Mediastinal lymphadenopathy and prognosis of COVID-19 disease

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ABSTRACT

Background and Objectives: There are conflicting studies on the prevalence of mediastinal lymphadenopathy (LAP) and its relationship to the prognosis of COVID-19 disease. The prevalence varied from 3.4 to 66 percent and more prevalent in patients who died. This study aimed to investigate the mediastinal lymphadenopathy and the disease progression in COVID-19 patients.

Materials and Methods: In this case-control study, 195 COVID-19 patients were divided into two groups, with the mediastinal lymphadenopathy and without it. In these groups, demographic characteristics, underlying diseases, laboratory results, and outcomes were compared.

Results: The median age in the LAP group was higher than the opposite group (62 vs. 58.5; p= 0.037). SpO2 (85% vs. 90%; P <0.001), lymphocyte count (760 vs. 969; p= 0.02), Neutrophil-to-Lymphocyte Ratio (5.53 vs. 4.41; p= 0.02), and ESR (36 vs. 29; p= 0.03) were significantly correlated with the presence of lymphadenopathy, using the Mann-Whitney Wilcoxon rank test. ICU admission (65.71% vs. 36.87; p= 0.003), mechanical ventilation (31.42% vs. 13.75%; p= 0.022), disease severity (65.71% vs. 40%; p <0.01), length of hospital stay (9 vs. 7; p= 0.039) and mortality rate (40% vs. 21.25%; p= 0.034) were more predominantly observed in the LAP group, using the $\chi 2$ test. There was no apparent difference in sex and the underlying diseases among the two groups.

Conclusion: This observation showed a relatively high prevalence of mediastinal lymphadenopathy in COVID-19 patients, which was more common in the elderly with low oxygen saturation. Therefore, LAP may lead to further intensive care needs, more use of mechanical ventilation, high severity of disease, and mortality rate.

Keywords: COVID-19; Hematologic disease; Lymphadenopathy; Mediastinal disease; Prognosis

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INTRODUCTION

The pandemic of Coronavirus Disease 2019 (COVID-19) first began in December 2019 from China and spread worldwide (1). The severity of infection could vary from asymptomatic infection to severe disease. The Clinical severity of COVID-19 was categorized in 5 groups as asymptomatic, mild, moder-

ate, severe, and critical (2). The commonly reported symptoms are fever, cough, myalgia, fatigue, headache, diarrhea, runny nose, dyspnea, and pneumonia. In clinical reports, patients with mild symptoms recovered after one week. At the same time, severe cases experience progressive respiratory failure due to alveolar damage, leading to death (3-5). Age and comorbidities such as diabetes, hypertension, cardiovascular disease, chronic kidney disease, chronic lung disease, cancer, smoking, and obesity are the most significant risk factors for COVID-19 disease severity (6, 7). Studies suggest that high temperature and respiratory rate, dyspnea, leukopenia, lymphocytopenia, elevated levels of Neutrophil-to-Lymphocyte ratio, D-dimer, procalcitonin, C-reactive protein (CRP), lactate dehydrogenase (LDH), and decreased albumin are the factors associated with poor prognosis of COVID-19 infection (4, 8-11). Chest computed tomography scan (CT scan) findings such as bilateral, multilobar ground-glass opacity with a peripheral or posterior distribution (or both), mainly in the lower lobes, are known as the hallmarks of COVID-19 patients. In addition, consolidation, septal thickening, bronchiectasis, pleural thickening, and subpleural involvement are less common, mainly in the later stages of the disease. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, and pneumothorax are uncommon but can be seen by disease progression stage (12-14). Mediastinal lymphadenopathy, one of the CT findings, can be caused by benign or malignant disorders (15). Primary lung cancer, lymphoma, metastatic malignancies to the mediastinum from other sites, lymphomatoid granulomatosis (like sarcoidosis), interstitial lung disease, and infective etiologies such as pneumonia, pulmonary tuberculosis, pulmonary fungal infection, and thoracic histoplasmosis are the most common cause of mediastinal lymphadenopathy (16, 17). Several studies have recently suggested that mediastinal lymphadenopathy (LAP) prevalence in patients with COVID-19 ranges from 3·4% to 5·4%, while its prevalence in patients with severe COVID-19 has been seen a sharp rise to 66% (14, 18, 19). Three retrospective studies in China reported a prevalence of mediastinal lymphadenopathy in 43.5%, 41.7%, and 19.8% of 154, 192, and 499 patients with COVID-19, respectively (20-22). Also, lymphadenopathy at admission was significantly more common in patients who died during hospitalization than those discharged (23) and was associated with increased mor-

tality (24). This epidemiological evidence indicates the correlation of mediastinal lymphadenopathy with COVID-19 severity. Our study investigates patients' clinical characteristics and laboratory findings with COVID-19 and mediastinal lymphadenopathy and its association with disease outcomes.

MATERIALS AND METHODS

Patient and procedures. The ethics committee approved this study of the Shahid Beheshti Medical University (No.: IR.SBMU.MSP.REC.1399.386.).

This study included all patients who were sufficiently ill to require hospital admission at Taleghani Hospital (Tehran, Iran) from April 20, 2020, to August 20, 2020, diagnosed by their Chest CT scan based on the standard criteria (25). All CT images were reviewed and evaluated by expert radiologists. The criterion for significant lymph node enlargement of mediastinal lymph nodes was considered a short-axis dimension ≥10 mm (22). Information of 213 patients was recorded, including demographic characteristics, clinical symptoms, underlying diseases, and laboratory findings. According to the restriction method, eighteen patients with a history of previous or concurrent cancer and tuberculosis were excluded from the study so as to eliminate the impact of confounding variables.

The rest of 195 patients were divided based on the mediastinal lymphadenopathy presence into two groups. This study explored three objectives: 1. Comparisons of essential characteristics between two groups, including demographic characteristics, current medical histories, and physical signs.   2. Comparisons of initial laboratory results and risk factors for severity of disease 3. Comparisons of admissions to the intensive care unit (ICU), using invasive mechanical ventilation, and clinical outcomes (discharge, length of hospital stay, and mortality) between groups. It is worth mentioning that admission to the intensive care unit, using invasive ventilation, or death was defined as severity.

Statistical analysis. Data were analyzed using R (V.3.6.0). A value of p< 0.05 was considered statistically significant. The Kolmogorov-Smirnov test carried out the distribution of continuous variables. Mann-Whitney Wilcoxon rank test was applied to compare the median in non-normally distributed

data. The χ2 test was applied to examine categorical data. Boxplots were used to compare the median of two groups' numerical data, and a bar plots were used to compare the proportions of categorical variables. Also, statistical control (regression models) was employed for explaining confounding variables.

RESULTS

Our study included 195 hospitalized patients with COVID-19. The median age was 60 years (IQR 46.5–71; Table 1), and 118 (60.51%) patients were men. The most common symptoms were fever (69.74%), cough (52.23%), shortness of breath (49.23%), and myalgia (44.10%). Other symptoms were diarrhea (25.12%), nausea (20.51%), headache (14.35%), chest pain (11.25%), vomiting (10.25%), and non-massive hemoptysis (4.10%). Nobody had symptoms of dysphasia, flushing, or superior vena cava syndrome.

Among them, 87 (44.61%) patients had severe disease, and 82 (42.05%) patients were admitted to ICU. During hospitalization, 33 (16.92%) patients received invasive mechanical ventilation treatment, and 48 (24.61%) critically ill patients died. The median length of hospital stay was seven days (IQR 4.5-10), and SpO2 on admission reached 89% (IQR: 84-91).

67 (34.35%) patients had a hypertension history, and 58 (29.74%) patients had diabetes. Other comorbidities were cardiovascular disease (23.58%), chronic kidney disease (6.66%), neurologic disorder (6.15%), dyslipidemia (6.15%), chronic respiratory disease (5.64%), hypothyroidism (4.61%), Rheumatic diseases (3.07%) and history of heart valvuloplasty (3.07%) and organ transplantation (2.05%).

Thirty-five patients (17.94%) had mediastinal lymphadenopathy ≥10 mm. Compared between the two groups, patients with mediastinal lymphadenopathy had a higher male proportion but without a significant difference (65.71% vs. 59.37%; p= 0.61). The median age in the LAP group was 62 (IQR 53-74 years), which was higher than the opposite group 58.5 (IQR 43.75-69.5; p= 0.037).

There was no apparent difference in the underlying diseases among the two groups. Also, the patient's initial vital signs were not significantly different except oxygen saturation. Oxygen saturation was significantly lower in the mediastinal lymphadenopathy group

Table 1. Demographics and baseline characteristics of patients infected with COVID-19 and Comparison of them between the two groups

	Total (n=195) Number (%)	With LAP (n=35) Number (%)	Without LAP (n=160) Number (%)	P-value
Age, median (IQR), (years)	60 (46.5-71)	62 (53 to 74)	58.5 (43.75 to 69.5)	0.037
Sex				
Female	77 (39.48%)	12 (34.28%)	65 (40.62%)	0.614
Male	118 (60.51%)	23 (65.71%)	95 (59.37%)	
Comorbidities:				
Diabetes	58 (29.74%)	12 (34.28%)	46 (28.75%)	0.656
Hypertension	67 (34.35%)	15 (42.85%)	52 (32.5%)	0.331
Ischemic heart disease	46 (23.58%)	9 (25.71%)	37 (23.12%)	0.914
Severity				
ICU patients	82 (42.05%)	23 (65.71%)	59 (36.87%)	0.003
Mechanical ventilation	33 (16.92%)	11 (31.42%)	22 (13.75%)	0.023
Length of hospital stay, median (IQR), (days)	4.5 (7 to 10)	9 (6 to 11)	7 (4 to 10)	0.039
Severity	87 (44.61%)	23 (65.71%)	64 (40.0%)	<0.01
Mortality	48 (24.61%)	14 (40%)	34 (21.25%)	0.034
Vital sign	Normal range	Median (IQR)	Median (IQR)	p-value
Systolic BP	90-120	125 (110 to 137.5)	120 (110 to 135)	0.490
Diastolic BP	60-80	75 (70 to 82.5)	80 (70 to 85)	0.399
Pulse rate	60-100	89 (80 to 111)	88 (80 to 100)	0.244
Temperature	36.5-37.5	37 (37 to 38)	37 (36.8 to 37.5)	0.210
Oxygen saturation	>93	85 (75.5 to 88.5)	90 (85 to 92)	<0.001

(85% vs. 90%; P< 0.001).

The median duration of hospitalization in the LAP group was nine days (IQR 6-11 days) compared with the opposite group seven (IQR 4-10 days; p= 0.039). Fig. 1 shows the comparison of age, oxygen saturation, and length of hospital stay in both groups.

As shown in Fig. 2, ICU admission more predominantly occurred in the LAP group than in the group without it (65.71% vs. 36.87%; p= 0.003). Eleven of the 35 patients in the group with mediastinal lymphadenopathy were treated with mechanical ventilation (31.42% vs. 13.75%; p= 0.022). Also, in this group, the disease was significantly more severe (65.71% vs. 40%; p< 0.01), and the mortality rate was higher than another one (40% vs. 21.25%; p= 0.034).

More biochemical abnormalities and hematological parameters were seen in the LAP group compared to the opposite group (Table 2), such as lymphocyte count (760 vs. 969; p= 0.02), Neutrophil-to-Lymphocyte Ratio (5.53 vs. 4.41; p= 0.02), and ESR (36 vs. 29; p= 0.03), which is shown in Fig. 3. Total bilirubin, lactate dehydrogenase (LDH), and prothrombin time (PT) were different between the two groups but not significantly.

DISCUSSION

This study collected clinical characteristics, laboratory results, severity of disease, and mortality of COVID-19 patients with mediastinal lymphadenopathy ≥10 mm and without it.
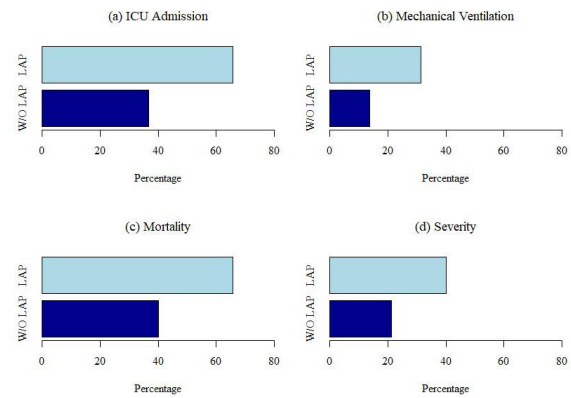
Contrary to previous studies, our study illustrated

Fig. 2. Comparison of (a) ICU admission, (b) using mechanical ventilation, (c) mortality and, (d) severity of disease in the two groups

that the prevalence of mediastinal lymphadenopathy in COVID-19 disease was 17.4%, which is more common than mentioned in previous researches, 3.38 and 5.4% (14, 26).

Sardanli et al. observed no association between age, sex, history of cancer, ICU admission, ventilator use, length of hospital stay, laboratory findings, and other CT scan complications in patients with or without mediastinal lymphadenopathy (23). Nevertheless, they noted that mediastinal lymphadenopathy was more common in patients who died in the hospital than those discharged. In our investigation, corresponding to the previous study, sex, comorbidities such as diabetes, hypertension, and cardiovascular disease have not been associated with mediastinal lymphadenopathy. However, as we observed,
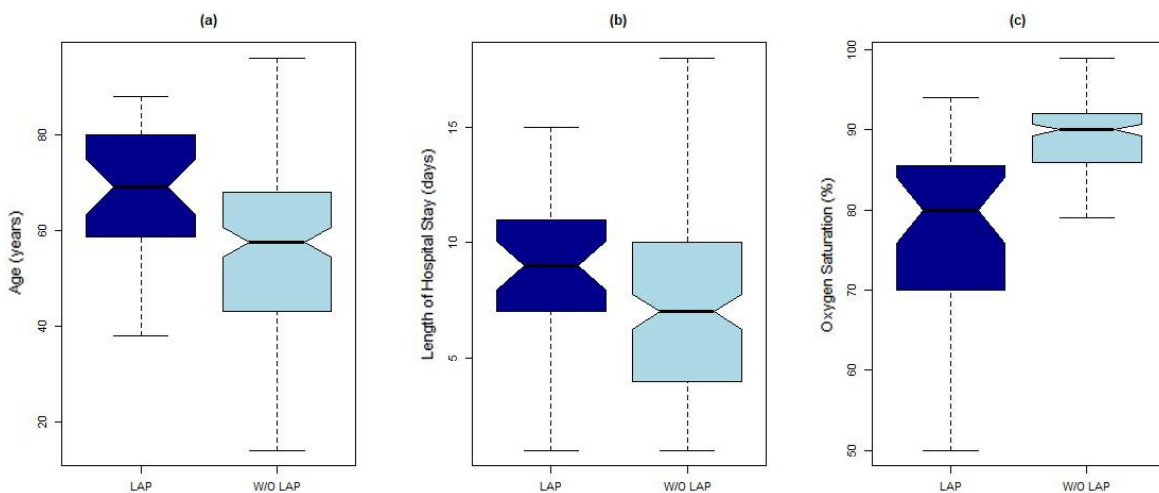

Fig. 1. Comparison of (a) Age (b) length of hospital stay (c) oxygen saturation in the mediastinal lymphadenopathy group to the opposite group

Table 2. Comparisons of laboratory investigations on admission between two groups

| Lab test	Normal range	Median (IQR) (With LAP)	Median (IQR) (Without LAP)	P-value
WBC	4000-10000	6000 (4350 to 9050)	5800 (4575 to 8125)	0.285
Lymphocyte count	1000-4800	760 (655 to 1069)	969 (720 to 1333)	0.026
Neutrophil-to-Lymphocyte Ratio	0.78 and 3.53	5.53 (3.77 to 9.44)	4.41 (2.90 to 7.20)	0.022
Hb	13-16	11.80 (11.35 to 13.05)	12.20 (11.27 to 13.10)	0.305
PLT	150-400*10^3	188 (142 to 257)	175 (146 to 240)	0.449
Cr	0.7-1.3	1.1 (1 to 1.4)	1.1 (0.9 to 1.2)	0.171
AST	<41	38 (29 to 60)	39.5 (28 to 59.5)	0.490
ALT	<41	33.5 (22.5 to 50.5)	33 (22 to 57)	0.525
Total Bill	<1.2	0.7 (0.5 to 0.9)	0.74 (0.6 to 1)	0.099
CPK	25-190	197 (102 to 310)	178 (96 to 348)	0.445
CK_MB	<24	21.5 (14 to 31.5)	24 (16 to 32)	0.163
Troponin	<0.5	0.020 (0.011 to 0.037)	0.020 (0.010 to 0.039)	0.274
LDH	<480	708 (570 to 935)	625 (492 to 809)	0.067
PT	11-13.5	13 (12 to 14)	13 (12 to 13.3)	0.075
ESR	0-20	36 (24 to 49)	29 (15 to 43)	0.031
CRP	0-6	19 (6.5 to 52)	21 (7 to 46)	0.344
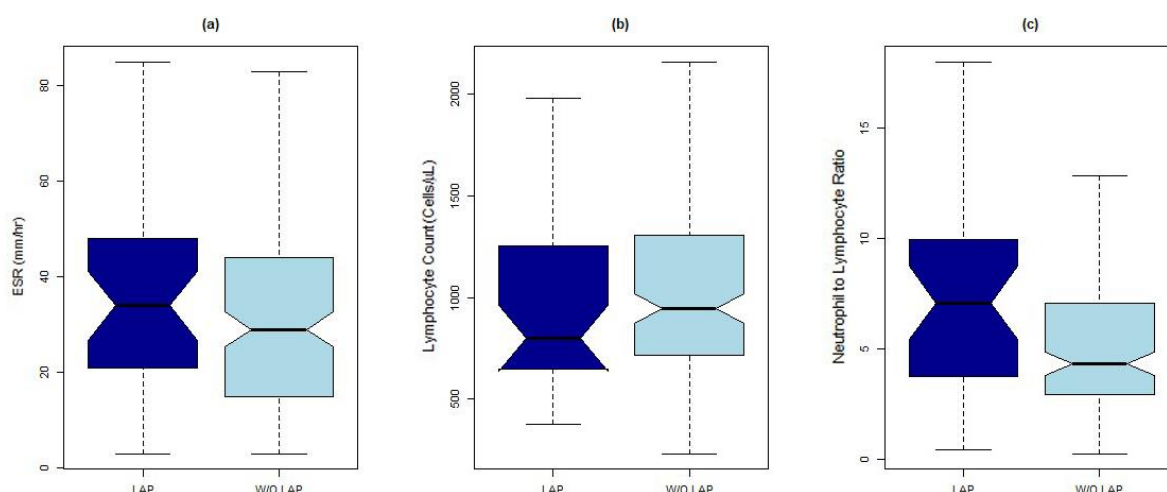
Fig. 3. Comparison of (a) ESR (b) the median lymphocyte count (c) neutrophil to lymphocyte ratio in the mediastinal lymphadenopathy group to the opposite group

patients with LAP were older, with a median age of 62 (IQR 53-74 yrs.). Furthermore, we found significant differences between patients with and without lymphadenopathies regarding oxygen saturation, length of hospital stay, invasive ventilation, ICU admission during hospitalization, disease progression, and severity of COVID-19.

As Valette et al. observed a higher prevalence of mediastinal lymphadenopathy in critically ill patients and considered it as a risk factor for disease severity (19), we detected mediastinal lymphadenopathies significantly more frequent in patients who died during hospitalization than those discharged (14 [40%] of 35 vs. 34 [21%] of 160, p= 0·03).

In a study of 650 patients, mediastinal lymphadenopathy reflected increased inflammation in patients with COVID-19 disease and may be predicted 30-day mortality (24). In addition, we observed laboratory tests indicating significantly lower absolute lymphocyte count, higher Neutrophil-to-Lymphocyte

Ratio, and higher ESR levels in the lymphadenopathy group. However, according to our observation, there was no evidence of these laboratory findings between the two groups: hemoglobin, platelets, liver enzymes, Creatine Phosphokinase (CPK), cardiac enzyme, lactate dehydrogenase (LDH), prothrombin time (PT), and C-reactive protein (CRP).

A few limitations in this case-control study, such as its relatively small sample size, may lead to biased results. In addition, the mechanism of development of mediastinal lymphadenopathy and its relationship with bacterial or fungal infection was not investigated due to the lack of lymph node sampling facilities, which requires further studies. Also, since the study was performed in one hospital where almost all its patients have a comparably higher socio-economic level, it may not translate to other social classes.

CONCLUSION

In summary, our study showed a relatively high prevalence of mediastinal lymphadenopathy in COVID-19 patients, which was more common in the elderly with low oxygen saturation.

In this observation, COVID-19 patients with mediastinal lymphadenopathy were relatively required to receive intensive care and mechanical ventilation. As a result, these patients show a higher mortality rate. Therefore, mediastinal lymphadenopathy can be considered a poor prognostic factor.

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