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Anemia predicts poor outcomes of COVID-19 in hospitalized patients: A Prospective study in a tertiary care hospital from South India

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ABSTRACT

Background: Hemoglobin plays a vital role in tissue oxygenation. Hence anemia might significantly affect the prognosis of COVID 19 pneumonia, where in there is development of tissue hypoxia due to the disease pathogenesis. **Aims and Objectives:** To correlate the severity of anemia in COVID 19 patients with disease outcomes in patients admitted in a tertiary care setting. **Materials and Methods:** The prospective single-center study considered adults patients of both the gender, diagnosed with COVID-19 infection by RT-PCR technique. Necessary demographic, clinical data and Hemoglobin level were collected and selected subjects were followed-up until discharge or death. Subjects were classified as those who survived and succumbed to death. t-test was used for comparing continuous variables and chi-square test for categorical data between the groups. **Results:** The study included 1212 patients, where in there was a statistically significant correlation between low hemoglobin level and the disease outcome. The hemoglobin levels were significantly lower in patients who died than the patients who were discharged. **Conclusion:** Severe anemia as noted by low hemoglobin level was associated with higher mortality than subjects with normal hemoglobin.

Keywords: COVID-19; Hemoglobin; RT-PCR

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INTRODUCTION

The COVID-19 pandemic was reported first, as a cluster of pneumonia from Wuhan, China, in December 2019.[1] This disease has been named coronavirus disease 2019 (COVID-19) by WHO. SARS-CoV-2 has been shown to cause disease via a mechanism analogous to the SARS coronavirus, with potential damage to vital organs such as lung, heart, liver, and kidney, and infection poses a considerable risk to patients by the high prevalence of pneumonia.[2] COVID-19 disease is known to cause severe hypoxemia, which plays a key role in the severity of the illness. The mechanism of hypoxia has been attributed to various mechanism including ventilation perfusion mismatch, intravascular thrombi and impaired diffusion capacity.[3] In the setting of hypoxia, anemia can worsen the already compromised tissue perfusion.

Hemoglobin concentration is one of the most important determinants of the oxygen-carrying capacity of the blood. Low hemoglobin in COVID-19 patients, especially on populations at risk of complications and mortality, could indicate that the patients could suffer from a decreased capability of hemoglobin to support the increased peripheral tissue demands for oxygen due to the hyper-metabolic states during infection.[4] This in turn might worsen the prognosis with accompanying complications like multi organ dysfunction and acute respiratory distress syndrome. Also, COVID-19 by itself is known to cause iron dysmetabolism and cause anemia by various mechanisms especially in patients with severe

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COVID 19 infections, which further accelerates the disease progression.[5]

Hence this study is being done to correlate the severity of anemia with the disease outcome in patients suffering from COVID 19 infection.

MATERIALS AND METHODS

The prospective study was carried out between March and May 2020 at a Bengaluru-based hospital setting. Approval and clearance were obtained from the institutional ethics committee. The study included patients aged ≥ 18 years of both the gender, diagnosed with COVID-19 infection by RT-PCR technique. The study excluded patients <18 years and those not willing to provide signed informed consent prior to the study. Case record form with follow-up chart was used to record the demographic data, clinical features of the disease and investigation.

The demographic and clinical data collected were age, sex, socioeconomic status, occupation, travel/contact history, blood group, vaccination details, clinical symptoms and incidence of comorbidities like hypertension, diabetes, and metabolic renal cardiac and respiratory disorders. Hemoglobin levels of the included subjects were measured and recorded in the case proforma. All the selected participants were followed up until discharge or death.

Statistical analysis

SPSS version 20 was used to perform the statistical analysis. Data was entered in the excel spread sheet. Descriptive statistics of the explanatory and outcome variables were calculated by median and IQR (based on normalcy test- Shapiro Wilk test - data was not normally distributed, hence non-parametric tests are applied) for quantitative variables, frequency and proportions for qualitative variables. Inferential statistics like Mann-Whitney test was applied to check the statistical difference of Hb levels between the groups (Discharged and Death). The level of significance was set at 5%.

RESULTS

The study considered 1212 patients admitted to the hospital and was diagnosed positive for COVID-19. The demographic and clinical characteristics considered for the analysis are given in Table 1. The average age of the patients was 43.89±15.58 years. The gender distribution has been depicted in Table 2. The average levels of hemoglobin and other blood parameters including inflammatory markers in discharge group and death group has been depicted in Table 3 and Table 4 respectively. The median

Table 1: Baseline and Clinical characteristics of the participants

Variable	Total (n= 1212)
Age (years)	43.89±15.58
Age Group	
<30 years, n (%)	256(21.19)
30-39 years, n (%)	277(22.86)
40-49 years, n (%)	226(18.66)
50-59 years, n (%)	218(18.01)
60-69 years, n (%)	145(12.04)
≥70 years, n (%)	75(6.22)

Table 2: Gender Distribution

Gender	n = 1212
Male	746
Female	466

Hb level in the discharge group was 13.1 while that of the death group was 11.85. Mann whitney test done showed significant correlation between the Hb level and the disease outcome ($p < 0.05$) as depicted in Table 5. The Hb level was significantly lower in the patients who died than the patients who were discharged.

DISCUSSION

There are several mechanisms proposed to correlate the iron dysmetabolism in COVID 19 infection. A viral interaction with hemoglobin molecule, through ACE2, CD147, CD26 and other receptors located on erythrocytes and/or blood cell precursors, has been highlighted. it has been argued that hemoglobinopathy would derive from viral endocytosis, through a linkage between spike proteins and cell receptors causing hemolysis.[6,7] SARS-CoV was previously shown to interfere with hemoglobin at erythrocyte and bone marrow level; in fact, through CD147 and/or CD26, the new SARS-CoV-2 attack to bone marrow erythroblasts.[8] The progressively decreased hemoglobin level may lead to a sideroblastic-like anemia pattern, with myelodysplastic features, as per the acute need to replace dysfunctional erythrocytes. Red cell distribution width (RDW) represents a reliable marker of myelodysplasias, being higher when immature cells are produced. COVID-19 literature repeatedly highlights a generally increased RDW, which is significantly higher (>14.5%) in deceased or critical patients.[9,10]

The GRP78 receptor has been considered another SARS-CoV-2 entry facilitator. [11]This endoplasmic reticulum heat shock protein is also located in bone marrow stem cells. Putatively, this additional receptor would facilitate anti-hemoglobin viral action on hematopoietic stem cells.[12] Mimicking hepcidin action, SARSCoV-2 might

Table 3: Basic parameters (Discharged patients)

	Discharge					P value
	Mean	SD	Q1	Median	Q3	
Hb	13.01	2.17	11.80	13.20	14.60	<0.005 Statistically significant for all parameters using Mann Whitney test
TLC	7868.62	3100.70	5800.00	7300.00	9300.00	
N	64.29	29.90	55.00	63.00	73.00	
L	27.14	11.47	19.00	27.00	34.00	
NLR	2.65	2.18	1.50	2.10	3.10	
LDH	281.01	143.01	196.00	240.00	323.00	
D-Dimer	1.16	5.66	0.30	0.60	1.00	
CRP	62.31	835.18	1.00	4.20	20.50	
Ferritin	288.79	391.87	60.23	153.90	337.13	
Hospitalization Duration	9.31	4.86	7.00	8.00	11.00	

Table 4: Basic Parameters (Death patients)

	Death					P value
	Mean	SD	Q1	Median	Q3	
Hb	11.17	2.62	9.25	11.85	13.20	< 0.005 Statistically significant for all parameters using Mann Whitney test
TLC	14078.54	33879.38	6975.00	9650.00	13225.00	
N	80.35	11.57	73.75	84.00	89.00	
L	13.45	9.02	7.00	12.00	17.00	
NLR	9.22	8.16	3.75	6.50	13.85	
LDH	548.38	278.47	358.50	513.00	696.00	
D-Dimer	1.98	3.03	0.50	1.10	2.18	
CRP	122.07	103.43	43.25	99.15	169.68	
Ferritin	939.84	711.02	311.00	932.00	1616.00	
Hospitalization duration	5.65	6.53	1.00	3.50	8.00	

Table 5: Comparison of Hemoglobin levels between the groups (Discharged and Death)

	N	Minimum	Maximum	Median	IQR	P value
Discharged	1130	4	137	13.1	2.8	<0.001 Statistically significant for all parameters using Mann Whitney test
Death	82	3.9	17.2	11.85	3.95	

remarkably increase circulating and tissue ferritin (affecting liver, spleen, bone marrow and muscles mainly), while inducing serum iron deficiency and lack of hemoglobin, by consequence. Hyperferritinemia gives rise to ferroptosis, with high oxidative stress and lipoperoxidation, ultimately increasing mitophagy with accelerated cell apoptosis/necrosis.[13] In fact, cell iron overload is tolerated up to a threshold, as with silent hypoxia (COVID-19 first phase). The increasing ferroptosis- linked multi-organ oxidative stress can precipitate the inflammatory/immune over-response (the so-called *interleukine storm*) in later, most critical stages. Laboratory data show a relevantly lower hemoglobin level and higher ferritin levels in non-surviving patients, over the survivors. [9,14,15]

Hence all these various mechanisms might contribute to a state of iron dysmetabolism and anemia especially in severe COVID 19 infections. In a meta-analysis by Taneri et al.,[16] hemoglobin levels were found to be significantly lower in patients with severe COVID-19 as opposed to mild to moderate cases. A similar study done by Henry et al.,[17] also showed similar results. The results of our study were also concurring with the results of the above-mentioned studies. Although these mechanisms have been proposed wherein the COVID 19 infection itself leads to a state of anemia, these are to be substantiated with further evidence. There is also a contrary assumption that the anemia in COVID 19 can be as a result of a precipitated anemia of chronic disease of the underlying comorbid conditions rather than COVID 19 infection by itself causing the anemia. Hence further study needs to be done to elucidate the mechanism correlating the severity of COVID 19 infection and the level of anemia

CONCLUSION

Our study has emphasized the clinical utility of Hemoglobin level as a significant predictor of outcome of COVID 19 disease. Severe anemia as noted by low hemoglobin level was associated with a poorer outcome in the form of increased mortality. It provides an indication to the prognosis of the illness and can ensure prioritized treatment of such patients who might develop a severe disease.

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Author's Contribution:
AHR-Concept and design of the study; prepared first draft of manuscript; **RS**- Interpreted the results; reviewed the literature and manuscript preparation and revision of the manuscript**;** Statistically analyzed and interpreted, preparation of manuscript; **RK-** Concept, coordination, review of literature and manuscript preparation.

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