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RESEARCH ARTICLE

# Correlation of Hematological Findings with Severity of COVID-19

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ABSTRACT

SARS-COV-2 emerged as pneumonia of unknown etiology and transforming into global pandemic leading mass casualties globally. It leads to serious complications with a wide range of symptoms and laboratory and radiological abnormalities.

Methodology:

This retrospective study included 191 admitted patients was conducted between 15 April 2020 and 31 August 2020 at university of Lahore teaching hospital, Lahore, Pakistan. Baseline demographics, clinical, laboratory and radiological characteristics were compared amongst disease severity categories with One way ANOVA and comparison amongst recovered and non-recovered was carried out by independent t test, Fisher's exact and chi-square test respectively. All data were analysed in SPSS 25 and p-value <0.05 was considered significant.

Results:

Out of 191 patients enrolled in this study, majority were male and above 50 year age. Fever (68%) was the most common symptom though dyspnea was statistically significant (p-value<0.05) and diabetes (41.4%) being the most common comorbidity. A statistical significant downtrend in eosinophil counts were observed in critical and severe disease from non-severe disease and similar trend was observed in non-recovered (died) patients than recovered. A significant rise in neutrophil to lymphocyte ratio, crp, ferritin and d-dimer were observed amongst critical and severe disease and non-recovered patients (p-value<0.05). Patients with eosinopenia had low survival proportion at day 5 and 10 than those with relatively normal eosinophil counts.

Conclusion:

Patients with advanced age, multiple comorbidities, elevated hematological, deranged coagulation markers presented with more severe disease and had poor outcome. In particular, eosinopenia can play key role in early diagnosis, disease severity recognition and disease surveillance as it is an independent risk factor for prognosis.

Keywords: COVID-19, eosinopenia, critical disease, outcome, prognosis.

**Authors' Contribution:**

WR conceived and designed the study. WR, AU, BR, RF were involved in data acquisition. WR, AU, BR, FAB, SA, AM summarized the data. WR did the data analysis. WR, AU, BR, FAB, SA, AM and RF did the data interpretation. WR drafted the manuscript. AU, BR, FAB, SA, AM, RF, KS, FI critically revised the manuscript for important intellectual and scientific input. All the authors contributed to the article and approved the submitted version.

**Conflict of Interest:**

All the authors declare no conflict of interest.

**Funding Statement:**

All the authors declare that they did not receive any financial grants for the study from any source.

**Introduction:**

A pneumonia of unknown etiology emerged as an outbreak in Wuhan City, Hubei Province, China in December 2019.[1] In January 2020 World Health Organization named the etiological agent as "novel coronavirus 2019" (2019-nCov) responsible for causing this pneumonia like illness.[2] SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) have been epidemics caused by coronaviruses in 2002 and 2012, respectively.[3] This 2019-nCov also belongs to the Coronaviridae family which has been transmitted to humans from bats after mutations.[4] The 2019-nCov later named by World Health Organization as SARS-CoV-2 was responsible for coronavirus disease (COVID-19) which rapidly spread globally compelling it to be declared as a pandemic on 11 March 2020 by World Health Organization.[5]

COVID-19 disease presents with wide spectrum of disease severity with majority being asymptomatic or having mild illness at one end whilst few progresses to develop moderate, severe or critical disease.[6] COVID-19 does not limit itself to respiratory tract rather it causes systemic inflammatory responses presenting with variety of organ dysfunctions including hematological problems.[7] Currently, there are no established treatments available for COVID-19 disease, so risk factors which predict guarded prognosis need to be elucidated.[8] Hematological disturbances such as leukocytosis, lymphopenia, increased neutrophil to lymphocyte ratio (NLR), thrombocytopenia and coagulopathy have been observed in patient populations of COVID-19.[9,10,11] Thromboembolic phenomenon have been noted in many publications across the globe.[12]

Complete blood count and coagulation profile are the most readily performed tests for patients presenting to the hospital and to gauge disease severity at the earliest to improve prognosis is the need of the hour. The objective of our study is to evaluate which hematological disturbances are commonly encountered in COVID-19 patients in our local population and whether they can serve as valuable independent predictors of disease severity and in-hospital mortality.

**Materials and Methods:**

This retrospective study was done including all the males and females, 18 years of age or older admitted to University of Lahore Teaching Hospital between 15 April 2020 and 31 August 2020. The institutions Ethical Review Board approved the study (Reg. No. ERC 08/20/08) and granted the waiver from informed written consent from the study participants. A total 200 patients admitted in the hospital out of which 191 met the inclusion criteria (one patient below 18 years of age and eight with incomplete data were excluded) included in the study. Non-probability consecutive sampling method was applied. All the patients had confirmed diagnosis of COVID-19 disease by RT-PCR on nasopharyngeal swab. Medical records of these patients were collected which included demographics, medical history, comorbidities, laboratory parameters including complete blood count, liver function tests, renal function tests, D-dimers, Ferritin, C-reactive protein (CRP), Lactate dehydrogenase (LDH), Pro-BNP, Troponin I (Trop I), Creatine Kinase (CK), coagulation profile, chest X-rays, disease severity and their clinical outcome (discharged from hospital labelled as Recovered and dead recorded as Non-Recovered). The modified Radiographic Assessment of Lung Edema

score (mRALE) was used to assess the extent of lung involvement (0=none, 1=<25%, 2=25-50%, 3=50-75%, and 4=>75% involvement) in chest x-rays. This score is multiplied with the density score for each lung (1=hazy, 2=moderate, 3=dense) and sum of score from each lung gives the final mRALE score within a range of 0 score for normal and 24 being the maximum score for chest x-ray with complete bilateral dense opacification.[13] All COVID-19 diagnosed patients were classified into:

i) Non-severe (oxygen saturation above 94% with respiratory rate below 25 breaths/minute)
ii) severe (oxygen saturation below 94% with respiratory rate above 25 breaths/minute and not requiring NIV, HFNC or mechanical ventilation)
iii) critical category (Respiratory compromise enough to require NIV, HFNC or mechanical ventilation) according to the clinical management guidelines issued by Ministry of National Health Services; Government of Pakistan.[14]

It was hypothesized that difference might exist in epidemiological, clinical and laboratory parameters amongst disease severity and outcome. Quantitative variables were presented as mean/median (standard deviation/range: minimum-maximum). Qualitative variables were presented as frequencies and percentages. The independent t-test, Chi-square, Fisher's exact and ANOVA test were applied to evaluate the differences amongst the groups depending upon the data. All the tests were two sided with 95% confidence interval. *P*-value less than 0.05 was considered significant for differences amongst the groups. IBM SPSS statistics software version 25 (IBM Corp., Armonk, NY, USA) was utilized for statistical analyses.

**Results:**

From April 15, 2020 until August 31, 2020, 2,456 patients were diagnosed with COVID-19 in an electronic medical record system from university of Lahore teaching hospital. One hundred ninety one patients' data out of two hundred admitted patients were analysed. Data was trifurcated as per disease severity categories that is non-severe, severe and critical disease. Furthermore, laboratory and radiological parameters were further bifurcated to evaluate their significance as per patient outcome status (recovered and non-recovered). The mean age was 50.71 ± 15.49 year with 48.80 ± 16.19 year in non-severe, 46.58 ± 10.76 year in severe and 53.59 ± 16.42 year in critical disease categories respectively ($p$=0.026). Male to female ratio was 2:1. (Table 1).

Diabetes (41.4%) was the most common comorbidity followed by hypertension (20.4%), cardiovascular disease (11%) and chronic kidney disease (1.6%) (Table 1). Fever (68.6%), cough (66.5%) and dyspnea (57.1%) were the most common symptoms amongst the cohort followed by headache (19.9%), ageusia (7.9%), anosmia (4.7%) and diarrhoea (3.1%) (Table 1). A statistical significant difference was observed for comorbidities (diabetes p=0.006, hypertension p<0.001, cardiovascular disease p<0.001), dyspnea (p<0.001), heart rate (p=0.028), respiratory rate (p=0.043) and blood oxygen saturation (p=0.039) respectively (Table 1). There was no statistical significant difference with respect to the gender, BMI, chronic kidney disease, fever, cough, diarrhea, ageusia, anosmia, sick contact, travel history, systolic and diastolic blood pressure (Table1).

**Table 1:** Baseline Characteristics of COVID-19 patients with respect to disease severity

| | Total (n=191) Mean ± SD or n(%) | Non-Severe (n=50) Mean ± SD or n(%) | Severe (n=43) Mean ± SD or n(%) | Critical (n=98) Mean ± SD or n(%) | P-value |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 50.71 ± 15.49 | 48.80 ± 16.19 | 46.58 ± 10.76 | 53.59 ± 16.42 | 0.026 |
| **Sex** | | | | | |
| Male | 131(68.6) | 31(62) | 30(69.8) | 70(71.4) | 0.505 |
| Female | 60(31.4) | 19(38) | 13(30.2) | 28(28.6) | |
| **Comorbidities** | | | | | |
| Diabetes | 79(41.4) | 22(44) | 09(20.9) | 48(49) | 0.006 |
| Hypertension | 39(20.4) | 03(6) | 03(7) | 33(33.7) | <0.001 |
| Cardiovascular Disease | 21(11) | 1(2) | 1(2.3) | 19(19.4) | <0.001 |
| Chronic Kidney Disease | 3(1.6) | 1(2) | 0(0) | 2(2) | 1 |
| **Symptoms** | | | | | |
| Fever | 131(68.6) | 40(80) | 27(62.8) | 64(65.3) | 0.117 |
| Cough | 127(66.5) | 29(58) | 25(58.1) | 73(74.5) | 0.055 |
| Dyspnea | 109(57.1) | 18(36) | 20(46.5) | 71(72.4) | <0.001 |
| Headache | 38(19.9) | 11(22) | 08(18.6) | 19(19.4) | 0.915 |
| Diarrhoea | 6(3.1) | 0(0) | 0(0) | 6(6.1) | 0.069 |
| Anosmia | 09(4.7) | 04(8) | 03(7) | 02(2) | 0.166 |
| Ageusia | 15(7.9) | 03(6) | 05(11.6) | 7(7.1) | 0.599 |
| **Contact Tracing** | | | | | |
| Sick Contact | 59(30.9) | 18(36) | 18(41.9) | 23(23.5) | 0.062 |
| Travel History | 22(11.5) | 07(14) | 4(9.3) | 11(11.2) | 0.544 |
| **Body Mass Index (BMI)** | 26.02 ± 3.47 | 25.96 ± 3.57 | 26.19 ± 3.59 | 25.97 ± 3.41 | 0.934 |
| **Vitals** | | | | | |
| Systolic BP(mmHg) | 110.75 ± 8.8 | 107.62 ± 6.6 | 108.65 ± 4.5 | 109.72 ± 7.8 | 0.095 |
| Diastolic BP(mmHg) | 78.82 ± 8.8 | 74.64 ± 6.6 | 76.60 ± 7.6 | 78.86 ± 6.8 | 0.245 |
| Heart Rate(beats/minute) | 112.65 ± 10.8 | 98.56 ± 8.8 | 106.45 ± 6.5 | 110.65 ± 6.8 | 0.028 |
| Respiratory Rate(breaths/minute) | 25.52 ± 4.52 | 22.35 ± 3.65 | 25.45 ± 5.65 | 30.66 ± 6.86 | 0.043 |
| Blood Oxygen Saturation (SpO2 %) | 90.65 ± 9.35 | 92.65 ± 5.65 | 85.90 ± 11.65 | 80.89 ± 12.56 | 0.039 |

**Table 2 Laboratory and radiological parameters of COVID-19 patients with respect to Disease Severity**

| | Total (n=191) Mean ± SD or n(%) | Non-Severe (n=50) Mean ± SD or n(%) | Severe (n=43) Mean ± SD or n(%) | Critical (n=98) Mean ± SD or n(%) | P-value |
|---|---|---|---|---|---|
| **Hematological markers** | | | | | |
| Haemoglobin (g/dL) | 12.95 ± 1.79 | 12.82 ± 1.66 | 13.18 ± 1.93 | 13.00 ± 1.75 | 0.61 |
| Hematocrit (%) | 38.37 ± 5.87 | 37.46 ± 4.42 | 39.67 ± 6.48 | 38.29 ± 6.10 | 0.18 |
| White Cell Count (x $10^3$/µL) | 9.42 ± 5.95 | 9.02 ± 5.16 | 7.51 ± 2.92 | 10.53 ± 6.95 | 0.01 |
| Platelets (x $10^3$/µL) | 218.53 ±108.78 | 257.40±91.91 | 226.64 ±88.41 | 198.15 ±119.26 | 0.001 |
| Neutrophils (%) | 71.38 ± 13.86 | 69.20 ± 13.65 | 62.56 ± 12.51 | 76.63 ± 12.28 | 0.001 |
| Lymphocyets (%) | 19.51 ± 11.97 | 20.82 ± 12.69 | 27.37 ± 11.36 | 15.26 ± 9.88 | 0.001 |
| N/L Ratio | 6.48 ± 5.24 | 6.70 ± 1.81 | 3.04 ± 2.18 | 7.94 ± 7.62 | 0.01 |
| Eosinophils (x $10^3$/µL) | 0.03 ± 0.02 | 0.05 ± 0.01 | 0.04 ± 0.01 | 0.01 ± 0.01 | 0.001 |
| **Inflammatory markers** | | | | | |
| CRP (mg/L) | 97.43 ± 82.17 | 13.94 ± 16.25 | 33.30 ± 58.86 | 166.56 ±104.01 | 0.001 |
| Ferritin (ng/mL) | 867.36 ±814.81 | 186.68±164.87 | 452.39±570.30 | 1582.47±1133.77 | 0.001 |
| Procalcitonin (ng/mL) | 0.87 ± 0.15 | 0.07 ± 0.03 | 0.08 ± 0.03 | 1.63 ± 1.02 | 0.34 |
| **Coagulation markers** | | | | | |
| D-Dimer (ng/mL) | 1053.19±766.67 | 161.94±94.18 | 476.95±122.25 | 1768 ± 261.39 | 0.001 |
| Prothrombin Time | 13.77 ± 1.91 | 13.46 ± 1.54 | 13.26 ± 1.35 | 14.11 ± 2.17 | 0.02 |
| Partial Thromboplastin Time | 31.39 ± 9.96 | 27.78 ± 3.84 | 27.05 ± 4.35 | 34.92 ± 12.25 | 0.001 |
| INR | 1.04 ± 0.17 | 1.00 ± 0.001 | 1.00 ± 0.002 | 1.066 ± 0.02 | 0.03 |
| **Biochemical markers** | | | | | |
| Total Bilirubin (mg/dL) | 0.56 ± 0.27 | 0.52 ± 0.19 | 0.56 ± 0.21 | 0.59 ± 0.32 | 0.35 |
| Alanine Aminotransferase (U/L) | 101.99 ± 65.36 | 42.04 ± 21.46 | 56.00 ± 36.46 | 153.45 ± 35.77 | 0.02 |
| Aspartate Aminotransferase (U/L) | 98.49 ± 32.77 | 35.02 ± 15.44 | 49.77 ± 30.31 | 152.92 ± 65.27 | 0.001 |
| Serum Sodium (mmol/L) | 131.74 ± 5.56 | 131.50 ± 2.56 | 131.95 ± 3.58 | 131.88 ± 7.22 | 0.91 |
| Serum Potassium (mmol/L) | 3.81 ± 0.59 | 3.76 ± 0.47 | 3.74 ± 0.38 | 3.87 ± 0.71 | 0.39 |
| Serum Creatinine (mg/dL) | 1.04 ± 0.79 | 0.90 ± 0.30 | 0.84 ± 0.43 | 1.18 ± 0.96 | 0.02 |
| Creatine Kinase (U/L) | 260.67 ±182.60 | 78.30 ± 56.73 | 123.53 ±99.59 | 416.69 ±269.09 | 0.001 |
| Lactate Dehydrogenase (U/L) | 456.81 ±356.00 | 152.34±99.39 | 305.23±147.37 | 676.45 ±425.85 | 0.001 |
| **Cardiac markers** | | | | | |
| Troponin I (ng/mL) | 7.77 ± 3.77 | 0.001±0.0001 | 0.004 ± 0.001 | 15.14 ± 7.29 | 0.13 |
| Pro-BNP (pg/mL) | 335.36 ±229.44 | 58.28 ± 24.05 | 128.84 ± 26.99 | 571.48 ± 99.58 | 0.001 |
| **Radiological parameters** | | | | | |
| mRALE score | 13.90 ± 7.39 | 3.44 ± 3.72 | 12.46 ± 2.34 | 19.81 ± 2.58 | 0.001 |
| Bilateral Radiological Lung Involvement (%) | 47.35 ± 31.08 | 4.58 ± 5.51 | 37.91 ± 13.51 | 73.06 ± 12.57 | 0.001 |
| **Admission duration** | | | | | |
| Hospital Stay (days) | 9.28 ± 6.39 | 9.54 ± 5.16 | 10.16 ± 6.43 | 8.71 ± 6.92 | 0.44 |

**Table 3 Laboratory and radiological parameters of COVID-19 patients with respect to Outcome**

| | Total (n=191) Mean ± SD or n(%) | Recovered (n=145) Mean ± SD or n(%) | Non-Recovered (n=46) Mean ± SD or n(%) | *P*-value |
|---|---|---|---|---|
| **Hematological markers** | | | | |
| Haemoglobin (g/dL) | 12.95 ± 1.79 | 13.02 ± 1.73 | 12.82 ± 1.98 | 0.51 |
| Hematocrit (%) | 38.37 ± 5.87 | 38.27 ± 5.48 | 38.67 ± 6.93 | 0.69 |
| White Cell Count (x $10^3$/µL) | 9.42 ± 5.95 | 7.86 ± 4.52 | 14.34 ± 7.14 | 0.001 |
| Platelets (x $10^3$/µL) | 218.53 ±108.78 | 204.97±101.03 | 259.64±121.48 | 0.002 |
| Neutrophils (%) | 71.38 ± 13.86 | 68.05 ± 13.59 | 82.06 ± 8.00 | 0.001 |
| Lymphocyets (%) | 19.51 ± 11.97 | 22.05 ± 12.08 | 11.30 ± 6.65 | 0.001 |
| N/L Ratio | 6.48 ± 5.24 | 5.19 ± 7.99 | 10.50 ± 9.58 | 0.001 |
| Eosinophils (x $10^3$/µL) | 0.03 ± 0.02 | 0.03± 0.02 | 0.01 ± 0.01 | 0.001 |
| **Inflammatory markers** | | | | |
| CRP (mg/L) | 97.43 ± 82.17 | 62.73 ± 83.82 | 202.59±104.97 | 0.001 |
| Ferritin (ng/mL) | 867.36 ±814.81 | 724.85±68.29 | 1730.34±1382.35 | 0.001 |
| Procalcitonin (ng/mL) | 0.87 ± 0.15 | 0.13 ± 0.03 | 3.17 ± 2.11 | 0.01 |
| **Coagulation markers** | | | | |
| D-Dimer (ng/mL) | 1053.19±766.67 | 878.34±166.04 | 1567.13±277.69 | 0.04 |
| Prothrombin Time | 13.77 ± 1.91 | 13.53 ± 1.70 | 14.55 ± 2.29 | 0.001 |
| Partial Thromboplastin Time | 31.39 ± 9.96 | 28.90 ± 9.11 | 38.95 ± 8.55 | 0.001 |
| INR | 1.04 ± 0.17 | 1.01 ± 0.16 | 1.10 ± 1.92 | 0.002 |
| **Biochemical markers** | | | | |
| Total Bilirubin (mg/dL) | 0.56 ± 0.27 | 0.54 ± 0.21 | 0.65 ± 0.34 | 0.015 |
| Alanine Aminotransferase (U/L) | 101.99 ± 65.36 | 75.77 ± 26.52 | 186.11 ± 74.41 | 0.01 |
| Aspartate Aminotransferase (U/L) | 98.49 ± 32.77 | 60.07 ± 53.26 | 216.47±135.79 | 0.04 |
| Serum Sodium (mmol/L) | 131.74 ± 5.56 | 130.94 ± 3.67 | 134.50 ± 8.87 | 0.001 |
| Serum Potassium (mmol/L) | 3.81 ± 0.59 | 3.75 ± 0.47 | 3.99 ± 0.85 | 0.02 |
| Serum Creatinine (mg/dL) | 1.04 ± 0.79 | 0.88 ± 0.34 | 1.49 ± 1.31 | 0.001 |
| Creatine Kinase (U/L) | 260.67 ±182.60 | 155.24±21.46 | 598.98±141.611 | 0.001 |
| Lactate Dehydrogenase (U/L) | 456.81 ±356.00 | 329.87±223.66 | 852.24 ± 529.26 | 0.001 |
| **Cardiac markers** | | | | |
| Troponin I (ng/mL) | 7.69 ± 3.73 | 0.24 ± 0.21 | 31.52 ± 15.25 | 0.001 |
| Pro-BNP (pg/mL) | 335.36 ±229.44 | 217.63±20.26 | 715.26±207.98 | 0.001 |
| **Radiological parameters** | | | | |
| mRALE score | 13.90 ± 7.39 | 3.44 ± 3.72 | 12.46 ± 2.34 | 0.001 |
| Bilateral Radiological Lung Involvement (%) | 47.35 ± 31.08 | 4.58 ± 5.51 | 37.91 ± 13.51 | 0.001 |
| **Admission duration** | | | | |
| Hospital Stay (days) | 9.28 ± 6.39 | 9.54 ± 5.16 | 10.16 ± 6.43 | 0.44 |

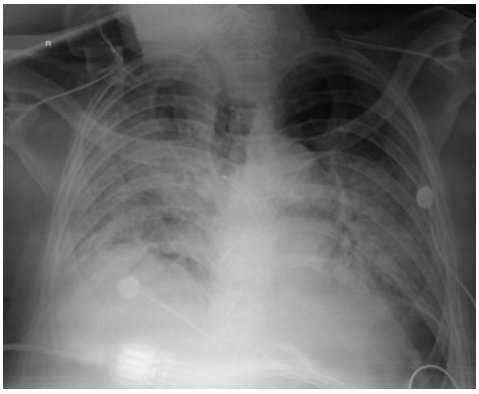
Laboratory and radiological parameters, and hospital stay were evaluated against the disease severity and patient outcome as shown in table 2 and Table 3. With respect to the disease severity, we found that there was statistical significant mean difference amongst the mild, moderate and severe disease groups for hematological biomarkers [white blood cells (p=0.01), platelets (0.001), neutrophilia (0.001), lymphopenia (0.001), high neutrophil to lymphocyte ratio (0.01) and eosinopenia (0.001)]. Furthermore, biochemical biomarkers [Total Bilirubin p=0.003, Alanine Aminotransferase p=0.001, Aspartate Aminotransferase p=0.02, serum creatinine p= 0.02, creatine kinase p=0.001, lactate dehydrogenase p=0.001 and Pro-BNP p=0.02)] were found to have statistical significant mean difference. Analysis of coagulation profile showed statistical significant mean difference for Prothrombin time, activated prothrombin time and D-dimer with p value <0.01 respectively. Infective markers CRP, Ferritin had statistical significant mean difference with p value 0.001 for each. Radiological parameters, modified radiographic lung edema (mRALE) score had statistical significant mean difference (p=0.001) and bilateral radiological lung involvement (p=0.001). Hospital stay also had significant mean difference (p=0.02). mRALE score guidance is illustrated in figure 1.

**Figure 1:** mRALE scoring system

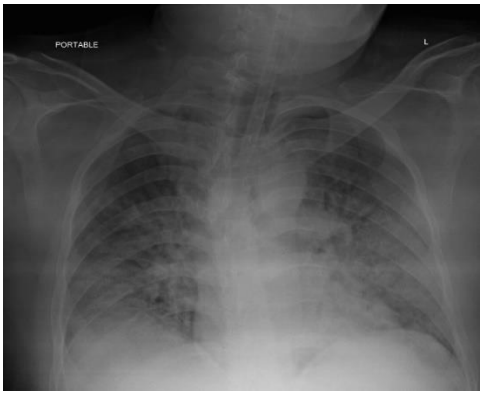
**A** mRALE score guidance

| **Consolidation** | |
|---|---|
| **Consolidation Score** | **Extent of alveolar opacities (%)** |
| 0 | None |
| 1 | <25% |
| 2 | 25-50% |
| 3 | 50-75% |
| 4 | >75% |
| **Density** | |
| **Density Score** | **Density of alveolar opacities** |
| 1 | Hazy |
| 2 | Moderate |
| 3 | Dense |
| **Final mRALE Score** | |
| **Right Lung** | **Left Lung** |
| Cons x Density = Right Lung score | Cons x Density = Left Lung score |
| **Total mRALE score = Right Lung score + Left Lung Score** | |

**B Calculation of mRALE score of Radiograph [B]**



**C Calculation of mRALE score of Radiograph [C]**



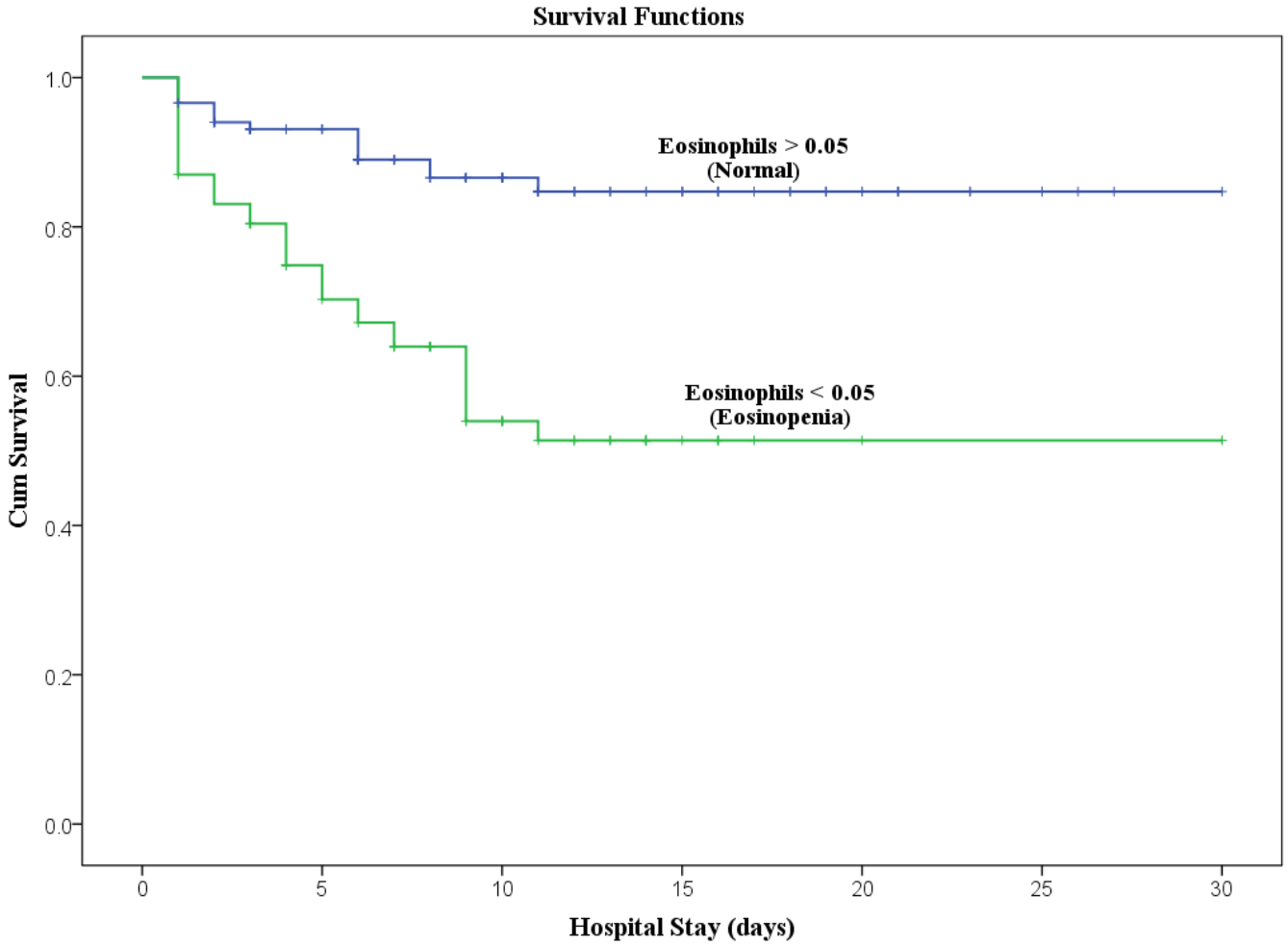

| Calculation of mRALE score of Radiograph [B] | | | |
|---|---|---|---|
| **Score** | **Right Lung** | **Left Lung** | **Total** |
| **Consolidation** | **4** | **3** | |
| **Density** | **3** | **3** | |
| **Lung Score** | **4 x 2 = 12** | **3 x 3 = 9** | **21** |

| Calculation of mRALE score of Radiograph [C] | | | |
|---|---|---|---|
| **Score** | **Right Lung** | **Left Lung** | **Total** |
| **Consolidation** | **4** | **4** | |
| **Density** | **2** | **3** | |
| **Lung Score** | **4 x 2 = 8** | **4 x 3 = 12** | **20** |

About the patient's outcome, a statistical significant mean difference was observed amongst the recovered and non-recovered patients for hematological biomarkers (white blood cells, platelets, neutrophilia, lymphopenia, high neutrophil to lymphocyte ratio, eosinopenia), biochemical markers (hyponatremia), coagulation biomarker (high D-dimer), inflammatory biomarkers (crp and ferritin) and radiological biomarkers high mRALE score and mean percent bilateral radiological lung involvement on chest radiographs. Procalcitonin levels were observed to be high in the patient who died (p-value 0.02) in comparison to those who recovered and discharged from the hospital.

Overall survival was compared amongst the cohort who had eosinopenia and normal eosinophil count. There was statistical significant difference ($p<0.001$) between two groups. Furthermore, at day 5 and 10 from admission, patients with eosinopenia had lower survival proportion that is 70% and 54% than those who had relatively normal eosinophil count that is 94% and 86% respectively as shown in figure2.

**Figure 2:** A Kaplan-Meier Survival plot depicting overall comparison analysis amongst patient with normal eosinophil counts eosinopenia.




**Discussion:**

This retrospective study conducted at university of Lahore teaching hospital is one the largest case series from Pakistan representing comparative analysis of hematological, biochemical, coagulation, inflammatory and radiological parameters against disease severity and patient outcome (discharged from the hospital and died) groups. The study demonstrated that older age group with multiple comorbidities, cough and dyspnea, eosinopenia, high Neutrophil to Lymphocyte ratio and high inflammatory markers on presentation had more severe to critical disease course throughout the admission than those who had non-severe disease at presentation. Furthermore, patients in severe and critical category had unfavorable outcome (died) than those who had non-severe disease recovered and discharged from the hospital. In particular, we identified eosinopenia as new independent prognostic marker of disease severity and mortality.

We found that our cohort had leukocytosis, thrombocytopenia, neutrophilia, lymphopenia and eosinopenia. Of note, these parameters were more profound amongst the severe, critical disease category and the non-recovered patients. These findings are in keeping with already published literature.[15-17] Lymphopenia and hyper-activated inflammatory cascade carries significant prognostic value; though underlying mechanism still remains limited. Based on the observations driven from clinical practice, it has been postulated that

coronaviruses may directly infect bone marrow precursors, resulting in abnormal hematopoiesis, or trigger an autoimmune response against the host blood cells.[15-17]

Neutrophils to lymphocyte ratio progressively rises with the disease severity and in those who did not recover as described in previously published literature. [17-20] We observed that our cohort in the category of severe and critical disease and those who did not recover had high Neutrophil to lymphocyte ratio. [17-20] Neutrophil to lymphocyte ratio elevation could be due to dysregulated expression of inflammatory cytokines, abnormal increase in low-density neutrophil and upregulation of genes involved in lymphocyte cell death pathway due to COVID-19 infection.[19-20]

Only few publications previously reported eosinopenia in patients with COVID-19 in regards to disease severity and patient outcome.[21] We observed a significant downtrend of eosinophil counts as the disease progressed from non-severe to severe and critical categories. Furthermore, there was significant eosinopenia in patients who died than who recovered and were discharged from the hospital.[22,23] Overall survival comparison analyses in our study further consolidated this fact, as there was low survival proportion in patients with eosinopenia than with relatively normal eosinophil count.

Two biologic functions may explain eosinophil's anti-viral effect. First, on activation by viruses, eosinophils release molecules such as neurotoxin/ribonuclease 2 and cationic proteins that can kill viruses. Second, eosinophils stimulate an immunological response by expressing toll-like receptors, CD80, CD86 and major histocompatibility complex MHC I/II. To support this fact, it was illustrated that influenza-A virus infected eosinophils can act as antigen presenting cells and stimulate virus specific CD8 T cell mediated anti-viral immune response in vivo. This fact is important because, if we hypothesize that eosinophils can generate immune defense against COVID-19, then strategies to correct eosinopenia may prove beneficial to lessen COVID-19 fatality.[21-23]

SARS-COV-2 causes coagulation disorder, a finding quite common in most of the patients. Our study supports this fact as we found elevated D-Dimer levels in severe and critical disease when compared to non-severe disease. Furthermore, significantly elevated D-dimer levels were observed in deceased patients with a positive correlation to mortality than those who recovered. Inflammatory markers, C-reactive protein, Ferritin and Procalcitonin had positive correlation to the disease severity and mortality, a finding from our study also described in already published literature.[18,20,24-26] One possible rason could be that pro-inflammatory markers induce cytokine storm related to COVID-19 induced endothelialitis.[24-26]

Transaminitis, elevated serum creatinine, LDH, Trop I, CK , LDH and Pro-BNP levels were also important findings in our study with positive correlation with disease severity. However, in our study, hyponatremia was common to deceased group of our cohort. We also found that mRALE score and percent bilateral radiological lung involvement had positive correlation to disease severity and fatality. These observations are in keeping with already published studies.[24-26]

There are few limitations in our study. First, it is a retrospective study. Second, this is single institution study with a relatively small sample size. Multi-institutional study with a large sample size would have increased the strength of study. Third, it represents laboratory data from admission time only and hence follow up of patients and laboratory data to evaluate recovery pattern would have improved the study strength significantly.

**Conclusion:**

This study represents comprehensive comparative analysis of the clinical characteristics, laboratory and radiological data against disease severity and outcome. It also highlighted eosinopenia may serve as an independent marker for early diagnosis, recognition of disease severity and prognosis. More vigilance is required in addition for elevated inflammatory and coagulation markers. The parameters presented in this study might help the clinicians to identify the patients at risk of developing severe and critical disease. Further research to assess time and pattern of eosinophil

count during disease course and recovery might help to define an algorithm for triaging patient management unit (outpatient, inpatient ward, high dependency unit, intensive care unit).

**Data Availability Statement:**

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

**Ethics Statement:**

The study involving human participants was reviewed and approved (Reg. No. ERC 08/20/08) by the Ethical Review Board, University College of Medicine and Dentistry. Informed written consent was not required in accordance with national legislation and institutional requirement.

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