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Editorial Board Member of *World Journal of Clinical Cases*, Jing Liu, MD, PhD, Chief Doctor, Professor, Department of Neonatology and NICU, Beijing Chaoyang District Maternal and Child Healthcare Hospital, Beijing 100021, China. liujingbj@live.cn

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Mediastinal lymphadenopathy in COVID-19: A review of literature

Pahnwat Tonya Taweeseedt, Salim Surani

ORCID number: Pahnwat Tonya Taweeseedt 0000-0002-5791-6920; Salim Surani 0000-0001-7105-4266.

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Pahnwat Tonya Taweeseedt, Department of Medicine, Corpus Christi Medical Center, Corpus Christi, TX 78404, United States

Salim Surani, Department of Pulmonary Critical Care and Sleep Medicine, Texas A and M Health Science Center, Bryan, TX 77807, United States

Corresponding author: Salim Surani, FACC, FACP, FCCP, MD, Professor, Department of Pulmonary Critical Care and Sleep Medicine, Texas A and M Health Science Center, 8441 Riverside Pkwy, Bryan, TX 77807, United States. srsurani@gmail.com

Abstract

A novel coronavirus disease 2019 (COVID-19) is a progressive viral disease that affected people around the world with widespread morbidity and mortality. Patients with COVID-19 infection typically had pulmonary manifestation but can also present with gastrointestinal, cardiac, or neurological system dysfunction. Chest imaging in patients with COVID-19 commonly show bilateral lung involvement with bilateral ground-glass opacity and consolidation. Mediastinal lymphadenopathy can be found due to infectious or non-infectious etiologies. It is commonly found to be associated with malignant diseases, sarcoidosis, and heart failure. Mediastinal lymph node enlargement is not a typical computer tomography of the chest finding of patients with COVID-19 infection. We summarized the literature which suggested or investigated the mediastinal lymph node enlargement in patients with COVID-19 infection. Further studies are needed to better characterize the importance of mediastinal lymphadenopathy in patients with COVID-19 infection.

Key Words: Mediastinal lymphadenopathy; Lymph node enlargement; COVID-19; Novel corona virus; Long term coronavirus disease-sequela; Coronavirus disease complications

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Core Tip: This reviewed summarized the articles with mediastinal lymphadenopathy evaluation in the patients with a novel coronavirus disease 2019. The content will help understand more regarding current prevalence of mediastinal lymphadenopathy in this population.

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INTRODUCTION

A novel coronavirus disease 2019 (COVID-19) is a progressive viral disease caused by the severe acute respiratory syndrome coronavirus 2 which initially was reported as a severe flu-like illness related to seafood in wet animal wholesale market in Wuhan, Hubei province, China in December 2019^[1]. In January 2020, severe acute respiratory syndrome coronavirus 2 was identified as the causative pathogen and in February 2020 COVID-19 was named by the World Health Organization^[2]. Person-to-person transmission is the main route of COVID-19 transmission and it can occur even during the incubation period^[3]. COVID-19 rapidly spreads worldwide reaching the pandemic level. COVID-19 has affected people around the world with widespread morbidity and mortality especially in the elderly population with co-morbidities^[4]. COVID-19 has a mean incubation period of approximately 5 d^[5]. Patients with COVID-19 infection typically had mild symptoms or even asymptomatic^[5]. Thus, early diagnosis of COVID-19 infection is very crucial. For symptomatic cases, fever, dry cough, fatigue, and dyspnea are commonly reported. Pulmonary manifestation is frequently found and progresses rapidly but other organ dysfunction such as gastrointestinal, cardiac, or neurological system dysfunction can also present^[6]. The high level of inflammatory markers, cytokines, and chemokines in the serum of patients with COVID-19 was reported. The reverse transcription-polymerase chain reaction is considered the gold standard of diagnosis for COVID-19 infection^[7].

IMAGING MODALITIES

Imaging of the chest is an important diagnostic and follow-up tool for the pulmonary manifestation of COVID-19. Chest X-ray (CXR) is commonly used as it provides faster information than reverse transcription-polymerase chain reaction. However, the CXR finding can be normal in the early stage of COVID-19 infection^[8-10]. CXR generally reveals pure ground glass, mixed ground-glass opacities-consolidation in bilateral peripheral and lower lungs zones^[11]. Specificity and sensitivity of CXR for COVID-19 infection increased with time (sensitivity of 55% at ≤ 2 d increased to 79% at > 11 d) while specificity decreased with time (specificity of 83% decreased to 70%)^[9]. The increase false negative of COVID-19 infection on CXR was found in young age and African-American ethnicity^[9]. When compare to CXR, computer tomography (CT) of the chest in patients with COVID-19 showed higher sensitivity in detecting lung abnormality (CT chest 86.2% *vs* CXR 49.1%)^[8] (Figure 1).

CT chest frequently showed bilateral lung involvement with bilateral multi-lobar ground-glass opacity (GGO) with peripheral or posterior distribution especially lower lobes and less commonly in the right middle lobe (Figure 2)^[12]. Consolidation may be found on the presentation or superimposed on GGO, mainly in older age cases^[3,4]. Less common findings were septal thickening, bronchiectasis, and pleural involvement^[12]. Rare findings include lymphadenopathy, pleural effusion, cavitory lesion, and pneumothorax were reported.

The point-of-care ultrasonography performing bedside can also use to evaluate pulmonary pathology at the bedside without the necessity of transporting the patients. In a retrospective single-center study of a total of 22 patients with COVID-19 infection, diffuse B line patterns were found by ultrasonography in all cases^[13]. Ultrasonography can also be used to monitor the disease response to prono-supination maneuvers in patients with COVID-19. However, it requires a longer operator-patient contact time than other imaging studies which may prevent it from being the imaging of choice. High definition transthoracic ultrasonography was used to evaluate mediastinal lymphadenopathy in sarcoidosis patients with sensitivity and specificity of 89% and 76%, respectively^[14]. In COVID-19 cases, ultrasonography has not yet reported the finding of mediastinal lymphadenopathy.

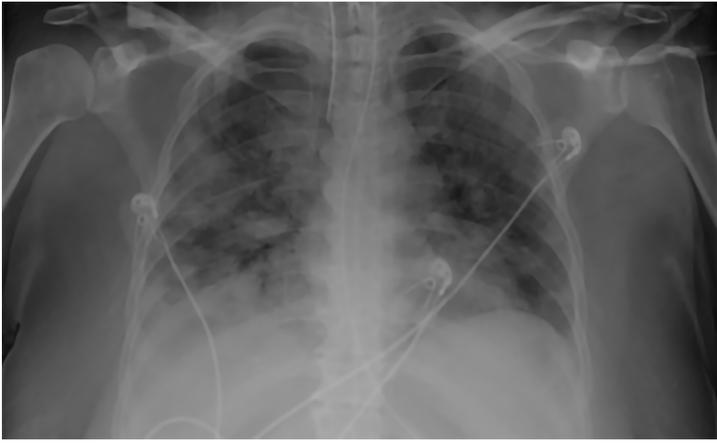


Figure 1 The typical chest X-ray finding of a patient with coronavirus disease 2019 infection showing bilateral infiltration.

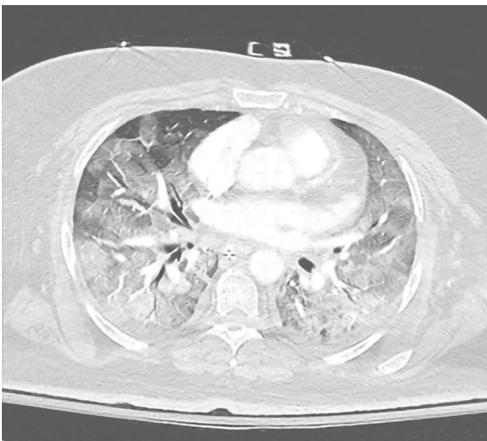


Figure 2 The typical computer tomography of the chest finding of a patient with coronavirus disease 2019 infection showing bilateral ground-glass opacity.

MEDIASTINAL LYMPHADENOPATHY

Mediastinal lymph nodes are seen in the anterior, middle, and posterior mediastinal compartments of the thorax. Mediastinal lymph nodes receive its drainage from the thoracic viscera. Mediastinal lymphadenopathy was defined as mediastinal lymph nodes enlargement with a ≥ 10 mm in short axis^[15]. The incidence of mediastinal lymphadenopathy was noted to be 1%-6%^[16]. Mediastinal lymphadenopathy can be found due to malignant or benign etiologies such as inflammation or infection. Evison *et al*^[17] reported that the size of hilar or mediastinal lymph node was the strongest predictor of etiology, with the size of 15 mm or less always reactive and the size of larger than 25 mm predict pathologic etiology. It is commonly found to be associated with malignant diseases, sarcoidosis, and heart failure^[18]. Lymphoma is the most common cause of mediastinal lymphadenopathy. Unlike other lymphadenopathies, mediastinal lymphadenopathy is uncommonly caused by infection. Histoplasmosis, coccidioidomycosis, and tuberculosis were reported to cause mediastinal lymphadenopathy. Exposure history, endemic location along with patients' symptoms and physical examination are helpful with the diagnosis. Mediastinal lymphadenopathy is commonly asymptomatic. However, it may contribute to pain, cough, wheezing, dysphagia, airway erosion leading to hemoptysis, obstruction of the airway leading to atelectasis, and the obstruction of the great vessels leading to superior vena cava syndrome. Mediastinal lymphadenopathy can be detected from chest X-ray, but a CT scan of the chest is usually performed as the next step to evaluate the lymph nodes as CT chest gives better delineation and characteristics of the lymph nodes such as calcification and necrosis.

MEDIASTINAL LYMPHADENOPATHY IN CORONAVIRUS DISEASE 2019 INFECTION

Mediastinal lymph node enlargement was not considered a typical CT chest finding of patients with COVID-19 infection. We summarized the literature which investigated mediastinal lymph node enlargement in patients with COVID-19 infection. Further studies are needed to better investigate the importance of mediastinal lymphadenopathy in patients with COVID-19 infection. We conducted a literature review of mediastinal lymphadenopathy evaluation in patients with COVID-19 infection from inception to November 2020 in PubMed (Figure 3). Keywords of "mediastinal lymphadenopathy" or "mediastinal lymph node" or "lymphadenopathy" and "COVID" or "coronavirus" were used. A total of 19 articles with a total of 1155 patients were included (Table 1).

Mediastinal lymphadenopathy was found in 0%-66% of the cases with COVID-19 infection. Subjects from a total of 8 articles (7 retrospective reviews and 1 case report) were noted to have mediastinal lymphadenopathy. In 4 case reports and 8 retrospective reviews with assessment of lymphadenopathy among patients with COVID-19, no mediastinal lymphadenopathy was found. In the case report of 2 cases by of elderly female and male 1/6/10R and 2R/4R/4L respectively on the both their first CT chest and their repeat CT chest after 6 d^[19]. In a retrospective review of CT chest in pediatric patients with COVID-19, mediastinal lymphadenopathy was found in 0%-8.1% of the cases^[20,21]. Mediastinal lymphadenopathy was not reported in pregnancy patients with COVID-19^[22]. The mediastinal lymphadenopathy detected on high-resolution CT chest was 1.3% in a review of 80 patients with COVID-19^[23]. In Italy, a review of 418 patients and a recent retrospective study of 134 patients with COVID-19 revealed a prevalence of mediastinal lymphadenopathy of 18.2% and 54.8% respectively^[24,25]. No significant difference between patients with and without lymphadenopathy in terms of gender, age, cancer history, non-invasive ventilation, intensive care unit admission, length of hospital stay, laboratory results^[25]. Lymphadenopathy was seen more in inpatient with a crazy-paving pattern on CT than those without and in those who died during hospitalization^[25]. In China, 3 retrospective reviews of 154, 192, and 499 patients with COVID-19 revealed a prevalence of hilar/mediastinal lymphadenopathy of 43.5%, 41.7%, and 19.8% respectively^[26-28]. Valette *et al*^[29] reported that apart from a typical GGO, reticulation, or consolidation features found in all 9 patients with severe COVID-19 who were under invasive mechanical ventilation in intensive care unit in France, 6 patients were found to have mediastinal lymphadenopathy giving this finding the highest percentage of (66%) of mediastinal lymphadenopathy prevalence^[29]. The onset of symptoms and CT findings had the median number of days of 7 (interquartile range 6-8). The subcarinal location of lymphadenopathy was noted in several patients up to 30 mm in the short axis.

The strength of this review is this is the first up-to-date review focusing on mediastinal lymphadenopathy in COVID-19. We used PubMed which is a reliable database. This review has limitations in that we used only published articles that are indexed in the PubMed database. Additionally, we have not reviewed the articles with COVID-19 imaging that may have the data of mediastinal lymph node without having our keywords.

CONCLUSION

Albeit rare in initial reports, mediastinal lymphadenopathy can be found in A novel COVID-19 infection especially in critically ill patients with COVID-19. Evaluating overall clinical condition is important to help with diagnosis, treatment, and prevention in this COVID-19 pandemic era.

Table 1 Summarization of included articles

Ref.	Country	Type of article	n	Age (yr)	Male (%)	Findings	n (%) of ML
Valette <i>et al</i> ^[29]	France	R	9	NA	NA	GGO, reticulation, or consolidation (100%)	6 (66)
Peng <i>et al</i> ^[20]	China	R	201	Median (range); 6 (3 h-15 yr)	118 (58.7)	GGO (69.7%), consolidation (37%)	0 (0)
Bayramoglu <i>et al</i> ^[21]	Turkey	R	37	Median (IQR); M 12.5 (8-15.5); F 15 (10-16)	18 (48.6)	GGO with/without consolidation (45.9%)	3 (8.1)
Grassi <i>et al</i> ^[24]	Italy	R	134	Mean (range); 69.3 (29-93)	89 (71)	GGO and consolidation (71%), crazy-paving pattern (75%)	69 (54.8)
Pakdemirli <i>et al</i> ^[30]	United Kingdom	R	18	mean (SD); 53.3 (NA)	9 (50)	GGO (44%), pleural thickening (50%), focal vascular engorgement (83%), B/L lesion (100%)	3 (17)
Li <i>et al</i> ^[31]	China	R	19	Mean (range); 63 (25-80)	11 (57.9)	GGO (100%), consolidation (73.7%), interlobular septal thickening (63.2%)	0
Gong <i>et al</i> ^[22]	China	R	10	Mean (range); 30 (26-40)	0 (0)	GGO (100%), B/L lesion (80%)	0
Sardanelli <i>et al</i> ^[25]	Italy	R	410	Median (IQR); 68 (57-78)	288 (70)	NA	76 (19)
Luo <i>et al</i> ^[32]	China	R	70	NA	NA	GGO (39%), GGO and consolidation (59%), B/L lesion (84%)	2 (2.8)
Huang <i>et al</i> ^[33]	China	C	7	Median (range); 56 (49-64)	3 (42.9)	GGO (100%)	0 (0)
Guan <i>et al</i> ^[34]	China	R	54	mean (SD); 44.8 (16.7)	25 (46)	GGO (100%), crazy-paving pattern (90%), B/L lesion (82%)	0 (0)
Doroudinia <i>et al</i> ^[35]	Iran	C	1	56	0 (0)	GGO both lungs	0 (0)
Lu <i>et al</i> ^[36]	China	C	9	mean (SD); 7.8 (5.3)	5 (55.6)	GGO (44.4%)	0 (0)
Lei <i>et al</i> ^[37]	China	R	14	mean (SD); 47 (19)	8 (57.1)	GGO (90%), irregular linear (90%), consolidation (90%)	0 (0)
Himoto <i>et al</i> ^[38]	Japan	R	6	Median (range); 58.5 (45-81)	5 (83.3)	B/L lesion (100%), GGO without consolidation (66.7%)	0 (0)
Guan <i>et al</i> ^[39]	China	R	53	Mean (range); 42 (1-86)	25 (47)	GGO (100%), crazy-paving pattern (89%), B/L lesion (79%)	0 (0)
Zhao <i>et al</i> ^[23]	China	R	80	mean (SD); 44 (11.7)	43 (54)	GGO (71%), B/L lesions (95%), subpleural lesion (90%)	1 (1.3)
Albarelo <i>et al</i> ^[19]	China	C	2	66 and 67	1 (50%)	GGO and ML were found in both cases	NA
Chung <i>et al</i> ^[40]	China	R	21	mean (SD); 51(14)	13 (62)	GGO (57%), multi-lobar lesion (71%), B/L lesion (76%)	0 (0)

B/L: Bilateral; C: Case report/series; F: Female; GGO: Ground-glass opacities; IQR: Interquartile range; M: Male; ML: Mediastinal lymphadenopathy; n: Number of coronavirus disease 2019 case with chest imaging; NA: Not applicable; R: Retrospective review; SD: Standard deviation.

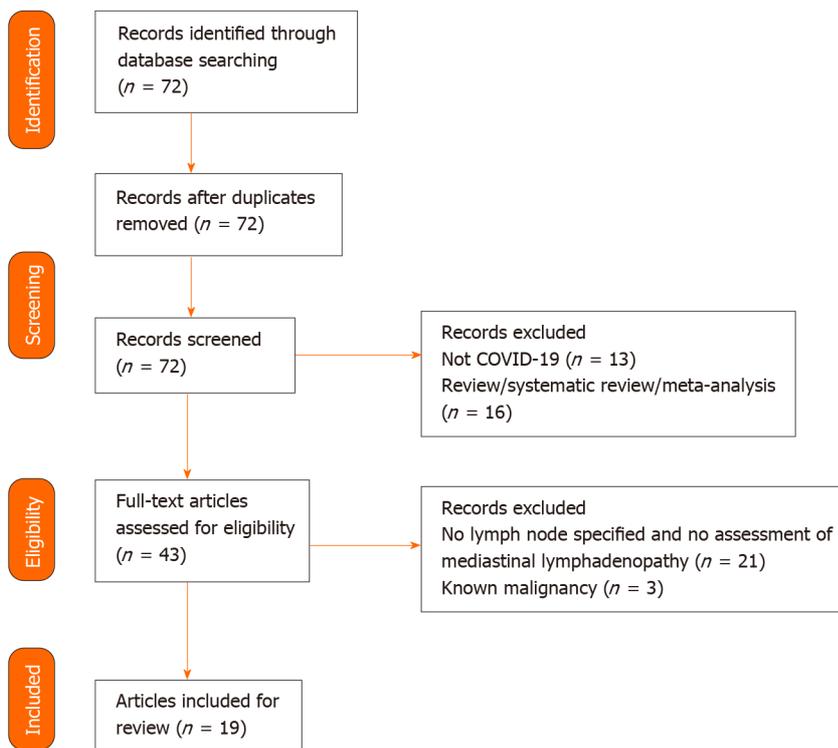


Figure 3 Flow diagram for study selection according to PRISMA 2009 guideline. COVID-19: Coronavirus disease 2019.

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