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Association of Innate and Adaptive Immune Cell Response with Survivors and Non-survivors Infected by SARS-COV-2

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Abstract

The emergence and after effects of SARS-CoV-2 virus led to a huge global health crisis. The disease caused by SARS-CoV-2 (COVID-19) is not only just a respiratory illness, but also the one causing significant haematological alterations. In order to find out the trends related to clinical outcomes in the years of its active existence (Year 2020 and 2021), the Complete Blood Count (CBC) parameters of recovered and deceased patients were observed. The observations reported that Total Leucocyte Count (TLC) was not fluctuating in case of survived cases of 2020, however, it was comparatively high in non-survived cases. Monocytes were high in recovered compared to non-survived. Levels of MCV (low), MCH, platelets (low) and ESR (high) were changeable during the year 2020 in case of recovered cases. Interestingly, recovered (year 2020) patients showed increased ESR and monocytes. Monocytes play the front line in the defence against foreign invasion by microorganisms and providing the first virus-cell contact upon infection. Monocytes are professional antigen-presenting cells with a broad repertoire of receptors on the cell surface and high phagocytic activity, which can be exploited by viruses. These changes are consistent with earlier research showing haematological prognostic markers and immunological dysregulation in COVID-19. Therefore, CBC patterns particularly TLC, Monocytes, ESR, and platelet abnormalities need to be linked to clinical profile and infection pattern, highlighting their predictive value. This will also improve COVID-19 early risk assessment and management.

Keywords: CBC, COVID-19, Haematology, Lymphocytes, Neutrophils.

Introduction

The Severe Acute Respiratory Syndrome-Coronvairus-2 (SARS-CoV-2) appeared in the year 2019 and caused a major health pandemic situation worldwide. The disease caused i.e. COVID-19 was declared as a public health emergency by the World Health Organization (W.H.O). From 2019 till date, there are around 778,994,897 cases and 7,106,996 deaths reported from various parts of the world according to the W.H.O. records. The Global healthcare system faced huge challenges as the virus was mutating fast within very short intervals (1-3). This led to the appearance of many variations of SARS-CoV-2 virus during the pandemic time which were referred as Variants of Concern (VOC). The W.H.O. classified these as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) owing to their transmissibility and pathogenic impact. The SARS-CoV-2 is known to affect multiple organs, because the receptor it interacts i.e. ACE2 (angiotensin converting enzyme 2) is found on organs such as lungs, heart, brain, kidneys, liver, etc (4, 5). It is also found on the vascular endothelial cells. This suggests that there is quite a possibility that the virus interacts with the blood cells and create a chaos in the blood system. This has been observed by researchers across the world and some have reported presence of extra pulmonary abnormalities specifically that of the lymphatic and the circulatory system (6-8). The COVID-19 affected people of all age groups. People with previous history of illness, hypertension, diabetes, immunosuppressed patients etc faced serious consequences. People who had the habit of smoking, alcohol intake and respiratory distress also reported severity. Elderly individuals with respiratory issues were found to be among the susceptible group (9-11). The array of tests which were recommended by the treating physicians included, Point of Care testing of related

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antigens, ELISA based assays, diagnosis via qRT-PCR, imaging techniques, routine tests like CBC, LFT, KFT, CRP protein, etc. (12). Thus, while managing individual patients of COVID-19, there is a need to check the overall effect on various organs. The important point is that though these instabilities in the blood components are seen, but they may take some time to appear. Besides finding ways to combat the virus entry into the host, it also became important to stabilize the body vitals and strengthen the immune system. Of the various parameters, the haematological profiling (CBC) was the crucial disturbing factor (13, 14). It was also estimated that the disease is not merely due to presence of virus, but also an impact of abnormal immune cells (15). Studies were done by two research groups to check the importance of various parameters in the blood of the infected individuals. However, they did not report any significant changes when conducted a comparative study between infected and non-infected individuals (16, 17). Yet another study showed significant observation in the comparative group. The changes were seen in the neutrophil-to-lymphocyte ratio (NLR), platelet count, haemoglobin levels, and leukocyte count (11). Looking into the ongoing waves of COVID-19, these soon began to be looked upon as biomarkers of prognosis (18-21).

Other studies done on the COVID-19 infection reported increased neutrophil counts (neutrophilia), decreased lymphocyte counts (lymphopenia), anaemia, thrombocytopenia etc. as the few important markers of disease progression and risk for mortality (22-24). According to one cross-sectional investigation, severe/critical COVID-19 cases had noticeably higher total leukocyte counts, neutrophil percentages, and Neutrophil Lymphocyte Ratio (NLRs) (25, 26). Another characteristic of COVID-19, particularly in severe cases, seen was lymphopenia (27, 28). Since there were variations observed in the study done by researchers, hence few also considered observations on WBC, as difficult to interpret (29-31). It was also considered that might be the haematological indices were getting modified due to virus presence and hence variations were seen in the observation of immune cells among various categories of patients (32-34). One recent study of 2025 had looked into the comparisons of immune cells that were affected during different variants of SARS-CoV-2. The study was a random hospital-based survey of the records of 2020-2022 in Connecticut, USA (data of 575 COVID-19 and 950 control patients). They observed different immune responses (innate and adaptive cells) among the initial (ancestral) COVID-19 strains compared with Delta and Omicron strains (15).

Since most of the studies as mentioned above were seen in limited number of patients or in a specific study area, hence continuous monitoring of such parameters in more of the resource settings is required. The disease of global pandemic level and where mutations are reported, a constant check of the crucial factors is important. With this aim, the present study was formulated. The study provides a better understanding of the systemic haematologic responses in survivors as opposed to death, by placing these findings within the existing prognostic framework of CBC parameters in COVID-19. Also, this will add to the existing knowledge of the importance of blood parameters in other respiratory diseases also.

Materials and Methods

The clinical profile of the patients who reported to Sharda hospital during the year 2020 and 2021 were studied. The patients were categorized into "Recovered" and "non-survivors" as per the various parameters and clinical conditions observed. The various parameters of Complete blood count (CBC) data were recorded and compared. For this, 2-3 ml of venous blood samples of the infected patients were collected in EDTA coated vials and subjected to Hematology Analyzer (XN-10/20) (m/s Sysmex, Singapore) (35). The machine is first calibrated and a control check is done. There is a place to hold the sample. The blood is mixed properly in the EDTA vial prior to insertion into the machine. An amount of 20-30µl is taken by the machine automatically from the vial. After sometime, the results appear on the monitor. The results obtained from the automated machine were then analysed, category wise. The ethical approval for conducting this study was taken prior hand (SU/SMS&R/76-A/2021/112).

Results

A total of 936 COVID-19 infections were recorded during the year 2020 from Sharda Hospital, UP, India. Out of these, 880 had recovered while 56 did not survive. During the year 2021, a total of 697

COVID-19 infections were recorded, out of which 446 individuals had recovered while 251 did not survive.

The CBC parameters of the patients recovered (during the year 2020) showed interesting results. The Haemoglobin (Hb) was found to be low (lower than the reference level) in 181 female patients while high in only 5 patients. Similarly, in case of Male patients also it was low in 173 while high in 4 cases. The Total Leucocyte Count was seen to be more or less similar; it was low in 74 cases and high in 87 cases. Neutrophil levels were toward the higher side; higher in 190 patients (high values compared to reference level) and low in 64 whereas Lymphocytes were low in 172 cases and high in 100 cases. The Eosinophil was high in 41 cases and no low levels were observed; similarly, monocytes were high in 413 patients but low only in 4. There were no major differences in the basophils from the normal range. Only one patient had high level whereas no patient had low levels. The Red Blood Cell (RBC) count was found to be on the lower side in 71 cases, while 98 patients had this count on the upper side. Hematocrit value indicated 180 patients with values on the lower side (compared to reference level) and 55 in the upper side (compared to reference levels shown in Figure 1.

The Mean Corpuscular Volume (MCV) levels indicated 145 patients with low levels and 85 with high levels. Similarly, Mean Corpuscular Haemoglobin (MCH) values were on lower side in 134 patients and in 35 patients, it was on the higher side. The Mean Corpuscular Haemoglobin Concentration (MCHC) values were high in 4, whereas it was low in 67 patients of the COVID-19. Platelet count indicated a low value in 219 patients whereas it was found to be high in 31 cases. There were no low levels of Erythrocyte Sedimentation Rate (ESR) however high values were seen in 124 patients. The RDW-SD varied from the reference level. 22 had lower levels while 79 had higher levels. The Red Cell Distribution Width-Standard Deviation (RDWSD) had only high levels in 98 cases. The Platelet Distribution Width (PDW) showed low levels in only 2 cases while 168 patents had high levels. In 10 patients, the Mean Platelet Volume (MPV) had low levels whereas in 114 patients it depicted high values. The Platelet-Large Cell Ratio (PLCR) results shown in Figure 1 indicated only 5 patients in lower range while a total of 178 in higher range.

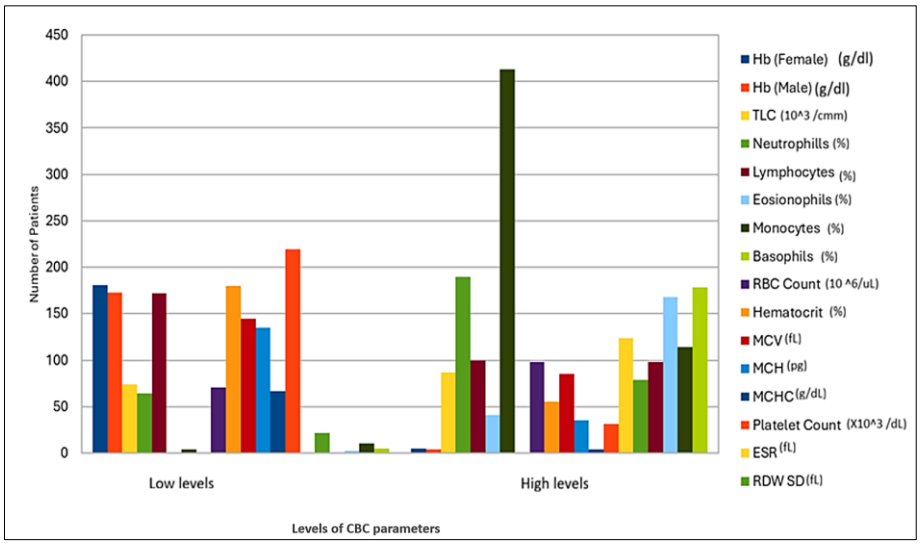

Figure 1: Graphical Representation of the CBC Parameters Indicating Number of Cases (Recovered, Year 2020) which had Levels Below and Above the Reference Value

In case of patients who did not survive, the Haemoglobin showed low values for 21 female patients and 7 male patients. While higher Haemoglobin values were seen for 4 female and 2 male patients. The TLC counts were higher in 30 patients while only 1 had low and others were within reference level. Neutrophils also indicated a high rise in 43 patients and 6 had low levels. Whereas Lymphocytes were seen to be low in 49 patients. Eosinophils were reported to be within range while monocytes and basophils had 3 and 5 patients respectively within the high range. The RBC count was also normal except in 8 patients

wherein low levels were observed, and in 10 patients' high values were observed in Figure 2.

Hematocrit values showed 16 persons with low levels and 12 patients with high values.

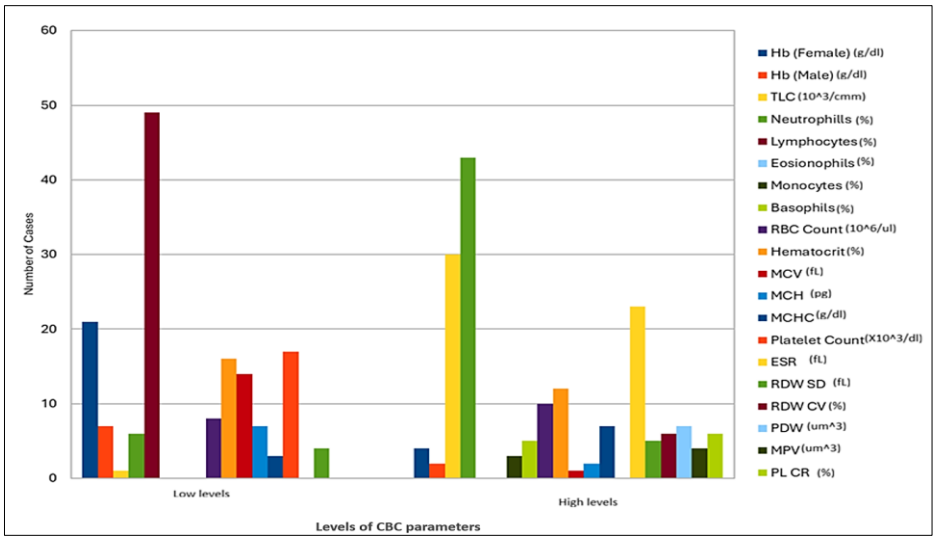

Figure 2: Graphical Representation of the CBC Parameters Indicating Number of Cases (Not- Survived, Year 2020) which had Levels Below and Above the Reference Value

The MCV, MCH and MCHC were also checked. Their values were found to be low in 14, 7 and 3 patients respectively while high in 1, 2 and 7 patients respectively. Talking about the platelet counts, all were within range expect in 17, which showed low levels. The ESR count showed a rise in 23 patients. RDWSD values were normal, expect for being low in 4 and high in 5 patients. The other parameters like RDWCV, PDW, MPV, PLCR were seen to be high in very few patients.

The Complete Blood Count (CBC) parameters of the recovered and non-surviving patients during the year 2021 were also studied. The results of the recovered patients indicated a wide variation. The haemoglobin level in males showed that 73 patients had values below average and 6 patients had values above average. In females, 108 patients had levels below average and only 1 patient had level above average. The Total Leucocyte Count was seen to be low in 36 patients and 105 patients had higher levels than the normal range. None of the patients showed lower levels of Neutrophils and Eosinophils, however higher levels were seen in 215 and 4 patients respectively. Lymphocytes were seen lower than normal range in 32 patients and high in 6 patients. Monocytes were found to be below average in 17 patients and above average in 123 patients. Basophils were seen normal in all the patients.

RBC count was recorded to lower in 22 patients and higher in 62 patients whereas PCV, RDW SD, RDW CV, MPV was low in 9 patients for each of the parameters. Higher levels were observed in 32, 38, 41 and 24 patients respectively. Low levels of MCV, MCH, MCHC and Platelet Count was seen in 53, 75, 49, 70 patients respectively, while high levels were seen in 33, 3, 3 and 19 patients respectively. No patient showed low levels in ESR while 105 patients had high levels. The PDW and P LCR was low in 8 and 9 patients while high in 24 and 35 patients respectively in Figure 3.

The results from the non-surviving individuals (year 2021) indicated a different pattern than recovered individuals. The hemoglobin in men was low in 71 patients and in females, 27 patients had low levels. The Total Leucocyte Count was lower in 8 patients and higher in 132 patients. 46 patients showed low values of Neutrophils whereas 167 patients had higher than usual levels. The higher levels of Eosinophils, ESR, PDW, MPV and P LCR were seen in 2, 75, 36, 33 and 27 patients respectively while all the others were within the normal range. Lymphocytes were seen lower than normal range in 206 patients and high in 2 patients only. Monocytes were recorded below average in 44 patients and above average in 15 patients.

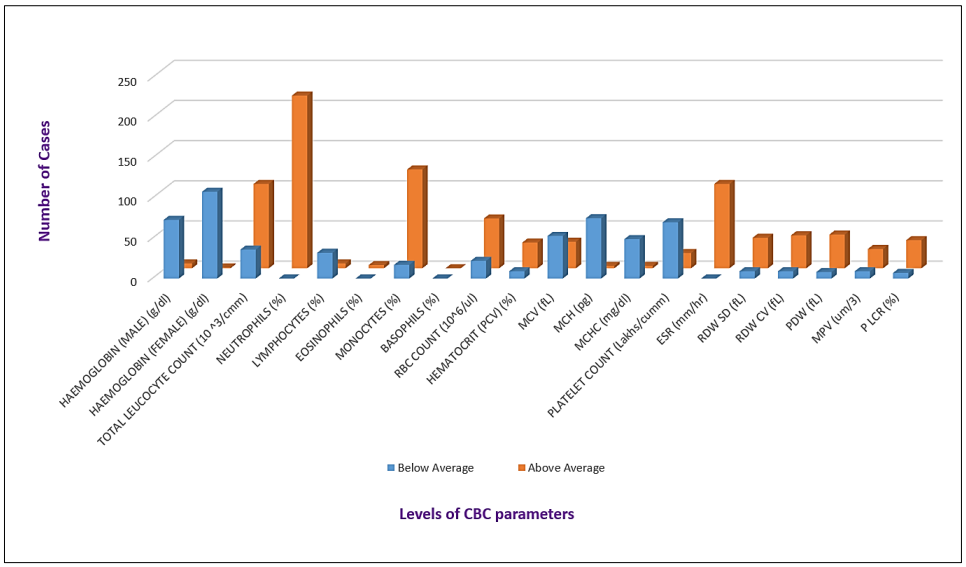

Figure 3: Graphical Representation of Complete Blood Count (CBC) among Recovered Cases (Year 2021) Indicating Below and Above Average Values

The low levels of Basophils were seen in none of the patients while 34 patients showed up the higher levels. RBC count was recorded lower in 17 patients and higher in 72 patients whereas PCV was lower in 39 patients and higher in 56 patients. Similar pattern in lower levels of MCV and Platelet Count was seen in 70 and 67 patients respectively while it was high in 16 and 5 respectively. MCH and MCHC values were low in 43 and 36 patients while the higher levels had 7 and 34 patients each respectively. The RDW SD and RDW CV levels were low in 32 and 1 patient resp., while high in 26 and 48 patients respectively shown in Figure 4.

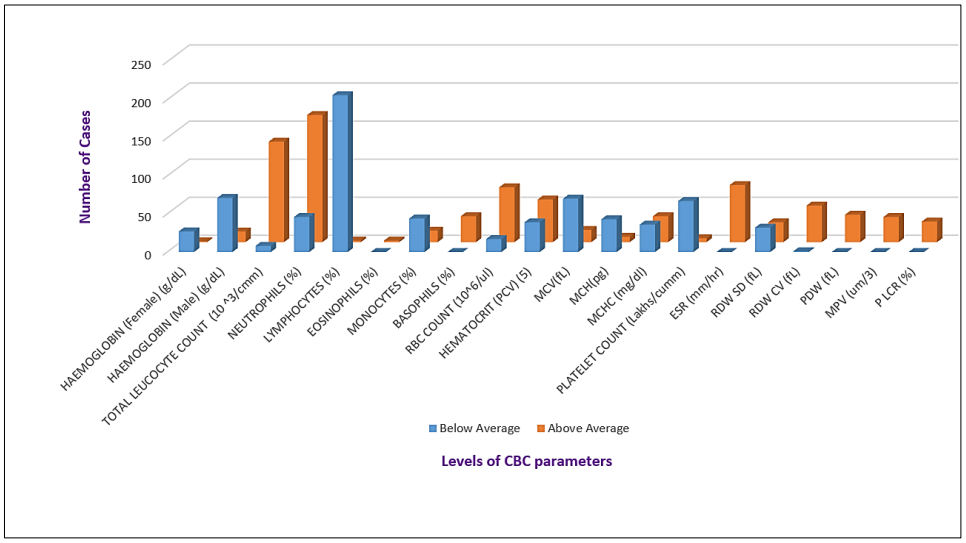

Figure 4: Graphical Representation of Complete Blood Count (CBC) among Non-Surviving Cases (Year 2021) Indicating Below and Above Average Values

Discussion

The retrospective analysis of CBC parameters of years 2020 and 2021 among recovered versus non-surviving COVID-19 patients unveils several notable haematological trends. These trends have been studied by researchers across the world and many new insights have been found to play a role during infection (36-38). Lymphocytes were found to be below average or lower in non-surviving patients and in recovered patients, Haemoglobin (in male) and platelet count were below average during the year 2020. Monocytes were elevated in recovered while in non-surviving category of the year 2020, TLC and neutrophils were above average. In non-surviving patients, lymphocyte

levels were found to be below average. Whereas in recovered patients of the year 2020, haemoglobin levels (in males) and platelet counts were also below average. Monocyte counts were elevated in the recovered (2020 year) group, while total leukocyte count (TLC) and neutrophil levels were above average in the non-surviving group of the year 2020. This is because, patients who recovered showed higher lymphocyte levels which reflect a strong adaptive immune response and the development of protective memory cells.

On the other hand, patients who did not survive had reduced lymphocytes but elevated neutrophils and total leukocyte count, pointing to excessive inflammation and a weakened adaptive defense. It means survival was linked to a well-regulated, lymphocyte mediated immune response, while poor outcomes were associated with uncontrolled inflammatory responses. In non-surviving male patients reported in the year 2021, hemoglobin and lymphocyte level was less than average, revealing a poor adaptive immune response among non survivors, whereas in this cohort of patients, innate immune response especially that of inflammation supported by elevated neutrophils count was evident.

Monocytes are at the front line in the defence against foreign invasion by microorganisms, providing the first virus-cell contact upon infection. Monocytes are professional antigen-presenting cells with a broad repertoire of receptors on the cell surface and high phagocytic activity, which can be exploited by viruses (39, 40). Studies done in the past report that monocytes are specifically susceptible to viral infection and may help in enhancing and activating the phagocytic innate antiviral function (41, 42).

The haematological patterns seen in both years and outcome groups in particular show anaemia (low levels of Haemoglobin), thrombocytopenia, neutrophilia, and lymphopenia as well as elevated RDW and platelet indices, which are in good agreement with findings from around the world that these characteristics are associated with a higher risk of death and a more severe form of the disease (43-45). These haematologic measures, particularly those obtained from CBC, such as NLR, platelet profiles, and lymphocyte counts, are not only easily available but also may be considered as effective tools for tracking the course of the disease, guiding treatment choices, and early risk classification in COVID-19 (46-48).

Conclusion

Over the course of two pandemic years, significant haematological differences were observed among COVID-19 patients. We report two important observations; TLC were comparatively high in non-survived cases than in recovered cases and secondly, Monocytes were high in recovered compared to not survived. Thus, it is important to keep a track of these, especially in case of critically ill and immunosuppressed patients, such that host immunity can be boosted.

Abbreviations

CBC: Complete blood count, ESR: Erythrocyte Sedimentation Rate, Hb: Haemoglobin, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Corpuscular Haemoglobin Concentration, MCV: Mean Corpuscular Volume, MPV: Mean Platelet Volume, NLR: Neutrophil Lymphocyte Ratio, PDW: Platelet Distribution Width, PLCR: Platelet-Large Cell Ratio, RDW-SD: Red Cell Distribution Width-Standard Deviation, SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronvairus-2, TLC: Total Leucocyte Count.

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None.

Author Contributions

All the authors contributed equally to conceptualization, data analysis, and manuscript writing for this study.

Conflict of Interest

The authors have no competing interests (financial or otherwise) to declare.

Declaration of Artificial Intelligence (AI) Assistance

The authors declare no use of artificial intelligence (AI) for the write-up of the manuscript.

Ethics Approval

The study has been approved by the Institutional Ethical Committee, Sharda University, India (SU/SMS&R/76-A/2021/112).

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