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Original Research Article

Biochemical and haematological parameters predicting severity of Covid 19 infection: Lessons from first wave of pandemic

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ABSTRACT

Context: Corona virus disease 2019 (COVID-19) was declared as pandemic by WHO on March 10, 2020. Several countries around the globe have seen a two-wave pattern of reported cases. India is witnessing unprecedented spike in COVID-19 cases again since March 2021 especially in Maharashtra. Newer insights in pathogenesis of diseases, diagnosis and treatment modalities continue to evolve in case of novel infection.
Aim: To study and compare laboratory parameters in COVID cases in first wave in 2020.
Design: Retrospective cross-sectional observational study.
Materials and Methods: Total 400 cases; 354 RTPCR and 46 RAT confirmed cases of COVID-19 done at dedicated COVID Hospital.
Statistical Analysis: Comparison of laboratory parameters was done between 72 Severe and 328 Non-Severe cases by unpaired t-test.
Results: Statistically significant differences were seen in severe cases as compared to non severe cases in Lymphocyte count, Eosinophil count, Neutrophil Lymphocyte Ratio, CRP, D-dimer, Ferritin levels. WBC count, Platelet count and ALT did not show significant difference between severe and non severe cases.
Conclusion: Lymphopenia, raised N/L ratio, Eosinopenia, increased D-dimer, Ferritin, CRP are associated with severe COVID disease. The routine laboratory tests can diagnose the disease, predict prognosis and complications and monitor treatment response.

1. Introduction

The Coronavirus disease 2019(COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), has adversely affected almost all countries in the World.[1] Several new kinds of covid variants emerge due to mutations leading to multiple waves or spikes of the pandemic.[2] Cases in second wave are rapidly increasing in European Continents, South Africa and United States of America.[2] India witnessed unprecedented spike in COVID-19 cases again since March 2021. Newer insights in pathogenesis of diseases, treatment modalities continue to evolve in case of novel infection. Clinical laboratory has a crucial role in mitigating this new pandemic. Timely and accurate diagnosis of COVID-19 is of paramount importance for early detection of cases and to prevent transmission. Clinical Laboratories have adopted different test modalities and processes to tackle this unprecedented situation with directives from regulatory bodies such as

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ICMR (Indian Council of Medical Research), WHO (World Health Organization). Different routine and uncommon parameters have been shown to have the diagnostic and prognostic capacity.[1] This study analyses and compares the laboratory parameters in severe and non severe cases.

2. Materials and Methods

2.1. Study design

This is a retrospective cross-sectional observational study. It was done at Tertiary care teaching hospital in Western India in Mumbai which was designated as dedicated COVID Hospital from April 2020. Informed consent was obtained from each patient included in this study. The data has been used in anonymised form, without revealing identity of any subject. This study was reviewed and approved by the institutional ethics committee. ICMR approved kits were used for nasopharyngeal swab testing. Real time Reverese Transcriptase Polymerase Chain reaction (rRT-PCR) and Rapid Antigen Test (RAT) testing was done according to ICMR.

2.2. Data collection

We have included total 400 cases; 354 rRTPCR and 46 RAT confirmed cases of COVID-19 patients, in which data of both laboratory parameters and disease severity was available from April to October 2020. Cases were divided into mild, moderate and severe based on MoHFW (Ministry of Health and Family Welfare) criteria. We included mild and moderate cases into Non severe category. There were 72 severe cases and 328 non severe cases. Comparison of parameters was done in these two groups. We studied total WBC count, Lymphocyte count, Eosinophil count, Platelets, Neutrophil Lymphocyte Ratio (NLR), D-dimer, Ferritn and C –Reactive Protein (CRP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST). As per ICMR protocol all laboratory parameters were tested in COVID positive cases on day of admission. Reports generated from Sysmex SF 3000 5 part cell counter and Cobas 6000 modular analyser by Roche. We obtained data from the Laboratory Information System (LIS) exclusively.

2.3. Statistical analysis

The data was systematically collected, compiled and entered in MS Excel version 2016. It was statistically analyzed using Graph pad prism online calculator. The observations were tabulated and p value was obtained by unpaired t- test to analyze variables. The p value of ≥ 0.05 as non-significant.

3. Results

Four hundred cases with the mean age of 50 (range: 2-90 years) were studied. All patients received antiviral and supportive therapy after diagnosis. Leucopenia was found in 15% of cases. Leucocytosis was seen in15% of cases. Lymphocytopenia was seen in 26.6% of cases. Eosinopenia was found in 30.8% of cases. Average NLR was 4.6. Thrombocytopenia was seen in 19.6% of cases. 78% had normal platelet count. D-Dimer elevation was seen in 82.8% of cases. The mean D-Dimer was 1021ng/ml. CRP levels were in range of 0.1 to 91. Average levels were 7.63. Elevated levels were seen in 74.5% of individuals. Average level of ferritin was 539ng/ml. Average Alanine aminotransferase (ALT) was 58 U/L, Aspartate aminotransferase (AST) was 62U/L.

Average value and standard deviation in both groups are tabulated (Table 1). Statistically significant Lymphocytopenia, Eosinopenia and increased NLR, D-Dimer, Ferritin, CRP, AST was seen in severe cases as compared to non severe cases. WBC count, Platelet count and ALT did not show statistically significant difference severe and non severe cases. (Table 1)

4. Discussion

Covid 19 is a systemic infection with a significant impact on the hematopoietic and the immune system. Examples of markers of systemic inflammation are ESR, CRP, Ferritin, alpha 1 antitrypsin, alpha 1 acid glycoprotein, Serum Amyloid A, Ceruloplasmin, Hepcidin, Hepatoglobin, Cytokines, Interleukin-6. Biochemical and hematological parameters have been investigated to assess their role in diagnosis and prognosis. We evaluated CRP, Ferritin, D-dimer and hematological parameters as they are inexpensive, easily available and results available within short period of time. We compared results of our study with studies across the globe. (Table 2)

Our study showed leucopenia in 15% of cases and leucocytosis in 15% of cases. Leucopenia was noted in 29% cases in study by Li LQ et al.,[3] 29.2% in Fan BE et al.,[4] Ferrari D et al.,[5] Mardani R et al.,[6] Najim R et al.[7] Agrawal A et al.[8] study showed higher mean leukocyte count. In our study significant difference was not seen in levels of WBC of severe cases as compared to non severe cases. This is concordant with studies done by Gao Y et al.[9] (4.26 ± 1.64 in severe group and $4.96\pm1.85 \times 10^9$/L in mild group) (p value 0.220) and discordant with studies done by Archana B et al.[10]

Variable results of studies can be explained on clinical severity of diseases, sample size, day of illness, comorbidities and treatment received. Most of studies showed leucopenia in moderate and severe cases of the disease. Henry et al.[11] study indicates that the increase in WBCs is driven by elevated neutrophils, as decreasing trends were observed for lymphocytes, monocytes and eosinophils.

In our study significant difference was seen in Absolute Lymphocyte Count of severe cases as compared to non severe cases. (p value<0.001) This is concordant with

Table 1: Laboratory findings of COVID-19 Severe and non-severe cases

Laboratory parameters	Severe	Non severe	p-value
WBC count (/mm^3)	4384 ± 1254	5018±2893	0.0694
Absolute Lymphocyte Count (/mm^3)	400±220	1050±480	> 0.0001
Eosinophils (/mm^3)	124 ± 98	230± 124	> 0.0001
Platelets (/mm^3)	230000±90000	280000±90000	0.1886
NLR	6.4±1.3	3.8±1.2	> 0.0001
CRP (mg %)	32±6	8±5	> 0.0001
D-Dimer(ng/ml)	2186±964	1034±892	> 0.0001
Ferritin (ng/ml)	1083±464	597±388	> 0.0001
AST(U/L)	87±25	43±24	> 0.0001
ALT(U/L)	62±28	55±31	0.0785

studies done by Archana B et al.[10] (p value 0.04, survivors 23% and non survivors 8.2%) & Huang et al.[12] while Gao Y et al.[9] found no significant difference between mild cases ($1.07\pm0.40\times10^9$/L) and severe cases ($1.20\pm0.42\times10^9$/L) (p value 0.309). Fan BE et al.[4] found that Absolute lymphocyte count on admission stood out as discriminating index between the ICU and non-ICU patients (P value of <.001).

Our study showed lymphocytopeni**a** in 40.5% of cases. Lymphocytopenia was seen in studies done by Li LQ et al.[3](64.5%), Liu M et al.[13] (40%) Siordia JA et al.[14] (68.7%) Mo P et al[15] (73.5%) Zhang JJ et al.[16] (75.4%) Fan BE et al.[4] (36.9%).

In patients with severe disease, a decrease in both CD4 and CD8 was observed in the study done by He Z et al.[17] Henry B further hypothesized that survival may be dependent on ability to replenish lymphocytes which are killed by the Corona virus.[18] As such, lymphocyte count, especially CD4, may serve as a clinical predictor of severity and prognosis.

In our study eosinopenia was seen in 30.8% of cases, and in 78.8% cases in Siordia JA et al.[14] study, 52.9% cases in Zhang JJ et al.[16] study. Average eosinophil count was 20 in Ferrari D et al.[5] study. In our study significant difference was seen in Absolute Eosinophils Count of severe cases as compared to non severe cases (p<0.001). Archana B et al[10] study showed higher eosinophils count in survivors 0.7 (0.0-2.0)% as compared to non-survivors 0.0 (0.0-2)% with p value 0.01.

Eosinopenia has been observed during infection with the SARS-CoV 2. Recently eosinophils have been shown to have various other functions including immunoregulation and antiviral activity apart from proinflammatory effects. In some studies, eosinopenia is reported to be associated with worsening of respiratory symptoms.[19] Tanni F suggested that persistent eosinopenia after admission correlates with low rates of recovery.[20]

Thrombocytopenia was seen in 19.6% of cases in our study. There was no significant difference seen in platelet count of severe cases as compared to non severe cases (p value 0.1886). This is concordant with studies done by Archana B et al[10] and Fan BE et al.,[4] Ferrari D et al.[5] In studies by Siordia JA,[14] Fan BE et al[5] thrombocytopenia was seen in 36.2% & 20.0% cases respectively.

Neutrophil to lymphocyte ratio (NLR) is a simple parameter to assess the inflammatory status of a subject. In a study by Forget P et al.,[21] it was identified that normal NLR values in an adult, non-geriatric and population in good health, are between 0.78 and 3.53. In our study significant difference was seen in levels NLR of severe cases as compared to non severe cases, This is concordant with studies done by Archana B et al[10] (Non survivors 8.40 vs survivors 2.95, p=0.04),and Agrawal A et al.[8] (symptomatic cases 6.17±6.11 and in asymptomatic was 2.67±1.32, p value 0.0001).

Jingyuan L et al.[22] study showed that NLR was the most significant factor affecting the severe illness incidence and it had significant predictive value. The incidence of severe ill ones with NLR ≥ 3.13 and aged ≥ 50 years old was 50%, and 9.1% in age ≥ 50 and NLR < 3.13 patients. Patients with age < 50 years old and NLR < 3.13 who are no risk should be treated in a community hospital or home isolation. Patients with age ≥ 50 and NLR ≥ 3.13 who are high risk should actively transfer to ICU with invasive respiratory support equipment. NLR may also have prognostic value in determining severe cases and in risk stratification.

CBC can be easily performed and is inexpensive. Parameters such as leukocytes, lymphocytes, eosinophils, platelets and NLR, individually and in combination can be used as indexes of systemic immune response. In our study severe cases had higher leukocytes, lower lymphocytes, lower eosinophil count and high NLR.

This study showed elevated CRP in 74.5% of cases. Average level was 7.63mg%. CRP levels were in range of 0.1 to 91mg%. (Normal range is 0.5 to 1). Other studies also showed elevated CRP Mardani R et al[6](77.1% of cases), Li LQ et al[3] (44% of cases) Mo P et al[15] (100% cases), Chen et al.[23] (93.1% cases) and in a review article by Siordia JA et al.[14](60.7%). Our results were comparable to all the studies.

In our study significant difference was seen in levels of CRP of severe cases as compared to non severe cases. This is concordant with studies done by Gao Y et al.[9] (p value 0.011; severe group 39.37±27.68 mg/L, and mild group

Table 2: Comparision of laboratory findings in other studies

Haematological parameters	**Covid 19 cases**	**Interpretation**	
White blood cell count (WBC)	302 (287 survivors, 15 nonsurvivors	↑ in non survivors normal or # in 23/29 increase in ICU cases	(Archana B et al, 2021) (Chen et al., 2020)
	15 mild, 14 severe	normal in all cases	(Huang et al., 2020)
	41 cases (13 ICU cases)		(Gao Y et al., 2020)
	43 (28 mild, 15 severe)		
Lymphocyte count	69 (26 ICU, 43 non ICU)	↓ more In ICU patients	Fan BE et al
	302 (287 survivors, 15 nonsurvivors)	↓ more In non survivors patients	(Archana B et al, 2021) (Chen et al., 2020a)
	15 mild, 14 severe	cases>60 years	(Huang et al., 2020)
	41 cases (13 ICU cases	↓ in 20/29	(Gao et al., 2020)
	43 (28 mild, 15 severe)	↓ in ICU cases normal in cases	(Li et al., 2020a)
	1,994 cases (meta-analysis)		(Mo P et al., 2020)
	70 mild, 85 severe cases	↓in most cases	
		↓ in most cases	
Eosinophil count	302 (287 survivors, 15 nonsurvivors	↑ in survivors	(Archana B et al, 2021)
	140 cases	↓ in most cases	(Zhang et al., 2020b)
Platelet count	302 (287 survivors, 15 nonsurvivors	↓ in non survivors	(Archana B et al, 2021)
	70 mild, 85 severe cases	normal; slightly lower in severe cases	(Mo et al., 2020) Fan BE et al
	69 (26 ICU, 43 non ICU)	normal in most cases	
Biochemical parameters			
C-reactive protein (CRP)	1,994 cases (meta-analysis)	↑ in 44% of cases	(Mo et al., 2020
	302 (287 survivors, 15 nonsurvivors	More ↑ in non survivors higher in severe cases	(Archana B et al, 2021) (Chen et al., 2020b))
	126 mild, 24 severe cases	↑ in 27/29	(Chen et al., 2020a))
	15 mild, 14severe	↑in severe cases	(Wang et al., 2020b)
	69 cases,	↑ in severe cases	(Zhang et al., 2020b)
	140 cases	↑ in severe cases	(Gao et al., 2020)
	28 mild, 15 severe cases	↑ in all cases, higher in severe	(Li et al., 2020a)
	70 mild, 85 severe cases	cases	
Ferritin	302 (287 survivors, 15 nonsurvivors	↑ in non-survivors	(Archana B et al, 2021)
	150	↑ in non-survivors	(Mehta et al., 2020)
Coagulation parameters			
d-dimers	302 (287 survivors, 15 nonsurvivors	↑ in non-survivors	(Archana B et al, 2021)
	191 cases,	↑ in non-survivors ↑in cases vs. controls	(Zhou et al., 2020) (Han et al., 2020)
	91 with comorbidities	↑ in severe cases	(Zhang et al., 2020b)
	94 cases	↑ in severe cases	(Gao et al., 2020)
	140 cases	normal; slightly higher in	(Mo et al., 2020)
	43: 28 mild, 15 severe cases	severe cases	(Tang et al., 2020)
	70 mild, 85 severe cases	↑ higher in non-survivors	
	183 cases; 21 non-survivors		
Liver enzymes			
Alanine aminotransferase (ALT)	102 (85 asymptomatic, 17 symptomatic)	↑in symptomatic patients ↑ in ICU cases	Agrawal A et al (Huang et al., 2020)
	41 cases (13 ICU cases)		
Aspartate aminotransferase (AST)	102 (85 asymptomatic, 17 symptomatic)	↑in symptomatic patients	Agrawal A et al

18.76±22.20); and Mo P et al[15] [in refractory patients 46 (22-106) as compared to General patients 23 (10-47 mg/L (p value P=0.001)]; while Archana B et al.[10] study analysed that even though CRP levels were much lower in survivor group (18 vs 62, p value= 0.08), it was not statistically significant.

CRP is an acute-phase reactant that is synthesized by the liver in response to inflammation or infection. Unlike most acute-phase proteins that undergo large variations in plasma levels (depending on the synthesis, consumption, and catabolism rates), plasma CRP levels remain nearly constant. During acute inflammation, serum concentrations increase dramatically, making it a more accurate marker for sepsis.[24] CRP also contributes to the proinflammatory cycle by activating inflammatory cytokines in the body.[25]

In a study by Smilowitz et al.[26] initial high CRP concentrations were associated with clinical outcomes. Patients with the highest quartiles of CRP measured had the greatest likelihood of Venous Thromboembolism, Acute Kidney Injury, critical illness, and mortality.

Ferritin, produced in inflammatory conditions of the body (infectious, malignant, hematologic, and rheumatologic), is an important acute phase reactant. In our study average level of ferritin was 539ng/ml (Normal level is 30-400 ng/ml). In a study by Nazim R et al.[7] average ferritin levels were 986±126.4 in 65 RTPCR positive cases. In our study significant difference was seen in levels of ferritin of severe cases as compared to non severe cases. This is concordant with studies done by Archana B et al.,[10] they found significant difference between two groups in ferritin levels 222 (5.54-3000) ng/ml in survivors and 480 (310-2000) ng/ml with p value 0.02 and Mehta et al.[27] study of 150 confirmed COVID-19 cases (mean 1297·6 ng/ml in nonsurvivorsvs, 614 ng/ml in survivors).

D-dimer is a sign of ongoing active fibrinolysis and, therefore, also of coagulation. It assesses the severity of the host response. In our study D-dimer elevation was seen in 82.8% of cases. The mean D-Dimer was 1021ng/ml. Liu et al[13] (17% cases) showed, Han H et al[28] (10.36±25.31mg/L), Siordia JA et al[14] (46.4%) and Tang N et al.[29] (0.66μg/mL) studies also showed similar results to our study.

In our study significant difference was seen in levels of D-dimer of severe cases as compared to non severe cases. This is concordant with studies done by Gao Y et al.[9] showing statistical significant difference between severe group 0.49 (0.29, 0.91) and mild group 0.21 (0.19, 0.27) ug/L with p value 0.007 and Archana B et al.[10] study with D- dimer levels (307 vs 604 ng/ml, p value 0.021). A study by Bhutta ZA[30] showed that the higher the D-dimer levels, the greater the risk of sepsis and septic shock for the patient. D-dimer found to be especially predictive of disease progression.

D-dimer, ferritin, CRP play an important role in the risk stratification of patients, predicting prognosis and improve clinical management. Their routine monitoring would appear advisable in patients with COVID-19.

In our study significant higher levels of AST were seen in severe cases as compared to non severe cases; while no association was seen in levels of ALT. In a study of Agrawal A et al.[8] showed mean AST values were significantly higher in symptomatic patients (AST (U/l) 30.62±23.98) as compared to asymptomatic patients 66.06±59.68 (p values <0.0001) and ALT values were (U/l) 37.02±36.53 in symptomatic patients and 68.71±52.94 in asymptomatic patients with p value 0.003. Guan Y et al.[31] observed that 18.2% patients with non-severe disease and 39.4% patients with severe disease had elevated AST level, whereas elevated ALT levels were observed in 19.8% of patients with non-severe disease and 28.1% of patients with severe disease. Nucleic acid amplification tests (like r RTPCR) are currently the gold standard for diagnosing suspected cases of COVID-19. Thus, based on current evidence, an initial negative NAAT result does not rule out SARS-CoV-2 infection due to potential pre-analytical and analytical issues or time of testing. The importance of rapid and reliable molecular testing for the initial diagnosis of SARS-CoV-2 infection is well recognized. However due to the relatively short research and development time for both lab-based and point-of-care (POC) molecular assays, in many cases uncertainties regarding their clinical accuracy and sensitivity persist.

As identified by Lippi et al.,[32] preanalytical issues include inadequate procedures for collection, Handling, transport and storage of the specimens (especially OP and NP swabs), as well as inadequate sample material in terms of poor quality or volume. The diagnostic testing window is perhaps one of the most important factors impacting test sensitivity. False negatives may be caused by low viral loads in the early and late stages of infection. Viral recombination or mutation may represent an analytical issue. Lack of harmonization between primer and probe sets limits comparison of assay performance between different platforms. Further analytical issues include inadequate assay validation, instrument malfunction, inaccurate cut-off definition, result misinterpretation, and others.[32]

Serology assays currently available from diagnostic manufacturers vary significantly in their methodology, antibody target, and acceptable specimen type.[33] The diagnostic performance of serology assays has not been systematically evaluated, and more data are urgently needed to support their clinical utility in different settings.[34]

Thus, based on current evidence, an initial negative NAAT result does not rule out SARS-CoV-2 infection due to potential pre-analytical and analytical issues or time of testing. Accordingly, combining NAAT testing with other methods may be key to improved patient diagnosis and

therapy monitoring. Although molecular tests are gold standard for diagnosis, routine laboratory tests are cheaper, affordable and available on large scale and useful for prognosis and making treatment decisions.

The role of routine laboratory testing is beyond initial diagnosis It is essential in assessing disease severity, selecting appropriate therapeutic options, and monitoring treatment response.The choice and combination of molecular, serological, hematological and biochemical tests by Clinicians should be practical, timely, judicious and relevant to set up especially in pandemic situation.

Limitation of our study is lack of correlation between days of illness and laboratory parameters. Confounding factors, Comorbidities, Age, medications were not taken into consideration. However, this study is a reflection of real-life clinical setting wherein a proportion of asymptomatic patients (admitted from positive RT-PCR results during contact tracing) may not have significant abnormalities.

5. Conclusion

Lymphocytopenia, raised NLR, Eosinopenia, increased D-dimer, Ferritin, CRP were associated with severe COVID disease. Assessment of different parameters and
dynamic trend in different stages of the disease is important.

The routine laboratory parameters have been shown to have the capacity to diagnose, predict prognosis & complications and have usefulness in monitoring treatment response.

High suspicion of COVID 19 disease is warranted in symptomatic cases based on these laboratory parameters where molecular assay are not available or possibilities of false negative RTPCR cases in subsequent waves of COVID Pandemic. This will help in early isolation, treatment and decreasing leed time and combating the pandemic.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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