

# Prevalence and significance of mediastinal lymphadenopathy in patients with Severe Acute Respiratory Syndrome Corona Virus-2 infection

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**Abstract.** – Severe Acute Respiratory Syndrome Corona Virus-2 is the causative factor of the Coronavirus Disease 2019. Early in the pandemic, mediastinal lymphadenopathy was not considered to be a significant radiologic finding of the SARS-COV-2 disease. Nevertheless, most recent studies associate mediastinal lymphadenopathy with more severe COVID-19 disease and poorer patient outcomes.

*Key Words:*

SARS-COV-2, Mediastinal lymphadenopathy, PET CT, Lung infiltrates.

## Introduction

Severe Acute Respiratory Syndrome Corona Virus-2 (SARS COV-2) is the cause of the Coronavirus Disease 2019 (COVID-19). Since the first cases were detected in Wuhan, China, the COVID-19 pandemic has evolved rapidly over the last 14 months<sup>1</sup>. As of now, 213 countries and territories outside of mainland China have reported SARS COV-2 infection<sup>2</sup>.

The clinical manifestations of the disease are variable. Clinical course can range from asymptomatic infection up to a wide variety of severe symptoms. The most common presenting symptoms include fever, malaise, dry cough, and dyspnea<sup>3</sup>.

In the early period of the pandemic, lymphadenopathy did not appear to be a common clinical or radiologic finding<sup>4-10</sup>, but later reports provided a different perspective<sup>11,12</sup>. The aim of this study is to review the existing literature regarding the presence of mediastinal lymphadenopathy (ML) in patients with SARS COV-2 infection and its clinical utility in characterizing disease progres-

sion, severity, and follow-up. Study results are summarized in Table I.

## *Lymphadenopathy Related to SARS-COV2 Infection*

COVID-19 virus causes inflammation of the nasopharynx and oropharynx, clinically presented as sore throat, nasal obstruction, tonsillitis, or nasopharyngitis. The inflammation causes a local immune reaction leading to the enlargement of Waldeyer's ring as well as to cervical and intraparotid lymphadenitis. Lechien et al<sup>13</sup> described the cases of three female patients diagnosed with pharyngeal COVID-19 infection<sup>13</sup>.

Hilar and mediastinal lymphadenopathy (ML) is commonly encountered in fungal and in mycobacterial infections, as well as sarcoidosis, but rarely seen in viral pneumonias. Valette et al<sup>14</sup> reported a high prevalence of ML, especially involving the subcarinal station, in 9 out of 15 patients with COVID-19 admitted to their Intensive Care Unit (ICU). In this case series lymphadenopathy was not related to longer ICU stay or mortality. Nevertheless, as stated by Sardanelli et al<sup>11</sup>, these findings reflect an 11-fold discrepancy with already existing literature<sup>11,14</sup>. In their case series, Sardanelli et al<sup>11</sup>, showed that ML was more common in patients that died during hospitalization and in those with extensive crazy paving infiltrates. Accordingly, in two Italian studies, ML was associated with a lower proportion of well aerated lung (WAL), higher inflammatory markers, lower lymphocyte count and higher death or ICU admission rates but were marginally not statistically significant ( $p=0.06$ )<sup>15,16</sup>. These results were confirmed by later studies, where ML was related to more ex-

**Table I.** Summary of publications regarding ML and COVID-19 infection.

Reference	Main findings
Valette et al <sup>14</sup>	High prevalence of ML, involving the subcarinal station, in 9 out of 15 patients admitted to ICU. Not related to longer ICU stay or mortality.
Sardanelli et al <sup>11</sup>	ML was more common in patients that died and in those with extensive crazy paving infiltrates.
Colombi et al <sup>15</sup>	ML was associated with a lower proportion of WAL, higher inflammatory markers, lower lymphocyte count and higher death/ICU admission rates.
Satici et al <sup>17</sup> , Leonardi et al <sup>18</sup>	ML was related to more extensive crazy paving infiltrates, increased CRP levels, and increased risk of death, critical illness, and ICU admissions.
Qin et al <sup>19</sup>	High <sup>18</sup> FDG avidity of ML in patients with SARS-COV-2 infection.

ML: Mediastinal Lymphadenopathy, WAL: Well Aerated Lung, ICU: Intensive Care Unit, CRP: C-Reactive Protein, <sup>18</sup>FDG:<sup>18</sup>FluoroDeoxyGlucose.

tensive crazy paving infiltrates, increased CRP levels, and increased risk of death or critical illness and ICU admission<sup>17,18</sup>.

The metabolic activity of ML in patients with SARS-COV-2 infection was described very early in the COVID-19 pandemic, where <sup>18</sup>FluoroDeoxyGlucose (<sup>18</sup>FDG)-avid ML was reported in 3 of 4 cases in Qin et al<sup>19</sup> case series. The increased metabolic activity can be attributed to enhanced immunological response in lymphoid tissues<sup>12</sup>, which may provisionally be associated with cytokine storm and subsequent lung damage<sup>20</sup>. In cases where the virus-eliminating immune response is inadequate, the long-term inflammatory activity may progress to lung fibrosis<sup>20</sup>. Of note, it is well documented that ML in patients with established Idiopathic Pulmonary Fibrosis (IPF) is related to poorer survival and increased risk of IPF exacerbations, revealing an underlying relation of lymphadenopathy and lung inflammation per se<sup>21</sup>.

## Conclusions

In summary, SARS-COV-2 viral infection can cause excessive inflammatory response, extensive lung infiltrates and ML. All the above findings may be related to worse outcomes and subsequent chronic post-inflammatory changes in lung parenchyma. It would be of great interest if future COVID-19 survivor studies focused on evaluating the presence of ML FDG-avidity and fibrotic lung parenchymal lesions. Of note bronchoscopic sampling of mediastinal lymph nodes in these patients could be useful in identifying chronic viral load carriage. This would provide

an extra treatment target in those patients that cannot effectively eliminate SARS-COV-2.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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