

# Role of Leukocytes Ratio in Predicting Survival with COVID-19

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## ABSTRACT

**Background:** Eosinophils, the main cells in the immune system, play a key role in parasitic and allergic diseases. However, their role in viral infections is still a matter of debate. Therefore, this study was conducted to evaluate the eosinophils, eosinophils to lymphocyte ratio, and lymphocyte to monocyte ratio in predicting survival in COVID-19 patients.

**Methods:** This retrospective study was conducted in the COVID-19 ward from August 2021 to January 2022. A total of 497 diagnosed patients of Covid-19 disease were enrolled aged >25 years of both genders. Quantitative variables were presented as percentages and frequencies. The Chi-square test was applied to evaluate the association.

**Results:** Of 497 patients infected with Covid-19, 311 (62.6%) were males and 186(37.4%) were females. The mean value of eosinophils was  $0.52 \pm 1.27$  and the eosinophils to lymphocyte ratio (ELR) was  $0.05 \pm 0.11$ . The association of age and hematological parameters with gender was found at  $52.25 \pm 27.52$  years in males and at  $55.20 \pm 25.77$  in females ( $p=0.114$ ). In addition, the mean value of ELR was observed  $0.05 \pm 0.11$  in males and  $0.04 \pm 0.11$  in females ( $p=0.627$ ), whereas, mean lymphocyte to monocytes ratio (LMR) was  $2.44 \pm 2.07$  in males and  $3.21 \pm 5.02$  in females ( $p=0.011$ ).

**Conclusion:** A significant association was reported in the lymphocyte-to-monocyte ratio ( $p < 0.011$ ) in both genders, whereas an insignificant association was found in Eosinophil to lymphocyte ratio. Thus, LMR, ELR, and CRP levels may be effective markers for survival in Covid-19.

**Keywords:** Eosinophils, Lymphocytes Ratio, Biomarker.

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## INTRODUCTION

The COVID-19 infection belongs to a wide range of viruses that caused common cold and serious disorders worldwide, such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). In December 2019, Wuhan city of China, reported 1<sup>st</sup> case of COVID-19 (unexplained viral pneumonia) while on March 11, 2020, World Health Organization (WHO) declared COVID-19 as an epidemic<sup>1</sup>. The expected mortality rate for COVID-19 has been revealed to be around 3.5%, which was related to Spanish influenza and had a very high increasing rate than seasonal influenza. In about 80% of COVID-19 pandemics, mild symptoms were observed and 10% to 20% of cases were reported to be severe infections. In severe cases, the condition of the patient abruptly results in acute respiratory distress syndrome, acute respiratory failure, bleeding disorder, metabolic acidosis, and sepsis<sup>2</sup>.

The first case of this pandemic virus was reported in Karachi, Pakistan on February 26, 2020. Gradually, the virus proliferated countrywide and at present has become widespread. In Pakistan, the number of COVID-19 patients had extended to 4601 till April 10, 2020, in which 727 patients recovered, however, 66 died<sup>3</sup>. Currently, the prevalence of Covid-19 in Pakistan, from 3<sup>rd</sup> January 2020 to 7<sup>th</sup> August 2021, there have been 1,058,405 confirmed cases of COVID-19 with 23,702 deaths, and 954,711 recoveries reported to WHO. As of 6<sup>th</sup> August 2021, a total of 35,306,892 vaccine doses have been administered<sup>4</sup>.

The main clinical manifestations of COVID-19 include fever, dyspnea (difficulty in breathing), cough, headache, rhinorrhea, sore throat, pneumonia, sepsis, hemoptysis, bilateral infiltrates on chest imaging which appear to be the most common serious clinical signs of infection<sup>5</sup>.

One recent pathological research on COVID-19 has revealed that CD3, CD4, CD5, CD8, CD20, CD38, and CD79a are positive in the spaces of the lung interstitial and the vessels of blood. In addition, the penetration of monocytes, lymphocytes, and plasma cells into the spaces of the lung interstitial is confirmed by the techniques of immunohistology<sup>6</sup>. These approaches recommended that the occurrence of infection stimulates the numerous resistant cells in the tissue of the alveolar epithelium. Many studies reported that peripheral lymphocytopenia is a common feature in patients suffering from COVID-19 and is usually associated with the severity and fatality of the virus<sup>7</sup>. Consequently, lymphocytes are thought to be the main marker for observing the patients' situation in the clinical management and diagnosis of COVID-19 infection<sup>7</sup>.

Eosinophils are a form of white blood cells in the immune system and work against multicellular organisms. In conjunction with the cells of the mast and basophils, they regulate systems associated with allergic diseases and asthma. These granulocytes grow in the course of hematopoiesis in the bone marrow and travel into blood<sup>8</sup>. In various studies, the function of eosinophils against viruses in the respiratory system has been noted<sup>9-11</sup>. Eosinophil-stimulated cytokines, for example, preexisted interleukin-2 (IL-2), interleukin-12 (IL-12), and interferon- $\gamma$  (IFN- $\gamma$ ) which is classic T-helper 1 (Th1) cytokines contained anti-viral reactions, generate molecules with anti-viral activity, comprising of RNases and reactive species of nitrogen and they have receptors allowing the recognition of viruses<sup>9-11</sup>. Further, eosinophils can move towards lymph nodes, where they can provide antigens to T cells<sup>9</sup>. The response of eosinophil anti-viral immune has been defined against certain viruses of respiration, containing respiratory syncytial virus<sup>10</sup> and influenza<sup>11</sup>. One study reported the role of peripheral blood eosinophil counts as an effective marker for the prognosis of COVID-19 patients<sup>12</sup>.

ELR is a novel indicator that has been assessed in several inflammatory illnesses and malignancies. An increased ELR is found in patients with cigarette smoking which can be a beneficial sign of systemic inflammatory activity<sup>13</sup>. Another study reported that the ELR may be supportive to differentiate patients with bronchial asthma with and without non-steroidal anti-inflammatory drugs (NSAIDs)<sup>14</sup>. Therefore, the present study was aimed at evaluating the association of eosinophils, eosinophils to lymphocytes ratio, and lymphocyte to monocyte ratio with Covid-19 patients.

## METHODS

This retrospective study was arranged in the COVID-19 ward of the tertiary care hospital, in Karachi. The duration of the study was four months i.e., October 2021 to January 2022. A total of 497 diagnosed patients of Covid-19 were enrolled aged >25 years for both genders. Non-probability consecutive sampling technique was used to collect the data.

Patients hospitalized with clinical presentation of lower respiratory infection and tested positive for COVID-19 by Polymerase Chain Reaction (PCR) test, were included in the study, however, those who have negative Polymerase Chain Reaction (PCR) results and refused to participate, were excluded from the study. Further, for the analysis, all the final test reports of all the patients whose blood samples were collected were taken from the hospital records to support our present study. The reports include Platelets count, Hb, Lymphocytes, Neutrophils,

Eosinophils, TCL, D-dimer, and CT- scans. The entire test was done in Dr. Ziauddin Hospital's laboratory.

For statistical analysis, the data extracted from the hospital files were then analyzed using SPSS version 22.0. Quantitative variables were presented as percentages and frequencies in the tables. The Chi-square test was applied to evaluate the association. A  $p$ -value < 0.05 was considered statistically significant.

## RESULTS

The present study enrolled 497 patients infected with Covid-19, including 311(62.6%) males and 186(37.4%)

females. The mean value of Hemoglobin (Hb) in patients was observed at  $12.40 \pm 5.38$  gm/dL, Mean Total Leucocytes Counts (TLC) were  $11.74 \pm 6.46$  ( $\times 10^3/L$ ), Mean Neutrophils were  $82.56 \pm 12.0$ , mean Lymphocytes were  $11.03 \pm 8.26$ , Mean Eosinophils were  $0.52 \pm 1.27$ , Mean Basophils were  $0.54 \pm 0.58$ , Mean Monocytes were  $5.25 \pm 6.74$ , Mean value of PLT were  $245.49 \pm 121.66$  ( $240 \times 10^6/L$ ), Mean of Eosinophils to lymphocyte ratio (ELR) was  $0.05 \pm 0.11$ , Mean of Lymphocyte to Monocytes Ratio (LMR) were  $2.73 \pm 3.50$ , Mean CRP were  $122.49 \pm 112.30$  gm/dL, and the mean value of D-Dimer in patients was found  $1905.29 \pm 2594.93$  (Table 1, Figure 1).

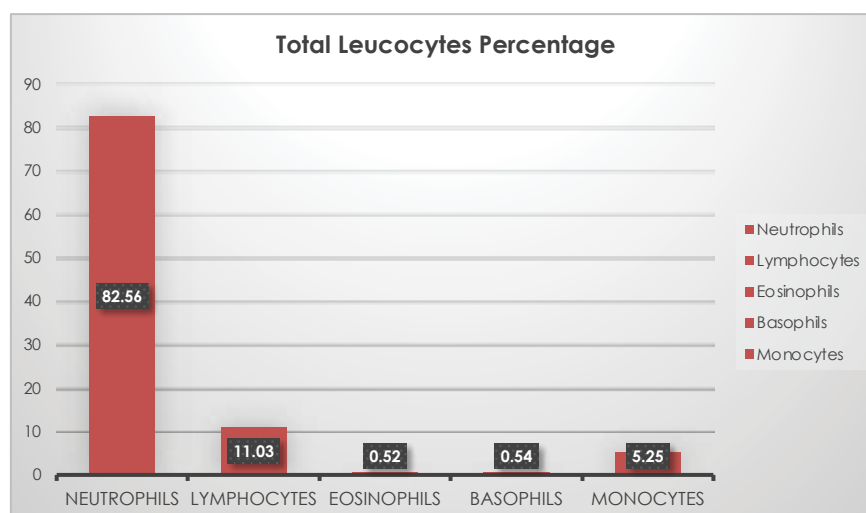


Figure 1: Total leucocytes percentage of the research participants.

Table 1: Mean of demographics and laboratory parameters to predict Covid-19 disease.

Variables		Mean $\pm$ SD/ Frequency n (%)
Gender	Male	311(62.6%)
	Female	186(37.4%)
Hemoglobin (Hb) (gm/dL)		12.40 $\pm$ 5.38
Total Leucocytes counts (TLC) ( $\times 10^3/L$ )		11.74 $\pm$ 6.46
Neutrophils (%)		82.56 $\pm$ 12.0
Lymphocytes (%)		11.03 $\pm$ 8.26
Eosinophils (%)		0.52 $\pm$ 1.27
Basophils (%)		0.54 $\pm$ 0.58
Monocytes (%)		5.25 $\pm$ 6.74
Platelets ( $\times 10^6/L$ )		245.49 $\pm$ 121.66
Eosinophil to Lymphocyte ratio (ELR)		0.05 $\pm$ 0.11
Lymphocyte to Monocytes ratio (LMR)		2.73 $\pm$ 3.50
C-reactive protein (CRP) (gm/dL)		122.49 $\pm$ 112.30
D-Dimer		1905.29 $\pm$ 2594.93

About the association of age and laboratory considerations with gender, the mean age of males was found 52.25±27.52 years, whereas in females it was observed 55.20±25.77 years with an insignificant difference ( $p=0.114$ ) between them. The results showed the value of Hemoglobin (Hb) 13.06±6.55 gm/dL in males and 11.30±1.92 gm/dL in females with an insignificant difference ( $p=0.332$ ) between them, Mean Total Leucocytes Counts (TLC) was observed 11.99±6.79 ( $\times 10^3/L$ ) in males and 11.32±5.87 ( $\times 10^3/L$ ) in females, the mean value of Neutrophils 82.91±12.36 in males and 81.98±11.40 in females, with insignificant difference between males and females ( $p=0.293$ ). The Mean value of Lymphocytes was observed at 10.49±8.11 in males and 11.93±8.47 in females with an insignificant difference ( $p=0.842$ ), between both genders, wherein the mean value of Eosinophils was found 0.53±1.24 in males and 0.51±1.34 in females with the insignificant difference ( $p=0.683$ ) between them. The mean value of

Basophils was 0.57±0.54 found in males and 0.49±0.63 in females with an insignificant difference ( $p=0.471$ ) between them. The mean value of Monocytes 5.40±8.17 % was observed in males and 4.99±3.14 in females, the mean value of PLT 248.70±130.61 ( $240 \times 10^6/L$ ) in males and 240.16±105.19 ( $240 \times 10^6/L$ ) in females, with the insignificant difference between them ( $p=0.189$ ). Moreover, the mean Eosinophil to lymphocyte ratio (ELR) was observed at 0.05±0.11 in males and 0.04±0.11 in females with an insignificant difference ( $p=0.627$ ), whereas the mean value of lymphocyte to monocytes ratio (LMR) were observed 2.44±2.07 in males and 3.21±5.02 in females with the significant difference ( $p=0.011$ ) between both the genders. Furthermore, an insignificant association was observed in the mean of CRP and D-Dimer in males and females, ( $p=0.902$  and  $p=0.416$  respectively) (Table 2).

**Table 2: Association of age and laboratory parameters with gender.**

Variable	Male Mean±SD	Female Mean±SD	p-Value
Age (years)	52.25±27.52	55.20±25.77	0.114
Hemoglobin (Hb) (gm/dL)	13.06±6.55	11.30±1.92	0.332
Total Leucocytes counts (TLC) ( $10^3/L$ )	11.99±6.79	11.32±5.87	0.116
Neutrophils (%)	82.91±12.36	81.98±11.40	0.293
Lymphocytes (%)	10.49±8.11	11.93±8.47	0.842
Eosinophils (%)	0.53±1.24	0.51±1.34	0.683
Basophils (%)	0.57±0.54	0.49±0.63	0.471
Monocytes (%)	5.40±8.17	4.99±3.14	0.446
Platelets ( $\times 10^6/L$ )	248.70±130.61	240.16±105.19	0.189
Eosinophil to Lymphocyte ratio (ELR)	0.05±0.11	0.04±0.11	0.627
Lymphocyte to Monocyte ratio (LMR)	2.44±2.07	3.21±5.02	0.011
C-reactive protein (CRP) (gm/dL)	125.68±111.51	117.0±113.78	0.902
D-Dimer	1847.85±2470.80	2010.85±2814.15	0.146

## DISCUSSION

The results of the present study showed that LMR, ELR, and CRP levels might be effective tools for diagnosis. It has also been observed that LMR, ELR, and CRP levels were found high in patients infected with COVID-19 due to pro-inflammatory cytokines that have also been revealed in some former

studies<sup>15,16</sup>. One study reported that the patients presented with critical illness, and the number of male patients were more significantly prone to the disease severity compared with female patients. Therefore, their eosinophil counts were checked, and it was found that the eosinophil counts and ratios in male patients had significantly lower levels

than those of female patients<sup>17</sup>. Inconsistent with that finding, the present study reported that statistically insignificantly lower levels of eosinophil counts were found between both male and female patients ( $p=0.683$ ).

Though, numerous studies have assessed the function of eosinophils in COVID-19 patients. Santotoribio et al. revealed that "blood counts of eosinophils levels might be a biomarker for the diagnosis of suspected COVID-19 patients"<sup>18</sup>. Another study by Zhao et al. has written: "there is a significant association between Eosinopenia and severe COVID-19 ( $p=0.006$ )"<sup>19</sup>. As far as the present study is concerned, it was reported that eosinophil count in the blood can be used as a biomarker for the diagnosis of suspected COVID-19 in patients but there was an insignificant association between males and females ( $p=0.683$ ).

One more study by Du et al. observed 85 serious COVID-19 cases in Wuhan, China, and concluded that "eosinopenia may perhaps demonstrate a poor prognosis"<sup>20</sup>. Sun et al. have reported that "a strong investigation of eosinophil counts supported the prognosis of severe cases of COVID-19"<sup>21</sup>. Lu and Wang have observed that "after admittance, eosinophils levels of patients with COVID-19 were extremely low during the first 10 days and their numbers were improved after admission at 12 days, earlier than other biomarkers that can be a significant marker for the progress of the disease"<sup>22</sup>. The present study was inconsistent with the above-cited studies and revealed that eosinophils help in the prognosis of severe COVID-19 cases but Eosinophil to lymphocyte ratio (ELR) had an insignificant association between males and females ( $p=0.627$ ).

Studies recommended that prolonged eosinopenia after admittance shows a relationship with low rates of improvement<sup>23,24</sup>. However, the eosinopenia resolution might be a sign of clinical status progression<sup>25,26</sup>. Likewise, in one study, an insignificant role of eosinophils in the prognostication of COVID-19 was observed. In this study, median eosinophil counts were found to be statistically insignificant between male and female patients<sup>27</sup>. The present study was in agreement with the above-mentioned study and revealed that the role of eosinophils in the prognosis of COVID-19 was found to be insignificant. There was no statistically significant difference between the median eosinophil counts in males and females ( $p=0.683$ ).

Currently, investigators have reported some ratios in the prognosis and diagnosis of many disorders of inflammation; platelet/lymphocyte, monocyte/lymphocyte, and neutrophil/lymphocyte ratios are some of the examples<sup>28</sup>. Yang et al. assessed confirmed 69 non-severe and 24 severe cases infected with COVID-19 and revealed that the association in age, WBC count, NLR, LMR, PLR, CRP, and d-NLR (derived NLR ratio) were found significantly higher in severe cases than the those of non-severe cases, however, the lymphocyte count

was observed to be significantly lower<sup>28,29</sup>. As far as the present study is concerned, there was a statistically insignificant age difference, WBC count, Eosinophil to Lymphocyte Ratio (ELR), and C-reactive protein (CRP) in both genders, whereas the statistically significant association was reported in lymphocyte to monocyte ratio (LMR) ( $p=0.011$ ) in both the genders.

Similarly, another study reported that the Hemoglobin level in confirmed COVID-19 patients was shown to be significantly higher as compared to the patients who had no COVID-19 infection. In addition, an insignificant difference was observed in female COVID-19 patients, while higher Hemoglobin levels were detected in male patients. The study also reported that in females, Hemoglobin level was also lower than in male COVID-19 patients<sup>30</sup>. Our study findings were inconsistent with the above-mentioned study and shows an insignificant difference ( $p=0.332$ ) between males and females regarding hemoglobin levels while the mean level of hemoglobin was slightly raised in males as compared to females. Therefore, more multicenter prospective studies need to elucidate the function of eosinophils and ELR as biomarkers in the clinical development of COVID-19 patients.

## CONCLUSION

The role of eosinophils as a diagnostic predictor is insignificant. Furthermore, an insignificant association was found in Eosinophil to lymphocyte ratio, whereas a significant association was reported in the lymphocyte-to-monocyte ratio between males and females. Further studies are needed to clarify the probable role of Eosinophils and Eosinophil to lymphocyte ratio as biomarkers in the early identification of COVID-19 infection.

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## CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

## ETHICS APPROVAL

The study approval was obtained by the institutional ethics review board.

## PATIENT CONSENT

Informed consent (written and verbal) was taken from all the parents included in the study.

## AUTHORS' CONTRIBUTION

All authors equally contributed to this research study.

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