenty and eight studies had a moderate and low risk of bias, respectively. Overall quality of evidence ranged from very low to moderate.

Definitions of electrolyte imbalances

Studies measured the respective electrolyte levels at hospital admission (15 studies), within 24 h (4 studies), 72 h (2 studies) or beyond 72 h of admission (2 studies). One study measured electrolyte levels at COVID-19 diagnosis and one study recorded the imbalance at any time during hospitalization [17, 45]. As some studies measured electrolyte levels beyond 24 h, [12, 19, 44, 51] we excluded them in sensitivity analyses. This did not did not alter our conclusions. We searched for but found no studies investigating dysphosphatemia in relation to COVID-19 outcomes.

Dysnatremia

Thirteen and ten studies investigated the association of hyponatremia and hypernatremia with the above specified COVID-19 clinical outcomes, respectively (Table 1) [12, 18, 20, 21, 33, 34, 36, 38–41, 43, 48, 49, 52]. Majority of studies defined hyponatremia and hypernatremia as having a serum sodium level of < 135 mmol/L or > 145 mmol/L, respectively. Two studies further stratified their sample based on dysnatremia severity [18, 39]. Three studies corrected their sodium measurements with glucose levels [12, 18, 36].

Dyskalemia

Nine and two studies investigated the association of hypokalemia and hyperkalemia with the same COVID-19 outcomes, respectively (Table 1) [17, 20, 21, 37, 41, 43–45, 49]. Majority of studies defined hypokalemia and hyperkalemia as having a serum potassium level of < 3.5 mmol/L or > 5.1 mmol/L, respectively. Three studies further stratified their sample based on hypokalemia severity [37, 44, 49].

Dyscalcemia

Ten studies investigated the association of hypocalcemia with the same COVID-19 clinical outcomes (Table 1) [20, 21, 35, 42, 46, 47, 50, 51, 53, 54]. Majority of the studies defined hypocalcemia as having a serum calcium level of < 2.20 mmol/L, with the exception of one study that

defined it as < 1.8 mmol/L [53]. There were no studies that investigated hypercalcemia.

Dysmagnesemia

Two studies investigated the association of dysmagnesemia including hypomagnesemia (2 studies) and hypermagnesemia (1 study) with ICU admission and respiratory support (Table 1). Hypomagnesemia and hypermagnesemia were defined as having a serum magnesium level of < 0.75 mmol/L or > 1.07 mmol/L, respectively [19, 49].

Dyschloremia

Two studies investigated the association of hypochloremia, defined as a serum chloride level of < 99 mmol/L, with prolonged hospitalization and mortality, respectively [20, 21].

Association of electrolyte imbalances with COVID-19 poor outcome

Overall poor outcome

Compared to the control group, participants with hyponatremia (OR = 2.08, 95% CI = 1.48–2.94, I^2 = 93%, N = 8), hypernatremia (OR = 4.32, 95% CI = 3.17–5.88, I^2 = 45%, N = 7) or hypocalcemia (OR = 3.31, 95% CI = 2.24–4.88, I^2 = 25%, N = 6) had, on average, significantly higher pooled odds of poor outcome, defined as a composite of mortality, ICU admission, respiratory support and ARDS (Fig. 2a). After adjustment, the associations were attenuated but remained significant for hyponatremia (aOR = 1.65, 95% CI = 1.09–2.51, I^2 = 91%, N = 5) and hypernatremia (aOR = 2.10, 95% CI = 1.80–2.44, I^2 = 0%, N = 3) (Fig. 2b). There was no significant association found for participants with hypokalemia (OR = 0.96, 95% CI = 0.62–1.51, I^2 = 0%, N = 4) or hypomagnesemia (OR = 1.43, 95% CI = 0.21–9.60, I^2 = 86%, N = 2) (Fig. 2a). Between-study heterogeneity was significant for hyponatremia (I^2 = 91%) and hypomagnesemia (I^2 = 86%) but expected due to the pooling of different clinical outcomes. As ICU admission criteria differ across countries, we performed sensitivity analyses excluding ICU admission, which did not change our findings. In studies excluded from meta-analysis, Ma et al. reported participants with hyponatremia and/or hypokalemia having an increased odds of unfavourable outcome, defined as mortality or disease progression from moderate to severe (OR = 19.44, 95% CI = 11.47–32.96), after adjusting for sex, age, BMI and first-onset COVID-19 symptoms [43]. Zhou et al. reported participants with low calcium levels tended to progress to a severe or critical infection [54].

Mortality

Looking at the specific poor outcome composites, participants with hyponatremia (OR = 2.15, 95% CI = 1.46–3.17, I^2 = 94%, N = 7), hypernatremia (OR = 5.60, 95% CI = 3.57–8.78, I^2 = 73%, N = 6) or hypocalcemia (OR = 2.72, 95% CI = 1.34–5.51, I^2 = 64%, N = 6) had, on average, significantly higher pooled odds of mortality compared to the control group (Fig. 3a). The adjusted association remained significant for hyponatremia (aOR = 1.48, 95% CI = 1.03–2.12, I^2 = 75%. N = 7) and hypernatremia (aOR = 3.32, 95% CI = 1.79–6.15, I^2 = 82%, N = 5) (Fig. 3b). There were insufficient studies that calculated the adjusted association for hypocalcemia. There were no significant associations found for participants with hypokalemia (OR = 0.92, 95% CI = 0.57–1.46, I^2 = 0%).

ICU admission

Compared to the control group, participants with hyponatremia (OR = 2.19, 95% CI = 1.36–3.52, I^2 = 44%, N = 4) or hypocalcemia (OR = 2.23, 95% CI = 1.60–3.11, I^2 = 6%, N = 3) had on average, significantly higher odds of ICU admission. There were no significant associations for hypernatremia (OR = 3.72, 95% CI = 0.14–99.22, I^2 = 82%, N = 3), hypokalemia (OR = 1.35, 95% CI = 0.25–7.30, I^2 = 90%, N = 3) or hypomagnesemia (OR = 1.43, 95% CI = 0.21–9.61, I^2 = 86%, N = 2) (Fig. 4).

Respiratory support

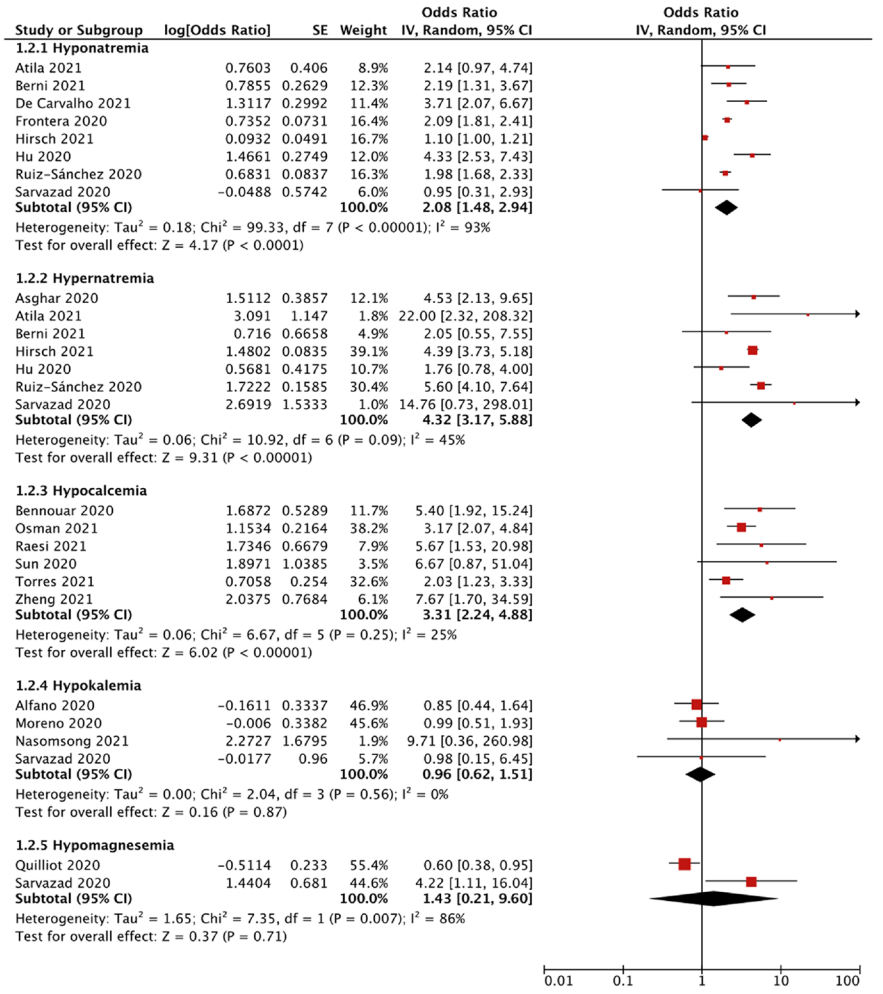
A total of 12 studies reported the use of respiratory support, defined as the need for either invasive ventilation or non-invasive ventilation [12, 33, 34, 36, 38–40, 44–46, 50, 51]. Compared to the control group, participants with hyponatremia (OR = 2.16, 95% CI = 1.91–2.45, I^2 = 0%, N = 5), hypernatremia (OR = 3.24, 95% CI = 1.24–8.50, I^2 = 70%, N = 4), hypocalcemia (OR = 2.99, 95% CI = 2.16–4.14, I^2 = 0%, N = 3) or hypokalemia (OR = 5.69, 95% CI = 2.81–11.54, I^2 = 0%, N = 2) had on average, a significantly higher odds of requiring respiratory support (Fig. 5a). The adjusted association remained significant for hyponatremia (aOR = 1.88, 95% CI = 1.56–2.26, I^2 = 0%, N = 2) (Fig. 5b).

Performance and prognostic value of electrolyte imbalances in predicting unadjusted odds of poor outcome

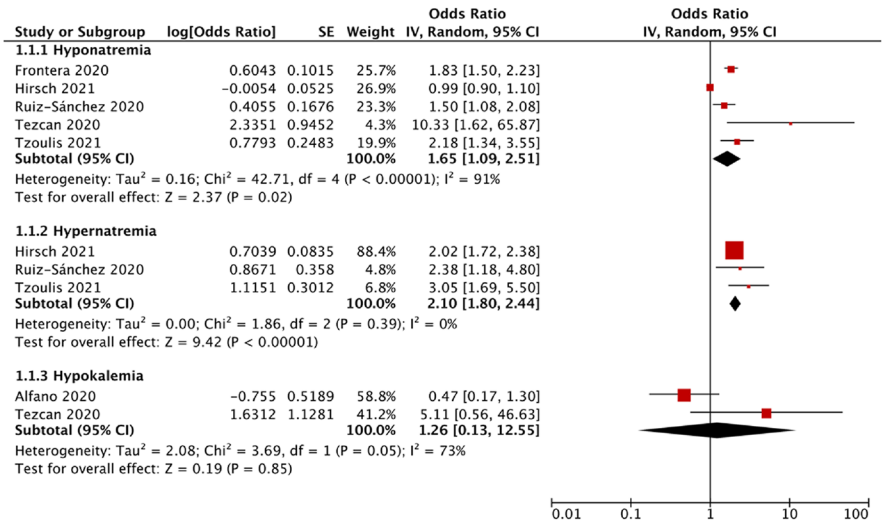
Based on the SROC curves generated for each electrolyte imbalance, hypernatremia (AUC = 0.80, 95% CI = 0.76–0.83) and hypocalcemia (AUC = 0.71, 95% CI = 0.67–0.75) performed adequately, with AUC > 0.70.

Fig. 2 Forest plot showing the (**a**) unadjusted and (**b**) adjusted association between electrolyte imbalances with poor outcome*, stratified by the type of electrolyte imbalance. Black diamonds are the estimated pooled odds ratios for each random-effects meta-analysis; red boxes reflect the relative weight apportioned to studies in the meta-analysis.*Poor outcome Is defined as a composite of mortality, ICU admission, respiratory support and acute respiratory distress syndrome

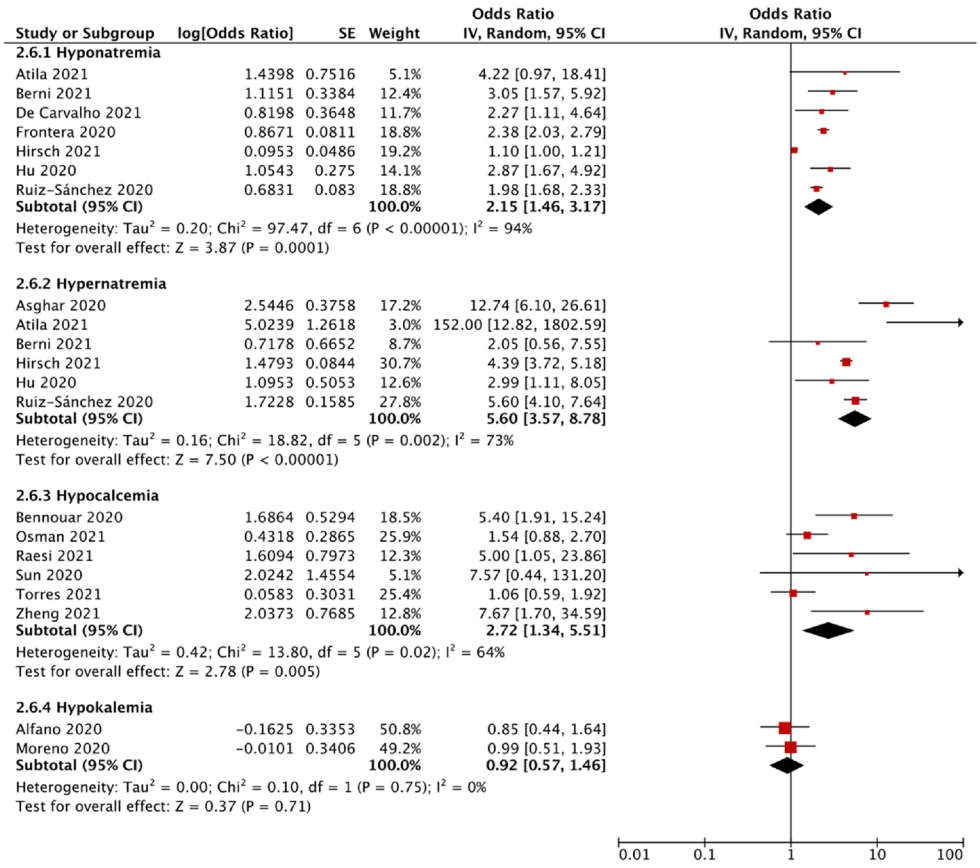
a Poor outcome, unadjusted association, stratified by the type of electrolyte imbalance



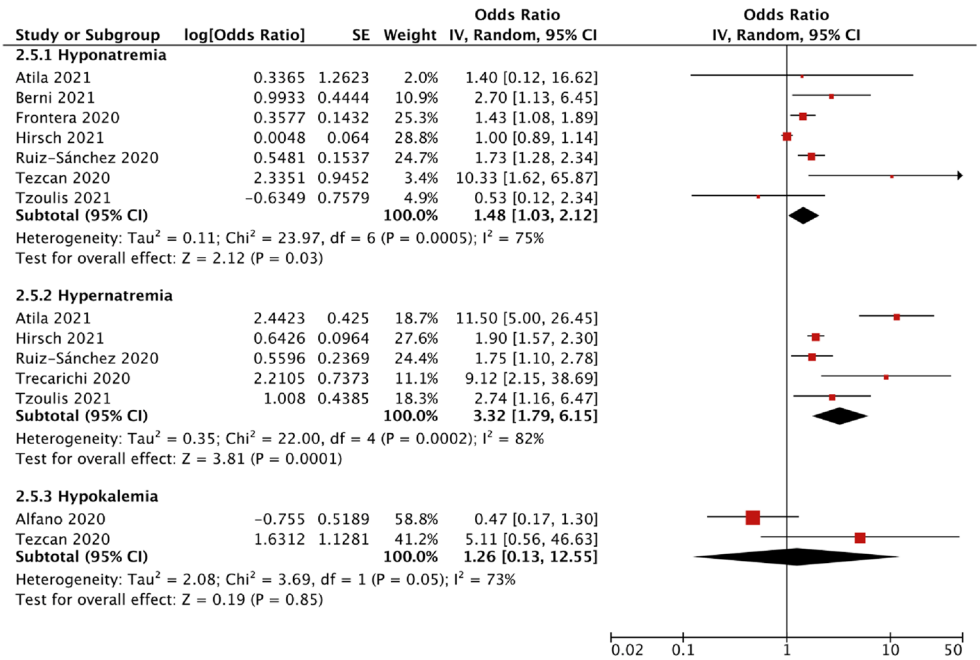
b Poor outcome, adjusted association, stratified by the type of electrolyte imbalance



a Mortality, unadjusted odds ratios, stratified by the type of electrolyte imbalance



b Mortality, adjusted odds ratios, stratified by the type of electrolyte imbalance



◂**Fig. 3** Forest plot showing the pooled unadjusted odds ratios (**a**) and adjusted odds ratios (**b**) of the association between electrolyte imbalances and mortality, stratified by the type of electrolyte imbalance. Black diamonds are the estimated pooled odds ratios for each random-effects meta-analysis; blue/red boxes reflect the relative weight apportioned to studies in the meta-analysis

In particular, hypernatremia was 97% specific (95% CI = 0.94–0.98; LR + 4.0) for a poor outcome with low sensitivity (0.13, 95% CI = 0.07–0.22; LR – 0.90), while hypocalcemia was 76% sensitive (95% CI = 0.53–0.90; LR – 0.44) for a poor outcome with low specificity (0.53, 95% CI = 0.26–0.78; LR + 2.0) (Fig. 6a and Fig. 7a). In contrast, hyponatremia and hypokalemia performed inadequately (AUC < 0.70) (Supplemental Results, Online Resource). Visual inspection of coupled funnel plots did not indicate a clear threshold effect (Fig. 6c and Fig. 7c).

Assuming a 25% pre-test probability of progression to severe COVID based on published estimates in the general population infected with COVID [55–57], the presence of hypernatremia (LR + 4.0) would be associated with a PPV of 55%, or a 55% post-test probability of progression to severe COVID based on Fagan's nomogram (Fig. 6b). Similarly, the absence of hypocalcemia (LR- 0.44) would be associated with a 13% post-test probability of severe COVID, or a NPV of 87% (Fig. 7b).

Association of electrolyte imbalances with Acute Kidney Injury (AKI) and serum creatinine levels

Participants with hyponatremia had a significantly increased odds ratio (OR = 1.63, 95% CI = 1.26–2.10, I^2 = 13%, N = 2) (Supplemental Figure S4, Online Resource) compared to the controls. In studies excluded from the meta-analysis, Sun et al. and Alfano et al. reported no significant association for hypocalcemia (OR = 4.67, 95% CI = 0.59–36.47) and hypokalemia (OR = 0.88, 95% CI = 0.49–1.60), respectively [12, 17, 50]. Additionally, Tzoulis et al. concluded that sodium values were not associated with the risk for AKI, although sufficient data was not provided. Compared to the control group, there was no significant difference in serum creatinine levels for dysnatremia, hypocalcemia and hypokalemia (Supplemental Figure S5a, Online Resource).

Association of electrolyte imbalances with C-reactive protein (CRP) levels

While patients with hyponatremia (MD = 27.92 mg/L, 95% CI = 16.97–38.86 mg/L, I^2 = 56%, N = 3), hypocalcemia (MD = 10.18 mg/L, 95% CI = 7.15–13.20 mg/L, I^2 = 0%, N = 4) and hypokalemia (MD = 5.82 mg/L, 95% CI = 0.26–11.37 mg/L, I^2 = 0%, N = 2) showed significantly higher CRP levels as compared to the control group, patients with hypernatremia (MD = 57.16 mg/L, 95% CI = – 27.12– 141.45 mg/L, I^2 = 98%, N = 3) showed no significant difference (Supplemental Figure S5b, Online Resource).

Association of electrolyte imbalances with Interleukin-6 (IL-6) levels

In studies excluded from meta-analyses, Berni et al. reported significantly higher (p-value < 0.001) baseline IL-6 levels in hyponatremic participants as compared to the control group. There was no significant difference in IL-6 levels between hypernatremic and normonatremic participants (p-value = 0.395) [36]. Liu et al. reported a significantly higher IL-6 levels (p-value = 0.0276) in hypocalcemic participants as compared to the control group [42].

Discussion

In this systematic review and meta-analysis of 28 observational studies comprising a combined cohort of 26,897 participants with COVID-19, we found that hyponatremia, hypernatremia and hypocalcemia were associated with a twofold, fourfold and threefold increased odds of poor clinical outcome, defined as a composite of mortality, ICU admission, ARDS and respiratory support. Participants with hyponatremia had a 63% increased odds of AKI. Hypernatremia and hypocalcemia performed adequately with an AUC score of more than 0.7. Hypernatremia had a specificity of 97% and hypocalcemia had a sensitivity of 76%, suggesting their predictive utility for a poor clinical outcome. The association of hypernatremia and poor outcome could not be explained by differences in CRP and IL-6 compared to normonatremic controls, thus highlighting its potential use as a unique clinical indicator of disease progression. These associations were robust to pre-specified sensitivity analyses and attenuated but remained significant upon adjustment for covariates. Hypokalemia, hypomagnesemia and hypochloremia was not significantly associated with a poor outcome and AKI.

To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis looking at multiple electrolyte imbalances and its associations with a poor clinical outcome. Our findings are consistent with recent meta-analyses that also reported significantly higher odds of poor outcome and severe infection amongst hyponatremic and hypocalcemic participants, respectively [15, 16]. We further add value to these studies by including ARDS and AKI as additional outcomes as well as by investigating additional electrolyte imbalances—hypernatremia, hypokalemia, hypochloremia and hypomagnesemia.

Legend: Black diamonds are the estimated pooled odds ratios for each random-effects meta-analysis; blue boxes reflect the relative weight apportioned to studies in the meta-analysis

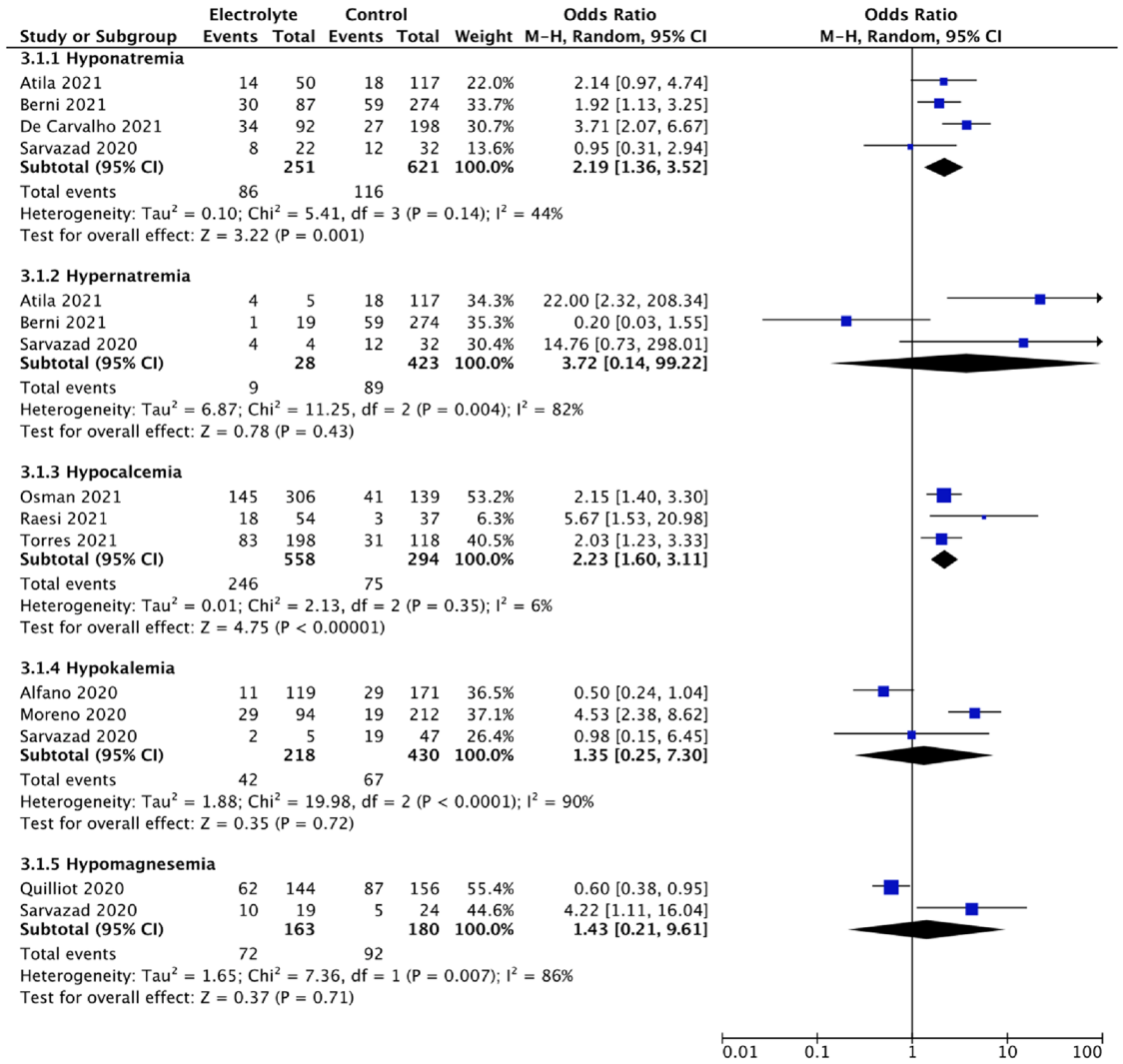
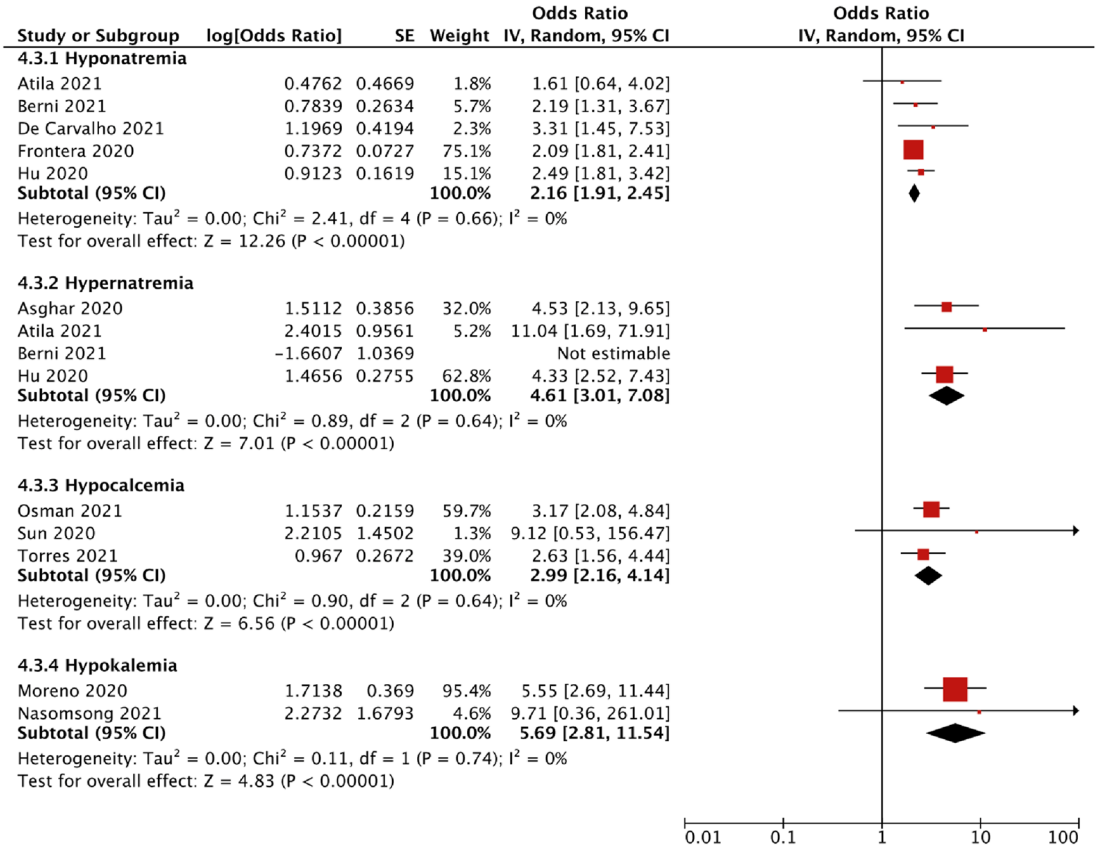


Fig. 4 Forest plot showing the unadjusted association between electrolyte imbalances with ICU admission, stratified by the type of electrolyte imbalance. Black diamonds are the estimated pooled odds ratios for each random-effects meta-analysis; blue boxes reflect the relative weight apportioned to studies in the meta-analysis

These associations may be confounded by the underlying disease process—either as part of a non-specific septic response or via mechanisms specific to COVID-19. Marked elevation of inflammatory cytokines have been described in COVID-19, manifesting in severe cases as cytokine storm [58]. This increase in cytokines such as IL-6 can result in syndrome of inappropriate secretion of antidiuretic hormone (SIADH) either through directly stimulating non-osmotic release of anti-diuretic hormone (ADH) or through injuring alveolar tissues which then triggers the hypoxic pulmonary vasoconstriction pathway [59–61]. Other potential mechanisms that can lead to increased ADH secretion include that of volume depletion from reduced oral intake or gastrointestinal losses. These processes lead to increased water retention, resulting in hyponatremia. In a small observational study of 26 COVID-19 patients by Berni et al. it was noted that IL-6 was inversely correlated with sodium levels and sodium was directly correlated with P/F ratio [59]. The correlation between active inflammatory processes and electrolyte imbalances is also observed in our results where hyponatremia, hypocalcemia and hypokalemia were significantly associated with higher baseline CRP levels, which itself is an established marker for inflammation and disease severity. [62] Electrolyte imbalances may also be a general

a Respiratory support, unadjusted association, stratified by the type of electrolyte imbalance



b Respiratory support, adjusted association

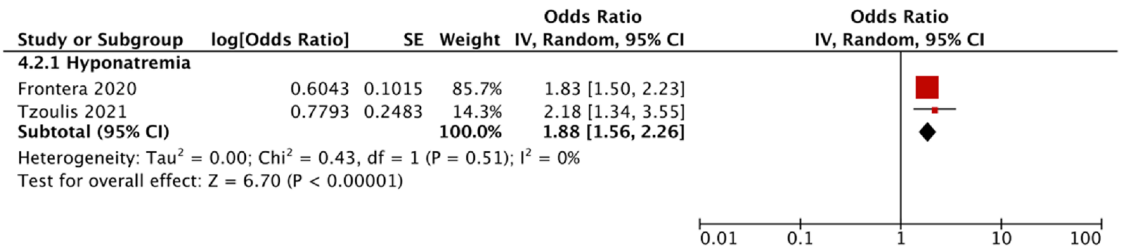
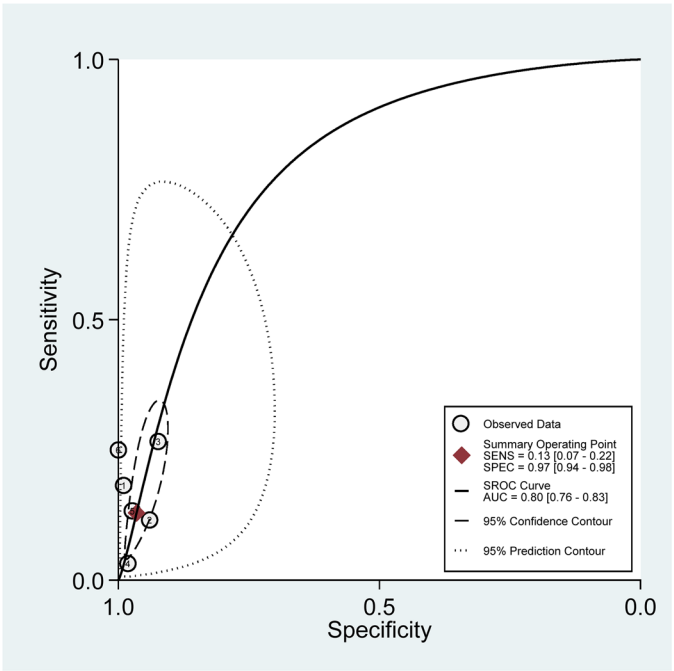


Fig. 5 Forest plot showing the **a** unadjusted and **b** adjusted association between electrolyte imbalances and respiratory support, stratified by the type of electrolyte imbalance. Black diamonds are the estimated pooled odds ratios for each random-effects meta-analysis; red boxes reflect the relative weight apportioned to studies in the meta-analysis

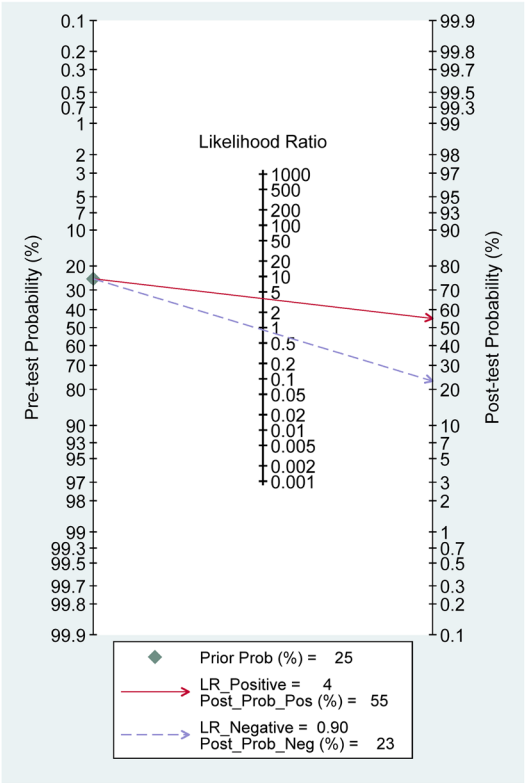
indication of kidney impairment as AKI has been reported to be prevalent in patients hospitalized with COVID-19 [63].

However, in a number of the included primary studies, the association of some electrolyte imbalances with poorer outcome in COVID-19 remained significant even after adjusting for inflammatory biomarkers. Furthermore, our study found that CRP levels were not significantly different between hypernatremic and normonatremic patients, which could suggest that the poor outcome associated with hypernatremia may be unrelated to the systemic inflammatory response. It has been proposed that hypernatremia can be caused by increased angiotensin II activity secondary to SARS-CoV-2-induced down regulation of ACE2 receptors in the proximal tubule after viral entry. [64] While hypernatremia in COVID disease likely represents dehydration from insensible water losses such as fever and tachypnea, it is not clear if dehydration alone can explain the observed poor prognosis, as a recent case series documented persistent

a Summary Receiver Operator Characteristic Curve of hypernatremia and poor outcome



b Fagan plot of hypernatremia and poor outcome



c Coupled funnel plot of hypernatremia and poor outcome

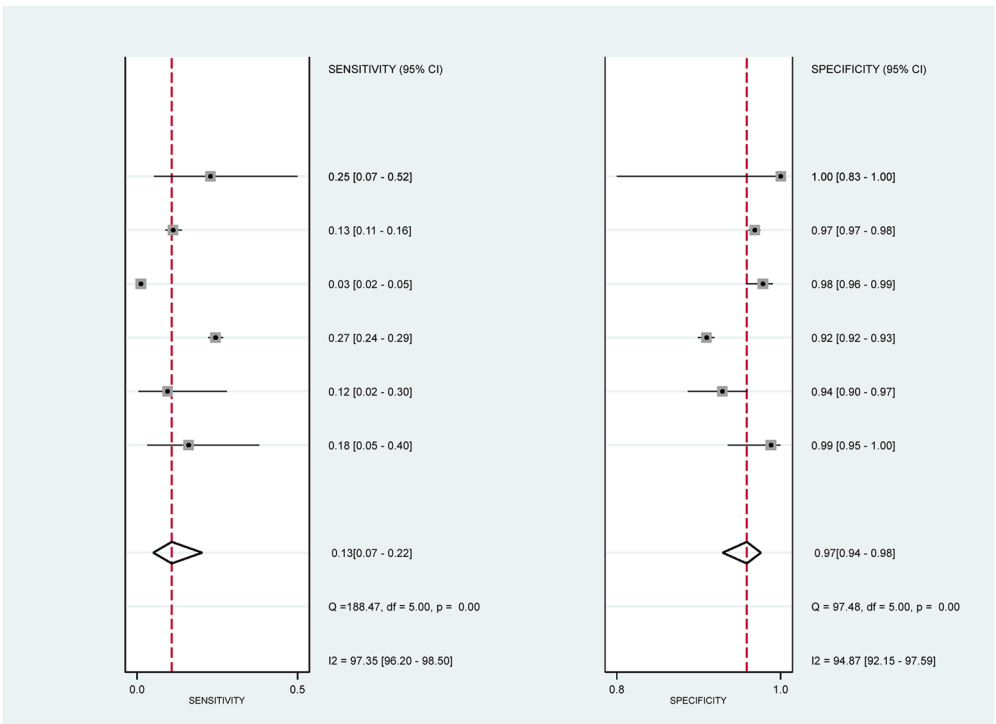


Fig. 6 **a** Summary receiver operator characteristic curve, **b** Fagan plot and **c** Coupled funnel plot of hypernatremia in predicting poor outcome

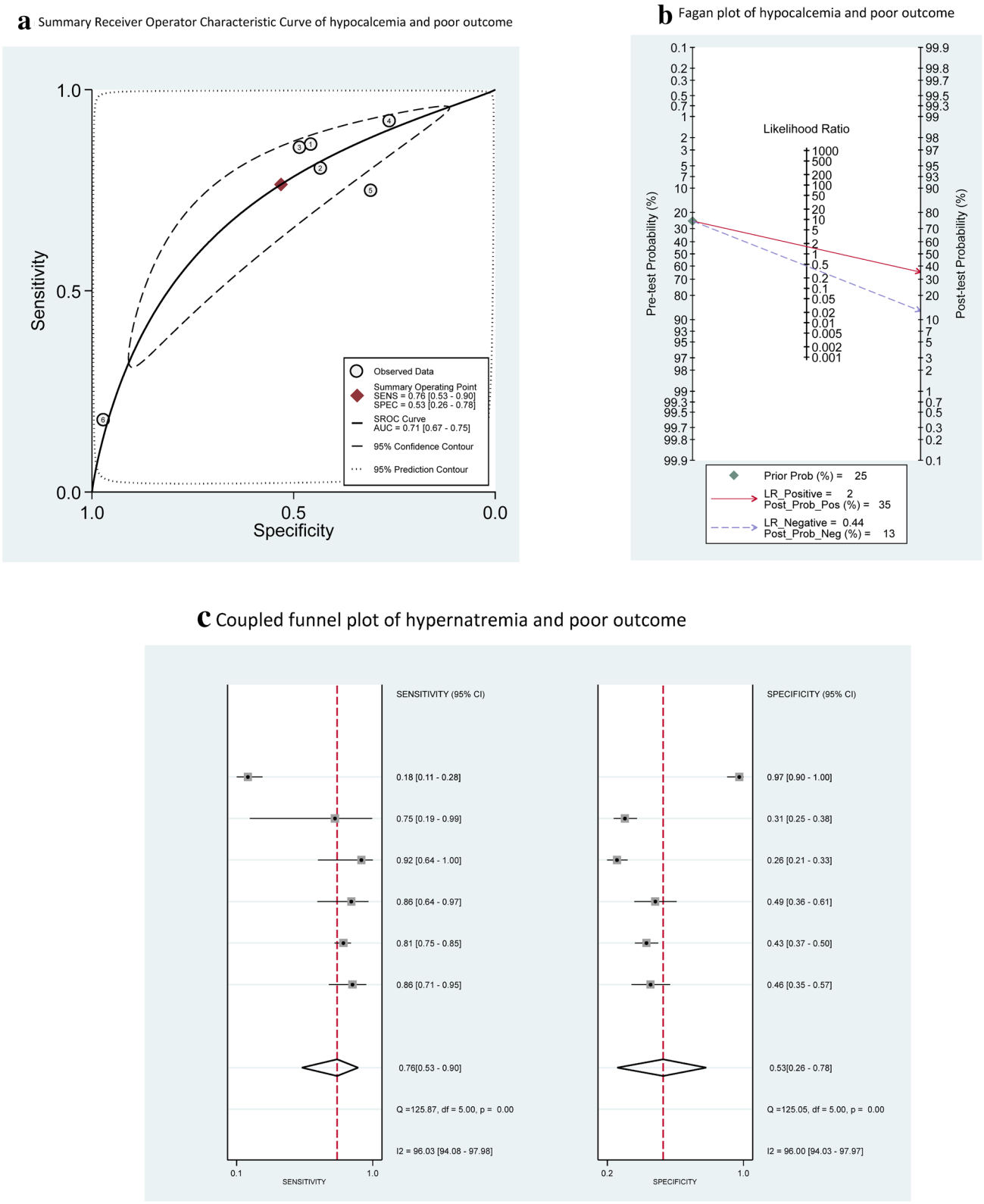


Fig. 7 **a** Summary receiver operator characteristic curve, **b** Fagan plot and **c** Coupled funnel plot of hypocalcemia in predicting poor outcome

hypernatremia despite adequate infusion of free water in 6 patients. [65] This could be consistent with a COVID-19-specific mechanism for hypernatremia rather than simple dehydration.

Electrolyte imbalances are a manifestation of the physiological derangement caused by COVID-19 infection though they likely do not exacerbate the disease process. These findings suggest a role for hyponatremia, hypocalcemia and hypernatremia to be used in the risk stratification, prognostication and clinical decision-making in the treatment of patients with COVID-19. As conventional biomarkers like IL-6 and CRP are expensive to test especially in rural healthcare centres, the measurement of electrolytes which is cheaper and more readily available, can serve as a valuable tool to triage scarce healthcare in these areas. Hypernatremia may be a clinically useful indicator of progression to a poor outcome due to its high LR + of 4.0 resulting in a PPV of 55% in the general population of COVID patients.

The strengths of our study lie in the large number of studies analyzed looking at a broad range of electrolyte imbalances. None of our included studies had a high risk-of-bias according to the NOS scale, increasing the quality of findings. We employed a rigorous methodology according to international guidelines pre-specified in our protocol. Additionally, we pooled maximally adjusted estimates to account for potential confounders and assessed the prognostic value of each electrolyte imbalance by calculating their overall sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and area the under curve scores. Our findings were also robust to pre-specified subgroup and sensitivity analyses.

Limitations

Firstly, there were insufficient studies looking at the same outcome and same electrolyte imbalance for a statistically-powered meta-regression and funnel plot for the assessment of publication bias. We were unable to conduct some meaningful subgroup analyses to explain heterogeneity, but this potentially could be explained by the differing impacts of the pandemic on different healthcare systems globally, as well as their varying management strategies. This may be confirmed using future studies for subgroup analyses stratified by country or region. Secondly, there is heterogeneity in the severity of disease at the time when data was collected in the studies. We are unable to separately analyse patients who were admitted with a severe disease requiring intensive care from those who deteriorate subsequently during hospitalization. This potentially introduces a source of bias as participants who had more severe disease from the start are more likely to have a poorer outcome. Nonetheless, we mitigated this by marking down the study's representativeness on the NOS scale. Thirdly, our results do not allow us to interpret the causality of the association as it is unclear whether the electrolyte imbalances further aggravate participants with COVID-19 or whether it's just a general indication of poor health. Furthermore, the temporal sequence between COVID-19 diagnosis and the presence of electrolyte imbalances is hard to establish. Studies also did not monitor the progression of these imbalances throughout the length of hospital stay. Additionally, we acknowledge that respiratory infections such as COVID-19 commonly result in dehydration because of pyrexia or tachypnea and that our association could be confounded by abnormalities such as blood volume and osmolarity. Not all our studies assessed the specific etiology of the electrolyte imbalance, whether it is hypovolemic, euvolemic or hypervolemic which could potentially influence management.

Conclusion

In this multi-adjusted observational meta-analysis of 26,897 participants with COVID-19, hyponatremia, hypernatremia and hypocalcemia were associated with a two-fold, fourfold and threefold increased odds of poor clinical outcome, respectively. We also observed that hypernatremia had a specificity of 97% independent of CRP and IL-6 levels, highlighting its potential use as a unique clinical indicator of poor disease progression. Our findings are pertinent to triaging and risk assessment of COVID-19 patients, especially since severe COVID-19 patients continue to take up significant healthcare resources. Future interventional studies and randomized controlled trials should look at whether correcting for these electrolyte imbalances via resuscitation strategies, fluid replacement or supplements can mitigate the odds of poor outcome.

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Author contributions Concept and design (HJJMDS, AZQC, BKJT, CBT), data collection (HJJMDS, AZQC), data analysis (HJJMDS, AZQC, BKJT, CBT), data interpretation (all authors), manuscript writing (HJJMDS, AZQC), critical revision (all authors), overall supervision (AK), approval for publication (all authors).

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Availability of data and materials Additional data may reasonably be requested from the corresponding author.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Research involving human participants and/or animals This article is a systematic review and meta-analysis, and hence does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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