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Serum nitrite and nitrate: A potential biomarker for post-covid-19 complications?

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ABSTRACT

Nitric oxide (NO) plays an important role in cardiovascular and immune systems. Quantification of blood nitrite and nitrate, two relatively stable metabolites of NO (generally as NO_x^-), has been acknowledged, in part, representing NO bioactivity. Dysregulation of NO_x^- had been reported in SARS-CoV-2 infected populations, but whether patients recovered from COVID-19 disease present with restored NO_x^- is unknown. In this study, serum NO_2^- and NO_3^- were quantified and analyzed among 109 recovered adults in comparison to a control group of 166 uninfected adults. Nitrite or nitrate levels were not significantly different among mild-, common-, severe- and critical-type patients. However, these recovered patients had dramatically lower NO_2^- and $\text{NO}_2^-/\text{NO}_3^-$ than the uninfected group ($p < 0.0001$), with significantly higher NO_3^- levels ($p = 0.0023$) than the uninfected group. Nitrate and nitrite/nitrate were positively and negatively correlated with patient age, respectively, with age 65 being a turning point among recovered patients. These results indicate that low NO_2^- , low $\text{NO}_2^-/\text{NO}_3^-$ and high NO_3^- may be potential biomarkers of long-term poor or irreversible outcomes after SARS-CoV-2 infection. It suggests that NO metabolites might serve as a predictor to track the health status of recovered COVID-19 patients, highlighting the need to elucidate the role of NO after SARS-CoV-2 infection.

1. Introduction

COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused substantial human life losses. As of August 22, 2021, the total number of confirmed infected cases of COVID-19 stood at 211 million worldwide, with a death toll of 4.4 million (from the Johns Hopkins Center for Systems Science and Engineering) [1]. The possibility of developing a severe case of disease and the mortality rate are reported to be influenced substantially by age and the presence of comorbidities, as well as sex [2–4]. Estimates of the influence of age

using data from 16 countries suggest that people aged 65 years and older were more susceptible to SARS-CoV-2 infection, with a higher admission rate to intensive care units (ICUs) and a higher fatality rate than younger individuals [5]. Multiple reasons for this age-related susceptibility have been proposed including a link to metabolic, respiratory, or cardiovascular comorbidities [6–11]. For example, COVID-19 patients with existing hypertension have been reported to be more vulnerable to severe disease progression and mortality [7,12], with evidence supported by numerous further larger studies and recent meta-analyses of 24 studies from across the globe [13]. Moreover, substantial organ

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