ORIGINAL ARTICLE

MEDIASTINAL LYMPHADENOPATHY AS A PREDICTOR OF WORSE OUTCOME IN SEVERE COVID-19 CASES

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Background: This cross-sectional study is aimed at evaluating the association of mediastinal lymphadenopathy with COVID-19 prognosis in severe cases. Place and Duration of Study: Department of Medicine, Pak Emirates Military Hospital, Pakistan, from June to July 2020. **Methods:** One hundred and fifty (150) laboratory-confirmed SARS CoV-2 infected, severe cases in Intensive Care Unit/ High Dependency Unit were included. These cases were divided into two categories, i.e., with and without mediastinal lymphadenopathy on High Resolution Computed Tomography chest. The two categories were compared on the basis of data obtained including age, gender, comorbid, White Blood Cell count, lymphocyte count, median days of hospitalization, need for invasive ventilation, Intensive Care Unit admission, clinical outcome and High-Resolution Computed Tomography chest findings. The data was compiled on a questionnaire and analysed on SPSS 24. **Result:** Total 155 severe COVID-19 patients were reviewed, out of which 36 (23.2%) had mediastinal lymphadenopathy (category 1) and 119 (76.8%) had no mediastinal lymphadenopathy (category 2). Laboratory findings including median of white blood cells and lymphocyte percentage had no significant change in both categories. Intensive care unit admissions were 12 (33.3%) and 56 (47.1%) in category 1 and 2 respectively. Median days of hospitalization (8 days) and mortality rate (16%) were almost the same in both categories. **Conclusion:** Our study concludes that presence of mediastinal lymphadenopathy in severe COVID-19 cases is not associated with worse outcome. However, overall prevalence of mediastinal lymphadenopathy in severe cases is high (23.2%).

Keywords: COVID-19; Mediastinal lymphadenopathy; Severe cases

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INTRODUCTION

Mediastinal Lymph Node (MLN) enlargement also known as mediastinal lymphadenopathy is a hallmark of ongoing protective immune response within the tissue that increases with disease severity.[1] This provides a strong rationale for measurement of MLN in thoracic diseases.[1] It can occur due to wide range of pathologies, either on its own or in association with other lung disorders that have immunologic response.[2,3] Mediastinal lymph nodes are considered significant if the size is greater than 10mm in short axis.[4–6] MLN assessment has been used as a prognostic factor and staging in many pulmonary disorders including sarcoidosis and lung cancer.[7,8] Increased MLN size has been strongly linked to more advanced stages of malignancy and greater mortality.[9,10] There is abundant evidence in health and disease that non-invasive CT assessment of MLN enlargement correlates fairly well with more invasive techniques such as endobronchial ultrasound measurements.[11,12]

Radiological assessment of lungs plays an important role in management of COVID-19 and includes chest X-ray, chest ultrasound and High Resolution Computed Tomography (HRCT) chest.[13] According to Fleischner Society consensus statement, HRCT chest is not indicated in mild or suspected COVID-19 cases or for screening/diagnosis of COVID-19.[13] It is only indicated if there is risk of disease progression in mild cases or in those suspected cases who are in moderate to severe category and have high pretest probability of disease.[13] HRCT chest has a sensitivity of 94% and a specificity of 37%.[14] In non-severe COVID-19 cases, CXR or HRCT chest is normal in approximately 18% cases, while this percentage drops to 3% in severe COVID-19 cases.[15,16]

Radiological Society of North America (RSNA) has proposed four categories for standardized reporting of chest HRCT findings related to COVID-19, i.e., "typical", "indeterminate", "atypical", and "negative".[17] A study among COVID-19 confirmed cases showed

76.9–96.6% had "typical" scans, 51.2–64.1% had "indeterminate" scans, 2.8–5.3% "atypical" scans and 20–25% had "negative" scans.[17,18] Typical findings of HRCT chest in COVID-19 include: ground-glass opacities (mostly bilateral, subpleural and peripheral), crazy paving appearance, broncho vascular thickening in the lesion and air space consolidation[19–21] Mediastinal lymphadenopathy is atypical finding on HRCT chest[22] other atypical findings include pleural effusions, pneumothorax, multiple tiny pulmonary nodules, tree-in-bud, cavitation and traction bronchiectasis. Various variables have been studied as prognostic factors in COVID-19. Currently, CALL score, using clinical parameters including comorbid, age, lymphocyte count and LDH, is used for prognosis in COVID-19 cases and its significance has been evaluated in various studies.[23,24] Our study aims to find significance of mediastinal lymphadenopathy as prognostic factor in severe COVID-19 cases. This variable, if found significant can be used as useful non-invasive parameter in predicting outcome of severe COVID-19 patients.

MATERIAL AND METHODS

Severe COVID-19 confirmed cases whose HRCT chest was done and were admitted in the intensive care unit (ICU)/ high dependency unit (HDU) of Department of Medicine Pak Emirates Military Hospitals, from Jun 2020 to July 2020, were included in this study. All these cases were laboratory confirmed using Reverse Transcriptase Polymerase Chain Reaction (RT PCR) on nasopharyngeal and oropharyngeal swabs samples. Those with mild and moderate COVID-19 and with history of heart failure and malignancies (especially haematological) were excluded from this study. Both males and females and adults with age ranging between 25–85 years were included in this study using convenience sampling technique. Study was started after taking approval from ethical review committee of the institute.

Severe COVID-19 case was defined as adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 <90% on room air. [25]

All the patients underwent HRCT Chest imaging by Toshiba Alexion 16-slice CT scan system. Patients were asked to lie in supine position and CT image was obtained while patient holding breathe in inspiration. Each HRCT was reviewed by a consultant radiologist blinded to the clinical and laboratory indicators. The scanning range was from the apex of the lung to costophrenic angle. CT scan parameters included X-Ray tube parameters of 120 KVp, 350 mAs; rotation time of 0.5 second; pitch of 1.0 with section thickness of 5 mm and intersection space – 5 mm. Mediastinal lymphadenopathy was defined as a mediastinal lymph node of greater than 10mm in short axis diameter.

These severe COVID-19 patients were divided into those with lymphadenopathy (category 1) and without lymphadenopathy (category 2). We recorded their age, gender, comorbid, White Blood Cell count (WBC count), lymphocyte count, median days of hospitalization, need for invasive ventilation during hospitalization, Intensive Care Unit (ICU) admission, clinical outcome and HRCT chest findings. All these variables of both category 1 and 2 were compared and *p*-value was calculated, to find any association with mediastinal lymphadenopathy. To find *p*-value, we applied Mann-Whitney test (non-parametric test) for variables including age, stay in hospital and laboratory parameters, while for rest of variables we applied Chi-square test. We obtained a *p*-value threshold of 0.05, above which *p*-values were not significant. Statistical analysis was performed by using SPSS 24.

RESULTS

In our study, data of a total of 155 severe COVID-19 patients was reviewed. Out of which, 36 (23.2%) had mediastinal lymphadenopathy (category 1) and 119 (76.8%) had no mediastinal lymphadenopathy (category 2). In category 1, 25 (69.4%) were males and 11 (30.6%) were females while 105(88.2%) were males and 14 (11.8%) were females in category 2. Median age was 52 years (IQR 43–69) for category 1 and 62 years (IQR 50–70) for category 2.

Out of total 155 patients, 95 patients (61.2%) had comorbid. ICU admissions were 12 (33.3%) and 56 (47.1%) in category 1 and 2 respectively. Median days of hospitalization (8 days) and mortality rate (16%) were almost the same in both categories. Similarly, laboratory findings including median of white blood cells and lymphocyte percentage had no significant difference in both categories. On HRCT chest, a total of 40 (25.8%) cases showed crazy pattern, Category 1 had 11 (30.6%) and category 2 had 29 (24.4%) cases. Thirty-one (20%) cases had atypical findings, Category 1 had 8 (22%) and category 2 had 23 (19%) cases (Table -1).

Frequencies of various comorbid are summarized in figure-1, most common comorbid being hypertension (37.1%). Frequency of various stations of lymph nodes involved, in 36 patients

with mediastinal lymphadenopathy are summarized in figure-2, most commonly involved station being precarinal area (38.7%). Among total of 155 severe cases, 31 cases showed atypical findings on HRCT chest. Frequency of these is summarized in figure-3, most common atypical HRCT chest finding being pleural effusion (61.3%).

Table-1: Demographic, clinical, laboratory and HRCT findings on admission

	Category 1	category 2	*p*-value
	Patients with Mediastinal Lymphadenopathy (n=36) 23.2%	Patients without Mediastinal lymphadenopathy (n=119) 76.8%	
Demographic and clinical findings			
Sex	Males 25 (69.4%)	Males 105 (88.2%)	
	Females 11 (30.6%)	Females 14 (11.8%)	0.007
Age (Years)	53 (IQR 43–69)	62 (IQR 50–70)	0.112
Median stay at Hospital (in days)	8.5 (6–11.5)	8 (6–12)	0.146
Comorbid	16 (44.4%)	79 (66.4%)	0.01
Invasive ventilation	3 (8.3%)	12 (10.1%)	0.75
ICU admission	12 (33.3%)	56 (47.1%)	0.708
Deaths	6 (16.7%)	19 (16%)	0.920
Laboratory findings			
White blood cells (×103 per µl)	10 (IQR 7–13)	10 (IQR 7–14)	0.902
Lymphocytes (%)	10 (IQR 5.25–13)	10 (IQR 5–20)	0.642
HRCT features			
Atypical features	8 (22%)	23 (19%)	0.619
Crazy pavings	11 (30.6%)	29 (24.4%)	0.457

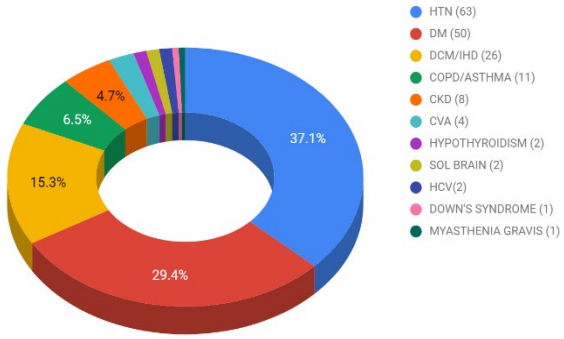

Figure-1: Frequency of various comorbids in 95 cases.

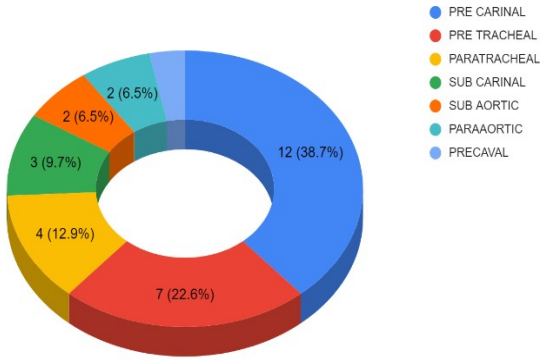

Figure-2: Frequency of lymph node stations involved in 36 patients having mediastinal lymphadenopathy

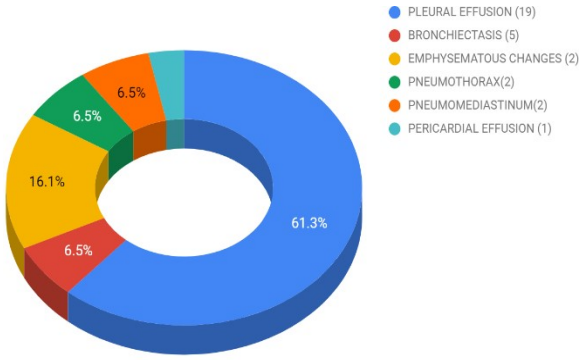

Figure-3: Frequency of atypical HRCT chest findings in 31 cases

DISCUSSION

SARS CoV-2 is a virus that was not previously known to human. Like any other new epidemic, this journey has started from knowing nothing about this virus to compiling a vast knowledge about its clinical spectrum, diagnosis, treatment options, prevention and factors associated with mortality. A study done by Aly MH *et al* concluded the risk factors associated with poor outcome of SARS-CoV-2 infection included old age, male gender, obesity and associated comorbid.[26] Laboratory parameters associated with critical COVID-19 disease were decreased lymphocyte count, platelet count and albumin, increased neutrophil, C reactive protein, ferritin, D dimer, ALT and/or AST, cardiac troponin and LDH.

In HRCT chest, severity score can be used as a predictor for mortality.[27] In this cohort, association of mediastinal lymphadenopathy with COVID-19 prognosis in severe cases is evaluated.

Previous studies have reported association of mediastinal lymphadenopathy with COVID-19 prognosis.[28,29] In our study, out of 155 severe COVID-19 cases 36 (23.2%) patients had significant mediastinal lymphadenopathy while in study done by Xavier valette *et al*[28], 9 (66%) patients showed significant lymphadenopathy. The difference in results can be explained by severity of cases included in this study and sample size. Whereas Xavier studied[15] patients of ICU, we studied 155 cases including both severe and critical cases in HDU and ICU of our hospital. Our study results comply more with the study done by F Sardanelli and colleagues[29] in which 19% (76) patients had mediastinal lymphadenopathy out of total 410 patients at emergency department admission. Li K and colleagues[30] reported that 28% (7) out of total 25 severe/critical COVID-19 cases had significant mediastinal lymphadenopathy while in comparison no mediastinal lymph node was seen in 58 mild/moderate COVID-19 cases. Our findings and those of Li K support the hypothesis that mediastinal lymphadenopathy is common in severe/critical cases.

In our study out of total 155 severe COVID-19 cases, 31 (20%) cases had atypical findings, these findings are in consistent with Li K *et al*[30] study (Table-3 of this study) in which atypical findings were higher in severe/critical cases than in another category. In our study the most common localization of enlarged mediastinal lymphadenopathy was pre carinal station (39%) followed by pre tracheal (22.6%) while C Satici *et al,*[31] reported subcarinal station (37%) to be the commonest followed by paratracheal station (29%).

We could not find any significant association of these two categories with variables including age, comorbid, need for invasive ventilation, ICU admission, deaths, laboratory findings of WBCs and lymphocytes and HRCT Chest features of atypical features and crazy pavings. C Satici *et al*, included 650 patients in study and found that variables including age, comorbid, laboratory finding of CRP and HRCT features of crazy paving had association with mediastinal lymphadenopathy, however no association was found among variables of gender, clinical severity status, HRCT features except crazy paving and laboratory finding of serum ferritin and procalcitonin.[31]

There are some limitations to our study. First, in our study bronchoscopy was not done in patients with mediastinal lymphadenopathy to rule out other causes of this lymphadenopathy. Variables like comorbid and age been associated with poor outcome in COVID-19 patients.[26] These variables can be considered as a confounding factor in assessing mediastinal lymphadenopathy as a predictor of poor outcome. As in category 2 (those without mediastinal lymphadenopathy) frequency of males (88.2%) is greater than in category 1 (69.4%). Similarly comorbid are present in 66.4% cases versus 44.4% in category 2 and category 1 respectively.

CONCLUSION

The presence of mediastinal lymphadenopathy in severe COVID-19 cases is not associated with worse outcome. However, overall prevalence of mediastinal lymphadenopathy in severe cases is 23.2% that is higher than prevalence found in mild/moderate COVID-19 cases (0%).[30]

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

AUTHORS' CONTRIBUTION

UQ: Data collection, write up, proof reading. NA: Data collection. MI: Proof reading. AN: Conceptualization of study design. DHK: Data analysis, data interpretation. SS: Proof reading. SN: Proof reading

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