ORIGINAL ARTICLE

NEUTROPHIL-TO-LYMPHOCYTE RATIO, DERIVED NEUTROPHIL-TO-LYMPHOCYTE RATIO, PLATELET-TO-LYMPHOCYTE RATIO AND LYMPHOCYTE-TO-MONOCYTE RATIO AS RISK FACTORS IN CRITICALLY ILL COVID-19 PATIENTS, A SINGLE CENTERED STUDY

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Background: A lot remains anonymous about the characteristics and laboratory findings that may evaluate poor outcomes in patients with Coronavirus disease 2019. The aim of this study was to determine the relationship of change in the peripheral blood factors of Neutrophil-to-Lymphocyte Ratio, derived-Neutrophil-to-Lymphocyte Ratio, Lymphocyte-to-Monocyte Ratio, and Platelet-to-Lymphocyte Ratio in hospitalized patients with COVID-19 and its severity. **Methods:** Cross-sectional analytical study was performed at Department of Haematology in Pak Emirates Military Hospital affiliated with Army Medical College, Rawalpindi, Pakistan from March-July 2020. We included 735 patients confirmed by real-time reverse transcriptase polymerase-chain-reaction test for subacute respiratory syndrome corona virus-2 of all ages, irrespective of gender and were classified in groups of severe and non-severe groups. **Results:** Data of blood and baseline characteristics were compared in between the two groups and found to be significant (p-value <0.001). The median age was 46.3 years, and 82 cases were only females. Receiver operator curve demonstrated larger area under the curve of NLR, d-NLR, and PLR and showed them as independent diagnostic biomarkers which were significantly associated with the severity of illness. Binary logistic regression performed in the form of forest plot also showed these factors were significantly linked with the severity (p-value <0.001). **Conclusion:** NLR, d-NLR, and PLR along with pre-existing co morbidities can be used as an independent biomarker for the poor clinical outcome of COVID-19 illness.

Keywords: Corona Virus Induced Disease-19, COVID-19; Derived-Neutrophil-to-Lymphocyte Ratio; d-NLR; Lymphocyte-to-Monocyte Ratio; Neutrophil-to-Lymphocyte Ratio; NLR; Platelets-to-Lymphocyte Ratio

Citation: Noor A, Akhtar F, Tashfeen S, Anwar N, Saleem B, Khan SA, *et al*. Neutrophil-to-Lymphocyte Ratio, derived Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio as risk factors in critically ill COVID-19 patients, a single centered study. J Ayub Med Coll Abbottabad 2020;32(Suppl. 1):595–601.

INTRODUCTION

2019-Coronavirus disease (2019-nCoV) is an infectious disease caused by a novel corona zoonotic virus also known as Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2). Similar viruses have caused epidemics in the past two years such as the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002, H1N1 influenza (bird flu) in 2009 and the Middle East Respiratory Syndrome Coronavirus (MERS-COV) in 2012. Pneumonia of unknown cause was detected on 31st December 2019 in Wuhan city and reported to WHO country office in China, quickly spreading China and globally. The World Health Organization confirmed the epidemic to be a public health emergency of international concern on 30th January 2020, and recognised it as a pandemic on 11th, March 2020. As per today July 2020, more than 15,865,752 COVID-19 cases have been reported around the world, resulting in more than 641,574 deaths until now.[1] According to the WHO latest statistics of Pakistan the patients having COVID-19 disease, the patients count in Pakistan is 273113 which make the incidence of the disease 0.07%.[2]

About 81% of corona patients had mild symptoms and were self-limiting such as low-grade fever, fatigue, dry cough and abnormal chest findings but with good prognosis. 14% cases had severe disease and those who were critical were 5%. The course of severe illness included symptoms of dyspnoea and / or hypoxemia after 1 week of illness and had fatal outcome.[3] According to previous studies serious COVID-19 patients can develop acute respiratory distress syndrome (ARDS), severe pneumonia, metabolic acidosis, septic shock and multiple organ failure leading to death. Death rates were ranging between 4.3–15% according to the different studies. Elderly patients with pre-existing chronic diseases had much higher mortality rate with poor prognosis.[4–7] As there is no specific treatment and medication available for this disease, it is necessary to detect risk factors of severity and diagnosis for COVID-19 infection. Doctors

are searching for a reliable prognostic marker which can help patients developing severe forms of COVID-19 disease to be identified earlier on time, and also help in the management of hospital resources.

Infectious diseases like COVID-19 cause severe inflammation and till now various studies support this notion and also its significance in the progression of disease. Weak adaptive immune response is the result of severe inflammatory responses in the body, causing imbalance immune reactions. The circulating biomarkers of inflammation and immune status are prognostic predictors for the diagnosis of COVID-19 patients. In the systemic inflammatory response, the peripheral white blood cell count (WBC), Neutrophil-to-Lymphocyte ratio (NLR), derived Neutrophil-to-Lymphocyte ratio (d-NLR absolute neutrophil count / WBC – absolute neutrophil count), Platelet-to-Lymphocyte Ratio (PLR) and Lymphocyte-to-Monocyte ratio (LMR) are indicators of systematic inflammation and have a clinical relevance to determine the progress of disease. As per previous studies the blood routine parameters of NLR, d-NLR, and PLR have shown to be of clinical importance in calculating the development of infectious diseases.[8–10] These are widely examined as useful prognostic biomarkers for the disease severity. These typical laboratory changes detected during extremely pathogenic coronavirus disease, such as SARS-CoV and MERS-CoV infections, and are believed to be associated with disease severities.[8] We have studied the independent prognostic risk factors, its relationship with the clinical parameters and severity of COVID-19 disease. These factors play a major role in calculating the severity and outcome of COVID-19 infection.

MATERIAL AND METHODS

This was a cross-sectional analytical study carried out in the Department of Haematology / Pak Emirates Military Hospital affiliated with Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan from March to July 2020 after approval from Ethics Review Committee of the Institute with ERC number ERC/ID/43. Patients of all age groups irrespective of their gender were included after informed consent. The confidentiality of the patients was maintained by giving codes. Non-purposive consecutive sampling technique was used with inclusion criteria of COVID-19 patients confirmed by real-time reverse transcriptase polymerase-chain-reaction test (RT-PCR) of SARS-CoV-2. Sample size was calculated using WHO calculator. We enrolled a total of 735 patients of all age groups. Data was collected on a pre-designed *Proforma* to endorse epidemiological, demographic, clinical signs and symptoms, laboratory haematological findings and outcome of the disease. Peripheral venous blood sample of corona patients was collected in an EDTA tube. The routine complete blood count (CBC) test was performed with an automated haematology analyser. The ratios of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR) and d-NLR ratio were calculated using formulas. NLR ratio was calculated by Neutrophil / Lymphocyte, PLR by Platelet / Lymphocyte, LMR by Lymphocyte / Monocyte and derived-NLR was calculated (neutrophil count divided by the result of WBC minus neutrophil count). The general characteristics, status of the patients and laboratory haematological results were collected during the period of admission from electronic medical records of the hospital.

According to the latest 3rd version Clinical Management Guidelines for COVID-19 Infections, Ministry of National Health Services Regulations and Coordination, Government of Pakistan[11] the cases were classified according to the clinical condition into mild, moderate, severe and critical. The clinical condition of mild and moderate symptoms was classified in non-severe group while those having severe and critical sign and symptoms were classified in the severe group. The severity of the disease is accessed by non-severe and severe groups. This is the primary outcome variable against the haematological markers and socio-demographic variable are study in this study.

For continuous variables means and standard deviation were calculated whereas counts and percentages were summarized for each category of categorical variables. Socio-demographic variables were compared across two categories of outcome variables by using chi-square and Fisher's exact tests. Receiver operating curve (ROC) analysis was calculated and optimal cut-off values were calculated for the continuous variable of NLR, d-NLR, LMR and PLR between the severe and non-severe groups. Binary logistic regression analysis was also performed by using forest plot using NLR, d-NLR, LMR and PLR with the severity of the disease. (https://www.evidencepartners.com/resources/forest-plot-generator/#forest_plot_7_graph). All statistical calculation was done using SPSS 26.0 software.

RESULTS

We enrolled total 735 of corona positive cases. The mean age of the patients was 46.30±16.3 years. The range of a minimum age is 1 year and maximum age is 92 years. Out of 735 cases male predominance was quite evident with 653 (88.8%) cases of male and only 82 (11.2%) females. There were 232 (31.6%) mild, 132 (18%) moderate, 227 (30.9%) severe and 144 (19.6%) critical cases. These were merged into two main categories of the study outcome variable into 370 (50.3%) severe and 365 (49.7%) non-severe cases. Baseline demographic data of age, gender along with

clinical sign and symptoms are calculated and comparison done with respect of severe and non-severe groups. All of these mentioned variables were found to be strongly significant with *p*-value of <0.001 (Table-1). Co morbidities were found in 264 (35.9%) cases and those without comorbidities were 471 (64.1%). Comorbidities were more than double in severe group of patients (n=193, 52.2%) as compared to non-severe (n=71, 19.5%) cases and were significantly associated with the severity of COVID-19 (*p*-value <0.001). The co morbidities, clinical sign and symptoms along with their frequencies and *p*-value were calculated by using chi-square test are given in table 1. The patients were followed up and final clinical outcome of the patients was assessed at the end showing 428 (58.2%) recovered patients, 112 (15.2%) under treatment, 62 (8.4%) on mechanical support of ventilators, 58 (7.9%) on nasal prong and 75 (10.2%) expired. There was a significant difference in the outcome of the patients in severe and non-severe groups (*p*-value of <0.001). The cause of death in expired patients of 75 (10.2%) was acute respiratory distress syndrome (ARDS), multiple organ damage (MOD), disseminated intravascular coagulation (DIC) and pulmonary embolism (PE). Number of ARDS cases was found to be highest, i.e., 32 (4.4%), MOD was 20 (2.7%) DIC was 13 (1.8%) and PE was a total of 10 (1.4%) (*p*-value <0.001).

The routine blood parameters were calculated between the two groups of severe and non-severe. Means and standard deviation were calculated for platelets, white blood cells, neutrophils, lymphocytes, monocytes, NLR, d-NLR, LMR and PLR shown in Table-2. All these haematological parameters are significantly associated with the disease severity (*p*-value of <0.001).

Receiver operating characteristic curve (ROC) was obtained for various blood parameters and disease groups (severe and non-severe) as shown in Figure-1. Severe was taken as one and non-severe was taken as negative. The ROC curve helps in establishing the affectivity of these haematological variables in the diagnosis of severe COVID 19. The area under curve (AUC) of these factors is given in Table-3. According to the criteria of assessing the AUC, NLR, d-NLR, PLR can be regarded as excellent predictor of disease severity whereas LMR has insignificant value.

To identify the risk association of haematological factors of NLR, d-NLR, LMR and PLR that may affect the severity of COVID 19, we performed binary logistic regression (Table-4). The results are also represented in the form of forest plot (Figure-2). All factors except LMR were shown to have significant *p*-values (<0.001) (Table-4).

Table-1: Demographic and baseline characteristics of COVID-19 positive cases.

Parameters	Total n=735	Severe group n=370 (50.3%)	Non-severe group n=365 (49.7%)	*p*-value
Gender Male; **(n, %)**	653 (88.8%)	330 (89.2%)	323 (88.5%)	0.76
Female; **(n, %)**	82 (11.2%)	40 (10.8%)	42 (11.5%)	0.76
Age; years (M±SD)	46.30+16.35	48.11±16.96	44.47±15.52	0.01
Comorbidities (n, %)	264 (35.9%)	193 (52.2%)	71 (19.5%)	<0.001
Hypertension	191 (26.0%)	145 (39.2%)	46 (12.6%)	<0.001
Diabetes	128 (17.4%)	111 (30.0%)	17 (4.7%)	<0.001
Chronic obstructive pulmonary disease (COPD)	42 (5.7%)	27 (7.3%)	15 (4.1%)	0.04
Ischemic heart disease (IHD)	99 (13.5%)	70 (18.9%)	29 (7.9%)	<0.001
Chronic kidney disease (CKD)	25 (3.4%)	22 (5.9%)	3 (0.8%)	0.001
Chronic liver disease (CLD)	21 (2.9%)	18 (4.9%)	3 (0.8%)	<0.001
Malignancy	12 (1.6%)	11 (3.0%)	1 (0.3%)	0.003
Signs and symptoms (n, %)				
Fever	668 (90.9%)	370 (100%)	298 (81.6%)	<0.001
Cough	581 (79.0%)	353 (95.4%)	228 (62.5%)	<0.001
Myalgia	560 (76.2%)	356 (96.2%)	204 (55.9%)	<0.001
Shortness of breath	424 (57.7%)	355 (95.9%)	69 (18.9%)	<0.001
Pneumonia	460 (62.6%)	333 (90.0%)	127 (34.8%)	<0.001
Leucopoenia	10 (1.4%)	7 (1.9%)	3 (0.8%)	<0.001
leucocytosis	162 (22.0%)	145 (39.2%)	17 (4.7%)	<0.001
Thrombocytopenia	97 (13.2%)	81 (21.9%)	16 (4.4%)	<0.001
Thrombocytosis	115 (15.6%)	66 (17.8%)	49 (13.4%)	<0.001
Lymphopenia	244 (33.2%)	188 (50.8%)	56 (15.3%)	<0.001
Neutrophilia	200 (27.2%)	180 (48.6%)	20 (5.5%)	<0.001
Outcome (n, %)				
Recovered	430 (58.5%)	111 (30.0%)	319 (87.4%)	<0.001
Under treatment	111 (15.1%)	66 (17.8%)	45 (12.3%)	<0.001
Ventilators	62 (8.4%)	61 (16.5%)	1 (0.3%)	<0.001
Nasal prongs	57 (7.8%)	57 (15.4%)	0	<0.001
Expired	75 (10.2%)	75 (20.3)	0	<0.001
Cause of Death (n, %)				
Acute respiratory distress syndrome (ARDS)	32 (4.4%)	32 (8.6%)	0	<0.001
Multiple organ damage (MOD)	20 (2.7%)	20 (5.4%)	0	<0.001
Disseminated intravascular coagulation (DIC)	13 (1.8%)	13 (3.5%)	0	<0.001
Pulmonary embolism (PE)	10 (1.4%)	10 (2.7%)	0	<0.001

Demographic and baseline data are expressed as n (%), mean±standard deviation. *p*-values calculated chi-square test.

Table-2: Laboratory blood parameter comparison between patients of severe and non-severe group

Parameters	Total (n=735) M±SD	Severe group (n=370) M±SD	Non-severe group (n=365) M±SD	*p*-value
Platelets (10^9/L)	259.98±135.20	263.65±147.90	256.260±121.06	<0.001
White blood cells (10^9/L)	9.419±5.42	11.495±6.52	7.314±2.71	<0.001
Neutrophils (10^9/L)	7.124±5.49	9.440±6.53	4.776±2.57	<0.001
Lymphocyte (10^9/L)	1.844±0.73	1.558±0.72	2.135±0.63	<0.001
Monocyte (10^9/L)	0.278±0.13	0.299±0.14	0.257±0.11	<0.001
NLR	5.584±6.43	8.544±7.63	2.584±2.51	<0.001
d-NLR	3.811±3.60	5.554±4.18	2.044±1.52	<0.001
LMR	8.578±7.31	6.635±6.67	10.548±7.41	<0.001
PLR	18.303±22.36	25.936±26.88	10.566±12.49	0.026

Data of haematological parameters are expressed as mean±standard deviation. P values calculated using chi-square test. Abbreviations: NLR: Neutrophil-to-Lymphocyte Ratio; d-NLR: derived-Neutrophil-to-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; MLR: Monocyte-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte-Ratio.

Table-3: Association of disease severity in COVID with various haematological parameters by Area Under Curve (AUC).

Test result variable	Area	Std. Error [a]	Asymptotic Sig. [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NLR	.773	.018	.001	.739	.808
d-NLR	.768	.018	.001	.734	.803
LMR	.262	.018	.001	.225	.296
PLR	.733	.019	.001	.697	.769

The test results variables: NLR, d-NLR, LMR and PLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption. b. Null hypothesis: true area= 0.5

Table-4: Binary logistic regression analysis for association of blood parameters with severity of disease.

Variable	Odds ratio(95%CI)	*p*-value
NLR	0.755 (0.714–0.797)	<0.001
LMR	1.117 (1.081–1.155)	<0.001
PLR	0.948 (0.935–0.961)	<0.001
d-NLR	0.627 (0.576–0.684)	<0.001

Abbreviations: NLR: Neutrophil-to-Lymphocyte Ratio, d-NLR: derived-Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte-Ratio.

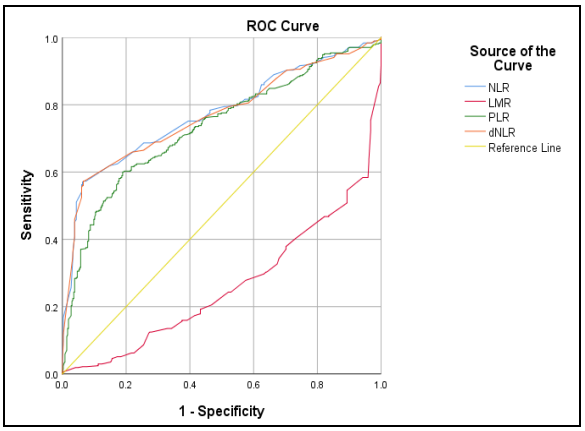

Figure-1: The ROC curves of various blood parameters with severity of COVID-19. NLR: Neutrophils-to-lymphocytes ratio; d-NLR: derived Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-lymphocytes ratio; LMR: lymphocyte-to-monocyte ratio

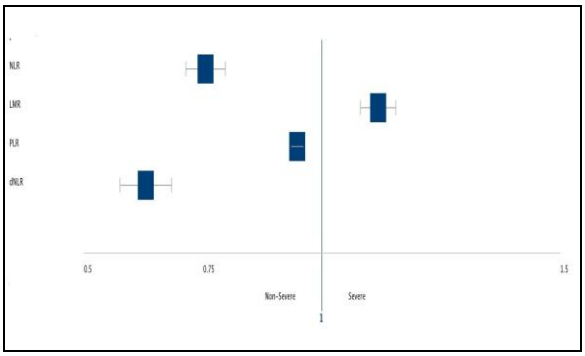

Figure-2: To identify the risk association of haematological factors of Neutrophil-to-Lymphocyte Ratio, derived-Neutrophil-to-Lymphocyte Ratio, Lymphocyte-to-Monocyte Ratio, Monocyte-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio that may affect the severity of COVID-19

DISCUSSION

Corona viruses that infect human are of six types; out of them four are more common and less pathogenic. Out of these two SARS-COV-1 and MERS-COV caused severe respiratory disease and mortality in the last twenty years. The mortality rate of SARS-COV-1 and MERS-COV is 10% and 35% respectively.[7,12] SARS-COV-2 virus belongs to beta coronavirus, known as the seventh human corona virus. The outbreak of this infection spreads rapidly with human-to-human transmission with a mortality of hospitalized cases to be 4.3–15%[13–16], which was similar to our study (10.2%) in hospitalized patients.

The comparison of results of demographic data of baseline characteristics of clinical sign and symptoms among the two groups of severe and non-severe showed significant results (*p*-value <0.0001) similar to recent studies done.[8–10,17,18]

In the recent studies[3,19] the clinical features of COVID-19 are identical to influenza, SARS-COV-1 and MERS-COV[20]. In our study the symptom of fever occurred in 668 (90.9%) and non-febrile cases were 67 (9.1%), as compared with SARS-COV-1 (1%) and MERS-COV (2%).[20,21] SARS-COV-2 causes systemic multiple organ damage with lung as the central target organ. It causes severe lung injury and ARDS in severe cases causing death.[22–24]

Frequency of severe cases has been reported to be higher in older age associated with underlying co morbidities of hypertension and diabetes[21,25,26], similar to the results in our study. Among the co morbidities of hypertension was highest in frequency followed by diabetes. Our results also reconfirmed that the patients having co morbidities had severe corona infection leading to dependency on mechanical support or expiry. Laboratory tests reported the main characteristics of COVID-19 was decrease in lymphocyte count resulting in lymphopenia and increase in neutrophil count (neutrophilia) making it main characteristic of severe group COVID-19 patients. Lymphopenia is common and seen in severe group of patients as per recent researches too.[21]

This infection causes systemic multiple organ damage with lung being the main affected organ. Severe lung injury and ARDS in critical cases lead to mortality.[23] The virus enters the alveolar epithelial cells by binding to the ACE-2 receptors and inflammatory factors are released by the cells which activates the macrophages in the alveolar tissue.[27] Abundant number of mononuclear inflammatory cells is aggregated and penetrates the lung tissue which leads to the heavy storm release of chemokine and cytokines causing severe inflammation and tissue damage.[14]

According to a research done by Xu *et al* also concluded that the inflammatory penetration of mononuclear cells mainly lymphocytes was in increase number seen by a pathological anatomy results of the deceased cases having corona infection.[28] Abnormal results of peripheral blood parameters were noted in severe group of COVID-19 cases. Among them significantly decrease in the lymphocyte count number in the above-mentioned research showed that this may be associated with redistribution of lymphocytes and increased consumption of lymphocytes due to ineffective erythropoiesis.[3] Superimposed bacterial infection was reported in the death cases by Li *et al*.[13] Significant increase in leucocyte count and neutrophils count was caused by bacterial infection.[13] The same haematological change was also seen in the MERS. Leucocytosis was shown by increase in neutrophils and monocytes, which was observed in all the MERS patients, and all the expired cases showed a drop of lymphocyte counts.[29–31] Bacterial infections play an important role in COVID-19 disease and in its outcome. Similar findings were seen in our study too in group of severe patients. Monitoring the changes in the blood routine parameters has important clinical significance. Peripheral blood combined parameters of NLR, d-NLR and PLR in the patients raised significantly. The blood parameter of NLR and d-NLR revealed this situation and we also concluded that these factors can assess the severity of corona infection. NLR and PLR is an inflammatory indicator, not only reveal the role of neutrophils in infection but also indicate the changes in the lymphocytes in vivo. These indicators of blood parameters have been considered as a systemic inflammatory biomarker and a valid prognostic factor in number of solid tumours and chronic diseases of kidney, cardiovascular and lungs, influenza virus, inflammatory and malignant disease.[32–37]

Our results showed NLR, d-NLR and PLR all had strong diagnostic values. The area under the ROC curve of NLR was the largest area. It was followed by d-NLR and PLR combined were had significant diagnostic value in the severity of the infection. The area under the curve reached 0.77, with highest sensitivity and specificity. LMR calculated could not be accessed as a diagnostic factor for severity of disease because the AUC was less than 0.50. Binary logistic regression analysis performed for these haematological parameters shown them to be significant (*p*-value <0.001). Our results showed that the patients of severe groups had low lymphocyte counts, low platelets count and a high neutrophil counts similar with the results of other studies.[7,9,17–19,38]

In summary NLR, d-NLR and PLR are the diagnostic markers and can measure the severity of the COVID-19 infection. These three biomarkers can also predict the clinical outcome of the disease severity. There is no particular treatment for this infection and mortality rate is still very high. The doctors need to carry out these simple blood parameters to timely assess the disease severity at an initial stage and diagnose the severe patients and take necessary steps to avoid and reduce mortality.

CONCLUSION

NLR, d-NLR and PLR along with and pre-existing co morbidities can be used as an independent biomarkers for the poor clinical outcome of COVID-19 illness.

Funding Source: There was no funding of any material support or monetary for this research purpose.

Acknowledgements: All the authors want to sincerely thank all the health workers and staff members of our department and hospital in helping us in our research work. We want to thank special thanks Dr. Omama Abbasi (trainee haematology) who helped in the data collection of the patients.

AUTHORS' CONTRIBUTION

AN: Designed the basic concept and methodology. AN, NA: Helped in data collection. AN, ZA: Analysed the data. BS: Critically reviwed the manuscript. FA, ST, SS: Proof reading. SAK: Final approval for publication. All authors were involved in the conceptualization of the study.

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Submitted: October 18, 2020	*Revised: October 25, 2020*	*Accepted: November 23, 2020*

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