IJCRR
Section: Healthcare
ISI Impact Factor
(2019-20): 1.628
IC Value (2019): 90.81
SJIF (2020) = 7.893

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Laboratory Findings in Treatment & Prognostication of COVID-19

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ABSTRACT

Introduction: Majority of COVID-19 patients present with mild disease. 20% of patients progress to severe disease and have high mortality, because of hyperinflammation, cytokine storm development, viral mutation and lack of specific targeted medication. Critical analysis of laboratory parameters and potential biomarkers aids in assessing the evolution of disease, rapid identification of severe cases, identification of possible impending cytokine storm and guide appropriate medical management.

Aim: The aim of the current study is to identify the significance of laboratory parameters that assist in disease categorization, so as to initiate early medical management.

Materials and Methods: Between April 1 to April 15 2021, we retrospectively and prospectively included 200 patients admitted with COVID-19 infection (COVID-19 RTPCR positive and CORADS >3). Clinical assessment including history and associated comorbidities were noted at admission. Correlation of laboratory parameters was performed with disease category along with duration of hospitalization and clinical outcome.

Results: Out of 200 COVID-19 patients, there were 145 males (72.5%). Severe disease patients had significantly higher neutrophil percentage, ESR, lower absolute lymphocyte count, elevated serum Ferritin and LDH. Non-survivors had low oxygen saturation, high absolute neutrophil count, Neutrophil to lymphocyte ratio (NLR), ferritin, D-dimer, IL-6 and low platelets at admission.

Conclusion: Laboratory parameters are rapid, simple, cost-effective that aid in early diagnosis in assessing the severity of disease by indicating changes in immune and clotting system. Dynamic measurements help in timely institution of treatment strategies.

Key Words: Biomarkers, COVID-19, CORADS, Fibrinolysis, Hypoxia, Pandemic

INTRODUCTION

COVID-19 infection due to SARS-CoV-2 is a fifth documented pandemic, declared as global health emergency by WHO.¹

Due to sudden drastic increase in numbers of COVID-19 patients worldwide, treatment in intensive care units has become a challenge, and seriously affected the health resources all over the globe. SARS-CoV-2 in minor population of elderly patients and with preexisting clinical comorbidities such as cardiovascular diseases, diabetes, respiratory disease

and other conditions show critical disease progression to severe stage involving lung and other organs and few of these patients require ventilation, plasma and ECMO therapy. Early identification of severe forms is essential for triaging of patients and control progression of the disease.²

Currently majority of COVID-19 patients have mild self-limiting disease due to vaccination and mild herd immunity. 20% of COVID-19 are complicated and develop bacterial superinfections, organ dysfunction and progress to severe acute respiratory distress syndrome.³

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ISSN: 2231-2196 (Print) ISSN: 0975-5241 (Online)

Received: 07.09.2021

Revised: 22.10.2021

Accepted: 18.11.2021

Published: 03.01.2022

Cytokines are released by immune system cells and have a role in intercellular signaling. COVID-19 has an aggressive dysregulated inflammatory response of pro-inflammatory cytokines leading to hyperinflammation known as cytokine storm which causes tissue damage resulting in multiorgan failure including heart failure, septic shock, DIC, thromboembolism and death. Common laboratory parameters and potential biomarkers aid in assessing the disease evolution, effective and rapid identification of severe cases and for therapeutic management and particularly for home isolation patients.⁴

MATERIALS & METHODS

STUDY DESIGN

A prospective and retrospective study was conducted over a period of 15 days (between April 1 to April 15). A total 200 COVID-19 patients have been included in our study who were admitted in AIG hospital. All the symptomatic patients with RTPCR positive, CORADS ≥ 3 were included. Clinical history with associated comorbidities, laboratory parameters at different points of time (day 0, 3, 5, 10), treatment and outcome were analyzed. Correlation of laboratory parameters was done with disease categorization along with duration of hospitalization and treatment provided. Patient details were kept confidential.

INCLUSION AND EXCLUSION CRITERIA:

All patients with confirmed COVID-19 positive by RTPCR from nasal and throat swab and HRCT Chest findings CORADS 3 or more along with clinical symptoms were included. Associated co-morbidities documented include - Hypertension, Diabetes mellitus, Respiratory illness, cardiovascular disease, immunosuppression, patients on chemotherapy.

COVID-19 positive without any clinical symptoms or having CORADS < 3, those under home quarantine were excluded. Any readmitted patients after discharge were also excluded.

Ethical clearance was obtained from the Hospital ethical committee.

DATA COLLECTION:

Throat and nasal swabs for molecular identification of SARS-CoV-2 using nucleic acid amplification tests. Reverse transcriptase quantitative polymerase chain reaction (RTPCR) were obtained from COVID-19 patients using standard techniques as per ICMR recommendations.

Investigations included - complete blood picture (CBP), Erythrocyte sedimentation rate (ESR). Coagulation profile which includes Prothrombin time (PT)/ Activated partial thromboplastin time (APTT) / D-dimer, Liver function tests

(LFT), Renal function tests (RFT). Inflammatory markers included serum Ferritin, Interleukin-6 (IL-6), Lactate dehydrogenase (LDH), Troponin and C reactive protein (CRP). Fasting blood glucose was not included in analysis. All investigations were done at hospital using standard procedures on fully automated analyzers.

An analysis of presenting symptoms, CT Chest, laboratory parameters over the days of admission (repeated based on clinical condition), treatment and outcome were noted (from electronic medical records).

For patients with mild disease, investigations were done once in 5 days. For patients with moderate or severe disease and those with clinical deterioration, the laboratory parameters were done more frequently (usually once in 2 to 3 days).

DEFINITION OF CLINICAL SEVERITY OF COVID-19:

According to clinical management protocol of COVID-19 published by the Government of India, Ministry of Health and Family Welfare, the infection has been classified into 4 categories based on clinical manifestations - mild, moderate, severe category and severe with sepsis. In this study, patients were categorized into three - mild, moderate and severe disease. Mild disease patients have symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache with no breathlessness or Hypoxia (normal oxygen saturation) and no imaging symptoms of pneumonia. Moderate diseases are patients with fever and or hypoxia, dyspnea, cough, including SpO₂ < 94% (range 90 -94%) on room air, respiratory rate ≥ 24 per minute (pneumonia with no signs of severe disease). Severe diseases are patients with clinical signs of pneumonia plus anyone of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO₂<90% on room air.⁶

RESULTS

The data of 200 patients was analyzed. Mean age was 55.8 years (IQR 43-47 years) in mild disease, 57.1 years (IQR 52-67years) in moderate disease and 57.2 years (IQR 45-68 years) in severe disease. 145 males were infected (72.5%). 158 (79%) subjects had mild COVID 19 infection, 19 (9.5%) had moderate infection, and 23 (11.5%) had severe infection. The most common symptoms were fever, cough, sore-throat (59.5%) followed by shortness of breath (33.5%) and few with anosmia (6 %).

There was significantly lower neutrophil percentage in patients with mild disease 70.11(14.21) compared to moderate 79.58(7.19; p 0.008) and severe 79.22 (19.43; 0.005). Absolute lymphocyte count was higher in mild disease compared to moderate and severe disease (p 0.011). ESR was signif-

icantly higher in severe disease compared to mild disease (67.11 (15.46) Vs 43.38 (27.86); p 0.047). Also, at admission, serum ferritin and serum LDH were significantly higher in severe disease compared to mild and moderate diseases (p 0.004 for ferritin, 0.0001 for LDH). Other laboratory parameters CRP, IL-6, Bilirubin, ALT, AST, albumin, D-dimer, prothrombin and activated partial thromboplastin time were not significantly different in three categories of disease at presentation (Table 1).

Patients who succumbed to the illness during hospital stay had low oxygen saturation at admission (85.88 (11.5) vs 95.67 (4.58); p 0.03); higher absolute neutrophil count (p 0.03); higher NLR (p value 0.02); lower platelets (p 0.011) compared to survivors (Table 2).

Patients with higher ferritin (p 0.046), IL-6 (p 0.001), creatinine (p 0.04), BUN (p value 0.004), LDH (p value 0.001), INR (p value 0.027) died during hospital stay.

At day 3, patients with higher WBC, ANC, LDH, D-dimer and ferritin died during hospital stay (p value < 0.05). At day 5, patients with Higher TLC, ANC, NLR and low haemoglobin died (p value < 0.05).

Median hospital stay was 8 days (range 1-49) days. Favipiravir was prescribed to 26 (13%). Remdesivir was prescribed to 71 (35.5%). Steroids, heparin and tocilizumab were used in 79 (39.5%), 24 (12.0%) and 4 (2.0%) patients respectively. and plasma therapy was given in one patient.

Mortality rate was 8.5% (17/200). Mortality rate in mild disease at admission 3.8% (6/158), in moderate disease 15.79% (3/19) and in severe disease is 34.8% (8/23). There was no difference in mortality in male and female patients (7.59% vs 10.91%, p 0.570).

DISCUSSION

The intent of this paper is to identify the relation between the COVID-19 disease severity and its outcome by clinical and laboratory parameters in local population. This would benefit in early recognition of more aggressive disease, triaging accordingly to predict disease severity, and early institution of treatment, including newer options to reduce mortality. Severity of disease with the comorbid conditions may change with the viral mutation, status of vaccination and probable some amount of herd immunity but these factors were not analyzed.

DIAGNOSTIC VALUE OF CT CHEST

Patients with COVID-19 may have normal CT chest findings, if imaging is done in early stage after onset of symptoms. CT findings peak around 9-13 days after onset. 5th to 7th day is recommended in order to not significantly delay treatment and in clinically moderate to severe disease. The

hallmark CT findings for suspected COVID-19 patients are bilateral and peripheral lung disease with ground glass appearance, consolidation, total lung involvement and are seen more frequently as the duration of disease increases.

DIAGNOSTIC AND PROGNOSTIC VALUE OF HEMATOLOGICAL PARAMETERS:

In the early stages of viral infection, there is a reduction in the circulating leukocytes, including neutrophils, and platelet count due to either bone marrow suppression or peripheral destruction. This phenomenon may increase the susceptibility to secondary bacterial infection.⁸ However, severe COVID-19 is marked by leukocytosis.⁶ Retrospective analysis from one study shows patients with leukocytosis were significantly older, probably associated with chronic disease, develop severe illness and may require ventilation. Zhou et al. reported that leukocyte counts were higher among non-survivors when compared to recovered patients.⁷ Data from our study shows leukocyte count increases as the severity increases and is higher in non-survivors when compared to recover. Monocytes are increased and eosinophil are reduced during infection. Eosinophil increase in recovery phase.

Absolute lymphocyte count is an important parameter to discriminate between severe and non-severe disease. Prolonged lymphocyte depletion is a predictor of imminent death and a key marker of increased severity.⁷ Persistence of low lymphocyte count throughout the disease have been associated with critical illness and death.⁸ The possible reason for lymphopenia include direct effect of virus on lymphocyte, disordered inflammatory cytokines leading to lymphocyte apoptosis and inhibition of lymphocytes by metabolic molecules. Yang et al. reported lymphopenia in 80% of critically ill adult COVID 19 patients.⁸ In our study too, the lymphocyte percentage is lower in severe disease when compared to mild disease.

Neutrophil to lymphocyte ratio is a significant prognostic biomarker of outcome in critically ill patients which integrates 2 subtypes of WBC. The ratio is calculated from the values generated by automatic blood cell coulter by dividing absolute number of neutrophils with absolute number of lymphocytes.⁹ Normal NLR value is 1-3. High NLR predicts bacteremia and suggests severe disease. This information at admission will help in prognostication and instituting aggressive management strategies. De Jager et al. reported that NLR predicts bacteremia and is better than conventional inflammatory markers like C-reactive protein, WBC count, and neutrophil count. A recent analysis shows the probability of severe illness in patients with $NLR \geq 3.13$ and age ≥ 50 years old was 50% (compared to modest 9.1% in patient age ≥ 50 years and $NLR < 3.13$). Severe COVID-19 disease had higher NLR values (standard mean difference (SMD): 2.80, 95% CI: 2.12 - 3.48, $P < 0.00001$) when compared to patients with non-severe disease. In the subgroup analysis,

non-survivors have higher NLR values when compared to survivors (SMD: 3.72, 95% CI: 0.53 - 6.90, $P = 0.02$).¹⁰ Our analysis also shows NLR is higher in severe disease and is non survivors when compared to moderate and mild disease and survivors.

Platelet count is useful for diagnosis and prognostication. Thrombocytopenia occurs due to invasion of bone marrow by virus infecting progenitor cells and activation of thrombocytes by virus triggered immune complexes along with increased consumption by lung damage due to excessive thrombosis. A significant decrease in platelet count is indicator of worsening of illness.¹¹ Our study shows no significant difference between three categories.

ESR is a non-specific inflammatory marker and indicates the changes of plasma protein type. In our analysis, ESR is higher in severe cases when compared to mild cases. This may be due to more inflammation in severe group. Older patients had higher ESR that may be explained by ESR level which increases with age.¹²

DIAGNOSTIC VALUE OF COAGULATION MARKERS

Dynamic changes of peripheral blood coagulation function are D-dimer, PT, APTT. Severe COVID-19 has elevated D-dimer, FDP levels and longer PT. D-dimer correlate with clinical classification of patients at first and last test. D-dimer is product of fibrinolytic degradation which predicts the severity and prognosis of disease. Elevated levels help in diagnosis of thrombotic diseases and is an indication for therapeutic anticoagulation rather than prophylaxis with $>800\text{ng/ml}$ in normal individual and $>1000\text{-}1200\text{ng/ml}$ in 60-70 years of age.¹³

Potential risk factors during hospitalization are DIC, infection, dehydration, mechanical ventilation and use of central venous catheter.¹⁴ Terpos et al. reported hypercoagulability is common and patients with elevated PT, APTT, FDP and D-dimer are associated with life threatening DIC which needs continuous vigilance and prompt intervention.¹⁵ Our study shows no significant difference in D-dimer, PT, APTT between mild, moderate and severe cases. This may be due to small number of patients in our study.

INFLAMMATORY BIOMARKERS

Dysregulation of cytokines and chemokines leads to pathological activation of innate and adaptive immunity that causes 'cytokine storm' syndrome (CSS). IL-6 is a cytokine which controls the immune response, cell proliferation and differentiation and associated with pleiotropic functions such as acute-phase response. Increased levels of IL-6 (cut off- 80pg/L) in COVID-19 patients are associated with inflammation and extensive lung damage. IL-6 acts as a therapeutic target and using IL-6 inhibitors (Tocilizumab) can arrest the cytokine storm and cytokine storm-associated organ dam-

age.¹⁶ Our study shows that the level of IL-6 was low in mild cases when compared with the moderate and severe cases, and also high in non-survivors. WBC in collected blood samples on storage continue to release interleukins leading to erroneous high values. Repeat testing may be sent to same lab for comparison.¹⁶

CRP is an acute phase reactant and a sensitive marker of inflammation, infection, tissue damage and production is stimulated by cytokines. Significant elevation is seen in early stages of infection, especially the severe grade reflecting lung lesions. Elevation of CRP often may precede CT findings. CRP value correlate with level of inflammation and acts as early prognosticator for severe cases.¹² In our study, there was no statistically significant difference between severe and mild cases. However, mean level of CRP was higher in severe group.

Procalcitonin is a glycoprotein and its synthesis is increased due to cytokines. Higher procalcitonin (PCT) concentrations (usually $\geq 0.05\text{ ng/ml}$) can distinguish between severe and non-severe disease due to Covid-19, suggesting its prognostic significance. However, a recent meta-analysis reported marginal benefit (by 0.2 ng/ml).¹⁷ Among critically ill COVID-19 patients, PCT and CRP elevation may be associated not only with the inflammatory response, but also with the higher frequency of bacterial super-infections (up to 50% rate among non-survivors).¹⁸ In our study, procalcitonin was not included in analysis.

Ferritin is an acute phase reactant elevated in inflammatory conditions and is a direct indicator of cellular damage. Ferritin synthesis is controlled by cytokines. Extreme higher values leads to increased expression of pro and anti-inflammatory cytokines, a hallmark of hyperferritinemic syndrome (macrophage activation syndrome). Values over 800ng/ml is directly related to organ damage and is an indication for steroid initiation with clinical correlation values over 2000ng/ml portend poor prognosis in hospitalized COVID-19 patients.¹⁹ Henry et al. reported ferritin as a surrogate marker of immune dysregulation and prognosis and shows a direct correlation between serum ferritin and poor survival.⁷ Zhou et al. reported that both ferritin and IL-6 concentrations showed higher values in non-survivors in comparison to discharged patients, and increased as the patient deteriorates.²⁰ Our study shows an increase of IL-6 in non-survivors when compared to survivors, and increase in moderate and severe cases when compared to mild cases.

ACE2 is a receptor which mediates virus entry into host cell and its expression is increased in patients with diabetes mellitus which enhances susceptibility to COVID-19. We have not analyzed variations of blood glucose in current study. Increased ALT, AST, Total bilirubin and decreased albumin in COVID-19 patients might be due to viral cytopathic effects, drug induced or systemic inflammatory response.²¹

Mortality rate among admitted patients with COVID-19 was 8.5% in our study, higher in severe disease 34.8% (8/23). Mortality rate is more due to selection bias as more sick patients got admitted. The categorization into mild, moderate & severe changed over time with more proper definition of disease. As observed in other parts of country in initial phase of pandemic, lack of patient awareness in approaching hospital for early treatment could also be the reason. There was no difference in mortality in male and female.

LIMITATIONS OF STUDY

This was a single-centre study with small number of study subjects and thus might have a selection bias. This study finding need to be corroborated with a large population

CONCLUSION

Laboratory parameters have diagnostic and prognostic value. Dynamic measurements of laboratory parameters correlate with disease severity and will be predictors for the clinical evaluation of COVID-19 patients for better monitoring and therapeutic interventions.

ACKNOWLEDGMENT

Authors would like to thank technical and hospital staff for providing material for publication.

DECLARATIONS:

Source of funding: Granules India Grant

Conflicts of interest: None declared

Ethical approval: Approval letter is attached.

Author's Contribution Statement:

1. Anuradha Sekaran - Conception of study, Data analysis, Interpretation and critical revision
2. Swapna S - Data analysis and Review of manuscript
3. Shruthi Dulala – Data collection, Analysis
4. Maddipati Veda Ganga Ritesh – Data collection, Analysis
5. Jagadeesh Kumar V – Review of manuscript
6. Nitin Jagtap - Statistical analysis and manuscript review
7. Naveen Chandra Reddy - Clinical data analysis
8. Sandeep Lakhtakia - Review of manuscript
9. Duvvur Nageshwar Reddy - Review of manuscript

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Table 1: Demographic and baseline laboratory data in patients classified as mild, moderate and severe disease at admission.

	Total (200)	Mild (158)	Moderate (19)	Severe (23)	p value			
					Overall	Mild Vs Moderate	Moderate Vs Severe	Mild Vs Severe
Age	56.09 (14.78)	55.80 (15.02)	57.05 (13.87)	57.22 (12.90)	0.873			
Hemoglobin	12.51 (2.60)	12.48 (2.54)	12.69 (3.19)	12.57 (2.58)	0.938			
Total Leucocyte Count	7761.54 (4383)	7501.31 (4647)	8189.47 (4024)	9139.13 (4494)	0.256			
Neutrophils	72.11 (14.85)	70.11 (14.21)	79.58 (7.19)	79.22 (19.43)	0.001	0.008	0.936	0.005
Lymphocytes	21.25 (13.61)	22.76 (12.88)	14.95 (6.53)	16.35 (19.44)	0.011	0.017	0.736	0.033
Eosinophils	1.89 (1.58)	1.93 (1.53)	2.11 (2.59)	1.48 (0.51)	0.368			
ALC	1371.97 (899.40)	1470.57 (957.40)	1054.84 (384.34)	978.09 (602.23)	0.013	0.055	0.780	0.014
ANC	5908.25 (4322)	5530.70 (4327)	6686.32 (3785)	7777.00 (4295)	0.047	0.268	0.412	0.020
AEC	145.10 (152.68)	141.73 (142.59)	183.06 (265.10)	136.78 (86.30)	0.537			
NLR	6.86 (10.61)	6.16 (11.03)	6.96 (4.29)	11.48 (10.52)	0.080			
Platelets	2.174 (0.91)	2.139 (0.90)	2.274 (0.94)	2.317 (0.99)	0.605			
ESR	48.82 (25.49)	43.38 (27.86)	47.86 (13.41)	67.11 (15.46)	0.047	0.663	0.123	0.014
CRP	9.30 (28.14)	7.93 (25.81)	3.43 (2.43)	22.54 (45.94)	0.206			
Ferritin	651.94 (647.72)	581.60 (635.43)	617.19 (467.81)	1100.08 (668.10)	0.004	0.846	0.032	0.001
IL 6	78.22 (147.23)	67.48 (146.55)	88.30 (166.38)	133.94 (132.83)	0.171			
Bilirubin	1.339 (3.00)	1.366 (3.19)	1.507 (3.05)	0.982 (0.53)	0.863			
ALT	41.01 (49.57)	39.02 (43.65)	37.20 (19.02)	59.53 (92.76)	0.265			
AST	57.84 (83.17)	56.81 (89.28)	55.53 (54.21)	67.71 (52.21)	0.875			
ALP	86.39 (57.07)	90.01 (61.52)	67.67 (25.76)	75.47 (33.83)	0.254			
Albumin	3.58 (0.60)	3.60 (0.63)	3.53 (0.47)	3.53 (0.41)	0.856			
Creatinine	1.13 (0.82)	1.06 (0.57)	1.70 (1.90)	1.09 (0.40)	0.007	0.002	0.024	0.876
BUN	33.88 (19.66)	31.79 (18.18)	42.36 (25.28)	43.18 (21.93)	0.042	0.057	0.916	0.065
LDH	663.81 (249.02)	616.77 (229.37)	664.86 (127.24)	914.00 (268.43)	0.0001	0.458	0.0001	0.002
D-Dimer	677.05 (1145)	685.52 (1255)	740.08 (865)	582.33 (286)	0.922			
PT	14.98 (6.14)	14.69 (6.38)	14.69 (4.09)	17.89 (5.58)	0.378			
APTT	35.79 (14.83)	34.92 (14.82)	32.90 (6.19)	44.96 (20.83)	0.332			
INR	1.26 (0.53)	1.23 (0.55)	1.23 (0.35)	1.50 (0.48)	0.400			

Table 2: Comparison of laboratory parameters between live and dead patients

Parameter	Alive	Death	p value
SP O ₂ (n, mean (SD))	183 95.67 (4.58)	17 85.88 (11.5)	0.003
Hemoglobin	178 12.70 (2.45)	17 10.54 (3.26)	0.016
ANC	178 5700 (3828)	17 8082 (7672)	0.03
NLR	178 6.32 (10.26)	17 12.54 (12.75)	0.02
Platelets	177 2.23 (0.91)	17 1.64 (0.82)	0.011
Ferritin	143 623 (640)	11 1026 (655)	0.046
IL 6	134 65.96 (126.36)	13 204.62 (260.29)	0.001
Albumin	150 3.62 (0.57)	11 3.12 (0.73)	0.006
Creatinine	153 1.02 (0.49)	15 2.21 (2.03)	0.04
BUN	121 31.11 (15.90)	10 67.3 (29.44)	0.004
LDH	134 642.82 (238.17)	13 880.23 (264.81)	0.001
INR	79 1.22 (0.49)	8 1.65 (0.75)	0.027
WBC at 3 day	138 9418 (4862)	13 14130 (8740)	0.003
ANC at 3 day	137 7483 (4526)	13 12398 (8297)	0.001
Ferritin at 3 day	100 571.82 (579)	8 1475.86 (668.93)	0.006
LDH at day 3	53 594.62 (197.33)	6 5926 (12445.76)	0.001
D dimer at day 3	91 606.54 (1065.77)	5 1983.8 (2360.79)	0.011
Hb at Day 5	79 13.74 (11.18)	12 10.39 (2.56)	0.025
WBC at day 5	79 11878.48 (5278.80)	12 19083.33 (5917.90)	0.001
ANC at day 5	79 9816.54 (4923.56)	12 17164 (5946.45)	0.001
NLR at day 5	79 9.90 (7.51)	12 21.18 (17.05)	0.044

ABBREVIATIONS

1. ALC - Absolute Lymphocyte Count;
2. ANC - Absolute Neutrophil Count;
3. AEC - Absolute Eosinophil count;
4. NLR - Neutrophil lymphocyte ratio;
5. ESR - Erythrocyte sedimentation rate;
6. CRP - C reactive protein;
7. IL-6 - Interleukin 6;
8. ALT - Alanine aminotransferase;
9. AST - Aspartate transaminase;
10. ALP - Alkaline phosphatase;
11. BUN - Blood urea nitrogen;
12. LDH - Lactate dehydrogenase;
13. PT - Prothrombin time;
14. APTT - Activated partial thromboplastin time;
15. INR - International normalized ratio