Original Research Article

Correlation of Hematological Parameters in Covid Positive Patients with The Severity of their Illness at A Teaching Hospital in India

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Abstract

Introduction: This study was done to evaluate importance of hematological parameters to identify severity of covid 19 positive patients. So that, it will be evaluated who need ICU or emergency treatment. A comparison of biomarkers from the peripheral blood between the covid 19 and non-covid 19 has been done. A comparable study with respect to age, gender and clinical complaints between covid 19 and non-covid 19 patients has been performed. **Materials and Methods**: A retrospective study was conducted at Autonomous government medical college society of Firozabad on 150 covid positive confirmed patients who were admitted in the covid hospital. Data was collected from the record section of this institute.

Result: As covid 19 is a systemic infection involving multiple systems of the body but the hematopoietic system and hemostasis showed the major impact. Leukocytosis with neutrophila, lymphocytopenia, thrombocytopenia along with raised PT, APTT and D-dimer were reported with poor prognostic potential. Biomarkers such as serum ferritin, serum pro-calcitonin, CRP, interleukin 6 proved to be the important inflammatory marker, which are associated with the severity of the covid 19 positive patients so that proper intervention should be taken at the appropriate time.

Conclusion: Laboratory tests were found to be useful in the diagnosis and management of the disease. Hematological abnormalities included lymphopenia, neutrophilia, thrombocytopenia, and slight fall of hemoglobin. $CD4^+$ and $CD8^+$ T lymphocytes count declined as the disease aggravated.

Keywords: Retrospective, Study, Haematological, Covid19.

Introduction

Since December 2019, an increasing number of pneumonia cases of unknown reason emerged in Wuhan, China [1]. Deep-sequencing analysis from nasopharyngeal swabs, sputum, lower respiratory tract samples, and blood indicated a novel coronavirus, known as 2019-nCoV [2]. Coronavirus can cause multiple system infections and mainly respiratory infections in human, such as severe acute respiratory syndrome and Middle East respiratory syndrome [3-5]. The novel virus was named 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by WHO, due to more than 79% homology with SARS-CoV, SARS-CoV-2 was responsible for coronavirus disease 2019 (COVID-19) [2].

Differences in hematological manifestations were detected between severe and non-severe patients. The severity of COVID-19 is defined according to the clinical management of severe acute respiratory infection when COVID-19 disease is suspected by WHO (version1.2) [2]. Severe illness is designated when the patients have fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or pulse oximeter oxygen saturation ≤ 93% on room air [2]. Critical illness is defined as patients with acute respiratory distress syndrome or sepsis with acute organ dysfunction [2]. Non-severe type represents patients with the exception of the above conditions [2]. A blood workup as well as continuous tracking hematological changes could reveal the risks of disease progression.Complete blood counts (CBC) are easily performed and inexpensive. Included in the CBC are values such as white blood count, neutrophil, lymphocyte and platelet count (PLT), mean platelet volume and certain ratios of these values. These can be used as inflammatory markers. Neutrophils are the most characteristic cell type among the white blood cells and are an important component of the immune system. Regulated by mast cells, epithelial cells and macrophages, neutrophils also take part in inflammatory processes. The role of lymphocytes in both inflammation and infections is evident. Additionally, thrombocytes also have importance in the regulation of various inflammatory

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processes. While these parameters may be used as inflammatory markers by themselves, their ratios to one another may also be indicators of early inflammation [6-8]. Circulating leukocytes respond to stress by increasing neutrophils and reducing lymphocytes; the ratio of these two parameters is also used as an inflammatory marker [9].

Methodology

A retrospective study was conducted at Autonomous government medical college society of Firozabad with full approval of ethical committee of this institution. This study was carried out in the period of May 20 to September 20. This study includes 150 covid positive confirmed patients, who were admitted in covid hospital. This study included both symptomatic and asymptomatic patients who were found to be positive in RT-PCR out of which few patients had history of travel from other countries. This study belonged to the hematological parameters, serological parameters and coagulative parameters whose findings were noted during the study period. Data was collected from the record section of this institution.

Result

Table 1: Chief complaints of symptomatic patients admitted in covid hospital

Serial no.	Chief complaints of symptomatic patients	Percentage
1	Fever	58
2	Cough	47
3	Sore-throat	68
4	Chest pain	10
5	Myalgia or fatigue	70
6	Loss of taste	47
7	Loss of smell	40
8	Breathlessness	25
9	Loose motions	02

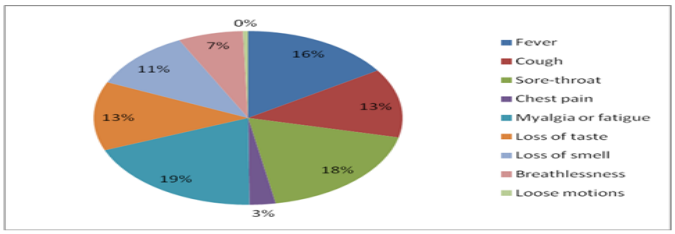

Fig 1: Chief complaints of symptomatic patients admitted in covid hospital

Table 2: Changes in hematological parameters in covid positive admitted patients

Serial no.	Hematological parameters	Asymptomatic patients	Symptomatic patients
1	Fall in hemoglobin	Nil	07%
2	Raised TLC	02%	56%
3	Lymphocytopenia	03%	49 %
4	Reduced platelet	Nil	15%

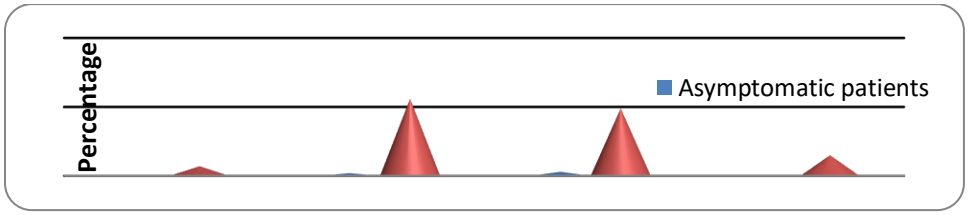

Fig 2: Changes in hematological parameters in covid positive admitted patients

Table 3: Changes in inflammatory biomarkers markers of covid 19 positive patients

Serial no	Inflammatory markers	Asymptomatic patients (45) 45%	Symptomatic patients (105) 55%
1	C reactive protein	02%	78%
2	Serum ferritin	01%	85%
3	Serum procalcitonin	Nil	12%
4	Interleukin - 6	03%	55%

Table 4: Changes in coagulative markers of covid 19 positive patients

Serial no.	Coagulative markers	Asymptomatic patients	Symptomatic patients
1	PT	Nil	05%
2	APTT	Nil	01%
3	D dimer	Nil	06%
4	Fibrinogen	Nil	07%

Discussion

Gender wise and age wise comparable study of Covid 19 positive patients: This study included 150 RT-PCR confirmed covid positive patients out of which 73 percentage were males and 27 percentage were females. Male to female ratio was 2.7:1 .

Age ranged from 15 years to 90 years. The median age was 49 years. In a study conducted by Guan et al., the median age was 47 and 52.1% of the patients were male [10]. Another study by Li et al. revealed that 56% of all patients were male and the median age was 59 [11]. Furthermore, another study conducted by Xu et al. showed a median age of 41 and 56% of the patients were male [12].

A comparable study of clinical complaints of covid positive patients: In our study fever, cough and sore-throat were the predominant complaints, followed by myalgia, loss of sensation and smell, breathlessness and chest pain. Rare complaints noticed were loose motions, nausea and vomiting, etc. The research conducted by Yang et al. also revealed fever and cough to be the most common complaints [13]. In a study by Guan et al., fever and cough and less frequently nausea, vomiting and diarrhea, were observed [10]. The study by Huang et al. showed that fever (40/41 patients [98%]), cough (31/41 patients [76%]) and myalgia or fatigue (18/41 patients [44%]) were the most commonly seen symptoms at onset of the disease [14].

Comparable study of haematological parameters in covid 19 positive patients: In this study, lymphocytopenia was seen in 48% of symptomatic patients and 3% in asymptomatic patients. Similary other studies also revealed the similar findings.Regarding the level of lymphocytes in COVID-19 infected patients, normal or slightly low level was reported among patients during the incubation time [15]. However, low level of lymphocytes was detected in 83.2% of hospital admitted patients [15]. A significant association between low lymphocytes count and requirement of intensive care unit (ICU) admission was reported by Wu and his colleagues [16]. In Washington state, decreased level of lymphocytes was highly reported with seriously ill COVID-19 patients in ICU [17]. Also, low lymphocytes count was more commonly reported in ICU patients compared to the non-ICU patients. Thus, low lymphocytes level might be considered as an important indicator for early admission for supportive ICU care.Another retrospective cohort study summarized the initial laboratory indices of patients with COVID-19 and proposed that more than half of them hadlymphopenia (126 of 197, 64%) [18]. Lymphocytes, the major antiviral cells, were found to be prone to decrease continually and severely in ICU and dead patients when Zhongnan Hospital of Wuhan University kept track of the lymphocyte changes in COVID-19 patients[19]. The median lymphocyte count of early reported COVID-19 cases was 0.8×109/L, demonstrating a high proportion of severe cases or a high risk of course progression among hospitalized patients in Wuhan [19,20].The counts of CD4+ and CD8+ T cells fell early during the course of SARS, which was associated with adverse outcomes [21]. It was manifested that the CD4+ T lymphocytes were rapidly activated to be T helper (Th) 1 cells and induced inflammatory CD14 CD16 monocytes with high expression of interleukin-6 (IL-6) and accelerated the inflammation [22].

A comparable study of total leukocyte count with differential count in covid-19 patients: In this study, Leukocytosis with increased neutrophil count was seen in 56% of symptomatic patient and Neutrophil lymphocytic ratio was found to be increased in symptomatic patients while in asymptomatic patients ratio was in normal range.A series of COVID-19 reports suggested that ICU cases were more likely to appear neutrophilia, which is an indicator associated with disease progression [19,20,23]. Furthermore, among patients with ARDS, higher neutrophils were detected in those who had died [18]. Hematological parameters were tracked from day 1 to day 19 after the onset of COVID-19 at an interval of 2 days, and it was found that non-survivors developed more severe lymphocytopenia and higher neutrophils counts than survivors [19]

Corona virus and thrombocytes level:In this study, Thrombocytopenia was noted in 15% of symptomatic covid positive patients while in asymptomatic patients, platelet count was found in normal range. In Beijing, 72.5% of COVID-19 patients developed thrombocytopenia among 13 patients from three hospitals, however, the reduction on platelet count did not reach to the level at which bleeding happens [16, 24]Xu and colleagues were reported three hypothesized mechanisms causing thrombocytopenia. The first mechanism by causing direct viral infection of bone marrow cells and impairing of platelet synthesis.Also, the decrease of platelet synthesis indirectly as a result of lung injury. The second mechanism is through the body's immune system. The third hypothesized mechanism is by aggregation of platelet in the lungs, leading to platelet consumption and microthrombi[18].A large sample size study of 1099 patients with COVID-19 demonstrated a higher incidence of thrombocytopenia (platelet count $< 150 \times 109$/L) of 36.2% [25]. Further analysis found that severe cases (57.7%) exhibited an increased susceptibility to thrombocytopenia than non-severe one (31.6%) [25].The investigation identified the lung as an organ with potential hematopoietic function and a primary site of terminal platelet production, which accounting for approximately 50% of the total platelet production [26]. On the basis of previous work proposing that the lungs are a reservoir for resident megakaryocytes and hematopoietic progenitor cells, suggesting thrombocytopenia could be caused by damage to the lungs [26]. Lung damage in COVID-19 could also induce the activation of RAS and cause abnormal functions of vascular endothelial cells and coagulation system, and platelet activation and aggregation, which might further increase consumption of platelet.

Decline of haemoglobin: Decline of haemoglobin is seen in 7% patients of symptomatic covid positive patients.Anaemia was not a common laboratory finding of patients with SARS-CoV-2 infection, but the hemoglobin showed a descending tendency in fact in 41 patients with COVID-19 pneumonia, the hemoglobin level of severe patients was lower, although the difference was not marked (122.0 g/L (111.0–128.0) vs 130.5 g/L (120.0–140.0) [14]. In the study of 1099 patients with COVID-19, the hemoglobin level of 128.0 g/L (111.8–141.0) in severe group was lower than that of 135.0 g/L (120.0–148.0) in non-severe one [10]. It is noteworthy that the reduction of hemoglobin was more pronounced in patients who reached composite endpoint (included admission to ICU, requirement of invasive ventilation and death) than in those who did not (125.0 g/L (105.0–140.0) vs 134.0 g/L (120.0–148.0) [10].

Hemoglobin was below the normal range in 51% of 99 patients with SARS-CoV-2 infection reported by Jin Yin-tan Hospital [26]. In the report of Zhou et al., although there was no difference in the incidence of anemia, the hemoglobin of the patients with severe cases decreased more significantly (125.42 g/L (97–144) vs 145.24 g/L (111–162) [22].

Inflammatory changes caused by SARS-CoV-2 infection could interfere with erythropoiesis, resulting in a decrease in hemoglobin. The low incidence of anemia in COVID-19 may relate to the long life span of erythrocyte and the compensatory proliferation of erythrocyte induced by pneumonia-associated hypoxia. For COVID-19, the reduced hemoglobin levels might be an indicator of disease progression, and it would be more worthy to focus on the decline of hemoglobin level, not on anemia.

A comparable study of coagulation parameters in covid 19 positive patients: Coagulation parameters proved to be very helpful in identifying severity of covid 19 positive patients. In our study APTT and d- dimer is prolonged in mostlyseverely ill patients. Along with these PT is prolonged in few very severe patients. Several studies have been reported abnormality in D-dimer levels [19,26]. It has been shown that 28.6% of COVID-19 patients investigated with high Ddimer levels in the University of Hong Kong-Shenzhen Hospital [21]. Additionally, the complications and severity of the disease among patients with community-acquired pneumonia was

significantly associated with D-dimer elevated levels [28]. Thus, higher D-dimers level is associated with patients WHO requiring ICU treatment and more severe cases [26]. D-dimer elevation and prolonged prothrombin time were observed in severe COVID-19 cases [5,19]. In the early report of Jin Yin-tan Hospital, prothrombin timeand D-dimer level on admission were higher in ICU cases than non-ICU cases [5]. The same outcome of D-dimer level was detected in Zhongnan Hospital that patients with critically condition had significantly elevated D-dimer level than common patients [19]. The difference of prothrombin time between ICU and non-ICU patients was not proposed by the research of Zhongnan Hospital [19]. The latest study of 1099 cases with COVID-19 demonstrated that 46.4% of them had increased D-dimer levels, and the severe patients were more prone to develop an elevation in D-dimer than non-severe patients; the rate of D-dimer elevation was as high as 69.4% in those who reached the composite endpoint [4].

Comparative study of biomarkers-procalcitonin, serum Ferritin, C-reactive protein and interleukin-6 in covid 19 patients with other studies: In our studies, serum procalcitonin is elevated in 12% of symptomatic patients. Increased procalcitonin proved to be the very important biomarker which helped the clinician in judging the critical condition of patients. Similarly, in the study done by Guan, disease severity was associated with elevated procalcitonin- 13.7% (16/117) of severe cases vs 3.7% (19/516) non-severe cases presented with elevated procalcitonin. [10]. Study done by Huang showed that 25% of patients (3/12) necessitating ICU care presented with elevated procalcitoninvs 0/27 non-icu patients, Overall, procalcitonin levels were elevated in ICU patients vs non-ICU patients [20].

Thus, more the severe condition of the patient is more the increase in procalcitoninis seen in all studies including ours study. CRP is raised in 78% of symptomatic patients and 2% in symptomatic patients in our study. Similarly, Guan (2020) study also found that disease severity was associated with elevated CRP- 81.5% (110/135) of severe cases vs 56.4% (371/658) of non-severe cases presented with elevated CRP[10]. Deng (2019) also found out that patients in the death group exhibited significantly higher CRP levels [29]. Serum Ferritin was raised in 85% of symptomatic patients in our study. Similarly, more the value raised , more critical the condition of the patient is .

Similarly, Wu (2020) studies found out that higher serum ferritin were associated with ARDS development [16]. Zhou (2020) also found out that higher serum ferritin levels were associated with higher odds of death [30]. In our studies, Interleukin 6 biomarker also helped clinicians like more the value is increasing, the severity of the illness increases .Studies done by Chen et al [26] and Wu et al [16] also found out the similar results.

Conclusion:

COVID-19 is a new human infectious disease caused by a novel coronavirus SARS-CoV-2. Laboratory tests proved to be very useful in the diagnosis and management of the disease. According to the literature review, haematological parameters are variable during the period of COVID-19 infection and that few of them can be a sign of lethal outcomes leading to death. Hematological abnormalities include lymphopenia, neutrophila, thrombocytopenia, and slight fall of hemoglobin. $CD4^+$ and $CD8^+$ T lymphocytes count declined as the disease aggravates. Increased neutrophil count and neutrophil-to-lymphocyte ratio were used to correlate with the severity of illness. Studies found out that the activation of monocyte-macrophage system aggravates the immune damage that of the lung and other tissues, which causes changes in the serological parameters of D-dimer, and prothrombin time. The effects of SARS-CoV-2 on hematopoiesis are still poorly understood, which needs more research work to be done in future.

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