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Original Research Article

A Retrospective Analysis of Changes in Clinical and Laboratory Parameters in COVID-19 and it's Relation with Severity of the Disease

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Abstract:

Background: The Severe acute respiratory syndrome coronavirus-2 pandemic has been affecting the health, economic, as well as social life of the entire globe since the end of 2019. There are only a few studies done in India on the changes in clinical and hematological parameters on covid19 and its relationship with disease severity. The study aimed to determine the changes in clinical and laboratory parameters in COVID-19 and also to correlate the changes in clinical and laboratory parameters with the severity of the disease.

Material and Methods: Laboratory parameters of 217 covid positive patients were retrieved from hospital record section and correlated with the severity of the disease by stratifying cases into four categories mild, moderate, severe and critical.

Results: In total 217 cases, prevalence of disease was higher in males. Similarly, severity of the disease was more in males and increases with higher age group. Leukocytosis, neutrophilia, elevated Neutrophil to lymphocyte ratio(NLR), activated partial thromboplastin time(activated PTT), D-dimer, Lactate dehydrogenase(LDH) ,serum ferritin and C-reactive protein (CRP) are significantly increased in patients with severe and critical disease. On Peripheral smear(PS) examination, hypersegmented neutrophils and toxic changes in neutrophils were seen in severe and critical patients.

Conclusion: LDH and D-Dimer could be used as a prognostic indicator for COVID-19 disease which are also easily available and cheap. Peripheral smear examinations can also predict the severity by showing hypersegmented neutrophils and toxic changes in neutrophils.

Keywords: COVID-19 disease, Severity, NLR Ratio, Hematological parameters, *coronaviridie,* D-dimer

Introduction

The World Health Organization (WHO) first reported the emergence of COVID-19 infection in Wuhan City, China in late December of 2019 [1]. Subsequently, the disease caused by this novel virus was declared to be a pandemic on March 12, 2020. As of July 2023, the virus affected more than 76 crores individual over 221 countries [2]. Covid-19 is a systemic viral infection with a remarkable bang on the hematopoietic system, hemostasis as well as immune system. As hematological tests help in quick diagnosis, treatment evidence, low detection costs and high automation, hematological tests have become the primary choice for disease monitoring and the evaluation of general conditions. Hematological abnormalities in COVID-19 are related with advancement of the disease, severity and mortality. Progression of the disease can be well documented by the means of complete blood count (CBC) assays, investigating coagulation and fibrinolysis cascades [Prothrombin Time, activated partial thromboplastin time, D-dimers] and inflammation-related parameters [Erythrocyte sedimentation time (ESR), CRP, S.ferritin,] [3]. Therefore, Laboratory medicine plays a pivotal role in early interpretation of disease severity providing a better guide for prompt management of patients, thus, can help in decreasing the disease morbidity and mortality. In this study, we aim to investigate the

changes of hematological parameters with COVID-19 disease, to evaluate the role of hematological parameters in stratification of COVID-19 disease severity.

Material and Methods

This is a retrospective observational study, conducted in Department of Pathology, Ispat General Hosptial in western part of Odisha of eastern India. Datas were recruited after taking approval from Scientific and Ethical committee. We were granted a waiver of informed consent as this was a retrospective study and all patients were discharged from the hospital. Datas from April 2020 to May 2021 was taken from hospital record section. All covid positive inpatients with both genders included in our study. All Patients with age less than 18 years, pregnant population, outpatients, cases with insufficient datas and referred cases are excluded from our study. By applying these criteria total 217 patients selected. But, Sample size for certain parameters like PT, aPTT, LDH, S.ferritin, S.calcium, S.albumin are 70 [due to insufficient data]. Patients were categorized into mild, moderate, severe and critical disease according to their clinical features and X-ray findings. Mild disease was defined as symptoms of fever, sore throat, cough and no sign of pneumonia on X-rays. Moderate disease was defined as fever and respiratory symptoms with oxygen saturation≤ 93% and first chest X ray showing non homogenous patchy infiltrates with peripheral dominance and improvement on repeat X-ray after 5 days of supportive treatment. Patients with respiratory distress (respiratory rate >30 breath per min, O2 saturation less than 93%) and no improvement in repeated chest X-ray were classified as severe disease while patients with respiratory failure requiring mechanical ventilation, shock or other organ failure were classified as patients having critical disease. CBC was performed on beckman coulter act 5 diff cp hematology analyzer. Biochemical parameters were performed in Auto analyzer AU5800 and Beckman coulter. Coagulation parameters including PT(Prothrombin time), activated PTT were performed on C-4 coagulation analyser under strict quality control. In our lab, ESR performed by Westegren method, CRP by Immunoturbidometric method(quantitative), S.Ferritin by CMIA method, LDH by Lactate→Pyruvate method, D-dimer by Latex Agglutination method (semi-quantitative), S.albumin by Bromocresol green method, S.calcium by Arsenazo 3 method, S.creatinine by jaffe rate blanked method and S.urea by urease method.

Result

In total 217 cases, prevalence of disease was higher in males 146(67.3%). Similarly, severity of the disease was more in males and increases with higher age group (more than 40 years). Association of severity with age was statistically significant (p< 0.001). In our study, 24 (11.1%) patients were afebrile, and 193 (88.9%) patients were febrile. But Association of severity with temperature was not statistically significant (p=0.185). Current study showed 75 (34.56%) patients had no Comorbidities and 142 (65.44%) were with comorbidities. Most of the patient with comorbidities 64(45.1%) came under critical group. Association of severity with Presence of comorbidities was statistically significant (p<0.001). Study showed that most of the patients came under critical group 66(43.4%) with less than 93% Oxygen(O2) saturation and similarly 63(96.9%) patients came under mild group with more than 93% saturation. Study showed Association of severity with O2 saturation was statistically significant (p< 0.001). Out of 217 cases, 64 (29.5%) patients were died. Out of it, most of the patients were from severe and critical group ;5(17.2%) and 57(85.1%) respectively. Hence; our study shows severity having significant association with mortality (p value <0.001).

Table 1: Demographic data and clinical findings of patients

	Mild	Moderate	Severe	Critical	P-Value
Age (years) - n (%)					
≤40	13 (54.2)	6(25)	2(8.3)	3(12.5)	
>40	53(27)	49(25)	27(14)	64(33)	<0.001
Gender- n (%)					
Males	32(21.9)	39(26.7)	19(13)	56(38.4)	<0.001
Females	34(47.9)	16(22.5)	10(14.1)	11(15.5)	<0.001
Temperature- n (%)					
Afebrile	8(33.3)	9(37.5)	4(16.7)	3(12.5)	=0.185
Febrile	58(30.1)	46(23.8)	25(13)	64(33.2)	
Co-morbidities- n (%)					
No	54(72)	16(21.3)	2(2.7)	3(4)	
Yes	12(8.5)	39(27.5)	27(19)	64(45)	<0.001
O2 Saturation- n (%)					
<93%	2(3)	54(35.5)	29(19.1)	66(43.4)	
>93%	63(96.9)	1(1.5)	0	1(1.5)	<0.001
Mortality- n (%)					

No	65(98.5)	54(98.2)	24(82.8)	10(14.9)	
Yes	1(1.5)	1(1.8)	5(17.2)	57(85.1)	<0.001

The hematological parameters in mild, moderate, severe and critical disease are shown in Table2. Hemoglobin and hematocrit was significantly higher in mild group compared to moderate, severe and critical groups. White blood cell (WBC), Absolute neutrophils count (ANC) and NLR are significantly higher in severe and critical groups compared to mild and moderate groups. Absolute lymphocyte count (ALC) shows no significant difference between the four groups. But standard deviation shows that there are high variations in ALC among moderate, severe and critical groups. No significant difference in ESR was found between four groups. However, it was in above normal range in all groups. There is a significant decrease in platelet count was noticed from mild to severe groups.

Table 2: Comparison of changes in haematological parameters according to severity of the disease (one way ANOVA with Duncan Multiple range test as post hoc test was done for comparing the variables between different severity group)

Variable	Severity Level				P-value
	Mild	Moderate	Severe	Critical	
Hemoglobin (g/dl)	11.92 ± 1.66^{a}	10.73 ± 1.64^{b}	10.36 ± 1.66^{b}	10.23 ± 1.44^{b}	< 0.001**
Hematocrit (%)	35.37 ± 5.23^{a}	31.94 ± 4.67^{b}	31 ± 4.82^{b}	30.80 ± 4.57^{b}	< 0.001**
White blood cell (cells/microliter)	6.72 ± 1.92^{c}	10.54 ± 3.82^{b}	13.62 ± 4.27^{a}	14.41 ± 5.20^{a}	< 0.001**
Absolute neutrophil count(cells/microliter)	3876.3 ± 1338.71^{c}	7281.58 ± 3275.15^{b}	10498.55 ± 3978.39^{a}	11298.51 ± 4628.12^{a}	< 0.001**
Absolute lymphocyte count(cells/microliter)	2100.56 ± 608.8	2275.82 ± 1677.61	2246.76 ± 2097.97	2049.61 ± 1539.53	0.819^{ns}
Neutrophil lymphocyte ratio	1.89 ± 0.71^{c}	4.09 ± 3.05^{b}	6.25 ± 4.11^{a}	6.92 ± 4.26^{a}	< 0.001**
Erythrocyte sedimentation rate (mm/hour)	90.53 ± 35.23^{b}	95.31 ± 46.32^{ab}	102.83 ± 40.47^{ab}	106.72 ± 36.60^{a}	0.100^{ns}
Platelet count(cells/microliter)	178.67 ± 39.82^{a}	145.36 ± 31.53^{b}	125 ± 23.3^{c}	112.58 ± 26.39^{c}	< 0.001**

** Significant at 0.01 level; ns non-significant. Means having different letter as superscript differ significantly within a row

Results given in Table 3 reveals that both PT and aPTT is significantly low in mild category of disease group compared to other three groups. Even though there is slight increase in these two variables in moderate to critical category, no significant difference was noted between moderate, severe and critical groups.

Table 3: Comparison of Change in Coagulatory Profile Parameters According to Severity of the Disease [PT & APTT] (N=70) (One Way Anova with Duncan Multiple Range Test as Post HOC Test was Done for Comparing the Variables between Different Severity Group)

Variable	Severity Level				P-value
	Mild	Moderate	Severe	Critical	< 0.001**
PT (seconds)	12.72 ± 0.92^{b}	17.33 ± 3.87^{a}	17.97 ± 2.23^{a}	18.19 ± 3.71^{a}	0.009**
aPTT(seconds)	30.8 ± 6.04^{b}	33.88 ± 2.35^{a}	34.19 ± 1.55^{a}	34.66 ± 2.04^{a}	< 0.001**

** Significant at 0.01 level. Means having different letter as superscript differ significantly within a row

In Table 4, Comparison of change in D-Dimer according to severity of the disease. Kruskall Walli's ANOVA was done.

Table 4:

Variable	Severity Level [median (Interquartile range)]				P-value
	Mild	Moderate	Severe	Critical	
D-dimer(mg/L FEU)	0^{c} (0)	400^{b} (400)	800^{a} (800)	1600^{a} (800)	< 0.001**

** Significant at 0.01 level. Medians having different letter as superscript differ significantly within a row

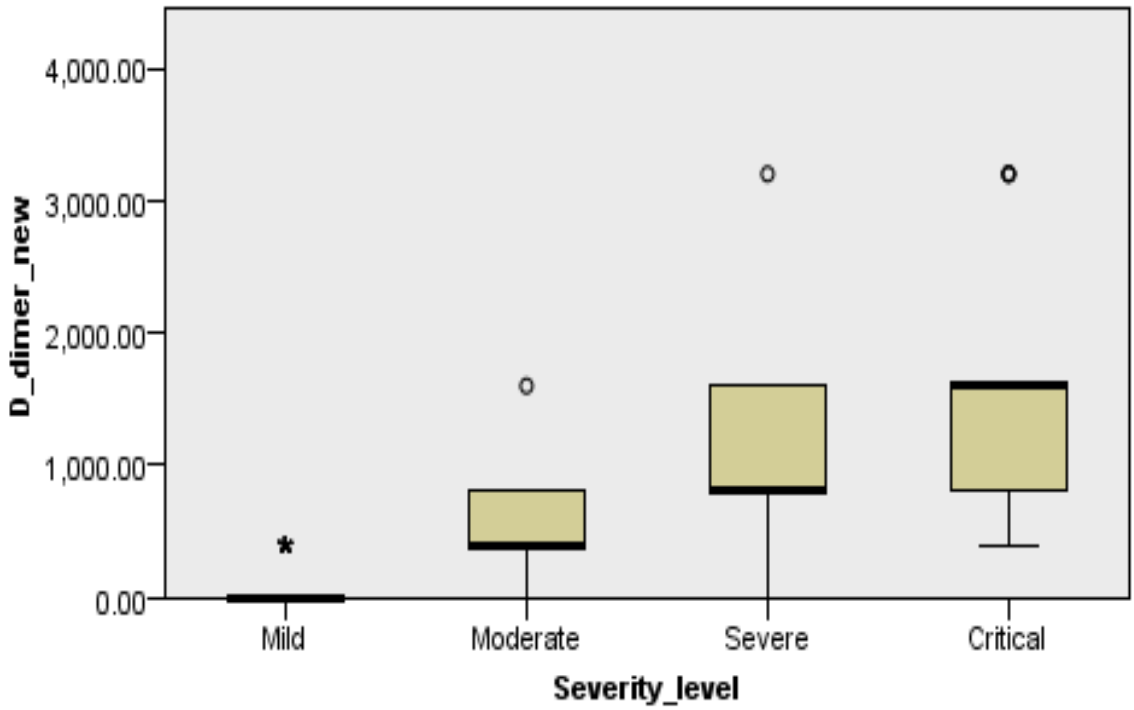

Figure 1: Plot showing the distribution of D-dimer in different severity groups

The median (IQR) values of statistically significant parameter D-dimer level was compared with patient severity levels (Table:4). The Figure shows D-dimer level increased with the severity (Fig 1).

Biochemical parameters as mentioned in Table 5 shows significant difference between mild, moderate, severe and critical group except for the variable's serum calcium and serum albumin. Serum ferritin significantly higher in severe and critical groups compared to mild and moderate groups. Results shows that LDH is increasing as the severity increases.

CRP was significantly higher in severe and critical groups and lower in mild group. Serum urea was significantly increased from moderate to severe and severe to critical groups. Serum creatinine was significantly higher in critical group compared to other three groups.

Table 5: Comparison of change in biochemical parameters according to severity.(one way ANOVA with Duncan Multiple range test as post hoc test was done for comparing the variables between different severity group)

Variable	Severity Level				P-value
	Mild	Moderate	Severe	Critical	< 0.001**
Serum ferritin(ng/ml)	475.68 ± 155.33^{b}	479.42 ± 117.03^{b}	767.92 ± 169.57^{a}	849.86 ± 102.86^{a}	< 0.001**
Lactate dehydrogenase(U/L)	322.88 ± 67.42^{d}	244.53 ± 44.49^{c}	406.67 ± 58.44^{b}	500.79 ± 62.48^{a}	< 0.001**
C reactive protein(mg/L)	28.92 ± 20.77^{c}	48.9 ± 17.99^{b}	60.03 ± 11.75^{a}	60.78 ± 12.52^{a}	< 0.001**
Serum Urea(mg/dl)	22.92 ± 7.3^{c}	31.4 ± 15.3^{c}	44.69 ± 23.84^{b}	63.42 ± 49.58^{a}	< 0.001**
Serum creatine(mg/dl)	0.83 ± 0.17^{b}	1.07 ± 0.47^{b}	1.03 ± 0.31^{b}	1.74 ± 2.07^{a}	< 0.001**
Serum calcium(mg/dl)	8.49 ± 0.25	8.20 ± 0.40	8.37 ± 0.29	8.15 ± 0.65	0.053^{ns}
Serum albumin(g/dl)	3.43 ± 0.33	3.38 ± 0.21	3.33 ± 0.26	3.45 ± 0.29	0.683^{ns}

** Significant at 0.01 level; ns non-significant. Means having different letter as superscript differ significantly within a row

Table 6: Association of severity with Toxic changes

Toxic Changes	Level of severity							
	Mild		Moderate		Severe		Critical	
	Count	Per cent	Count	Per cent	Count	Per cent	Count	Per cent
No	65	54.6	39	32.8	6	5.0	9	7.6
Yes	1	1.0	16	16.3	23	23.5	58	59.2
Chi Square Value = 116.54**; P-value < 0.001								

** Significant at 0.01 level

Table 7: Association of severity with Hyper segmented neutrophils

Hyper segmented neutrophils	Level of severity							
	Mild		Moderate		Severe		Critical	
	Count	Per cent	Count	Per cent	Count	Per cent	Count	Per cent
No	65	40.9	51	32.1	17	10.7	26	16.4
Yes	1	1.7	4	6.9	12	20.7	41	70.7
Chi Square Value = 75.872**; P-value < 0.001								

** Significant at 0.01 level

On PS examination of 217 patients, study showed that most of the patients in critical group showed hypersegmented neutrophils and toxic granules in cytoplasm of neutrophils 41(70.7%) and 58(59.2%) respectively. Study showed that there is Association of severity with hypersegmented neutrophils and toxic changes were statistically significant (p<0.001) (Table 6 and 7).

Discussion

Results of our study demonstrating hematological, coagulatory, biochemical manifestations and their correlation with the severity of the disease in covid19 patients. In our study, as mentioned in Table no: 1 most covid positive patients belonged to the >40 years of age group and severity is significantly higher in higher age groups compared to lower age groups. According to study conducted by Jakhmola S et al stated that Population groups of 20-49 years of age and 50 years-above were highly vulnerable to infection [4]. Low ACE-2 expression in the children's nasal epithelium may be responsible for reduced SARS-CoV-2 susceptibility. Our study, on Severity with age group correlates with Wang M et al [5] (2021) study which showed that median age was obviously higher in severe and critically severe cases than in non-severe cases. In our study, 146 (67.3%) patients were Male, and 71 (32.7%) patients were Female. Also, we demonstrate association of severity with gender was statistically significant (p< 0.001). Our study correlates with George M B et al who have stated that, generally, females are more resistant to infections than men, and this is possibly mediated by several factors including sex hormones and high expression of coronavirus receptors (ACE 2) in men but also life style, such as higher levels of smoking and drinking among men as compared to women[6].

Our study showed that, Most of the patients were with comorbidities 117(65.44%) and 75 (34.56%) patients had no Comorbidities. On stratification with severity level; Most of the patient, that is; 64(45.1%) came under critical group. Association of severity with Presence of comorbidities was statistically significant (p< 0.001). All deaths were in severe and critical disease.

Our study demonstrated that Leukocytosis, neutrophilia and increased neutrophil to lymphocyte ratio, which might be due to inflammatory response, have a significant association with the disease severity. Neutrophil to lymphocyte ratio was highest in patients with critical disease. Liao D et al. were also found in their respective studies elevated neutrophil to lymphocyte ratio as a useful predictor for severity and mortality of SARS-CoV-2 infection[7]. In our study, hemoglobin and hematocrit was significantly higher in mild group compared to moderate, severe and critical groups. However no significant difference was noticed between moderate severe and critical groups. Similarly, a prospective study conducted in Iran by Masood [8] et al stated that prevalence of anemia in hospitalized patients with Covid19 was high, and it was associated with poor outcomes. However, they observed a significant association after assessing the disease severity, presence of comorbidities, age, sex, and hypoxia status. This may be partly due to the effect of anemia on immunity, which leads to increases the probability of poor outcomes in patients with COVID-19 [9]. We observed, there is a significant decrease in platelet count was noticed from mild to severe groups. But no significant difference in platelet count was noticed between severe and critical groups. Our study correlates with Liao D et al. [7]. Thrombocytopenia in COVID-19 may be explained by the irreversible consumption of platelets during the execution of procoagulant and immune modulation functions. Other possibility is Viral infection of megakaryocytes can increase their apoptosis and decrease maturation and ploidy [10]. We didn't observe any significant difference in Absolute lymphocyte count between the four groups. Our study contradicts with the study of J. Wagner et al who discovered that lymphocyte count is lower and a marker of disease severity [11]. The mechanism of this lymphocytopenia seems to be due to the cytotoxic action of virus and endothelial dysfunction in older age group. We did not notice any significant difference in ESR which contradicted with the study of F Zeng et al they found a higher ESR level in the severe group than in the nonsevere group [12]. It can be due to patients in the severe group had higher inflammation. On Peripheral examination of 217 patients we observed that most of the patients in critical group showed hypersegmented neutrophils and toxic cytoplasmic changes in neutrophils 41(70.7%) and 58(59.2%) respectively. We found that there is an association of severity with hypersegmented neutrophils and toxic changes. Salib et al. also demonstrated presence of hyper-

segmented neutrophils in covid19 patient [13]. But they have not correlated association of hypersegmented neutrophils with disease severity. Few studies have reported hypersegmented neutrophils in cases of severe viral respiratory infection [14]. The hypersegmented morphology of the neutrophil implies increased maturation compared with banded and normal neutrophils [15]. Maturation is thought to occur in hyperinflammatory state due to the presence of a cytokine-rich environment consisting of prosurvival mediators[16]. Similar to our study on toxic changes in neutrophils S. Jain et al reported Most of the critical patients had significant leucocytosis with marked neutrophilia and toxic granulation as compared to survivors, indicating that these patients might have a secondary bacterial infection as an underlying cause of death [17].

In our study LDH, C-reactive protein and S.ferritin showed significant association with severity which correlates with the study of S.Taj et al [18]. Active ferritin production during the course of inflammatory diseases is due to cytokines such as IL-6 which is secreted by macrophage [19]. Severe infections may cause cytokine mediated tissue damage and LDH release. Since LDH is present in lung tissue (isozyme 3), patients with severe COVID-19 infections can be supposed to release higher amounts of LDH in the circulation. [20]. In the study by Chen et al., although no statistically significant difference was found in the level of CRP between the nonsevere and the severe group, the mean level of CRP was higher in the severe group than in the nonsevere group [21]. The raised levels of CRP production are due to the inflammatory cytokines and by tissue destruction in patients with COVID-19 [7].

In our study we observed Serum urea was significantly increased from moderate to severe and severe to critical groups. But no significant difference was noticed between mild and moderate groups. Serum creatinine was significantly higher in critical group compared to other three groups and no significant difference in serum creatinine was noticed between mild moderate and severe groups. Our study correlates with the study of Y M Liu et al [22]. The mechanism of increase level Serum urea and creatinine after SARS-CoV-2 infection has not been fully explained. However, it can be elucidated as, that angiotensin-converting enzyme 2 (ACE2) is the primary cellular receptor of SARS-CoV-2 and highly expressed in renal epithelial cells, it is possible that the viral infection may directly lead to an interaction of SARS-CoV-2 with its receptor in the kidney to reduce ACE2 expression, resulting in abberent activation of the renin angiotensin-aldosterone system (RAAS). The activated RAAS can significantly increase the absorption of water by kidney tubules while increasing the resorption of urea, leading to elevated levels[23].

In our study no significant difference was noticed in serum calcium and serum albumin among the four different groups. However, Based on the results of meta-analysis done by E Alemzadeh et al in people with lower calcium, mortality and complications are higher, therefore, serum calcium is a prognostic factor in determining the severity of the disease[24]. Similarly, a retrospective study done by G Turcato et al observed that, albumin levels may serve as a potentially useful marker of disease severity and prognosis in SARS-CoV-2 [25].

In our study we found that Association of severity with D- Dimer was statistically significant, which correlates with the study of H Long et al [26] . The increase of D-dimer may be an indirect manifestation of inflammatory reaction, as inflammatory cytokines could cause the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system [27]. But in case of PT and aPTT is significantly low in mild category of disease group compared to other three groups. Even though there is slight increase in these two variables in moderate to critical category, no significant difference was noted between moderate, severe and critical groups. Similar findings were observed by Iba T et al. These parameters depended upon the extent of coagulopathy as well as its association with other co-morbidities like Thrombotic Thrombocytopenic Purpura, Disseminated Intravascular Coagulopathy, Hemolytic Uremic Syndrome and Sepsis Induced Coagulopathy [28].

Conclusion

The study concluded that Leukocytosis, neutrophilia, elevated NLR, APTT, D-dimer, LDH, serum ferritin and CRP are significantly increased in patients with severe and critical disease. However, we observed as the severity increases, the values of LDH and D-Dimer increase from mild to critical. So, clinicians should prefer LDH and D-Dimer as prognostic indicators, which are also easily available and cheap. PS examinations can also predict the severity by showing hypersegmented neutrophils and toxic changes in neutrophils as these appears in mostly in severe and critical patients.

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Limitations of the Study

The current study has certain limitations that have to be kept in mind before making any final inference.

- As our our study is retrospective, it is having inferior level of evidence when comparing with prospective.
- The small sample size was a limiting factor of this study. The frequency and total number of samples collected for estimation of different laboratory parameters were not uniform.
- The study was carried out in a tertiary care hospital, so hospital bias cannot be ruled out.
- The most of the patient's blood group were we collected from already registered patients data in our hospital and for few of the patients collected by contacting over by phone call. It may create information bias.
- If we have compared the covid19 positive cases with the negative cases, strength of the study might increase.
- We couldn't include the datas of referred cases, which may also increase the sample size as well as strength of the study.
- Hematological complications of the coronavirus disease are associated with bad prognosis. However, due to low resources we could not explore the other hemostatic parameters like fibrinogen, ADAM-TS 13, von Willebrand factor antigen etc. in our.

References

1. P.C. Woo, S.K. Lau, Y. Huang, K.Y. Yuen, Coronavirus diversity, phylogeny and interspecies jumping, Exp. Biol. Med. (Maywood) 234(10) (2009) 1117–1127.
2. World health organisation-covid UpToDate-https://covid19.who.int/
3. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics Microbes and New Infections, September 2020;37: 100738.
4. Jakhmola S, Baral B, Jha HC. A comparative analysis of COVID-19 outbreak on age groups and both the sexes of population from India and other countries. J Infect Dev Ctries. 2021; 15:333-341.
5. Wang et al Association of clinical and immunological characteristics with disease severity and outcomes in 211 patients with COVID-19 in Wuhan, China. Frontiers in cellular and infection microbiology. 2021;11.
6. Bwire, George M. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? SN comprehensive clinical medicine, 2020;2:7: 874-876.
7. Liao D., Zhou F., Luo L., Xu M., Wang H., Xia J. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020;7(9):e671–e678
8. Faghih Dinevari M, Somi MH, Sadeghi Majd E, Abbasalizad Farhangi M, Nikniaz Z. Anemia predicts poor outcomes of COVID-19 in hospitalized patients: a prospective study in Iran. BMC Infect Dis. 2021 Feb 10;21(1):170.
9. Iron-deficiency anemia in infant development: implications for growth, cognitive development, resistance to infection, and iron supplementation. Am J Phys Anthropol. 1997;104(S25):25–62.
10. Terpos E., Ntanasis-Stathopoulos I., Elalamy I., Kastritis E., Sergentanis T.N., Politou M. Hematological findings and complications of COVID-19. Am. J. Hematol. 2020;95(7):834–847.
11. Wagner J, DuPont A, Larson S, Cash B, Farooq A. Absolute lymphocyte count is a prognostic marker in Covid-19: A retrospective cohort review. Int J Lab Hematol. 2020; 42(6): 761-765.
12. Furong Zeng, Yuzhao Huang, Ying Guo, Mingzhu Yin, Xiang Chen, Liang Xiao, Guangtong Deng, Association of inflammatory markers with the severity of COVID-19: A meta- analysis, International Journal of Infectious Diseases, 96,2020;96.
13. Salib C, Feldstein JT. Hypersegmented granulocytes and COVID-19 infection. Blood. 2020; 135:2196.
14. Lakhdari N, Tablet B, Boudraham L, et al. Red blood cells injuries and hypersegmented neutrophils in COVID-19 peripheral blood film. medRxiv.
15. Juss JK, House D, Amour A, et al. acute respiratory distress syndrome neutrophils have a distinct phenotype and are resistant to phosphoinositide 3-kinase inhibition. Am J Respir Crit Care Med. 2016;194(8):961-973.
16. Pillay J, Kamp VM, van Hoffen E, et al. A subset of neutrophils in human systemic inflammation inhibits T cell responses through Mac-1. J Clin Invest 2012; 122:327–36.
17. Swasti Jain, Rachana Meena. Comparison of hematologic abnormalities between hospitalized coronavirus disease 2019 positive and negative patients with correlation to disease severity and outcome; Journal of medical Virology. 94:8.
18. Taj, Sadia et al. Role of hematological parameters in the stratification of COVID-19 disease severity. Annals of medicine and surgery 2012;62 (2021): 68-72.
19. Rosário et al The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med. 2013; 11:185.
20. Henry BM, Aggarwal G, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med. 2020;38(9):1722-1726.
21. Chen L., Liu H.G., Liu W., Analysis of clinical features of 29 patients with 2019 novel corona-

virus pneumonia (In Chinese) Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(3):203–208.
22. Ye-Mao Liu, Jing Xie, Ming-Ming Chen, Xiao Zhang, Xu Cheng, et al Kidney Function Indicators Predict Adverse Outcomes of COVID-19, Med, 2021; 2(1).
23. M. Soleimani Acute Kidney Injury in SARS-CoV-2 Infection: Direct Effect of Virus on Kidney Proximal Tubule Cells Int. J. Mol. Sci., 21 (2020), p. 3275.
24. E.alemzadeh et al The effect of low serum calcium level on the severity and mortality of Covid patients: A systematic review and meta-analysis. Immunity, inflammation, and disease. Vol 1; Issue 4.
25. F.Turcato G, Zaboli A, Kostic I, et al Severity of SARS-CoV-2 infection and albumin levels recorded at the first emergency department evaluation: a multicentre retrospective observational study. Emergency Medicine Journal 2022; 39:63-69.
26. Long H, Nie L, Xiang X, et al. D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. Biomed Res Int. 2020; 2020:6159720.
27. Tang N., Bai H., Chen X. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J. Thromb. Haemost. 2020 May; 18(5):1094-1099.
28. Iba T., Levy J.H., Levi M., Thachil J. Coagulopathy in COVID-19. J. Thromb. Haemostasis.2020;18(9):2103–21.