Original Research Article

A study of the association of leukopenia with disease severity and mortality in patients diagnosed with COVID-19

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ABSTRACT

Background: It has been observed in patients suspected with COVID-19 or presenting as confirmed cases of COVID-19 that a decreased total white blood cell count (leukopenia) is quite a common haematological presentation. In this study we aimed to determine the effect of leukopenia on the progress and severity of COVID-19, as well as to establish the association of leukopenia with disease severity and overall mortality.
Methods: This was a longitudinal study conducted at Guru Teg Bahadur hospital, New Delhi from 1st July 2020 to 3rd August 2020. A sample size of 34 cases each in two groups (group A and B) was taken as one random case each day for the duration of the study; group A consisting of the patients presenting with leukopenia, while group B comprising of the patients with a normal leukocyte count.
Results: The mean duration of hospital stay in group A was found to be 5.5±2.23 days, while the mean duration of stay in group B was found to be 2.9±1.17 days, showing a significant difference in the two groups with a p<0.001. It was also seen that a total of 8 out of 34 cases in group A and 2 out of the 34 cases in group B had expired during their hospital stay; a significant difference seen among the two groups with a p=0.04.
Conclusions: Thus, in conclusion, this study demonstrates a definite and significant association between a decreased leukocyte count (leukopenia) and disease severity and mortality in patients with COVID-19.

Keywords: COVID-19, Hospital stay, Leukopenia, Mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease which was first identified in Wuhan, China in December 2019, and was proposed to be caused by a novel coronavirus.[1,2] This virus was reported to be a member of the β group of coronaviruses, and was named as the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) by the international committee on taxonomy of viruses (ICTV).[3,4] It has now led to a full blown pandemic and as of 14th August 2020, more than 21 million cases have been reported across 188 countries and territories, resulting in more than 758,000 deaths.

Although infected birds and animals in the Wuhan seafood markets were initially suggested to be the source of primary infection, many cases which were found subsequently had no history of contact with these animals. This suggested that the virus had a confirmed potential for human to human spread in the community; a phenomenon subsequently reported in more than 100 countries all over the world. The human to the human spread of the virus has been shown to occur via respiratory droplets or aerosols from close contact with an infected person who is actively coughing or sneezing. These virus laden aerosols enter the lungs via inhalation through the nose or mouth.[5,6]

It has been observed in patients suspected with COVID-19 or presenting as confirmed cases of COVID-19, that a decreased total white blood cell count (leukopenia) is quite a common haematological presentation.[7] Although a few studies from China have demonstrated the prevalence of leukopenia in severe and critically ill cases of COVID-19, no significant study has been done in the Indian subcontinent till date to demonstrate this abnormality or to show its association with disease severity or prognosis in patients diagnosed with COVID-19.[8]

Therefore, in this study aim to determine the effect of leukopenia on the progress and severity of COVID-19, as well as to establish the association of leukopenia with disease severity and overall mortality.

METHODS

Study design and population

This was a longitudinal study conducted at Guru Teg Bahadur hospital, New Delhi from 1st July 2020 to 3rd August 2020. The inclusion criteria for the population selected for this study consisted of confirmed COVID-19 positive cases diagnosed by reverse transcription polymerase chain reaction technique (RT-PCR), who were at least 18 years of age or above. Exclusion criteria included pregnant patients, patients of pediatric age group, and patients who left the hospital premises without completing their treatment. Considering the logistical constraints of time and resources for the present study, in absence of any data for sample size estimation pertaining to this study from literature, the subjects were taken in two groups; group A consisting of the patients presenting with leukopenia and group B comprising of the patients presenting with a normal leukocyte count. A sample size of 34 cases each in both the groups was taken as one random case each day for the duration of the study, by using the random number table.

The necessary data was collected from all 68 patients along with their clinical examination, blood pressure, oxygen saturation and the relevant blood tests and investigations. The physician looking after the patients was not aware about the two groups allotted for the study, and the patients were followed up till the date of discharge or the date of expiry. All the 68 participants provided a written informed consent. The blood tests for all the 68 patients were done in the pathology lab of Guru Teg Bahadur hospital, New Delhi. As the differential leukocyte counts were unavailable at the time, a total leukocyte count (TLC) was taken for all the subjects. A research flowchart for the study has been shown below in figure 1.

Statistical Analysis

All continuous variables were presented as mean ± SD, and categorical variables were presented in frequency or percentage. The data thus collected using the study tools was converted into a computer-based spreadsheet and analyzed. Appropriate statistical tests of significance like the chi-square test were used to test the difference in categorical measures, while the Mann Whitney U test was used for finding out the association between leukopenia and the various clinical and laboratory parameters. A $p<0.05$ was considered to be statistically significant.
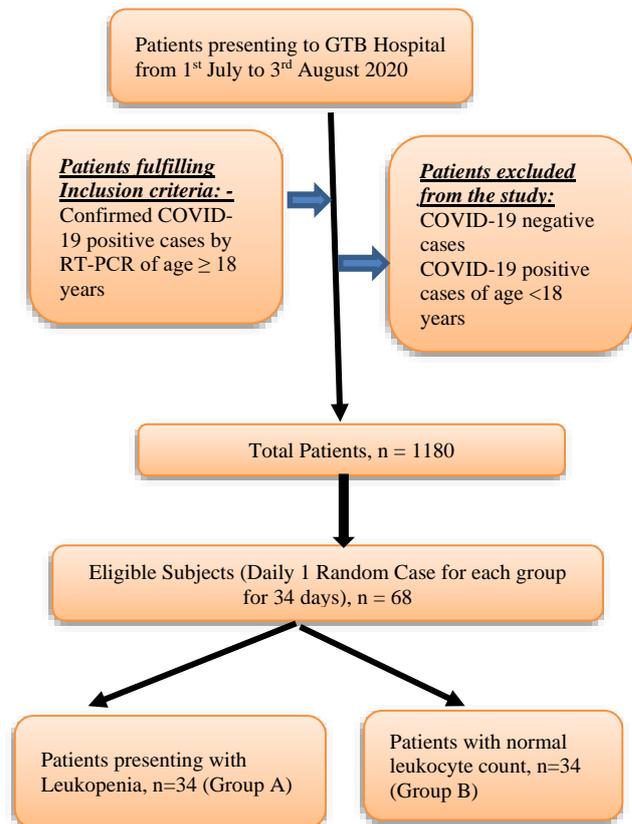

Figure 1: The study flowchart.

RESULTS

Baseline characteristics

A total of 68 patients (34 cases each in group A and group B) were selected for the study after fulfilling all the inclusion and exclusion criteria. The mean age of patients presenting with leukopenia was found to be 49.9±19.11 years, while mean age in patients presenting with a normal white cell count was found to be 46.4±14.97 years. No significant difference was observed in their mean age of both the categories. The mean absolute leukocyte count at presentation in group A and group B were 3032.3±684.34 per mm^3 and 6588.2±1598.62 per mm^3 respectively, showed a statistically significant difference with a $p<0.001$.

Association of leukopenia with morbidity and mortality

After applying the Mann Whitney U test for comparing the duration of hospital stay in the two groups, the mean duration of hospital stay in group A was found to be 5.5±2.23 days, while the mean duration of stay in group B was found to be 2.9±1.17 days, showing a significant difference in the two groups with a p<0.001. The mean oxygen saturation levels in group A and group B were seen to be 87.8±6.84 and 93.1±2.87 respectively, showing a statistically significant difference between the two patient categories.

On observing the outcomes of the patients admitted to the hospital after best possible treatment, it was seen that a total of 8 out of 34 patients in group A and 2 out of 34 patients in group B had expired during their hospital stay. After applying the chi-square test, there was a significant difference seen among both the groups with a p=0.04. No significant difference was observed amongst the males and females of both groups. The comorbidities (Diabetes, Hypertension, Hypothyroidism etc.) were observed to be similar in the two groups; the chi square test showing no significant difference with a p=0.604. The baseline characteristics of the study population and association of leukopenia with increased hospital stay and mortality have been shown below in table 1.

Table 1: Baseline characteristics of the study population and association of leukopenia with increased hospital stay and mortality.

Variables	Group A (n=34) (Mean ± SD)	Group B (n=34) (Mean ± SD)	P value
Age (years)	49.9±19.11	46.4±14.97	0.425
SpO2 (%)	87.8±6.84	93.1±2.87	< 0.001
Duration of hospital Stay (days)	5.5±2.23	2.9±1.17	< 0.001
TLC at time of presentation (mm^3)	3032.3±684.34	6588.2±1598.62	<0.001
TLC at time of discharge (mm^3)	3524.3±1353.39	6782.3±1601.75	<0.001
Random blood sugar (RBS) (mg/dl)	152.4±98.7	140.8±75.6	0.672
Blood sodium level (Na$^+$) at time of admission (mEq/L)	134.2±5.34	138.2±4.13	0.002
Blood sodium level (Na$^+$) at time of discharge (mEq/L)	137.7±3.23	139.4±3.33	0.066
Aspartate aminotransferase level at time of admission (U/L)	41.9±31.34	27.6±23.67	0.017
Aspartate aminotransferase level at time of discharge (U/L)	50.8±39.08	29.9±19.44	0.014
Alanine aminotransferase level at time of admission (U/L)	46.4±39.08	25.9±19.09	0.004
Alanine aminotransferase level at time of discharge (U/L)	59.7±59.3	29.7±35.54	0.009
Total mortality	8	2	0.04

DISCUSSION

In this study, found that COVID-19 patients who had a decreased white blood cell count on presentation to the hospital were seen to have poorer oxygen saturation levels and a longer duration of hospital stay as compared to the patients having a normal leukocyte count on presentation. In addition to these findings, the patients with leukopenia also had a higher percentage of deaths as compared to the control group with normal leukocyte levels, showed a statistically significant association between leukopenia and mortality in patients with COVID-19.

The findings in this study were in accordance with the study done by Guan et al in China among 1099 COVID-19 patients, of whom 33.7% showed leukopenia on admission, and the vast majority (83.2%) had presented with lymphopenia.[9,10] These findings were observed to be more prominent among the severely ill cases as compared to the mild to moderately ill cases (96.1 vs 80.4% for lymphopenia, 61.1 vs 28.1% for leukopenia). These results were similar to a few other studies conducted during the same period in China and including only confirmed cases with COVID-19.[11-14] In two other studies from China and Singapore, lymphopenia was reported in 85% of critically ill patients and in approximately 40% of hospitalized patients respectively.[15,16]

An association was also seen between lymphopenia and the need of ICU care in the same patient population in two separate studies done by Huang et al and Wang et al.[11,13] It was observed in both these studies that majority of the patients needing ICU care were seen to have lymphopenia on presentation, and conversely lymphopenia was also seen to be prevalent amongst the

severely ill COVID-19 patients already in ICU care. In Singapore, a study done by Fan et al observed that the patients of COVID-19 requiring ICU support had significantly lower lymphocyte levels (p<0.001) as compared to the non-ICU patients.[17] Wu et al also showed an association between decreased lymphocyte count and the development of acute respiratory distress syndrome (ARDS) in COVID-19 patients; the incidence of ARDS seen to be significantly associated with an increased neutrophil (P<0.001), and a decreased lymphocyte count (p<0.001).[14]

In a couple of studies from Washington, USA, it was observed that lymphopenia was common among critically ill patients with COVID-19.[18,19] It was also seen that that the patients who had expired during the course of hospital stay in those studies, demonstrated a more significant deterioration in lymphopenia in comparison to patients who survived.[13] Along with these findings, it was also reported that severely ill patients as well as those with fatal outcomes had initially presented with a decreased lymphocyte/white blood cell ratio both at the time of admission (p<0.001) and during hospitalization (p<0.001), as compared to the patients who survived and recovered from the disease.[20,21]

In another study done in 90 patients by Tan et al it was observed that a lymphocyte percentage of <20% on day 10-12 was indicative of a pre-severe disease and a percentage of <5% on day 17-19 denoted a severe illness with poor patient prognosis.[22]

In the present study, attempted to show the association of leukopenia on presentation with the severity of disease and mortality in patients diagnosed with COVID-19. Most of the previous studies had focused on the relationship of a decreased lymphocyte count with prognosis and disease severity in COVID-19, due to the fact that as lymphocytes express the ACE2 receptor on their surface, they are more prone to lysis secondary to infection and penetration by the coronavirus.[23] Unfortunately due to laboratory constraints, we were only able to receive the TLCs of our test subjects and not the differential count, permitting our study to only show the association of leukopenia with the COVID-19 severity and mortality.

There were several limitations in our study. Firstly, we could not get the differential lymphocyte counts and could only use the TLC in the test subjects. Secondly, it was a study of limited duration, which might lead to the significant association between leukopenia and disease severity to be somewhat controversial.

CONCLUSION

In conclusion, this study demonstrated a definite and significant association between a decreased leukocyte count (leukopenia) and disease severity and mortality in patients with COVID-19. This finding is mostly

attributed to the proposed destruction of the lymphocytes by viral entry and subsequent cell lysis. These findings also raise certain questions regarding the importance of segregation and intensive management at presentation of patients diagnosed with COVID-19, and presenting with leukopenia.

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