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Comparative Study of Physiological and Haematological Parameters among Mild and Severe COVID-19 Patients Admitted in Tertiary Care Hospital of Pune District, India

Suchita Sachin Palve[1*] and Pallavi Sachin Chaudhari[1]

[1]Symbiosis Medical College for Women, Symbiosis International (Deemed University), Pune, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: The COVID-19 pandemic has put global health at stake by creating havoc all over the world, due to which the world, as well as health agencies, are experiencing the greatest challenges. This disease is a health emergency due to its high level of infectiousness and the non-availability of any specific treatment [1].
Objectives: To determine and compare the significance of physiological and haematological parameters in the diagnosis of COVID 19 infection and compare the association of physiological and haematological parameters among mild and severe COVID-19 patients.
Methodology: The present comparative, observational study was carried out in a designated tertiary care hospital, where admission of COVID19 patients in Pune district, India. Various parameters like age, height, weight, BMI, various physiological variables, haematological parameters, and CRP levels were assessed among 202 Mild and 50 severe COVID 19 diagnosed

**Corresponding author: E-mail: drsuchitrapalve11@gmail.com;*

patients on day one of the hospital's stays.
Results: Pearson's correlation coefficient showed a significant correlation among physiological and haematological variables compared to both groups, especially physiological parameters like SBP and DBP. The results showed that TLC, CRP, NLR, PLR, among COVID 19 patients cans work as important biomarkers to understand the disease prognosis.
Conclusion: Study of physiological and haematological parameters and their interrelation will help in understanding the impact of COVID 19 infection on the reactive inflammatory responses and help in understanding the prognosis of the disease among mild and severe patients.

Keywords: COVID 19; mild; severe; comorbid; diabetes mellitus; haematological; physiological.

ABBREVATIONS

COVID-19	*: Corona Virus Disease 2019*
WHO	*: World Health Organisation*
SARS COV	*: Severe Acute Respiratoy syndrome Corona Virus*
MERS COV	*: Middle East Respiratoy syndrome Corona Virus*
TLC	*: Total leukocyte count*
NLR	*: Neutrophil to lymphocyte ratio*
LMR	*: Lymphocyte-to-Monocyte ratio*
PLR	*: Platelet to lymphocyte ratio*

1. INTRODUCTION

Hubei province of China has reported many pneumonia cases of unknown aetiology around December 2019 [2]. On January 7, 2020, the CDC of China had published a statement stating that a new virus is extracted from the sample of a throat swab, which has a close resemblance with the previously confirmed (SARS-CoV) [3] and MERS-CoV and named by WHO as COVID 19 or the 2019-novel coronavirus disease [4].Various strains of the corona, which are known till now, like MERS and SARS-CoV, can cause systemic infection among different animals like bats, pigs, camels, etc. This can lead to infections related to the respiratory tract of various grades in humans [5]. New coronavirus (COVID-19) has a high case fatality rate among critically ill patients. Ever since India's first case was diagnosed on January 30, 2020, there are around 1200000 cases, around 30,000 deaths have occurred due to this novel virus. Many Indian cases have been reported from the state of Maharashtra, which accounts for just over a third of the country's cases that are nearly 360000 and 12,000 deaths [6]. Literature from other countries such as Italy, Spain, France, and the United States have suggested high mortality associated with this disease and overburdening intensive care units [7]. Transmission of the disease usually occurs among the closed contact family members and hospital staff members [8]. Most of the patients exhibit mild or no symptoms, and few represents a worse prognosis [9].Patients usually have a wide range of symptoms depending on the severity of the illness, maximum patients who are infected with this novel infection usually don't have any symptoms, certain clinical manifestations may appear around the first 14 days of virus exposure, which includes fever and chills or without chills, headache, cough, difficulty in breathing or shortness of breath, easy fatigability, body aches or muscular pain [10]. New symptoms may vary from loss of smell and taste sensation, running nose and congestion, diarrhoea, nausea, vomiting [11]. In India, around 80% of the Covid-19 patients either have mild symptoms, or most of them are asymptomatic [12]. Most of them (about 96% approximately) recover from the disease without needing special treatment in India [13]. The vulnerable population includes old aged (>55 years). Those who have underlying comorbid medical conditions like diabetes, hypertension, chronic kidney diseases, and respiratory disorders like bronchial asthma are more prone to develop severe symptoms due to COVID 19 [14]. As the disease transmission rate is very fast, there is a need for continuous improvement and advancement in its clinical diagnosis and treatment. Also, there is a need to do extensive research to understand the disease progression and the expected treatment modalities [15].It is also necessary to explore various biochemical and physiological parameters that are still in the exploratory stage and can help understand the prognosis of the disease [16]. Suppose any disease progression in the body is to be understood. In that case, one should know that it's the severe inflammatory responses that contribute heavily to the host's weak acquired immune response that can lead to the immune system imbalance [17]. Inflammation can occur due to various infectious diseases and can mark an important predictor of the disease progression [18]. Thus, circulating biomarkers are representatives of inflammatory and immune

system response and are also potential predictors for understanding the prognosis and the disease progression among COVID-19 patients. Total leukocyte count (TLC), (NLR) neutro Phil to lymphocyte ratio, lymphocyte-to-monocyte ratio (LMR), and (PLR) platelet to lymphocyte ratio are frontline predictors used in the prognosis of any viral infection and also the related response to inflammation. The liver secretes CRP (C-reactive protein) as a response to various inflammatory cytokines. The CRP level increases rapidly with the response to infection, inflammation, and trauma and reduces rapidly as the underlying condition resolves. Thus, CRP levels are widely used to monitor various inflammatory disorders. The present study was planned to analyse and compare the laboratory results and clinical characteristics among mild and severe COVID 19 patients. This study will help identify the risk factors associated with mortality among these patients and help determine the significance and correlation of physiological variables with haematological parameters among patients with mild and severe symptoms of COVID-19.

2. MATERIAL AND METHODS

2.1 Study Design

This comparative observational study was carried out in a designated tertiary care hospital to address COVID19 patients in the Pune district. The random purposive sampling technique was used based on the study's duration (2 months), based on which recruitment of 202 mild patients and 50 severe patients was done**.** After obtaining prior informed consent, the retrospective data were collected from the admitted patients' medical records. Positive patients were randomly selected based on the RT-PCR lab reports, either nasal or pharyngeal swab specimens, about the World Health Organization's standard guidelines (WHO).

2.2 Inclusion Criteria

- Lab confirmed cases of COVID 19 (with mild and severe symptoms as per standard guidelines prescribed by WHO)
- Patients with age >18 years

2.3 Exclusion Criteria

- Patients with age <18 years
- Patients with hematological diseases, chronic kidney and liver disease
- Patients undergoing radiotherapy and chemotherapy were excluded from the present study.

3. METHODOLOGY

3.1 Clinical Characteristics and Laboratory Data

A detailed patient profile screening was done based on the records, including recent exposure history, clinical signs and symptoms, and association of any comorbid conditions. Various parameters which were obtained for Analysis includes,

3.1.1 Physiological variables

Temperature, pulse, blood pressure, respiratory rate was obtained from the patients' records.

3.1.2 Hematological parameters

TLC, NLR, LMR, PLR, CRP, ANC, ALC, AMC, PL values were obtained from electronic medical records. The patient's complete blood count was done on a fully automated five-parthematology analyser: Beck man Coulter DXH 800, and peripheral blood smear examination was performed under a microscope. Records for all the parameters were obtained for day one of the admission. Neutrophil lymphocyte ratio (NLR), Lymphocyte monocyte ratio (LMR), and Platelet lymphocyte ratio (PLR) were subsequently derived using standard formulae. CRP test was performed by a quantitative method which is based on the principle of Nephelometry. (MISPA-AGAPPE Diagnostics limited, Kerala, India).Serum samples were analysed for the same on the day of admission and repeated on day 10. CRP test was considered positive if the value was >6mg/L and negative if the value was <6mg/L.

3.2 Statistical Analysis

Grouping of the patients was done based on Age, Sex, BMI, severity, and comorbidities. Study variables were expressed as means and standard deviations. Descriptive and inter variable Analysis was performed to assess parametric variations during the disease progression using one-way ANOVA analysis; values ≤0.05 were considered statistically significant. Pearson's correlation coefficient was obtained to determine the correlation between haematological and physiological parameters; a

level of significance for r values was set between 0.5 to1.0 and values in this range were considered statistically significant.

4. RESULTS

Out of the total study participants in the mild group (n=202), 112 were male, and 90 were females with an average age (43.43±15.07), (51.8±16.35) and BMI (25.48±3.85), (24.37±3.55). Out of 202 subjects, n=58 was hypertensive, n=54 were diabetics, and n=28 was diabetic and hypertensive. Among the severe group (n=50), 37 were male, and 13 were females with an average age of (58.8±16.35) (47±16.07) and BMI (27.37±3.55), (26.59 ±4.69) for male and female respectively. Out of 50 severe patients, n=31 was hypertensive, n= 37 were diabetics, and n=34 had both diabetes and hypertension; n= 23 patients had renal dysfunctions. Significantly, higher numbers of patients were found suffering from comorbid conditions, like hypertension, diabetes, and renal disorders among the severe category. ($p<0.01$)The age, BMI, TLC, PCT ANC, AMC, ALC count, NLR, LMR, PLR, ratios, and CRP levels of severely ill patients were significantly higher than those of mild patients. Significant variations were seen in gender ratio among severe patient's data's shown in Figure 1. Highly significant variations were found in the physiological variables, like Pulse, SBP, DBP, RR, and haematological parameters like CRP, TLC, PCT ANC, AMC, ALC, NLR, PLR, LMR, when both groups were compared. Significant variation in DBP was found among mild and severe patients. Distribution of study population based on Analysis of study variables for entire population shown in Table 1 Analysis of study variables among both groups in correlation with comorbidities As shown in Table 2. Analysis of the correlation of physiological and haematological variables for all the study populations is based on gender and comorbid conditions shown in Table 3. A highly significant variation for ALC and ANC was also seen among both groups. Significant variation was seen in the respiratory rate and platelet count among both categories. Pearson's correlation coefficient showed a significant correlation among physiological and haematological variables compared to both groups, especially physiological parameters like SBP and DBP, which were significantly correlated with gender.

In contrast, haematological parameters were significantly correlated among severe patients when compared among both groups. To understand the markers that will help understand the disease's prognosis, after performing the regression analysis, we got the crude odds ratio (OR). After excluding the probable effect of age and gender on the haematological parameters, we tried to analyse the adjusted OR ratio. The results showed that TLC, CRP, NLR, PLR, among COVID 19 patients, can work as important markers to understand the disease prognosis in shown in Table 4.

Pearson's correlation coefficient was obtained to determine the correlation between haematological and physiological parameters; the level of significance for r values was set between 0.5 to1.0 and values in this range were considered statistically significant.

5. DISCUSSION

The most affected organ due to COVID 19 is the lung, and also it causes damage to the immune system of the body. The majority of the patients will not show any symptoms in the initial stage of the disease. If present, too, 80% will exhibit mild symptoms, around 14% of patients suffer pneumonia, and 5% may land up in a septic shock leading to respiratory failure and death. This novel infectious disease exhibits around 3 to 4 % of the case fatality rate, too. Some of the primary symptoms of COVID 19 infected patients are mild to severe fever with or without chills, giddiness, and feeling of breathlessness, headache, and dry cough. Few novel types of symptoms include loss in smell and taste sensation; few severe category patients have also reported diarrhoea. Easy fatigability 80% of the patients will show no symptoms or have mild symptoms, 14% of the infected patients may develop pneumonia, 5% of the patients will develop a septic shock and land up in multi-organ failure (mostly respiratory failure) and considering these complications the overall case fatality rate remains between 3 to 4%. The study's major aim was to analyse and the physiological and haematological parameters among mild and severe COVID 19 patients and to understand if these parameters are going to get affected due to disease progression. Our study showed a significant correlation of physiological and haematological parameters compared with gender and compared with comorbid conditions like *Diabetes mellitus* and hypertension. Our study results showed significant relevance of the clinical characteristics with the previous literature. We tried to assess

the immunological characteristics of COVID-19 patients using haematological parameters. Our study takes account of the inflammatory processes in disease prognosis, where we tried to analyse the values of not only NLR, PLR, ratios as compared with the previous studies, but also the levels of ANC, AMC, ALC, PCT, TLC, and the ratio of LMR too, as these parameters are nowadays increasingly preferred to be investigated in the current COVID 19 scenarios. Our hypothesis is based on the fact that the human immune responses, which are notoriously triggered due to the viral load or infection, mainly rely on the lymphocytes' support system. On the other hand, the cellular immune responses are suppressed due to systemic inflammatory responses leading to a decrease in T lymphocytes and CD4+ cells and increased levels of the suppressor T lymphocyte or CD8. The inflammation triggered by the virus will lead to elevated NLR levels, which will lead to COVID-19 progression. Lymphocytes are first-line markers to produce the immune response in the patients, while the destructive inflammatory response results from neutrophils' responses. These ratios try to work as a reflection of acute inflammatory responses (increase in neutrophils and platelets) and acute physiological stress (decrease in lymphocyte), which leads to an increase in the heart rate and respiratory rate. In the present study, our results helped us to prove that neutrophil to lymphocyte ratio (NLR), Platelet to lymphocyte ratio (PLR) as well as lymphocyte to monocyte ratio (LMR) can be utilized as an independent prognostic biomarker to assess the prognosis in these patients. Also, the integration of elevated neutrophil-to-lymphocyte ratio (NLR), Platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and physiological variables like pulse and blood pressure in the nomograms of prognosis will lead to improved prediction of morbidity as well as morality. Our findings of the significant correlation of NLR ratio with gender and comorbid conditions follow the previous literature. In addition to this finding, we also found that NLR and PLR, CRP, and TLC also contribute equally to this process. Neutrophils, most abundant among the leukocyte pool, get activated and migrate to the immune system from the venous drainage system that helps release the virus from cells due to DNA damage and the release of a large number of Reactive Oxygen Species (ROS). In addition to these changes, neutrophils try to produce many cytokines and effectors molecules with the help of interaction with the perceptible cell population. This may destroy the virus directly by antibody-dependent cell-mediated cell (ADCC), leading to exposure to the virus's antigen and stimulation of various immune responses. Not limited to this function, neutrophils perform the same function of production of cytokines and effectors molecules like VEGF, which can stimulate the growth, setting metastasis and tumour angiogenesis. When compared with other tissues, VEGF-A and VEGF-C tend to possess a significantly high level of activity or expression among patients suffering from COVID 19. In the conditions where the expressions of VEGF and VEGFR are limited or reduced, there is less tissue and damage to the organs. Furthermore, the neutrophil response is usually triggered due to inflammatory factors related to the virus, including granulocyte colony-stimulating factor, interferon-gamma factors interleukin-6, alpha tumour necrosis factor, which are usually produced by the endothelial cells and the lymphocytes. C reactive protein (CRP), a widely accepted marker to annotate the acute-phase inflammatory response, marks the inflammatory level and is never affected by factors related to physical condition. Our results showed the significant contribution of CRP levels in the assessment of the disease progression, especially among the patients with comorbid conditions like diabetes mellitus, based on the fact that elevated CRP levels tend to activate the complement system and can lead to phagocytes is, ultimately clearing off the microorganisms from the body.

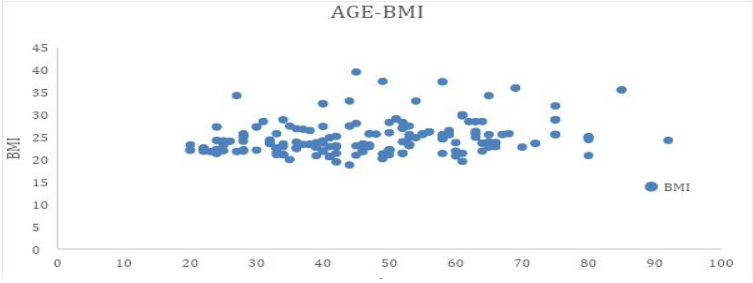

Fig. 1. Distribution of study population based on BMI

Table 1. Distribution of study population based on analysis of study variables for the entire population

	Characteristics	Mild Patients	Severe Patients	P-value
Physiological variables	Age	43.43±15.07(M)	58.8±16.35(M)	0.001***
		51.8±16.35(F)	47±16.07(F)	0.001***
	BMI	25.48±3.85(M)	27.37±3.55(M)	0.001***
		24.37±3.55(F)	26.59 ±4.69(F)	0.001***
	Pulse	74.59 ± 5.24	75.16 ± 4.87	0.0037*
	SBP	126.92±11.15	140.83±10.64	0.001***
	DBP	76.82±5.76	80.02±5.32	0.001***
	RR	20.96±2.00	23.63±2.00	0.009***
Haematological parameters	CRP	20.1±24.5	53.9±66.1	0.003***
	TLC	5.78±2.19	6.76±2.16	0.002***
	PCT	249.70±82.65	122.89±103.62	0.001***
	ANC	3.38±1.65	3.77±1.71	0.002***
	ALC	1.78±0.69	3.32±10.32	0.740
	AMC	0.56±0.25	0.59±0.31	0.001***
	NLR	4.6±3.5	29.7±24.1	0.001***
	PLR	177.7±83.2	386.5±329.2	0.001***
	LMR	3.44±1.39	2.10±2.04	0.001***

Abbreviations'- male, F- female, BMI- body mass Index, Pulse (P), SBP-systolic blood pressure, DBP- diastolic blood pressure, RR-respiratory rate, CRP- C-reactive protein, TLC- total leukocyte count, PCT- platelet, ANC- absolute neutrophil count, ALC- absolute lymphocyte count, AMC- absolute monocyte count, NLR- neutrophil to lymphocyte ratio, PLR- platelet to lymphocyte ratio, LMR- lymphocyte to monocyte ratio

Table 2. Analysis of study variables among both groups in correlation with comorbidities

	Characteristics	Mild Patients	Severe patients	P-value
Comorbidities	Diabetes mellitus	54 (24.73%)	37 (74%)	p<0.01
	Hypertension	58 (28.71%)	31 (62%)	p<0.01
	Renal disorders	12 (5.94%)	23 (46%)	p<0.01
Physiological variables	Pulse	78.43 ± 5.55	86.09 ± 5.24	p<0.09
	SBP	134.12±11.24	140.87±10.64	p<0.06
	DBP	76.14±4.63	82.81±4.60	p<0.02
	RR	21.96±1.81	24.70±1.81	p<0.03
Haematological parameters	CRP	32.1±24.5	74.9±260.1	P<0.001
	TLC	4.78±2.13	8.76±2.16	P<0.001
	PCT	179.70±82.65	112.89±233.12	P<0.001
	ANC	3.18±1.65	4.77±1.71	0.0045
	ALC	1.78±0.69	3.32±10.32	0.043
	AMC	0.56±0.25	0.59±0.31	0.003
	NLR	4.6±3.5	24.7±26.1	P<0.001
	PLR	167.7±83.2	486.5±329.2	P<0.001
	LMR	3.74±1.39	2.12±2.04	P<0.001

Note: P values ≤0.05 were considered statistically significant

Table 3. Analysis of correlation of physiological and haematological variables for all the study population based on gender and comorbid conditions

	Characteristics	Entire Population (252)	Mild (202)	Severe(n=50)
Physiological variables	RR	0.43	0.36	0.76**
	Pulse	0.20	0.32	0.58**
	SBP	0.72**	0.68**	0.77**
	DBP	0.73**	0.69**	0.74**

Haematological parameters	CRP	0.64**	0.69**	0.74**
	TLC	0.71**	0.71**	0.92**
	PL	0.67**	0.72**	0.80**
	ANC	0.55**	0.52**	0.51**
	ALC	-0.02 ns	-0.04 ns	0.52**
	AMC	0.31	0.33	0.37
	NLR	0.80**	0.88**	0.99**
	PLR	0.76**	0.71**	0.94**
	LMR	0.42	0.55**	0.76**

Table 4. Analysis of the odds ratio and the adjusted ratio for various haematological parameters

Haematological parameters	Odds ratio (OR)	P-value	Adjusted odds ratio (aOR)	P-value
Total leucocyte count	1.226 (0.895～1.755)	0.057	1.116 (0.868～1.537)	0.044
Neutrophil to lymphocyte ratio	2.466 (1.978～4.463)	0.047	2.876 (2.054～4.780)	0.020
Platelet to	1.0241 (0.934～1.744)	0.066	1.021 (0.991～1.759)	0.027
CRP	1.327 (0.968～2.065)	0.079	1.203 (0.871～2.032)	0.033

Note: Adjustment for age and gender was done based on which odds ratio and adjusted odds ratio for TLC, NLR, PLR, and CRP were derived

6. CONCLUSION

The present study will help in understanding the impact of COVID 19 infection on the reactive inflammatory responses. It will help understand the prognosis of the disease based on an estimation of various physiological and haematological parameters proving their significant role in understanding the disease progression. While the COVID 19 pandemic is entirely sweeping around the entire world, it is a prime concern to understand the process of transmission of the disease as well as to study the major adverse effects which occur in the body and also to analyse which has made it to convert into a global pandemic. COVID 19 is a novel type of virus that belongs to the coronavirus family, which includes the Levels of TLC, NLR, PLR, LMR, CRP, heart rate, respiratory rate can work as an independent prognostic biomarker as well as dependent physiological variable among COVID 19 patients. Ours is an observational study that shows or proves the temporal correlationship between the exposure and the outcome. In contrast, the demographical and prospective epidemiological study would have been more beneficial in providing accurate inflammatory mediators' accurate levels.

7. LIMITATION OF STUDY

The present study does not mention about the Ach receptors which help in predicting the prognosis of COVID 19 patients. Both haematological and physiological parameters alone will not help in understanding the inflammatory responses.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical clearance taken from Symbiosis Medical College for Women, Symbiosis International (Deemed University) (SIU), Pune, Maharashtra, India.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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