Histo-Pathological Findings of Critical COVID-19 Pneumonia: A Case Series

Farrukh Shehzad, Arshad Naseem, Hafeez Ud Din*, Kaswar Sajjad, Asad Zaman Khan, Bushra Zafar

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Armed Forces Institute of Pathology/ National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

***Objective*:** To study the histo-pathological findings in lung biopsies of critical COVID-19 cases.
***Study Design*:** Case series.
***Place and Duration of Study*:** Pakistan Emirates Military Hospital, Rawalpindi Pakistan, from Jul to Dec 2020.
***Methodology*:** Deceased patients who remained on ventilatory support with a confirmatory diagnosis of SARS-CoV-2 both by PCR and radiological evidence on HRCT and clinically established severity of disease as per CALL scoring were included in the study. Written informed consent for lung biopsy was taken from the deceased's next of kin
***Result*:** Mean age of the study group was 67.20 ± 6.01 years. The patients had a mean high resolution computed tomography score of 36.73 ± 1.59, and the mean CALL score was 12.73 ± 0.691 on admission. The average time after intensive care unit admission to intubation was 1.23 ± 0.50 days. Histopathological examination of the lung biopsy showed 27 (87.1%) patients had the exudative stage of adult respiratory distress syndrome while three (9.7%) patients had a proliferative stage of adult respiratory distress syndrome.
***Conclusion*:** Histopathological findings of an exudative stage of adult respiratory distress syndrome in the lung biopsies of critical COVID-19 showed no significant difference with typical adult respiratory distress syndrome and are correlated with very high mortality rates in critical COVID-19.

Keywords: Adult respiratory distress syndrome (ARDS), COVID-19, Call score, Histopathology, HRCT, Lung biopsy.

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INTRODUCTION

Critical COVID-19 presents as viral pneumonia from severe acute respiratory syndrome coronavirus,[2] (SARS-CoV-2) infections resulting in ARDS. It can manifest alone or in two processes, viral pneumonia and ARDS.[1,2] COVID-19 ARDS is an ongoing global threat as this virus can infect non-immune populations and spread very rapidly. It calls for strict prevention, social distancing and supportive ICU management for those having critical COVID-19 infection.[3,4]

The patients who require ICU care are significantly older and more likely to have underlying comorbid conditions, such as hypertension, diabetes, and cardiovascular disease, as evident from a highly accurate risk-estimation model in a CALL score.[5] The imaging modality HRCT chest of critical COVID patients is helpful to deepen the understanding of the severity of illness, promote early intervention and imply treatment strategies accordingly.[6,7] Respiratory support management, including non-invasive and invasive ventilation, now remains the mainstay of treatment and ICU supportive care in critical COVID 19 cases.[8,9]

The purpose of this research was to find out the difference between histopathological findings and stages of critical COVID-19 ARDS compared to typical ARDS due to other causes. This will help us assess the disease severity, plan early respiratory support intervention for better patient care and decrease significant morbidity and mortality associated with critical COVID-19.

METHODOLOGY

After approval from the Hospital Ethical Committee (letter-number A/28/EC/260/2020), 30 patients were recruited in this case series from July to Decenber 2020. The patients were treated in the established COVID-ICU of PEMH Rawalpindi.

Inclusion Criteria: Deceased patients who remained on ventilatory support with a confirmatory diagnosis of SARS-CoV-2 both by PCR and radiological evidence on HRCT and clinically established severity of disease as per CALL scoring were included in the study.

Exclusion Criteria: Patients with other respiratory illnesses like bronchial asthma and chronic obstructive pulmonary disease (COPD) were excluded from the study.

Correspondence: Dr Farrukh Shehzad, Department of Critical Care Medicine, PEMH Rawalpindi, Pakistan
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Written informed consent for lung biopsy was taken from the deceased's next of kin. All these patients of critical COVID-19 were of age ≥55 years and had comorbid conditions like hypertension, ischemic heart diseases and diabetes mellitus. All the patients complained of fever either with dry cough or shortness of breath on presentation in ICU. These patients were ventilated within 24 to 36 hours of presentation in ICU. The high-resolution computerised topography, (HRCT) severity indexes of all the critical COVID-19 patients included in the study were significantly higher ≥35. The CALL score for all the patients was ≥11. Lung tissue biopsy was obtained by transthoracic 18-gauge monopty disposable core biopsy needle from areas coinciding with maximum ground-glass opacities on high chest resolution computed tomography (HRCT) after the patient's death. Two samples for biopsy were taken the single patient maximum affected lung. The biopsy specimen was fixed in 10% neutral buffered formalin and sent for histopathological reporting at the Armed forces institute for pathology (AFIP). Standard processing with hematoxylin and eosin staining was done.

Statistical Package for Social Sciences (SPSS) version 22 was used for the data analysis. Quantitative variables were summarized as mean ± SD and qualitative variables were summarized as frequency and percentages. To compare disease severity with histopathological findings, one-way analysis of variance (ANOVA) was applied. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Out of the total 30 patients, the mean age was of the study participants was 67.20 ± 6.01 years (range 56 to 78 years). There were 21 (67.7%) male patients and 9 (29%) female patients in our study. All 30 patients had clinically significant comorbidities (Figure).

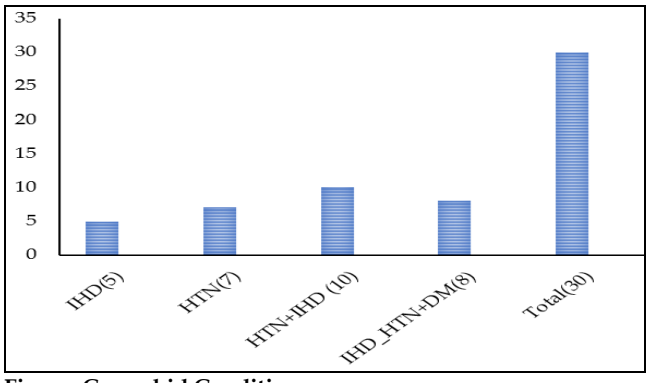

Figure: Comorbid Condition.

The most frequent presenting symptoms were shortness of breath with fever in 23 (74.2%) patients and shortness of breath with dry cough in 7 (22.6%) patients.

The mean time from the onset of illness to ICU admission was 6 ± 0.67 days (ranging from 5–8 days). All the patients had an HRCT chest score of more than 35 on admission to ICU with a mean score of 36.73 ± 1.59, and a mean CALL score was 12.73 ± 0.69. All the thirty patients required intubation and mechanical ventilation within 24-36 hours of presentation in ICU. The mean duration of ICU admission to intubation was 1.23 ± 0.50 days. Mean ferritin levels on day 1 in ICU were 1267.2 ± 500.1, and on day 3, it was 2696.8 ± 1223.1 micrograms per liter (Table).

Table: Rising serum ferritin levels.

Parameter	Day 1	Day 2	Day 3	*p*-value
	(n=30)	(n=30)	(n=30)	
Serum Ferritin levels (µg/L)	1267.2 ± 500.1	1986.1 ± 948.5	2696.8 ± 1223.1	0.040

In patients with critical COVID-19 duration to death after the onset of illness varied from day 8 to 11, with a mean time of 9.2 ± 0.80 days. Histopathological examination of the lung biopsy showed 27 (87.1%) patients with the exudative stage of ARDS and diffused alveolar damage in pulmonary tissue, 3 (9.7%) patients with the proliferative stage ARDS along with diffuse alveolar damage in pulmonary tissue. Vasculitis or endothelins were not evident. The lung biopsy histopathological findings corresponding with disease severity, as evident from the HRCT chest score and Call score, were statistically significant (*p*-value=0.03).

DISCUSSION

Our study results showed that histopathological findings of an early exudative stage of ARDS in lung biopsies of patients with critical COVID-19 were not different from COVID-19 ARDS and typical ARDS and was supported by high HRCT chest score and CALL score with very high mortality rates. ARDS, a predictable serious complication of COVID-19, requi-res early identification and a proper management plan. These histopathological findings provide an in-depth insight for clinical observations and help characterise the disease severity leading to intervention with early ventilatory management strategies with non-invasive or invasive ventilation and novel therapies.[10,11]

The critical patients in our study population were significantly older (mean age 67.20 ± 6.01 years). They had comorbid conditions like hypertension, Ischemic

heart disease, and diabetes mellitus, compared to a study by Li *et al,* the mean age of patients was 53.7 ± 12.3 years, and they had a comorbid illnesses like diabetes mellitus and chronic obstructive pulmonary disease.[8]

In our study mean time of illness onset to hospital admission in critical patients was 5.97 ± 0.85 days. The mean time from ICU admission to intubation was 1.23 ± 0.50 days, with most intubations occurring within 24 hours of admission. Our patients with critical COVID-19 died at mean 9.20 ± 0.80 days after onset of illness. Our study population had a shorter interval from symptoms onset to death because all the reported cases had severe respiratory distress on admission to ICU and the disease was already in a critical stage.

COVID-19 predominantly affected the respiratory system with minor damage to other organs. The reported incidence of ARDS was 15.6–31%, higher than other organ involvement in COVID -19.[12,13]

In intensive care units, ARDS frequently remains underdiagnosed.[14] 42% of COVID-19 patients present with ARDS, out of which 61–81% require intensive care.[15] The outcome of COVID-19 ARDS is worse than typical ARDS from other causes. The intensive care unit and hospital mortality from typical ARDS are 35.3% and 40%, respectively.[16] For Older age, presence of comorbidities such as hypertension, cardiovascular disease and diabetes mellitus are poor prognostic factors. Death from COVID-19 ARDS is due to respiratory failure 53%, respiratory failure combined with cardiac failure 33%, myocardial damage and circulatory failure 7%.[17]

Oxygen saturation and respiratory rate are important parameters for disease severity recognition and assessing the ARDS stage. Any patient fulfilling any one of the following criteria may have severe/ critical disease and require further evaluation by the critical care outreach team and ICU admission: respiratory rate ≥30 breaths/min; SpO2 ≤92%; and PaO2/ FiO2 ≤ 300 mmHg.[18]

COVID-19 ARDS disease spectrum is similar to typical ARDS from different aetiology ranging from diffuse alveolar damage in the lung to hyaline membrane formation in the alveoli in the acute stage, followed by interstitial widening, oedema and then fibroblast proliferation which represents the organising stage.[19] As patients progress through the course of their illness, the long term complications of ARDS start setting in, like lung fibrosis appearing as part of COVID-19 ARDS.[16, 17]

Ye *et al*, reported that 17% of patients had fibrous stripes in HRCT chest scans and considered that the fibrous lesions might form during the healing of chronic pulmonary inflammation or proliferative diseases, with the gradual replacement of cellular components by scar tissues.[17]

Histopathological examination of pulmonary tissues in our study found a spectrum of diffuse alveolar damage in two different stages of ARDS in 30 patients with lung biopsies. 27 (87.1%) out of 30 patients with diffuse alveolar damage showed acute early exudative stage of ARDS, and 3 (9.7%) patients showed proliferative stage of ARDS with organising diffuse alveolar damage.

In contrast to our study, a case report by Xu *et al*, reported that the most common histopathologic correlation of COVID 19 ARDS is diffuse alveolar damage, characterised by hyaline membrane formation in the alveoli in the acute proliferative stage, fibroblast proliferation in the organising stage and interstitial widening by edema.[19]

Menter *et al*, reported 21 cases of COVID-19 patients. Autopsy findings showed pulmonary capillary congestion 21/21 (100%), diffuse alveolar damage exudative 16/21 (76%), diffuse alveolar damage proliferative 8/21 (38%); the data of the study was comparable to our results, with predominant early exudative stage of ARDS.[20]

Comparable to our study, Lax *et al*, performed autopsies of 10 COVID-19 cases. Histologically, the lungs showed a variable pattern of changes, with different stages of diffuse alveolar damage with oedema, hyaline membranes, and proliferation of pneumocytes and fibroblasts.[21]

No histopathology finding of endothelins was observed in our study. COVID-19 patients are at increased risk for endothelial injury-causing pulmo-nary micro thrombi. This results in an increased mismatch of V/Q ratio in ventilated patients, which causes refractory hypoxemia in patients.[22]

CONCLUSION

Histopathological findings of an exudative stage of adult respiratory distress syndrome in the lung biopsies of critical COVID-19 showed no significant difference with typical adult respiratory distress syndrome and are correlated with very high mortality rates in critical COVID-19.

Conflict of Interest: None.

Authors' Contribution

FS: Data writing, data collection, AN: Data analysis, HUD: Supervision, KS: Interpretation of data, AZk:, BZ: Data analysis.

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