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CORRELATION OF LEUKOCYTE PARAMETERS AND D-DIMER LEVEL IN COVID-POSITIVE PATIENTS – AN INSTITUTIONAL STUDY.

Pathology

Dr. Megha Hasmukh Lalcheta* *Corresponding Author
Dr. Thejasvi Krishnamurthy
Dr. S R Niveditha
Dr. Parth Hasmukh Lalcheta
Dr. Khushali Kotecha

ABSTRACT

Introduction: Simple, effective leukocyte parameters like Neutrophil Lymphocyte Ratio (NLR) and Lymphocyte monocyte ratio (LMR) etc have gained importance as inflammatory prognostic markers in many conditions including COVID-19. Additionally D-dimer levels help in upstaging covid-19 patients for additional treatments though expensive. Could cost effective NLR, LMR predict alterations in D-dimer and thereby clinical severity? **Objective:** To study the role of leukocyte parameters in predicting the severity of covid-19 and to correlate the D-dimer levels with NLR & LMR. **Materials and Methods:** This prospective, single centered study was conducted in the department of pathology, Kempegowda institute of medical sciences (KIMS), Bangalore. After approval from ethical committee clearance, 322 RT-PCR confirmed patients with Covid-19 admitted in the KIMS hospital from June'20 to Dec'20 were included in the present study. Samples received in the laboratory for various parameters related to COVID-19 which also included Complete Blood Count (CBC) and D-dimer levels. From these data, NLR & LMR were derived and correlated with D-dimer through appropriate statistical tests. The results were tabulated. Based on D-dimer, patients were grouped into three categories (<0.5µg/ml: Category-A, 0.5-1.0 µg/ml: Category-B, >1.0µg/ml: Category-C) and compared with respective NLR & LMR. The ROC curve was applied to determine the cut-off level for NLR which can help to predict the disease severity (based on discharge and death). **Results:** With a mean age of 53.1 years, 193 cases were males. As severity of illness increased, D-dimer and NLR increased, while LMR reduced. D-dimer showed positive correlation with NLR. D-dimer levels ≥1 had higher incidence of mortality when compared to those with D-dimer <1µg/ml. ROC curve analysis identified cutoff point of NLR (3.95) & LMR (3.38) between discharged and dead patients. **Conclusion:** Elevated D-dimer & NLR are independent biomarkers, indicating poor clinical outcomes. NLR acts as a cost effective tool predicting increasing D-dimer, thereby identifying severe cases early, for effective management.

KEYWORDS

Coronavirus, Prognostic biomarker, Severity.

INTRODUCTION

Corona virus disease 2019 (COVID-19), a highly infectious disease caused by Severe Acute Respiratory Syndrome Corona virus - 2 (SARS-CoV-2), has been rapidly spreading all over the world and remains a great threat to global public health. Patients with severe acute respiratory syndrome (SARS), dysregulated inflammation begin to cytokine storm which is associated with worsening clinical outcomes in COVID-19 patients [1]. The common clinical manifestations of the covid-19 patients are fever, dry cough, headache, fatigue, sputum production, dyspnea and sore throat [2]. Early identification of high risk patients who with poor clinical outcomes is of great importance in saving the lives of patients with COVID-19 in the context of limited medical resources [3].

Neutrophil-to-lymphocyte ratio (NLR) and Lymphocyte monocyte ratio (LMR) are readily available biomarker that can be calculated from components of the differential white cell count (dividing neutrophil by lymphocyte count and dividing lymphocyte by monocyte count). Emerging evidences suggested that peripheral blood (NLR) can be used as a marker of systemic inflammation [4]. NLR has shown good predictive values on progression and clinical outcomes in various disease, such as solid tumors, chronic obstructive pulmonary disease (COPD), cardiovascular disease and pancreatitis [5, 6].

Furthermore, NLR may differentiate between mild, moderate and severe groups & probability of death in patients with COVID-19 infected patients. Lian J et al concluded NLR as a reliable predictor of COVID-19 progression and elevated NLR is associated with high mortality [7]. Indeed, NLR is a low-cost marker compared to cytokines, since in the clinical routine it is common to use the blood count. So NLR is a useful systemic inflammation marker for screening COVID-19 infected patients and may be used as a useful indicator of a poor prognosis at the initial moment of hospitalization [8]. D-dimer is a specific degradation product which is produced by fibrin hydrolysis [9]. It may reflect the effects of infection on coagulation in various infectious diseases including COVID-19 [10]. The current study evaluated the prognostic utility of NLR, LMR and D-dimer on disease severity in patients with COVID-19 and to provide a reliable marker for early identification of potentially severe cases.

The current study was aimed to correlate the D-dimer levels with NLR & LMR and in turn to predict of COVID-19 also to investigate the association between D-dimer levels and the severity of COVID-19.

MATERIALS AND METHODS

Patient selection: The present prospective observational study was conducted in the department of Pathology, KIMS hospital, Bangalore from June'20 to December'20 in the first wave of covid-19 pandemic after obtaining approval from the institutional ethical committee (Ref no. KIMS/IEC/A038/M/2020). This is an observational study. It does not involve any control group or any follow up. The obtained results of the said parameters were tabulated and subjected to statistical evaluation and results were derived. The duration of the study was also for a short period and the sample size is also around 300. Hence in this context the power of the study would not be applicable. However, there is a p value that is derived from correlating the high D-dimer levels to the NLR which is significant.

Inclusion Criteria: The current study 322 included COVID-19 RTPCR positive patients admitted in KIMS hospital, Bangalore.
Exclusion Criteria: Admitted COVID-19 positive patients with incomplete laboratory tests specifically D-dimer & pediatric age group (<14 years).

Data Collection & Laboratory Testing: Demographic data like age and gender were noted down. Differential count (neutrophil, lymphocyte, eosinophil and monocyte) were determined by electrical impedance method by Sysmex XN-1000 hematology analyzer (seven

part differential count). NLR (dividing the % of neutrophils by % of lymphocytes) & LMR (dividing % of lymphocytes by % of monocytes) were calculated using data obtained from the Complete Blood Count (CBC).

Venous sample blood (9vol) and 0.11mol/L (3.2%) sodium citrate (1vol) was collected and mixed carefully. Samples were centrifuged for 10 minutes at 3000rate/min to obtain plasma and tested D-dimer within 2 hours. Test of D-dimer was done by nephelometry by the specification of D-dimer detection kit Neph plus-1 protein specific analyzer (mfg by Genrui Biotech Inc., Shenzhen, China imported by Deep Meditech Pvt. Ltd.). Antiserum and buffer were brought to room temperature (18-25°C) before the use. Stirrer was added to the cuvette followed by 300 µl buffer solution and 6 µl plasma (sample). Cuvettes were inserted to the test channel and with the help of pippettor 100 µl antiserum was added within 5 seconds. When the test finished and test results were noted down. (Reference range: 0-0.5 mg/L) Based on D-dimer, patients were grouped into 3 categories.

Review of literature [9,10,11] revealed various methods and parameters to gauge the severity of disease process in covid 19 infected patients. It included multiple parameters like c-reactive protein (CRP), Lactate Dehydrogenase (LDH) [11], Serum ferritin, D-dimer, etc, which actually are expensive and to correlate with leukocyte parameters was cumbersome. In the quest of exploring various cost effective and simple methods to predict the severity of the disease process, one significant parameter like D-dimer was selected and based on the values dividing the patients into 3 categories was attempted and in turn compared with leukocyte parameters like LMR and NLR. The following were the 3 categories.

- <0.5 mg/L: Category-A,
- 0.5-1.0 mg/L: Category-B,
- >1.0 mg/L: Category-C

Statistical Analysis

Statistical Package for Social Sciences [SPSS] for windows Version 22.0 Released 2013. Armonk, NY:IBM Corp. was used to perform statistical analyses. Mean values of parameters (NLR, LMR & D-dimer) we're compared based on the Severity of COVID-19 using Kruskal Wallis test followed by Mann Whitney Post hoc Test. Spearman's correlation test was applied to assess the relationship between D-dimer, NLR, LMR values. The receiver operative characteristic (ROC) curve analysis was performed for NLR & LMR parameters for determining the cut-off between discharged & dead patients which can help to predict the survival status of the patient. The level of significance was set at $p<0.05$.

RESULTS

In current study, majority of COVID-19 patients were seen in 41-50 age group (21.4%). The mean age was 53.1 years old & males were predominantly affected (193/322). Kruskal Wallis test followed by Mann Whitney post hoc test was put in an application to compare mean values of D-dimer based on severity of Covid-19 (Table 1). 161 patients of category A show mean D-dimer level of 0.30, 98 patients of category B show mean D-dimer level of 0.99 seemed increased compared to category A patients. Mean D-dimer value of category C (63) patients showed much higher than both mild and moderate category patients which is 3.73, which has statistically significant differences (p value <0.001). Henceforth, disease illness increased, as D-dimer values were increased. Same as D-dimer, mean values of NLR were compared based on severity of Covid-19 (Table1). Mean value of NLR in category A patients is 3.2 which is lower compared to category B patients (5.5). In severe & incubated patients mean NLR value seemed so higher 10.9 which had statistically significant difference. With disease illness increased, NLR values shoot up. In case of LMR, mild, minor symptomatic cases shows higher mean LMR compared to category B and category C which is statistically significant (p value - <0.001). Henceforth, unlike NLR & D-dimer, LMR showed values going down as disease progression because of lymphopenia. With the help of chi square test, D-dimer levels were compared based on survival status of patients. 225 patients were included in category A & all were discharged. In case of category B of 28 patients, 96.6 % patients survived, only 1 patient died. While, intubated& severe cases, 45 patients couldn't survive, which is 66.2% with the p value <0.001. Based on survival status of patients, mean values of NLR & LMR were calculated by Mann whitney test. For survival group (276/322), Mean NLR & LMR values are 4.43 & 7.91 respectively which are statistically significant. NLR value of 11.57 for the deceased patients seemed an indicator of severity. In case of LMR value, survival group showed higher value compared deceased patients with mean difference of 3.8 (p value <0.001). To assess the relationship between D-dimer, NLR & LMR values – spearman's correlation test was applied (Table 2). As the D-dimer values increases, corresponding NLR values were also increased & rho value is 0.42. D-dimer shows significant positive moderate correlation with NLR but with LMR, D-dimer showed very weak negative correlation. Correlation coefficient value between NLR & LMR is 0.33 which again showed weak negative correlation. Receiver operative characteristic (ROC) curve analyzed and predicted the survival of COVID-19 patients with NLR & LMR values (Table 3). The current study have a cut-off value for NLR & LMR with the help of sensitivity analysis which seemed statistically significant. For NLR, cut-off value is 3.95 with 80% sensitivity & 63.7 % specificity. For LMR, cut-off value is 3.38 with 56% sensitivity & 75.3 % specificity. Figure 1 showing comparison of ROC curves between D-dimer, NLR & LMR with 100- specificity on X-axis & sensitivity on Y-axis. Dotted line indicates reference line. Higher the area under the curve (AUC) gives more prognostic importance. D-dimer shows AUC 0.99 and gives very high prognostic importance. NLR has 0.77 AUC and moderate correlation with D-dimer reflects prognostic importance in COVID-19 patients. LMR shows 0.73 AUC value and has negative correlation with both D-dimer and NLR, ultimately gives less prognostic importance.

DISCUSSION

The current study included 322 cases admitted to the hospital with a RTPCR confirmed diagnosis of COVID-19 from June to December 2020, which was in the relatively early to mid phase of the pandemic in India. The SARS-CoV- 2 virus can infect human race irrespective of age categories and gender [12]. However, there exist individual variations in physiological functions, immune responses and risk factors across age and gender. Therefore, the chances of getting infected might vary among gender and different age. In the present study, the male (59.90%) COVID 19 patients were higher than females (40.10%) which are similar to Kushwaha S et al &Jin J et al study findings [13, 14].

D- dimer was usually measured on admission, and serial D-dimer measurement was not part of the routine management. The present study found that a higher D-dimer value on hospital admission was significantly associated with inhospital mortality in COVID-19 patients. D-dimer is a fibrin degradation product and its main utility is in the diagnosis and management of thrombotic disorders [15]. In addition to thrombosis and pulmonary embolism, the increase of D-dimer may be an indirect manifestation of inflammatory reaction, as inflammatory cytokines could cause the imbalance of coagulation and fibrinolysis in the alveoli [16] and D-dimer greater than 1 µg/ml was found to be a risk factor of poor prognosis for COVID-19 patients [17]. Before the COVID-19 pandemic, D-dimer was not considered a useful biomarker for Bacterial or viral pneumonia despite some evidence to the contrary [18].

E- A study done by Zhang et al in China including 343 patients concluded that D-dimer could be an early useful marker for predicting in-hospital mortality in patients. They found the optimal cutoff point for D-dimer to be 2 µg/ml [19]. Qeadan F et al found that the trajectory of lab values including D-dimer in hospitalized patients had good accuracy in predicting severity and mortality of COVID-19 [20]. In current study d-dimer levels increased with severity of disease which was also comparable with study conducted by Soni M et al in Chennai and S D et al in Bangalore [21, 22]. D-dimer showed positive moderate correlation with NLR and weak negative correlation with LMR. Elevated D-Dimer and NLR were seen in deceased patients than discharge group, which was comparable with study conducted by W Ye et al [10]. NLR was found to have greater prognostic power than traditional infection markers, such as CRP, white blood cell (wbc) count and neutrophil count, in community-acquired pneumonia [23, 24]. At the early stage of COVID-19, wbc count in peripheral blood is normal or decreases, while the lymphocyte count decreases [25]. It is still not clear how lymphocyte count changes as the disease progresses. As expected, in our study, inflammation was important in COVID-19 patients, and alongside other inflammatory markers, NLR had significantly higher values in these patients. The optimal cut-off values of NLR and LMR were calculated by the ROC analysis evaluated and those values were 3.95 (AUC = 0.77, 95%CI (0.72–0.82), p<0.001, Se = 80%, Sp = 63%) and 3.38 (AUC = 0.73, 95%CI (0.68–0.78), p<0.001, Se = 56%, Sp = 75%) respectively in

patients with SARS-COV2 infection. These values facilitate early prediction of disease severity.

F- The increase of neutrophils often indicates that the patients have bacterial infection and the infection is aggravated. The decrease of lymphocyte means that the immune function is poor [26]. This suggests that the aggravated condition and the infection is difficult to control. Generally, it is necessary to pay attention to the COVID-19 patients with increased NLR, who may have a poor prognosis, even a risk of death. As expected, in our study, inflammation was important in COVID-19 patients, and alongside other inflammatory markers, NLR had significantly higher which is similar to Man M et al [27] study findings and LMR has lower values in these patients. LMR does not have a strong correlation with NLR and D-dimer. The correlation is stronger between NLR and D-dimer suggesting the importance of coagulation disturbances. This is an attempt were in cost-effective NLR can be tracked down the dynamic changes of D-Dimer level and in turn predict disease severity. Meta analysis of Simadibrata DM et al [28] and Li X et al [4] demonstrated that NLR on admission is predictive of severity and mortality in COVID-19 patients, and higher values of NLR are associated with poor clinical outcome which was also seen in our study.

The current study is a single center prospective study. All of data were collected from patients in a single tertiary care hospital. The results showed much higher values of the D-Dimer and NLR in the deceased patients than in the survival group. If the test result of patients was higher than the critical value that might indicate poor prognosis of patients. Second, our data may be subjected to recall bias and selection bias due to the nature of our study. Patients' co morbidities might affect D-dimer and NLR levels. The strength of the current study is that it is the first study in Karnataka which correlated D-dimer, NLR and LMR in COVID-19 patients.

CONCLUSION

D-dimer levels are significantly higher in patients with severe COVID-19 when compared to those with non-severe forms. Elevated NLR and D-dimer are independent biomarkers, indicating poor clinical outcomes. NLR is a cost effective tool predicting increasing D-dimer, thereby identifying severe cases early, for effective management.

Table 1

Table 1 - Comparison of mean values of different study parameters based on the Severity of COVID-19 using Kruskal Wallis test followed by Mann Whitney Post hoc Test

Parameter	Severity	N	Mean	SD	P-Value [a]	Sig. Diff	P-Value [b]
D-dimer	Category A	161	0.305	0.559	<0.001*	A vs B	<0.001*
	Category B	98	0.991	1.959		A vs C	<0.001*
	Category C	63	3.735	4.722		B vs C	<0.001*
NLR	Category A	161	3.266	3.276	<0.001*	A vs B	<0.001*
	Category B	98	5.536	6.028		A vs C	<0.001*
	Category C	63	10.927	9.933		B vs C	<0.001*
LMR	Category A	161	8.769	7.976	<0.001*	A vs B	0.02*
	Category B	98	6.820	5.201		A vs C	<0.001*
	Category C	63	4.587	6.461		B vs C	<0.001*

Table 2

Table 2 - Spearman's correlation test to assess the relationship between D-dimer, NLR, LMR values among patients

Parameters	Values	D-dimer	NLR	LMR
D-dimer	rho	1	0.42	-0.16
	P-Value		<0.001*	0.003*
NLR	rho	0.42	1	-0.33
	P-Value	<0.001*		<0.001*
LMR	rho	-0.16	-0.33	1
	P-Value	0.003*	<0.001*	

The correlation coefficients are denoted by 'rho' & minus sign denotes negative correlation.
Correlation coefficient range
0.0 - No Correlation
0.01 - 0.20 - Very Weak Correlation
0.21 - 0.40 - Weak Correlation
0.41 - 0.60 - Moderate Correlation
0.61 - 0.80 - Strong Correlation
0.81 - 1.00 - Very Strong Correlation

Table 3

Table 3 - ROC Curve analysis for NLR & LMR Parameters for determining the cut-off between Discharged & Dead Patients

Variable	AUC	Std. Error	95% Conf. Interval		P-Value	Cut off	Sn (%)	Sp (%)
			Lower	Upper				
NLR	0.77	0.04	0.72	0.82	<0.001*	3.95	80.43	63.77
LMR	0.73	0.04	0.68	0.78	<0.001*	3.38	56.52	75.36

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