VOLUME - 12, ISSUE - 05, MAY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Internal Medicine

A STUDY ON HEMATOLOGICAL MANIFESTATIONS IN PATIENTS INFECTED WITH SARS COV 2 DURING ILLNESS AT TERTIARY CARE CENTRE

Dr Gourav Sahu	MBBS PGT M.D. in Department of Medicine, Mahatma Gandhi Memorial medical college and maharaja Yashwant Rao and associated group of hospitals, Indore, MP, India
Dr Manoj Gupta*	MD Medicine, Associate Professor, Department of Medicine, Mahatma Gandhi Memorial medical college and maharaja Yashwant Rao and associated group of hospitals, Indore, MP, India*Corresponding Author
Dr Monika Porwal	MD, DNB Neurology, Assistant Professor, Department of Medicine, Mahatma Gandhi Memorial medical college and maharaja Yashwant Rao and associated group of hospitals, Indore, MP, India
Dr Dipali Agarwal	MD, DNB Neurology, Assistant Professor, Department of Medicine, Mahatma Gandhi Memorial medical college and maharaja Yashwant Rao and associated group of hospitals, Indore, MP, India
Dr Ved Prakash Pandey	MD Medicine, Professor and head, Department of Medicine, Mahatma Gandhi Memorial medical college and maharaja Yashwant Rao and associated group of hospitals, Indore, MP, India

ABSTRACT **Background** – COVID 19 is a systemic infection which results a disease spectrum ranging from mild respiratory involvement to life threatening multi-organ involvement. COVID 19 has significant impact on hemostasis and hematopoietic system and hematologic manifestations like lymphopenia, neutrophilia, thrombocytopenia, monocytopenia, elevated LDH, elevated ferritin, elevated D-dimers, prolonged PT, prolonged APTT, elevated fibrinogen are more common with severe disease.Therefore, we selected COVID19 infected patients to study their clinical and investigational profile. **Methods** -500 COVID 19 positive patients in age group of 18-85 yrs admitted in our 500 bedded covid dedicated hospitals associated with Maharaja Yashwant Rao Hospital, Indore, were observed for their clinical profile, laboratory parameters, inflammatory markers, radiological parameters etc. **Results** – Hematological manifestations are very common among COVID19 patients. It is frequently associated with anemia, thrombocytopenia, leukopenia, lymphopenia, high Neutrophil to Lymphocyte ratio and high platelet to Lymphocyte ratio. It also associated with raised inflammatory markers and deranged coagulation profile. Various hematological manifestations like lymphopenia, thrombocytopenia, high NLR and PLR, raised inflammatory markers are associated with severity of disease. **Conclusionn** -Hematological manifestations plays significant role in COVID19 disease course .Various hematological parameters are reliable markers for disease severity and prognosis . These parameters also helps in triage of patients and further management.

KEYWORDS : COVID 19, hematological manifestations, severity, prognosis, inflammatory markers.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) affected millions of patients worldwide. It rapidly evolved from an epidemic outbreak in Wuhan, China1 into a pandemic infecting more than 63.5million individuals all over the world. This pandemic has caused disruption in communities and hospital services, as well as straining blood product supply, affecting chemotherapy treatment and haematopoietic stem cell transplantation schedule.

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-strand RNA virus belonging to the family Coronaviridae with about 80% genomic similarities with SARS-CoV[1-3]. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a betacoronavirus which is transmitted mainly via droplets and contaminated surfaces[4,5]. Covid-19 is a respiratory infection, but it has a significant impact on the hematopoietic system and hemostasis. Hematologic manifestations include lymphopenia, neutrophilia, thrombocytopenia, monocytopenia, elevated LDH, reactive and plasmacytoid lymphocytes on blood film, elevated ferritin, coagulopathy associated with COVID-19, elevated D-dimers, prolonged PT, prolonged APTT, elevated fibrinogen. Severe disease is commonly complicated by lymphopenia[16], thrombocytopenia[17] and coagulopathy, which often progresses to disseminated intravascular coagulation (DIC)[18]. A characteristic feature of the pathogenesis of SARS-CoV-2 is a cytokine storm. Indeed, plasma concentrations of interleukin-6, interleukin1 , TNF- , but also granulocyte colony-stimulating factor (G-CSF) or interferon -inducible protein (IP10) appear to be very high in patients with Covid-19 and even higher in the intensive care unit (ICU) patients than non-ICU patients. This cytokine release syndrome in Covid-19 patients is associated with reduced lymphocyte counts[19]. Lymphopenia is present in more than 80% of Covid-19 patients on admission[20] and could predict the severity of Covid-19 disease[21].

Hematologic abnormalities were more prominent in patients with severe disease compared to non-severe: 96.1% versus 80.4% for lymphopenia, 61.1% versus 28.1% for leukopenia, and 57.7% versus 31.6% for thrombocytopenia[51].

A study from Wuhan revealed that more severe cases had higher neutrophil counts (4.3 × 109/L vs 3.2 × 109/L; P < 0.001) and lower lymphocyte counts (0.8 vs 1.0 × 10^9/L; P < 0.001) a higher ratio of neutrophils to lymphocytes (5.5 vs 3.2; P < 0.001) and also a lower percentage of monocytes, eosinophils and basophils[83].

Yang et al.[115] analyzed the predictive role of PLR and showed

that higher PLR was observed in severe patients (436.5 ± 329.2) compared to non-severe patients (176.7± 84.2; p < 0.001). Increased PLR showed a trend for association with disease progression (hazard ratio [HR] 1.023, 95% CI 0.921–1.756 in multivariate Cox regression), but statistical significance was lost after adjusting for gender and age, limiting its clinical utility[115].

Patients with severe disease from COVID-19 often show abnormal laboratory markers that reflect a systemic inflammatory response. Some of the inflammatory biomarkers like ESR, CRP, LDH, PCT, D-dimer, IL 6 are associated with adverse clinical outcomes and are emerging as reliable prognostic parameters.

CASE STUDY

In this study, out of 500 patients ,17.4% are below 30yrs of age, 24% are in 31- 45yrs, 31.4% are in 46-60yrs, 22.6% are in 61-75yrs and 4.6% are >75yrs age group. The mean age is 49.11±17.24 (Range 18-85 years) and median age is 50yrs. Among all patients, 65.8% are males and 34.2% are females. 29.4%patients have mild anemia while 13.2% and 4.4% have moderate and severe anemia respectively.10% patients have leukopenia while 18% have leukocytosis and 13% have thrombocytopenia.

As per the clinical evaluation and CT severity score, 70.8% cases had mild infection whereas 19.8% and 9.4% cases had moderate and severe COVID 19 infection respectively.

In our study, data was skewed and thus median and interquartile range were taken into consideration. Median hemoglobin levels were 12.75 (IQR-11.4 to 14.1) gm%, whereas median WBC count was 6785 (IQR-5200-9615) cells/mm^3.Median neutrophils and lymphocyte counts were 74% and 19% respectively. Median Neutrophil to lymphocyte ratio and median platelet to lymphocyte ratio were 3.8 and 12.78 respectively.

Other investigations such as ESR, PT INR, CRP, LDH, PCT etc. were done in few cases. Median ESR was 21 mm, whereas median PT INR was 1.05. Median CRP, LDH, PCT and D-dimer were 82, 326.5, 0.05 and 576 respectively. However, median IL6 was 8.75 whereas median ferritin levels were 245.14.

Median WBC count, neutrophil, NLR as well as PLR were found to be significantly higher in cases with severe infection and moderate infection whereas lymphocytopenia and thrombocytopenia worsened with increase in severity of infection (p<0.05).

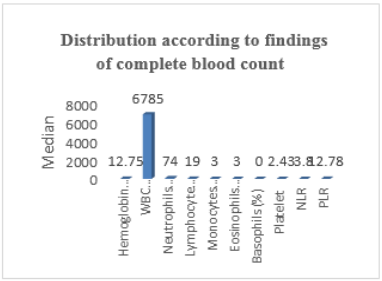
We reported median ESR, LDH, PCT, D-dimer, IL 6 as well as serum ferritin levels to be significantly higher in severe COVID 19 infection as compared to moderate and mild infection (p<0.05).

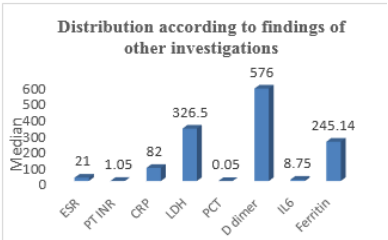
Area under the curve was maximum for Neutrophil to lymphocyte ratio (AUC-0.712; p<0.05) suggesting NLR to be fair predictor of severity with sensitivity of 70.2% and specificity of 63.4% at cut off of 5.27. AUC of PLR, WBC and neutrophil showed these parameters were helpful in predicting severity, but the diagnostic accuracy was in poor range (AUC- 0.60-0.70; p<0.05).

Median WBC count, neutrophil, NLR as well as PLR were found to be significantly higher in cases with severe infection and moderate infection whereas lymphocytopenia and thrombocytopenia worsened with increase in severity of infection (p<0.05).

We reported median ESR, LDH, PCT, D-dimer, IL 6 as well as serum ferritin levels to be significantly higher in severe COVID 19 infection as compared to moderate and mild infection (p<0.05).

Area under the curve was maximum for Neutrophil to lymphocyte ratio (AUC-0.712; p<0.05) suggesting NLR to be fair predictor of severity with sensitivity of 70.2% and specificity of 63.4% at cut off of 5.27. AUC of PLR, WBC and neutrophil showed these parameters were helpful in predicting severity, but the diagnostic accuracy was in poor range (AUC- 0.60-0.70; p<0.05).





Association of routine hematological parameters with severity of COVID 19 infection

CBC	Mild (n=354)		Moderate (n=99)		Severe (n=47)		Kruskal Wallis Test	P value
	Median	IQR	Median	IQR	Median	IQR		
Hemoglobin	12.9	11.6-14.2	12.8	11.1-13.7	12.5	11-13.1	3.9	0.56
WBC	6185	4872.5-8410	9200	6090-14250	11000	7440-16000	90.9	0.001
Neutrophils	68	60-76	84	74-94	89	86-90	224.9	0.001
Lymphocytes	24.5	16-31	10	3-19	7	6-8	234.8	0.001
Monocytes	4	2-6	4	1-5	3	2-5	6.8	0.064
Eosinophils	3	2-5	3	1-4	3	1-4	2.3	0.65
Basophils	0	0-0	0	0-0	0	0-0	1.9	0.81
Platelet	2.7	1.9-3.84	2.4	1.8-3	1.9	1.5-2.7	12.99	0.001
NLR	2.8	1.9-4.8	8.4	3.9-31.3	12.8	10.6-15.2	235.7	0.001
PLR	10	6.7-15.5	23.3	9.6-56.6	41	26.4-52.5	188.7	0.001

Association of inflammatory markers with severity of COVID 19 infection

Other	Mild		Moderate		Severe		Kruskal Wallis Test	P value
	Median	IQR	Median	IQR	Median	IQR		
ESR (n-263)	20	14-31	19	15-29	36.5	17.7-88	14.7	0.001
PT INR (n=50)	1.06	0.99-1.12	0.94	0.7-1.1	1.03	1.02-1.04	4.8	0.09
CRP (n=50)	74.5	13.11 39.5	86.5	33.3-139	112.6	69.5-153.3	2.5	0.28
LDH (n=124)	304	234-398	336.5	260.8-420.5	437	351.5-507	11.05	0.004
PCT (n=62)	0.03	0.02-0.37	0.02	0.01-0.08	0.27	0.08-32.3	10.5	0.005
D dimer (n=195)	477	345-808.5	660	463-1150	1102	728-8820	24.2	0.001
IL6 (n=190)	6.89	4.24-20.9	12	5.7-31.7	19.9	9.03-62.4	15.1	0.001
Ferritin (n=142)	156.9	70.2-372.6	210.3	105.4-718.2	1005.4	563.7-1576	31.85	0.001

CONCLUSIONS

In the current study, we have considered 500 COVID-19-infected patients in age group 18-80 years and considered their hematological parameters. From the different observations, we concluded that COVID 19 infection is frequently associated with various hematological manifestations like anemia, thrombocytopenia, leukopenia, lymphopenia, high Neutrophil to Lymphocyte ratio and high platelet to Lymphocyte ratio. It also associated with raised inflammatory markers and deranged coagulation profile. This study also concludes that various hematological manifestations like lymphopenia, thrombocytopenia, high NLR and PLR are associated with severity of disease and the severity of disease increases with increasing degree of lymphopenia and thrombocytopenia. This study also concludes that COVID 19 infection is associated with systemic inflammatory reaction and the inflammatory biomarkers are associated with severity of disease and poor clinical outcomes. These biomarkers can be used as reliable prognostic parameters.They will help in triage of patients and early intervention.

REFERENCES:

1. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020 Apr;92(4):424–32.
2. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar;579(7798):265–9.
3. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270–3.
4. Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-733.
5. World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations 2020. https://www.who.int/publications-detail/modes-of-trans mission-of-virus-causing-covid-19-implications-for-ipc-precaution -recommendations. Accessed May 11, 2020
6. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID19. Am J Hematol. 2020;95(7):834–847.
7. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–148.
8. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–1099.
9. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., et al. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, 395(10224), 565–574
10. Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., et al. (2020). Clinical characteristics of coronavirus disease 2019 in China. The New England Journal of Medicine.
11. Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y. Q., et al. (2020). Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduction and Targeted Therapy, 5, 33.
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA. 2020;323(13):1239.
13. Qin C, Zhou L, Hu Z et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clinical Infectious Diseases. 2020; http://dx.doi.org/10.1093/cid/ciaa248
14. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020 Jul;84:106504