Introduction

The COVID-19 pandemic caused by SARS-CoV-2 originated in Wuhan, China, in December 2019. The disease spread was rapid to most of the countries across the globe. The disease not only posed an enormous global health threat but also had an adverse socio-economic effect that is expected to be exacerbated in the future. Multiple strategies like lockdown, travel restrictions, and potential treatment initiatives and approaches were developed. Vaccines were developed and mass vaccination along with COVID-appropriate behavior is offering hope. Coronavirus derived its name due to its crown-like appearance on electron microscopy. It belongs to the beta coronaviridae family. Recent evidence highlights transmission by even asymptomatic individuals through aerosol.
Mortality, as well as morbidity, due to COVID-19 is found to be more in the elderly and in those with pre-existing co-morbid conditions. But it is also observed that young and healthy individuals unpredictably succumbed to COVID-19. While the clinical examination and assessment of the patient are indispensable, the laboratory parameters can aid in providing additional information and insight into the patients’ disease, and thus, improve patient management.1,2

Viral infectious diseases like Influenza, varicella, dengue, and acquired immunodeficiency virus, middle east respiratory syndrome coronavirus (MERS Co-V) are associated with hematological changes. The changes have not only aided in monitoring the infectious process but also predicted severity.4 A study by Cataudella et al.5 on 195 patients admitted with community-acquired pneumonia successfully used the neutrophil to lymphocyte ratio as a marker in predicting the prognosis. Similarly, a study on 58 patients with influenza in 2009 by Merkoulias et al.6 has proposed a lymphocyte to monocyte ratio of less than 2 and can be a better screening tool for influenza as compared to rapid tests.

A hematology investigation comprising of complete blood count is the most widely requested and performed test. The COVID-19 disease has a wide social presence and most patients present themselves to primary care physicians at first. Family medicine care providers have a large role in reporting and providing treatment to these patients. A complete blood count (CBC) is a simple test which can be done in most of the clinical laboratories even with limited resources. It is done not only in outpatient settings or small clinics but also in inpatients and multispeciality hospitals. The CBC is widely available, inexpensive, and can provide the clinicians with reliable information regarding the patients’ condition, that in turn, will be helpful in making a reasonable allocation of medical resources.1,7 Our understanding of the pathophysiology of SARS-CoV-2 infection is incomplete, however, rapidly evolving with each day. The correlation of the clinical features with the available biomarkers and radiological investigations and the effect of the treatment are yet to be studied in detail. The study was undertaken to assess the trend of routine hematology parameters and their ability to predict the severity and mortality in COVID-19.

**Material and Methods**

The study is a retrospective observational study conducted at a tertiary care referral hospital with a dedicated COVID-19 care facility. A total of 251 consecutive patients were admitted to the hospital with a diagnosis of COVID-19 from January 1, 2021, to January 31, 2021. Out of these, only 240 patients with complete data were included in the study while 11 patients were excluded due to the unavailability of complete medical data. The confirmation of COVID-19 was done by testing the nasopharyngeal and oropharyngeal swabs by the reverse transcription-polymerase chain reaction (RT-PCR) method. Our hospital is a tertiary care hospital that caters to a large population area and referrals from near and far. Many patients with co-morbid conditions who require regular and continuous care are treated. In the COVID-19 pandemic, many patients with end-stage renal disease, oncological diseases, and other medical and surgical emergencies were diagnosed to have COVID-19 despite being asymptomatic for the COVID-19 infection symptoms. These patients were also admitted to our setup and treated for the respective diseases alongside under observation for COVID-19. The hematology analysis consisting of hemoglobin, total and differential leukocyte count, platelet count, and erythrocyte sedimentation rate was done on a five-part fully automated hemogranalizer (Ruby Cell Dyn, Abbot). A tri-level quality check was done before processing the samples. No separate sample was collected from the patient for the study. The data regarding the patient’s clinical and laboratory status during hospitalization were collected from the Hospital Informatics System. The hematology results were divided into four groups: asymptomatic, mild, moderate, and severe on which the analysis was performed. Data related to hematology investigation were collected from the first day of hospitalization till the discharge or death of the patient. Due to the limitations in analyzing the vast data obtained it was thought appropriate to assess the hematology parameters on three occasions viz. on admission, median day of hospitalization, and last day of hospitalization.

**Ethical clearance:** Ethical approval was obtained from the Institutional Ethical committee with a waiver of consent (IEC-2020-230-IP-EXP-27; PGI/BE/545/2020).

**Statistical analysis:** Continuous variables were presented in median (interquartile range) (mean) whereas categorical variables in frequency (%). The demographic and hematological variables were compared between the severity of the infection (asymptomatic, mild, moderate, and severe infection) using the Kruskal–Wallis H test for continuous variables, whereas the proportions were compared using the Fisher's exact test as the expected frequency in at least one cell was less than 5 followed by multiple comparisons. The receiver operating characteristics curve (ROC Curve) was used to assess the diagnostic accuracy of the inflammatory variables in terms of the area under the receiver operating characteristics curve (AUROC) and for each significant variable, the three most suitable cut-off values were identified with a strategy to obtain the maximum sensitivity or specificity with at least >50% sensitivity and specificity. The classification and regression tree (CART) analysis was used to represent the association between binary outcomes with the most significant variables. A P value <0.05 was considered statistically significant. Statistical package for social sciences, version-23 (SPSS-23, IBM, Chicago, USA) and Med Cals Software were used for data analysis.
A total of 240 patients were included in the analysis. The mean and median age of the patients was 54.5 and 58 years (range: 6 months to 91 years), 164 (68.3%) were males. As per the severity of the disease, 25% were asymptomatic whereas 44.6, 15.4, and 15% were mild, moderate, and severe, respectively. The distribution of the demographic variables, duration of hospital stay and symptoms, frequency of hematological investigation, and the presence of co-morbidity were compared between the disease severities of COVID-19 and are presented in Table 1. The results showed that there was a significantly higher age of the patients with moderate and severe disease compared to the asymptomatic patients’ group with a statistically significant difference ($P < 0.001$). The duration of hospitalization was more as the disease severity increased and so were the number of times the hematology investigation was done. The difference in the duration of stay and number of hematology investigations done was more in the severe disease group with a statistically significant difference ($P < 0.001$). Mortality was seen only in the group with the severe disease 30 (83.3%). The presence of co-morbidity was observed to be increasing with an increase in the severity of the disease. The difference between the asymptomatic and severe disease was statistically significant ($P$-value = 0.002).

The alteration in the hematological variables as compared to the COVID-19 disease severity is shown in Table 2. Multivariate analysis was used to demonstrate the difference across different grades of COVID-19 severity. The multivariate comparison was done to assess the difference across different severity of the disease. Each investigation was done at three points for the assessment on admission, on the median day of hospitalization, and on the last day of hospitalization (death/discharge). The median day and last day are different for each patient depending on the duration of hospitalization.

The total leukocyte count (TLC) and absolute neutrophil count increased as the disease progressed to severity while the lymphocyte and monocyte count decreased with severity. To potentiate the usefulness of CBC, individual leucocytes were clubbed as ratios.

### Table 1: Baseline characteristics of the patients as per the severity of the disease ($n=240$)

| Variables                          | Asymptomatic ($n=60$, 25%) (a) | Mild ($n=107$, 4.6%) (b) | Moderate ($n=37$, 15.4%) (c) | Severe ($n=36$, 15%) (d) | Group-wise comparisons with $P$-value |
|------------------------------------|-------------------------------|--------------------------|------------------------------|--------------------------|-------------------------------------|
| Age (years) Median (IQR)           | 49 (35.3, 61.5)              | 57 (42, 64)              | 62 (53, 69)                  | 62 (51.3, 72.6)          | a-c, a-d (<0.001)                   |
| Gender (male) (%)                  | 39 (65)                      | 72 (67.3)                | 26 (70.3)                    | 27 (75)                  |                                     |
| Duration of symptoms (days) Median (IQR) | 2 (0, 5)                  | 5 (3, 8)                 | 7 (3, 13)                    | 8 (6.3, 14)              | a-c, a-d, b-d & c-d (<0.001)       |
| Duration of hospital stay (days) Median (IQR) | 10 (7, 13)                | 12 (9, 17)               | 17 (13, 20.5)                | 9.5 (5.3, 15.6)          | a-c, b-c, b-d (<0.001)             |
| Frequency of hematological investigation | 2 (1, 5)                        | 5 (3, 8)                  | 12 (9, 15.5)                 | 7.5 (3.128)              | a-c, a-d, b-c, b-d (<0.001)       |
| Median (IQR)                       |                              |                          |                              |                          |                                     |
| Presence of co-morbidity (%)       | 31 (51.7)                    | 66 (61.7)                | 27 (73)                      | 32 (88.9)                | a-c, a-d (0.002)                   |

Kruskal-Wallis H test used. *P*<0.05 significant.

### Table 2: Distribution of hematological parameters between diagnosis ($n=240$)

| Parameters                          | Timing of sampling | Asymptomatic (a) | Mild (b) | Moderate (c) | Severe (d) | Group-wise Comparisons with $P$-value |
|------------------------------------|-------------------|-----------------|---------|--------------|------------|-------------------------------------|
| Hemoglobin (g/dL)                  | On admission      | 12.6 (10.2, 14) | 11.7    | 11.7 (9.9, 12.6) | 11.0 (9.1, 12.3) | - (0.03)                          |
|                                    | Median day        | 12.8 (9.8, 14.1)| 11.8    | 11.8 (10.1, 13.2) | 10.8 (9.1, 11.5) | - (0.02)                          |
|                                    | Last day          | 11.8 (9.7, 13.8)| 11.8    | 12 (9.95, 13.1)  | 9.8 (8.7, 11.7) | b-d (0.002)                        |
| Total leucocyte count ($\times10^3$ cells/mm$^3$) | On admission | 6.75 (5.6, 8.5) | 6.75    | 9.05 (6.6, 12.1)  | 11.9 (8.4, 15.2) | a-c, b-d (<0.001)                |
|                                    | Median day        | 7.2 (5.5, 9.8)  | 7.6     | 11.5 (9.5, 14.2)  | 12.6 (9.1, 16.2) | a-c, b-c, b-d (<0.001)            |
|                                    | Last day          | 7.2 (6.5, 8.7)  | 8.6     | 10.2 (8.1, 12.9)  | 10.5 (7.4, 23.7) | a-d, b-d, c-d (<0.001)            |
| Absolute neutrophil count ($\times10^3$ cells/mm$^3$) | On admission | 4.5 (3.3, 6.0)  | 4.6     | 6 (4.1, 10.1)     | 9.7 (6.4, 13.7) | a-b, a-c, a-d (<0.001)            |
|                                    | Median day        | 5.1 (3.2, 7.3)  | 5.8     | 10.3 (7.9, 12.9)  | 12 (8.2, 15.5) | a-b, a-c, b-c, b-d (<0.001)       |
|                                    | Last day          | 4.4 (2.8, 5.7)  | 5.3     | 7 (1.8, 11.2)     | 9.3 (5.6, 18.0) | a-d, b-d, b-c (<0.001)            |
| Absolute lymphocyte count ($\times10^3$ cells/mm$^3$) | On admission | 1.5 (0.9, 2.2)  | 1.2     | 1.1 (0.6, 1.4)    | 0.7 (0.5, 0.9) | - (0.12)                          |
|                                    | Median day        | 1.4 (0.8, 2.3)  | 1.2     | 0.9 (0.6, 1.4)    | 0.5 (0.3, 1.0) | b-d (<0.001)                      |
|                                    | Last day          | 1.4 (1, 2.3)    | 1.3     | 0.8 (0.3, 1.6)    | 0.6 (0.3, 0.9) | - (0.06)                          |
| Absolute monocyte count ($\times10^3$ cells/mm$^3$) | On admission | 0.5 (0.3, 0.7)  | 0.4     | 0.5 (0.2, 0.8)    | 0.3 (0.2, 0.7) | - (0.31)                          |
|                                    | Median day        | 0.4 (0.2, 0.6)  | 0.4     | 0.5 (0.3, 0.6)    | 0.3 (0.2, 0.6) | - (0.45)                          |
|                                    | Last day          | 0.4 (0.3, 0.6)  | 0.5     | 0.3 (0.1, 0.7)    | 0.3 (0.1, 0.7) | - (0.73)                          |
| Platelets ($\times10^3$ cells/mm$^3$) | On admission | 150 (132, 198)  | 150     | 164 (122.5, 214.5)| 155 (86.25, 242.5)| - (0.74)                         |
|                                    | Median day        | 164 (133, 242)  | 192     | 203 (164, 245)    | 136 (79, 224) | b-d, c-d (0.002)                  |
|                                    | Last day          | 212 (157, 265)  | 220     | 166 (117, 221)    | 99 (53, 153) | a-d, b-d (<0.001)                 |
| Erythrocyte sedimentation rate (mm in 1$^\text{st}$ h) | On admission | 49 (6, 96)      | 65      | 87 (62, 98)       | 85 (44, 97) | - (0.05)                          |
|                                    | Median day        | 33 (9, 77)      | 43      | 51 (27, 95)       | 58 (19, 90) | - (0.80)                          |
|                                    | Last day          | 44 (13, 73)     | 24      | 24 (8, 38)        | 25 (7, 57) | - (0.72)                          |
The ratio between various leukocyte cells was calculated. The neutrophil-lymphocyte ratio and neutrophil-monocyte ratio was observed to be increased while the lymphocyte-monocyte ratio was observed to be decreased. A statistically significant difference was observed between the values for all the ratios between the milder forms of the disease from moderate to severe disease as depicted in Table 3. The error bar depicting the distribution of LMR between diagnosis—on admission, median day, and last day of hospitalization is shown in Figure 1.

Table 4 shows the diagnostic accuracy of the hematological variables on admission for the depiction of severity and mortality.

The elevated NMR and NLR along with decreased LMR at admission were found to be good predictors of severity and mortality in COVID-19. The CART representing the association of mortality with NLR and TLC (x10^3 cells/mm^3) on admission is shown in Figure 2.

**Discussion**

The hematological parameters consist of hemoglobin, leukocytes, and platelets and their subtypes with derived indices. During the disease, these parameters and changes in their values can help in disease monitoring. Also, some hematological parameters or a combination of them can be used to predict severity or outcome. In our study, we observed that the patients who developed moderate to severe disease and required critical care support were a decade older than the patients with milder disease severity. This can be attributed, in part, to the presence of co-morbidities in the higher age groups.

In a retrospective study by Bellman et al. on 259 patients with COVID-19, anemia along with altered homeostasis were found to be common in patients who were hospitalized, and there...
The platelet count was found to be normal as also seen in the present study, while as the severity of the disease increased the lymphocyte count was found to be further decreasing. Other studies by the authors have also found a low lymphocyte count in the patients requiring critical care as well as in the non-survivors. In patients with severe disease, the flow cytometric analysis of the lymphocytes revealed a decrease in CD3, CD4, CD8 T lymphocytes. Lympohpenia was found to be an effective and reliable indicator for not only hospitalization but also predicting severity in the COVID-19 infection. The possible mechanisms include inhibition of the lymphocytes by metabolites like lactic acid, apoptosis due to inflammatory cytokines. A study by Yang et al. on 37 patients concluded that for the detection of COVID-19 pneumonia, a low percentage of eosinophils can be used as a biomarker. Also, a lesser number of eosinophils were seen in the group with severe COVID-19. However, in the present study, no difference was observed in the eosinophil or basophil cells.

A lesser number of monocytes were seen in a severe disease due to selective recruitment at the site of inflammation in the lungs. Contrary to this, studies by a few authors found an increase in the number of monocytes.

The platelet count was observed to be within range with a slight marginal decrease in the patients with severe disease in the present study. Thrombocytopenia was seen in the non-survivors while the normal platelet count was seen in the survivors in the study by other authors. Similarly, the severe patients had a lower platelet count as compared to the non-severe patients. The platelet count was found to be an independent risk factor for mortality in COVID-19. The erythrocyte sedimentation rate was increased as also seen in the present study.

Along with the quantitative changes in the hemoglobin, leucocyte, and platelets, various morphological changes are reported in COVID-19. The peripheral blood smear changes in the neutrophils included pseudo pelgerhuet anomaly, apoptotic neutrophils, and immature and dysplastic granulopoiesis while reactive lymphocytes, some with plasmacytoid appearance were also observed by some authors. Giant platelets were common features. These findings were more pronounced in the severe disease and attributed it to the cytokine storm. While in the present study, the morphological changes were not studied. The qualitative, as well as quantitative changes in the various leucocytes, viz. neutrophil, lymphocyte, and monocyte, are found to be associated with severe COVID-19 disease as well as mortality. These cells have a potent role in the immune response and COVID-19 is associated with the

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prominent systemic inflammatory response. The lymphocytes are involved in the activation of pathogen-specific adaptive immunity, especially in response. Neutrophils are thought to play a role in the primary defense at the respiratory epithelium level and the acute inflammatory response by locally stimulating the release of cytokines IL-1, IL-6, tumor necrosis factor (TNF)-alpha, and reactive oxygen species. The monocytes with their ability to differentiate into alternatively-activated macrophages release interleukin-10 (IL-10) and transforming growth factor (TGF)-beta 1 which regulate hyperactivation of the inflammatory response. Thus, the interplay of neutrophils, lymphocytes, and monocytes is important in regulating the systemic inflammatory response seen in COVID-19.\textsuperscript{[24]}

The NLR is useful in diseases of the respiratory tract like community-acquired pneumonia.\textsuperscript{[5]} A high ratio on admission (NLR $>4$) was found to be a biomarker for COVID-19 as compared to the SARS-negative patients (NLR 2.4).\textsuperscript{[10,22]} Similarly, an increasing ratio was found to be a bad prognostic marker.\textsuperscript{[7]} An NLR value of more than 5 is associated with mortality as also seen in the present study.\textsuperscript{[27,28]} The prognostic role of lymphocyte to monocyte ratio has been well studied in cancers of the bladder and lung and respiratory tract illness caused by influenza while not much has been studied about its role in COVID-19.\textsuperscript{[5,26]} The decreasing value of the ratio can be attributed to a decrease in the lymphocyte and monocyte cell count as the disease becomes severe. The neutrophil to monocyte ratio was found to be increasing with more severe disease. Similarly, an NMR $>17$ was found to be an independent risk factor for mortality in severe COVID-19 as also seen in the present study.\textsuperscript{[28]} Along with the various biomarkers available, the hematology parameters are expected to aid in the understanding of the pathophysiology of the SARS-CoV-2 infection. So, our study shows that primary care physicians can prove a great force in combating this disease and its morbidity and mortality outcomes by asking the patient to be evaluated for a hematological picture. In the absence of sophisticated laboratory facilities and costly tests, a simple test of hematological parameters advised by family medicine clinicians can help us in predicting further clinical outcomes, and the patient can be accordingly managed or transferred to an appropriate health care facility.

Conclusion: The CBC is an easily available, inexpensive, and reliable investigation that can help in providing insights into the patients' COVID-19 status. The combinations of ratio and serial trends of hematology parameters along with clinical assessment can aid in precise decision-making in COVID-19 patient management. With an increase in severity, there is an increase in the TLC and absolute neutrophil count while the absolute lymphocyte count decreases. On admission, the cut-off value of NLR $>5.2$, NMR $>12.1$ while LMR $<2.4$ may predict severity and mortality in COVID-19.

Limitations: The limitations of the study are the small sample size and retrospective nature of the study from a single center.

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How this paper is relevant to the practice of primary care physicians:
- This study is conducted using CBC as a research parameter.
- CBC is a routinely done test, be it OPD or inpatient, primary health center or tertiary health care facility.
- CBC can be done with minimal workforce training in a resource-limited laboratory.
- CBC along with the derived ratios, that is, NMR, NLR, and LMR gives information that has been found to predict disease severity and mortality.
- Thus, CBC, with the derived ratios done on presentation, can aid in COVID-19 patient triaging at the primary assessment itself.

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Conflicts of interest
There are no conflicts of interest.

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