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Direct Correlation of Lymphopenia with Severity Scores and Chest CT Findings in COVID-19 Patients

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Abstract

Background: As COVID-19 severity and related death is a challenging issue, the protective effect and predictive value of lymphocyte count are critical.

Objectives: The present study investigated the importance of lymphopenia on disease severity and death rate.

Methods: This retrospective cross-sectional study was performed from April 2020 to June 2020 on a total of 300 patients with confirmed COVID-19 who attended the Firoozgar Hospital affiliated with the Iran University of Medical Sciences, Tehran, Iran. All of the COVID-19 patients referred to the hospital during the study period and met the inclusion criteria were enrolled and divided into two groups of lymphopenia (lymphocyte count less than 1.0×109/L) (n=138) and non-lymphopenia (n=162). All patient data from the medical records were acquired and utilized for statistical analysis.

Results: Of 300 patients 63.3% were male and 72% had underlying disease. The most common symptoms were dyspnea (50%), cough (41%), and lethargy (40%). Lymphopenia was associated with male gender (P=0.01). Additionally, mean age (P=0.02), ventilator need (P=0.03), and death (P=0.05) were significantly associated with lymphopenia compared to the non-lymphopenia group. The Lymphopenia group had lower levels of O2 saturation (P=0.04), AST (P=0.001), and ALT levels (P=0.02). Based on the chest CT scan results, there was a significant relationship between lymphopenia and the extent of pulmonary involvement (P=0.004)

Conclusion: Lymphopenia could clinically predict the severity of COVID-19. Lymphopenia was associated with male gender, older age, ventilator need, and death. Lymphopenia status had a significant relationship with reduced levels of O2 saturation, AST, ALT, and the extent of pulmonary involvement.

Keywords: COVID-19, Lymphopenia, Severity of illness index

1. Background

As of December 2019, COVID-19 was first reported in Wuhan, China, and then rapidly spread throughout the entire world. It is noteworthy that the clinical manifestations of COVID-19 are varied. These include asymptomatic carriers, those with mild symptoms, and with severe forms of acute viral pneumonia that can lead to acute respiratory distress syndrome. It has been found that hospitalization in the intensive care unit increases the risk of death (1).

Lymphocytes play an important role in the regulation of cellular immunity, especially in viral infections. As lymphopenia is associated with the severe acute respiratory syndrome coronavirus 2 infection, it adversely affects the mortality of patients with the disease (2). In COVID-19, major causes of lymphopenia include low activity of lymphatic organs, as well as lymphocyte exhaustion by apoptosis or other mechanisms by cytokines and the virus. These conditions could exacerbate the patient presentations and outcomes (3).

The lymphocyte count as a simple, cheap, routine, and available tool in each laboratory is used for COVID-19 diagnosis as first described (4). Generally, lymphopenia is associated with more severe cases of COVID-19 and mortality (5, 6). It has been reported that there was a lower amount of CD3+, CD4+, and CD8+ lymphocytes in severe cases compared to those with a milder disease (1). Lymphopenia could be a useful predictive factor for assessing the severity and recovery process of a disease (7). In severe cases, lymphocyte count increased before C-reactive protein (CRP) and chest radiograph elevation, indicating that it can help predict disease improvement. Lymphopenia is also clinically important for forecasting the severity and recovery of COVID-19, which highlights the need to keep track of lymphocyte count changes (8). Additionally, patient mortality may be linked to lymphocyte count below 20% and more than 50% lung involvement in chest computed tomography (CT) scan. These may serve as laboratory and clinical markers of disease severity, mortality, and outcome (9).

In this study, we aimed to examine the association between the level of lymphopenia and the severity and lung lesions of COVID-19 patients, using a retrospective cross-sectional design. We hypothesized that patients with lower lymphocyte counts would have more severe disease and more extensive lung involvement, as measured by the CT scan, than patients with higher lymphocyte counts. We also hypothesized that the changes in lymphocyte count over time would correlate with the changes in lung lesions and clinical outcomes. To test these hypotheses, we analyzed the data of 300 COVID-19 patients who were admitted to our hospital between April and June 2020, and who underwent blood tests and chest CT scans at admission and discharge. We compared the lymphocyte counts and the CT findings between different groups of patients based on their disease severity and outcome. We performed regression analyses to explore the relationship between these variables.

2. Objectives

The present study investigated the importance of lymphopenia on disease severity and death rate.

3. Methods

Patients and setting

In this retrospective cross-sectional study, 300 patients who were admitted to Firouzgar Hospital affiliated with Iran University of Medical Sciences, Tehran, Iran, from April 2020 to June 2020 were enrolled. Eligible patients were COVID-19 cases diagnosed by positive reverse transcription polymerase chain reaction and CT scan results, and those who had complete data in the hospital's records, filled out informed consent forms, and were over 18 years old. All COVID-19 patients that referred to the hospital during the study period and met the inclusion criteria were enrolled. Patients with a history of blood malignancies and lung disease (except for asthma and chronic obstructive pulmonary disease) were excluded. A checklist including laboratory and clinical data was filled out for each participant. This checklist included the duration of symptoms before hospitalization, age, the clinical signs and symptoms, underlying diseases, smoking status, and laboratory tests (white blood cell count [WBC], CRP, erythrocyte sedimentation rate [ESR], Red blood cell distribution width [RDW], lymphocyte count and percentage, aspartate aminotransferase [AST], alanine transaminase [ALT], dehydrogenase lactate [HDL], total bilirubin, creatinine, platelets, and hemoglobin).

Based on the CT scan, the number of lung foci, lobes, the volume and extent of involvement, opacities glass ground, pattern paving-crazy, consolidation, nodule, cavity, and fibrosis and scar were included. Patients were divided into two groups according to lymphocyte count: the lymphopenia group (lymphocyte count was 1.0×10^9/L) and the non-lymphopenia group.

Statistical analysis

SPSS version 25 software was used for statistical analysis. Quantitative variables were described as mean, standard deviation, median, and range of changes, while qualitative variables were expressed as frequency statistics and frequency percentages. To compare quantitative data, an independent t-test was performed, and if the data were not normal, a Mann-Whitney test was applied. The comparison of qualitative data was achieved by performing a Chi-square test or Fisher's exact test. A p-value of < 0.05 was considered significant. The SPSS software was used to collect and analyze the obtained data.

4. Results

Among 300 cases, the mean age was 64.04±16.2 years (range 24 to 93 years). The majority of patients (63.3%) were male. According to the study, 72% (n=216) of the participants had underlying diseases, with the highest rates of co-morbidities being hypertension (n=120, 40%), diabetes (n=88, 29%), and heart disease (n=68, 22%) (Table 1). The most common symptoms reported by patients were dyspnea (n=150, 50%), cough (n=124, 41%), and lethargy (n=122, 40%) (Table 1).

The patients were categorized into two groups: 138 (46%) of the patients were in the lymphopenia group (lymphocyte $<1.0\times10^9$/ul), while 162 (54%) of the patients belonged to the non-lymphopenia group (lymphocyte $>1.0\times10^9$/ul). It was shown that gender played an important role in lymphopenia (P=0.01), and lymphopenia was more commonly found in men (63.3%) (P=0.01). Additionally, it was found that there was a significant association between the two groups in terms of mean age (P=0.02), ventilator need (P=0.03), and death (P=0.05), which was higher in the lymphopenia group (36.2%). The results of this study demonstrated that the lymphopenia group had lower levels of O_2 saturation (P=0.04), AST (P=0.001), and ALT levels (P=0.02), compared with the non-lymphopenia group. There was no relationship between lymphopenia and smoking, need for vasoconstrictive drugs, duration of disease onset to hospital admission, the level of CRP, creatinine, platelets, and other laboratory variables (P>0.05) (Table 2). Medication before referral was reported in 24.6% (74/300) cases, for which azithromycin was administered in 55.4% (41/74), hydroxychloroquine in 44.5% (33/74), and glucocorticoid in 40.5% (30/74).

Table 1. Patient's comorbidity and symptoms at the baseline

Comorbidities; (n=216)	n (%)	COVID19 symptoms	n (%)
Hypertension	120 (40)	Dyspnea	150 (50)
Diabetic	88 (29)	Cough	124 (41)
Heart disease	68 (22)	Lethargy	122 (40)
Cancer	34 (11.3)	Weakness	114 (38)
Chronic Kidney Disease	14 (4.6)	Fever	110 (36.6)
Chronic Obstructive Pulmonary Disease	12 (4)	Gastrointestinal symptoms	104 (34.6)
Asthma	11 (3.6)	Myalgia	65 (21.66)
Hypothyroid	9 (3)	Chills	55 (18.33)
Parkinson	7 (2.3)	Anorexia	35 (11.66)
Alzheimer	5 (1.6)	Dizziness	34 (11.33)
Gout	5 (1.6)		
End-stage renal disease	5 (1.6)		
Others*	10 (3.3)		

* 1 case per each of these diseases: Cerebrovascular Accident, Bronchitis, Thalassemia major, Posttraumatic Growth, Coaching, Rheumatoid Arthritis, Pulmonary Thromboembolism, Psoriasis, Kidney stone, Intrinsically Disordered Proteins (IDP)

Table 2. Characteristics of COVID-19 patients in total and between lymphopenia and non-lymphopenia groups

Variables	Total (n=300)	Lymphopenia	Non-lymphopenia	p-value
Age (year); Mean±SD	64.04±16.233 (24, 93)	67.16±15.456 (29,93)	61.32±16.5 (24,92)	**0.02**$^{\delta}$
Gender; n (%) Male	190 (63.3)	102 (73.9)	88 (54.3)	**0.01**$^{¥}$
Female	110 (36.7)	36 (26.1)	74 (45.7)	
Smoker; n (%)	30 (10)	14 (10.14)	16 (9.8)	0.99$^{¥}$
Ventilation need; n (%)	60 (20)	38 (27.5)	22 (13.5)	**0.03**$^{¥}$
Vasoconstrictive drug use; n (%)	52 (17.3)	32 (23.18)	20 (12.34)	0.22$^{¥}$
Death; n (%)	82 (27.3)	50 (36.23)	32 (19.75)	**0.05**$^{¥}$
Duration of disease onset to hospital admission (day); Mean±SD	7.43±7.18 (0, 30)	7.48±7.22 (1,30)	7.40±7.20 (0,30)	0.97^
Hospitalization (day); Mean±SD	11.05±6.23 (1,43)	10.71 (3,43)	11.33 (1,30)	0.33$^{€}$
Laboratory indexes; Mean±SD				
AST (U/l)	48.17±82.341 (10, 933)	48.07±31.688	48.26±108.51	**0.001^**
ALT (U/l)	41.30±64.28 (8, 745)	42.25±32.238	40.49±82.537	**0.02^**
WBC (µl/Cell)	8.78±6.09 (1.8, 43.8)	7.843±4.63	9.579±7.02	**0.011^**
RDW (%)	22.91±14.86 (11.7, 75.4)	23.46±15.84	22.46±14.06	0.52^
Hb (mg/dl)	12.06±2.51 (3.6, 21.3)	12.28±2.49	11.87±2.52	0.31^
LDH (U/l)	675.5±415.66 (203, ,2869)	733.97±454.11	626.06±376.205	0.17^
Total Bill (mg/dl)	0.963±1.34 (0.4,12.1)	0.939±0.81	0.984±1.69	0.09^
CRP (mg/l)	71.67±45.27 (6,194)	70.21	59.14	0.09^
Creatinine (Cr) (mg/dl)	1.515±1.39 (0.5-8)	1.68±1.56	1.37±1.22	0.09^
Platelet (×1000/mm^3)	214.41±99.99 (4,605)	201.43±94.65	225.44±103.63	0.09^
Vital parameters; Mean±SD				
Oxygen saturation	90.33±7.327 (60,100)	89.12±8.233 (60,100)	91.35±6.34 (68,98)	**0.04^**
Pulse rate	85.89±15.333 (25,150)	86.65±14.89 (60,150)	85.23±15.75 (25,126)	0.82^
Respiration rate	18.49±3.595 (12,30)	18.36±3.56 (12,30)	18.59±3.64 (12,30)	0.75^
Diastolic blood pressure	74.79±11.202 (25,115)	74.97±10.15 (55,115)	74.64±12.08 (25,100)	0.63^
Systolic blood pressure	121.56±18.051 (90,215)	122±18.764 (90,215)	121.19±17.53 (90,190)	0.97^

^ Mann-Whitney U; $^{¥}$ Chi-square; $^{€}$ Wilcoxon W; $^{\delta}$ t-test

CT imaging finding

Based on the radiographic changes among the subjects, the majority of cases had three foci in the lungs (66%), all of the two lungs were involved (82%), all of five lobes of the lungs were involved (42%), the extent of the lesions was about 25% (37.3%), and pleural effusion (80.6%) was observed. However, there was a significant relationship between lymphopenia and the extent of pulmonary involvement (P=0.004). There was a broader extent of pulmonary involvement in the lymphopenia group than in the non-lymphopenia group (Table 3).

Table 3. Different findings of CT images between two clinical groups

Variables n (%)	Total n=300	Lymphopenia n=138	non-lymphopenia n=162	P-value*
Number of foci in lungs				0.27
0	26 (8.6)	16 (11.59)	10 (6.17)	
1	16 (5.4)	6 (4.34)	12 (7.4)	
2	60 (20)	20 (14.49)	40 (24.69)	
3	198 (66)	96 (69.56)	102 (62.96)	
Number of involved lungs				0.1
0	24 (8)	16 (11.59)	6 (3.7)	
1	30 (10)	8 (5.79)	24 (14.81)	
2	246 (82)	114 (82.6)	132 (81.48)	
Number of involved lobes				0.51

Table 3 Continue				
0	26 (8.6)	18 (13.04)	8 (4.93)	
1	18 (6)	6 (4.34)	14 (8.64)	
2	42 (14)	14 (10.14)	28 (17.28)	
3	38 (12.6)	16 (11.59)	22 (13.58)	
4	50 (16.6)	20 (14.49)	30 (18.51)	
5	126 (42)	64 (46.37)	62 (38.27)	
Extent of involvement				0.004
<25%	30 (10)	24 (17.39)	6 (3.7)	
25%	112 (37.3)	34 (24.63)	78 (48.14)	
25-50%	88 (29.3)	38 (27.53)	50 (30.86)	
50-75%	40 (13.3)	24 (17.39)	16 (9.87)	
>75%	30 (10)	18 (13.04)	12 (7.4)	
Accompanying findings				
Ground glass opacities	82 (27.3)	39	43	0.1
Pleural effusion	242 (80.6)	38 (27.5)	44 (27.16)	0.34
Adenopathy	2	0	2	0.3
*Chi-square was used for analysis				

Discussion

The findings of this study revealed that lymphopenia was a good predictor of the severity of COVID-19. Particularly, we found that lymphopenia was associated with older age, being male, the need for a ventilator, and death (P<0.05). In addition, O_2-sat, ALT, and AST levels were significantly lower in the lymphopenia group (P<0.05). Based on the CT imaging, the extent of pulmonary involvement was higher in the lymphopenia group than in the non-lymphopenia group.

As COVID-19 may present asymptomatic (4, 10, 11), the majority of our patients reported no fever at the time of diagnosis, and common symptoms included dyspnea (50%), cough (41%), and lethargy (40%) in descending order. These findings were similar to those of previous studies. A study conducted in China by Liu et al. showed that lymphopenia was more prevalent in patients with high blood pressure, coronary heart disease, and severity of pulmonary involvement, compared to the non-lymphopenia group (7). According to the results of our study, 72% of patients had underlying diseases that included hypertension (n=120, 40%), diabetes (n=88, 29%), and heart disease (n=68, 22%).

The findings of studies by Francone M. et al. (12) and Wan S. et al., (13) showed that CT scan scores could be used to predict the outcome and disease severity of patients suffering from COVID-19. Our study revealed similar radiographic changes by the broader extent of pulmonary involvement in the lymphopenia group, which had a significant association. This finding was in line with those of previous studies. These patients had a more severe disease in terms of the extent of pulmonary involvement compared to others.

Saeed (14) reported that lymphopenia, elevated CRP, and D-dimer were linked to the severity of lung injury. Moreover, the ferritin levels, chest CT scoring, and O_2 saturation had a positive correlation with the outcome of COVID-19 disease. In comparison with our study, we found that O_2 saturation, ALT, and AST levels had a direct association with severe outcomes in the lymphopenia group, while CRP and D-dimer were not significantly correlated.

The results of a study on patients with lung cancer (2) showed the T cell count (CD3+, CD4+, CD8+) in patients with COVID-19 was low, whereas interleukin (IL)-6 and IL-10 levels were high and the severity of the lung lesions was shown to be an indicator of a worse clinical disease. However, we could not characterize the T cell in our studied patients and this might apply to our population as well. Amin et al. (3) conducted a study on Iranian patients with hematological deficiencies and COVID-19 infection and reported that inflammatory cytokines did not increase. Accordingly, TNF-beta induced apoptosis in lymphocytes, resulting in lymphopenia and platelet depletion, indicating its potential for treatment.

The current study found that around 50% of patients had lymphopenia upon admission, comparable to the frequency reported in SARS (15). However, this rate was significantly lower than that of COVID-19 patients in Hubei Province (7). As we found in our study, lymphopenia was positively related to the severity of acute lung injury in patients with COVID-19, which was in agreement with the results of a study by Liu et al. (16). According to the mentioned study, there was a positive relationship between lymphopenia and the severity of acute lung injury in patients with COVID-19.

Our study also demonstrated that the severity of lung involvement as indicated by chest CT scan had a direct correlation with the extent of lymphopenia. In cases of more severe disease, the lymphocyte count proved to be a more sensitive indicator compared to CRP or chest CT.

Our study had some limitations, including participants who failed to follow up within the study timeframe, which could have provided more comprehensive results. Another limitation was related to the retrospective setting, which did not allow us to use a broader range of laboratory tests, such as ferritin or procalcitonin levels. Moreover, we could not use the data from certain cases due to missing information, and they were excluded from the analysis for the purpose of matching.

In conclusion, lymphopenia was correlated with older age, being male, the need for a ventilator, and death. The O_2 saturation as well as ALT and AST

levels were statistically lower in the lymphopenia group than in the non-lymphopenia group. In addition, lymphopenia was directly related to the extent of pulmonary involvement and therefore can serve as an indicator of the severity of the disease. Lymphopenia is a good predictor of the severity of COVID-19. However, further studies are needed to be performed with a larger sample size to obtain more comprehensive results.

6. Conclusion

Drawing from the primary discoveries of the present investigation, the strategic defensive position of healthcare waste management in the Kermanshah and Varzaqan-Ahar earthquakes indicated that the formulated and prioritized strategies, including developing national and local regulations and guidelines, applying green management, preparing a database of facilities and equipment in order to increase capacity, attracting operational budget, and paying due attention to ensuring the health and safety of waste management employees need to be carefully considered. In the Kermanshah and Varzaqan-Ahar earthquakes, healthcare waste management was in a defensive position that required waste management managers to mitigate threats by addressing vulnerabilities and weaknesses. Thus, based on the study's results, the most effective approach for establishing an appropriate healthcare waste management system during an earthquake is to utilize "the insights of waste management professionals, researchers, and experts to develop national guidelines and regulations", as indicated by the high attractiveness score in the QSPM matrix.

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Footnotes

Conflicts of Interest: The authors declare that they have no conflict of interest.

Author Contribution: Conceptualization: MR and FD; Data collection: RE and SKA. Formal analysis: KS, and RE. Funding acquisition: MR. Project administration: FD, MR. Writing original draft: NSK, KS and MHKN. Writing-review & editing: FD, MHKN and SKA.

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