Introduction

The COVID-19 pandemic caused by the novel zoonotic coronavirus is a serious health concern for mankind and health care professionals globally. Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) is the gold-standard test for the diagnosis of this viral illness. Though affection of lungs resulting in severe acute respiratory syndrome (SARS-COV2) is the major cause of death, the virus also affects hematopoiesis with several hematological abnormalities. Hematological work-up, such as complete blood count, peripheral smear, reticulocyte count, and G6PD activity, was tested. The pattern of hematological abnormalities was assessed across disease severity groups to identify predictors of severe illness from basic investigation. Also, the interplay between iron deficiency and possible hemoglobinopathy trait and COVID was explored. We intend to study the pattern of hematological abnormalities in COVID-19-positive patients and their correlation with severe illness. Our preliminary findings suggest the need to explore the protective role of hemoglobinopathy traits and iron deficiency against severe COVID illness.

Keywords: Complete blood count, COVID-19, G6PD, hematological parameters, hemoglobinopathy
in the presence of an inflammatory storm. Physiologically, nitrous oxide generated during inflammation or tissue injury combines with Hb, displacing oxygen.\[9\] We shall be testing COVID patients for G6PD activity to assess the relation between G6PD deficiency and severe COVID if any. We also intend to assess if there is an association between possible hemoglobinopathies trait and disease severity using available information.

This study helps to find easily available prognostic markers on complete blood count to predict severe illness in COVID patients. It will also help family physicians to better interpret this data and identify patients with increased risk of severe illness to offer them intensive care.

Initial findings of G6PD activity and hemoglobinopathy trait association with COVID will benefit medical science by paving the way for large-scale studies to understand the relationship between these pathologies if any.

**Materials and Methods**

This is a prospective observational study where 801 RT-PCR-proven COVID-19-positive patients presenting to the COVID care center were included. Pregnant patients and patients with underlying hematological disorders or systemic illnesses causing deranged CBC were excluded from the study. Among the study cohort, 383 (47.8%) were asymptomatic and advised home isolation, and 418 (52.2%) were admitted for hospital care. They were categorized as asymptomatic, mild, moderate, and severe at admission as per national guidelines. For further analysis, asymptomatic and mild versus moderate and severe categories were clubbed as the intention was to identify the patients with moderate and severe illness requiring hospitalization and intensive management. EDTA sample was collected for all the patients at first visit to the hospital or at admission after testing positive. CBC was performed using Mindray BC-6000 fully automated hematology analyzer. Various parameters such as Hb; total leucocyte count (TLC) and platelet; absolute counts for neutrophils, lymphocytes, monocytes, and eosinophils; and neutrophil/lymphocyte ratio (NLR) were calculated and analyzed among different groups of disease severity. Peripheral smear examination was done in case of any abnormal flag or CBC abnormality. Quantitative G6PD assay was done by measuring change in absorbance after addition of substrate in 114 patients.

In patients with mean corpuscular volume (MCV) <76 fl (125 patients), Mentzer’s index was calculated as MCV/RBC count × 10. Serum iron studies were also checked for this group of patients. Among them, patients with Mentzer’s index of less than 13 and normal serum ferritin were taken as probable heterozygous beta thalassemia. To confirm cation exchange, Hb HPLC was done using Bio Rad D10 for five such patients and all confirmed to be carriers of hemoglobinopathy (Supplementary data). Distribution of such patients was analyzed among different groups of COVID patients to analyze if there is any protective role of such hemoglobinopathy traits or iron deficiency anemia for severe illness.

**Statistics**

Patient demographic and clinical characteristics such as age group, gender, and severity of COVID-19 were presented as frequencies and percentages. Similarly, all the hematological parameters were summarized as percentages. To identify factors associated with severity of illness, the COVID-19 illness was initially categorized into non-severe (asymptomatic and mild illness) and severe (moderate and severe) illnesses. The categorized severe and non-severe COVID-19 were cross-tabulated across a range of demographic, clinical, and laboratory parameters. The independent association of each factor with the severity of illness factors was determined by multivariate logistic regression analysis. Factors that were statistically significant in univariate analysis were subjected to logistic regression modeling. In the logistic regression, severe illness was the dependent variable, and demographic, clinical (comorbidities), and laboratory parameters were considered as independent variables. Association of these significant factors was presented as odds ratio with 95% CI. Statistical significance was considered at \( P = 0.05 \).

**Results**

In total, 801 RT-PCR-positive patients were enrolled in the study. The mean age of our study cohort was 42.8 years with a male: female ratio of 1:8:1 (518:283). Out of them, 283 patients (35.3%) were more than 50 years of age. Figure 1 summarizes the population characteristics and distribution of these patients as per disease severity and subset of patients with various comorbidities.

Table 1 summarizes the mean values of various parameters in the study cohort and distribution of abnormal values in the study group (n = 801), with G6PD activity noted in 114 patients. All 114 patients had normal G6PD activity with a mean value of 7.66.

Peripheral smear examination was done in cases where CBC showed flagging. Common findings encountered in such patients were activated lymphocytes (virocytes), pseudo Pelger–Huet neutrophils, and a few showing toxic granules and large granular lymphocytes [Figure 2].

Various patient characteristics were analyzed across disease severity categories to look for any parameter having an association with disease severity. It was observed that patients having comorbidities such as diabetes hypertension; ischemic heart disease, and asthma were more likely to suffer from moderate to severe illness than patients having no comorbidities. \( (P < 0.01 \) for each comorbidity). Female patients and patients aged less than 50 years were more likely to have milder illness with \( P < 0.01 \).

Laboratory parameters of these patients were analyzed for any correlation with severity to identify the predictors of severity in COVID patients from basic investigations done routinely for all patients. Table 2 summarizes the distribution of various
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abnormalities in laboratory parameters and their distribution across disease severity groups.

Leukocytosis, neutrophilia, lymphopenia, monocytopenia, eosinopenia, and thrombocytosis were the hematological parameters identified to be associated with more severe illness with \( P < 0.05 \) as summarized in Figure 3.

Multivariate analysis was done using these laboratory parameters, and statistically significant demographic characters were identified as predictors of severe COVID illness. Results of this analysis are summarized in Table 3 showing parameters that were found to be associated with or protective for moderate and severe illness with adjusted \( P < 0.05 \).

On multivariate analysis, only old age, male gender, diabetes, neutrophilia, lymphopenia, monocytopenia, and eosinopenia showed association with moderate to severe illness with \( P < 0.05 \). Similar multivariate analysis was done to identify lab parameters as predictors of mortality in 18 patients of the study cohort. Only age >50 years and diabetes were found to be a predictor of mortality. The rest of the lab parameters were not found statistically significant.

Discussion and Conclusion

SARS-COV-2 has developed significant concerns about morbidity and mortality. The focus is to identify demographic and laboratory markers that help us in better triaging COVID patients. We studied the hematological parameters of 801 COVID patients presented to the COVID care center; 176 (~22%) patients had moderate and severe illness, and 18 succumbed to death.

Similar to the studies by Liao et al.,[7] Shi et al.,[8] and Ejaz et al.[9] we found increasing age and comorbidities (DM, IHD, asthma, and HTN) to be associated with severe illness with \( P < 0.05 \);

| Parameter with normal range | Mean | Std. deviation | Normal (%) | Below normal (%) | Above normal (%) |
|-----------------------------|------|----------------|------------|-----------------|-----------------|
| Total leucocyte count (4-10×10⁹/micro l) | 6.7 | 4.14 | 626 (78.15) | 100 (12.48) | 75 (9.36) |
| ANC (2-7×10⁹/micro l) | 4.3 | 3.1 | 692 (86.39) | 23 (2.87) | 86 (10.74) |
| Lymphocytes (20%-40%) | 27.9 | 11.9 | 484 (60.4) | 211 (26.34) | 106 (13.2) |
| ALC (1-3×10⁹/micro l) | 1.75 | 1.46 | 611 (76.28) | 142 (17.73)* | 48 (5.99) |
| N/L ratio (high is >4) | 3.57 | 9.19 | 634 (79.15) | 167 (20.85) |
| Monocytes (2-10%) | 7.42 | 2.70 | 689 | 49 | 63 |
| Absolute monocyte count (0.2-1×10⁹/micro l) | 470 | 30 | 755 (94.26) | 34 (4.24) | 12 (1.5) |
| Eosinophils (1%-6%) | 1.53 | 1.99 | 104 | 17 | 551 (68.79) |
| AEC (0.02-0.5×10⁹/micro l) | 0.279 | 0.2120 | 0.94 | 0.55 | 133 |
| RBC (5±0.5 million/micro l) | 4.85 | 0.73 | 194.313 | 138.0081 |
| Hb (15.2 g/dl- Males) (13±1.5 g/dl-Females) | 13.5 | 1.8 | 689 (86.02) | 49 (6.12) | 63 (7.87) |
| Plts (1.5-4.5 lac/micro l) | 269.74 | 89.60 | 727 (90.76) | 46 (5.76) | 28 (3.5) |
| PL RATIO | 7.66 | 1.32 | 7.66 |
| Reticulocyte count (0.5%-2.5%) (n=141) | 0.94 | 0.55 | 0.94 |
| G 6PD activity (n=114) (U/g of Hb) | 7.66 | 1.32 | 114 (100) |

*Out of 142 patients having lymphopenia 17 patients (2.12%) had severe lymphopenia with values <500/mm³

Figure 1: Demographic and patient characteristics of the study cohort (n = 801)

Figure 2: (a) Leishman stained peripheral smear showing hypogranular and hypolandate-pseudo Pelger–Huet neutrophil (400×). (b and d) Activated lymphocyte with moderate dark blue cytoplasm (1000×). (c) Large lymphocyte with many azurophilic granules in cytoplasm (1000×)
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however, only diabetic status was found to be a predictor of mortality. Increased expression of ACE‑2 receptor and impaired immunity in chronic illnesses facilitate the entry of the virus, causing more severe illness.

**Basic hematological parameters**

Many studies and meta‑analyses[10‑12] have found CBC parameters such as leukocytosis, lymphopenia, and thrombocytopenia as predictors of severe illness and even as predictors of mortality. Out of several parameters, lymphopenia is persistently found to be associated with severe illness. Letícia de Oliveira Toledo et al.[13] summarized the various mechanisms of lymphopenia in COVID patients as direct cytolysis of lymphocytes expressing ACE‑2, immune‑mediated destruction of lymphocytes, and atrophy of lymphoid organs. Our study echoes with the literature in identifying neutrophilia, lymphopenia, and high NLR ratio at baseline as biomarkers predicting severe illness and helpful in triaging patients.

In addition to this, we found that patients with eosinopenia (227, 28.34%) and monocytopenia (34, 4.24%) are likely to have more severe illness. SARS‑COV‑2 is known to be associated with eosinopenia, with several underlying mechanisms such as reduced eosinophilopoeisis, decreased release from marrow, or type 1 IFN induced direct apoptosis.[11] Human eosinophils express several endosomal Toll‑like receptors (TLRs) that detect viral microbe‑associated molecular patterns and mount an antiviral response. Also, eosinophilic NO synthase mediated NO and extracellular traps have a direct antiviral effect.[14] Some studies have proved eosinophilia to be protective against severe COVID illness.[15] These are potential explanations of how eosinopenia creates a state of impaired antiviral immune response and hence

| Table 2: Distribution of various abnormal hematological parameters across COVID disease severity groups (n=801) |
|-----------------|-----------------------------------------------|----------------------------------|-----|
| Parameter       | Asymptomatic and mild illness | Moderate and severe illness | P   |
| No Leukocytosis | 577 (79.48)                  | 149 (20.52)                    | <0.01|
| Leukocytosis    | 48 (64)                      | 27 (36)                        | 0.43 |
| No Leucopenia   | 550 (78.4)                   | 151 (21.54)                    | 0.43 |
| Leucopenia      | 75 (75)                      | 25 (25)                        |     |
| No Neutrophilia | 583 (81.54)                  | 132 (18.46)                    | <0.01|
| Neutrophilia    | 42 (48.84)                   | 44 (51.16)                     |     |
| No neutropenia  | 605 (77.76)                  | 173 (22.24)                    | 0.294|
| Neutropenia     | 20 (86.96)                   | 3 (13.04)                      |     |
| No Lymphocytosis| 577 (76.63)                  | 176 (23.37)                    | <0.01|
| Lymphocytosis   | 48 (100)                     | 0 (0)                          |     |
| No lymphopenia  | 559 (84.83)                  | 100 (15.17)                    | <0.01|
| Lymphopenia     | 66 (46.48)                   | 76 (53.52)                     |     |
| NLR not high    | 551 (86.91)                  | 83 (13.09)                     | <0.01|
| NLR high        | 74 (44.31)                   | 93 (55.69)                     |     |
| No Monocytosis  | 618 (78.33)                  | 171 (21.67)                    | 0.09 |
| Monocytosis     | 7 (58.33)                    | 5 (41.67)                      |     |
| No Monocytopenia| 607 (79.14)                  | 160 (20.8)                     | <0.01|
| Monocytopenia   | 18 (52.94)                   | 16 (47.06)                     |     |
| No Eosinophilia | 604 (77.6)                   | 174 (22.37)                    | 0.12 |
| Eosinophilia    | 21 (91.3)                    | 2 (8.7)                        |     |
| No cosinopenia  | 496 (86.41)                  | 78 (13.59)                     | <0.01|
| Eosinopenia     | 129 (56.83)                  | 98 (43.17)                     |     |
| No Anemia       | 590 (78.4)                   | 162 (21.54)                    | 0.25 |
| Anemia          | 35 (71.4)                    | 14 (28.57)                     |     |
| No Polycythemia | 575 (77.91)                  | 163 (22.09)                    | 0.78 |
| Polycythemia    | 50 (79.37)                   | 13 (20.63)                     |     |
| NO Microcytic hypochromic anemia | 519 (76.78%) | 157 (23.2%)                    | 0.047|
| Microcytic hypochromic anemia | 106 (84.8%) | 19 (15.2%)                     |     |
| No IDA          | 566                          | 166                            | 0.11 |
| IDA/Anemia due to inflammation | 59 (85.5%) | 10 (14.5%)                     |     |
| No beta thal trait | 578 (77.58) | 167 | 0.269 |
| Likely Beta thalasemia trait* | 47 (83.9%) | 9 (16.07%) |     |
| No Thrombocytopenia | 593 (78.54) | 162 (21.4) | 0.15 |
| Thrombocytopenia | 32 (69.57)                  | 14 (30.43)                     |     |
| No Thrombocytosis | 611 (79.04)                | 162 (20.96)                    | <0.01|
| Thrombocytosis  | 14 (50)                      | 14 (50)                        |     |

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severe illness. The prevalence of eosinopenia in our study cohort was still lower than >50%\cite{16,17} in the literature.

Though increased contribution in both inflammation and thrombosis by platelet has been documented, reactive thrombocytosis is not often described in COVID patients.\cite{18} However, in our study, cohort thrombocytosis was documented in 28 (3.5%) of patients. This difference can be attributed to other secondary infections developing in our patients and hyperactive inflammation. Supportive microbiological data for that is not available; however, 17 patients had raised markers of inflammation as IL-6, CRP. Also, thrombocytosis was found to be associated with moderate and severe illness with P < 0.05. This needs to be verified in a large dataset.

According to the literature, COVID patients are likely to develop thrombocytopenia more than thrombocytosis due to decreased production and increased destruction. Similar to Liao et al.,\cite{7} only 5.76% of study cohort showed thrombocytopenia, which is less than MERS and SARS. None of our patient had severe thrombocytopenia and bleeding.

The primary physician attending most of the patients in pandemic can use these simple CBC-based markers of severe illness and perform a crucial role by offering more intensive therapy to patients with these derangements on CBC.

**Newer hematology insights**

It has been hypothesized that SARS-COV-2 attacks one of the beta-globin chain molecules and captures porphyrin to inhibit haem metabolism. A group has found heterozygous beta-thalassemia protective against COVID.\cite{19} On the contrary, patients with homozygous hemoglobinopathy are considered high-risk patients and advised strict home isolation to avoid infection.\cite{20}

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**Table 3: Results of multivariate analysis of various statistically significant parameters with disease severity. Only parameters with an adjusted P<0.05 shown in the table**

| Parameter                  | n  | Asymptomatic and mild illness | Moderate and severe illness | P      | Adjusted OR 95% CI | Adjusted P |
|----------------------------|----|-------------------------------|----------------------------|--------|--------------------|------------|
| Gender Female              | 283| 248 (87.63%)                  | 35 (12.4%)                 | <0.01  | 0.39 (0.24-0.63)   | <0.01      |
| Male                       | 518| 377 (72.78%)                  | 141 (27.2%)                | <0.01  | 2.46 (1.57-3.85)   | <0.01      |
| Age <50                    | 518| 453 (87.45)                   | 65 (12.55)                 |          |                    |            |
| Age >50                    | 283| 172 (60.78)                   | 111 (39.22)                | <0.01  | 3.8 (2.1-7.08)     | <0.01      |
| Non-diabetic               | 630| 535 (84.92%)                  | 95 (15.1%)                 |          |                    |            |
| Diabetes                   | 171| 90 (52.63%)                   | 81 (47.37%)                | <0.01  |                    |            |
| No Neutrophilia            | 715| 583 (81.54)                   | 132 (18.46)                | <0.01  |                    |            |
| Neutrophilia               | 86 | 42 (48.84)                    | 44 (51.16)                 | <0.01  | 3.1 (1.7-5.7)      | <0.01      |
| No lymphopenia             | 659| 559 (84.83)                   | 100 (15.17)                | <0.01  | 2.6 (1.6-4.3)      | <0.01      |
| Lymphopenia                | 142| 66 (46.48)                    | 76 (53.52)                 | <0.01  |                    |            |
| No Monocytopenia           | 767| 607 (79.14)                   | 160 (20.8)                 | <0.01  |                    |            |
| Monocytopenia              | 34 | 18 (52.94)                    | 16 (47.06)                 | <0.01  | 2.8 (1.1-7.2)      | 0.02       |
| No eosinopenia             | 574| 496 (86.41)                   | 78 (13.59)                 | <0.01  |                    |            |
| Eosinopenia                | 227| 129 (56.83)                   | 98 (43.17)                 | <0.01  | 2.8 (1.8-4.4)      | <0.01      |

**Figure 3:** Bar diagram showing lab parameters associated with moderate to severe illness with P < 0.05 (n = 801)
We tried to study if there is any association between disease severity and heterozygous beta-thalassemia. In the study cohort, 125 patients had microcytic hypochromic RBC indices, and it was statistically found to be protective against severe illness and mortality (P = 0.04). P values were more than 0.05 for further analyses for IDA and suspected heterozygous beta-thalassemia. Small study group and lack of definitive testing modality for hemoglobinopathy are the shortcomings of our data.

Iron and COVID

Functional iron overload contributing to inflammation, hypercoagulation, hyperferritinemia, and immune dysfunction has been implicated in the pathogenesis of COVID-19. This made us use hyperferritinemia as a biomarker of disease severity in inflammatory diseases such as COVID-19 and provoked the thought of using iron chelators as a therapeutic agent. We pondered if iron deficiency which is the most common cause of anemia in our country could be playing a protective role against severe COVID illness. Our data lacked statistical significance for the same, with P > 0.05. Literature is divided on this issue as the study by Zhao et al showed lower serum iron level to be associated with severe illness.

However, these findings suggest the potential of research in the field of interplay between iron hemostasis and hemoglobinopathy trait and COVID infection.

Summary

Our study describes various abnormalities found in the hematological parameters of COVID patients. We found old age, male gender, diabetes, neutrophilia, lymphopenia, monocytopenia, and eosinopenia at presentation to be associated with moderate to severe illness and may help in triaging with other inflammatory and radiological parameters. Our small data is a novel attempt to explore the protective role of hemoglobinopathy and iron deficiency from severe illness and warrants further studies to evaluate the same.

Take-home messages from the study are

- Patients with old age, male gender, diabetes, neutrophilia, lymphopenia, monocytopenia, eosinopenia, and COVID presenting to the family physician should be hospitalized and managed more intensively.
- The interplay between hemoglobinopathy and iron and COVID is complex and needs further research.

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Conflicts of interest
There are no conflicts of interest.

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