Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Mediastinal lymph node enlargement in COVID-19: Relationships with mortality and CT findings

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ABSTRACT

Background: The presence of mediastinal lymph node enlargement (MLNE) in computed tomography (CT) of Coronavirus disease 2019 (COVID-19) patients can be associated with disease severity.
Objectives: To investigate the relationship between MLNE with intensive care unit admission (ICU), mortality rates, and CT findings, especially in early-stage COVID-19 patients.
Methods: This single-center retrospective case-control study, included aged ≥18 years, 250 COVID-19 patients with positive RT-PCR tests. We included two patient groups, 125/250 with and without MLNE. Demographic information of the patients, laboratory findings, length of stay in hospital or ICU, mortality rates, initial CT imaging findings and CT severity scores (CT-SS) were recorded and their relationship with MLNE was investigated.
Results: Patients with MLNE were older (69.61 ± 11.16; $p < 0.001$) and had a higher CT-SS (14.67 ± 7.55; $p < 0.001$). There was a significant difference between the presence of MLNE with mortality (58/77, 75.3%; $p < 0.001$) and ICU admission (49/61, 80.3%; $p < 0.001$). Also, a statistical association was found between MLNE with ICU admission ($p = 0.001$) and ($p < 0.001$) mortality rates in patients with CORADS≤2 CT findings. In multivariate logistic regression analysis, MLNE was 8.8-fold (95% CI: 1.62–47.86, $p = 0.01$) more correlated with linear opacity and 0.25-fold with bronchial wall thickening (95% CI: 0.07–0.92, $p = 0.04$).
Conclusion: Mediastinal lymph node enlargement is an important CT finding that can predict the severe prognosis of COVID-19 patients. Even in patients without lung involvement on initial CT, the presence of MLNE should be carefully examined as it is associated with disease severity.

Introduction

COVID-19 is a progressive viral disease that can cause widespread morbidity and mortality worldwide.[1] This disease has typical pulmonary symptoms and can be severe, affecting many extrapulmonary systems.[2] For this reason, the patient should be diagnosed in the early phase and the imaging findings showing the progression of the disease should be known. Some of these factors are older age, male gender, and comorbidities.[3–5] A computed tomography (CT) performed in the first 4 days after the onset of symptoms may be negative.[6] This may make it difficult to predict the prognosis of patients with a positive reverse transcription-polymerase chain reaction (RT-PCR) test. The presence of typical thorax CT findings of COVID-19 pneumonia provides early diagnosis without waiting for RT-PCR test results. The typical CT findings are bilateral peripheral, multifocal ground-glass opacities (GGOs), consolidation, crazy paving pattern, halo and reverse halo signs. GGOs with or without consolidation is the most common CT finding of COVID-19.[7] Among the atypical features, the most common are mediastinal lymph node enlargement (MLNE), linear opacities, tree-in-bud sign, inter and intralobular septal thickening, cavitation and pleural effusion.[8]

MLNE can occur as a result of infectious and non-infectious causes and is defined as enlargement of the lymph node short axis is ≥ 10 mm.[9] It is often associated with comorbidities such as heart failure, malignant diseases, and sarcoidosis. In addition, it has been found that the district where the person lives and smoking history are associated with the occurrence of MLNE. MLNE is not the typical chest CT finding in COVID-19 pneumonia.[10] However, atypical findings such as MLNE are associated with the prognosis of patients with COVID-19.[11]

The incidence of MLNE in patients with COVID-19 pneumonia is 0%–66%, and the relationship between CT findings has not been demonstrated in the literature yet.[10] The higher mortality rate in hospitalized COVID-19 patients with MLNE than those without MLNE suggested that it should be investigated as a prognostic factor for serious disease.[12] The presence of MLNE in patients with idiopathic pulmonary fibrosis (IPF) is thought to be a result of a higher degree of

Abbreviations: MLNE, mediastinal lymph node enlargement; CT-SS, computed tomography severity score; ICU, intensive care unit; GGO, ground-glass opacity

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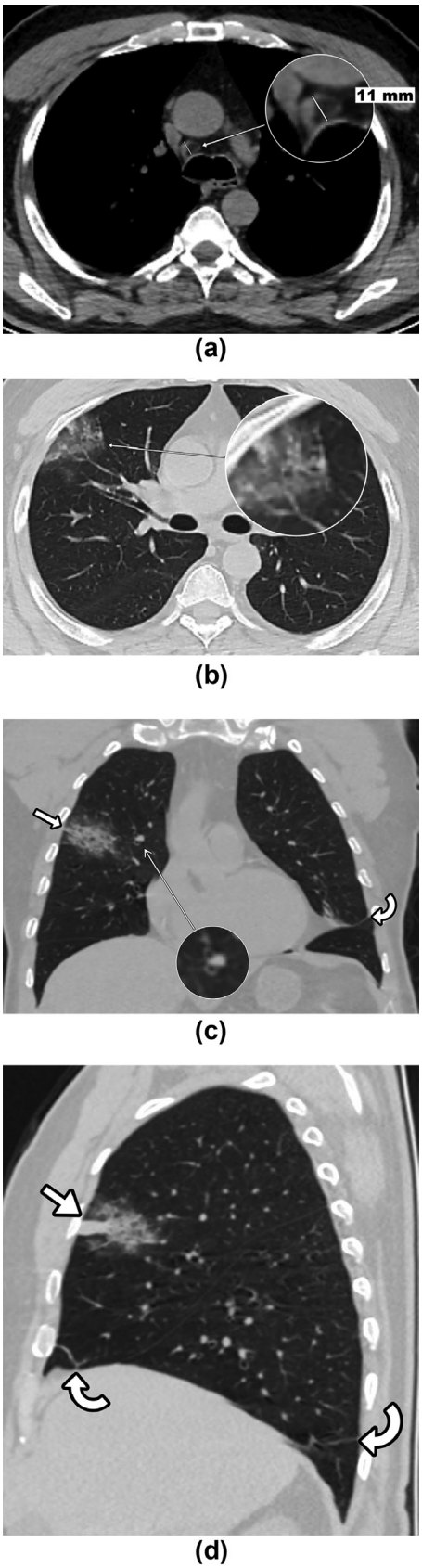

Fig. 1. a–d A 66-year-old male patient with COVID 19 has a positive RT-PCR test. In the first CT, CT-SS:3, CORADS 3 (a) In the axial non-contrast CT, the short axis of the subcarinal lymph node was measured 11 mm in the mediastinal window. (b) In the axial parenchyma window, right lung upper lobe peripheral localized interlobular septal thickening and GGO accompanied by an increase in bronchial wall thickness were observed. (c) In the coronal parenchyma window, interlobular septal thickening located peripherally in the right lung upper lobe and GGO accompanied by an increase in bronchial wall thickness were observed. The GGO area indicated by the arrow and the bronchial wall thickness increase is shown are magnified. The arrow shows the linear opacity area in the left lung lower lobe. (d) In the sagittal parenchyma window, the GGO area (arrow) accompanied by peripheral localized consolidation in the right lung upper lobe, linear opacity areas (oblique arrows) were observed.

chronic inflammation, and a correlation has been shown between disease severity of IPF and MLNE in the literature.[13]

We aimed to investigate the relationship between MLNE with intensive care unit admission (ICU), mortality rates, and intraparenchymal CT findings, especially in early-stage COVID-19 patients.

Methods

This study was approved by the Ethical Committee of Amasya University Faculty of Medicine and was conducted according to the Declaration of Helsinki and Good Clinical Practice (06 January 2022, number: 04). The study is retrospective, patient information was obtained from electronic records and censored. Since the study was retrospective, the ethics committee did not find it necessary to obtain written informed consent from the patients.

Study population and data collection

Our study is a single-center, retrospective, case-control study. Our study analyzed the data of 250 patients who applied to our hospital's Emergency Service and COVID-19 polyclinic between January 2021 and May 2021. Patients over the age of 18 with at least one positive RT-PCR test were included in our study. Patients with negative RT-PCR test, with lung and other malignancies, under 18 years of age, pregnant women and patients who had image artifacts on their CT scans were excluded from the study. Demographic information, laboratory findings, length of stay in hospital or ICU, mortality rates, first CT imaging findings and CT-SS were recorded.

Sample size

The study sample was determined as a total of 228 patients, with at least 114 in both groups, with an effect size of 0.40, α = 0.05, and power (1-β) = 0.85 using the G-power program. Two groups were performed, 125 patients with MLNE and 125 without MLNE (control).

Clinical and laboratory data

The laboratory results obtained within 1 day from the initial chest CT date and comorbidities such as diabetes, chronic lung and cardiovascular diseases, admission to the hospital and/or ICU, and the dates of death were scanned from our hospital's electronic medical records. The patient's length of stay in the service and ICU and their survival were recorded.

CT protocol

The non-contrast chest CT scans were performed using the multidetector CT (MDCT) scanners 128-slice GE Healthcare Revolution EVO CT (GE Medical Systems; Milwaukee, WI). Tube voltage, 120 kV; tube current, 100–450 mA; beam collimation, 64 mm $\times$ 0.625 mm; beam pitch, 1.375; gantry rotation, 0.4 s; acquisition direction, craniocaudal; reconstruction kernel, standard; slice thickness, 0.625 mm; and section overlap, 0.625 mm. All chest CT scans were assessed at lung window of 1500 WW and −450 WL and mediastinal window of 400 WW and 40 WL. The non-contrast chest CT is acquired during a single breath-hold. Craniocaudal axial images were obtained from the beginning of the thorax to the abdomen (middle part of the kidneys) with the patient in deep inspiration and supine position.

Image analysis

The chest CT scan at admission to the hospital was evaluated for the presence of COVID-19 pneumonia and MLNE by a radiologist with 8 years of experience. Initial CTs were reported using the Coronavirus disease 2019 Reporting and Data System (CO-RADS) based on suspicions of COVID-19 lung involvement, 1 to 5 (1 = very low, 2 = low, 3 = uncertain, 4 = high, and 5 = very high, i.e. typical findings). GGOs, which are the typical finding of COVID-19 pneumonia, were present in CORADS≥ 3.[14] The CT-SS was calculated visually using a previously defined semi-quantitative CT severity scoring system ranging from 0-25. Scoring was done in the range of 0–5 according to the percentage of involvement of each lobe (0 = 0%, 1 = 1–5%, 2 = 6–25%, 3 = 26–50%, 4 = 51–75% and 5 = >75%), and the scores of the 5 lobes were summed to obtain a total CT-SS.[15–17] The mediastinal lymph node short axis was measured on routine axial CT images. If the short axis was ≥ 10 mm, it was accepted as MLNE (Fig. 1).[9] Intraparenchymal radiological findings were defined according to Fleischner Society guidelines.[18]

Statistical analysis

Statistical analysis were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2017. Armonk, NY). The conformity of the variables to the normal distribution was examined using Kolmogorov-Smirnov. In descriptive analyses, mean and standard deviation were used for normally distributed variables, median and interquartile range (IQR) were used for non-normally distributed variables. In the comparison of continuous variables according to MLNE groups, Student's t-test was used for those with normal distribution, and the Mann-Whitney U test for those who were not normally distributed. Pearson Chi-square or Fisher tests were used instead of comparing categorical variables according to MLNE groups (in cases where the values displayed in the cells did not meet the assumptions of the Chi-Square test). The main factors related to mortality were evaluated by univariate binary logistic regression analysis. Explanatory variables with p value < 0.25 in the univariate logistic regression analysis were included in multivariate logistic regression analysis.[19] The Hosmer-Lemeshow test was used for model fit. $p < 0.05$ was considered statistically significant.

Table 1
Comparison of the presence of MLNE with demographic data and CT findings.

		Mediastinal lymph node enlargement		Total	P value
		Absent - n (%)	Present - n (%)		
Age≥65	P	52 (36.9)	89 (63.1)	141	<0.001
	A	73 (67.0)	36 (33.0)	109	
Gender	Male	63 (46.7)	72 53.3)	135	0.253
	Female	62 (53.9)	53 (46.1)	115	
Mortality	Death	19 (24.7)	58 (75.3)	77	<0.001
	Alive	106 (61.3)	67 (38.7)	173	
Mortality (CORADS≤2)*	Death	5 (35.7)	9 (64.3)	14	<0.001
	Alive	28 (96.6)	1 (3.4)	29	
Intensive care unit (ICU)	ICU	12 (19.7)	49 (80.3)	61	<0.001
	Non ICU	113 (59.8)	76 (40.2)	189	
ICU (CORADS≤2)*	ICU	4 (36.4)	7 (63.6)	11	0.001
	Non ICU	29 (90.6)	3 (9.4)	32	
GGOs	P	93 (45.1)	113 (54.9)	206	0.001
	A	32 (72.7)	12 (27.3)	44	
Consolidation	P	24 (29.3)	58 (70.7)	82	<0.001
	A	101 (60.1)	67 (39.9)	168	
Crazy paving pattern	P	33 (29.5)	79 (70.5)	112	<0.001
	A	92 (66.7)	46 (33.3)	138	
Reticular pattern	P	70 (37.2)	118 (62.8)	188	<0.001
	A	55 (88.7)	7 (11.3)	62	
Intralobular septal thickening	P	40 (30.8)	90 (69.2)	130	<0.001
	A	85 (70.8)	35 (29.2)	120	
Interlobular septal thickening	P	76 (39.2)	118 (60.8)	194	<0.001
	A	49 (87.5)	7 (12.5)	56	
Linear opacities	P	91 (42.5)	123 (57.5)	214	<0.001
	A	34 (94.4)	2 (5.6)	36	
Subpleural curvilinear line	P	51 (39.2)	79 (60.8)	130	<0.001
	A	74 (61.7)	46 (38.3)	120	
Adjacent pleural thickening	P	54 (35.8)	97 (64.2)	151	<0.001
	A	71 (71.7)	28 (28.3)	99	
Vascular thickening	P	87 (42.2)	119 (57.8)	206	<0.001
	A	38 (86.4)	6 (13.6)	44	
Bronchial wall thickening	P	72 (39.6)	110 (60.4)	182	<0.001
	A	53 (77.9)	15 (22.1)	68	
Bronchiectasis	P	46 (32.4)	96 (67.6)	142	<0.001
	A	79 (73.1)	29 (26.9)	108	
Bronchus distortion	P	25 (26)	71 (74)	96	<0.001
	A	100 (64.9)	54 (35.1)	154	
Reversed Halo sign	P	29 (31.5)	63 (68.5)	92	<0.001
	A	96 (60.8)	62 (39.2)	158	
Halo present	P	47 (39.8)	71 (60.2)	118	0.002
	A	78 (59.1)	54 (40.9)	132	
Tree in bud sign	P	9 (29.0)	22 (71.0)	31	0.013
	A	116 (53.0)	103 (47.0)	219	

n: Number; A: Absent; P: Present.
* Pearson Chi-square or (*) Fisher tests were used to compare categorical variables according to MLNE groups.

Results

The mean age of the total 250 patients included in the study was 64.84 ± 13 years, and the mean age was 69.61 ± 11.16 years in the group with MLNE. MLNE was associated with older age ($p < 0.001$). 89/141 (63.1%) of the patients older than 65 years had MLNE and there was a significant difference ($p < 0.001$). A total of 135/250 (54%) patients were male in the study. 72/135 (53.3%) male patients had MLNE in their CT imagings and there was no significant difference ($p = 0.253$) between gender and presence of MLNE. 26/250 (10.4%) patients were treated as outpatients. 61/250 (24.4%) patients were admitted to ICU; 77/250 (30.8%) patients died in our study. Of the patients without MLNE, 19 (24.7%) died. 49/61 (80.3%) of the patients admitted to the ICU had MLNE and statistically association ($p < 0.001$) was found between MLNE and ICU admission. 58/77 (75.3%) deceased patients had MLNE and there was a significant difference between MLNE and mortality ($p<0.001$). In our study, CTs of 43 patients were reported as CORADS≤2 and 35/43 (81.4%) were reported as CORADS 1. According to the Chi-Square Tests analysis of this group, there was a statistical difference in terms of the presence of MLNE in 7/11 patients with ICU admission (63.6%; $p = 0.001$) and 9/14 (64.3%; $p < 0.001$) mortality. CTs of 207 patients were reported as CORADS≥ 3 and 177/207 (86.35%) were reported as CORADS 5. According to the Chi-Square Tests analysis of this group, there was a statistical association in terms of the presence of MLNE in 42/50 (84%; $p < 0.001$) patients with ICU admission and 49/63 (78.8%; $p < 0.001$) mortality (Table 1).

The mean CT-SS value in the group with MLNE was 14.67 ± 7.55, MLNE was associated with a higher CT-SS value ($p <$ 0,001). GGO (113/206, 54.9%; $p = 0.001$) and consolidation (58/82, 70.7%; $p < 0.001$) which were the typical chest CT findings were significantly higher in the CTs of the group with MLNE. The presence of MLNE was statistically associated with all parenchymal CT findings except the tree-in-bud sign (22/125, 17.4%; $p = 0.013$). The median value of time

Table 2
Comparison of MLNE presence and laboratory data.

	MLNE	n	Mean	SD	25th quarter	50th quarter (Median)	75th quarter	P value
Age	A	125	60.06	14.39				<0.001
	P	125	69.61	11.16				
	T	250	64.84	13.72				
Length of stay in hospital (days)	A	101	15.14	10.67				0.88
	P	123	14.93	9.73				
	T	224	15.03	10.14				
Length of stay in ICU (days)	A	12	13.75	10.00				0.86
	P	50	13.14	10.40				
	T	62	13.26	10.25				
Time between admission to ICU and death (days)	A	10	12.70	9.11				0.97
	P	43	12.56	10.93				
	T	53	12.58	10.53				
Time between hospitalization and death (days)	A	19	25.37	11.57				0.14
	P	58	20.29	13.03				
	T	77	21.55	12.80				
Time from hospital admission to first CT	A	125	2.53	4.93	0	0	3	0.57
	P	125	1.54	2.98	0	0	1	
	T	250	2.03	4.10	0	0	2	
Time between first RT-PCR and first CT	A	125	2.50	4.90	0	1	3	0.95
	P	125	1.47	2.94	0	0	1	
	T	250	1.98	4.07	0	0	2	
CT-SS	A	125	7.66	7.09				<0.001
	P	125	14.67	7.55				
	T	250	11.17	8.11				
CRP (0-5; mg/L)	A	125	48.53	61.69				<0.001
	P	125	75.49	62.67				
	T	250	62.01	63.51				
Ferritin (22-322; ug/L)*	A	125	281.68	430.79	41.30	152.00	343.80	0.01
	P	125	482.51	1183.84	86.20	248.40	495.25	
	T	250	382.10	894.68				
ESR. (0-30; mm/H) First hour	A	125	43.66	25.40				<0.001
	P	125	67.82	86.76				
	T	250	55.74	64.93				
Neutrophil percentage (40.1%-67%)	A	125	68.88	13.88				<0.001
	P	125	75.44	11.95				
	T	250	72.16	13.34				
Lymphocyte percentage (23.6%-48%)	A	125	21.15	10.29				<0.001
	P	125	16.87	9.63				
	T	250	19.01	10.17				
LDH (135-225; U/L)	A	123	302.21	164.56				0.01
	P	124	353.69	156.92				
	T	247	328.06	162.50				
D-dimer (0-0.5; μg/mL)	A	124	1.81	5.34				0.60
	P	123	1.52	2.71				
	T	247	1.67	4.23				
Creatine (0.7-1.2; mg/dl)	A	125	0.96	0.30				0.01
	P	124	1.13	0.69				
	T	249	1.04	0.54				

n: Number; A: Absent; P: Present; T: Total; SD: Standard deviation.

* In the comparison of continuous variables according to MLNE groups, the Student's t-test was used for those with normal distribution and the Mann-Whitney U test for those who were not normally distributed (*).

Table 3
Logistic regression analysis of CT findings with the presence of MLNE.

	Univariate logistic regression analysis				Multivariate logistic regression analysis			
	p value	OR	95% CI		p value	OR	95% CI	
			Lower	Upper			Lower	Upper
GGOs	0.001	3.24	1.58	6.64	0.08	0.33	0.10	1.15
Consolidation	<0.001	3.64	2.07	6.42	0.09	1.86	0.90	3.84
pattern	<0.001	4.79	2.79	8.21	0.27	1.73	0.65	4.59
Reticular pattern	<0.001	13.25	5.72	30.69	0.14	2.57	0.74	8.88
Intralobular septal thickening	<0.001	5.46	3.18	9.40	0.14	2.09	0.78	5.65
Interlobular septal thickening	<0.001	10.87	4.68	25.25	0.21	2.40	0.62	9.33
Linear opacities	<0.001	22.98	5.38	98.12	**0.01**	**8.80**	1.62	47.86
Subpleural curvilinear line	<0.001	2.49	1.50	4.15	0.07	0.48	0.22	1.05
Adjacent pleural thickening	<0.001	4.56	2.63	7.89	0.47	0.71	0.28	1.79
Vascular Thickening	<0.001	8.66	3.51	21.40	0.11	3.52	0.77	16.10
Bronchial wall thickening	<0.001	5.40	2.83	10.30	**0.04**	**0.25**	0.07	0.92
Bronchiectasis	<0.001	5.69	3.27	9.87	0.15	2.07	0.76	5.60
Bronchus distortion	<0.001	5.26	2.99	9.24	0.32	1.51	0.67	3.42
Reversed Halo sign	<0.001	3.36	1.95	5.79	0.65	1.24	0.49	3.10
Halo sign	0.003	2.18	1.32	3.62	0.99	1.00	0.42	2.34
Tree in bud sign	0.015	2.75	1.21	6.25	0.25	1.78	0.66	4.77

OR: odds ratio; 95% CI: 95% confidence interval (Hosmer-Lemeshow test $p = 0.567$).

Table 4
Comparison of comorbidities by presence of MLNE.

		Mediastinal lymph node enlargement		Total	*P* value
		Absent n (%)	Present n (%)		
Chronic lung diseases	P	13 (30.2)	30 (69.8)	43	**0.004**
	A	112 (54.1)	95 (45.9)	207	
Cardiovascular diseases	P	65 (43.3)	85 (56.7)	150	**0.010**
	A	60 (60)	40 (40)	100	
Diabetes mellitus	P	41 (45.1)	50 (54.9)	91	0.237
	A	84 (52.8)	75 (47.2)	159	
Hyperlipidaemia	P	31 (41.9)	43 (58.1)	74	0.096
	A	94 (53.4)	82 (46.6)	176	
Rheumatological diseases*	P	6 (66.7)	3 (33.3)	9	0.308
	A	119 (49.4)	122 (50.6)	241	
Chronic neurological diseases*	P	4 (33.3)	8 (66.7)	12	0.376
	A	121 (50.8)	117 (49.2)	238	
Chronic liver diseases*	P	2 (33.3)	4 (66.7)	6	0.409
	A	123 (50.4)	121 (49.6)	244	
Chronic kidney diseases*	P	125 (50.6)	122 (49.4)	247	0.247
	A	0 (0)	3 (100)	3	

* **Pearson Chi-square or (*) Fisher tests were used to compare categorical variables according to MLNE groups.**

from hospital admission to first CT was 0 (IQR 0–2; $p = 0.57$) and the time between first RT-PCR to first CT was 0 (IQR 0–2; $p = 0.95$) (Table 2).

In the MLNE group, the mean CRP value was 75.49 ± 62.67 ($p < 0.001$); median ferritin value was 248.40 (IQR 86.2–495.25; $p = 0.001$); mean erythrocyte sedimentation rate (ESR) value was 67.82 ± 86.76 ($p < 0.001$) and presence of MLNE was related with higher serum CRP, ferritin and ESR values.

In multivariate logistic regression analysis, linear opacity was 8.8-fold higher [odds ratio (OR): 8.80; 95% CI 1.62–47.86, $p = 0.01$] and bronchial wall thickening 0.25-fold higher (OR: 0.25; 95% CI 0.07–0.92, $p = 0.04$) in the CT imaging of patients with MLNE (Table 3).

There was a statistical association between a history of chronic lung disease (30/43, 69.8%; $p = 0.004$) and cardiovascular diseases (85/150, 56.7%; $p = 0.010$) with MLNE (Table 4). Among the comorbidities, only chronic lung disease was statistically associated with MLNE in multivariate logistic regression analysis (OR: 2.44; 95% CI 1.99–5.01, $p = 0.01$) (Table 5).

In the multivariate logistic regression analysis of CT findings, comorbidities, and laboratory parameters, age was approximately 1.1-fold (OR: 1.105; 95% CI 1.060-1.151, $p < 0.001$) and MLNE was approximately 5-fold (OR: 4.954; 95% CI 1.986–12.362, $p = 0.001$), interlobular septal thickening approximately 21-fold (OR: 21.020; 95% CI 2.741–161.211, $p = 0.003$) and hyperlipidaemia approximately 3.3-fold (OR: 3.292; 95% CI 1.399–7.744, $p = 0.006$) were riskier in terms of mortality (Fig. 2) (Table 6).

Discussion

In our study, we evaluated the prognostic role of the presence of MLNE and its relationship with CT findings in patients with COVID-19. In addition, we evaluated the frequency of MLNE in patients with COVID-19, its relationship with the length of stay in the service and ICU, and its association with comorbidities. Our results showed an association between the presence of MLNE with older age, increased inflammatory markers, high CT-SS, increased death and ICU hospitalization rates. The presence of MLNE was found to be 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). There was no difference between MLNE and gender. Parenchymal chest CT findings were more common in the group with MLNE. In multivariate

Table 5
Logistic regression analysis of comorbidities with the presence of MLNE.

	Univariate logistic regression analysis				Multivariate logistic regression analysis			
	p value	OR	95% CI		P value	OR	95% CI	
			Lower	Upper			Lower	Upper
Chronic lung diseases	0.005	2.721	1.343	5.511	0.015	2.439	1.188	5.01
Cardiovascular diseases	0.01	1.962	1.173	3.28	0.117	1.607	0.889	2.905
Diabetes mellitus	0.237	1.366	0.814	2.291	0.667	1.131	0.645	1.984
Hyperlipidemia	0.098	1.59	0.919	2.752	0.673	1.146	0.608	2.16
Chronic neurological diseases	0.246	2.068	0.606	7.054	0.261	2.047	0.587	7.136
Rheumatological diseases	0.318	0.488	0.119	1.995				
Chronic liver diseases	0.418	2.033	0.366	11.306				

OR: odds ratio; 95% CI: 95% confidence interval (Hosmer-Lemeshow test $p = 0.476$)

Table 6
Multivariate analysis of CT findings, comorbidities and laboratory parameters for mortality.

	Univariate logistic regression analysis				Multivariate logistic regression analysis			
	P value	OR	95% CI		P value	OR	95% CI	
			Lower	Upper			Lower	Upper
Age	<0.001	1.105	1.071	1.139	<**0.001**	**1.105**	**1.060**	**1.151**
Gender (Male)	0.478	0.823	0.481	1.41				
CT severity score	0.004	1.051	1.016	1.087	0.963	1.002	0.940	1.067
MLNE	<0.001	4.83	2.646	8.815	**0.001**	**4.954**	**1.986**	**12.361**
GGOs	0.872	0.944	0.469	1.901				
Consolidation	0.167	1.485	0.847	2.604				
pattern	0.215	1.406	0.82	2.41				
Reticular pattern	<0.001	5.664	2.321	13.821	0.833	0.832	0.149	4.641
Intralobular septal thickening	0.103	1.572	0.912	2.71				
Interlobular septal thickening	<0.001	10.894	3.286	36.124	**0.003**	**21.020**	**2.741**	**161.211**
Linear opacities	0.005	5.814	1.725	19.596	0.493	0.469	0.054	4.082
Subpleural curvilinear line	0.057	1.699	0.983	2.934				
Adjacent pleural thickening	0.004	2.395	1.327	4.324	0.191	0.465	0.148	1.466
Vascular Thickening	0.022	2.721	1.154	6.415	0.732	0.722	0.111	4.685
Bronchial wall thickening	0.007	2.593	1.296	5.186	0.390	0.467	0.082	2.651
Bronchiectasis	0.011	2.084	1.182	3.674	0.355	0.608	0.212	1.745
Bronchus distortion	0.071	1.654	0.958	2.856				
Reversed Halo sign	0.85	1.055	0.605	1.838				
Halo sign	0.144	0.666	0.387	1.148				
Tree in bud sign	0.31	1.496	0.687	3.26				
Any_comorbidity	0.366	1.332	0.716	2.481				
Chronic lung diseases	0.319	1.418	0.714	2.819				
Cardiovascular diseases	0.106	1.592	0.906	2.798	0.192	0.552	0.226	1.347
Diabetes mellitus	0.994	0.998	0.571	1.743				
Hyperlipidemia	0.032	1.871	1.056	3.315	**0.006**	**3.292**	**1.399**	**7.744**
Rheumatological diseases	0.223	0.271	0.033	2.208				
Chronic neurological diseases	0.044	3.36	1.031	10.946	0.986	1.014	0.205	5.021
Chronic liver diseases	0.892	1.127	0.202	6.286				
CRP	0.028	1.005	1.000	1.009	0.871	0.999	0.993	1.006
Ferritin	0.014	1.001	1.000	1.001	0.495	1.000	0.999	1.001
ESR	0.994	1.000	0.996	1.004	0.115	0.988	0.973	1.003
Neutrophil percentage	<0.001	1.042	1.018	1.066	0.900	0.996	0.934	1.062
Lymphocyte percentage	<0.001	0.947	0.918	0.976	0.694	0.983	0.903	1.070
LDH	<0.001	1.004	1.002	1.006	0.064	1.003	1.000	1.006
D-dimer	0.014	1.156	1.029	1.299	0.108	1.110	0.977	1.262
Creatine (0.7-1.2; mg/dl)	0.007	2.999	1.352	6.652	0.316	1.335	0.759	2.345

OR: odds ratio; 95% CI: 95% confidence interval (Hosmer-Lemeshow test $p = 0.393$)

analysis, linear opacity and increased bronchial wall thickness on CT scans and a history of chronic lung disease were associated with a higher frequency of MLNE. In addition, older age, MLNE, interlobular septal thickening and hyperlipidaemia were riskier in multivariate logistic regression analysis for mortality. There was no significant difference in terms of the presence of MLNE with the time from hospitalization (service or ICU) to death.

During the peak of the COVID-19 pandemic, the most important problem in many health institutions was the lack of ICU and service beds. Especially at the beginning of the pandemic when PCR testing was not common, CT was more important in the diagnosis of COVID-19. It was reported that the typical CT findings are less common in the early period (0-4 days) and the CT-SS is mostly calculated as 0.[6] Therefore, we do not have enough information about the prognosis of PCR positive COVID-19 patients without lung involvement in the early period (CORADS 1 or 2). Satıcı et al. investigated the relationship between MLNE and mortality in their study. They reported that patients with MLNE were older, had at least one comorbidity, and were associated with increased mortality.[20] In our study, the presence of MLNE was associated with higher mortality rates and worse prognosis in COVID-19 patients with CORADS≤2 CT findings in the early period. In Satıcı et al.'s study, 60/650 patients (9.2%) had MLNE, which was less than our study. In addition, the mean age was lower than in our study. In our study 75.3% of the deceased patients had MLNE and in the study of Satıcı et al., 19.65% of deceased patients had MLNE. So, in our study, patients with MLNE were significantly

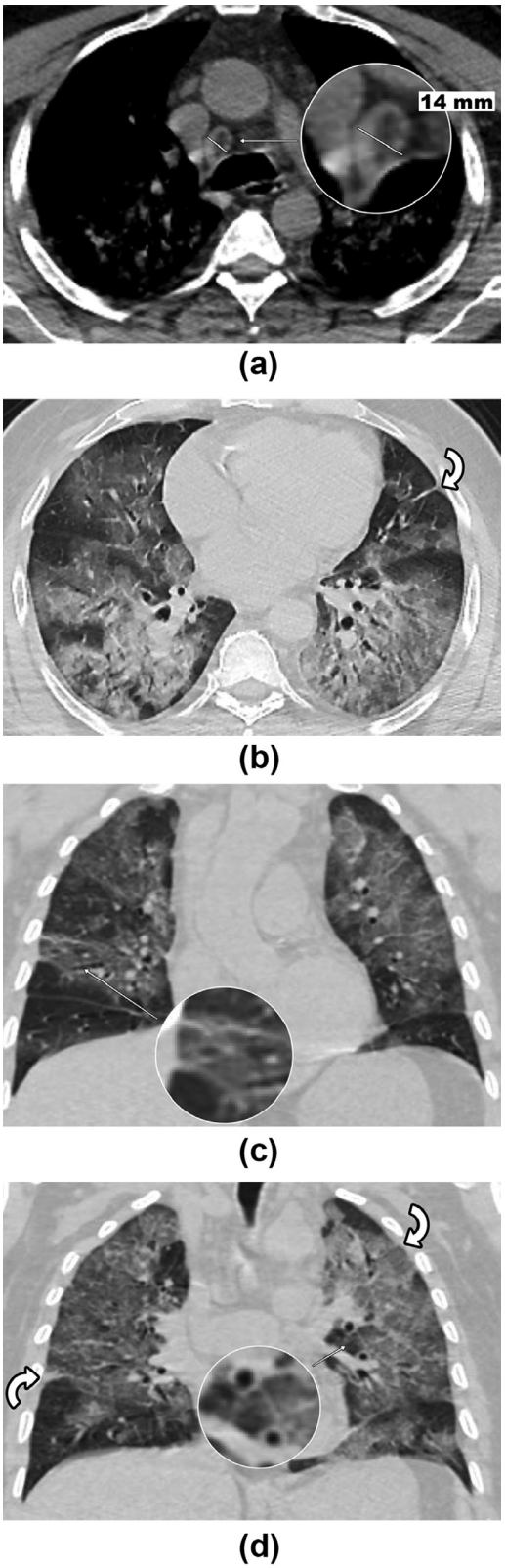

Fig. 2. a–d In the CT performed 8 days after hospitalization of the same patient, CORADS 5 and CT-SS increased to 25 points. He died on the 11th day of his admission to the ICU. On follow-up CT, typical findings of COVID 19 pneumonia commonly include GGOs, consolidation and crazy-paving patterns. (a) In axial CT, the short axis of the subcarinal lymph node in the mediastinal window increased and was measured 14 mm. Also, the number of mediastinal lymph nodes increased. (b) Diffuse crazy-paving patterns in both lungs and linear opacity in the anterior segment of the left lung upper lobe were observed in the axial parenchyma window. (c) GGO with linear opacity extending vertically to the parenchyma and increased bronchial wall thickness was observed in the magnified image of the right lung in the coronal parenchyma window. (d) In the coronal parenchyma window, oblique arrows show linear opacities in both lungs, while the magnified image shows the increase in bronchial wall thickness.

higher. In addition, in both studies, the presence of MLNE was associated with increased mortality in logistic regression analysis.[20]

Sardanelli et al. reported that there was no significant difference between the presence of MLNE with age, hospitalization in the ICU, length of hospital stay, laboratory results, but the frequency of death was high in the group with MLNE.[12] In our study, similar to Sardanelli et al. and Silva et al.'s studies, there was no significant difference between the presence of MLNE and gender, length of stay in hospital and ICU, but the frequency of death was significantly higher.[12,21] But, in our study, there was an equal number of positive and negative patient groups according to the presence of MLNE. Unlike the literature, we found that patients with MLNE had a higher value of age, infection laboratory findings (CRP, ESR and Ferritin), CT-SS, and intensive care unit admission.

Patients with severe or progressive COVID-19 pneumonia had a significantly higher frequency of consolidation, linear opacities, crazy laying pattern, bronchial wall thickening, MLNE, pericardial effusion, and pleural effusion.[22–26] The most common CT findings in patients with severe infection and ICU hospitalization are GGOs with consolidation.[23] Although interlobular septal thickening is not among the most common CT findings of COVID-19 pneumonia cases, it often occurs in severe pneumonia and prolonged disease.[27,28] In the multivariate logistic regression model in our study, interlobular septal thickening was approximately 21-fold increased the mortality risk. According to Hashemimadani et al.'s meta-analysis, there was no significant relationship between the presence of consolidation and the severity of the disease.[26] In our study, there was no significant relationship between the presence of consolidation and the prognosis of the patients. This may be due to the inclusion of chest CT at admission to our study. Consolidation is often seen in the mid-late stage of the disease. Satıcı et al. found that only the crazy-paving pattern was significantly higher in the group with MLNE in the study.[20] In our study, the incidence of all CT parenchymal findings (typical and atypical) except the tree-in-bud was high in the patient group with MLNE.

We found that linear opacities and bronchial wall thickening are riskier for the presence of MLNE. Linear opacities often observed on follow-up chest CT scans, indicate lower segment atelectasis or pneumonia and are indicative of fibrosis. This may be related to the increase in the severity of the disease.[29,30] Bronchial wall thickening due to increased vascular endothelial growth factor (VEGF) in severe disease is thought to increase the severity of the disease and airflow resistance.[31,32] Consistent with the literature, linear opacities and bronchial wall thickness was associated with an increased frequency of MLNE in our study.

In the literature, two studies except Sardanelli F. et al.'s study reported a relationship between older age and MLNE.[12,20,33] Angiotensin-converting enzyme 2 (ACE-2) is important in the entry of the virus into the cell, and its expression increases with age, so there is a higher risk for Covid-19 mortality in the elderly.[34] Consistent with the literature, the presence of MLNE was also associated with higher age in our study. In addition, in older patients, the possibility of comorbidities increases and immunity weakens. In Meyer et al.'s meta-analysis of the effect of their extrapulmonary findings on mortality, they reported that MLNE increased the risk of mortality approximately two-fold.[11] Consistent with the literature, in our study, we think that the relationship between chronic lung disease and cardiovascular diseases with the presence of MLNE is an important factor in the exacerbation of the infection.[24]

Like other studies in the literature, there was no relationship between gender and MLNE in our study.[12,25] This shows that gender is not a risk factor for the presence of MLNE. Satıcı et al. reported that there was no significant difference between MLNE and gender, as in

our study.[20] In addition, while comorbidities and MLNE were unrelated in their study, the frequency of MLNE was significantly higher in patients with chronic lung diseases and cardiovascular diseases in our study.

To our knowledge, our study is the first to examine the association between the presence of MLNE with mortality and ICU hospitalization in early-period COVID-19 patients with CORADS≤2 CT findings. A significant relationship was found between MLNE and ICU hospitalization and mortality. Our results suggested that we can have information about the prognosis of patients with COVID-19 by evaluating the presence of MLNE when the CT-SS is zero. In addition, we found that linear opacities and increased bronchial wall thickness, which is seen in severe disease, are common in patients with MLNE, consistent with the literature.

There were some limitations in our study. First of all, our study was a single-center retrospective study. No classification was made according to mediastinal lymph node stations. The smoking of the patients was not questioned in terms of pack/year. CTs at the time of admission were used, and some of our patients did not have follow-up CT. Therefore, the mediastinal lymph node size of the patients could not be evaluated after treatment.

In conclusion, the presence of mediastinal lymph node enlargement is associated with linear opacity and increased bronchial wall thickness, which are CT findings of severe disease. MLNE is a predictive factor of increased CT severity score and mortality risk in COVID-19. Therefore, evaluation of the mediastinum for the presence of MLNE on CT may be useful for prognosis.

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Ethical approval

This study was approved by the Ethical Committee of Amasya University Faculty of Medicine and was conducted according to the Declaration of Helsinki and Good Clinical Practice (06 January 2022, number: 04) and the requirement for informed consent was waived.

Declaration of Competing Interest

In this study, there were no competing interests or financial benefits to the authors.

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