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Inflammation Driven Dysregulation of Iron Homeostasis in COVID 19 Patients: An Insight into Anemia

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KEYWORDS

COVID 19, Inflammation, Iron homeostasis

ABSTRACT:

Introduction: COVID virus predominantly affects the respiratory system and can also affect other systems due to hematological pathologies .The cytokine surge in COVID19 inhibits erythropoietin leading to hematological pathologies like anemia.

Objectives: This study explores the effect of inflammatory markers on iron dysregulation in COVID patients with and without anemia. .

Methods: 100 COVID patients confirmed by RT- PCR were divided into anemic and nonanemic groups comprising 50 patients each. Patients with Hb ≤ 12g/dl were included in anemic group. Plasma iron regulatory proteins and inflammatory markers were estimated by spectrophotometric methods using Roche Cobas Pro autoanalyser.

Results: Hepcidin and erythropoietin were prominently higher in anemic patients compared to nonanemic patients (p=0.000).Compared to nonanemic patients markers of coagulation and hemolysis which included D Dimer and LDH showed a marked increase in the anemic group. Further indices of inflammation like CRP, IL6 and procalcitonin also increased significantly in anemic group (p= 0.027, p= 0.018) respectively. Significantly high plasma transaminases and creatinine in the anemic group point to the early onset of hepatic and renal dysfunction due to anemia. Low hemoglobin would have induced thrombotic changes that culminated in the elevation of D Dimer. IL6 released by the virus induces hepcidin synthesis resulting in hyperferritinemia and decreased erythropoiesis due to restricted availability of iron.

Conclusions: Dysregulation of iron homeostasis observed in COVID 19 patients with anemia is inflammation driven, emphasizing the important crosstalk between inflammatory molecules and iron regulatory proteins. Further, anemia along with coagulopathy may aggravate the organ dysfunction in these patients.

1. Introduction

The COVID virus largely affects the respiratory system but can also affect other systems which may have hematological pathologies. Anemia is one of the most common hematologic disorders. The existing body of literature shows a link between COVID 19 and anemia [1]. Anemic patients with COVID19 may experience severe morbidities due to various pathophysiological mechanisms like hemorrhagic and thrombotic etiologies, primarily caused by decreased hemoglobin [2]. Inflammation is the other mechanism in any infection that leads to alterations in the homeostasis of iron hallmarked by augmented iron sequestration by

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macrophages along with decreased iron absorption in the intestine [3]. Thus low circulating iron reduces its availability for hemoglobin synthesis and erythropoiesis. Cytokine surge in COVID19 inhibits erythropoiesis by decreasing biological activity of erythropoietin ultimately leading to development of anemia of inflammation [4].

2. Objectives

Our study aims to investigate the relationship between anemia and inflammation in COVID19 patients in addition, evaluation of its impact on the kidney and liver by analysis of biomarkers. Further determine proteins like hepcidin, erythropoietin and ferritin to explore the alterations in iron homeostasis.

3. Methods

This is a prospective cross-sectional study conducted ethically as per the Declaration of Helsinki on Biomedical research involving human beings and that was approved by the Institution Ethics Committee (IEC KMC MLR 08/2020/245). Informed consent was obtained from all the subjects enrolled in the study. This is a retrospective observational study conducted on a total of 100 COVID patients confirmed by RT- PCR admitted at K.M.C. Hospitals, Mangalore between March to December 2020. Demographic data such as age and gender, clinical features were noted at the time of admission. The patients were divided into two groups as anemic and nonanemic groups based on their hemoglobin value. 50 patients between the age group of 25-45 years were included in Group I with Hb ≤ 12g/dl and 50 age and sex matched patients were included in Group II with Hb >12 g/dl . The symptoms were not significantly different between patients with anemia and those without anemia at the time of blood collection. Random blood samples that tested positive for COVID-19 were collected in heparin vacuum tubes and centrifuged at 3000g for 10 mins to separate plasma. D-dimer assay was conducted in cases by particle enhanced immunoturbidimetric assay [5], plasma lactate dehydrogenase by measuring the increase in absorbance at 340 nm and serum ferritin by ECLIA [6, 7]. AST, ALT and creatinine were estimated spectrophotometrically using the COBAS Pro auto-analyser [6]. Procalcitonin and IL6 were estimated by sandwich ELISA [8, 9]. Hepcidin was calculated using the formula: Hepcidin (predicted) ng/mL = 23.76+0.396(IL6) + 0.448(ferritin) + 0.310(creatinine mg/dL)[10]. Formula to calculate erythropoietin was: Expected EPO mU/mL=2.5(140- Hb g/dL)[11].

4. Results

In COVID patients with anemia plasma ferritin remained elevated to the same extent as in the nonanemic group compared to normal reference range. Hence there was no statistical difference between the groups. Expected erythropoietin and hepcidin were significantly higher in anemic group when compared to the nonanemic group (Table1).

Inflammatory markers CRP, IL6 and procalcitonin increased significantly in the anemic group compared to COVID patients without anemia (p=0.027, p=0.018, p=0.002) respectively (Table 2). Though creatinine values were within the normal reference range in both the groups, anemic patients had significantly higher values compared to their nonanemic counterparts (p=0.022). Plasma transaminases and D Dimer were also significantly higher in COVID patients with anemia. The anemic patients showed an apparent increase in LDH compared to nonanemic COVID patients (Table 3).

Table 1: Comparison of Iron homeostasis proteins in COVID patients with and without anemia

	Covid without anemia N=50	Covid with Anemia N=50	p
Hb	14.02 ± 0.19	11.23 ± 0.16	0.000
Ferritin	703 ± 138	743 ± 123	0.200
Hepcidin	316 ±19	403± 62	0.000
Erythropoietin	20 ±11	69.2± 19	0.000

Table 2: Comparison of inflammatory markers in COVID patients with and without anemia

	Covid without anemia N=50	Covid with anemia N=50	p
CRP	54.52± 9.8	86± 13	0.027
IL6	65.13 ±14.17	115 ±22	0.018
Pc	0.34± 0.086	0.84± 0.212	0.002

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Table 3: Comparison of organ dysfunction markers in COVID patients with and without anemia

	Covid without anemia N=25	Covid with anemia N=25	p
Creatinine	0.91 ± 0.05	1.14 ± 0.098	0.022
D Dimer	0.95 ± 0.33	1.28 ± 0.27	0.013
LDH	407 ± 39	515± 39	0.058
AST	41± 5.8	110± 30	0.004
ALT	46 ± 11.6	60 ± 7.4	0.003

5. Discussion

The correlation between COVID-19 and anemia appears to be a complex process. In the current study, we have observed a prominent dysregulation of iron metabolism in anemic patients. There appears to be a progressive increase in ferritin levels in COVID patients with anemia compared to those without anemia. Even hepcidin and erythropoietin remained elevated in these patients. COVID-19 patients with anemia were at a higher risk of severe inflammatory reactions [12], which is evident from the results of the current study showing significant increase in IL6 and CRP levels compared to nonanemic patients. On the contrary, inflammation induces disruption of iron homeostasis characterized by decreased iron absorption and increased iron sequestration by macrophages [13]. Low circulating iron reduces its availability for hemoglobin synthesis and erythropoiesis. Further, cytokine-mediated inhibition of erythropoietin activity results in anemia of inflammation [14]. This study also confirms that the release of IL-6 by the virus induces synthesis of hepcidin, leading to high plasma ferritin and restricts erythropoiesis due to unavailability of iron [15]. The cytokine storm induced by SARSCoV-2 promotes changes in antigen presentation, shape and functions of erythrocytes leading to haemolysis [16]. Oxidative stress caused due to infection may enhance haemolysis and anemia. Elevation in LDH is found to be predominant in anemic patients than their nonanemic counter parts. This finding underlines a potential link between COVID19, inflammation and anemia. Immune dysregulation is seen both in anemia and COVID19 [17].High procalcitonin points to secondary infection and very poor immune response in anemic patients. In COVID-19, inflammation may bring about activation of the coagulation cascade and may promote intravascular thrombosis [18] resulting in multiorgan failure. Anemic patients demonstrated a greater degree of renal and hepatic dysfunction with an increase in serum creatinine and transaminases respectively. This is in accordance with several other studies [19]. Increased fibrinolysis in anemic patients would have increased D dimer in circulation, indicating worsened thrombotic status compared to nonanemic patients. Erythrocytes affect haemostasis by interaction with vessel wall, thrombin generation and inhibition of fibrinolysis [20]. The RBC lysate contributes to the pathogenesis of coagulopathy with increased LDH and ferritin in COVID [21] Thus anemia is aligned with abnormalities in coagulation, which emphasizes the interplay of erythrocytes and hemostasis in inflammatory processes seen in COVID19 [22].

The main limitation of this study is that only 50 anemic patients were studied and the diagnosis was based on hemoglobin levels at the time of admission without knowing the cause and duration of anemia.

On the whole it can be concluded that dysregulation of iron metabolism observed in COVID 19 patients with anemia is inflammation driven, emphasizing the important crosstalk between inflammatory molecules and iron regulatory proteins. Further, anemia along with coagulopathy may aggravate intravascular thrombosis resulting in the organ dysfunction in these patients.

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Conflict of Interest

The author(s) declares no conflict of interest.

References

1. Taneri P.E., Gómez-Ochoa S.A., Llanaj E., Raguindin P.F, Rojas LZ, Roa-Díaz ZM, 2020.Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol. 35(8),763-773.
2. Thomas M.R., Scully M., 2022. Clinical features of thrombosis and bleeding in COVID-19. Blood. 140(3):184-195.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(2), 300-303 | ISSN:2251-6727

3. Manoj H.P., Kuthethur S., Kumarchandra R., Pawar N.M., Gopalakrishnakurup A.K., Kollampare, S.,2024. Cross Talk between Iron Regulatory Proteins and Proinflammatory Molecules in Ovarian Cancer Patients Based on Menopausal Status. OnLine Journal of Biological Sciences, 24(4), 550-554.
4. Crooks C.J., West J., Morling J.R., Simmonds M., Juurlink I., Briggs S., 2023. Anemia of acute inflammation: a higher acute systemic inflammatory response is associated with a larger decrease in blood haemoglobin levels in patients with COVID-19 infection. Clin Med (Lond).23(3), 201-205.
5. Adema E., Gebert U., 1995. Pooled patient samples as reference material for D-Dimer. Thromb Res.80(1),85-88.
6. Adams D.H., Hubscher S.G, 2006. Systemic viral infections and collateral damage in the liver. Am. J. Pathol. 168, 1057–1059.
7. Blackmore S., Hamilton M., Lee A., Worwood M. , Brierley M., Heath, A., 2008. Automated immunoassay methods for ferritin: recovery studies to assess traceability to an international standard. Clin Chem Lab Med.:46(10),1450- 1457.
8. Ogbonna G., Atienza J.R., Singleton D.W., Ott-Vasconi A., Alvey S.A., 2025. Clinical and Analytical Performance Evaluation of an Automated Procalcitonin Assay. J Appl Lab Med. 10(2),359-369.
9. Schefold J.C., Hasper D., von Haehling S., Meisel C., Reinke P., Schlosser H.G.,2008. Interleukin-6 serum level assessment using a new qualitative point-of-care test in sepsis: A comparison with ELISA measurements. Clin Biochem. 41(10-11),893-8.
10. Suega K., Widiana G.R., 2019. Predicting hepcidin level using inflammation markers and iron indicators in patients with anemia of chronic disease. Hematol Transfus Cell Ther. 41(4),342-348.
11. Panjeta M., Tahirovic I., Karamehic J., Sofic E., Ridic O., Coric J.,2015. The Relation of Erythropoietin Towards Hemoglobin and Hematocrit in Varying Degrees of Renal Insufficiency. Mater Sociomed. 27(3),144-8.
12. Tao Z., Xu J., Chen W., Yang Z., Xu X., Liu L.,2021. Anemia is associated with severe illness in COVID-19: A retrospective cohort study. J Med Virol. 93(3),1478-1488.
13. Lanser L., Fuchs D., Kurz K., Weiss G., 2021. Physiology and Inflammation Driven Pathophysiology of Iron Homeostasis-Mechanistic Insights into Anemia of Inflammation and Its Treatment. Nutrients. 13(11),3732.
14. Bellmann-Weiler R., Lanser L., Barket R., Rangger L., Schapfl A., Schaber M.,2020. Prevalence and Predictive Value of Anemia and Dysregulated Iron Homeostasis in Patients with COVID-19 Infection. J Clin Med. 9(8), 2429.
15. Maira D, Duca L, Busti F, Consonni D, Salvatici M, Vianello A, 2022. The role of hypoxia and inflammation in the regulation of iron metabolism and erythropoiesis in COVID-19: The IRONCOVID study. Am J Hematol. 97(11),1404-1412.
16. Abu-Ismail L., Taha M.J.J., Abuawwad M.T., Al-Bustanji Y., Al-Shami K., Nashwan A., 2023. COVID-19 and Anemia: What Do We Know So Far? Hemoglobin. 47(3):122-129.
17. Azoulay E., Zuber J., Bousfiha A.A., Long Y., Tan Y., Luo S.,2024. Complement system activation: bridging physiology, pathophysiology, and therapy. Intensive Care Med. 50(11), 1791-1803.
18. Asakura H., Ogawa H., 2021. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol.113(1), 45-57.
19. Dufour J.F., Marjot T., Becchetti C., Tilg H., 2022. COVID-19 and liver disease. Gut. 71(11), 2350-2362.
20. Giannis D., Ziogas I.A., Gianni P., 2020. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 127,104362.
21. Cihakova D., Streiff M.B., Menez S.P., Chen T.K., Gilotra N.A., Michos E.D., 2021. High-value laboratory testing for hospitalized COVID-19 patients: a review. Future Virol. doi.10.2217/fvl-2020-0316.
22. Venter C., Bezuidenhout J.A., Laubscher G.J., Lourens P.J., Steenkamp J., Kell D.B., 2020. Erythrocyte, Platelet, Serum Ferritin, and P-Selectin Pathophysiology Implicated in Severe Hypercoagulation and Vascular Complications in COVID-19. Int J Mol Sci. 21(21), 8234. doi: 10.3390/ijms21218234.