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REVIEW

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Epidemiology, prognosis and management of potassium disorders in Covid-19

Maryam Noori[1] | Seyed A. Nejadghaderi[2,3] | Mark J. M. Sullman[4,5] | Kristin Carson-Chahhoud[6,7] | Ali-Asghar Kolahi[8] | Saeid Safiri[9,10]

[1]School of Medicine, Student Research Committee, Iran University of Medical Sciences, Tehran, Iran

[2]Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

[3]Systematic Review and Meta-analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[4]Department of Social Sciences, University of Nicosia, Nicosia, Cyprus

[5]Department of Life and Health Sciences, University of Nicosia, Nicosia, Cyprus

[6]Australian Centre for Precision Health, University of South Australia, Adelaide, SA, Australia

[7]School of Medicine, University of Adelaide, Adelaide, SA, Australia

[8]Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[9]Social Determinants of Health Research Center, Department of Community Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[10]Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence
Saeid Safiri and Ali-Asghar Kolahi, Social Determinants of Health Research Center, Tabriz University of Medical Sciences, Golgasht St, Attar Neishabouri Ave, Tabriz 5142954481, Iran; Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Koodakyar Ave, DaneshjuBlvd, Velenjak, Tehran, Iran.
Email: safiris@tbzmed.ac.ir and a.kolahi@sbmu.ac.ir

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Abstract

Coronavirus disease (Covid-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently the largest health crisis facing most countries. Several factors have been linked with a poor prognosis for this disease, including demographic factors, pre-existing comorbidities and laboratory parameters such as white blood cell count, D-dimer, C-reactive protein, albumin, lactate dehydrogenase, creatinine and electrolytes. Electrolyte abnormalities particularly potassium disorders are common among Covid-19 patients. Based on our pooled analysis, hypokalemia and hyperkalemia occur in 24.3% and 4.15% of Covid-19 patients, respectively. Potassium level deviation from the normal range may increase the chances of unfavorable outcomes and even death. Therefore, this article reviewed the epidemiology of potassium disorders and explained how hypokalemia and hyperkalemia are capable of deteriorating cardiac outcomes and the prognosis of Covid-19 for infected patients. The article finishes by highlighting some important considerations in the management of hypokalemia and hyperkalemia in these patients.

KEYWORDS
Covid-19, hypokalemia, review, SARS-CoV-2, serum potassium

Abbreviations: ACE2, Angiotensin-converting enzyme 2; ADH, Antidiuretic hormone; AKI, Acute kidney injury; CKD, Chronic kidney disease; CK-MB, Creatine kinase-myocardial band; Covid-19, Coronavirus disease; CRRT, Continuous renal replacement therapy; CVD, Cardiovascular disease; DKA, Diabetic ketoacidosis; ECG, Electrocardiogram; EVD, Ebola virus disease; ICU, Intensive care units; IHD, Intermittent hemodialysis; IMV, Invasive mechanical ventilation; MERS-CoV, Middle East respiratory syndrome coronavirus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PVN, Paraventricular nucleus; RAAS, Renin angiotensin aldosterone system; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SD, Standard deviation; SON, Supraoptic nucleus; TdP, Torsades de Points; WHO, World Health Organization..

1 | INTRODUCTION

In December 2019, an outbreak of an unknown origin respiratory illness in Wuhan City, Hubei Province, China, led to the identification of a new type of beta coronavirus genus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] On 11 February 2020, the World Health Organization (WHO) named the disease coronavirus disease 2019 (Covid-19) which is characterized by its high contagiousness, infectivity, and an asymptomatic incubation period,[2,3] resulting in more than 162 million confirmed cases and over 3.3 million deaths across the world, up to 17 May 2021.[4]

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus and the seventh confirmed coronavirus that is able to infect humans.[5] Two other members of this family are the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), which share 79% and 50% of their nucleotide identity with SARS-CoV-2, respectively.[5] Unlike these two viruses, SARS-CoV-2 is characterized by a lower mortality rate, but the absolute number of deaths is remarkably high.[4]

Covid-19 has a broad clinical spectrum of severity, ranging from asymptomatic infection and mild flu-like symptoms, in 80% of infected individuals, to severe and critical clinical presentations in 20%.[6] Aside from affecting the respiratory system, Covid-19 also has extra-pulmonary manifestations, which can affect the kidneys, digestive tract, heart and nervous system.[7] Older patients, males and those with preexisting comorbidities, such as diabetes, cardiovascular disease (CVD) and chronic kidney disease (CKD), are more likely to be infected with the virus.[8,9]

Recent studies have reported a high prevalence of electrolyte disorders in patients with SARS-CoV-2 infection, including sodium, potassium, chloride and calcium abnormalities.[10–13] There are many potential reasons for these electrolyte changes, which may result from prolonged hospitalization and the administration of multiple medications, changes in eating habits, multi-organ failure, drug-related side effects, fever, sweating and hyperventilation.[14] Electrolyte disorders are not only a common manifestation in Covid-19 patients, but are also positively associated with severe clinical outcomes.[10,11,13,15]

Potassium disorders are one of the most common electrolyte abnormalities among confirmed Covid-19 cases.[16–18] Both high and low serum potassium levels have been found to be important factors that independently affect disease prognosis.[13,19–21] Identifying the reason for potassium homeostasis impairment and attempting to resolve this may improve the clinical outcomes of infected patients. Therefore, this article is a review of the currently available literature regarding epidemiology, etiologies, outcomes and some points on the management of potassium abnormalities in Covid-19 patients.

2 | MATERIALS AND METHODS

The guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement was used for retrieving the results related to estimate the frequency of hypokalemia and hyperkalemia in patients with Covid-19.[22]

2.1 | Search strategy

The literature search was performed using electronic databases of PubMed and Scopus, as well as Google scholar search engine up to 1 March 2021 for identifying the articles that discussed potassium disorders in patients with Covid-19. Our query was (hypokalemia OR hypokaleamia OR hypokalaemia OR hyperkalemia OR hyperkaleamia OR hyperkalaemia OR potassium disorder) and (Covid-19 OR SARS-CoV-2 OR 2019-nCoV). No search filters on any fields such as article type, publication date, and language were implemented. To avoid missing relevant studies, backward and forward citation searching were implemented.

2.2 | Screening and eligibility

The yield of search was combined in EndNote X8.0 (Clarivate Analytics, Philadelphia, PA, USA) reference manager software and duplicate reports were removed. Title and abstract of final records were initially screened and relevant articles were potentially extracted. Full-text of selected publications were carefully assessed according to the inclusion and exclusion criteria. The screening and review processes were conducted independently by two reviewers (M.N. and S.A.N.). Discrepancies were resolved through consulting with a third reviewer (S.S.) to reach a consensus.

We included studies that met the following criteria: (1) studies reporting the prevalence of potassium abnormalities in patients with Covid-19; (2) studies reporting the prognosis and complications of potassium abnormalities in patients with Covid-19; (3) studies reporting how to manage the potassium abnormalities in patients with Covid-19. Studies were excluded if were conducted in a specific population such as, pregnant women, children, patients with epilepsy and other groups.

2.3 | Data extraction

The data extraction was performed by two independent reviewers (M.N. and S.A.N.) using standardized forms in Excel spreadsheets, which included the name of first author, date of publication, name of country, date of patients' enrolment, number of included patients, gender, mean age, definition of hypokalemia and hyperkalemia, number of patients developed potassium disorders, prognosis and complication of potassium disorders and methods for managing the potassium disorders.

2.4 | Statistical analysis

We used meta-analysis of proportions to generate pooled estimates and their 95% confidence intervals (95% CIs) for the prevalence of hypokalemia and hyperkalemia in patients with Covid-19. I2 statistic was used to evaluate heterogeneity between studies. In the case of little evidence of heterogeneity (i.e. $I^2 \leq 40\%$), a fixed-effect model was used to pool the proportions; otherwise, a random-effect model was used. All the analysis was conducted using Metaprop commend in STATA software, version 15.0 (STATA Corp, LLC.).

3 | POTASSIUM DISORDER: PREVALENCE AND ETIOLOGIES

Electrolyte balance keeps the internal environment in an optimal state, which is essential for general functioning and homeostasis. Sodium is the major cation in extracellular fluid, whereas potassium is the most abundant cation in the intracellular fluid, playing a vital role in numerous physiological processes.[23] Because an appropriate potassium balance is necessary for survival, several intra- and extrarenal mechanisms are involved in maintaining the serum concentration within a narrow range (3.5–5.0 mmol/L).[24] Potassium levels below 3.5 mmol/L and above 5 mmol/L are defined as hypokalemia and hyperkalemia, respectively.[25]

Generally, the etiology of decreased and increased serum potassium levels are multifactorial.[26] Hypokalemia may result from a reduction in potassium intake, the movement of potassium from extracellular to intracellular fluids, and excessive potassium loss through urine or the gastrointestinal tract.[26] Diuretic use and subsequently increased urinary potassium loss is a common cause of hypokalemia.[26] In contrast, hyperkalemia is more likely to be associated with impaired renal function and the use of medications, such as renin angiotensin aldosterone system (RAAS) inhibitors and potassium sparing diuretics, which avoid renal potassium excretion.[26]

Potassium balance disorders are common medical problems among hospitalized patients across disciplines.[27–32] The incidence of hypokalemia in hospitalized patients is up to 21% and from 2% to 3% in outpatients,[27,28,33] while hyperkalemia is less common, occurring in up to 3.3% of hospitalized patients and nearly 1% of outpatients.[30–33] Although, potassium disorders are often the consequence of an underlying disease, it can also be iatrogenic, such that one in six hospitalized patients with hypokalemia will subsequently develop hyperkaliemia, while correcting potassium levels, which highlights the need for close potassium monitoring in clinical settings.[34]

4 | POTASSIUM DISORDERS AND INFECTIOUS DISEASES

In order to determine the prevalence of hypokalemia in hospitalized patients with infectious diseases, Widodo et al. designed a cross-sectional study at Cipto Mangunkusumo General Hospital in Jakarta, Indonesia.[35] Out of 105 patients who were enrolled in this study, dengue fever was the most common infectious disease.[35] The frequency of hypokalemia among the hospitalized patients was 23% on admission which increased to 37% during hospitalization.[35] Nausea, vomiting, and anorexia were possible reasons for inadequate dietary intake and subsequent hypokalemia.[35] Tissue breakdown and potassium release during infectious diseases can mitigate low potassium levels, that is why most cases developed mild hypokalemia in this study.[35]

Similarly, another study reviewing clinical manifestations and management of Ebola virus disease (EVD) was conducted on 27 infected participants.[36] The prevalence of hypokalemia was 37% on admission and 67% during hospitalization.[36] Furthermore, hypokalemia was not isolated and it was associated with other electrolyte abnormalities such as hyponatremia, hypocalcemia and hypomagnesemia.[36] Close electrolyte monitoring and correction of its abnormalities along with other medical care improved survival of patients with EVD.[36]

HIV positive patients are at increased risk of developing hyperkalemia.[37] Trimethoprim-sulfamethoxazole which is usually given in high dose for *Pneumocystis jirovecii* pneumonia in immunocompromised patients is an important cause of hyperkalemia.[38] Elevated serum potassium levels above 5 mmol/L was reported in 24% and 48% of HIV-infected patients receiving low- and high-dose trimethoprim-sulfamethoxazole, respectively, such that 14% required therapeutic intervention for addressing the complications of hyperkalemia.[38]

4.1 | Serum potassium in SARS-CoV and MERS-CoV infections

Few studies have measured serum potassium levels in SARS-CoV patients, but hypokalemia seems to be a common presentation.[39–43] In a study investigating the clinical manifestations of 62 probable SARS-CoV cases in Vietnam, Vu and colleagues reported a hypokalemia prevalence rate of 14.8%.[40] However, there was no evidence of hyperkalemia among these patients.[40] Moreover, Booth et al. designed a study to describe the clinical characteristics and short-term outcomes of SARS-CoV.[41] Of the 144 patients diagnosed with suspected SARS-CoV, the frequency of hypokalemia was 26% at admission and 43% during hospitalization.[41] In addition to hypokalemia, other electrolyte abnormalities, such as hypocalcemia, hypomagnesemia and hypophosphatemia were observed during the study, and these deteriorated during hospitalization.[41] The natural history of the disease and medications like ribavirin, which affects renal tubular function, were among the suggested explanations for these electrolyte disturbances.[41]

To our knowledge, there is limited evidence for potassium disorders in patients affected by MERS-CoV.[44–46] However, the first case of MERS-CoV infection in the US was reported to have mild hyponatremia and hyperglycemia, while the serum potassium level was within the normal range.[44] In addition, in a retrospective cohort of 51 RT-PCR positive patients, 33% had serum potassium levels above 4.5 mmol/L.[46] Finally, in a case series of eight confirmed MERS-CoV patients, one of the two who died, had hyperkalemia, with associated ventricular tachycardia.[45]

4.2 | Serum potassium in Covid-19

Electrolyte imbalances, notably hyponatremia, hypokalemia and hypocalcemia, are common in Covid-19 patients and may increase the risk of adverse clinical outcomes.[10–13,15,17,18] In a retrospective cohort study, which gathered data from 274 acute care hospitals across the US, the clinical features and laboratory records of 21,676 hospitalized patients with Covid-19 were evaluated.[18] Electrolyte imbalances for hypokalemia, hyperkalemia, and hyponatremia were present in 15.8%, 13.2%, and 11.4% of patients, respectively.[18] In a Chinese study of 125 discharged patients who had recovered from Covid-19, the most common electrolyte abnormalities were hypocalcemia (64.8%), hypochloremia (30.4%), hyponatremia (17.6%) and hypokalemia (10.4%).[15] Tezcan et al. also reported the onset of an electrolyte disorder in 53% of their 408 individuals confirmed with Covid-19.[10] Hyponatremia was the most common electrolyte abnormality (35.8%), along with hypocalcemia (9.5%), hypokalemia (6.8%), hypochloremia (6.8%) and hyperkalemia (1.7%).[10]

It is worth noting that among potassium disorders, hypokalemia seems to be more prevalent than hyperkalemia in Covid-19 cases. According to the pooled analysis that we performed on data of the eligible studies, overall 30 and 15 relevant studies with total number of 91,945 and 89,166 Covid-19 patients were enrolled for estimating the prevalence of hypokalemia and hyperkalemia, respectively. The pooled hypokalemia prevalence rate was 24.31% (95% CI: 20.80%–28.00%), while the corresponding rate for hyperkalemia was 4.15% (95% CI: 2.37%–6.34%; Figures 1 and 2). There was a significant heterogeneity among studies. I^2 estimates were 98.44% and 98.70% for hypokalemia and hyperkalemia, respectively. The epidemiological data from Covid-19 patients with hypokalemia is summarized in Table S1 and for hyperkalemia in Table S2.

A numbers of studies have reported hypokalemia as an important clinical manifestation of this new coronavirus.[14,19,21,47–49] Chen et al. first proposed the idea of potassium disorders in SARS-CoV-2 infections, when designing a retrospective cohort study on 175 RT-PCR positive patients who were admitted from 11 January 2020 to 15 February 2020 to Wenzhou Central Hospital and the Sixth People's Hospital of Wenzhou, China.[19] Interestingly, severe hypokalemia (potassium <3 mmol/L) and mild hypokalemia (potassium <3.5 mmol/L) were detected in 31 (18%) and 64 (37%) patients, respectively.[19] Additionally, the onset of hypokalemia in this study was associated with the presence of underlying diseases; 25 patients (81%) with severe hypokalemia and 29 patients (45%) with mild hypokalemia had underlying diseases, such as diabetes and hypertension, compared with only 17 patients (12%) with normokalemia.[19] In a study in Italy, Szoke et al. reported that median potassium baseline levels were significantly lower in 874 confirmed cases of Covid-19, compared with 538 negative patients [3.9 (3.6–4.2) vs. 4.0 (3.7–4.3); $p < 0.001$], and that hypokalemia was more frequent in Covid-19 cases than among the controls ($p = 0.005$).[48] Furthermore, in a case-control study, consisting of 594 RT-PCR positive cases and 594 PCR negative controls, matched for age and sex, hypokalemia was found to be significantly associated with Covid-19 at emergency department admission (adjusted odds ratio [OR] = 1.76; 95% CI: 1.20–2.60).[13] An investigation of a cluster of patients with an established diagnosis of Covid-19, found hypokalemia in 25% of cases.[47] The duration of clinical symptoms of Covid-19, prior to diagnosis, was significantly shorter in the hypokalemic group, suggesting that hypokalemia is more likely to manifest itself earlier in the illness.[47] In a retrospective cohort study of 290 non-critically ill Covid-19 patients, hypokalemia was found in 171 cases (41%), with a mean level (±standard deviation [SD]) of 3.1 ± 0.018 mmol/L.[14] Of those patients, 36.6% presented with hypokalemia on admission and about half developed hypokalemia within 24 h of admission.[14] The duration of low serum potassium levels was, on average, 2.27 days per patient.[14] The findings of this study also showed that the presence of hypomagnesemia and hypocalcemia were significantly associated with lower potassium concentrations.[14] Furthermore, the most relevant risk factor for hypokalemia was being female, with a hazard ratio of 2.24.[14] Paice et al. made similar findings, and they concluded that the depleted serum potassium levels in women was unlikely to have arisen by chance, due to the strength of the statistical relationship.[28] Although the etiology of this association is unclear, hormonal influences and the physical characteristics of women might play a greater role in decreasing serum potassium levels than the natural history of the disease.[14,28]

However, these results differ from another study, which compared the laboratory findings of 59 Covid-19 and 83 non-Covid-19 cases in Japan.[50] This research found that the potassium level in the Covid-19 group was significantly higher than in the control group [4.10 (4.04–4.02) vs. 3.93 (3.89–3.97); $p < 0.05$].[50] Hyperkalemia was observed in only three patients with Covid-19 and it was not reported in any of the healthy controls ($p < 0.05$).[50] The percentage of patients with hypokalemia in the Covid-19 group was also significantly lower than in the control group (3.4% vs. 18.1%; $p < 0.01$).[50]

The potential mechanism of potassium homeostasis alteration in Covid-19 patients is a controversial issue. However, initial studies have suggested that kidneys could be a major source of potassium abnormalities in Covid-19 infection.[19,21] In the case of hypokalemia, a putative mechanism would be through utilization and subsequent degradation of angiotensin-converting enzyme (ACE2) as a receptor

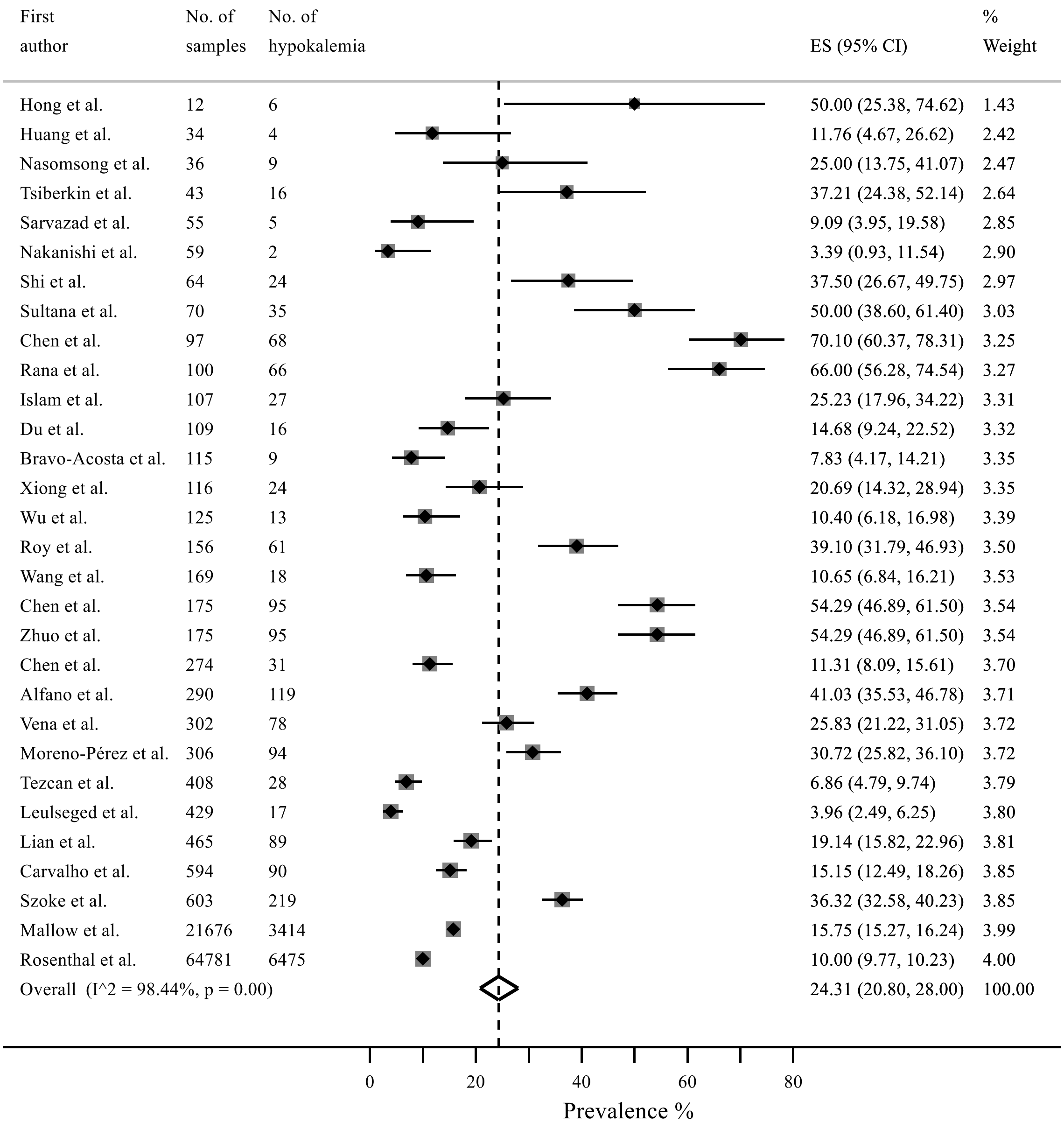

FIGURE 1 Hypokalemia prevalence in Covid-19 patients. Forest plot showing the prevalence of hypokalemia in Covid-19 patients. The squares indicate weight of each study in random-effect model. The vertical dashed line indicates the overall pooled estimate of hypokalemia prevalence and the diamond the 95% confidence interval around that pooled estimate. The forest plot was generated using STATA 15.0 (STATA Corp, LLC, TX)

for the cell-entry process.[51] RAAS has a key role in regulation of potassium concentration that could be counter-regulated by ACE-2. When ACE-2 is downregulated by the virus, increased activity of RAAS would be feasible which leads to potassium wasting through urine and hypokalemia in Covid-19 patients.[52] In addition, antidiuretic hormone (ADH) is a hormone that could also be important in potassium homeostasis. ADH is secreted from the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). It is hypothesized that either viral-mediated neurodegeneration or neuroinflammation of subfornical organ may cause dysfunction of PVN and SON, leading to excess urinary potassium loss and hypokalemia.[53] In the case of hyperkalemia, it has been reported that the incidence of acute kidney injury (AKI) is high in Covid-19 patients.[54] Impairing potassium excretion as common manifestation of AKI could induce potassium retention and increased serum potassium levels in Covid-19 patients.

Taken together, the difference between frequency of potassium disorders in Covid-19 patients may be due to the variations among laboratories and how they collect the samples, various therapeutic approaches, or even genetic factors such as population polymorphisms.[55] For instance, the East Asian populations have much higher allele frequencies in the expression quantitative trait loci variants associated with higher ACE2 expression compared to European populations.[56] This may suggest different susceptibility or

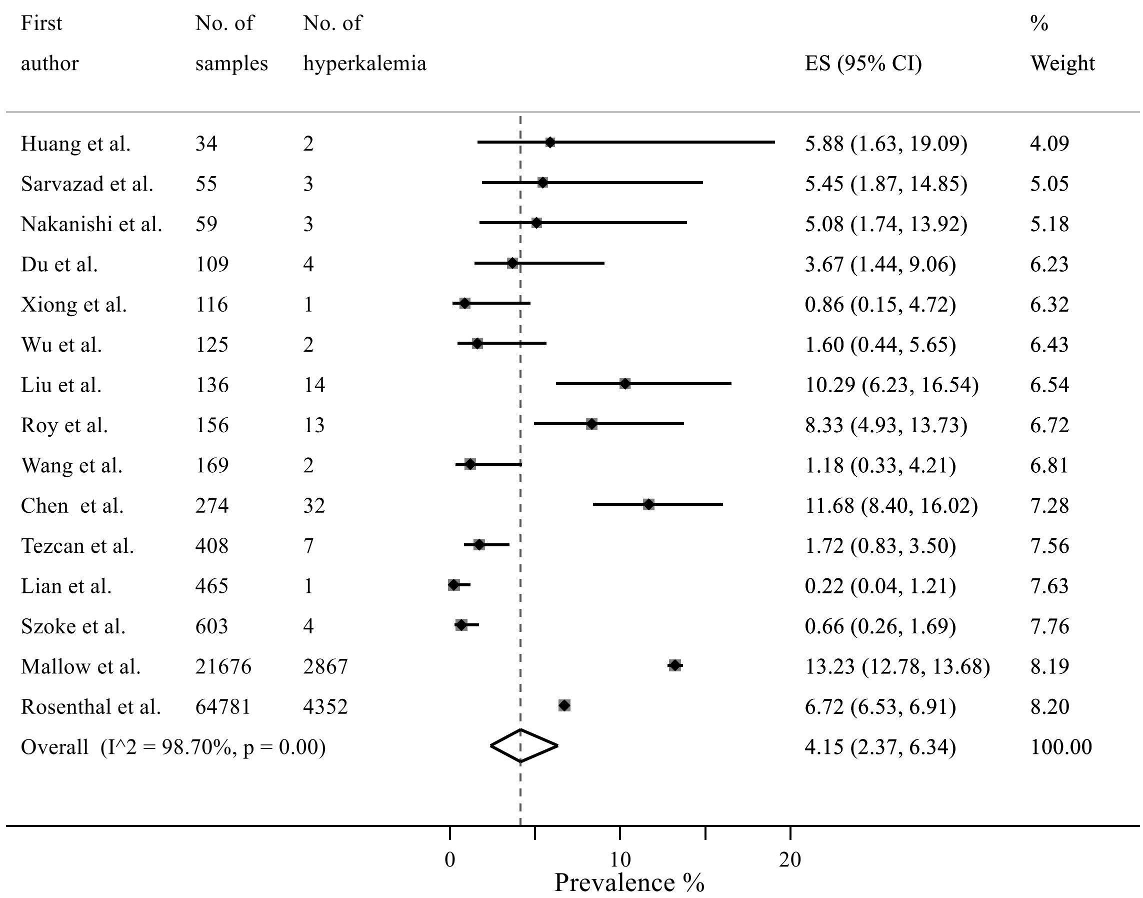

FIGURE 2 Hyperkalemia prevalence in Covid-19 patients. Forest-plot showing prevalence of hyperkalemia in Covid-19 patients. The squares indicate weight of each study in random-effect model. The vertical dashed line indicates the overall pooled estimate of hyperkalemia prevalence and the diamond the 95% confidence interval around that pooled estimate. The forest plot was generated using STATA 15.0 (STATA Corp, LLC, TX)

response to SARS-CoV-2 and even different serum potassium status from different populations.

4.3 | Prognostic implication of potassium disorders

In general, hypokalemia and hyperkalemia are both related to a poor prognosis. Numerous studies have found a U-shaped correlation between potassium levels and adverse outcomes.[57–59] A previous study of 57,874 hospitalized patients, with a mean ± SD baseline potassium level of 4.2 ± 0.6 mmol/L, demonstrated that both lower and higher potassium levels were associated with increased 1-year mortality, regardless of the main diagnosis.[59] Potassium levels of ≤2.9 and ≥5.5 mmol/L were associated with the highest mortality rate, while the lowest mortality rate occurred among those in the range of 4.0–4.4 mmol/L.[59] A similar relationship in the prognosis of Covid-19 was also noted by recent investigations (Table 1). Hypokalemic patients affected by SARS-CoV-2 tend to have longer stays in hospital and intensive care units (ICU) and more commonly require invasive mechanical ventilation (IMV).[14,21] Moreover, lower serum potassium levels have been showed to be related to prolonged SARS-CoV-2 RNA detection.[62,63] A number of studies have reported that critically or severely ill Covid-19 patients had serum potassium levels outside the normal range.[16,19,21,64–70] For example, in a study by Chen et al., 85% of critically ill Covid-19 patients also had hypokalemia.[19] Liu et al. described a J-shaped risk association between potassium concentration and the mortality rate among Covid-19 patients.[20] They found that, compared with potassium levels of 4.0 to 4.5 mmol/L, the adjusted hazard ratio for 30-day mortality during hospitalization was 4.14 (95% CI: 1.29–13.29; p = 0.017) for >5 mmol/L and 1.99 (95% CI: 0.54–7.35; p = 0.300) for <4 mmol/L.[20] Given that both hypokalemia and hyperkalemia may be sensitive predictors of a poor prognosis, early identification and correction are crucial, particularly in patients who are at a higher risk of becoming critically ill.

5 | POTASSIUM ABNORMALITIES AND CARDIAC DYSFUNCTION

A growing body of evidence has reported Covid-19 patients to be prone to cardiac damage, even if they do not have any underlying heart disease.[71] Elevated troponin enzymes and creatine kinase-myocardial band (CK-MB), as diagnostic markers of myocardial

TABLE 1 Association of serum potassium concentration with Covid-19 outcomes in recent studies

Reference	Country	Study design	Total number	Gender	Age	Categorization based on potassium level	Outcomes
Chen et al.[19]	China	Retrospective cohort	175	50% female	Mean: 45 (SD: 14)	• Sever hypokalemia (serum potassium <3 mmol/L) (n = 31) • Mild hypokalemia (serum potassium 3-3.5 mmol/L) (n = 64) • Normokalemia (n = 80)	(i) Patients with severe hypokalemia had higher body temperature, ECG abnormality, and the need for oxygen administration than the patients with mild hypokalemia ($p = 0.02$, $p = 0.001$, and $p = 0.004$, respectively) and normokalemia ($p = 0.005$, $p < 0.001$, and $p < 0.001$, respectively)(ii) Patients with higher levels of hypokalemia had higher CK levels, CK–MB fraction, LDH levels, and CRP levels ($p = 0.01$, $p = 0.04$, $p = 0.002$ and $p < 0.001$, respectively).(iii) Among 40 severely and critically ill patients 85% had hypokalemia
Moreno-pérez et al.[21]	Spain	Retrospective cohort	306	42.2% female	Median: 65 (IQR: 51.0–77.0)	• Sever hypokalemia (serum potassium <3 mmol/L) (n = 18) • Mild hypokalemia (serum potassium 3-3.5 mmol/L) (n = 76) • Normokalemia (n = 212)	(i) Patients with hypokalemia had higher Charlson comorbidity index ≥3, CURB65 severity score for community-acquired pneumonia, number of lymphocytes and serum levels of ferritin, IL-6, D-dimer, troponin T, and brain natriuretic peptide at baseline ($p = 0.027$, $p = 0.045$, $p = 0.018$, $p = 0.002$, $p = 0.046$, $p = 0.033$, and $p = 0.040$, respectively)(ii) Severe hypokalemia and mild hypokalemia were associated with ICU admission (OR = 4.48; 95% CI: 2.35–8.53) and the requirement for IMV (OR = 5.49; 95% CI: 2.66–11.33)(iii) Hypokalemia were associated with a longer length of hospital ($p = 0.000$) and ICU stay ($p = 0.018$)
Islam et al.[60]	Bangladesh	Cross-sectional	134	34.3% female	Mean: 51.74 (SD: 13.8)	• Sever hypokalemia (serum potassium <3 mmol/L) (n = 2) • Mild hypokalemia (serum potassium 3-3.5 mmol/L) (n = 24) • Normokalemia (n = 108)	Grades of hypokalemia was associated with shortness of breath ($p = 0.022$)

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Total number	Gender	Age	Categorization based on potassium level	Outcomes
Roy et al.[61]	India	Cross-sectional	156	42.9% female	Mean: 36.3	• Hypokalemia ($n = 61$) • Normokalemia ($n = 82$) • Hyperkalemia ($n = 13$)	(i) Approximately 70% of Covid-19 cases with ARDS were hypokalemic(ii) In total cases, potassium levels showed a significant negative correlation with CRP levels ($r = -0.463$; $p < 0.001$) but in ARDS cases, the correlation was significantly stronger ($r = -0.728$; $p < 0.001$)(iii) Potassium levels also showed a significant positive correlation with PaO_2:FiO_2 ratio in ARDS cases ($r = 0.660$, $p < 0.001$)
Alfano et al.[14]	Italy	Retrospective cohort	290	27.2% female	Mean: 64.8 (SD: 13.8)	• Hypokalemia ($n = 119$) • Normokalemia ($n = 171$)	Patients with hypokalemia had higher SOFA score ($p = 0.014$) and a longer follow-up duration ($p = 0.002$)
Tsiberkin et al.[49]	Russia	Retrospective cohort	43	44.1% female	Median: 56.0 (IQR: 42,0–63,0)	• Hypokalemia ($n = 16$) • Normokalemia ($n = 27$)	Patients with hypokalemia had a higher level of CRP ($p = 0.034$) and LDH ($p = 0.036$), lower O2 saturation ($p = 0.001$), and a greater tissue damage ($p = 0.019$) at the time of admission
Nasomsong1 et al.[47]	Thailand	Cross-sectional	36	39.1% female	Mean: 42.6 (SD: 16.3)	• Hypokalemia ($n = 9$) • Normokalemia ($n = 27$)	Fever in the hypokalemia group was higher than the normokalemia group ($p = 0.07$)
Liu et al.[20]	China	Prospective cohort	136	49.9% female	Mean: 62.1 (SD: 14.6)	• Serum potassium <4.0 mmol/L ($n = 20$) • Serum potassium ≥4, <4.5 mmol/L ($n = 57$) • Serum potassium ≥4.5, <5 ($n = 45$) • Serum potassium ≥5 ($n = 14$)	(i) Patients with serum potassium ≥5.0 mmol/L had higher creatinine ($p < 0.001$) and BUN ($p < 0.001$) and lower eGFR ($p < 0.001$)(ii) In the multivariate Cox regression model adjusted for potential confounders, 30-day mortality was 3.14 (95% CI: 1.29–13.29; $p = 0.017$) times higher in patients with potassium level ≥5.0 mmol/L than in patients with potassium level 4.0 to 4.5 mmol/L.

injury, have been reported in many SARS-CoV-2 cases.[72] Direct viral invasion through the ACE2 receptors, advanced release of inflammatory cytokines, and a mismatch between myocardial oxygen supply and demand are the possible mechanisms of myocardial damage and subsequent arrhythmia.[73] In a study of 4,526 patients with Covid-19 across the world, almost 18% had arrhythmia.[73] Atrial arrhythmia was the most frequent (81.8%), followed by bradyarrhythmia (22.6%), and ventricular arrhythmias (20.7%).[74]

Potassium plays a crucial role in modifying resting membrane potential, thus deviations from normal potassium levels results in electrophysiological perturbations and unfavorable effects on the cardiac electrophysiology.[75] An elevated serum potassium level is known to cause abnormal heart rhythms.[75] The electrocardiographic (ECG) signs of hyperkalemia vary from deadly sine waves and bradyarrhythmia in severe hyperkalemia, to nonspecific changes, such as a flattened P wave, widened QRS complex, and a peaked T wave in moderately increased potassium levels.[75]

Although both low and high levels of potassium are arrhythmogenic conditions, research has shown that the incidence of ventricular fibrillation is five-time higher in hypokalemic patients than in hyperkalemic.[76] Severe hypokalemia potentially contributes to QTc interval prolongation, life-threatening arrhythmia of Torsades de Points (TdP), and sudden cardiac death.[75] In addition to the high risk of hypokalemia in Covid-19 patients, and the ensuing increased risk of TdP, frequently prescribed drugs, including hydroxychloroquine, chloroquine, lopinavir/ritonavir and azithromycin are listed as definite causes of TdP.[77] Therefore, as infected patients are inherently, or as a consequence of various medications, susceptible to multiple arrhythmias, continuous ECG monitoring and the optimization of potassium balance are recommended in clinical settings.

5.1 | Some considerations in the management of hypokalemia and hyperkalemia

Both hypokalemia and hyperkalemia are often asymptomatic.[26] Patients with serum potassium levels below 2.5 mmol/L and above 6.0 mmol/L are predisposed to cardiac arrhythmias, muscle weakness, paralysis and respiratory failure.[26] The immediate goals of treatment are to prevent lethal cardiac conductance and muscular disturbances. Following this, interventions should diagnose and address the underlying causes. Although the management of potassium abnormalities does not differ greatly between Covid-19 and non-Covid-19 patients, below we focus on some important clinical considerations.

5.2 | Hypokalemia

- Regarding the high risk of TdP arrhythmia in patients with Covid-19, it is important to correct any electrolyte disturbances, with special attention to hypokalemia, before starting QTc prolongation drugs. If QTc exceeds the preset threshold of 500 ms, or 60 ms from baseline, unnecessary QT prolongation drugs should be withdrawn and serum potassium levels should be kept at >4.5 mmol/L.[73]
- Considering the hypokalemic state of some Covid-19 patients, those who are on digoxin therapy may be at an increased risk of developing hypokalemia-induced digoxin toxicity, so they should undergo close serum digoxin monitoring until potassium levels are normalized.[78]
- In cases where hypokalemia is due to intracellular shifting, given the fact that the total body reserves of potassium have not been depleted, less aggressive correction of the serum potassium level is proposed, in order to reduce the risk of rebound hyperkalemia.[26]
- Concomitant magnesium deficiency must be corrected, in order to optimally treat hypokalemia.[79]
- Serum potassium levels in diabetic ketoacidosis (DKA) management should be monitored carefully, for Covid-19 patients with diabetes. Upon initiation of insulin therapy and fluid resuscitation, the DKA patient is particularly vulnerable to depleted potassium levels. Because of the frequent occurrence of hypokalemia in Covid-19 patients, hypokalemia would be expected to be more profound during the management of DKA patients who are affected by SARS-CoV-2.[80]

5.3 | Hyperkalemia

- Administration of sodium polystyrene sulfonate as a potassium binder for hyperkalemic patients was shown to increase the risk of intestinal ischemia and thrombosis.[81] Clinicians must be alert to the incremental risk of thrombosis in patients with Covid-19, due to the thrombogenicity feature of the disease.[82]
- Hyperkalemic patients who do not respond to potassium lowering agents, or are suffering from severe kidney function impairment, are typically treated with hemodialysis. The preferable hemodialysis modality in patients with Covid-19 is continuous renal replacement therapy (CRRT), which is more easily tolerated in hemodynamically unstable patients. However, CRRT has a higher risk of circuit clotting, due to low blood flow, in comparison to intermittent hemodialysis (IHD).[83,84] Due to the procoagulable nature of Covid-19, the administration of anticoagulants is necessary during CRRT, but heparin-induced hyperkalemia may further deteriorate the elevated potassium levels in patients using this approach for improving hyperkalemia.[85] In contrast, IHD allows a rapid drop in serum potassium levels and reduces the need for anticoagulants.[84] In order to minimize the risk of rebound hyperkalemia, after hemodialysis, it would be better to keep the dialysate potassium concentrations above 2 mmol/L.[86] In comparison to hemodialysis, the rate of potassium removal is much lower in peritoneal dialysis and also its utilization is challenging in critically ill Covid-19 patients, owing to their prone position that will increase abdominal pressure,

reduce respiratory system compliance, and enhance the risk of fluid leakage.[87]

Finally, the correction of potassium abnormalities not only enhances the prognosis of patients with Covid-19, but research has also shown that potassium levels tend to become normalized at the same time as improvements in the disease.[19] Therefore, along with treating Covid-19, clinicians must also be careful to keep potassium levels within the normal range.

5.4 | Limitations

This study has some limitations that requires cautions when generalizing our findings. The main one being the marked heterogeneity of the pooled estimations, which probably was due to the differences in sample sizes and baseline characteristics of the patients. Furthermore, consistent threshold was not applied among included studies for defining hypokalemia and hyperkalemia, which may lead to misestimation of overall pooled analysis. In addition, the majority of included study were retrospective and analyzed the data of hospitalized patients that are more susceptible for electrolyte abnormalities, highlighting the risk of selection bias. Finally, there are several risk factors that might influence prognosis of Covid-19. Therefore, although the included articles have adjusted the outcome variables for several potential confounders, the observational studies are always prone to some unexpected confounding factors that should be considered when the association between potassium disorders and prognosis of Covid-19 patients is interpreted.

6 | CONCLUSION

Potassium disorders are prevalent in patients with Covid-19, with a proportion of 24.3% for hypokalemia and 4.15% for hyperkalemia. Both hypokalemia and hyperkalemia are correlated with a poor prognosis and outcomes. The early detection and management of potassium changes, along with close ECG monitoring, could prevent the incidence of life-threatening arrhythmias, particularly in critically ill patients. Future studies should consider characteristics of participants, including age, gender, comorbidities, existing pharmacotherapies, and poor lifestyle risk factors, such as cigarette smoking and obesity. Investigation of these factors will enable a better understanding of hypokalemia and hyperkalemia pathogenesis and more targeted treatment recommendations.

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AUTHOR CONTRIBUTIONS

Maryam Noori, Seyed Aria Nejadghaderi, Ali-Asghar Kolahi and Saeid Safiri designed the study. Maryam Noori and Seyed Aria Nejadghaderi wrote the first draft of the manuscript; Mark J. M. Sullman, Kristin Carson-Chahhoud, Ali-Asghar Kolahi and Saeid Safiri critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Seyed A. Nejadghaderi https://orcid.org/0000-0002-8692-9720
Ali-Asghar Kolahi https://orcid.org/0000-0003-0178-3732
Saeid Safiri https://orcid.org/0000-0001-7986-9072

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SUPPORTING INFORMATION

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