Original Article

On the relationship between mediastinal lymphadenopathy in chest CT scan in Covid-19 patients and mortality rate

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ABSTRACT

Little information exists about the effect of the presence of mediastinal lymphadenopathy on the prognosis of the 2019 coronavirus disease (COVID-19). This study investigates the relationship between mediastinal lymphadenopathy in the chest CT scan of Covid-19 patients and the mortality rate in Razi Hospital of Jundishapur University, Ahvaz. As a single-center retrospective case-control study, it included 300 COVID-19 patients over 15 years of age with positive RT-PCR test and lung involvement. We had two patient groups: 280 patients without lymphadenopathy and 20 patients with lymphadenopathy. We recorded the information of the patients, including age, sex, and mortality, and investigated their relationship with lymphadenopathy.

Out of 300 COVID patients, 280 (93.3%) had no lymphadenopathy and 20 (6.7%) had lymphadenopathy. From among the two groups without lymphadenopathy and with lymphadenopathy, 3 people died from the lymphadenopathy group (15%) and 22 people from the non-lymphadenopathy group (7.9%). It shows that although the mortality rate was higher in the group of patients with lymphadenopathy, but it was not statistically significant (p=0.22). Thus, age and gender were not associated significantly with lymphadenopathy and non-lymphadenopathy groups. The present study did not find a significant relationship between the lymphadenopathy and the variables of age, gender and mortality. Although enlarged mediastinal lymphadenopathy has been reported as an uncommon radiologic finding, the mediastinum should be evaluated for enlarged mediastinal lymphadenopathy and it may be useful as a biomarker for progressive disease.

Keywords: Mediastinal lymphadenopathy, Radiological findings, Covid-19, Mortality

Introduction

The 2019 coronavirus pandemic (COVID-19) is still a major health problem and threatens the entire world with high mortality. After discovering the first cases in Wuhan, China, COVID-19 is spreading rapidly. Since September 21, 2020, the World Health Organization has confirmed 30.6 million cases and reported 950,000 deaths in over 200 countries. Patients with COVID-19 fall into three groups: mild, moderate, and severe. A mild case is not of the symptoms of pulmonary infection. Moderate cases are accompanied with fever, respiratory symptoms and lung infection in lung images. In severe cases, the percentage of oxygen saturation and the relative arterial pressure of oxygen also decrease besides breathing problems. For testing suspected patients, the history of other diseases and clinical examinations of the patient are comprehensively analyzed. Symptoms in CT scan comprise ground glass opacity (GGO), consolidation, crazy paving, and pulmonary fibrosis (1). An unknown pneumonia case was reported in late December 2019 in Wuhan, Hubei Province, China, whose clinical features were very similar to viral pneumonia. The World Health Organization (WHO) named this virus as COVID-19 and the International Committee on Taxonomy of Viruses (ICTV) named it as SARS-CoV2. It belongs to the beta-coronavirus family, and like other viruses, it has many potential natural hosts that act as intermediate hosts or final hosts. This creates significant challenges for the prevention and treatment of COVID-19. Its transmission occurs through breathing/inhalation or contact with infected particles, and its recovery period lasts from 2 to 14 days. Its symptoms are usually fever, cough, Pharyngitis, shortness of breath, fatigue and body weakness. This disease is mild in most people and in some people (usually elderly people and people with underlying diseases) it may lead to lung

infection, acute respiratory distress syndrome (ARDS) and severe functional disorders in the major organs of the body.

Mediastinal lymphadenopathy was not a typical chest CT finding in patients with COVID-19 infection. Further studies are necessary to better investigate the significance of mediastinal lymphadenopathy in patients with COVID-19 infection. Mediastinal lymphadenopathy was found in 0–66% of cases with COVID-19 infection. As found from 8 reports (articles) (7 retrospective reviews and 1 case report), individuals had mediastinal lymphadenopathy. Mediastinal lymphadenopathy was not found in 4 case reports and 8 retrospective reviews evaluating lymphadenopathy in patients with Covid-19. A retrospective review of chest CT in children with COVID-19 observed mediastinal lymphadenopathy in 0%–8.1% of cases. No study has reported Mediastinal lymphadenopathy in pregnant patients with COVID-19. A review of 418 patients and a recent retrospective study of 134 patients with Covid-19 in Italy showed a prevalence of mediastinal lymphadenopathy by 18.2% and 54.8%, respectively. There is no significant difference between patients with and without lymphadenopathy in terms of gender, age, history of cancer, non-invasive ventilation, hospitalization in the intensive care unit, duration of hospitalization, and laboratory results. Lymphadenopathy was observable mostly in hospitalized patients with crazy-paving pattern in CT. 3 retrospective reviews of 154, 192, and 499 patients with COVID-19 showed in China a prevalence of hilum/mediastinal lymphadenopathy by 43.5%, 41.7%, and 19.8%, respectively. Valette *et al*. reported that apart from a typical GGO, reticulation, or consolidation in all 9 patients with severe Covid-19 who underwent invasive mechanical ventilation in an intensive care unit in France, 6 patients had mediastinal lymphadenopathy; this finding shows a highest percentage (66%) of the prevalence of mediastinal lymphadenopathy. The average of days for onset of symptoms and CT findings was 7 (interquartile range 6-8). A subcarinal location of lymphadenopathy was in several patients up to 30 mm in the short axis (2).

Materials and Methods

The current study was descriptive-analytical, conducted from July 2021 to August 2021 at Razi Hospital, affiliated to the Jundishapur University of Medical Sciences, Ahvaz. The sample size is 300 people. The people excluded from study are: individuals over 65 years old, cancer patients, CHF patients, and chronic lung patients like ILD. Mediastinal lymph node size cut-off is ≥10 mm in short axis. The study got from electronic medical records the demographic characteristics, comorbidities, onset of symptoms, vital signs at admission including heart rate, blood pressure, oxygen saturation and respiration rate, primary systemic inflammatory markers including CRP, ferritin and Procalcitonin. It got also Protocol and Imaging Techniques of Chest CT scan through the hospital's standard dose protocol with a 68-slice CT scan machine (EDP_essense; Iran; ehya darman pisrafteh). All CT scans were performed through a breath hold without contrast administration. Mediastinal lymphadenopathy was pathological if the short axis of mediastinal lymphadenopathy was ≥ 10 mm. In fact, this study examines the mediastinal lymph nodes, and since the shape of the lymph nodes is spherical or oval, it measures both diameters of these lymph nodes. If the smaller diameter is ≥ 10 mm, it is supposedly an important and pathological finding. Mediastinal lymph nodes were evaluated and measured in the usual axial plan. Whenever the lymph node was considered larger in other plans, the short axis of mediastinal lymphadenopathy was measured and recorded. Mediastinal lymph node stations are classified according to a new international map of lymph nodes (24). CT images were evaluated for distribution (bilateral/unilateral, predominance at the base of the lungs/predominance at the apex), lesion attenuation (GGO, crazy paving) and other radiological findings (bronchiectasis, subpleural band etc.). Radiographic findings were defined according to the guidelines of the Fleischner Society.

Probable findings outside of the checklist were also recorded. Data were analyzed after collecting and coding in SPSS statistical software version 13 (version 13, SPSS Inc., Chicago, IL). A statistically significant level was less than 0.05. This study is an extract of the thesis of Dr. Asma Javadipour (thesis code: U-00304). It has been approved by the Research Ethics Committee of the Ahvaz University of Medical Sciences with code IR.AJUMS.REC.2021.673.

Results and Discussion

This study examined 300 patients with the age range of 15 to 65, including 28 people from 15 to 25 years old, 57 people from 26 to 35 years old, 60 people from 36 to 45 years old, 77 people from 45 to 55 years old, and 78 people from 56 to 65 years old. 130 of them are women and 170 are men **(Table 1)**. 20 people had lymphadenopathy and 280 people were without lymphadenopathy, and 275 people fully recovered and 25 people died **(Table 2)**. The Chi-square test determined the relation of the last condition of the patient with the lymphadenopathy and non-lymphadenopathy groups. This relationship was not significant and 3 people died from the lymphadenopathy group (15%) and 22 people from the non-lymphadenopathy group (7.9%) **(Table 3)**. We have discussed also the relationship between gender and the group of lymphadenopathy and non-lymphadenopathy. There is no significant difference between gender and the group of lymphadenopathy and non-lymphadenopathy **(Table 4)**. 3 people (15%) died from the lymphadenopathy group and 22 people (7.9%) died in the non-lymphadenopathy group. The relationship between the age groups and the lymphadenopathy and non-lymphadenopathy groups was analyzed through the chi-square test. There is no significant difference between the age groups and the lymphadenopathy and non-lymphadenopathy groups. From the lymphadenopathy group, 7 people with 56-65 years old and from the non-lymphadenopathy group 71 people with 56-65 years old respectively have the highest frequencies **(Table 4)**.

Table 1. Frequency distribution of demographic indices

Variable	Classification	Frequency	Frequency percentage
Gender	Male	43.3	130
	Female	56.7	170
Age	15-25	9.3	28
	26-35	19	57
	36-45	20	60
	46-55	25.7	77
	56-65	26	78

Table 2. Frequency distribution of groups under study and final status

Variable	Classification	Frequency	Frequency percentage
groups under study	Without lymphadenopathy	280	93.3
	Lymphadenopathy	20	6.7
final status	Recovery	275	91.7
	Dead	25	8.3

Table 3. Examining the relationship between the final status and lymphadenopathy and non-lymphadenopathy groups

	Groups under study				p-value
Patient's final status	Non-lymphadenopathy		Lymphadenopathy		
	Frequency	Frequency percentage	Frequency	Frequency percentage	0.22
Recovery	258	92.1	17	85.0%	
Dead	22	7.9	3	15.0%	

Table 4. Examining the relation of gender and age with lymphadenopathy and non-lymphadenopathy groups

		Groups under study				
Variable	Patient's final status	Lymphadenopathy		Non-Lymphadenopathy		p-value
		Frequency	Frequency	Frequency	Frequency	
Gender	Male	8	40.0%	122	43.6%	0.75
	Female	12	60.0%	158	56.4%	
Age	15-25	0	0.0%	28	10.0%	0.4
	26-35	2	10.0%	55	19.6%	
	36-45	5	25.0%	55	19.6%	
	46-55	6	30.0%	71	25.4%	
	56-65	7	35.0%	71	25.4%	

The present study investigated the role of prognosis of mediastinal lymphadenopathy and its relationship with demographic characteristics in chest CT scan of Covid-19 patients. It examined also the frequency of lymphadenopathy in Covid-19 patients and its relationship with mortality. Out of 300 COVID patients, 280 (93.3%) had no lymphadenopathy and 20 (6.7%) had lymphadenopathy. As for comparing the mortality rate, 3 people died from among the lymphadenopathy group (15%) and 22 people from the non-lymphadenopathy group (7.9%). It shows that although the mortality rate was higher in the group of patients with lymphadenopathy, but it was not statistically significant (p=0.22). Most individuals in both groups were women, and therefore, no significant relationship was reported between the two groups in terms of gender (p=0.75). As for the age, the results showed that there is no significant difference between the age groups and the groups of lymphadenopathy and non-lymphadenopathy; the highest frequency in both groups is for the age group of 56-65 years (7 people with 35 percent in the lymphadenopathy group compared to 71 people with 25.4% in the group without lymphadenopathy). Mediastinal lymphadenopathy is a uncommon chest CT finding in patients with COVID-19 infection, and its prevalence in patients with Covid-19 is different in different studies and different regions of the world. According to reports, the prevalence of mediastinal lymphadenopathy has been from 0 to 66% in cases with COVID-19 infection (2). The present study reported by 6.7% the prevalence of lymphadenopathy in patients with COVID-19 infection. In an Iranian study conducted by Pilechian *et al*. (2021), the prevalence of mediastinal lymphadenopathy was 17.4% in 195 patients with Covid-19. A study of children with COVID-19 reported mediastinal lymphadenopathy in 0-1.8% of cases (3). No study observed any mediastinal lymphadenopathy in pregnant patients with COVID-19. Recent studies have also shown that even the prevalence of lymphadenopathy in Covid-19 patients is different in the same region. In China, for example, three studies on 154, 192, and 499 patients with Covid-19 reported the prevalence of hilum/mediastinal lymphadenopathy by 43.5%, 41.7%, and 19.8%, respectively. Overall, this difference in the prevalence of lymphadenopathy in patients with COVID-19 infection in different studies can be because of a difference in sample size, a difference in disease severity, and different identification methods (2). The present study did not observe significant relationship between age and gender with lymphadenopathy and non-lymphadenopathy groups. There was also no significant difference between the final status (in terms of recovery and death) and the lymphadenopathy and non-lymphadenopathy groups. In line with the results of the present study, the study of Ahmet Turan Kaya *et al*. did not observe statistically significant relationship between gender and lymphadenopathy and non-lymphadenopathy groups. However, there was a significant relationship between age and mortality in lymphadenopathy and non-lymphadenopathy groups, which contradicts the findings of the present study. Their results showed also a significant relationship between the lymphadenopathy and older age, increased inflammatory markers, high CT-SS, increased mortality and the rate of hospitalization in the intensive care unit. The lymphadenopathy was associated with the prognosis of early-stage COVID-19 patients without CT imaging findings of COVID-19 pneumonia (CT-SS = 0, CORADS 1 or 2). Parenchymal chest CT findings were more common in the group with lymphadenopathy. In multivariate analysis, linear opacity and increased bronchial wall thickness in the CT scan and history of chronic lung disease were associated with a higher rate of lymphadenopathy. Older age,

lymphadenopathy, interlobular septal thickening and hyperlipidemia were more dangerous for mortality in multivariate logistic regression analysis. There was no significant difference in the relation between the lymphadenopathy and the time of hospitalization (department or ICU) until death (4). Satıcı *et al*. investigated in their study the relationship between lymphadenopathy and mortality. They reported that patients with lymphadenopathy were older, had at least one comorbidity, and were associated with increased mortality (5).

Kaya's study showed the lymphadenopathy in association with a higher mortality rate and worse prognosis in COVID-19 patients with CORADS ≤2 CT findings in the early period. The frequency of mortality in the group of patients with lymphadenopathy was in the present study higher than the group of patients without lymphadenopathy. Two studies conducted by Kaya and Satıcı reported an association between lymphadenopathy and increased mortality (4, 5). Sardanelli *et al*. reported no significant difference between the lymphadenopathy and age, ICU admission, length of hospital stay, and laboratory results, but the frequency of mortality in the group with lymphadenopathy was high (6). Similar to Sardanelli *et al*. the studies of Silva *et al*. did not show significant difference between the presence of lymphadenopathy and gender, the duration of hospitalization and ICU, but the frequency of death was significantly higher (7). A reason for the unequal number of patients with or without lymphadenopathy can be a difference in various prognostic outcomes in Covid-19 patients. The patients with lymphadenopathy have older age, laboratory findings of infection (CRP, ESR and ferritin), CT-SS and hospitalization in the intensive care unit (4). Patients with severe or progressive COVID-19 pneumonia had a significantly higher frequency of consolidation, linear opacities, crazy laying pattern, bronchial wall thickening, lymphadenopathy, pericardial effusion, and pleural effusion (8). Bronchial wall thickening because of increased vascular endothelial growth factor (VEGF) in severe disease increases, supposedly disease severity and airflow resistance (9). Past studies, except for that of Sardanelli *et al.*, reported a relationship between older age and lymphadenopathy (5, 6, & 9). Angiotensin-converting enzyme 2 (ACE-2) is important in the virus's entry into the cell and its expression increases with age, so the risk of mortality from Covid-19 is higher in older adults (10). As in other studies, there was no relationship between gender and lymphadenopathy in the present study. This shows that gender is not a risk factor for lymphadenopathy. Satıcı *et al*. reported no significant difference between lymphadenopathy and gender, as in the present study (5). Because angiogenesis is one of the most important findings of inflammation, enlarged mediastinal lymphadenopathy is a significant finding in inflammatory diseases. Enlarged mediastinal lymphadenopathy is associated with clinical worsening in patients with IPF characterized by chronic inflammation (11, 12). The reason is that lymphangiogenesis and lymphatic remodeling caused by persistent chronic inflammation lead to progressive fibrosis. Thus, enlarged mediastinal lymphadenopathy may also reflect increased inflammation in patients with COVID-19 (13, 14).

The present study has some limitations: low sample size, cross-sectional design of the study, and lack of evaluation of CT scans in different stages, lack of certainty whether the patient previously had enlarged mediastinal lymphadenopathy, failure to perform a biopsy for excluding other causes of enlarged mediastinal lymphadenopathy such as sarcoidosis and Malignancy, lack of examination of the relationship between lymphadenopathy and clinical and radiological findings in patients and single-centeredness.

Conclusion

The present study did not observe significant relationship between the existence of lymphadenopathy and the variables of age, gender and mortality. Although researchers have reported enlarged mediastinal lymphadenopathy as an uncommon radiologic finding, the mediastinum should be evaluated for enlarged mediastinal lymphadenopathy and may be useful as a biomarker for progressive disease. However, studies with a higher sample size are necessary, and on the correlation of the lymphadenopathy with the factors that determine the severity and progress of the COVID disease, especially with clinical and radiological findings.

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Conflict of interest:

The authors declare that they have no competing interests.

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