Predicting Early Requirement of Invasive Ventilation in COVID-19 Patients Using Neutrophil-Lymphocyte Ratio

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Abstract: ***Background**: Coronavirus disease 2019 (COVID-19) pandemic has affected millions of people and overloaded the healthcare system. Hypoxemic respiratory failure is a common clinical picture requiring supplemental oxygen therapy as the first line of treatment. Neutrophil-lymphocyte ratio (NLR) reflects patient's inflammatory state indirectly. In this study, we aim to determine the efficacy of NLR for predicting early requirement of invasive ventilation in COVID-19 patients. **Methodology**: In this observational descriptive record based study, 80 patients with confirmed COVID-19 status hospitalized in our ICU in month of April through June 2021 were retrospectively analysed. For each patient demographic data, lab findings and inflammatory markers were collected from the medical records. The type of oxygen support needed in first 48 hours was noted. Their NLR was calculated from the blood investigations available within 24 hours of admission. **Results**: The ROC curve found the optimal cut-off value of NLR to be 5.316 which distinguishes patients in two groups. The area under the ROC curve for NLR was 0.546 (95% CI, 0.416-0.676). The sensitivity and specificity value of NLR was 0.674 and 0.568 respectively. High NLR (>5.316) was associated with more patients (n=29) (64.4%) requiring invasive ventilation (p value=0.03) **Conclusion**: Our study concludes that NLR is moderately good in predicting early requirement of invasive ventilation in COVID-19 patients and this simple biomarker can be used where lack of resources often prevents costly testing.*

Keywords: COVID-19; Neutrophil, lymphocyte, Ratio, Biomarker, Invasive ventilation

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS COV2) has caused the outbreak of pandemic. It has affected a vast majority of populations and continues to cripple the healthcare system. (1) Judicious ICU resources allocation is still a major challenge. Identifying early warning signs and timely intervention can lead to good outcomes. (2)

Key features in the pathophysiology of this disease are the overwhelming systemic inflammatory response leading to a rapidly progressive pneumonia, acute respiratory distress syndrome followed by multiple organ damage. (3) Respiratory distress and hypoxemic respiratory failure is a common clinical picture requiring supplemental oxygen therapy as the first line of treatment. (4, 5)

Biomarkers related to inflammatory status serve as a good indicator of the severity of the disease. A major change in the proportion of blood cell subsets has been recognized as a sensitive hallmark. (3) D-dimers, CRP, LDH, Ferritin have been associated and to aid in knowing the severity of the disease. (6) However, these tests are costly and increase the financial burden on patients.

Neutrophil-lymphocyte ratio (NLR) reflects patient's inflammatory state indirectly. It is validated as a prognostic marker in various disorders like solid tumours, ARDS, pneumonia, cardiac conditions. (1) Various studies have shown it to be associated with severity of COVID19, ARDS, requirement of admission to critical care unit and mortality. (2, 6, 7, 8)Very few studies are done on early requirement of invasive ventilation. In our study, we aim to determine the efficacy of NLR for predicting early requirement of invasive ventilation in COVID-19 patients.

2. Methodology

Our study comprised of 80 adult patients of age more than 18 years with confirmed COVID-19 status (RTPCR) hospitalized in Father Muller's ICU in month of April, May and June 2021. They were retrospectively analyzed using hospital records after obtaining institutional ethical clearance. Patients with carcinoma history were excluded from our study. For each patient demographic data, lab findings like complete blood count (CBC), liver function tests (LFTs), renal functional tests (RFTs), serum electrolytes and inflammatory markers such as d-dimer, ferritin, CRP, LDH were collected from the medical records. The type of oxygen support needed in first 48 hours was noted. Their NL ratio was calculated from the blood investigations available within 24 hours of admission using the simple formula: $\frac{Absolute\ \ number\ \ of\ neutrop\ hils}{Absolute\ \ number\ \ of\ lymp\ hocytes}$

Based on oxygen requirement in first 48 hours, patient were divided into two groups; who required invasive ventilation in first 48 hours and those who required non-invasive oxygen support. The collected data was analyzed by mean, standard deviation, frequency and ROC analysis. For analyzing the ability of NLR in predicting the requirement of the invasive ventilation the area under the receiver operating characteristic (ROC) curve was used. Based on the previous study conducted by Ma et al, using standard deviation of 6.695 in the observational study domain, 90% statistical power, 5% α error and 10% β error, sample size of 80 was found to be adequate.

3. Results

Our study was conducted on 80 COVID-19 positive patients admitted in the ICU. The demographic data and oxygen therapy required is listed in the table 1.

Table 1: Demographic data and oxygen therapy required by the patients

Parameters		Cases (N=43)	Controls (N=37)	P value
Age (in years)		61.28 ±13.50	56.92 ±16.33	0.195
Sex	Male	28 (56.0)	22 (44.0)	0.602
	Female	15 (50.0)	15 (50.0)	
DM	Yes	29 (60.4)	19 (39.6)	0.143
	No	14 (43.8)	18 (56.2)	
HTN	Yes	20 (52.6)	18 (47.4)	0.849
	No	23 (54.8)	19 (45.2)	
Pulmonary disease	Yes	4 (40.0)	6 (60.0)	0.509
	No	39 (55.7)	31 (44.3)	
Cardiovascular disease	Yes	10 (62.5)	6 (37.5)	0.433
	No	33 (51.6)	31 (48.4)	
Cerebrovascular disease	Yes	6 (75.0)	2 (25.0)	0.275
	No	37 (51.4)	35 (48.6)	
Renal disease	Yes	13 (81.2)	3 (18.8)	0.014*
	No	30 (46.9)	34 (53.1)	
Liver disease	Yes	0	1 (100)	-
	No	43 (54.4)	36 (45.6)	
HFNO	Yes	27 (79.4)	7 (20.6)	<0.001*
	No	16 (34.8)	30 (65.2)	
NRBM	Yes	10 (31.2)	22 (68.8)	<0.001*
	No	32 (68.1)	15 (31.9)	
NLR#	**<5.316**	14 (40.0)	21 (60.0)	0.030*
	≥5.316	29 (64.4)	16 (35.6)	

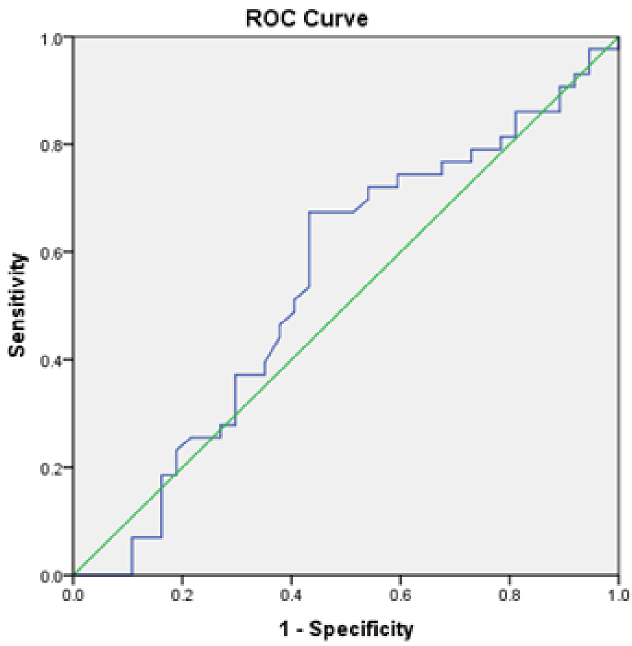

Figure 1: ROC curve for NLR (Area under the curve= 0.546, Std. error=0.066, p value=0.478, 95% Confidence Interval= 0.416, 0.676)

Majority of the study participants were male (62.5%, n=50). Out of the 80, 43 (53.8%) patients required invasive ventilation whereas 37 (46.3%) patients did not require invasive ventilation. Among various comorbidities, Diabetes mellitus was found in 48 patients (60%). Whereas renal disease had a statistically significant association among the two groups (p value =0.014), as majority of patients having renal disease (81.2%) required invasive ventilation (Table 1).

The ROC curve found the optimal cut-off value of NLR to be 5.316 which distinguishes patients in two groups, who require invasive ventilation from those who do not. Th**e** area under the ROC curve for NLR was 0.546 (95% CI, 0.416-0.676). The sensitivity and specificity value of NLR was 0.674 and 0.568 respectively. (fig1). High NLR (>5.316) was associated with more patients (n=29) requiring invasive ventilation (64.4%) (p value=0.03) (table1).

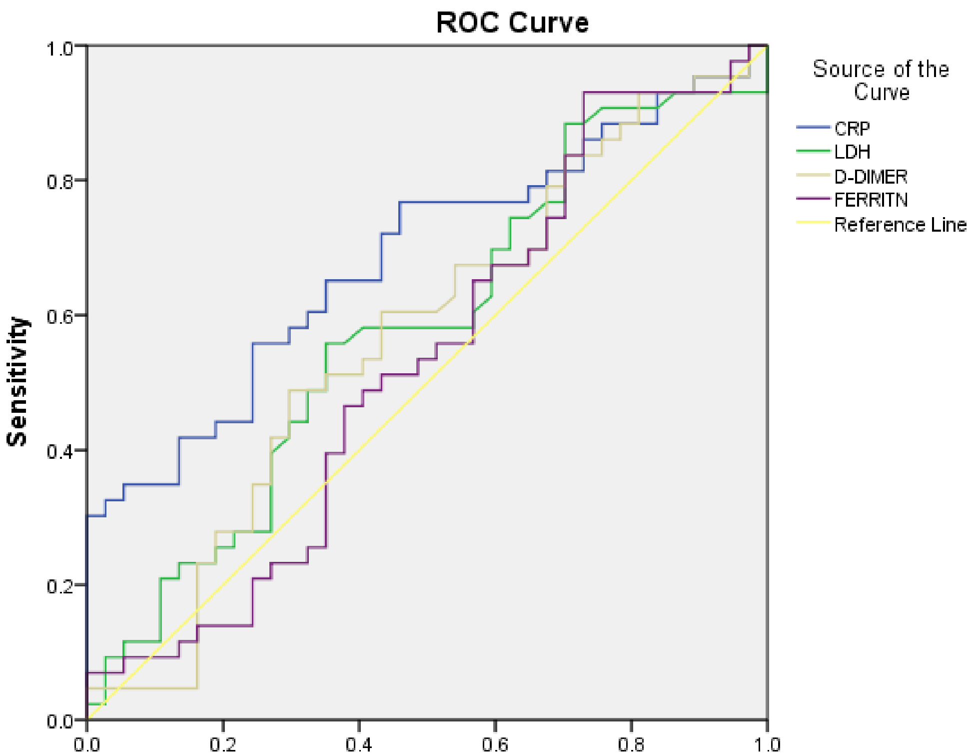

Figure 2: ROC curve for CRP, LDH, D-DIMER, FERRITIN ((AUC-0.686 (95% CI, 0.571-0.805), 0.580 (95%CI, 0.453-0.706), 0.569 (95%CI, 0.441, 0.697) and 0.530 (95%CI, 0.400, 0.660) respectively)

Figure 2, shows ROC curve plotted for the Inflammatory markers such as CRP, LDH, d-dimer and ferritin having area under the curve (AUC) 0.686 (95%, 0.571-0.805), 0.580 (95% CI, 0.453-0.706), 0.569 (95% CI, 0.441, 0.697) and 0.530 (95% CI, 0.400, 0.660) respectively. The optimal cut-off for CRP, LDH, d-dimer and ferritin were 70.85, 444.50, 332.00 and 690.55 respectively.

4. Discussion

Neutrophils are one of the immune cells which tend to rapidly chemo tactically gather to the infection site when a pathogenic microorganism invades the body. They play the role of host defense and immune regulation. (17) The risk of infection is significantly increased, when the body's neutrophils are reduced, the body's immunity is compromised. (18)Lymphocytes are the main cells of immune response in the human body. The number of lymphocytes in the body is closely related to the body's immunity and defense system against pathogenic microorganisms and is negatively correlated with the degree of inflammation. (13)

NLR reflects the degree of systemic inflammation and the balance of the body's neutrophil and lymphocyte count levels. More accurately, it reflects the balance between the severity of the inflammation and the body's immunity status. (19) Thus, it is considered an important marker of systemic inflammatory response. (10)

Neutrophil-to-lymphocyte ratio (NLR) is a simple blood test that can be measured during routine hematology. Multiple studies previously done have exhibited that higher NLR was associated with clinical deterioration and mortality for COVID-19 patients. (20) However, it remains unclear to what extent the significance of NLR would predict the occurrence of ventilator requirements for the COVID-19 crisis. (6)

Our study demonstrated that 43 patients required invasive ventilation out of which majority were male (65.1%). This was similar to Ma *et al.*, (6) study where male gender (63.6%) was associated with higher incidence of severe disease and Sagar *et al.*, (9) study where incidence of severe disease was higher in males (72%). Disparities in outcomes have been seen among various races/ethnicities and very few studies done on South-Asian population.

Our data suggested that NLR could be valuable marker to predict early requirement of invasive ventilation in COVID-19 patients because of mismatch of oxygenation and lung mechanics which makes severity of hypoxia not a good predictor of ventilation. High NLR was associated with early requirement of mechanical ventilation. In our study NLR value was found higher in patients requiring invasive ventilation 15.4 (mean) vs. those who did not 4.9 (mean). This was similar to the study conducted by Parvathy *et al.*, (5) where NLR was significantly higher in patients who required mechanical ventilation in first 24 hours than those who did not (5.8 vs. 3.9 respectively). Sagar *et al.*, (9) in their study have also reported higher NLR value of 8.45 which was associated with ICU admissions whereas non ICU admissions group had NLR of 2.32. In another study by Ma *et al.* (6), high NLR group (9.8) showed higher incidence of ARDS.

The area under roc curve found optimal cut off value of NLR to be 5.316 statistically significant which distinguishes patients in two groups (p value 0.03). The sensitivity was 67.4 % and specificity was 56.8% which is similar to Parvathy*et al.*, (5) study where the best cut off for NLR was 4.6 with sensitivity of 79.2% and specificity of 62.3%. Our study found NLR >5.316 moderately good in predicting early requirement of ventilation within first 48 hours and this can facilitate clinicians to give effective respiratory support to COVID-19 patients and allocate ICU resources.

Having a simple predictor like NLR can be very useful in overburdened health care system. NLR is cost effective and easily accessible in all laboratories. Hence moderate performance of NLR in predicting early requirement of invasive ventilation in first 48 hours warrants further studies from a larger data set.

5. Conclusion

Our study concludes that NLR is moderately good in predicting early requirement of invasive ventilation in COVID-19 patients and this simple biomarker can be used where lack of resources often prevents costly testing.

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Tables

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