COMMENTARY

Electrolytes and COVID-19: challenges and caveats in clinical research studies

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The Coronavirus Disease Pandemic (COVID-19) imposed a tremendous challenge on hospitals, health care facilities, health policy makers, and scientists, prompting action to limit the spread of infection, prevent its consequences, and understand as much as possible about the aetiology, prognostic factors, treatments, and vaccines. Along with population-level data on the spread of the pandemic, a large number of studies were published and readily made available in an unprecedented effort to share potentially useful information as quickly as possible. Many of these observational studies investigated demographic and clinical variables that could possibly represent risk factors for the severity and prognosis of COVID-19. Although under stress, hospitals began to collect data and biological samples in patients hospitalized for COVID-19 and to collaborate on research projects.

Recently, attention has focused on the incidence and clinical impact of electrolyte disorders in COVID-19 patients. Indeed, to date, a few studies with sufficiently large sample size evaluating a putative association between dysnatremia and outcomes have been published [1–3], whereas the prognostic role of disorders of serum potassium in COVID-19 patients was previously investigated only in a small cohort of patients [4]. Whilst a significant association between hypernatremia and increased mortality was reported in several studies [1–3], findings about a putative association between hyponatremia and increased risk of death are conflicting. In fact, notwithstanding the higher relative frequency of patients with hyponatremia than with hypernatremia, hyponatremia has not conclusively been shown to be a risk factor for death, except in the case of hypovolemic patients [2]. The association between hyponatremia and increased hazard of death reported by Hirsch et al. [1] in a large cohort of COVID-19 patients was no longer significant after correction of serum sodium for serum glucose values. On the other hand, the Kaplan–Meier curves in the study by Hu et al. [3] showed that both hypernatremia and hyponatremia were associated with decreased survival. Despite a high prevalence of hypokalemia during hospitalization in COVID-19 patients, studies failed to demonstrate any significant association between hypokalemia and the risk of death in this population. The lack of association between hypokalemia and the risk of death in COVID-19 patients is somewhat unexpected, since hypokalemia is associated with life-threatening ventricular arrhythmias in hospitalized patients. Thus, it is conceivable that in the studied COVID-19 cohorts serum potassium levels were not low enough to exert a clinically relevant pro-arrhythmic effect. On the contrary, in a small Chinese cohort in which a J-shaped relationship emerged between serum potassium values and mortality, patients with serum potassium levels ≥ 5.0 mmol/L had a significantly increased risk of death at 30 days [4].

All of these studies had a retrospective design, and most used multivariable analyses to adjust for potential confounders. However, further factors associated with both electrolyte disorders and adverse outcomes may have been unaccounted for. In other words, dysnatremias and dyskalemias may have been markers of greater severity of clinical conditions rather than being pathogenetically linked to poor patient outcomes. Indeed, electrolyte disorders are to be expected in patients with febrile illness, especially if metabolic and/or respiratory acidosis is present. Febrile patients may develop hypernatremia, and hyperkalemia is common when a patient is acidemic. COVID-19 patients are obviously no exception. Despite these caveats, both hypernatremia and hyperkalemia

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have been associated with increased mortality even in non-COVID patients. This is true both in patients admitted to general wards and to those admitted to the intensive care unit (ICU). In addition, the amount of fluid administered and the doses of diuretic are typically unavailable in retrospective observational studies. Clearly, vigorous resuscitation with crystalloids, and especially normal saline may promote the development of hypernatremia and hyperchloremia, whereas high doses of loop diuretics are more commonly associated with hypernatremia, hypokalemia and hypomagnesemia. In addition, acute kidney injury (AKI) can exacerbate fluid overload in ICU patients, especially when renal replacement therapy is postponed. AKI can be part of multi-organ failure caused by sepsis, and oliguric AKI is an important cause of electrolyte and acid–base imbalances, particularly hyperkalemia and metabolic acidosis. It is less clear whether electrolyte or acid–base disorders may impact outcomes independently of AKI. Finally, nephrotoxic antibiotics (e.g., aminoglycosides, colistin, amphotericin) are commonly used in ICU patients to treat infections with multidrug-resistant bacteria or fungi, and may contribute both to AKI and electrolyte imbalances, such as hyper- or hypokalemia and hypomagnesemia. Generally, accurate data on the use of nephrotoxic drugs are not available in retrospective studies.

Although the role of observational studies in treatment evaluation is a controversial topic, it is recognized that these studies are the main source of information on prognostic and risk factors [5]. Well-designed randomized controlled trials limit the possibility of bias in patient recruitment and estimates of treatment effect, whereas observational studies, in which patient treatment is deliberately chosen, have a high risk of selection bias and biased estimates of treatment effect [6]. Upon scrutiny of crucial aspects of the data analysis approaches used in the COVID-19 observational research on therapeutic interventions, many flaws were found in the statistical methods adopted for data analysis that could compromise the reported results and interpretation [7]. While the results of the analysis of prognostic and risk factors may be a by-product of randomized controlled trials (RCTs), RCTs are not designed to address this topic unless prognostic features are expected to have a predictive effect, that is, to interact with the treatment modifying its effect. Furthermore, in RCTs the view of prognostic features may be limited by strict eligibility criteria based on specific patients and specific disease characteristics. Observational studies, on the other hand, can be very useful for studying prognostic or risk characteristics that influence the course of a disease beyond treatment, especially if they are designed with a rigorous definition of the study cohort and data collection, and possibly with a prospective design. Large

observational cohorts, consisting of unselected consecutive patients hospitalized for COVID-19-confirmed infection, are well suited to answer questions about prognostic characteristics in a "real world setting" that reflects the context under study. However, we should be aware that hospitalized subjects usually have more severe clinical conditions than the total population of infected subjects [8]. Therefore, the identified risk factors for disease severity and selected clinical outcomes are useful in defining the management and treatment of hospitalized patients, but they may not necessarily be generalizable to the population of infected individuals. On the other hand, it is important that the association found in an observational study should provide a reliable estimate of a true causal effect at the individual level, which requires taking into account potential confounders in the data analysis. However, notwithstanding adjustment for potential confounders at multivariable analysis, observational studies are prone to residual confounding by unmeasured variables. For instance, observational studies may not collect time-varying exposure data that could better describe the association of changes over time of a given parameter with the outcome. Finally, missing data represent an important methodological problem in observational studies. If data are missing not completely at random for one or more exposure variables, this could introduce a significant bias in the analysis of outcomes.

Other studies in non-COVID-19 patients have shown that serum sodium and potassium values above normal limits are associated with increased mortality, both in patients with heart failure and in patients with chronic kidney disease. For the most part, these studies collected single electrolyte measurements taken at baseline, and demonstrated an association between electrolyte disorders and mortality. Thus, it advisable that special attention should be paid to patients who present with disorders of serum sodium or potassium at the time of admission because they may face an abrupt worsening of their clinical condition. This is probably true in COVID-19 patients as well. We cannot say, based on observational studies, whether the association between hypo/hyperkalemia or hypo/hypernatremia and mortality reflects a causal relationship or whether these electrolyte disorders are simply markers of the clinical severity of these patients. Nevertheless, patients with electrolyte disorders may face a worse outcome, and knowing this is an important clinical piece of information.

In conclusion, observational studies on electrolyte alterations have several limitations, especially when conducted in clinical emergency situations, but this should not prevent us

from using useful information derived from these studies to save the lives of our patients.

Declarations

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