Hepcidin Level Assessment in COVID-19 Patients Admitted to the Intensive Care Unit

Himani Dhiman*

Department of Life Sciences, J C Bose University of Scienece and Technology, YMCA, Haryana, India

*Corresponding Author**

Himani Dhiman
Department of Life Sciences, J C Bose University of Scienece and Technology, YMCA, Haryana, India
Email: Himani@centro.org

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Abstract

The clinical spectrum of 2019's coronavirus disease (COVID-19) spans from a little ailment to a serious illness. Patients with severe illnesses display multi-organ failure brought on by the so-called "cytokine storm," respiratory failure, septic shock, and/or septic shock. Inflammatory cytokines have an impact on iron metabolism, primarily through increasing the production of the hormone peptide hepcidin, which is not frequently tested. The severity of COVID-19 has been linked to high hepcidin levels. In this investigation, the levels of hepcidin in a sample of COVID-19 patients who had been hospitalised to the Intensive Care Unit (ICU) of the Policlinico Tor Vergata in Rome, Italy, were retrospectively analyzed. The trial recruited 38 participants between November 2020 and May 2021. Patients were divided into two groups—survivors and non-survivors—based on the clinical outcome. Additionally, while the patients were in the ICU, a number of standard laboratory parameters were checked, and the levels of these parameters were associated with the results. Hepcidin, D-dimer, IL-6, LDH, NLR, neutrophils, CRP, TNF-, and transferrin levels were statistically different amongst the groups. Hepcidin levels in particular indicated significantly different median amounts between survivors and non-survivors (88 ng/mL vs. 146 ng/mL). Hepcidin was found to be a good biomarker for predicting the severity and mortality of COVID-19 in ICU patients, with sensitivity and specificity values of 74% and 76%, respectively, at a cut-off of 127 (ng/mL), according to ROC curves analysis.

Keywords: Hepcidin • ICU • COVID-19

Introduction

The 2019 coronavirus disease (COVID-19), which is brought on by the recently discovered human coronavirus SARS-CoV-2 [1], has a clinical profile that can range from a minor illness to a life-threatening illness. The so-called "cytokine storm" causes respiratory failure, septic shock, and/or multi-organ failure in patients with critical disease. Increased levels of several cytokines, such as IL-2, IL-6, IL-7, interferon-c inducible protein-10, macrophage inflammatory protein 1, Tumour Necrosis Factor (TNF), monocyte chemoattractant protein 1, and granulocyte colony-stimulating factor, are indicative of this exaggerated inflammatory response. The primary regulator of iron absorption and distribution to tissues is the 25-amino acid peptide hepcidin, which is generated largely in liver cells by inflammatory cytokines. Hepcidin plays a key role in iron metabolism by promoting its synthesis. Another crucial indicator of iron status and a gauge of inflammation is serum ferritin. In COVID-19 patients, elevated ferritin levels are associated with high mortality, which is reflected in abnormal iron metabolism [1]. Through ferroportin, a hepcidin receptor and cellular iron exporter in vertebrates, hepcidin regulates the export of cellular iron to plasma and extracellular fluid. Iron and erythropoietic activity control the homeostatic regulation of hepcidin levels. When there is too much iron in the body, hepcidin is produced, which prevents the intestines from absorbing iron. Instead, iron insufficiency results in hepcidin suppression, which promotes dietary iron absorption and iron store replenishment.

Hepcidin levels can rise during inflammation and infection, which is probably related to the host's defense mechanism to remove iron from the infecting microorganisms. Iron is mostly sequestered by hepcidin using macrophages. While the relevance of this phenomena in viral infections is uncertain, it is well-established in bacterial infections. The immune system's operation is impacted by iron metabolism. Contact with the antigen-presenting cells primes lymphocytes, and they require iron to create a potent and successful cellular and humoral response. Hepcidin is not typically tested in the clinic laboratory despite its critical role in the regulation of iron metabolism. According to preliminary research, COVID-19 patients' elevated hepcidin levels are correlated with the severity of their condition. Similar to COVID-19, severe hypoxemia in intensive care unit (ICU) patients as well as low serum iron levels have been linked to COVID-19 severity and death [2]. Given this context, the study's objective was to retrospectively assess the levels of hepcidin in a group of COVID-19 patients who had been brought to the ICU at Rome, Italy's Policlinico Tor Vergata. Hepcidin levels and the prognosis of the illness were connected.

Discussion

Millions of people have died as a result of COVID-19 since it first surfaced at the end of 2019. A few people experience more serious clinical conditions, such as severe pneumonia, acute respiratory distress, or multiorgan failure with mortality, despite the fact that the majority of patients have moderate symptoms and a positive prognosis [3]. A "cytokine storm," or extreme inflammatory response accompanied by the production of many cytokines, can be seen in these seriously unwell patients. A number of haematological and biochemical indicators are changed by this inflammatory response. Hepcidin, a crucial regulator of iron metabolism, may have a predictive value for the severity of the disease and mortality in COVID-19 patients, according to recent research. Indeed, patients with severe disease or bad outcomes had increased serum levels of hepcidin. In this context, in this study, we assessed the usual haematological and biochemical profile as well as the hepcidin level in a group of COVID-19 patients admitted to the ICU with severe pneumonia. According to our findings, there are statistically significant variations between survivors and non-survivors in the level of various indicators. In comparison to the survivors, the non-survivors had greater levels of D-dimer, IL-6, LDH, NLR, CRP, TNF-, and transferrin. In COVID-19 patients, elevated D-dimer levels are associated with a poor prognosis and the requirement for ICU care [4]. In line with our findings, a recent meta-analysis found that patients who passed away had greater D-dimer levels than those who survived. A recognised indicator of the severity and mortality of COVID-19 is LDH. A subsequent meta-analysis that also found how LDH is significantly greater in ICU patients compared to non-ICU patients and in non-survival patients compared to survival patients supported this

conclusion. As a result, it can be used to predict survival. A sizable retrospective study that was released at the beginning of 2022 verified the significance of the predictive value of LDH level in COVID-19 patients. This latter point is supported by the higher level of LDH in the non-survivors' group compared to the survivors' group in our study. The relationship between IL-6 and TNF- and the severity and mortality of COVID-19 has been discussed in a number of research articles. As was recently evaluated in a study with a large sample size, elevated levels of these two biomarkers considerably raise the risk of disease severity and mortality. Patients who did not survive displayed a significantly different amount of IL-6 than those who did. The TNF level showed a same trend. Our findings support the notion that increased IL-6 and TNF- levels are linked to a poor prognosis. Additionally, elevated levels of CRP as well as increased NLR and neutrophil counts are indicators of a poor prognosis and illness severity. The higher levels of these laboratory indices in the nonsurvivors' group in our data support these observations. Increased inflammation and the course of the disease have been linked to lower levels of transferrin. According to our study, group non-survivors had median lower transferrin levels than group survivors, indicating that low transferrin levels might be a predictor of a more severe disease. Hepcidin has been examined in recent research as a potential predictor of death and disease severity in COVID-19 patients. Hepcidin levels were elevated in all of the patients in our study who were admitted to the ICU due to their severe pneumonia, and these levels were considerably higher in the patients who did not survive and required invasive mechanical ventilation. Finally, ROC curve analysis revealed that the best sensitivity and specificity are, respectively, IL-6 and LDH. However, at a cut-off value of >127 ng/mL, hepcidin had a sensitivity of 74% and a specificity of 76%, indicating that hepcidin measurement is a helpful biomarker for predicting the severity and outcome of COVID-19 in ICU patients. Additionally, Serum Amyloid Protein (SAA) and mid-regional proadrenomedullin (MR-proADM), two recent novel inflammatory biomarkers that have been tested for predicting mortality in COVID-19 patients, could be used with hepcidin to build an algorithm [5]. Patients who passed away had higher SAA levels than those who survived. Similar to this, individuals had a threefold increased chance of dying if their MR-proADM level was above 1105 nmol/L. Our investigation did not find any statistically significant differences in the levels of fibrinogen, AST, ferritin, leucocytes, lymphocytes, or sideremia between the survivors and non-survivors groups, despite the fact that these markers of disease severity are still crucial. The study's limited sample size, which may lower the power of the findings, is one of its limitations. However, this study provides crucial information about the value of hepcidin measurement in COVID-19 patients admitted to the ICU and verifies the efficacy of specific biomarkers in predicting the severity and mortality of the disease. A negative outcome was experienced by all patients who had high hepcidin levels.

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