

Prevalence of Anaemia and its Association with Severity of COVID-19 among Hospitalised Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) emerged as a global pandemic and was associated with various haematologic abnormalities. There are very few studies from India regarding the association between anaemia and disease severity of COVID-19.

Aim: To check the prevalence of anaemia and its association with severity of disease among hospitalised COVID-19 patients.

Materials and Methods: This was a cross-sectional study involving 203 patients admitted in general ward and Intensive Care Unit (ICU) of a tertiary care hospital in eastern India. Complete blood count at admission along with other relevant clinical and laboratory parameters was noted. Haematological parameters of the patients were described and then correlated with disease severity and death. Spearman's correlation and Chi-square test were used to determine the associations.

Results: Out of 203 patients with COVID-19, 145 (71.4%) had anaemia. The study included 107 males (52.7%) and 96 females (47.3%), of which 77 (80%) females had anaemia compared to 68 (63.5%) males. Co-morbidities were present in 73 patients. Haemoglobin levels were significantly negatively correlated with disease severity ($p < 0.001$). This was even true for patients without any other co-morbidities ($p < 0.05$). Haemoglobin was also negatively correlated with deaths in this study ($p < 0.05$).

Conclusion: The prevalence of anaemia in admitted patients of COVID-19 was very high and low haemoglobin levels were associated with more severe disease and death. So, low haemoglobin levels in COVID-19 may be considered as a risk factor for more severe disease and death.

Keywords: Blood count, Co-morbidity, Coronavirus, Death, Severe

INTRODUCTION

COVID-19 has emerged as a global pandemic with officially recorded over 628 million cases and over 6.5 million deaths as of November 2022 [1]. India also had to bear a major impact with more than 44 million cases and 0.5 million deaths till date [2].

Haematologic abnormalities in the form of reduced lymphocytes and increased neutrophil:lymphocyte ratio and its association with severity has been extensively studied and reported [3-5]. In a Chinese study in 2021, the association between anaemia and COVID-19 was described [6]. However, the association between haemoglobin levels of patients and their outcome has been less frequently described in the Indian context [7]. There is inadequate data with respect to this association in Indian patients across all classes of severities ranging from mild to severe COVID-19. Haemoglobin level as a risk factor for severe disease has not been studied adequately in the Indian context. The Indian study that has been found on this subject has shown increased severity of disease associated with low haemoglobin levels but it has included only patients from ICUs [7]. So, naturally that study included patients only with severe disease but not the vast majority of the patients with mild or moderate disease who were managed in general wards. This current study included patients from both general wards and ICU so that the subjects belong to all classes of severities and also included those with and without co-morbidities. This present study aimed to analyse the prevalence of anaemia on admission in hospitalised patients of COVID-19 and the association of haemoglobin levels with the severity of COVID-19 and death.

MATERIALS AND METHODS

This cross-sectional study was conducted on the hospitalised patients admitted between March 2021 and October 2021 in ESI-PGIMS and ESIC Medical College and Hospital, Joka, Kolkata, West Bengal, India. Ethical clearance was taken from the Institutional Ethics Committee (IEC) for the study {No. 412 (Dean Joka)/IEC (Joka)/2022}.

Inclusion criteria: All hospitalised patients who were tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus infection by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test or Rapid Antigen Test (RAT) were included in the study.

Exclusion criteria: Patients who had incomplete data (inadequate documentation of clinical parameters) to determine severity and incomplete investigation reports of complete blood count and patients who left hospital against medical advice were excluded from the study. The number of total exclusions were 36.

Procedure: After satisfying the inclusion and exclusion criteria, a total of 203 patients were included in the study. The clinical notes indicating the severity of COVID-19 (mild/moderate/severe) were studied and noted. The classification was based on the official COVID-19 management protocols issued by the Ministry of Health and Family Welfare, Government of India [8]. Mild cases had no shortness of breath or hypoxia, moderate cases had dyspnoea and/or hypoxia (oxygen saturation 90-93% on room air), respiratory rate of more or equal to 24/minutes. Severe cases had features of pneumonia along with either of Oxygen saturation $< 90\%$, respiratory rate > 30 and severe respiratory distress. The data studied were the clinical findings including the age, pulse rate, blood

pressure, sensorium, respiratory rate and oxygen saturation along with the presence of any co-morbidity.

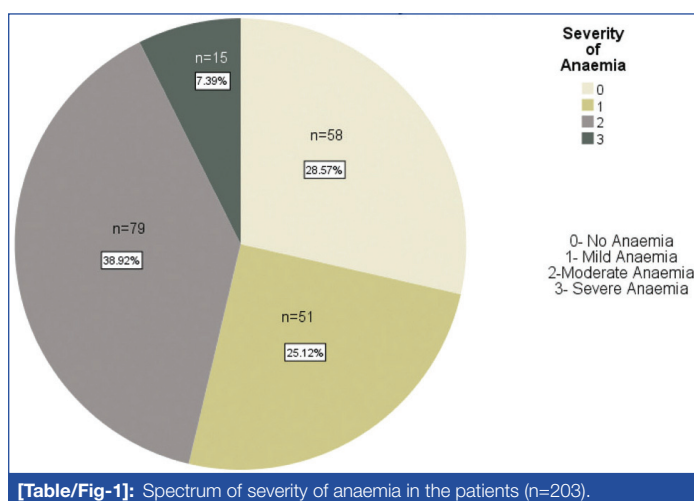
Laboratory data on complete blood count in the form of haemoglobin, neutrophil, lymphocyte and neutrophil:lymphocyte ratio was studied. Clinical outcomes were also noted in the form of death or discharge. The random capillary blood glucose, serum urea, creatinine and C-reactive protein on admission were noted. World Health Organisation (WHO) recommendations were followed for diagnosis and severity assessment of anaemia [9]. Anaemia is defined as haemoglobin <13 and 12 g/dL, respectively for adult males and non pregnant adult women respectively. The cut-off level is 11 g/dL for pregnant women. Anaemia is further classified into severe (<8 g/dL for men and non pregnant women, <7 g/dL for pregnant women), moderate (8<Hb<11 g/dL for adult men and non pregnant women, 7-10 g/dL for pregnant women) and mild (Hb=11-13 g/dL for adult men, 11-12 g/dL for adult non pregnant female and 10-11 g/dL for pregnant women).

STATISTICAL ANALYSIS

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 18.0. Descriptive statistics in the form of mean, median, range and standard deviation of the parameters were studied. Spearman correlation was done between the haemoglobin levels and the severity of COVID-19. Correlation between COVID-19 deaths and haematological parameters were also assessed. Chi-square test was done to see the association between severity of anaemia and severity of COVID-19. A p-value <0.05 was considered to be statistically significant.

RESULTS

The total number of patients recruited in the study were 203 with 107 males (52.7%) and 96 females (47.3%). The mean±SD age was found to be 55.7±15.34 years (range 18-88 years). The mean±SD haemoglobin level was 11.14±2.17 g/dL (range 4.3-16.6 g/dL). Anaemia was found in 145 patients (71.4%), 77 out of 96 (80%) female patients had anaemia, whereas 68 out of 107 (63.5%) male patients had anaemia. Anaemia was significantly associated with female sex (Chi-square value 6.88, p-value<0.01). Mild anaemia was found in 51 patients, moderate in 79 patients and severe was found in 15 patients [Table/Fig-1]. [Table/Fig-2] shows the descriptive statistics of the demographic, clinical and laboratory parameters of the patients.



[Table/Fig-1]: Spectrum of severity of anaemia in the patients (n=203).

The number of patients categorised as having mild, moderate and severe disease were 89 (43.8%), 38 (18.7%) and 76 (37.4%), respectively. The number of deaths was 41 (20.2%). [Table/Fig-3] shows a glimpse of co-morbidities found in the patients. The most common co-morbidities were hypertension 66 (32.5%) and Diabetes Mellitus 49 (24.1%). Eight of the included patients were pregnant out of which one had an abortion and four underwent caesarean section at term.

Variables	Range (Min-Max)	Mean	Median	Standard deviation	Standard error of mean
Age (in years)	70 (18-88)	55.73	58	15.34	1.08
Pulse (Heart Rate)/minute	66 (68-134)	93.3	92	10.5	0.74
Systolic blood pressure (in mm Hg)	120 (60-180)	131.1	132	17.6	1.23
Diastolic blood pressure (in mm Hg)	72 (40-112)	84.9	84	9.8	0.69
Respiratory rate (/minute)	28 (16-44)	26.36	24	7.7	0.54
SpO ₂ (Oxygen saturation at room air)	36 (64-100)	89.7	90	7.6	0.54
Haemoglobin (g/dL)	12.3 (4.3-16.6)	11.14	11.2	2.17	0.15
Total leukocyte count (/cmm)	34700 (1800-36500)	10208.9	9200	5460	384.17
Neutrophil %	55 (40-95)	71.76	72.5	10.74	0.76
Lymphocyte %	46 (4-50)	23.37	22.5	10.29	0.72
Neutrophil: Lymphocyte ratio	22.95 (0.8-23.75)	4.29	3.18	3.56	0.25
C-reactive protein (mg/dL)	182 (2-184)	24.63	12	28.4	1.99
Capillary blood glucose (mg/dL)	386 (70-456)	111	104	66.5	4.67
Urea (mg/dL)	164 (18-182)	39.39	33	28.04	1.97
Creatinine (mg/dL)	18.4 (0.6-19)	1.66	1.1	2.33	0.16

[Table/Fig-2]: Descriptive statistics of the demographic, clinical and laboratory parameters.

Co-morbidities	Total number (%)	No. of males	No. of females
Total patients with co-morbidities	73 (36)	41	32
Hypertension	66 (32.5)	37	29
Diabetes mellitus	49 (24.1)	22	27
Obstructive airway disease	15 (7.4)	11	4
Ischaemic heart disease	12 (5.9)	6	6
Acute kidney injury	14 (6.9)	9	5
Chronic kidney disease	10 (4.9)	4	6
Others	9 (4.4)	5	4

[Table/Fig-3]: Comorbidities and their percentages.

*Others: 1 Beta-Thalassaemia, 1 Carcinoma breast, 1 Pulmonary tuberculosis, 1 Seizure disorder, 1 Chronic liver disease, 2 Lower gastrointestinal bleeding, 2 Ischaemic stroke

Severity of anaemia	Severity of COVID-19 disease				χ^2 test
	Mild	Moderate	Severe	Total	
No anaemia	36	6	16	58	χ^2 -19.69, df-6, p-value<0.005
Mild	24	11	16	51	
Moderate	25	20	34	79	
Severe	4	1	10	15	
Total	89	38	76	203	

[Table/Fig-4]: Association between severity of anaemia and severity of COVID-19.

Significant positive association was found between the severity of anaemia and the severity of disease (Chi-square value: 19.68, p-value<0.005) [Table/Fig-4].

The analysis of data revealed that there was significant negative correlation between haemoglobin values and severity of COVID-19. (Spearman's rho-0.306, p-value<0.001). This was found to be true even in the 130 patients without any other co-morbidities (Spearman rho:-0.3, p-value<0.05). Haemoglobin level was also found to have mild negative correlation with death (Spearman rho: -0.154, p-value<0.05). The severity was found to have positive correlation with total leukocyte

count (Spearman rho: 0.267, p-value<0.01), Neutrophil count (Spearman rho: 0.375, p-value<0.001), neutrophil:lymphocyte ratio (Spearman's rho: 0.384, p-value<0.001). There was positive correlation between death and neutrophil:lymphocyte ratio (Spearman rho: 0.342, p-value<0.001). [Table/Fig-5] shows the associations of severity of COVID-19 and death with different laboratory parameters.

Variables		Spearman rho	p-value (2 tailed)
Correlation with COVID-19 disease severity	Haemoglobin level	-0.306	<0.001
	Total leukocyte count	0.267	<0.001
	Neutrophil	0.375	<0.001
	Lymphocyte	-0.386	<0.001
	Neutrophil: Leukocyte ratio	0.384	<0.001
Correlation with death	Haemoglobin level	-0.154	<0.05
	Total leukocyte count	0.175	<0.05
	Neutrophil	0.32	<0.001
	Lymphocyte	-0.344	<0.001
	Neutrophil: Lymphocyte ratio	0.342	<0.001

[Table/Fig-5]: Correlation of COVID-19 death and disease severity with haematological parameters.

DISCUSSION

This cross-sectional data from a tertiary care government hospital in eastern India shows that anaemia is highly prevalent with presence in 71.4% of patients admitted with COVID-19. Female sex had higher prevalence of anaemia than males. Other studies from India and abroad have shown high prevalence of in COVID-19 patients [6,7,10-12]. A study by Jha M et al., on 784 COVID-19 patients from India in 2022 showed anaemia prevalence of 44% [6]. Studies by: i) Chen C et al., from China in 2021 with 137 patients showed prevalence of 44.5%; ii) Oh SM et al., from USA in 2021 with 4356 patients showed prevalence of 43.3%; iii) Bergamaschi G et al., from Italy in 2021 with 206 patients showed prevalence of 61%; and iv) Faghih Dinevari M et al., from Iran in 2021 with 1274 patients showed prevalence of 48.3% [7,10-12]. So, anaemia can be considered as a common manifestation of COVID-19. Lower haemoglobin levels were found to be associated with increased severity of infections and also death. Haemoglobin level was found to be significantly associated with severity of disease even in patients who didn't have any other comorbidities suggesting that low haemoglobin levels can be considered as an independent risk factor for more severe disease. Among the co-morbidities, other than hypertension 66 (32.5%) and diabetes mellitus 49 (24.1%), renal impairment 24 (11.8%) in the form of AKI and CKD were found to be the most common associations.

Studies on anaemia in COVID-19 are few especially from India. One study published recently from western part of India has shown the association of anaemia with death in patients admitted in ICUs [6]. This study showed significant correlation between anaemia and disease severity and suggested that anaemia can be included as an independent risk factor for prognostication of COVID-19 but as stated earlier this study involved patients admitted only in the ICU and but didn't include patients from general wards. Another study from USA has also shown that anaemia on admission predicts mortality in COVID-19 patients. It showed that anaemia was independently associated with increased odds of all-cause mortality in hospitalised COVID-19 patients. Also, moderate-severe anaemia (Hb<11 g/dL) was found to be an independent risk factor for severe COVID-19 outcomes [10]. One study from Italy has however shown that though anaemia has been found to be a common manifestation of COVID-19, but it isn't associated with increased mortality [11]. A study from Iran evaluated the effects of anaemia on COVID-19 and was found to be associated with poorer outcomes

including increased mortality [12]. To the best of our knowledge, present study was probably the first study from India evaluating the haemoglobin levels in COVID-19 disease encompassing patients from all grades of severity and admitted in both ICU and general wards.

Hypothetically, anaemia in COVID-19 has been attributed to a number of factors. The major theories are: i) Interaction of SARS-nCov-2 with Haemoglobin by CD 147, CD 26 and some other receptors resulting in a haemoglobinopathy; ii) Hepcidin mimetic action of viral element with ferroportin blockage [13]. Haemoglobin denaturation and iron metabolism dysregulation are considered in some studies as resulting in anaemia in COVID-19 [13].

Limitation(s)

More number of patients could have presented a better analysis of the associations. There was no control group for comparison with patients who were negative for COVID-19. Some conditions like chronic kidney disease, thalassaemia and gastrointestinal bleeding would themselves contribute to the anaemia and increased severity of COVID-19. Co-morbid conditions like obstructive airway disease, diabetes mellitus, ischaemic heart disease themselves may increase the severity of the disease. Also, the haemoglobin level was taken at the time of admission of the patients, so records of past or future haemoglobin estimations indicating any dynamic change could not be evaluated from this study. So, a retrospective cohort or case-control study with larger sample size may provide more information on the causal relationships between risk factors and severity of COVID-19.

CONCLUSION(S)

This study describes the high prevalence of anaemia in COVID-19 in hospitalised patients due to all causes and also attempts to have a glimpse of its association with the severity and outcome. Low haemoglobin, high leukocyte count and high neutrophil:lymphocyte ratio have been found to be associated with increased severity and mortality. So, low haemoglobin levels in COVID-19 may be considered as a risk factor for more severe disease and death. Hence, in a developing country like India with limited resources, with a simple baseline blood test like complete blood count, poorer outcomes in the disease process can be predicted and prevented.

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