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Original Research Article

Retrospective study of inflammatory markers of COVID-19 in third wave of a tertiary covid care hospital of central India, Indore

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ABSTRACT

CONTEXT:

Acute respiratory distress syndrome (ARDS) and multiorgan dysfunction that results in death are significant in COVID-19 infection, with a greater mortality risk in elderly people with comorbidities. Along with inflammatory markers (like C-reactive protein, Pro-calcitonin, Lactate-dehydrogenase, Ferritin, D-Dimer, Interleukin-6), neutrophil-lymphocyte ratio(NLR), platelet-lymphocyte ratio(PLR), and absolute-lymphocyte count(ALC) are new adjuncts in COVID-19 management.

STUDY DESIGN: Retrospective cross-sectional study at a tertiary care hospital of Indore.

METHOD:

The study included patients in third-wave who tested positive (RT-PCR/RAT) for SARS-CoV2 and hospitalized with routine blood investigations like complete blood count and differential values of serum biochemical tests C-reactive protein, D-dimers, liver-function test, renal-function test and ABG were done at admission.

STATISTICAL ANALYSIS: chi square and fisher's exact test.

RESULTS:

A value >= 4.94 for NLR and >=263 for PLR was suggestive of severe COVID-19 disease. While absolute-lymphocyte count (<= 1210 lymphocytes/mcl) was suggestive of severe COVID-19 disease along with D-Dimer value of >0.6 ngFEU/l and C-reactive protein of > 16.6 mg/l.

CONCLUSION:

As COVID-19 pneumonia is secondary to inflammation, we showed that a more severe inflammation, as evaluated through inflammatory markers, correlates with more severe disease via different grading scores/systems (ARDS Grading, APACHE-2 Scoring, Covid-19 infection severity and Final outcome). Higher levels in NLR, PLR, CRP and D-Dimer while lower absolute-lymphocytes count should prompt the clinician to proceed aggressively in management of Covid-19 patients.

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KEY WORDS: Covid-19, inflammatory marker, severity, India.

KEY MESSAGE: NLR, PLR, CRP, D-Dimer and ALC are markers of inflammation and can be used prognostically in COVID-19 patients.

1. INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is an infectious disease that progresses quickly and can occasionally be fatal. It is brought on by coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). It was initially mentioned in China (Wuhan city, Hubei province) at the end of 2019, and the World Health Organization proclaimed it a pandemic in March 2020. [1]

Inflammation is linked to infectious diseases, and evidence suggests that it plays a key part in the development of several viral pneumonias, including COVID-19. The replication of the SARS-COV2 virus causes cellular damage, which causes the activated macrophages to release cytokines and chemokines. As a result, they trigger immunological reactions, which cause cytokine storms and aggravations. Immune response imbalance results from an imbalance between the adaptive immune response and the severity of the inflammatory response. Severe COVID19 infection has been linked to elevated levels of procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6). Circulating biomarkers that can provide data on immune function and inflammation may be helpful in determining a patient's prognosis for identifying COVID-19 patients. Absolute lymphocyte counts, the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR) are markers of the systemic inflammatory response. They have received extensive research in a number of additional disorders, including systemic diseases, acute coronary syndrome, intracerebral haemorrhage, haematological malignancies, and respiratory, gastrointestinal, and cardiovascular diseases. [1]

NLR & PLR are inexpensive, easily measured, and generally accessible as a component of regularly examined blood tests. Higher NLR and PLR values compared to a lower absolute lymphocyte count appear to be linked to more severe disease manifestations and admissions to critical care units. Lymphocytes and eosinophils are powerful pro-inflammatory cells, and recent research on mice have shown that they play a variety of pleiotropic activities, including moulding many physiological responses and contributing to protective immunity, including antiviral responses. Compared to patients with other kinds of pneumonia, those with pneumonia associated to COVID-19 experienced a significant decline in their peripheral blood level. As they tend to be decreased from NLR, they have a stronger predictive value when paired with it and could aid in COVID-19 diagnosis and risk classification. When combined with NLR, they have a higher predictive value and could help in COVID-19 diagnostic and risk stratification, as they tend to be diminished from the very beginning. [2,3,4]

The risk of death from COVID-19 is increased in some demographics (older persons and those with comorbidities, particularly cardiovascular comorbidities). COVID-19 is more contagious than seasonal flu. Even young patients with no underlying problems, however, can experience severe and occasionally fatal side effects such fulminant myocarditis or disseminated intravascular coagulopathy. The lungs, heart, and gastrointestinal tract are among the tissues that SARS-CoV-2 frequently affects. It is crucial to look for clinical and laboratory tests that might point to a bad result. [1,5]

The purpose of the present paper was to evaluate the correlation between inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocytes ratio (PLR),

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and absolute lymphocyte count (ALC), CRP, D-Dimer at admission with the severity of illness in patients with COVID-19 (via APACHE 2 scoring, Covid-19 severity grading, ARDS grading and Final outcome). The second objective was to reassess cut-off value for NLR, PLR, ALC, CRP and D-Dimer that could suggest severe COVID-19 infection.

2. MATERIAL & METHODS:

The study included all patients with confirmed SARS-COV 2 infection consecutively hospitalized between December 1, 2021 till February 22, 2022. COVID-19 diagnostics were confirmed using rapid antigen detection test (RAT) and/or real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay to test nasal and pharyngeal swab specimens. Inclusion criteria consisted of all hospitalized patients with confirmed COVID-19 infection. While exclusion criteria were age <18 years, pregnant females, patients of cancer or on cancer treatment and seropositive HIV patients.

➢ STUDY DESIGN:

It's a retrospective study done in a tertiary covid-19 care hospital of Central India with no sponsorship and conflict of interest. After approval from scientific and ethics committee, demographic, clinical and laboratory data were taken from the patients records at admission. Laboratory tests were collected from all the patients during entry in the hospital (before any intervention) and were recorded. Blood examinations involved measuring complete blood cell count and differential values of serum biochemical tests C-reactive protein, D-dimers, liver function test, renal function test and ABG were done for COVID-19 patients. Appropriate Absolute lymphocyte count was noted with a cutoff for mild/moderate/severe group as <890 / 891-1210 / >1210 lymphocytes/mcl respectively; [2] PLR ratio was calculated as the platelet count divided by the total count of lymphocytes with a cutoff for mild/moderate/severe group as <170 / 171-263 / >263 respectively; [2] while the NLR ratio was calculated as the absolute count of neutrophils divided by absolute count of lymphocytes with a cutoff for severe and non-severe group as >=4.94 / <4.94 respectively. [3] All laboratory tests were done in the hospital laboratory with standard procedures. The laboratory reference values of white blood cells, neutrophils, lymphocytes and platelets were 4 – 10, 1.6 – 7.3, 1.5 – 4 and 150 – 450 $*10^3$/ul, respectively. D-dimers were considered positive if they were above 0.6 ng FEU/l. Upper normal limit of CRP was 6 mg/l and but was considered significantly high if above 16.6 mg/l. [4]

STATISTICAL ANALYSIS: Data management was done on Microsoft excel spreadsheet and significance was calculated using appropriate analytical test (chi square and fisher's exact test).

3. RESULTS:

➢ NLR (Neutrophil lymphocyte ratio) study:

TABLE 1: NLR with Final outcome

NLR	Improved	Deaths	% mortality
Non- Severe	114	2	1.7%
Severe	44	15	25.4%
	P =0.001		

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TABLE 2: NLR with Covid-19 infection severity at admission (WHO criteria)

NLR	MILD			MODERATE			SEVERE		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
Non-Severe	66	1	1.5%	44	0	0%	4	1	20%
Severe	15	5	25%	24	1	4%	5	9	64.3%
	P = 0.001			***P = 0.362***			***P = 0.141***		

TABLE 3: NLR (non-severe) cases with Covid-19 infection severity at admission (WHO criteria)

	Improved	Deaths	% Mortality
Mild	68	1	1.4%
Moderate	44	0	0%
Severe	4	1	20%
	P = 0.083		

TABLE 4: NLR (severe) cases with Covid-19 infection severity at admission (WHO criteria)

	Improved	Deaths	% Mortality
Mild	15	5	20%
Moderate	24	1	4%
Severe	5	9	64.3%
	P = 0.002		

TABLE 5: NLR with APACHE 2 score at admission

NLR	APACHE 0-24			APACHE 25-34			APACHE >=35		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
Non-Severe	103	0	0%	9	2	18.2%	2	0	0%
Severe	23	0	0%	17	5	22.7%	4	10	71.4%
	P = 1			***P = 1***			***P = 0.125***		

TABLE 6: NLR (non-severe) with APACHE-2 scoring

	Improved	Deaths	% Mortality
0-24	103	0	0%
25-34	9	2	18.2%
>=35	2	0	0%
	P = 0.017		

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TABLE 7: NLR (severe) with APACHE-2 scoring

	Improved	Deaths	% Mortality
0-24	23	0	0%
25-34	17	5	22.7%
>=35	4	10	71.4%
	P = 0.001		

TABLE 8: NLR with ARDS grading

NLR	NO ARDS			MILD ARDS			MODERATE ARDS			SEVERE ARDS		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
Non-Severe	94	1	1.05 %	14	0	0%	5	0	0%	1	1	50%
Severe	11	2	15.4 %	18	5	21.7 %	8	4	33.3 %	7	4	36.3 %
	P = 0.038			***P = 0.135***			***P = 0.261***			***P = 1.0***		

TABLE 9: NLR (non-severe) with ARDS

	Improved	Deaths	% Mortality
No	94	1	1%
Mild	14	0	0%
Moderate	5	0	0%
Severe	1	1	50%
	P = 0.046		

TABLE 10: NLR (severe) with ARDS

	Improved	Deaths	% Mortality
No	11	2	15.4%
Mild	18	5	21.7%
Moderate	8	4	33.3%
Severe	7	4	36.3%
	P = 0.599		

- **PLR (Platelet lymphocyte ratio) study:**

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TABLE 11: PLR to final outcome

PLR	Improved	Deaths	% mortality
Mild	74	4	5.1%
Moderate	44	4	8.3%
Severe	41	9	18%
	P = 0.113		

TABLE 12: PLR to Covid-19 infection severity at admission

PLR	MILD			MODERATE			SEVERE		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
Mild	39	1	2.5%	30	0	0%	3	3	50%
Moderate	24	3	11.1%	19	0	0%	2	1	33.3%
Severe	18	2	10%	19	1	5%	4	6	60%
	P = 0.303			***P = 0.565***			***P = 0.836***		

TABLE 13: PLR (mild) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	39	1	2.5%
Moderate	30	0	0%
Severe	3	3	50%
	P = 0.001		

TABLE 14: PLR (moderate) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	24	3	11.1%
Moderate	19	0	0%
Severe	2	1	33.3%
	P = 0.088		

TABLE 15: PLR (severe) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	18	2	10%
Moderate	19	1	5%
Severe	4	6	60%
	P = 0.001		

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TABLE 16: PLR with APACHE 2 score at admission

PLR	APACHE 0-24			APACHE 25-34			APACHE >=35		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
Mild	64	0	0%	6	2	25%	2	2	50%
Moderate	36	0	0%	8	2	20%	1	2	66.6%
Severe	26	0	0%	12	3	20%	3	6	66.6%
	P = 1			***P = 1***			***P = 0.811***		

TABLE 17: PLR (mild) cases with APACHE-2 score at admission

	Improved	Deaths	% Mortality
0-24	64	0	0%
25-34	6	2	25%
>=35	2	2	50%
	P = 0.0002		

TABLE 18: PLR (moderate) cases with APACHE-2 score at admission

	Improved	Deaths	% Mortality
0-24	36	0	0%
25-34	8	2	20%
>=35	1	2	66.6%
	P = 0.0008		

TABLE 19: PLR (severe) cases with APACHE-2 score at admission

	Improved	Deaths	% Mortality
0-24	26	0	0%
25-34	12	3	20%
>=35	3	6	66.6%
	P = 0.0001		

TABLE 20: PLR with ARDS grading

PLR	NO ARDS			MILD ARDS			MODERATE ARDS			SEVERE ARDS		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
Mild	57	1	1.7%	8	2	10%	1	0	0%	0	1	100%
Moderate	31	2	6%	6	1	14.3 %	4	1	20%	3	0	0%
Severe	9	0	0%	18	2	10%	8	3	27.3 %	5	4	44.4 %

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	P = 0.470	***P = 0.817***	***P = 1***	***P = 0.315***

TABLE 21: PLR (mild) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	57	1	1.7%
Mild	8	2	20%
Moderate	1	0	0%
Severe	0	1	100%
	P = 0.006		

TABLE 22: PLR (moderate) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	31	2	6.1%
Mild	6	1	14.3%
Moderate	4	1	20%
Severe	3	0	0%
	P = 0.406		

TABLE 23: PLR (severe) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	9	0	0%
Mild	18	2	10%
Moderate	8	3	27.3%
Severe	5	4	44.4%
	P = 0.046		

- **ALC (Absolute lymphocyte count) study:**

TABLE 24: ALC to final outcome

ALC	**Improved**	**Deaths**	**% mortality**
Mild	106	6	5.3%
Moderate	27	3	10%
Severe	25	8	24.2%
	P = 0.008		

TABLE 25: ALC to Covid-19 infection severity at admission

ALC	**MILD**			**MODERATE**			**SEVERE**		
	Improved	**Death**	**% mortality**	**Improved**	**Death**	**% mortality**	**Improved**	**Death**	**% mortality**
Mild	58	3	4.9%	42	0	0%	6	3	33.3%
Moderate	14	1	6.6%	13	1	7.1%	0	1	100%

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Severe	9	2	11.2%	13	0	0%	3	6	66.6%
	P = 0.222			***P = 0.391***			***P = 0.580***		

TABLE 26: ALC (mild) cases with Covid-19 infection severity at admission

	Improved	**Deaths**	**% Mortality**
Mild	58	3	4.9%
Moderate	42	0	0%
Severe	6	3	33.3%
	P = 0.002		

TABLE 27: ALC (moderate) cases with Covid-19 infection severity at admission

	Improved	**Deaths**	**% Mortality**
Mild	14	1	6.6%
Moderate	13	1	7.1%
Severe	0	1	100%
	P = 0.100		

TABLE 28: ALC (severe) cases with Covid-19 infection severity at admission

	Improved	**Deaths**	**% Mortality**
Mild	9	2	18.2%
Moderate	13	0	0%
Severe	6	3	33.3%
	P = 0.071		

TABLE 29: ALC with APACHE 2 score at admission

ALC	**APACHE 0-24**			**APACHE 25-34**			**APACHE >=35**		
	Improved	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**
Mild	92	0	0%	10	2	16.6%	4	4	50%
Moderate	22	0	0%	5	2	28.5%	0	1	100%
Severe	12	0	0%	11	3	21.4%	2	5	71.4%
	P = 1			***P = 0.869***			***P = 0.755***		

TABLE 30: ALC (mild) cases with APACHE-2 score at admission

	Improved	**Deaths**	**% Mortality**
0-24	92	0	0%
25-34	10	2	16.6%
>=35	4	4	50%
	P = 0.001		

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TABLE 31: ALC (moderate) cases with APACHE-2 score at admission

	Improved	Deaths	% Mortality
0-24	22	0	0%
25-34	5	2	28.6%
>=35	0	1	100%
	P = 0.005		

TABLE 32: ALC (severe) cases with APACHE-2 score at admission

	Improved	Deaths	% Mortality
0-24	12	0	0%
25-34	11	3	21.4%
>=35	2	5	71.4%
	P = 0.002		

TABLE 33: ALC with ARDS grading

ALC	**NO ARDS**			**MILD ARDS**			**MODERATE ARDS**			**SEVERE ARDS**		
	Improved	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**
Mild	82	2	2.3%	16	4	20%	6	0	0%	2	0	0%
Moderate	15	1	6.2%	10	1	9.1%	1	0	0%	1	1	50%
Severe	8	0	0%	6	0	0%	6	4	40%	5	4	44.4 %
	P = 0.530			***P = 0.539***			***P = 0.300***			***P = 0.739***		

TABLE 34: ALC (mild) cases with ARDS

	Improved	Deaths	% Mortality
No	82	2	2.4%
Mild	16	4	20%
Moderate	6	0	0%
Severe	2	0	0%
	P = 0.027		

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TABLE 36: ALC (moderate) cases with ARDS

	Improved	Deaths	% Mortality
No	15	1	6.6%
Mild	10	1	9.1%
Moderate	1	0	0%
Severe	1	1	50%
	P = 0.277		

TABLE 37: ALC (severe) cases with ARDS

	Improved	Deaths	% Mortality
No	8	0	0%
Mild	6	0	0%
Moderate	6	4	40%
Severe	5	4	44.4%
	P = 0.041		

- **CRP (C-Reactive protein) study:**

TABLE 38: CRP with Final outcome

CRP	Improved	Deaths	% mortality
<=16.6	108	0	0%
>16.6	50	17	25.3%
	P = 0.001		

TABLE 39: CRP with Covid-19 infection severity

CRP	MILD			MODERATE			SEVERE		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
<=16.6	64	0	0%	41	0	0%	3	0	0%
>16.6	17	6	26.1%	27	1	3.5%	6	10	62.5%
	P = 0.0002			***P = 0.406***			***P = 0.087***		

TABLE 40: CRP (<=16.6) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	64	0	0%
Moderate	41	0	0%
Severe	3	0	0%
	P = 1		

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TABLE 41: CRP (>16.6) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	17	6	26%
Moderate	27	1	3.5%
Severe	6	10	62.5%
	P = 0.001		

TABLE 42: CRP with APACHE 2 scoring

CRP	**APACHE 0-24**			**APACHE 25-34**			**APACHE >=35**		
	Improved	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**
<= 16.6	101	0	0%	8	0	0%	0	0	0%
>16.6	25	0	0%	18	7	28%	6	10	62.5%
	P = 0.001			***P = 0.154***			***P = 1***		

TABLE 43: CRP (<=16.6) cases with APACHE-2 scoring at admission

	Improved	Deaths	% Mortality
Mild	101	0	0%
Moderate	8	0	0%
Severe	0	0	0%
	P = 1		

TABLE 44: CRP (>16.6) cases with APACHE-2 scoring at admission

	Improved	Deaths	% Mortality
Mild	25	0	0%
Moderate	18	7	28%
Severe	6	10	62.5%
	P = 0.001		

TABLE 45: CRP with ARDS grading

CRP	**NO ARDS**			**MILD ARDS**			**MODERATE ARDS**			**SEVERE ARDS**		
	Improved	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**
<= 16.6	89	0	0%	18	0	0%	1	0	0%	0	0	0%
>16.6	16	3	15.7 %	14	5	26.3 %	12	4	25%	8	5	38.4 %

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	P = 0.005	***P = 0.046***	***P = 1***	***P = 1***

TABLE 46: CRP (<=16.6) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	89	0	0%
Mild	18	0	0%
Moderate	1	0	0%
Severe	0	0	0%
	P = 0.500		

TABLE 47: CRP (>16.6) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	16	3	15.8%
Mild	14	5	26.3%
Moderate	12	4	25%
Severe	8	5	38.5%
	P = 0.550		

- **D-Dimer study:**

TABLE 48: D Dimer to Final outcome

D Dimer	**Improved**	**Deaths**	**% mortality**
<=0.6	104	3	2.8%
>0.6	54	14	20.6%
	P = 0.0001		

TABLE 49: D Dimer to Covid-19 infection Severity

D Dimer	**MILD**			**MODERATE**			**SEVERE**		
	Improved	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**	**Improved**	**Deaths**	**% mortality**
<=0.6	61	2	3.1%	39	0	0%	4	1	20%
>0.6	20	4	16.6%	29	1	3.3%	5	9	64.3%
	P = 0.026			***P = 0.435***			***P = 0.141***		

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TABLE 50: D Dimer (<=0.6) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	61	2	3.2%
Moderate	39	0	0%
Severe	4	1	20%
	P = 0.119		

TABLE 51: D Dimer (>0.6) cases with Covid-19 infection severity at admission

	Improved	Deaths	% Mortality
Mild	20	4	16.6%
Moderate	29	1	3.3%
Severe	5	9	64.3%
	P = 0.001		

TABLE 52: D Dimer to APACHE 2 scoring

D Dimer	APACHE 0-24			APACHE 25-34			APACHE >=35		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
<=0.6	96	0	0%	7	2	22.2%	1	1	50%
>0.6	30	0	0%	19	5	20.8%	5	9	64.3%
	P = 1			***P = 0.931***			***P = 1***		

TABLE 53: D Dimer (<=0.6) cases with APACHE-2 scoring at admission

	Improved	Deaths	% Mortality
Mild	96	0	0%
Moderate	7	2	22.2%
Severe	1	1	50%
	P = 0.001		

TABLE 54: D Dimer (>0.6) cases with APACHE-2 scoring at admission

	Improved	Deaths	% Mortality
Mild	30	0	0%
Moderate	19	5	20.8%
Severe	5	9	64.3%
	P = 0.001		

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TABLE 55: D Dimer to ARDS grading

D Dimer	No ARDS			Mild ARDS			Moderate ARDS			Severe ARDS		
	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality	Improved	Deaths	% mortality
<=0.6	85	2	2.3 %	13	1	7.1 %	5	0	0%	1	0	0%
>0.6	20	1	4.7 %	19	4	17.4 %	8	4	33.3 %	7	5	41.6 %
	P = 0.481			***P = 0.630***			***P = 0.261***			***P = 1***		

TABLE 56: D Dimer (<=0.6) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	85	2	2.2%
Mild	13	1	7.1%
Moderate	5	0	0%
Severe	1	0	0%
	P = 0.334		

TABLE 57: D Dimer (>0.6) cases with ARDS

	Improved	**Deaths**	**% Mortality**
No	20	1	4.7%
Mild	19	4	17.4%
Moderate	8	4	33.3%
Severe	7	5	41.6%
	P = 0.034		

4. DISCUSSION:

- **On assessing NLR:**

- We observed that the mortality was comparatively higher and statistically significant in patients of severe NLR (>4.94) group than non-severe NLR (<4.94) group. At admission, we observed that mortality was comparatively higher in severe NLR group in all categories of Covid19 infection severity than in non-severe NLR group cases. With highest mortality of 64.3% was seen in severe Covid19 infection cases with NLR of >4.94. While in both groups of non-severe and severe NLR cases comparatively higher mortality is seen in severe covid-19 infection cases., which is statistically significant in severe NLR group. At admission we observed that mortality rate was comparatively higher mortality was seen in APACHE 2 score of >= 25 with severe NLR than in non-severe group, but was statistically insignificant. While observing in both groups of non-severe and severe NLR cases comparatively higher and statistically significant mortality was seen in APACHE 2 score >= 25 than those with <25 score, while highest mortality is among cases with score >=35 and NLR

>4.94 (71.4%). At admission among all cases in both NLR groups, maximum mortality is seen in cases with severe ARDS in comparison to no/mild/moderate ARDS cases. But no statistically significant mortality difference is seen in any of the ARDS categories (Mild/moderate/severe) among both NLR groups. While in both groups of non-severe and severe NLR cases comparatively higher mortality is seen in severe ARDS cases, which is also statistically significant in non-severe NLR group. In a study done by Tatum et al 2020 [3], higher proportion of mortality, ARDS and renal failure were seen in cases with NLR > 4.94 at the day of admission.

- **On assessing PLR:**

- We observed that the mortality was comparatively higher in patients of severe PLR (>263) group than mild/moderate PLR (<170 and <263 respectively) group, but is statistically insignificant. At admission (according to WHO criteria) we observed that mortality was comparatively higher in moderate and severe PLR group in all categories of Covid19 infection severity than in mild PLR group cases, but are all statistically insignificant. With highest mortality of 60% was seen in severe Covid19 infection cases with PLR of >263. While in all three groups of mild, moderate and severe PLR cases comparatively higher mortality is seen in severe covid-19 infection cases, which is statistically significant in mild and severe PLR group. At admission we observed that mortality rate was comparatively higher mortality was seen in APACHE 2 score of >= 25 with moderate/severe PLR cases than mild PLR cases, but was statistically insignificant. While observing in all three PLR groups of mild, moderate and severe PLR cases comparatively higher and statistically significant mortality was seen in APACHE 2 score >= 25 than those with <25 score, while highest mortality is among cases with score >=35 and PLR >170 (66.6%). At admission among all cases in all PLR groups, maximum mortality is seen in cases with severe ARDS in comparison to no/mild/moderate ARDS cases. But no statistically significant mortality difference is seen in any of the ARDS categories (Mild/moderate/severe) among all PLR groups. While in all PLR groups, cases of mild and severe PLR cases shows comparatively higher and statistically significant mortality difference in severe ARDS cases, while statistically insignificant difference was observed in moderate PLR group. In a study by Koval et al 2021 [2], PLR for moderate and severe covid-19 cases were 170.6 and 263.3 respectively. In a study by Chaudhary et al 2021 [8], among moderate covid-19 cases, the mean PLR was 159.1 ± 113.7%, and among severe covid-19 cases, it was 288.9 ± 207.2%. The difference in PLR between moderate and severe cases was statistically significant ($p < 0.001$).

- **On assessing ALC:**

- We observed that the mortality was comparatively higher but statistically insignificant in patients of moderate (<890 lymphocyte/mcl) and severe (<1210 lymphocyte/mcl) ALC group than mild ALC group (1211-1500 lymphocyte/mcl). We observed that mortality was comparatively higher in moderate and severe ALC group in all categories of Covid19 infection severity than in mild ALC group cases, but are all statistically insignificant. With highest mortality of 70% was seen in severe Covid19 infection cases with ALC of <1210. While in all three groups of mild, moderate and severe ALC cases comparatively higher mortality is seen in severe covid-19 infection cases, which is statistically significant in mild ALC group. We observed that mortality rate was comparatively higher mortality was seen in APACHE 2 score of >= 25 with moderate/severe ALC cases than mild ALC cases, but was statistically insignificant.

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While observing in all three ALC groups of mild, moderate and severe ALC cases comparatively higher and statistically significant mortality was seen in APACHE 2 score >= 25 than those with <25 score, while highest mortality is among cases with score >=35 and ALC <1210 (75%). Among all cases in moderate and severe ALC groups, maximum mortality is seen in cases with severe ARDS in comparison to no/mild/moderate ARDS cases. But no statistically significant mortality difference is seen in any of the ARDS categories (Mild/moderate/severe) among all ALC groups. While in cases of moderate and severe ALC cases, comparatively higher mortality difference in severe ARDS cases, which statistically significant was observed in severe ALC group. In a study by Koval et al 2021 [2], ALC for moderate and severe covid-19 cases were 1210 and 890 respectively. In a study by Manal et al 2021 [9], patients with lymphopenia of (<1000) has higher mortality than without lymphopenia cases of 38.1 % and 28.6 % respectively.

- **On assessing CRP:**

- We observed that the mortality was comparatively higher and statistically significant in patients with CRP >16.6 mg/l. We observed that mortality was comparatively higher with CRP >16.6 in all categories of Covid19 infection severity than in CRP <16.6 cases, which is statistically significant in mild infection cases. With highest mortality of 62.5% was seen in severe Covid19 infection cases with CRP >16.6. While no mortality was seen in cases with CRP <=16.6. Cases with CRP >16.6 shows comparatively higher and statistically significant mortality is seen in severe covid-19 infection cases. We observed that mortality rate was comparatively higher mortality was seen in APACHE 2 score of >= 25 with CRP >16.6 cases, but was statistically insignificant. While observing both CRP groups of <16.6 and >16.6, comparatively higher and all mortalities were seen in APACHE 2 score >= 25 than those with <25 score, while highest mortality of 62.5% is seen in cases with score >=35 and CRP >16.6. Among all cases with CRP >16.6, maximum mortality is seen in cases with severe ARDS in comparison to no/mild/moderate ARDS cases. While statistically significant mortality difference is seen in no and mild ARDS categories among both CRP groups. While no mortality was seen in cases with CRP <=16.6. Cases with CRP >16.6 shows comparatively higher mortality in severe ARDS cases, but is statistically insignificant. In a study by Chen et al 2020 [10], yielded a discriminatory power of higher CRP levels in moderate-severe SARS-CoV-2 pneumonia patients from lower CRP levels in those with mild condition, with a cutoff level of 16.60 mg/L.

- **On assessing D-Dimer:**

- We observed that the mortality was comparatively higher and statistically significant in patients with D-Dimer more than normal upper limit (>0.6 ng FEU/l). We observed that mortality was comparatively higher with D-Dimer >0.6 in all categories of Covid19 infection severity than in D-Dimer <0.6 cases, which is statistically significant in mild infection cases. With highest mortality of 64.3% was seen in severe Covid19 infection cases with D-Dimer >0.6. While in both groups of D-Dimer <0.6 and >0.6, comparatively higher mortality is seen in severe covid-19 infection cases, which is statistically significant in D-Dimer >0.6 group. We observed that mortality rate was comparatively higher mortality was seen in APACHE 2 score of >= 25 with D-Dimer >0.6 cases, but was statistically insignificant. While observing both D-Dimer groups of <0.6 and >0.6, comparatively higher and statistically significant mortality were seen in APACHE 2 score >= 25 than those with <25 score, while

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highest mortality of 64.3% is seen in cases with score >=35 and D-Dimer >0.6. Among all cases with D-Dimer >0.6, maximum mortality is seen in cases with severe ARDS in comparison to no/mild/moderate ARDS cases. Which are statistically insignificant in all (no/mild/moderate/severe) ARDS categories among both D-Dimer groups. While no statistically significant mortality difference is seen in D-Dimer <0.6 cases. Cases with D-Dimer >0.6 shows comparatively higher and statistically significant mortality difference in severe ARDS cases. In a study by Guan et al 2020 [11], cutoff D-dimer of more than 0.5 μg/ml was found in 59.6% cases with severe covid-19 infection. A systematic review by Rostami et al 2020 [12] reported the mean D-dimer level to be 0.58 μg/ml in 1551 patients with mild disease and 3.55 μg/ml in 708 patients with severe disease. A similar meta-analysis by Simadibrata 2020 [13], found a relative risk of mortality of 4.60 (95% CI 2.72–7.79) taking 0.5 μg/ml as the cutoff value.

5. CONCLUSION:

This retrospective study focuses on haematological parameters in patients with COVID-19 disease. It evaluates several accessible and widely uses inflammatory markers (neutrophils, lymphocytes, NLR, PLR, D-dimers, and CRP) in COVID-19 patients. Some markers: NLR, PLR and Absolute lymphocytes count are determined in previous studies on COVID-19 patients, offering some cut-off values that could guide us in severity of covid-19 infection. NLR and PLR have proven to be reliable markers in several diseases that go with systemic inflammation. As shown, they have a higher value in COVID 19 patients, and even more, they correlated with classical inflammatory markers such as CRP and D Dimer of SARS-cov2 infection. A value of and above 4.94 for NLR and 263 for PLR seem to be suggestive for severe COVID-19 infection. While a decrease in number of absolute lymphocyte count (<1210 lymphocytes/mcl) seem to be suggestive of severe COVID-19 infection. Classical markers on inflammation like CRP and D-dimer were also suggestive as a predictor of severe covid-19 infection with a cut-off value of >16.6 mg/l and >0.6 ng FEU/l respectively. As COVID-19 pneumonia is secondary to inflammation, we showed that a more severe inflammation, as evaluated through the markers mentioned earlier, correlates with more severe disease via different grading scores/system (ARDS Grading, APACHE 2 Scoring, Covid-19 infection severity and Final outcome). Higher levels in NLR, PLR, CRP and D Dimer while lower number of absolute lymphocytes count should prompt the clinician to proceed aggressively in management of Covid-19 patients.

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LIST OF ABBREVIATIONS

ɒreviation	**Definition**
ARDS	Acute respiratory distress syndrome
CRP	C-reactive protein
PLR	Platelet lymphocyte ratio
ALC	Absolute lymphocyte count
NLR	Neutrophil lymphocyte ratio

Conflicts of interest: None.