Int.j.pathol.2021;19(3): 117-120

Original Article

Prognosis of Covid-19 Patients with Raised Neutrophil-Lymphocyte Ratio (NLR)

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ABSTRACT

Introduction: Covid-19 disease is a deadly contagious disease leading to acute respiratory failure, septic shock and even death. Literature study showed that in severe Covid-19 patients, high NLR ratios suggested that there can be a hyper-inflammatory response to initial Covid-19 infection, accelerating to a severe hyper-cytokinaemia that could lead to an underlying endothelial dysfunction. Thus, systemic inflammation has been declared as a new predictor for Covid-19 patients' outcomes.

Objective: To demonstrate the importance of Neutrophil to Lymphocyte ratio (NLR) in the treatment of severe Pneumonia caused by SARS-CoV2 and its impact on the general prognosis.

Methodology: Prospective analytical study, included 150 PCR positive patients admitted in Covid ITC, PAF Hospital from 1st February 2021 to 31st July 2021 including serving personnel and their dependents residing in the premises of PAF Air Base, Sargodha.

Results: Out of 150 patients, 120 (80%) were discharged while 30 (20%) patients died out of which 5 died while being on HFNO therapy (High Flow Nasal Oxygen Therapy) and 25 patients were mechanically ventilated after consent. A comparison between NLR value of non-survival group to that of the survival group with the outcome of ITC patients via Chi square test revealed that there is a significant relationship (P value <0.005) between higher NLR values (equal to or more than 3) with increase in-hospital mortality.

Conclusion: Our findings suggested that the NLR value appears to be a significant prognostic biomarker of multiple outcomes in critically ill Covid-19 patients.

Key Words: SARS-CoV2, Neutrophil-Lymphocyte ratio NLR, Systemic inflammation, Hyper-cytokinaemia

Introduction

Since mid-December 2019, worldwide Covid-19 outbreak caused by SARS-CoV2 was one of the worst infectious diseases in history with symptoms ranging from a mild self-limiting disease to a more severe form characterized by acute respiratory distress syndrome (ARDS), septic shock and even death.[1,2,3] Most Covid-19 patients with severe ARDS when assessed for hyper-inflammation to decrease mortality and improve survival rates showed high Neutrophils and low Lymphocyte counts suggesting that there can be a hyper-inflammatory response to initial Covid-19 infection, which further accelerates a severe hyper-cytokinaemia, that signals the presence of an underlying endothelial dysfunction.[4,5,6,7,8] In this context, literature review has reported systemic inflammation as a new predictor for Covid-19 outcomes. [9, 10, 11, 12]

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Thus, this study was conducted to highlight the importance of neutrophil to lymphocyte ratio (NLR) in the treatment of severe pneumonia caused by SARS-CoV2.

Materials and Methods

This was a prospective analytical study which enrolled 150 laboratory tested PCR positive patients from the time period of 1st February 2021 to 31st July 2021 (about 6 months) including serving personnel and their dependents, retired and the civilians of all age groups and both genders residing in the premises of PAF Air Base, Mushaf, Sargodha. All those patients who were laboratory tested PCR positive had been included in the study.

While patients using immunosuppressive drugs (including long-term steroids) and with negative PCR detection of n-CoV 19, suspected bacterial pneumonia (confirmed by sputum bacterial culture), interstitial pneumonia (previously diagnosed based on radiological findings), and heart failure associated with pulmonary oedema (non-COVID-19 heart disease) were excluded from our study.

Following data was collected: patient's age, gender, co-morbidities to see any significant association between their presence and NLR ratio with the final effect on the patient's outcome, degree of HRCT involvement, PaO2/FiO2 ratio (i-e the ratio of arterial oxygen partial pressure in mmHg to fractional inspired oxygen) to categorize Covid-19 patients into mild/ moderate or severe ARDS, their laboratory tests especially Total Leukocyte Count (TLC) with specific emphasis on neutrophil count and lymphocyte count so to divide the former by the latter to obtain NLR ratio, need of mechanical ventilation and the general patients' ITC stay outcome.

Patients presenting with fever, respiratory symptoms and radiological findings consistent with COVID-19 infection were classified as having mild disease according to W.H.O criteria if they have:

1. Respiratory rate ≤ 30/min at rest.
2. Oxygen saturation (SpO2) ≥ 93% on room air.
3. Arterial oxygen partial pressure (PaO2)/oxygen uptake concentration (FiO2) ≥ 300.

While patients presenting with the following were classified as moderate disease:

1. Respiratory rate ≥ 30/min at rest.
2. Oxygen saturation (SpO2) ≤ 93% on room air.
3. Arterial oxygen partial pressure (PaO2)/oxygen uptake concentration (FiO2) [PaO2/FiO2] (PF ratio) ≤ 300.

Patients with the following characteristics were classified as severe disease:

1. Oxygen requirement more than 15L for 90% saturation.
2. More than 50% involvement on HRCT chest.
3. Multi-organ dysfunction or failure.
4. Secondary bacterial infection as confirmed by blood culture test.
5. Use of inotropic to raise arterial pressure above 65mmHg.
6. PaO2/FiO2 ratio less than 100 mmHg.

Statistical Analysis

Data was analyzed using SPSS software version 16. Frequencies were calculated along with mean and standard deviation. Chi square test was applied to the data. P value <0.005 was considered statistically significant.

Results

Out of these 150 patients who got tested Real Time RT-PCR positive for Covid-19 disease, most (86.7%) of the patients were of the middle age group (50-70 years) of whom 113 (75.3%) were males and 37 (24.7%) were females. Majority of the subjects had co-morbidities such as Diabetes Mellitus (45.3%), Hypertension (3.3%), and Ischemic Heart Disease (20.7%) while Diabetes Mellitus and Hypertension both existed collectively in 16.7% of this study's population. A comparison between co-morbidities and NLR ratio via Chi square test revealed that patients with Ischemic Heart Disease (IHD) and Diabetes Mellitus (DM) had more higher NLR values (NLR ratio >3), thus a significant association (P value <0.005) was discovered between them [See Table 1]. Majority (40%) of Covid-19 patients had 50-70% lung involvement observed on Hyper Resonance Computed Tomography HRCT chest scans while mild ARDS was observed in 30 participants (20%) and 46% and 34% of subjects had moderate (n= 69) to severe (n= 51) ARDS respectively [See Figure 1]. Out of these 150 patients, 120 (80%) were discharged while 30 (20%) patients died out of which 5 (16.7%) died while being on HFNO therapy and 25 (83.3%) patients were intubated and put on mechanical ventilation after informed and written consent [Figure 2]. Another comparison between NLR value of non-survival group to that of the survival group with the outcome of the ITC patients revealed that there is a significant relationship (P value <0.005) between higher NLR values (equal to or more than 3) and increased in-hospital mortality of moderate to severe Covid-19 pneumonia patients [Table 2].

Table 1: Comorbidities and NLR Ratio

Comorbidities	Observed n	Expected n	Residual
DM	68	18.8	49.2
HTN+DM	25	18.8	6.2
HTN	5	18.8	-13.8
IHD	31	18.8	12.2
Prior respiratory disease	3	18.8	-15.8
CLD	5	18.8	-13.8
CKD	4	18.8	-14.8
None	9	18.8	-9.8
NLR ratio less than 3	12	75.0	45.0
NLR ratio equal to or more than 3	30	75.0	-45.0
Total	**150**		

Table 2: Test Statistics

	Co-morbidities	NLR ratio	Outcome of patients
Chi-Square	189.520[a]	54.000[b]	54.000[a]
Df	7	1	1
Asymp. Sig.	.000	.000	.000

a. 0 cells (.0%) have expected frequencies less than 5. The minimum expected cell frequency is 18.8.
b. 0 cells (.0%) have expected frequencies less than 5. The minimum expected cell frequency is 75.0.

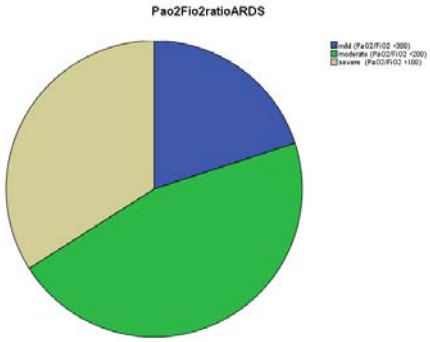

Figure 1: Patients with <300 PaO2/FiO2 ratio had mild disease
Patients with <200 PaO2/FiO2 ratio had moderate disease
Patients with <100 PaO2/FiO2 ratio had severe disease

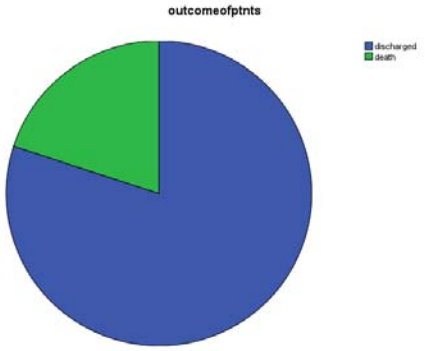

Figure 2: 120/150 patients were discharged while 30/150 died due to disease

Discussion

NLR is an easily measurable, daily available, cost-effective, and reliable laboratory marker that can be continuously monitored on a daily basis so to check the progression of disease in patients affected by Covid-19 pneumonia.[6,7,8] In this prospective analytical study, we found that association with Diabetes Mellitus and Ischemic Heart Disease can be considered independent biomarkers for indicating poor clinical outcomes in Covid-19 patients as higher NLR value (equal to or greater than 3) was observed in these patients.[11,12] Reason behind these observations can be that patients with Diabetes Mellitus and Ischemic Heart Disease often have systemic inflammation in their bodies which is further aggravated by the disease caused by SARS-CoV2. [(9,10,11)] Hence, raised inflammatory markers such as TLC count, LDH, CRP, D-Dimers and ferritin levels are observed in these patients. [(10, 11, 12)] This can be considered to be a very useful observation as it can give the attending physician a crystal clear insight about the concerned patient's disease progression, severity and their general ICU outcome compelling him to treat that patient very aggressively from the start with strong antibiotics and anti- inflammatory medications.

Conclusion

Neutrophil to Lymphocyte Ratio (NLR) appears to be a significant prognostic biomarker of multiple outcomes in critically ill patients with Covid-19. Patients already diagnosed with Diabetes Mellitus/ Ischemic Heart Disease are at more risk for developing severe pneumonia caused by SARS-CoV2 with raised NLR value. Furthermore, Higher NLR values (equal to or greater than 3) were found to have a significant impact on the outcome of these ITC patients with lesser survival and higher mortality rates.

Limitation of Study:

This study was conducted in a single center with a small sample size, therefore, more exploratory studies are necessary to apply these relationships in clinical practice.

Conflict of Interest:

This study has no conflict of interest to declare by any author.

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HISTORY	
Date received:	12-09-21
Date sent for review:	13-11-21
Date received reviewers comments:	24-12-21
Date received revised manuscript:	28-12-21
Date accepted:	09-01-21

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A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion