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ROUTINE HEMATOLOGICAL OR BIOCHEMICAL PARAMETERS AS COST-EFFECTIVE PREDICTIVE MARKER OF COVID-19 SEVERITY: A RETROSPECTIVE STUDY AT A TERTIARY CARE CENTRE.

Clinical Laboratory

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ABSTRACT

Introduction: From beginning as epidemic to becoming pandemic, COVID-19 has known no boundaries, spreading worldwide straining the health infrastructure globally. Significant infectivity, morbidity and mortality were reported. The present study was done with objective of evaluating simple, cost-effective haematological and biochemical biomarkers to identify high risk groups in early COVID-19 for better management outcome. **Methods:** In this retrospective study, adult patients admitted to isolation ward and intensive care unit (ICU) of the institute who fulfilled the WHO case definition of COVID-19 and confirmed to have SARS-CoV-2 infection by reverse transcription-polymerase chain reaction (RTPCR) were included. Demographics, clinical data, haematological and biochemical investigations were studied. **Results:** In the present study mean age were 56±15 yrs. It included 1232 patients, 62.9% males and 37.1% females. 80.6% patients had moderate disease and 19.4% patients had severe disease. 22.1% patients had a normal CBC at admission. Remaining showed abnormal counts affecting at least one cell line. Age and gender association with mortality was found to statistically significant. Amongst survivors and non-survivor there were significant differences in mean hemoglobin(Hb), absolute neutrophil count(ANC) and absolute lymphocyte counts (ALC)($P < 0.001$), Neutrophil lymphocyte ratio(NLR) and Platelet lymphocyte count(PLR)($P < 0.001$). Amongst severely deceased patients, significant leukocytosis, neutrophilia, lymphopenia and monocytopenia($P<0.001$) correlating with increased mortality. **Conclusions:** Neutrophilia, Lymphocytopenia, Increased NLR, Increased PLR are more reliable predictive, prognostic biomarker associated with increased morbidity and mortality in COVID-19 patients.

KEYWORDS

COVID-19, SARS-CoV2, Biomarker, Neutrophil Lymphocyte ratio.

INTRODUCTION

COVID-19 is highly contagious and infectious disease caused severe acute respiratory syndrome by Coronavirus-2 (SARS-CoV 2) with a very high case-fatality rate varying from 0-20%. There were around 83900 active cases,477422 deaths and over 34178940 recovered patients on 19 Dec 2021 in India.[1,2] After first wave of COVID-19 in 2020, second wave of the pandemic in India was experienced between April and June 2021, deadliest of all caused by the delta(B.1.617.2) and Kappa(B.1.617.1) variants of SARS-CoV2.Evolution of COVID-19 infection on a mass scale led to the need to discover simple, cost-effective biomarkers with easy interpretation, accessible in remotest part of India and other developing nations, helping to predict outcome.[1-3] These biomarkers allow risk stratification in early disease for preventing morbidity and mortality. Hence, the present study designed with objective to analyses various haematological and biochemical prognostic markers in patients with moderate disease in hospitalized COVID-19 patients to identify prognostic markers which correlate well with morbidity and mortality.

METHODS:

The current study was cross-sectional, retrospective study conducted in a tertiary care Centre. Adult patients with moderate to severe disease, admitted in COVID-ICU and COVID-Isolation-Ward of LLRM Medical College, Meerut, Uttar Pradesh, India between 15-May and 27-July 2021 who fulfilled WHO case definition of COVID-19 and confirmed have SARS-CoV-2 infection by oro-pharyngeal and nasopharyngeal swab samples by RTPCR were enrolled. Exclusion Criteria were: mild disease/asymptomatic cases, with age below 18 years, missing haematology/biochemical/coagulation data, transfer to other medical facilities with unknown outcomes, patients with death/discharge within 48 hours of admission, patients with hematological malignancies, immunodeficiency states. On admission, patients were categorised clinically into two groups – Group A: moderate disease and Group B: severe disease. Operational Definitions: moderate disease was defined as having pneumonia with no signs of severe disease respiratory rate >24/min, respiratory distress with SpO2<94% at room air, persistent fever, cough, constitutional symptoms, controlled comorbid. Severe disease was defined as: pneumonia respiratory rate > 30/min, respiratory distress requiring assisted ventilation with Spo2 <90% at room air, <94% with oxygen supplementation, uncontrolled comorbid conditions.

Basic Data and laboratory values extracted from laboratory software (VINMEDILAB III) of our hospital) and medical case-files of patients. The following variables recorded: age, sex, severity assessment, any comorbid illness [hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, asthma, chronic kidney or liver disease etc.Baseline investigations were obtained at admission: complete blood cell counter(CBC), Liver function tests(LFT), Renal function tests (RFT),electrolytes-Reactive protein(CRP), D-dimer, ferritin, procalcitonin, PT (Prothrombin time), aPTT (Activated Partial thromboplastin clotting time). Follow up CBC, LFT, RFT were repeated daily, CRP, D-dimer, ferritin, procalcitonin 48-72hrly. Radiological investigations (X-ray/CT-scan) were done as per protocol. Recovery and mortality regarded as endpoints. Haematological parameters: NLR, PLR were calculated. These parameters compared against normal healthy controls. Data was analyzed using SPSS.20 software for mean, median and standard deviation (SD) for comparison of variables in different groups.

OBSERVATION AND RESULTS

Total 1540 COVID-19 patients were admitted between may-2021 and july-2021 in LLRM medical college, Meerut, Uttar Pradesh, India. 308 patients excluded from the study as per criteria and 1232 patients studied. Age range between 19-82 years. Mean age was 56±15 yrs. Demographic profile of patients is seen in Table-1.

Table 1: Demographic Profile of COVID-19 patients in Group A and Group B patients

Age Range	Group A	Group B	Total (Percentage)
20-40	317	89	406 (33.0%)
40-60	459	115	574 (46.6%)
60-80	217	35	252 (20.4%)
Gender			
Males	624	152	776 (62.9%)
Females	369	87	456 (37.1%)
Comorbidities			
Present	248	119	367 (29.8%)
Absent	745	120	865 (70.2%)
Total Patients (Percentage)	993 (80.6%)	239 (19.4%)	1232

Age range survivors was 20-69 yrs and mean age was 48.6±4yrs. In non-survivors range was 28-81 years and mean age was 64±6. Mortality was seen in 287 patients (23.3% of total), which included 218 males (75.9%) and 69 females (24.1%). Mortality was 28% males and 15% females. Age and gender association with mortality was found significant.($P<0.001$) 272 patients (22.1%) had normal CBC within 48 hours of admission and 960 (77.9%) patients had abnormal CBC, showing low or high counts affecting at least one cell line.

Average hemoglobin were 11.32±2.2 g/dL. Low Hb (Hb< 11) was seen in 158 males (20.4%) and 277females (60.7%), As seen in Table-2.

Table 2: Comparison of Haematological and Biochemical characteristics profile findings in Group A and Group B patients

Laboratory Parameters	Range		Group A		Group B	
	Healthy Controls	Disease	Mean± SD	Median	Mean± SD	Median
Hb (g/dL) Males Females	15.0±2.0 13.2±1.5	8.8-15.2 7.2-13.5	12.4±+2.7 11.2±1.8	12.5 10.6	11.9±2.8 10.9±1.8	11.6 10.4
RBC count(1012/L) Males Females	5.0±0.5 4.5±0.5	3.3-6.2 2.4-5.2	4.0 ±1.4 3.1 ±0.4	4.39 4.1	3.8±1.1 2.9±0.7	4.1 3.2
MCV (fL)	92±9	72-126	83.2±6.2	83.5	82.2±4.5	82.3
RDW (CV%)	12.8±1.2	11.2-38.7	15.6±2.6	12.1	20.2±6.1	15.3
WBC Count (10 9/L)	3.5-4.5	3.4-33.6	9.76±.4.1	11.6	10.3±8.3	13.7
ANC (109/L)	1.6-7.8	5.2-29.6	7.4 ± 3.5	7.2	19.4±4.2	24.4
ALC (109/L)	1.2-4.3	1.0-3.6	1.8±1.4	2.7	0.8±1.2	1.7
AMC (109/L)	0.3-1.0	0.6-6.7	3.9 ±1.7	5.8	4.2±2.6	6.0
AEC (109/L)	0.02-0.5	1.5-3.0	1.2±0.5	1.2	1.9±0.7	2.1
ABC (109/L)	0.01-0.08	0.01-1.0	0.02±0.06	.02	0.01±0.08	0.0.04
Platelet Count (109/L)	280±30	186-420	194.21±128	210.3	128.4±120	116.22
PT (sec)	11-13 sec	11-14.6	12.97±4.4	13.3	19.75±9.5	19.3
aPTT (sec)	30-46	25.5-36.4	32.84±5.5	28.2	44.76±9.4	37.5
D-dimer (ng/mL)	(>2 mg/L	343-867	669±698.10	628	808,67±132	734.9
CRP (mg/L)	<10	2.46-79.6	62.64±45.96	30.15	186.67±109.71	167.5
LDH (U/L)	105-260	415.6-826	689.28±28	504.7	732±82	701.5
Procalcitonin (ng/mL)	<0.5	0.4-.10	0.3±0.2	0.5	0.4±0.4	0.8

Mean Hb values were low with Group-B as compared to Group-A, in males as well as females. However difference not clinically significant (p-value>.005). Hemoglobin were lower in females as compared to males with clinical significance (p<0.005). Higher RDW (>14%) was found in 229 patients (18.6%). Leucocytosis present in 247 patients (25.7%). Most of them showed neutrophilia (25.3%) followed by eosinophilia present in 4 patients (1.3%).The mean WBC count was 11.71 ± 3.6 $X10^9$/L. As shown in Table-2 neutrophilia was more prominent in Group B patients and showed statistical significance. The ALC was 2.55 ± 1.3 $X10^9$/L, absolute monocyte count was 1.0 ±0.7 and absolute eosinophil count was 1.4±0.3. These values in Group A and Group B are shown in Table-2. Cytopenias were noted in 527 patients (42.8%).Out of these, pancytopenia was seen in 149 patients (28.2%), lymphocytopenia in 78.4% patients. In early disease monocytopenia was seen in both Group A and Group B patients but difference was not statistically significant. Difference between survivor and non-survivor was found to be statistically significant (P<.001) with clinical improvement during later course of disease, monocyte count increased. Cut off for NLR was >3.5 based on previous studies. In present study increased NLR was seen in 788(82.1%) patients. Mean NLR was 4.2 in Group A and 5.8 in Group B. Survivors 3.86 and 6.2 in non -survivors, difference being statistically significant. Thrombocytopenia was seen in 354 patients (36.9%) and mean platelet count was 234.24 ± 192.38 $X10^9$. Comparison seen in Table-3. Mean PLR in survivors and non-survivors group 119.21 and 186.62 respectively.

Table 3: Comparison of Haematological and Biochemical profile of subcategories of covid patients based on survivor status.

Laboratory parameters	Survivors		Non-survivors	
	Mean± + SD	Median	Mean ± SD	Median
Hb (g/dL)	12.5±+5.7	11.8	10.06±2.7	10.1
WBCCount(10^9/L)	5.0±4.2	11.7	7.9±5.5	19.4
ANC (10^9/L)	6.7±13.20	12.1	8.0±2.2	21.4
ALC(10^9/L)	1.29 ±1.6	2.9	0.63±1.6	1.2
AMC(10^9/L)	3.4 ±1.4	5.2	4.4±1.8	6.9
AEC(10^9/L)	1.4±0.3	1.6	1.8±0.5	2.1
Platelet Count(10^9/L)	203.04±76.81	214.8	165.28±117.88	122.9
PT (sec)	12.97±4.42	12.1	19.75±9.54	24.4
aPTT(sec)	32.84±5.50	36.0	5476±41.94	42.3
D-dimer ng/mL	529±508.1	511	808.6±526	822.1
CRP mg/L	36.6±55.96	41.7	186.67±99.71	200.5
LDH(U/L)	672.28±66	655	840±56	81
Procalcitonin ng/mL	0.3±0.4	0.8	0.5±0.4	0.9

PT/aPTT and D-dimer were significantly elevated in Group B compared to Group A patients, but difference was not statistically significant. D-dimer difference was however significantly elevated in both survivor and non-survivors. C-reactive protein (CRP) was elevated in 834 patients (7.7%). Group B showed a more marked increase compared with Group A patients (86.5% vs 61.4%). Elevated procalcitonin was present in 45 patients (3.6%) and elevated lactate dehydrogenase (LDH) values were present in 406 patients (32.9%).

DISCUSSION

Inflammation plays a significant role in the progression of various infectious diseases: viral pneumonias including COVID-19. Cellular destruction because of viral replication leads to elaboration of cytokines and chemokines from the activated macrophages which leads to cytokine storm and is responsible for the development of acute respiratory distress syndrome (ARDS) and multiple organ failure. Inflammatory markers have been suggested for assessing severity of disease.[3,4,5] In the present study mean age was 56±15 yrs and most of the patients belonged to age group 40-60 yrs, 574 patients(46.6%). It included 776 males (62.9%). 993 patients (80.6%) had moderate disease admitted in isolation ward and 239 patients (19.4%) had severe disease. In study conducted by Kayina et al data from 235 adult patients was analyzed, mean age was 50.7±15 yrs of whom 68.1% were males. In their study patients were divided into four categories and patients with mild, moderate, severe and critical illness were 43(18.3%),76(32.3%), 73(31.1%) and 43(18.3%) respectively, at the time of presentation. [6] In present study mild cases were not admitted in hospital as per protocol and henceforth excluded. The mean Hb gender wise and in different comparative groups were similar to other studies. In study done by Anegundit et al mean Hb was 13.44 gm/dL with range 13.6gm/dL 5.8-18.5 gm/dL and RDW ranged 11.4-39.9%. Present study showed higher RDW in 229 cases (18.6 %) cases, higher in case of severe COVID-19 disease. In study by Ashgar et al higher RDW was predictive of severe hospital complications, infections and prognosis than WBC counts.[14,15] Studies suggest that hematological profiles change during the course of SARS-CoV-2 illness as also seen in the present study. Leukocyte count in COVID-19 is an important consideration as a predictive and prognostic marker. In the present study leucocytosis was present in 247 patients(25.7%). Out of these, most of the patients showed neutrophilia (25.3%) followed by eosinophilia which, was in 4 patients (1.3%). Neutrophils were the predominant cell type involved in early anti-viral defense. However, during severe pneumonia, neutrophils become cytotoxic through degranulation and lysis. Studies have suggested neutrophil recruitment may exacerbate COVID-19 immunopathology. Hence neutrophilia seen in early disease serves as predictor of grim prognosis. Neutrophilia was more prominent in severely ill patients and non-survivors compared to survivors P<0.0001). As seen in present study neutrophilia as evident by ANC correlated with increased morbidity, mortality and showed statistical significance(p<0.001), on comparison in Group A and Group B patients as well as between survivors versus non-survivors. The mean ANC was 17.14±2.4 $X10^9$/L and ALC was 2.55 ± 1.3 $X10^9$/L which was in agreement by studies by Anegundit et al. Leucocytosis, neutrophilia, lymphocytopenia and monocytopenia were characteristic findings observed in COVID-19 patients.[4,7,9]

In present study cytopenias were noted in 527 patients (42.8%).

Lymphocytopenia was most consistent finding seen in patients (78.4%). Similar results were seen in study by Guan et al in which lymphocytopenia was present in 83.2% case. In study conducted by Agbuduwe et al most commonly blood count abnormality was lymphopenia noted in 35%-83% patients.[5,10,11,12] The white cell parameters are altered as a result of cytokine release syndrome and destruction of the T-lymphocyte leads to a bad clinical outcome. Inflammatory states of body triggers excessive yield of neutrophils and simultaneously bringing about apoptosis of lymphocytes thus proceeding towards immunological aberration. In one study in hospitalised COVID-19 patients in Singapore, the median ALC was significantly lower in patients requiring admission to ICU (0.4 vs 1.2 $x10^9$ /L) as was neutrophilia (11.6 vs 3.5 $x10^9$) /L). Another study involving 90 hospitalized COVID-19 patients reported an association between lymphopenia and disease severity.[13,14] In present study thrombocytopenia was seen in 354 patients(36.9%) which was in very close agreement with study by Guan et al showing 36.2% cases of thrombocytopenia. These hematological abnormalities were more prominent among severe vs non-severe cases and survivors versus non-survivors. These results were consistent in four other descriptive studies that were conducted in China and included 41,99,138 and 201 patients respectively. Thrombocytopenia common in viral infections, which might be explained by immunological platelet destruction, inappropriate platelet activation, consumption, and impaired megakaryopoiesis..Decreased platelet count, reflecting their consumption and thrombin generation, is helpful in recognizing the presence and severity of coagulopathy.[5,9,11,15] In the present study increased NLR was seen in 788(82.1%) patients the mean NLR was 4.2 in moderate disease versus 5.8 in severe disease and 3.86 in survivors versus 6.2 in non-survivors, the difference being statistically significant(P<.0001). Elevating NLR projects towards the prediction of mortality among sufferers of acute coronary syndrome, intracerebral hemorrhage, polymyositis, dermatomyositis, and cancers. It is a prominent predictor of severity of disease, high mortality and poor prognosis within patients of ICU. Normally, NLR should be below 3, but a ratio of above 3 signifies acute stress, and a ratio of more than 9 signifies sepsis. But variability occurs in populations regarding the cut-off value of NLR with some studies suggesting a cut-off value of 3, 3.5 and even 4. NLR, were found in COVID-19 patients and serve as useful indicators for diagnosis and predictive markers. PLR has also emerged as a potential tool for risk stratification in sepsis patients and a prognostic predictor in COVID-19 patients. Metaanalysis by Sarkal of various studies in literature showed deceased and critically ill patients had higher PLR correlating with more mortality and morbidity. In present study PLR was raised in severe disease and non-survivors group, as were seen by Man et al study. Another study from Wuhan revealed more severe cases having higher neutrophil counts, lower lymphocyte counts, higher NLR as well as lower percentages of monocytes, eosinophils and basophils.[19,25,26] Procalcitonin, serum ferritin, CRP, and interleukin-6 (IL-6) have been associated with high risks for severe COVID-19 infection . Regarding ferritin, Wu et al. showed that higher serum ferritin was associated with ARDS development, but the association with survival did not reach significance. Zhou et al. supported an association between higher serum ferritin levels and death.[15] In present study CRP was elevated in 834 patients(67.7%) Increased CRP correlation was seen to correlate well with clinical features, disease severity in COVID-19 patients. Higher CRP has been linked to unfavourable aspects of COVID-19 disease, such as ARDS development, myocardial injury, and death. Procalcitonin levels help in differentiating COVID-19 from sepsis in which the levels are increased, whereas in COVID19, the levels remain normal. Elevated procalcitonin which may also be suggestive of a secondary bacterial infection complicating the clinical course of COVID-19 disease, was found in 5.5%, and elevated lactate dehydrogenase (LDH) in 41% of patients. More severe cases showed a more marked increase compared with the moderate ones (81.5% vs 56.4% for CRP, 13.7% vs 3.7% for procalcitonin and 58.1% vs 37.2% for LDH). Accordingly in a retrospective cohort study including 191 patients with COVID-19 from Wuhan, China, non-survivors, as compared with survivors, presented more often with high LDH , high procalcitonin, increased serum ferritin levels and elevated IL-6. In the study by Wang et al, 40% of patients presented with elevated LDH. Increased LDH has been associated also with higher risk of ARDS, ICU support and death.[9,15,17]

CONCLUSION

Male gender, increasing age, Neutrophilia, Lymphocytopenia, Increased NLR and PLR are associated with grim prognosis in COVID-19 patients. Absolute neutrophil count, absolute lymphocyte count, neutrophil lymphocyte ratio(NLR) and platelet lymphocyte ratio(PLR), can independently, serve as reliable predictive and prognostic marker in COVID-19 disease.

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