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ORIGINAL RESEARCH

Neutrophilic lymphocyte ratio and lymphocyte monocyte ratio: prognostic significance in COVID 19

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ABSTRACT

Aim: To evaluate neutrophilic lymphocyte ratio and lymphocyte monocyte ratio as prognostic markers in COVID 19.

Material and method: The present retrospective observational studyconducted in the department of Medicine, Government Medical College, Jammu for a period of one year. The study comprised of 100 Covid 19 RT PCR positive cases admitted patient in ICU as well as Ward, in covid care centre of Government Medical College, Jammu. Patients characteristics were obtained from the hospital covid care centre satisfying inclusion criteria from electronic medical records and demographic, clinical, laboratory data were extracted included age, sex clinical features, signs and symptoms, comorbidities, exposure history, oxygen support during hospitalization, duration of oxygen support during hospitalization,imaging features of the chest (CT scoring), laboratory findings (Hemogram, Total leucocyte count, differential counts, NLR and LMR. Complete blood count including NLR and LMR collected at day of admission and day 3 of admission and documented on a standardized proforma. Two outcomes were evaluated: "discharge" or "died."

Results:In majority (53%) of patients, ventilation given was high flow followed by bipap (21%), ventimask (19%) and ventilator (5%). Ventilation given was room air in only 2 out of 100 patients (2%). In present study, only 10 out of 100 patients (10.00%) died.Discriminatory power of neutrophil lymphocyte ratio (AUC 0.865; 95% CI: 0.781 to 0.925) was excellent and discriminatory power of lymphocyte monocyte ratio (AUC 0.791; 95% CI: 0.698 to 0.867) was acceptable. Among both the parameters, neutrophil lymphocyte ratio was the best predictor of CTSI severity at cut off point of >3.57 with 86.50% chances of correctly predicting CTSI severity.

Conclusion: It can be concluded from the results that NLR may be a rapid, widely available, useful prognostic factor in the early screening of critical illness in patients with confirmed COVID-19.

Keywords: COVID, NLR, LMR, Mortality

INTRODUCTION

The coronavirus disease (COVID-19) caused by virus of family coronaviridae, severe acute respiratory syndrome and middle east respiratory syndrome affecting humans belongs to same family. COVID-19 was first found as unexplained atypical pneumonia in Wuhan city of the China. They found that COVID-19 was caused by novel coronavirus which causes

infections similar to severe acute respiratory syndrome, so it was named as SARS COV 2. This novel virus is highly contagious and spread rapidly throughout the world and as per now no effective treatment available. Recognised human to human transmission significantly increases the risk of much wider transmission. The WHO named it as COVID 19 on 11th February 2020 and they declared the covid 19 as pandemic on 11th March 2020.[1-7] In India more than 30 million confirmed cases of COVID-19 reported in which more than 400000 patients died due to COVID-19. In India recovery rate of COVID-19 patients is 97.5%, Overall case fatality rate is 2.3% with no fatality in mild cases.

The COVID-19 has variable presentations like asymptomatic, upper respiratory tract symptoms, gastrointestinal symptoms, atypical pneumonia, respiratory failure.[2] Some patient develops early symptoms of severe respiratory infection with acute respiratory distress syndrome and other serious complication leads to multiple organ failure even death.[8] So it is necessary to identify the factors which are associated with poor outcome in the patient with COVID-19.

Few studies were conducted to know these risk factors and laboratory parameters association with prognosis of COVID-19 infection. These includes old age, comorbidities (hypertension, cardiovascular diseases, diabetes mellitus etc), sequential organ failure assessment score and few laboratory parameters such as higher baseline white blood cell count, neutrophils, D dimer, C-reactive protein, NLR (Neutrophil to lymphocyte ratio), LMR (lymphocyte monocyte ratio) and PLR (Platelet to Lymphocyte ratio) and lower absolute lymphocyte count, association with prognosis of COVID-19 patient[2,8]. According to some studies inflammation is one of the important factor in COVID-19 pathophysiology, both neutrophil to lymphocyte ration and lymphocyte to monocyte ratio indirectly indicate inflammatory state of patient[9].

In small towns and small hospital it's very difficult to do all hematological test like D dimer, interleukin levels but hemogram is easily available blood test in all places and using its subset we can identify the risk for worse outcome of Covid 19 patients. A better understanding of early prognostic clinical laboratory parameters could save many lives by enabling timely intervention and better resource allocation since ICU capacity is limited in most countries. In this study we will determine clinical outcome and its association with Neutrophilic lymphocyte ratio and lymphocyte monocyte ratio in COVID-19 patient.

MATERIAL AND METHODS

The present retrospective observational studyconducted in the department of Medicine, Government Medical College, Jammufor a period of one year.

STUDY POPULATION

Covid 19 RT PCR positive cases admitted patient in ICU as well as Ward, in covid care centre ofGovernment Medical College, Jammu.

INCLUSION CRITERIA

a. Covid 19 RT PCR positive admitted patients,
b. >18 years of age and
c. Both genders.

EXCLUSION CRITERIA

a. Having haematological diseases, cancers and underwent recent chemo for same.
b. Patient who went against medical advice

SAMPLE SIZE

During the study, a total of 100 patients were recruited for the present study.

DATA COLLECTION PROCEDURE

After obtaining approval from scientific committee, Institutional review board the patients characteristics were obtained from the hospital covid care centre satisfying inclusion criteria from electronic medical records and demographic, clinical, laboratory data were extracted included age,sex clinical features, signs and symptoms, comorbidities, exposure history, oxygen support during hospitalization, duration of oxygen support during hospitalization,imaging features of the chest (CT scoring), laboratory findings (Hemogram, Total leucocyte count, differential counts, NLR and LMR. Complete blood count including NLR and LMR collected at day of admission and day 3 of admission and documented on a standardized proforma**.** Two outcomes were evaluated: "discharge" or "died." The criteria for rehabilitation discharge or being cured is (1) no fever without antipyretics (2) substantial improvement in clinical symptoms and (3) ability to maintain oxygen saturation without support for 3 consecutive days.

SAMPLE COLLECTION

At the time of admission, 3 mL of venous blood sample was collected into vacutainers containing ethylene-diamine-tetraacetic acid (EDTA) and plain vaccutainers under aseptic precautions. After calibration and performing internal quality control checks, the blood samples were analyzed using a five-part automated hematology analyzer (Sysmex xn1000 automated cell counter), and the following findings were noted: hemoglobin level (Hb), total leucocyte count (TLC), neutrophil count (NC), lymphocyte count (LC), and monocyte count (MC). Neutrophil to lymphocyte ratio(NLR) was calculated by dividing NC by LC, and lymphocyte to monocyte ratio (LMR) was calculated by dividing LC/MC. The interpretation of all hematological parameters was done as per the Lab standards. As of now there is no standardised cutoff or normal values available, Receiver Operator Curve (ROC curve) analysis was done to derive the cutoff values for NLR and LMR. Sensitivity and specificity, positive predictive value and negative predictive value analysis was done for NLR and LMR cutoff with outcome.

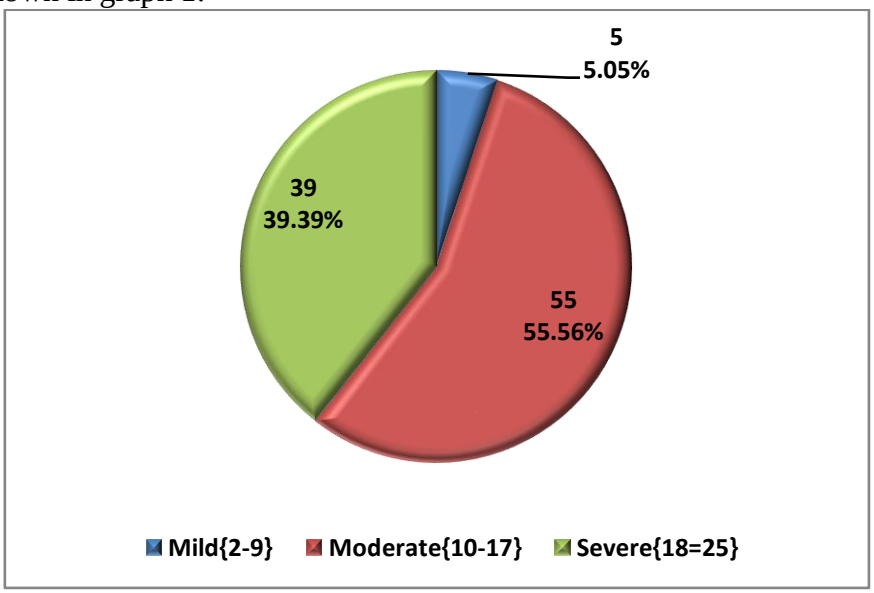
STATISTICAL ANALYSIS

Data were analysed using SPSS (Statistical packages for social sciences) version 20.0, Proportion of patients those who got discharged and died is the primary outcome, and association of PLR and LMR ratio,comorbidities with clinical outcome were analysed using Chi square test.Lab values hemogram (NLR,LMR on day 1and day 3 were analysed using independent t test (mean values) and compared between discharge and died patients. P value is considered significant if p is <0.05.Receiver Operator Curve (ROC curve) analysis was done to derive the cutoff values for NLR and LMR. Sensitivity and specificity, positive predictive value and negative predictive value analysis was done for NLR and LMR cutoff with outcome. p value considered significant if p is <0.05.

RESULTS

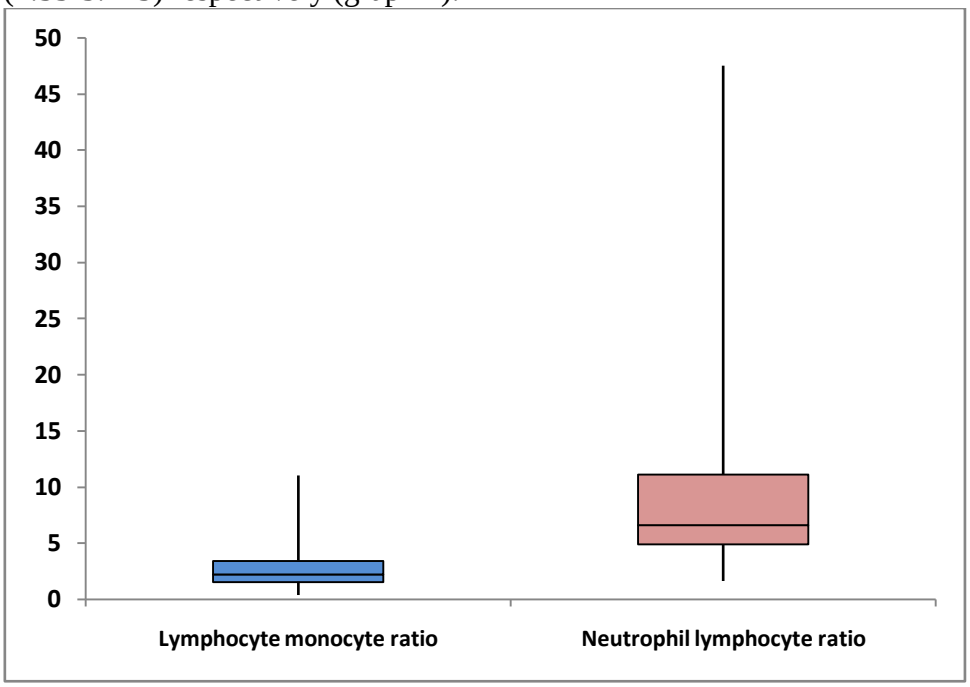
In present study, 51% of patients were males and 49.00% of patients were females. Mean age (years) among the study subjects was 60.19±13.1 with median of 60.5 (53.5-70). In the present study; hypertension was present in 44% of the patients followed by T2DM (35.00%) and hypothyroid (16.00%). Post CABG, pregnancy, COAD, depression, alcoholic, psychiatric illness and ishemic heart disease was present in only 1 out of 100 patients (1.00%) each. In majority (55.56%) of patients, CTSI was moderate (10-17) followed by severe

(39.39%). Mean value of CTSI among the study subjects was 15.95±3.39 with median of 16 (14-18) as shown in graph 1.



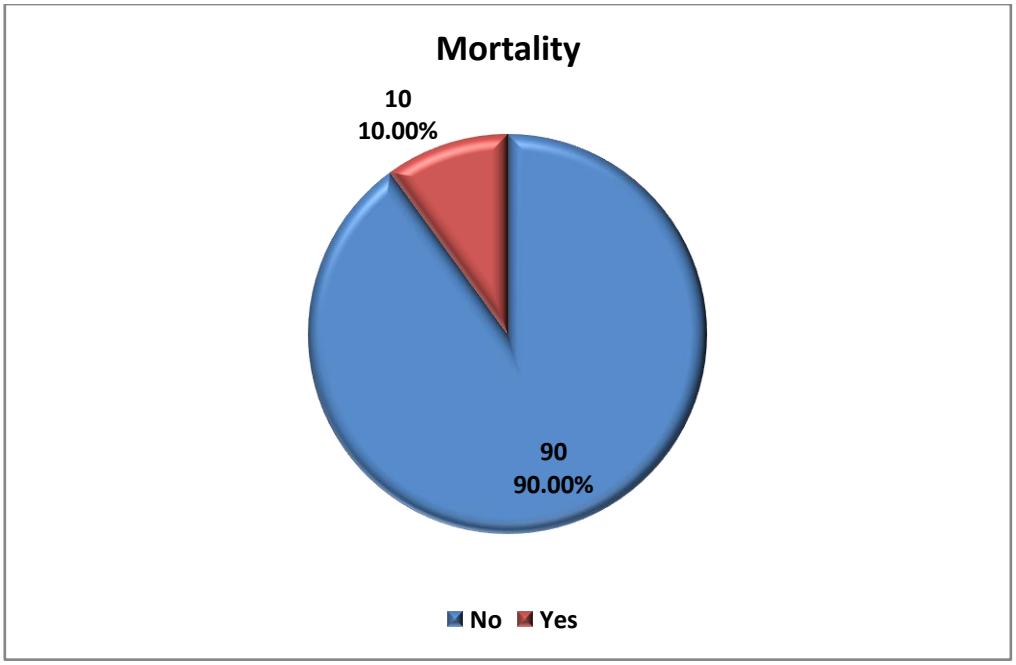
Graph 1: Distribution of CTSI of study subjects

Mean value of neutrophil lymphocyte ratio and lymphocyte monocyte ratio among the study subjects was 10.4±9.68 and 2.72±1.82 with median (25th-75th percentile) of 6.58 (4.87-11.1) and 2.25 (1.53-3.425) respectively (graph 2).



Graph 2: Descriptive statistics of lymphocyte monocyte ratio and neutrophil lymphocyte ratio of study subjects

In majority (53%) of patients, ventilation given was high flow followed by bipap (21%), ventimask (19%) and ventilator (5%). Ventilation given was room air in only 2 out of 100 patients (2%). In present study, only 10 out of 100 patients (10.00%) died (graph 3).



Graph 3: Distribution of mortality of study subjects

Table 1: Association of NLR and LMR with CTSI

Variables	CTSI			p value	p value (Odds ratio)
	Mild	Moderate	Severe		
NLR					
Mean±SD	3.38±1.86	6.67±4.19	16.68±12.28	<.0001*	Mild vs Moderate: 0.048(1.686) Mild vs Severe:0.017(2.208)
Median(25th-75th percentile)	3.36 (1.9-3.57)	5.78 (4.6-8.06)	12.28 (7.35-23.2)		
Range	1.7-6.35	1.6-27.6	3.31-47.5		
LMR					
Mean ± SD	5.23 ± 3.47	2.99 ± 1.73	2 ± 1.28	0.0006*	Mild vs Moderate: 0.043(0.689) Mild vs Severe:0.028(0.538)
Median(25th-75th percentile)	4.6 (3.4-5.25)	2.5 (1.675-3.605)	1.66 (1-2.45)		
Range	1.9-11	0.75-8	0.35-6.5		

Kruskal Wallis test

Taking mild as reference, Neutrophil lymphocyte ratio was significantly high in moderate and severe with odds ratio of 1.686 and 2.208 respectively. Similarly taking mild as reference, Lymphocyte monocyte ratio was significantly low in moderate and severe with odds ratio of 0.689 and 0.538 respectively (table 2).

Table 2: Association of NLR and LMR with mortality

Variables	Mortality			p value	p value (Odds ratio)
	Alive	Dead	Total		
NLR					
Mean±SD	9.23 ± 8.76	20.94 ± 11.54	10.4 ± 9.68	<.0001*	1.082 (1.027 to 1.139)
Median(25th-75th percentile)	6.28 (4.765-10.438)	19.6 (12.8-23.238)	6.58 (4.87-11.1)		

Range	1.6-47.5	9.6-47.5	1.6-47.5		
LMR					
Mean ± SD	2.85 ± 1.85	1.54 ± 0.91	2.72 ± 1.82	0.0006*	0.418 (0.188 to 0.927)
Median(25th-75th percentile)	2.34 (1.6-3.5)	1.33 (1.075-2.02)	2.25 (1.53-3.425)		
Range	0.66-11	0.35-3.5	0.35-11		

Mann Whitney test

Median (25th-75th percentile) of neutrophil lymphocyte ratio in died was 19.6(12.8-23.238) which was significantly higher as compared to alive (6.28(4.765-10.438) with odds ratio of 1.082 (1.027 to 1.139). Similarly median (25th-75th percentile) of lymphocyte monocyte ratio in alive was 2.34(1.6-3.5) which was significantly higher as compared to died 1.33(1.075-2.02) with odds ratio of 0.418(0.188 to 0.927) taking alive as reference.

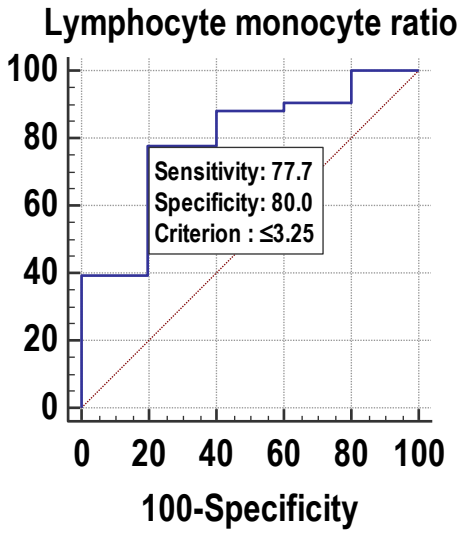


Figure: 1a

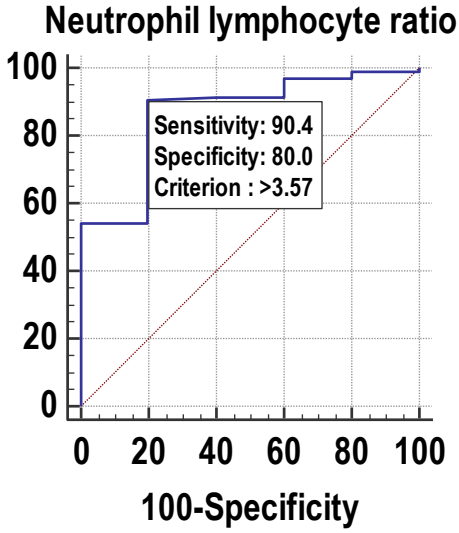


Figure: 1b

Figure 1: Receiver operating characteristic curve of LMR and NLR to predict predicting CTSI severity

Discriminatory power of neutrophil lymphocyte ratio (AUC 0.865; 95% CI: 0.781 to 0.925) was excellent and discriminatory power of lymphocyte monocyte ratio (AUC 0.791; 95% CI: 0.698 to 0.867) was acceptable. Among both the parameters, neutrophil lymphocyte ratio was the best predictor of CTSI severity at cut off point of >3.57 with 86.50% chances of correctly predicting CTSI severity. Neutrophil lymphocyte ratio had sensitivity of 90.43% followed by lymphocyte monocyte ratio (77.66%). On the other hand, neutrophil lymphocyte ratio had specificity of 80.00% followed by lymphocyte monocyte ratio (80.00%). Highest positive predictive value was found in neutrophil lymphocyte ratio (98.80%) and highest negative predictive value was found in neutrophil lymphocyte ratio (30.80%). Maximum diagnosticaccuracy to predict CTSI severitywas neutrophil lymphocyte ratio (figure 1).

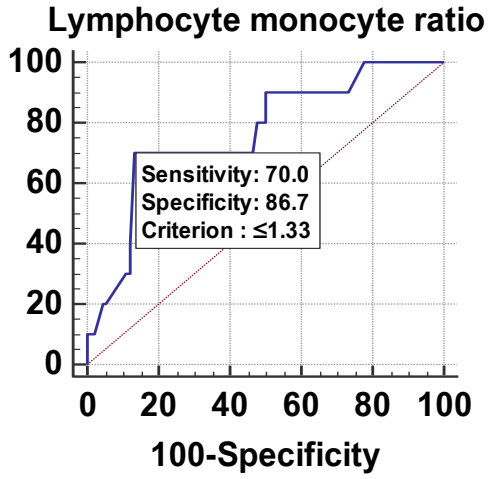


Figure: 2a

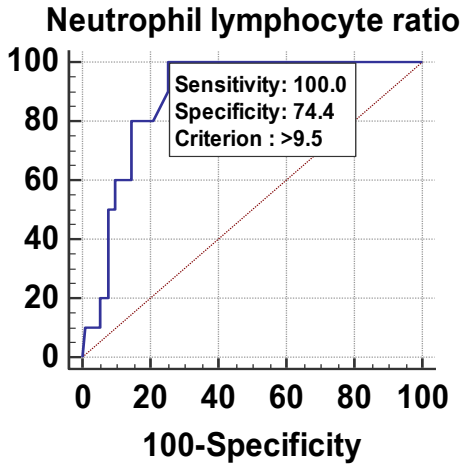


Figure: 2b

Figure 2: Receiver operating characteristic curve of LMR and NLR to predict predicting mortality

Discriminatory power of neutrophil lymphocyte ratio (AUC 0.883; 95% CI: 0.803 to 0.938) was excellent and discriminatory power of lymphocyte monocyte ratio (AUC 0.765; 95% CI: 0.670 to 0.844) was acceptable. Among both the parameters, Neutrophil lymphocyte ratio was the best predictor of mortality at cut off point of >9.5 with 88.30% chances of correctly predicting mortality (figure 2).

DISCUSSION

Inflammation is caused by infectious diseases, and growing evidence supports its significant role in the progression of COVID-19. Severe inflammatory responses contribute to weak adaptive immune response, thereby resulting in immune response imbalance. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients. NLR and LMR are indicators of the systematic inflammatory response that are widely investigated as useful predictors for the prognosis of patients with viral pneumonia.[5,10]

In our study males were slightly more as compared to females. Mean age (years) among the study subjects was 60.19±13.1 with median of 60.5 (53.5-70).Shivakumar BG et al[40] in their study found similar age and gender distribution i.e. there were 57 males and 43 females with mean age of 59.1 years.In a study by Arturo Cicculloet al[11], of the 74 patients analysed, 51 (68.9%) were male, the median age was 63 years.Ai-Ping Yang et al[10] in their study revealed that the average age was 58 years old, with 83 years old as the maximum. They revealed more males too as compared to females in their study. The findings of above mentioned studies are similar to our study. Differences in the male and female immune-system response could explain the divergent risks. The female immune system might have an edge by detecting pathogens just a bit earlier. The immune system might also explain the much higher risk of older people dying from the virus. As the body ages, it develops low levels of inflammation, and COVID-19 could be pushing the already overworked immune system over the edge. Since the number of comorbid conditions steadily increases with age, this could be another logical explanation of the observed increased mortality in older patients.

In the present study; hypertension was present in 44% of the patients followed by T2DM (35.00%) and hypothyroid (16.00%). Post CABG, pregnancy, COAD, depression, alcoholic, psychiatric illness and ishemic heart disease was present in only 1 out of 100 patients (1.00%) each.Mortality was reported more in subjects with multiple co-morbidities as compared to subjects having none or single comorbidity.Shivakumar BG et al[12] in their study revealed that

diabetes mellitus was the most common accompanying morbidity, followed by hypertension and other conditions. The difference in co-morbidities might be due to the difference in study area and associated life style. Regarding pre-existing co-morbidities, Arturo Cicculloet al[11] found that 24 patients (32.4%) had hypertension, 15 (20.3%) had a pre-existing heart condition and 8 (10.8%) had type 2 diabetes mellitus. López-Escobar A et al[13] in their study reported that comorbidities were significantly more prevalent among patients who died.

Our findings are similar to the above mentioned studies. Comorbidity may also relate to reduced immune function. Since natural immunity is declined profoundly in comorbid conditions and as patients are taking more drugs concurrently, the notorious adverse drug reactions (ADRs) alongside down-regulation of immune function may expected to occur in these patients and may increase risk of mortality eventually.

Mortality was reported among 10% of the patients in our study.Ai-Ping Yang et al[10] in their study revealed mortality >2.5%. López-Escobar A et al[13] in their study showed that three hundred and twenty-one (15.3%) patients died.The difference in outcome might be due to the difference in study area and population.

In our study; mean value of neutrophil lymphocyte ratio among the study subjects was 10.4±9.68 with median (25th-75th percentile) of 6.58 (4.87-11.1). Median (25th-75th percentile) of neutrophil lymphocyte ratio in died was 19.6(12.8-23.238) which was significantly higher as compared to alive (6.28(4.765-10.438) with odds ratio of 1.082 (1.027 to 1.139).Discriminatory power of neutrophil lymphocyte ratio (AUC 0.883; 95% CI: 0.803 to 0.938) was excellent and discriminatory power of lymphocyte monocyte ratio (AUC 0.765; 95% CI: 0.670 to 0.844) was acceptable. Neutrophil lymphocyte ratio was the best predictor of mortality at cut off point of >9.5 with 88.30% chances of correctly predicting mortality. Thereforeelevated NLR was an independent prognostic biomarker that affected pneumonia progression in COVID-19 patients. In addition, the integration of elevated neutrophil-to-lymphocyte ratio (NLR) to prognostic nomograms may lead to improved prediction. The following reasons may account for the findings. On the one hand, neutrophil (NEU) is a major component of the leukocyte population that activates and migrates from the venous system to the immune organ or system. Neutrophil releases large amounts of reactive oxygen species that can induce cell DNA damage and free the virus from the cells. Thus, antibody dependent cell mediated cell (ADCC) may kill the virus directly, expose virus antigen, and stimulate cell-specific and humoral immunities.[14]

Our findings were consistent with those of previous studies[10,11,15] on the relationship between NLR and prognosis of many other infectious diseases.Ai-Ping Yang et al[10] in their study found that optimal cut-off values were 3.3 for NLR with specificity and sensitivity of 0.636 and 0.88 respectively. According to Arturo Cicculloet al[11] too, patients with severe disease had a significantly higher NLR. Admission to the ICU was instead predicted by a NLR of > 4.Meanwhile, a recent study by Qin et al[15] showed a significantly higher NLR in patients with severe forms of COVID-19 in a cohort of 452 hospitalised patients.

Shivakumar BG et al[12] in their study reported that NLR was significantly higher in patients who survived the disease, with a p-value of 0.004. This is in contrast to our study. The derived NLR was not found to be significantly associated with mortality in the study.Xiaoming Li et al[16] in their meta-analysis too revealed that NLR can not only be a good biomarker predicting disease severity in patients with COVID-19 (AUC = 0.85, SEN = 0.78 and SPE = 0.78), but also have value in predicting mortality (AUC = 0.90, SEN = 0.83 and SPE = 0.83).

In this study; mean value of lymphocyte monocyte ratio among the study subjects was 2.72±1.82 with median of 2.25 (1.53-3.425) respectively.Median(25th-75th percentile) of lymphocyte monocyte ratio in alive was significantly higher as compared to died (p value=0.006)) with odds ratio of 0.418(0.188 to 0.927) taking alive as reference.To predict

mortality, discriminatory power of lymphocyte monocyte ratio (AUC 0.765; 95% CI: 0.670 to 0.844) was acceptable. LMR had sensitivity and specificity of 70% and 86.67% respectively. Highest positive predictive value was found in lymphocyte monocyte ratio (36.80%).

Yang et al[10] reported that age LMR value was significantly higher in severe patients than the other patients. Murat Seyitet al[17] in their study too revealed similar findings.

In summary NLR was the best predictor for CTSI severity and mortality. Similarly Yang et al[10]compared the crude odds ratio with the adjusted oddsratio after logistic regression analysis by excluding possible effects ofage and gender in order to identify the factors that could affect the progression of the disease and the researchers concluded that NLR positivelycorrelated with the risk of COVID-19. Murat Seyitet al[17] agreed with the same observation too.

LIMITATION OF STUDY

Several notable limitations existed in this study. First, the data were obtained from a single clinical research center and not from multiple clinical research centers.Finally, due to some limitations, patients with the mild illness who are in home isolation and not admitted to hospital not included in this study.

CONCLUSION

Although further studies with a larger sample size will be needed to properly assess this matter, the current study shows that NLR may be a rapid, widely available, useful prognostic factor in the early screening of critical illness in patients with confirmed COVID-19.

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