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Association between lymphopenia and disease severity in Covid 19 patients with single pulmonary nodule

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Introduction: Based on the results of recent studies, the presence of lymphopenia has been suggested as a predictor factor in patients with Quid-19. This study aimed to evaluate the association between lymphopenia and disease severity in Covid 19 patients with single pulmonary nodule.
Materials & Methods: This study is a descriptive-correlational study that was performed on 32 Covid-19 patients with single pulmonary nodule. In this study, demographic characteristicsand information about laboratory data such as lymphopenia as well as radiological findings of patients were collected and analyzed using Chi-square, independent t-test and regression logistics.
Results: The results showed that most of the patients participating in the study (68.8%) were male with a mean age of 38.9 years. There was a statistically significant association between lymphopenia and disease severity (P = 0.039), while there was no significant association between age, sex, and nodule type with disease severity (P> 0.05).
Conclusion: Lymphopenia is a valid predictor for disease severity and mortality in patients with Covid-19.

Keywords: Lymphopenia, Disease severity, Covid-19, single pulmonary nodule

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), was found for the first time from Wuhan, China, in December 2019, For this reason called Coronavirus Disease 2019 (COVID-19) by World Health Organization (WHO) [1]. This viral disease is an acute respiratory illness with unknown etiology, and highly contagious [2]. Lymphocyte dysfunction, especially lymphopenia, is one of the most common disorders in patients with Covid-19 [3].Significant cytokine activation in patients with Covid-19 can be associated with atrophy of lymphoid organs such as the spleen and further impair lymphocyte circulation [4]. Recent studies showed that the Covid-19 virus can directly destroy lymphatic organs and cause a severe decrease in lymphocytes. This decrease in lymphocytes can be the result of a dysfunction of lymphocytes and therefore can directly destroy organs such as the thymus and spleen and in these studies lymphopenia introduced as a predictor of disease severity in patients with Covid-19 [5. 6].Some other studies have shown that the incidence of lymphopenia is a marker for the severity of infection and acute lung damage, and therefore improved lymphocyte counts may indicate an improvement in pulmonary involvement and a criterion for patient discharge[7]. Also, in some recent studies, the role of single pulmonary nodule, especially in cases with a halo sign, has been mentioned as more specific symptoms for Covid-19[5. 6]. Due to the high prevalence of the Covid-2019 pandemic in the world and the contradictory results regarding the causes and factors affecting it, the present studyaimed to evaluate the association between lymphopenia and disease severity in Covid 19 patients with single pulmonary nodule.

Method & Material:

Study design and participants

A Prospective cohort study was performed in Imam Hossein Educational and Medical Center, Tehran, Iran, in the period of 2020 February 26 to 2020 march 22. Purpose population was including all Covid 19 patients with single pulmonary nodulereferred to Imam Hossein Educational and MedicalCenter. The study population was including Covid 19 patients with single pulmonary nodulewho had inclusion criteria for this study. 32patients participated in this study.

Inclusion and exclusion criteria

Inclusion criteria were including patients with definitive diagnosis of Covid 19 who had single pulmonary nodule in their chest CT scan and exclusion criteria were including patients who had no sufficient information in their clinical document.

Sample size and sampling method

Sample size in this study was 32 Covid 19 patients with single pulmonary nodule, andsampling method in was easy, continuous and available sampling.

Definition of disease severity

Disease severity was defined as patient that their single pulmonary nodule got progressed and became hospitalized or died.

Definition of Lymphopenia

Lymphopenia was defined as the number of lymphocytes less than 800 per / ML of blood or the percentage of lymphocytes less than 18% of all white blood cells.

Data collection

Datawere collected by demographic checklist, including questions related to demographic characteristics such as age, sex, etc., as well as radiological and laboratory findings including single pulmonary nodule in the patient's chest CT scan, and the number and percentage of lymphocytes in laboratory tests.

Statistical analysis:

Data were analyzed by using the software SPSS v26. Descriptive statistics such as mean, Standard deviation (SD) and percentage were used to present the data. Independent T test, Chi-square or Fisher's exact test used to compare frequently between classification variables. Univariate logistic regression was used to explore the association between lymphopenia anddisease severity. A p-value less than 0.05 were considered significant.

Ethical Approval: This study has taken from a research project with Ethical code (IR.SBMU.MSP.REC.1399.689), approved by the Vice President of Research of Shahid Beheshti University of Medical Sciences, Tehran, Iran. Ethical considerations in this study have been confirmed by obtaining the ethics code from the Vice President of Research of Shahid Beheshti University of Medical Sciences.

Result: Demographic characteristics in this study showed that most of the patients participating in the study (68.8%) were men with a mean age of 38.09 ± 12.06. Mean size of single pulmonary nodule was 11.93 ± 4.77 mm (Tabel1).

Table1: Mean, standard deviation, minimum and maximum age and size of nodules in participating patients.

variable	Mean	ST. deviation	Max	Min
Age (year)	38.09	12.06	72	22
Nodule size(mm)	11.93	4.77	22	3

The frequency of nodule type showed that 29 (90.6%) patients hadground glass noodles and 3 (9.4%) patients had soiled. The frequency of lymphocyte counts showed that 19 (59.4%) patients had lymphocytes in normal range and 13 (40.6%) patients had less than normal range (Lymphopenia).

Table2: Frequency of gender, nodule type, and lymphocyte counts in participating patients.

Variable		Frequency	Percent
Gender	**Male**	22	68.8
	Female	10	31.2
Nodule Type	**Ground – Glass**	29	90.6
	Soiled	3	9.4
lymphocyte count	**Normal Range**	19	59.4
	Lymphopenia	13	40.6

Data analysis results used Logistic regression showed that there was a statistically significant association between lymphopenia and disease severity (P = 0.039), while there was no significant association between age, sex, and nodule type with disease severity (P> 0.05) (Table3).

Table3: Association between disease severity with age, sex, nodules type, and lymphocyte count of patients participating in the study by using logistic regression test.

Variable	All patients (frequency)	Severity disease Frequency (percent)	B	S.E	Logistic Wald	Regression P-value
		Gender				
Male	22	3 (13.6)	0.999	0.929	1.156	0.282
Female	10	3 (70)				
		Age				
< 40 year	17	3 (17.6)	0.154	0.906	0.029	0.865
> 40 year	15	3 (20)				
		Nodule Type				
Ground-glass	29	4(18.8)	2.526	1.338	3.567	0.059
Soiled	3	2 (66.7)				
		Lymphopenia				
Yes	13	5 (38.5)	2.42	1.175	4.243	0.039
No	19	1 (5.3)				

Discussion: Lymphopenia is one of the most common laboratory abnormalities reported in patients with SARS Covid-2, and recent studies have shown that this disorder is more common in patients with severe disease in comparative with non-severe disease [8].Lymphopenia also observed in about 60% of Patient with Covid-19 [3]. A systemic review and meta-analysis study reported that lymphopenia is a common disorder in patients with acute respiratory syndrome caused by Covid-19 virus with a prevalence of 54 to 69.6%, which can act as a rapid tool to identify Covid-19 patients with severity disease quickly [9].

In the present study data analysis results used Logistic regression showed that there was a statistically significant association between lymphopenia and disease severity that is in line with the most of studies: Toori et al, in their study reported thatthere is a significant association between lymphopenia and disease severity and lymphopenia has been considered as a valid predictor of disease severity and mortality in patients with Covid-19 [10], Huang et al, stated that Lymphopenia is statistically significantly associated with higher incidence of ARDS, more need for ICU hospitalization, and severity of Covid-19 disease[3], Zhaoa & his colleague said Lymphopenia can be useful in predicting the severity of clinical consequences of Covid-19 [9], Liu et al, reported that Lymphopenia is a strong criterion for predicting the severity and recovery of patients with Covid-19 [11], and Shireen and his co-worker showed that lymphocyte counts can be used to assess the severity of Covid 19 [9]. Also Wu et al [12], and Wang& his colleague[13],approved the association between lymphopenia and the incidence of acute respiratory syndrome in patients with Covid-19.

Covid-19 virus often affects tissues that express high levels of the angiotensin-converting enzyme, such as the heart, lungs, and digestive system, causing inflammatory mediators [14], and cytokines, which cause lymphopenia and

increased inflammatory factors in plasma [15]. Therefore, it can be concluded that the Covid-19 virus can directly infect these cells and lead to their lysis. In addition, cytokine storms can accelerate lymphocyte apoptosis by significantly increasing interleukin levels [16. 17]. On the other hand significant activation of cytokines can cause atrophy of lymphoid organs such as spleen and impair lymphocyte circulation [4].

Conclusion: The results of this study showed that there is a statistically significant association between lymphocyte countand disease severity in patients with Covid-19,so that the decrease in the number of lymphocytes leads to more severity of disease.so we conclude that lymphopenia is a valid predictor for disease severity and mortality in patients with Covid-19.

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Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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