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Study of comparison between Lymphocyte to neutrophil ratio and neutrophil to monocyte ratio as a predictor of mortality in COVID19 infection.

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Abstract
Background and objectives: *COVID 19 causes infection ranging from mild self-limiting illness to severe cases of ARDS (Acute respiratory distress syndrome) with multi-organ dysfunction syndrome. The objective of this study is to compare LNR and NMR in predicting mortality due to COVID19.*
Methods: It is a cross-sectional study, done from June 2020 to August 2020. All are COVID 19 diagnosed patients admitted to KIMS hospital.
Results: The mean LNR value was 0.399 in patients of category C, which was significantly lower compared to patients of category A and B which was 0.69 and 0.423 respectively. And the mean NMR value was 35.27 in category C patients which was significantly higher compared to Category A and B patients, which was 17.75 and 24.18 respectively.
Interpretation: This study demonstrates that an LNR less than 0.399 and an NMR greater than 35.27 at the time of admission can predict the in-hospital severity of patients with Covid-19.
Conclusion: NMR is a better predictor of severity and mortality than LNR.
Keywords: *COVID19, LNR, NMR*

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I. Introduction:

The outbreak of coronavirus disease 2019 (Covid-19) is an ongoing global pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has affected the lives of millions of people worldwide[1]. Although more than 85% of patients with Covid-19 show a self-limiting illness some patients develop severe pneumonia that can progress to acute respiratory distress syndrome, multiple organ failure, and death[2].There have been many biochemical markers to predict in-hospital mortality. Many studies have suggested the use of hematological parameters like neutrophil, lymphocyte, and monocyte counts to predict mortality[3]. Some have also proposed the use of ratios of neutrophils, lymphocytes, and monocytes to predict mortality[4]. There have been many studies on the use of Lymphocyte to the neutrophil ratio (LNR) as a predictor, hence this study aims to compare the efficacy between LNR and NMR (Neutrophil to Monocyte ratio) in predicting mortality in COVID 19.

II. Materials and Methods:

This was a single-center cross-sectional study, done in a tertiary care hospital in Bangalore. Data of 120 RTPCR confirmed COVID 19 cases admitted in KIMS hospital Bangalore was collected between the months June 2020 and August 2020. Patients with hematological malignancy, HIV, Hepatitis B, C, end-stage kidney, and liver disease were excluded.

Data collection: patient's age, sex, vital parameters, co-morbidities, and relevant laboratory parameters i.e. lymphocyte count, neutrophil count, and monocyte count at the time of admission was collected. LNR and NMR were calculated with the data. The patients were assigned to the respective category of disease severity according to the clinical management protocol released by the Ministry of Health and Family Welfare, Government of India, version 3 (Table 1) at the time of admission. They were re-categorized during the course

of treatment in case of improvement/ worsening in the condition. The outcome of the patient i.e. discharge/death was noted.

Statistical analysis: The data was collected in MS excel sleet and was analyzed at the end using SPSS for windows version 22.0. The comparison of the sensitivity of LNR and NMR in different categories was done using the Kruskal Wallis test, Mann Whitney post hoc test, and chi-square test. Statistical significance was set as $p<0.05$.

III. Results:

Of 120 COVID patients, 65 were male and 55 were female and 102 were survivors, and 18 were non-survivors. Age and gender-wise distribution among the study patients is given in table 3. The presence of comorbidities among the study patients is shown in table 4.

Among the survivors, 44 were in category A, 29 in category B, and 28 in Category C. Among the 18 non-survivors, 12(30.0%) were from Category C, 4(12.1%) were from category B and 3(6.4%) were from category A (Table 2)

The mean LNR value among the survivors was 0.399 in patients of category C, which was significantly lower compared to patients of category A and B which were 0.698 and 0.423 respectively (p-value <0.001).In the case of non-survivors, the mean LNR was 0.954 in Category A, 0.341 in Category B, 0.584 in category C. Even though LNR is a very good parameter in predicting the severity of COVID 19, it did not prove to be a good parameter in predicting mortality as the values were lower in case of Category B than in Category C among non-survivors.

As for the mean NMR values in survivors, it was 36.66 in category C patients, which was significantly higher compared to Category A and B patients, which were 17.83 and 23.86 respectively. In the case of non-survivors, the mean NMR values were 16.56 in Category A, 26.49 in Category B, and 32.03 in Category C (table 6). The values were significantly higher in the case of Category C patients compared to that of Category A and B in both survivors and non-survivors.

IV. Discussion:

Neutrophil: Neutrophils are now considered one of the most important immune cells in defending the airway epithelium against the SARS-CoV-2 infection by locally stimulating the production of IL-1 beta, IL-6, tumor necrosis factor-alpha (TNF-alpha), and reactive oxygen species (ROS). Paradoxically, neutrophil hyper-activation and recruitment intensify the acute inflammatory response and worsen epithelial tissue damage thus leading to disease progression. As a contributor to pathological inflammation of pneumonia, excessive neutrophils lead to tissue injury by oxidative burst, phagocytosis, and the formation of neutrophil NETs (Neutrophil extracellular traps) known as NETosis[5].

Lymphocytes are the cells that specifically recognize and respond to foreign antigens and are mediators of humoral and cellular immunity. They have a major role in viral infections. Zhang et al. reported that the number of T lymphocytes including both CD4 and CD8 subtypes and especially NK cells are much lower than expected in patients with the severe disease course of COVID 19[6]. The number of regulatory T cells is also very low. Severe lymphopenia is a very early sign of the disease, preceding pulmonary problems, and tends to normalize as the patient improves.

Monocytes constituting about 5–9% of the total peripheral leukocytes remain in the circulation for 1–2 days, following which these cells may differentiate to tissue-resident macrophages. The primary activities of the macrophage include phagocytosis, antigen presentation, secretion of cytokines, production of antibacterial compounds, and releasing enzymes that remodel the extracellular matrix[7].

However, the improper hyper-activation of macrophages may contribute to the development of immunopathologic reactions. The lung injury of SARS-CoV-infected patients appears to happen directly through viral disruption of alveolar and bronchial epithelial cells and macrophages, and indirectly via triggering inflammatory mediators. Both infected- and uninfected-macrophages exist in large numbers in the lungs of severe SARS patients and are causally related to the severity of coronavirus infections[8].

In other words, neutrophils and the cell populations of lymphocytes and monocytes seem to have typical antagonistic roles in multiple inflammatory scenarios including that provoked by the SARS-CoV-2 infection. Thus, it is feasible to assume that LNR and NMR might reflect an imbalance among these immune cells that in turn could be related to excessive inflammation and poorer survival in patients with severe Covid-19.

Many studies have reported an association between the baseline leukocyte counts and the severity of COVID 19 disease. Qin C et al[9] reported that severe cases of COVID-19 were likely to have higher neutrophil count but lower lymphocyte count compared with non-severe patients. A meta-analysis done by Huang z et al identified NLR as a prognostic biomarker in sepsis[10]. A study was done by Yang AP et al which also reported

NLR as an independent biomarker in predicting poor COVID19 outcome[11]. Many studies have been done on NLR as a risk factor for poor COVID 19 outcomes, but less has been done on NMR.

A study done by Salma A[12] demonstrated for the first time that NMR is also a better and independent risk factor for the prediction of mortality in COVID 19. Hence this study aimed to compare LNR and NMR as independent risk factors in the prediction of mortality of COVID 19 patients.

In our study, an overall (survivors and non-survivors) LNR value of less than 0.399 and an NMR value greater than 35.27 at the time of admission can predict the in-hospital severity of patients with Covid-19.

And NMR values increased with the increase in severity in the case of both survivors and non-survivors of the disease and was a better predictor of mortality compared to LNR. There was a significant association between the values of NMR and the severity of the disease.

Strengths of our study: The use of the NMR parameter in predicting the severity of COVID 19 disease was never done, before this study in India.

Limitations: Due to limited sample size and as this is a single-center study, even though the NMR values correlate with mortality, the significance is less. Hence this requires further multicenter study with a larger sample size and has a considerable advantage over other COVID severity markers by its cheaper and faster testing method.

V. Conclusion:

A baseline NMR value at the time of admission can predict the disease severity in case of COVID 19 infection and can be used for triaging of patients in centers where other biomarkers like CRP, ferritin, and LDH is not available. It is a better biomarker than LNR.

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Table 1 – Categorization of COVID 19 patients according to disease severity as per MoHFW version-3

Clinical Category	Description	Parameters
Asymptomatic	No symptoms	SPO2 >/= 94% in room air , RR </= 24/min, no evidence of hypoxemia or breathlessness
Category A (Mild)	Patients with uncomplicated upper respiratory tract infection	SPO2 >/= 94 % in room air , RR of </= 24/min, no evidence of hypoxemia or breathlessness
Category B(Moderate)	Pneumonia with no signs of severe disease	SPO2: 90-94% in room air, RR 24-30/min
Category C (Severe)	Severe Pneumonia	SPO2 : <90% room air , RR >30/min

Table 2 – mortality among patients of COVID 19 in different categories.

Comparison of Mortality among patients between different categories using Chi Square Test								
		Category A		Category B		Category C		
Variable	Category	n	%	n	%	n	%	P-Value
Mortality	Yes	3	6.4%	4	12.1%	12	30.0%	0.009*
	No	44	93.6%	29	87.9%	28	70.0%	

Table 3- Age and gender distribution among the study groups is given below

Age and Gender distribution among different study groups								
		Category A		Category B		Category C		
Variable	Category	Mean	SD	Mean	SD	Mean	SD	P-Value
Age	Mean & SD	48.64	14.90	55.21	14.96	55.33	15.49	0.07[a]
	Range	19 - 81		20 - 91		30 - 87		
		n	%	n	%	n	%	
Gender	Males	29	61.7%	22	66.7%	24	60.0%	0.83[b]
	Females	18	38.3%	11	33.3%	16	40.0%	

Table 4 - Co-morbidities among the study patients.

Comparison of comorbidity conditions between categories using Chi Square Test								
		Category A		Category B		Category C		
Variable	Category	Mean	SD	Mean	SD	Mean	SD	P-Value
DM	Yes	17	36.2%	7	21.2%	17	42.5%	0.15
	No	30	63.8%	26	78.8%	23	57.5%	
HTN	Yes	11	23.4%	5	15.2%	13	32.5%	0.22
	No	36	76.6%	28	84.8%	27	67.5%	

Table 5 – Comparison of mean LNR and NMR between different categories

Variable	Category	N	Mean	SD	P-Value [a]	Sig. Diff	P-Value [b]
LNR	Category A	47	0.698	0.367	<0.001*	A vs B	0.001*
	Category B	33	0.423	0.327		A vs C	<0.001*
	Category C	40	0.399	0.326		B vs C	0.61
NMR	Category A	47	17.75	14.82	<0.001*	A vs B	0.001*
	Category B	33	24.18	11.33		A vs C	<0.001*
	Category C	40	35.27	19.61		B vs C	0.01*

Table 6 – Comparison of mean LNR and NMR between different categories in survivors and non-survivors.

		Not Survived		Survived		
Parameter	Category	Mean	SD	Mean	SD	P-Value
LNR	Category A	0.954	0.393	0.680	0.364	0.24
	Category B	0.341	0.305	0.434	0.333	0.76
	Category C	0.584	0.422	0.320	0.243	0.49
NMR	Category A	16.56	7.08	17.83	15.25	0.51
	Category B	26.49	8.70	23.86	11.73	0.47
	Category C	32.03	14.51	36.66	21.52	0.54