DOI: 10.7860/JCDR/2022/51211.15874

Original Article

Pathology Section

High Resolution Computed Tomography Findings of Pulmonary Fibrosis in COVID-19 Survivors and its Association with Inflammatory Markers- A Retrospective Study

TARANG PATEL[1], VIRENDRAKUMAR MEENA[2], SWATI JINDAL[3], ANJANA VERMA[4], ASHISH SHARMA[5], RISHI SHARMA[6]

ABSTRACT

Introduction: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection enters human body through respiratory tract and then rapidly spread to involve lungs and multiply swiftly leading to severe hypoxic pneumonia. Clinically, Coronavirus Disease-2019 (COVID-19) infection is identified by three stages based on viral infection, lung involvement with inflammation and pulmonary fibrosis. High resolution Computed Tomography (HRCT) lung play an important role in diagnosis and management of lung fibrosis in coronavirus disease patients.

Aim: To study association between inflammatory markers and development of lung fibrosis in post COVID-19 patients. Study also aimed at assessment of chest Computed Tomography (CT) Involvement Score (CT-IS) and COVID-19 Reporting and Data System (CO-RADS) for chest CT in post COVID patients presented with lung fibrosis.

Materials and Methods: This retrospective study included elaborate evaluation of HRCT findings and inflammatory markers of 54 patients presented with pulmonary fibrosis at tertiary care centre for duration of six months from 1st June to 30th November 2020. Only those patients were included in which both HRCT findings and clinical laboratory parameters were available. Interleukin-6 (IL-6), C-Reactive Protein (CRP), serum ferritin, Lactate Dehydrogenase (LDH), Erythrocyte Sedimentation Rate (ESR) and Procalcitonin (PCT) markers were studied. Statistical analysis was conducted using Chi-square test to compare the inflammatory markers with CT-IS score with p-value <0.05 was considered significant.

Results: Total 536 COVID positive patients were admitted in hospital and underwent HRCT lung from June 2020 to November 2020. Out of 536, 54 (10.07%) patients showed findings of lung fibrosis on follow-up CT scan. Among 54 patients with lung fibrosis, CRP, serum ferritin and IL-6 levels were high in 46 (85.19%), 42 (77.77%) and 48 (88.89%) patients respectively. Lactate dehydrogenase, ESR and PCT were increased in 12 (22.22%), 15 (27.78%) and 06 (11.11%) patients respectively. These levels were higher in fibrotic phase compared to prefibrotic phase. Erythrocyte sedimentation rate was significantly associated with the severity of lung fibrosis, having significant p-value=0.004.

Conclusion: Among all inflammatory markers, ESR value may be useful as a surrogate marker to predict the pulmonary fibrosis in COVID-19 patients. C-reactive protein, IL-6, LDH, serum ferritin and PCT levels do not show significant association with lung fibrosis on HRCT scan.

Keywords: Acute respiratory syndrome, Coronavirus disease-2019, C-reactive protein, Ferritin, Ground-glass opacity, Inflammatory biomarkers, Interleukin-6

INTRODUCTION

Coronavirus Disease-2019 (COVID-19) is a pandemic that started in 2019. It is an acute respiratory illness caused by a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was first identified in Wuhan city of Hubei Province, China and then spread to other provinces of China. From China it outspread globally to involve countries all over the world [1]. Millions of people have been infected by this virus throughout the world. The SARS-COV-2 is the seventh member of viruses, which are known to cause human respiratory tract infections. Four of these pathogenic viruses cause mild infections of upper respiratory tract, whereas three coronaviruses cause lower respiratory tract infections and also responsible for lung complications [2].

At the time of writing this article, globally infected cases are 55,946,862 with 13,44,557 global deaths and overall case fatality rate 2.40% [3]. SARS-CoV-2 swiftly spread throughout the world in 2002. The SARS-CoV-2 has been more infective than SARS-CoV, showing doubling time of 2.3-3.3 days and basic reproductive number (R0) of 5.7 [4]. The Angiotensin Converting Enzyme 2 (ACE 2) is receptor for the SARS-CoV-2 plays a crucial role in human infections [5]. Drugs increasing the ACE2 expression may enhance the infection, such as Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB) [6]. Smoking could be a risk factor for SARS-CoV-2 because it can enhance ACE2 expression [7].

Both innate and adaptive immunity play a pivotal role to fight against COVID-19 infection [8]. One theory suggest that severe COVID-19 progression could be due to insufficient adaptive immunity and imprudent innate immunity response leading to increased proinflammatory cytokines and chemokines [9,10]. Varied inflammatory markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), serum ferritin and Procalcitonin (PCT) have been reported to be remarkably associated with the escalating risks of severe COVID-19 progression [11,12]. Initial studies indicated vascular aetiology induced by activation of proinflammatory cytokines and complement pathway, is accountable for underlying organ damage in seriously sick COVID-19 patients [13,14].

High resolution Computed Tomography (HRCT) lung plays a pivotal role in the diagnosis and treatment of COVID-19 pneumonia [15]. Some studies demonstrated the varied HRCT findings, with the prime features being ground-glass opacities and pulmonary consolidation [16,17]. COVID-19 Reporting and Data System (CO-RADS) is an assessment system based on chest Computed Tomography (CT) and used to evaluate suspicion for lung involvement by COVID-19.

The CO-RADS was introduced by Dutch Radiological Society [18]. Study of clinical, radiological and autopsy findings in COVID-19 patients suggest lung fibrosis being a common occurrence following infection, and current evidence suggests that lung fibrosis might complicate the SARS-CoV-2 infection [19].

It is the need of hour to identify important inflammatory biomarkers which may be helpful in identifying patients in early clinical stage and proper clinical management may be provided to decrease the likelihood of clinical deterioration. The aim of this study was to analyse HRCT lung findings in COVID-19 patients with attention on development of pulmonary fibrosis and recognising those biomarkers with the help of understanding of progression of CT findings.

MATERIALS AND METHODS

This retrospective study of COVID-19 cases, showing pulmonary fibrosis on HRCT scan (admitted between 1st June 2020 to 30th November 2020) was conducted in month of February 2021 at Geetanjali Medical College and Hospital, Udaipur, a tertiary care centre in Udaipur, Rajasthan, India. A total of 536 COVID patients were admitted during the study period and were confirmed cases with at least one positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) report. Out of 536 cases, 54 patients (10.07%) had fibrosis on HRCT scan. The laboratory reports of these patients were retrieved from their medical records and analysed. Inflammatory biomarkers utilised in this study were IL-6, CRP, serum ferritin, Lactate Dehydrogenase (LDH), Erythrocyte Sedimentation Rate (ESR) and PCT. Measurements during lung fibrosis on scan were compared with prefibrotic measurements of inflammatory markers.

Ethical Committee approval was obtained (no.1949) dated 01-02-2021. All data was anonymised before the analyses. No informed consent was required due to the characteristics of the design.

Inclusion criteria

1. Patients with at least one positive RT-PCR for SARS-CoV-2.
2. Patients admitted at our hospital who had undergone testing for inflammatory markers and CT scan findings.
3. Patients who developed lung fibrosis on subsequent follow-up radiology.

Exclusion criteria: Patients with negative RT-PCR for SARS-CoV-2 or patients without follow-up CT scan findings or patients with incomplete investigation profile were excluded from the study.

CT Scan Protocol

The HRCT chest was done on 64 slice CT scanner (Siemens Somatom sensation, Germany) in supine position by using standard HRCT protocol. The scans were obtained by utilising 120 kvp and final images were reconstructed in axial, sagittal and in coronal sections. Scans were performed for both prefibrotic and fibrotic stages.

Prefibrotic phase is characterised by ground-glass opacity and consolidation patches, whereas fibrotic phase is defined by reticular opacities, fibrotic strands and traction bronchiectasis. Prefibrotic phase was considered for 0-4 days from clinical onset and fibrotic phase was considered for 7-10 days after onset of symptoms [15].

COVID-19 Reporting and Data System (CO-RADS)

- CO-RADS 0 imply incomplete scan or insufficient quantity.
- CO-RADS 1 and CO-RADS 2 implies chosen in case of very low level and low level of suspicion for COVID-19 infection respectively.
- CO-RADS 3 implies in case of equivocal findings of lung involvement by COVID-19.
- CO-RADS 4 and 5 correspond to high level and very high level of suspicion.
- CO-RADS 6 is given in case of positive COVID-19 case confirmed by RT-PCR test [18].

All the patients were categorised according to Computed Tomography-Involvement Score (CT-IS) developed by Chung M et al., [20]. CT-IS was calculated using number of involved lung lobes and percentage of involvement [18,20].

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for the Social Sciences version 16.0 (IBM Corp. Released 2012, IBM SPSS statistics for Windows, Armonk, NY). Quantitative variables were presented as mean values. Frequency distribution was done for categorical variables and determined as proportions. Chi-square test or Fisher's-exact test was used to compare the laboratory parameters with CT-IS on CT scan. The p-value <0.05 was considered as significant.

RESULTS

Total 536 patients were confirmed as COVID-19 positive by RT-PCR test and had undergone HRCT scan procedure. Out of 536 patients, 54 patients developed pulmonary fibrosis on follow-up CT scan findings [Table/Fig-1,2].

Computed Tomography- Involvement Score (CT-IS)	Grade	No. of patients
01-08	Mild	04
09-15	Moderate	15
16-25	Severe	35

[Table/Fig-1]: Study of Computed Tomography- Involvement Score (CT-IS) in COVID-19 patients (n=54).

Inflammatory marker	Normal range (Unit)	Mean prefibrotic phase value	Mean fibrotic phase value
IL-6 (pg/mL)	0-10	15.12	67.13
CRP (mg/L)	0-10	6.08	54.21
Serum ferritin (ng/mL)	15-150	172.6	284.3
ESR (mm/hr)	0-20	14.3	16.4
PCT (ng/mL)	0.10-0.50	0.088	0.183
LDH (U/L)	200-400	233	262

[Table/Fig-2]: Study of inflammatory markers.
IL-6: Interleukin-6; CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; LDH: Lactate dehydrogenase

Inflammatory biomarkers were studied in 54 patients of lung fibrosis. CRP, Ferritin and IL-6 levels were high in 46 (85.18%), 42 (77.78%) and 48 (88.89%) patients out of 54 patients. LDH, ESR and PCT were increased in 12 (22.22%), 15 (27.78%) and 6 (11.11%) patients out of 54 patients [Table/Fig-3].

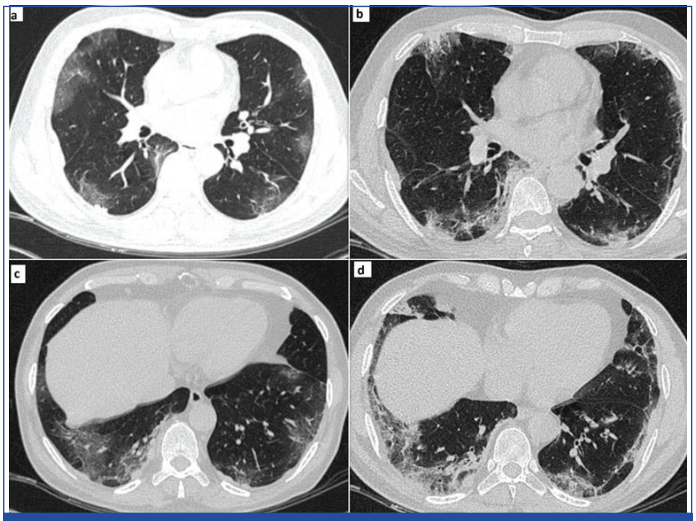
Laboratory parameter	n, %	With mild CT-IS (n=4)	With moderate CT-IS (n=15)	With severe CT-IS (n=35)	p-value
IL-6, >10 pg/mL n (%)	48 (88.89)	3 (75)	12 (80)	33 (94.2)	0.22
CRP, >10 mg/L n (%)	46 (85.18)	2 (50)	15 (100)	29 (82.9)	0.11
Serum ferritin, >150 ng/mL n (%)	42 (77.78)	4 (100)	11 (73.3)	27 (77)	0.95
ESR, >20 mm/hr n (%)	15 (27.78)	1 (25)	9 (60)	5 (14.3)	0.004*
PCT, >0.5 ng/mL n (%)	6 (11.11)	0	2 (13.3)	4 (11.4)	0.7
LDH, >400 U/L n (%)	12 (22.22)	1 (25)	5 (33.3)	6 (17.1)	0.4

[Table/Fig-3]: Laboratory parameters association with CT-IS.
IL-6- Interleukin-6; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; LDH: Lactate dehydrogenase; CORAD-COVID-19 reporting and data system; Test used- Chi-square test or Fisher's-exact test; p-value <0.05 was considered statistically significant

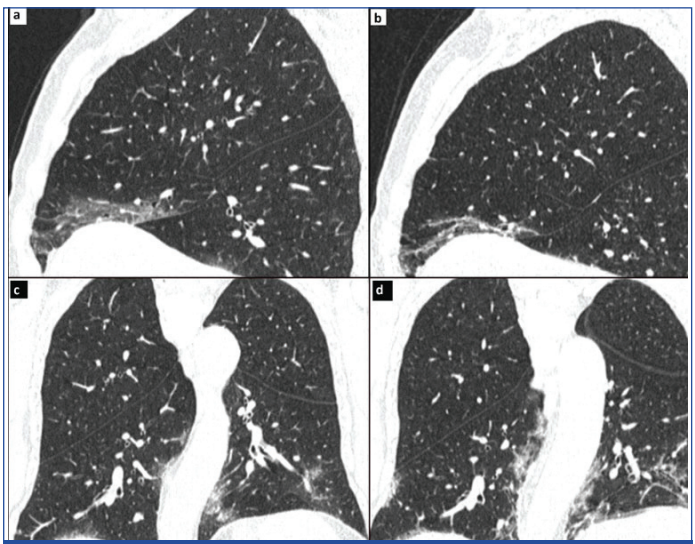
The CT-IS was associated with laboratory parameters. Evaluation of the inflammatory markers in severe category (severe CT-IS) patients revealed that 94.2% patients had raised IL-6 levels, 82.9% had raised

CRP levels, 77% had raised Ferritin levels, 14.3% had raised ESR levels, 11.4% had raised PCT levels and 17.1% had raised LDH levels. About 80% of patients with moderate CT-IS, showed raised IL-6 levels, 73.3% had raised Ferritin levels, 60% had raised ESR levels, 13.3% had raised PCT levels and 33.3% had raised LDH levels. All patients with moderate CT-IS had raised CRP levels. Amongst all the inflammatory markers, only ESR value was found to be significantly associated with CT-IS, with p-value of 0.004 [Table/Fig-3].

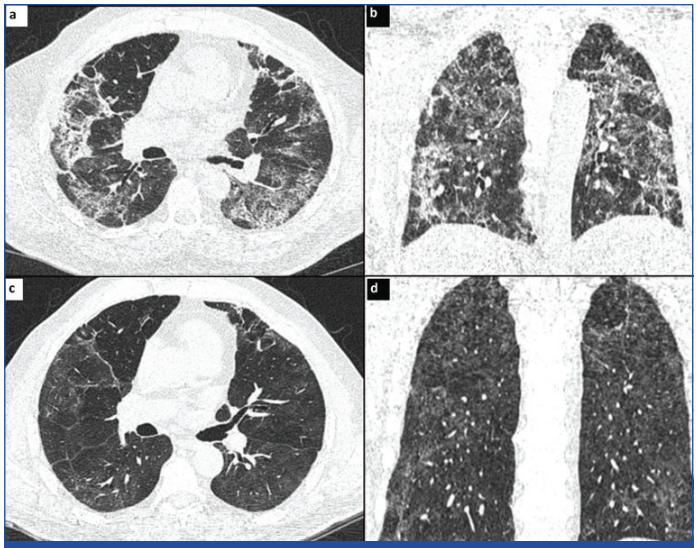
Out of 54 patients of lung fibrosis, 42 (77.78%) patients had bilateral lung lesions on HRCT lung. Bilateral lower lobes were the most common site to be involved, followed by upper lobes and middle lobes. Peripheral region or sub pleural ground glass opacities were the most common form of lesion distribution on HRCT scan in prefibrotic stage. Reticular opacities, parenchymal bands and traction bronchiectasis findings are seen in lung parenchyma of post COVID fibrosis patients. Initial changes of pulmonary ground glass opacities were present at 0-4 days from clinical onset. Maximum involvement of lung on CT was seen at 7-10 days from symptoms onset [Table/Fig-4-7].



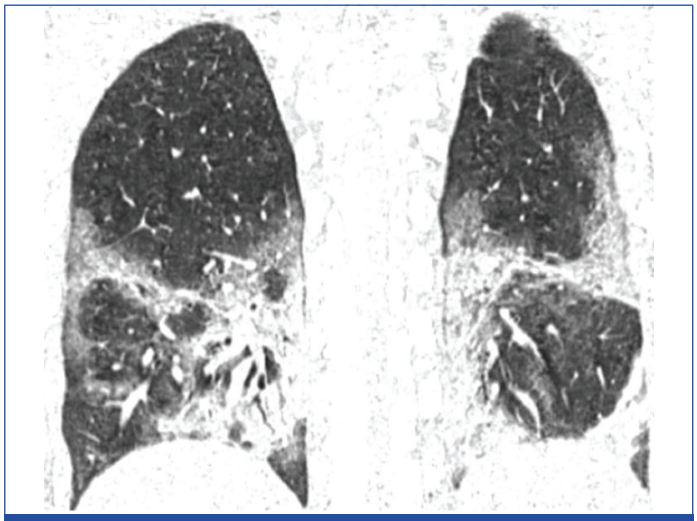
[Table/Fig-4]: HRCT lung of COVID-19 patient (a) On patient admission, axial sections of HRCT lung show ground glass opacities mainly in peripheral and in sub pleural region of upper lobes of bilateral lungs; (b) One week later axial sections of HRCT lung at same level shows fibrotic changes in form of parenchymal bands and reticular opacities in peripheral and in sub pleural region; (c) Axial sections of HRCT lung shows ground glass opacities mainly in peripheral and in sub pleural region of basal segments of bilateral lungs; (d) One week later axial sections of HRCT lung at same level shows fibrotic changes in form of reticular opacities and parenchymal bands in peripheral and in sub pleural region.



[Table/Fig-5]: HRCT lung of COVID-19 patient. (a) Sagittal reformatted image of HRCT lung shows ground glass opacities in basal segment; (b) 15 days later sagittal reformatted image of HRCT lung shows fibrotic changes in form of reticular opacities in basal segment; (c) Coronal reformatted image of HRCT shows ground glass opacities in lower lobes of bilateral lungs mainly in peripheral and in sub pleural region; (d) 15 days later coronal reformatted image of HRCT shows fibrotic changes in form of reticular opacities in lower lobe of bilateral lungs.



[Table/Fig-6]: HRCT lung of post COVID-19 patients before and after steroid therapy. a,b: (before steroid therapy) Axial and Coronal image of HRCT lung shows ground glass opacities with significant fibrotic changes and few foci of minimal bronchiectasis; c,d: (after steroid therapy) One month after starting steroid therapy showed significant reduction in fibrotic changes.



[Table/Fig-7]: HRCT lung of COVID-19 patient. Coronal reformatted image of HRCT shows ground glass opacities and fibrotic changes in lower lobe of bilateral lungs with traction bronchiectasis in lower lobe of right lung.

DISCUSSION

The COVID-19 pandemic, caused by SARS-CoV-2, is rapidly expanding throughout the world. Albeit it is widely known that most cases have mild symptoms with a good prognosis, COVID-19 disease may develop into Acute Respiratory Distress Syndrome (ARDS) or may culminate in death. Till date, there is no efficacious treatment for COVID-19 [21,22]. Several studies have demonstrated increased serum levels of proinflammatory cytokines in COVID-19 patients. Even, anti-inflammatory reagents therapy among COVID-19 patients also focusses on the scathing role of inflammation in the progressive pathogenesis of COVID-19 [23,24].

In the present study, all the patients were categorised according to CT-IS score [20]. CT-IS was assessed using each of the five lobes of the lung (three right lobes and two left lobes) and percentages of involvement. Lobe score 1 equals to less than 5% involvement, Lobe score 2 equals to 5-25% involvement, Lobe score 3 equals to 26-49% involvement, Lobe score 4 equals to 50-75% involvement and Lobe score 5 equals to 76-100% involvement [20]. Whereas, CO-RADS system is used to categorised patients radiologically, depending upon degree of suspicion for COVID-19 lung involvement. CO-RADS system has a significant role in COVID-19 pneumonia diagnosis [18]. As per the classification, patients with very high suspicion for COVID-19 are categorised into CO-RADS 5. In our

study, we included only COVID-19 positive patients confirmed by RT-PCR test, corresponding to CO-RADS 6 category.

Nevertheless, the role of inflammatory markers in monitoring the severity of COVID-19 is still questionable. In our study, we concluded that among inflammatory markers, only ESR was positively associated with the severity of COVID-19. Interleukin 6 has been also implicated in the H5N1 avian influenza infections and 2003 SARS outbreak [25,26]. Recent study unveiled that in COVID-19 patients, activated T-cells may secrete IL-6 and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF). Also, GM-CSF could activate monocytes (CD14 and 16 positive), which would further enhance secretion of IL-6 and other proinflammatory cytokines [27].

C-reactive protein is a crucial systemic marker of acute-phase response, which is very sensitive in tissue inflammation, tissue damage and infections. So, it can be used as a benchmark of systemic inflammation in COVID-19 patients [28]. However, Chen L et al., did not reveal any statistically significant difference in CRP levels between the severe and the non severe group, the mean CRP level was higher in the severe group compared to the non severe group [29]. PCT is also an important inflammatory marker measured in routine clinical practice. Chang Z et al., reported that, levels of PCT were all higher in the critical patients in comparison to the non critical group [30]. Erythrocyte sedimentation rate is another non specific inflammatory marker. Essentially, it reflects the changes of plasma protein types. Zeng F et al., in their study, found a higher ESR level in the severe group compared to the non severe group (p-value=0.005). Exuberant inflammation in severe group patients could be the reason for the above results [27]. Zeng F et al., also found higher levels serum ferritin in the severe group of corona patients than those in the non severe group (p-value <0.001) [27].

The present study revealed that almost all inflammatory markers were raised in patients showing fibrotic changes in HRCT lung. Inflammatory markers were predominantly increased in patients in the moderate and severe category namely IL-6 (80% and 94.2%), CRP (100% and 82.9%), ESR (60% and 14.3%), PCT (13.3% and 11.4%) and LDH (33.3% and 17.1%), respectively. This finding is similar to the results shown in a study done by Bhandari S et al., which revealed that inflammatory markers CRP, LDH, ferritin and PCT were elevated in the severely ill patients [31]. The radiological findings of COVID-19 patients on HRCT lung reflected typical features of viral pneumonia, and it was characterised by a rapid change similar to that in middle-east respiratory syndrome and severe acute respiratory syndrome [32-34]. Present study shows that utmost pulmonary findings on HRCT scan were found around 7-14 days from onset of symptoms. Results were comparable to studies by Wang Y et al., and Pan F et al., [15,35].

Follow-up studies using HRCT scans in COVID-19 patients showed fibrotic changes. Zhou S et al., revealed that fibrotic changes were seen in 21 patients (33.9%) out of total 62 patients. Moreover, his study also concluded that fibrotic changes were more likely to take place in late phase of corona disease (8-15 days after symptoms onset) than early phase of the disease (<8 days after the symptoms onset) [36]. Likewise, study by Pan Y et al., showed fibrotic changes in 11 out of 63 patients on HRCT lung performed on COVID-19 confirmed patients. [16]. These HRCT lung findings are reinforced further by autopsy reports. One study reported that four patients who died of COVID-19 pneumonia revealed microscopic picture of diffuse alveolar damage along with consolidation by fibroblast proliferation. ECM and fibrin deposition in the alveolar spaces was seen in postmortem core biopsy [37]. Nevertheless, it is precocious in the course of the disease to figure out if this finding would undergo resolution or in the course of time or may develop pulmonary fibrosis [38].

Limitation(s)

Limitation of study includes lack of data regarding therapeutic application against inflammatory markers positively associated with severity of lung disease in COVID-19 patients. Further studies need to be conducted for new drugs invention utilising the laboratory parameter data.

CONCLUSION(S)

In conclusion, among studied inflammatory markers, only ESR was positively associated with the severity of COVID-19 and changes of pulmonary fibrosis on HRCT scan. The association of serum ferritin levels with the severity of COVID-19 needs to be further clarified. Study of inflammatory biomarkers may be helpful to treating physicians in predicting the prognosis of disease. In the absence of any proven established target therapy, aim of the clinician should be at restricting the disease grievousness and prevent any major pulmonary complications.

REFERENCES

[1] Shang Y, Xu C, Jiang F, Huang R, Li Y, Zhou Y, et al. Clinical characteristics and changes of chest CT features in 307 patients with common COVID-19 pneumonia infected SARS-CoV-2: A multicenter study in Jiangsu, China. Int J Infect Dis. 2020;96:157-62.

[2] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for COVID-19: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.

[3] COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available at: https://coronavirus.jhu.edu/map.html. Accessed 19 November 2020.

[4] Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis. 2020;26(7):1470-77.

[5] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seqdata analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-92.

[6] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21.

[7] Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco smoking increases the lung gene expression of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med. 2020;201(12):1557-59.

[8] Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: The perspectives on immune responses. Cell Death Differ. 2020;27(5):1451-54.

[9] Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). Front Immunol. 2020;11:827.

[10] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-39.

[11] Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791-96.

[12] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020;;71(15):762-68.

[13] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-47.

[14] Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727-32.

[15] Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: A longitudinal study. Radiology. 2020;296(2):E55-64.

[16] Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): A study of 63 patients in Wuhan, China. Eur Radiol. 2020;30(6):3306-09.

[17] Kanne JP. Chest CT Findings in 2019 Novel Coronavirus (2019-nCoV) Infections from Wuhan, China: Key Points for the Radiologist. Radiology. 2020;295(1):16-17.

[18] Özel M, Aslan A, Araç S. Use of the COVID-19 Reporting and Data System (CO-RADS) classification and chest computed tomography involvement score (CT-IS) in COVID-19 pneumonia. Radiol Med. 2021;126(5):679-87.

[19] Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: Host-directed therapies should be an option. Lancet. 2020;395(10224):e35-36.

[20] Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. Ct imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020;295:202-07. Doi: 10.1148/radiol.2020200230.

[21] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19(3):149-50.

[22] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473-75.

[23] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-34.

[24] Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400-02.
[25] Law HK, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, et al. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood. 2005;106(7):2366-74.
[26] Saito LB, Diaz-Satizabal L, Evseev D, Fleming-Canepa X, Mao S, et al. IFN and cytokine responses in ducks to genetically similar H5N1 influenza A viruses of varying pathogenicity. J Gen Virol. 2018;99(4):464-74.
[27] Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis. 2020;96:467-74.
[28] Pepys MB, Hirschfield GM. C-reactive protein: A critical update. J Clin Invest. 2003;111(12):1805-12.
[29] Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia (In Chinese) Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(3):203-08.
[30] Chang Z, Yang W, Wang Q, Liao G. Clinical significance of serum hs-CRP, IL-6, and PCT in diagnosis and prognosis of patients with COVID-19 (In Chinese). Drugs Clin. 2020;35(3)
[31] Bhandari S, Sharma S, Bhargava A, Keswani P, Sharma R, Shekhawat A. Inflammatory markers in COVID-19. Ann Acad Med Singap. 2020;49(6):393-97.
[32] Ooi GC, Khong PL, Müller NL, Yiu WC, Zhou LJ, Ho JC, et al. Severe acute respiratory syndrome: Temporal lung changes at thin-section CT in 30 patients. Radiology. 2004;230(3):836-44.
[33] Antonio GE, Ooi CG, Wong KT, Tsui EL, Wong JS, Sy AN, et al. Radiographic-clinical correlation in severe acute respiratory syndrome: Study of 1373 patients in Hong Kong. Radiology. 2005;237(3):1081-90.
[34] Das KM, Lee EY, Enani MA, Al Jawder SE, Singh R, Bashir S, et al. CT correlation with outcomes in 15 patients with acute Middle East respiratory syndrome coronavirus. AJR Am J Roentgenol. 2015;204(4):736-42.
[35] Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes at chest CT during recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-21.
[36] Zhou S, Wang Y, Zhu T, Xia L. CT Features of Coronavirus Disease 2019 (COVID-19) pneumonia in 62 Patients in Wuhan, China. AJR Am J Roentgenol. 2020;214(6):1287-94.
[37] Tian S, Xiong Y, Liu H, Niu L, Guo J, Liao M, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol. 2020;33(6):1007-14.
[38] Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): A pictorial review. Eur Radiol. 2020;30(8):4381-89.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, All India Institute of Medical Sciences, Rajkot, Gujarat, India.
2. Assistant Professor, Department of Radiology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
3. Assistant Professor, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
4. Associate Professor, Department of Community Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
5. Professor, Department of Biochemistry, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
6. Professor, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Tarang Patel,
Assistant Professor, Department of Pathology, All India Institute of Medical Sciences,
Temporary Campus, Civil Hospital, Rajkot-360001, Gujarat, India.
E-mail: tarangpatelmddnb@outlook.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 22, 2021
- Manual Googling: Nob 08, 2021
- iThenticate Software: Dec 16, 2021 (12%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 14, 2021**
Date of Peer Review: **Sep 02, 2021**
Date of Acceptance: **Nov 11, 2021**
Date of Publishing: **Jan 01, 2022**