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Association of Lymphopenia Severity with Clinical Outcomes in Patients with COVID-19

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ABSTRACT

Lymphopenia is a decrease in the number of circulating lymphocytes. Often, the number of lymphocytes decreases in patients with COVID-19. This study aimed to investigate the association between lymphopenia severity and clinical outcomes in patients with COVID-19. A total of 196 COVID-19 patients with a mean age of 53.18 years were included in this cross-sectional study. Patients were over 18 years of age with a positive PCR test or arterial blood oxygen less than 92% requiring oxygen who referred to the emergency department of Payambar-e-Azam Kerman Hospital in 2021. Then the patients were classified and matched into 4 groups based on the number of lymphocytes. Demographic variables, clinical information related to lymphocyte count, length of hospitalization, disease severity, need for ventilation, patient outcome, and arterial blood oxygen saturation were recorded using patient records. Patients with mild lymphopenia had a higher average age (57.33 years) than the other groups. Patients with severe lymphopenia were mostly in the acute respiratory phase (42.9%). A total of one person among the examined people was admitted to the ICU, who was placed in the severe category in terms of lymphopenia. 173 of the examined people needed ventilation. Interestingly, patients with severe lymphopenia had a lesser mean arterial blood oxygen saturation (90.71) than the other groups. Patients with severe lymphopenia had a higher average length of hospitalization than the other groups and had a higher average high-resolution computed tomography (HRCT) than the other groups. The severity of lymphopenia was not significant according to gender, but it was significant according to age, disease severity, disease severity, ICU hospitalization, disease outcome, arterial blood oxygen, length of hospitalization, and HRCT. These results suggest that lymphopenia and its severity may serve as reliable predictors for clinical outcomes in managing COVID-19 patients.

Keywords: Absolute lymphocyte count, COVID-19, ICU, Lymphopenia, HRCT, Oxygen saturation.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent behind the highly infectious and deadly disease known as coronavirus disease 2019 (COVID-19) (1). Based on the latest data from the World Health Organization (WHO), as of March 15, 2024, there have been over 774 million reported cases of COVID-19 globally since the start of the pandemic, and the total number of excess deaths due to COVID-19 is estimated to be two to four times higher than the reported number of confirmed deaths, with a global figure of around 18 million excess deaths (2). COVID-19 is transmitted through droplets, close contact, aerosol, and perhaps fecal-oral transmission, and patients can transmit the virus to other people during the incubation period (3, 4). The clinical signs of COVID-19 include fever (82.0 % prevalence), cough (54.3% prevalence), dyspnea or shortness of breath, which is a significant symptom, particularly in severe cases, fatigue (30.2% prevalence), sputum production (28.5% prevalence), sore throat (21.7% prevalence), and headache (11.0% prevalence). Laboratory signs of COVID-19 include abnormal creatinine levels, high blood pressure, high glucose levels, high CPK levels, high ALT values, lymphopenia, and eosinopenia, which are all significant indicators of the severity of the disease (2, 5-8).

Lymphopenia, a condition characterized by a significant decrease in lymphocyte count, has been identified as a prominent feature of severe coronavirus disease 2019 (COVID-19) infections. The association between lymphopenia and the severity of COVID-19 has been extensively studied, and the results consistently indicate that lymphopenia is a strong predictor of poor outcomes in patients with COVID-19 (9, 10). The clinical significance of lymphopenia in COVID-19 is significant, as it can be used as a biomarker to predict disease severity and outcomes (11, 12). A study by Tan et al. found that lymphopenia was a strong predictor of disease severity and 30-day mortality in patients with COVID-19 (13). Similarly, a meta-analysis by Huang et al. showed that patients with lymphopenia had a nearly threefold increased risk of severe COVID-19 compared to those without lymphopenia (10).

The mechanisms underlying lymphopenia in COVID-19 are not yet fully understood, but several factors have been implicated. One key factor is that the virus may directly infect lymphocytes, causing their death, as lymphocytes express the coronavirus receptor ACE2, making them potential targets for the virus. Also, the virus might directly damage lymphatic organs. Acute lymphocyte decline could be linked to lymphocytic dysfunction, and the novel coronavirus might directly harm organs like the thymus and spleen. This hypothesis requires future confirmation through pathological dissection. Moreover, disordered inflammatory cytokines may lead to lymphocyte apoptosis. Basic research has shown that pro-inflammatory cytokines such as tumor necrosis factor (TNF)α and interleukin (IL)-6 can induce lymphocyte deficiency. Finally, metabolic molecules produced by metabolic disorders, such as elevated lactic acid levels, may inhibit lymphocytes. Severe COVID-19 patients often have high blood lactic acid levels, which might suppress lymphocyte proliferation (13-16).

Lymphopenia is a common feature of severe COVID-19, with studies reporting lymphopenia in up to 80% of patients admitted to intensive care units (ICUs). The severity of lymphopenia has been linked to various clinical outcomes, including the need for mechanical ventilation, ICU admission, and mortality. One study found that patients with severe lymphopenia (lymphocyte count < 200 cells/μL) had a significantly higher risk of developing severe COVID-19 and requiring ICU admission compared to those with mild lymphopenia (lymphocyte count 200-500 cells/μL).

Several studies have investigated the association between lymphopenia severity and clinical outcomes in COVID-19 patients. A study examined the effect of baseline immunosuppression on COVID-19 mortality

and the role of severe lymphopenia in immunocompromised individuals. The study included patients admitted with COVID-19 to a tertiary hospital in Madrid between March 1st and April 30th, 2021. Researchers analyzed and compared epidemiological and clinical data, including cases of severe lymphopenia (<500 lymphocytes/μL) during admission, based on patients' baseline immunosuppression status. The study involved 1594 patients with COVID-19 pneumonia, of whom 166 (10.4%) were immunocompromised.

Immunocompromised patients were younger (64 vs. 67 years, p = 0.02) but had higher rates of hypertension, diabetes, and heart, neurological, lung, kidney, and liver diseases (P<0.05). The study concluded that immunosuppression is an independent risk factor for mortality in COVID-19 and that severe lymphopenia in these patients should be promptly identified (17). Other studies found that severe lymphopenia was associated with a longer duration of hospitalization and a higher risk of developing secondary infections (18, 19). Given the emergence of new variants of the COVID-19 virus, the lack of complete immunity to this virus despite vaccination, and the high mortality rates associated with it, there remains a need to clarify potential approaches that can reduce the number of severe COVID-19 cases and consequently decrease the mortality rate of this disease. Therefore, identifying biomarkers that can predict disease severity and prognosis is essential for guiding clinical care. Therefore, early identification of lymphopenia can help clinicians identify high-risk patients who may require more aggressive treatment and closer monitoring.

Additionally, monitoring lymphocyte counts can provide valuable information for guiding treatment decisions, such as the use of immunomodulatory therapies to mitigate the cytokine storm. Considering the impact of COVID-19 on the immune system and the decrease in lymphocyte count in predicting and assessing the progression of this disease, the present study aimed to investigate the relationship between lymphopenia and prognosis in COVID-19 patients at Payambar-e-Azam Hospital in Kerman during the first six months of 2021.

MATERIAL AND METHODS

Patients and Grouping

The present study is a descriptive-cross-sectional study, conducted on COVID-19 patients referring to Payambar-e-Azam Hospital in Kerman in the year 2021. The inclusion criteria for participation in the research comprised individuals aged over 18 years, with a positive PCR-RT test for COVID-19 virus, or patients necessitating oxygen therapy with blood oxygen saturation less than 92%. Exclusion criteria encompassed patients with a history of previous lymphopenia due to other pathologies such as AIDS, tuberculosis, lupus, sarcoidosis, Hodgkin's lymphoma, aplastic anemia, etc., as well as incomplete medical records and patient information in the study. Based on these criteria, 196 patients were recruited.

Study Parameters

The research variables included depression, age, gender, platelet count, disease severity, arterial blood oxygen saturation, length of hospital stay, admission to intensive care units, need for ventilation, patient outcome, and lung involvement severity. After obtaining ethical approval from the Research Deputy of the Azad University Kerman Branch University (IR. IAU. KERMAN. REC. 1401. 029), the researcher commenced the study by presenting the necessary documents to the hospital's clinical supervisors and managers. The study population comprised all COVID-19-infected patients hospitalized at Payambar-e-Azam Hospital from April to September 2021. Sampling will be random from the available samples. After sample selection, the researcher will gather demographic data (age, gender) and clinical information related to their first CBC test (lymphocyte count) using patient records. Then, patients will be categorized into four groups based on lymphocyte count. Group 1: Severe lymphopenia (absolute lymphocyte count (ALC) < 500 cells/μL), group 2: moderate lymphopenia

(ALC 500-1000 cells/µL), group 3: mild lymphopenia (ALC < 1500 cells/µL), and the fourth group without lymphopenia (ALC >1500 cells/µL). Subsequently, clinical symptoms and patient pre-notification information, including disease severity, arterial blood oxygen saturation upon admission, length of hospital stay, admission to intensive care units, need for ventilation, and patient outcome, will be extracted from patient records. Then, along with a radiologist and an infectious disease specialist, the researcher will examine the findings of the first chest CT scans of the samples, calculate the severity of radiographic findings for each sample, and record them in the questionnaire. A scoring system based on the involvement area, according to the study by Wang et al., will be assigned to determine the extent of lung involvement.

Statistical Analysis

The analysis of the data involves describing the research variables using frequency distributions and descriptive statistics. In the data analysis section, the research hypothesis was examined. Before hypothesis testing, the normality (having a normal distribution) of the study variables was assessed using the Kolmogorov-Smirnov test. To investigate the research questions, an independent t-test and chi-square test were used. For data analysis, SPSS version 20 software was utilized, and a significance level of 0.05 was considered as a statistical difference.

RESULTS

Relationship between lymphopenia and demographic data in patients

In this study, 196 patients with COVID-19 were enrolled, of whom 103 (52.6%) were male and 93 (47.4%) were female, with a mean age of 53.18 years. Most patients were in the moderate respiratory phase, with 92 individuals (46.9%). One patient was admitted to the ICU, and 173 patients (88.3%) required ventilation. 174 patients (88.8%) were discharged, while 22 patients (11.2%) died. In terms of lymphopenia, 102 patients (52%) did not have lymphopenia, 3 patients (1.5%) had mild lymphopenia, 84 patients (42.9%) had moderate lymphopenia, and 7 patients (3.6%) had severe lymphopenia. According to Table 1, in patients with mild and moderate lymphopenia, the frequency of males was higher than that of females, but in severe lymphopenia, the frequency of females was higher than that of males. However, no significant relationship was found between lymphopenia and gender. Regarding age comparison, patients with mild lymphopenia had a higher average age (57.33 years) compared to the other groups, and this relationship was statistically significant (P < 0.01).

Table 1

Determining the association between lymphopenia and gender and age in COVID-19 Patients.

Demographic information	Lymphopenia					P value
	Normal	Mild	Moderate	Severe	Total	
Male No. (%)	50 (49)	2 (66.7)	48 (57.1)	3 (42.9)	103 (52.6)	0.632
Female No. (%)	52 (51)	1 (33.3)	36 (42.9)	4 (57.1)	93(47.4)	
Age ± SD	50.93±15.19	57.33±10.78	56.82±15.52	40.57±11.10	53.18±15.53	**0.008**

Relationship between lymphopenia and stage of the disease

Table 2 shows that in patients without lymphopenia, most were in the initial stages of infection (9.52%), in patients with mild lymphopenia mostly in the moderate respiratory phase (100%), in patients with moderate lymphopenia mostly in the moderate respiratory phase (56%), and in patients with severe

lymphopenia mostly in the acute respiratory phase (9.42%).

The results indicate a significant difference between lymphopenia and the severity of the disease (P value = 0.001).

Table 2

Determining the association between lymphopenia and stage of the disease in COVID-19 Patients.

Stage of the disease	Lymphopenia					P value
	Normal No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)	Total No. (%)	
Early stages of infection	54 (52.9)	0	16 (19)	0	70 (35.7)	**0.001**
Moderate respiratory phase	40 (39.2)	3 (100)	47 (56)	2 (28.6)	92 (46.9)	
Critical phase	1 (1)	0	6 (7.1)	3 (42.8)	10 (5.1)	
Severe phase	7 (6.9)	0	15 (17.9)	2 (28.6)	24 (12.2)	

Relationship between lymphopenia and ventilation, ICU admission, and mortality

173 individuals (125 nasal cannula, 8 intubation, 38 mask, and 2 Non-invasive ventilation (NIV)) required ventilation. Among them, 82 individuals (65 nasal cannula, 16 mask, and 1 NIV) did not have lymphopenia, 3 individuals in the mild lymphopenia group (2 nasal cannula and 1 NIV), 82 individuals in the moderate lymphopenia group (57 nasal cannula, 5 intubations, 19 mask, and 1 NIV), and 6 individuals in the severe lymphopenia group (1 nasal cannula, 3 intubations, and 2 mask) required ventilation. This relationship was statistically significant (P value = 0.003). From a recovery or mortality point of view, 174 individuals (8.88%) of the samples were discharged. Among them, 97 individuals did not have lymphopenia, 3 individuals had mild lymphopenia, 70 individuals had moderate lymphopenia, and 4 individuals with severe lymphopenia were discharged. On the other hand, 22 patients died, 42% of whom were from the severe lymphopenia group.

This association was statistically significant (P value= 0.003). All data in this section are summarized in Table 3.

Table 3

Determining the relationship between lymphopenia with ICU admission, need for ventilation, and percent of recovery/death in COVID-19 Patients.

Outcome	Lymphopenia					P value
	Normal No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)	Total No. (%)	
Ventilator +	82 (84)	3 (100)	82 (97.6)	6 (85.7)	173 (88.3)	**0.003**
Ventilator -	20 (19.6)	0	2 (2.4)	1 (14.3)	23 (11.7)	
ICU +	0	0	0	1 (14.3)	1 (0.5)	**0.001**
ICU -	102 (100)	3 (100)	84 (100)	6 (85.7)	195 (99.5)	
Recovery	97 (95.1)	3 (100)	70 (83.3)	4 (57.1)	174 (88.8)	**0.003**
Death	5 (4.9)	0	14 (16.7)	3 (42.9)	22 (11.2)	

Relationship between lymphopenia and clinical parameters of patients

According to Table 4, patients with severe lymphopenia had the lowest mean arterial oxygen saturation level (84.89±11.84) compared to the other groups, and this relationship was statistically significant (P value < 0.05). Moreover, patients with severe lymphopenia had a higher mean length of hospital stay (10.14±8.23 days) compared to the other groups, and this relationship was statistically significant (P value < 0.001). The relationship between high-resolution computed tomography (HRCT) severity and lymphopenia was also determined. The result of this part showed patients with severe lymphopenia had a higher mean HRCT score (12.42±4.39) compared to the other groups, and this relationship was statistically significant.

Table 4

Determining the relationship between lymphopenia with arterial blood oxygen saturation level, length of hospitalization, and HRCT Severity in patients with COVID-19.

Clinical Parameters	Lymphopenia					P value
	Normal ± SD	Mild ± SD	Moderate ± SD	Severe ± SD	Total ± SD	
Blood oxygen saturation level (%)	89.28±8.99	90.71±3.25	86.33±12.66	84.89±11.84	87.40±10.42	**0.029**
Length of hospitalization (Day)	4.61±2.32	7.33±1.15	5.51±2.97	10.14±8.23	5.23±3.13	**0.001**
HRCT Severity	4.71±3.7	3.66±0.57	7.92±4.99	12.42±4.39	6.34±4.71	**0.001**

DISCUSSION

In this study, 196 patients with COVID-19 were investigated from the point of view of lymphopenia and the severity of clinical outcomes. The mean age of the patients was 53.18 years, and the frequency of males was higher than that of females, but not significantly so. Almost all patients were in the moderate respiratory phase, and just one patient was admitted to the ICU, who was classified as having severe lymphopenia, while 173 patients (88.3%) required ventilation. Finally, 174 patients (88.8%) were discharged, and 22 patients (11.2%) died. Regarding lymphopenia, 102 patients (52%) had no lymphopenia, 3 patients (1.5%) had mild lymphopenia, 84 patients (42.9%) had moderate lymphopenia, and 7 patients (3.6%) had severe lymphopenia. In patients with mild and moderate lymphopenia, the frequency of males was higher than that of females, but in severe lymphopenia, the frequency of females was higher than that of males. Patients with mild lymphopenia had a higher mean age (57.33 years) compared to other groups. In patients without lymphopenia, most were in the early infection stages (52.9%), and in patients with mild lymphopenia, most were in the moderate respiratory phase (100%), in patients with moderate lymphopenia, most were in the moderate respiratory phase (56%), and in patients with severe lymphopenia, most were in the acute respiratory phase (42.9%). Patients with severe lymphopenia had a longer mean hospital stay (10.14 days) compared to other groups. Patients with severe lymphopenia had a higher mean HRCT score (12.42) compared to other groups. The severity of lymphopenia was not significant by gender, but by age, disease severity, ICU admission, disease outcome, arterial blood oxygen, length of hospitalization, and HRCT were significant. Several similar studies connect the severity and clinical signs of

COVID-19 to lymphopenia. Lee and colleagues in 2021 conducted a study to investigate lymphopenia as a biological predictor in COVID-19 patients throughout Korea. The study findings showed that mortality was significantly associated with the severity of lymphopenia: 40% in the severe lymphopenia group, 22.7% in the moderate lymphopenia group, and 13% in the mild lymphopenia group. 40% of patients with severe lymphopenia, 24.5% of patients with moderate lymphopenia, and 14% of patients with mild lymphopenia required ventilation. Therefore, their study results indicated that lymphopenia and its severity may serve as a reliable predictor for clinical outcomes in managing COVID-19 patients (11). The results of their study are consistent with the current study.

Ghizlane and colleagues in 2021 enrolled 589 patients, with one group having lymphopenia with 357 cases (60.6%) and the non-lymphopenia group with 232 cases (39.4%). The mean age of patients with lymphopenia was 65 years (range 56-76). High blood pressure and diabetes were observed in most patients with lymphopenia compared to the non-lymphopenia group. Lymphopenia was significantly associated with COVID-19 inflammatory biomarkers. Moreover, a significant association was observed between the lymphopenia group and CT scans, and lymphopenia was observed as a long-term hospitalization indicator, but it was not significant (20). Similarly, Tan Li *et al*. analyzed dynamic changes in blood lymphocyte percentage (LYM%) in 15 deceased cases, 15 severe cases, and 40 moderate cases of COVID-19 patients in a retrospective manner. The results showed that LYM% in blood tests had an inverse correlation with the severity and prognosis of COVID-19 (13). In another study conducted by Wagner *et al*., lymphocytopenia, with an odds ratio of 3.40, was more common in patients admitted to the ICU, indicating severe disease, compared to those not in the ICU (12). A similar result could be obtained from our study.

Elhassadi *et al*. (2020) reported that 150 (20%) patients with COVID-19 required hospitalization due to severe illness. Among these, 11 patients (1.4%) were admitted to the ICU. The mortality rate in this group was 2.4% (35 patients), with 29 of these individuals being over 60 years old. The impact of lymphopenia on disease severity and mortality was more pronounced in older populations. Therefore, older age and lymphocytopenia may collectively serve as predictors of poor prognosis in COVID-19 patients (21). Likewise, Huang *et al*. found that 25% of COVID-19 patients had leukopenia and 63% had lymphocytopenia. Abnormalities in chest CT images were observed in 100% of the patients. Lymphocytopenia was associated with disease severity (22).

In a retrospective study conducted by Chen *et al*., at the time of admission, the number of lymphocytes, T cell subsets, eosinophils, and platelets was significantly reduced, especially in severe/critical and fatal patients. An increase in neutrophils and the neutrophil-to-lymphocyte ratio (NLR) was predominant in severe/critical or non-surviving patients. During hospitalization, eosinophils, lymphocytes, and platelets showed an increasing trend in survivors, indicating that the recovery of these levels could predict recovery, whereas the gradual increase in neutrophils, basophils, and IL-6 was associated with fatal outcomes (23).

Yuan *et al*. attempted to identify changes in hematologic and immunologic parameters in COVID-19 patients by collecting and analyzing data from 117 patients with laboratory-confirmed SARS-CoV-2 infection. Based on China's sixth edition of the COVID-19 diagnosis and treatment plan, patients were categorized into normal, severe, and critical groups. Laboratory tests included routine blood tests, cellular and humoral immunity indicators, biochemical diagnostics, and inflammatory biomarkers. Compared to normal patients, severe and critical patients had significantly lower lymphocyte counts, red blood cells, hemoglobin, and immunoglobulin G levels, while levels of D-dimer, fibrinogen, white blood cells, neutrophils, and interleukin-6 were significantly higher (24). Liao *et al*. found that the incidence of thrombocytopenia was significantly higher in patients with severe

disease (49% vs. 6%), and increased D-dimer levels, a higher neutrophil-to-lymphocyte ratio, and thrombotic and hemorrhagic events were common complications in deceased patients (25). Similarly, in the Fan *et al*. study, 69 Chinese patients with COVID-19 demonstrated leukopenia (29.2% of patients) (26). In a study of 1099 patients in China, 33.7% had leukopenia; this rate was 61.1% in severe cases (173 individuals) and 28.1% in non-severe cases (926 cases) (27). In agreement with the results of the present study, it can be concluded that all studies have found a significant association between lymphopenia and outcomes in COVID-19 patients. Minor differences between studies may arise from variations in the frequency of different admission criteria, definitions of lymphopenia, and sample sizes.

CONCLUSION

The study had some limitations, including its retrospective nature of the study, short follow-up period, and lack of information on treatment types and timing. Moreover, the study could not establish the cause of lymphopenia among confirmed individuals. Nonetheless, the study focused on the association between COVID-19 outcomes and limited variables, including laboratory findings. Despite these limitations, the study found a significant association between lymphopenia and severity of illness and mortality in COVID-19 patients, even after adjusting for confounding factors. In our study, the severity of lymphopenia was not significant based on gender, but it was significant based on age, disease severity, ICU admission, patient outcomes, arterial blood oxygen levels, duration of hospitalization, and HRCT. Our results indicated that lymphopenia could be a critical parameter. Therefore, lymphopenia and its severity levels can serve as reliable predictors of clinical outcomes in the management of COVID-19 patients. Dynamic monitoring of lymphocyte counts upon admission and during hospitalization is necessary. Additionally, for patients with severe lymphopenia, early hospital admission and consideration of current treatment options should be prioritized.

Transparency declaration

There is no conflict of interests.

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