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Original Article

Correlation of ferritin with the duration of illness, disease severity, oxygenation status, ventilatory requirement, and lung fibrosis in COVID-19 pneumonia: A single-center experience of 1000 cases in tertiary care setting in India

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ABSTRACT

Objective: Robust data of ferritin are available as prognostic marker in bacterial infection and we have analyzed its usefulness in COVID-19 pneumonia in predicting severity of illness, response to treatment, and final outcome.

Materials and Methods: A prospective and observational study included 1000 COVID-19 cases confirmed with reverse transcription-polymerase chain reaction. All cases were assessed with lung involvement documented and categorized on high-resolution computed tomography (CT) thorax, oxygen saturation, inflammatory marker, ferritin at entry point, and follow-up during hospitalization. Age, gender, comorbidity, and use Bi-level positive airway pressure (BIPAP)/Non invasive ventilation (NIV) and outcome as with or without lung fibrosis as per CT severity were key observations. Statistical analysis is done using Chi-square test.

Results: In a study of 1000 COVID-19 pneumonia cases, age (<50 and >50 years) and gender (male vs. female) have significant association with ferritin ($P < 0.00001$) and ($P < 0.010$), respectively. CT severity score at entry point with ferritin level has significant correlation in severity score ($P < 0.00001$). Ferritin level has significant association with the duration of illness ($P < 0.00001$). Comorbidities have significant association with ferritin level ($P < 0.00001$). Ferritin level has significant association with oxygen saturation ($P < 0.00001$). BIPAP/NIV during hospitalization has significant association with ferritin level ($P < 0.00001$). Timing of BIPAP/NIV requirement in critical care setting has significant association with ferritin level ($P < 0.00001$). Follow-up ferritin titer during hospitalization as compared to entry point normal and abnormal ferritin has significant association in post-COVID lung fibrosis, respectively ($P < 0.00001$).

Conclusion: Ferritin is easily available, and universally acceptable inflammatory marker in COVID-19 pandemic, documented very crucial role in predicting severity of illness and assessing response to treatment and follow-up ferritin titer during hospitalization, can be used as early predictor of post-COVID lung fibrosis.

Keywords: COVID-19 pneumonia, Ferritin, Oxygen saturation, Inflammatory marker, Post-COVID lung fibrosis

INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, originally emerged from China, has documented 274,628,461 confirmed cases and 5,358,978 deaths globally, and 34,752,164 confirmed cases 478,007 deaths in India.[1] The International

Federation of Clinical Chemistry and Laboratory Medicine Task Force on COVID-19 has been established to synthesize up-to-date information on the epidemiology, pathogenesis, and laboratory diagnosis and monitoring of COVID-19, as well as to develop practical recommendations on the use of molecular, serological, and biochemical tests in disease diagnosis and management.[2,3]

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways, and vasculature, leading to long-term effects on lung functions. Although lung is the primary target organ involvement in COVID-19, many patients were shown pulmonary and extrapulmonary manifestations of diseases variably during the first and second wave, which occurred as resultant pathophysiological effects of immune activation pathway and direct virus-induced lung damage. In COVID-19 pneumonia, pathophysiology constitutes different pathways such as immune activation, inflammatory, thrombogenic, and direct viral affection to lungs and extrapulmonary tissues.[4,5]

Ferritin is highly ubiquitous iron-binding protein first isolated in 1937 from horse spleen since then its isolation methodology and role as acute-phase reactant and role as marker of inflammation have been evolved over decades. Various inflammatory markers such as ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), interleukin (IL)-6, and D-dimer have been evaluated in this pandemic, and now, robust data are available regarding its usefulness in analyzing severity, decision-making in critical cases, assessing response to interventions, and predicting outcome. Cytokine syndrome is defined as "A group of conditions sharing same pathological mechanisms with different etiologies, causing massive release of pro-inflammatory cytokines resulting into aberrant activation of immune and coagulation systems."[6] Cytokine storms have direct association with raised ferritin level, and indirectly, it will help in predicting ongoing inflammatory surge resulting in cytokine storm. Cytokine storm is most dreadful event in pathophysiology of COVID-19 pneumonia, and ultimately, it will lead to either direct cytokine-induced lung injury manifesting as ALI/ARDS or extrapulmonary systemic secondary hemophagocytic lymphohistiocytosis.[7] Studies have documented significantly raised ferritin with other inflammatory markers in COVID-19 pneumonia,[8] and now, COVID-19 has been included in conditions causing hyperferritinemia.[7]

Ferritin analysis found to be very crucial in this COVID-19 pneumonia, apart from routine inflammatory marker, its usefulness as marker of underlying immunosuppression.[9] In addition, it is useful in predicting severity of illness in patients suffering with comorbidity as diabetes mellitus and in geriatric cases and marker of increased morbidity in these cases.[10-12]

In the present study, we have utilized ferritin as basic marker in laboratory panel workup in all COVID patients and analyzed as core marker during follow-up in all admitted patients to assess response to therapy and predictor of post-COVID fibrosis as dismal outcome of this pandemic of pneumonia in tertiary care setting.

MATERIAL AND METHODS

Ethical approval

This study was approved by the Institutional Review Board/ Ethics Committee at Venkatesh Hospital and Critical Care Center, Latur, India, and MIMSR Medical College, Latur, India (Approval # VCC/90-2020-2021; approval date July 4, 2020).

Data source

A prospective, observational, 12 weeks follow-up study conducted during July 2020–May 2021, in MIMSR Medical College, Latur, and Venkatesh Hospital, Latur, India, included 1000 COVID-19 cases confirmed with reverse transcription-polymerase chain reaction (RT-PCR), to find out role of ferritin in predicting severity of illness, assessing response to therapy, and outcome as post-COVID fibrosis in diagnosed COVID-19 pneumonia cases admitted in critical care unit. A total of 1000 cases were enrolled in study after IRB approval and written informed consent of all included cases was taken at respective center of study in Venkatesh Hospital and MIMSR Medical College, Latur.

Inclusion criteria

COVID-19 patients confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, including those with comorbidities and irrespective of severity and oxygen saturation were included in the study.

Exclusion criteria

Those not willing to give consent, not able to perform ferritin, and not willing to remain in follow-up and cases died during hospitalization or before 12 weeks of discharge from hospital were excluded from the study.

Study design

Prospective, observational, 12 weeks follow up study.

All study cases were undergone following assessment before enrolling in study

COVID-19 RT-PCR test was performed on nasopharyngeal samples collected with all standard institutional infection control policies, if the first test results were negative and radiological features clearly documenting pneumonia,

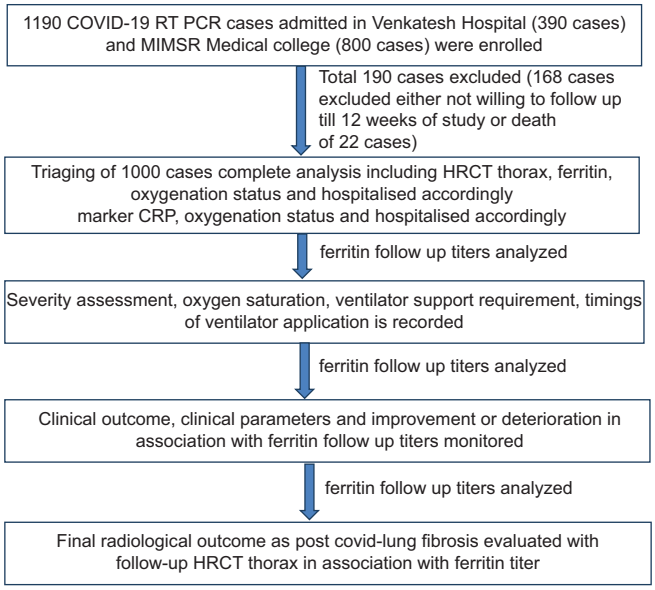

Figure 1: Flow of the study.

we have repeated RT-PCR test and enrolled all cases with positive COVID-19 RT-PCR test. High-resolution computed tomography HRCT Thorax was done in all cases to assess severity of lung involvement as per COVID-19 Reporting and Data System (CO-RADS)[13] and categorized as Mild if score <7, moderate if score 8-15 and severe if score >15 or 15-25. We have performed clinical assessment and routine biochemistry analysis with hematological workup including viral inflammatory markers such as CRP, Ferritin, LDH, IL-6 titers in all study cases. Entry point ferritin titer was utilized as assessment tool of severity of illness with clinical parameters. If ferritin analysis was normal at entry point, then ferritin titer was repeated on day of discharge from hospital or done during hospitalization if clinical course deteriorates. If ferritin analysis was abnormal at entry point, we repeated on every 72 h as follow-up to assess severity, progression of illness, and also titer utilized to assess response to medical treatment. Follow-up HRCT thorax was done after twelve weeks of discharge from hospital for analysis of post covid lung fibrosis in selected cases with abnormal ferritin titer at discharge and required BIPAP/NIV during hospitalization and cases required oxygen supplementation at home [Figure 1].

Methodology of ferritin titer assessment

Principle

Sandwich immunoluminometric assay:

Interpretation of results with reference values

1. Male: 14–250 ng/mL
2. Female: Age <45 years old 6–160 ng/mL and age ≥45 years old 5–200 ng/mL
3. Results may differ between laboratories due to variations in population and test method. Each laboratory should establish its own reference range.

Interpretation of results

1. Negative: Values with in normal limit as per gender
2. Positive: Value above reference range as per gender
3. Significant: Two-fold raised value as per gender
4. Highly significant: Four-fold raised as per gender
5. Follow-up significance: Values raised or decreased in 2-to-4-fold change as per gender.

Statistical analysis

The statistical analysis was done using Chi-square test in R-3.4 software. Significant values of χ^2 were seen from probability table for different degree of freedom required. *P* value was considered significant if it was below 0.05 and highly significant in case if it was <0.001.

RESULTS: COVARIATES

In the present study, 1000 COVID-19 pneumonia cases confirmed by COVID-19 RT-PCR, males were 650/1000 and females were 350/1000, age >50 was 600 cases, and age <50 was 400 cases.

Significant association in ferritin and COVID-19 pneumonia has been documented with variables such as age, gender, diabetes mellitus, ischemic heart disease (IHD), hypertension, chronic obstructive pulmonary disease (COPD), and obesity ($P < 0.00001$) [Table 1].

RESULTS: CORE OBSERVATIONS

Computed tomography (CT) severity score at entry point has significant correlation with ferritin level ($P < 0.00001$) [Table 2]. Ferritin level has significant association with the duration of illness (Doi) ($P < 0.00001$) [Table 3]. Ferritin level has significant association with oxygen saturation in COVID-19 pneumonia cases ($P < 0.00001$) [Table 4]. BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with ferritin level ($P < 0.00001$) [Table 5]. Timing of BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with ferritin level ($P < 0.00001$) [Table 6]. Follow-up ferritin titer during hospitalization as compared to entry point abnormal ferritin has significant association in post-COVID lung fibrosis ($P < 0.00001$), that is, ferritin at entry point to 4-fold raised cases in the presence or absence of pulmonary fibrosis was 40/170 and 360/110 cases, respectively ($P < 0.00001$) [Table 7]. Follow-up ferritin titer during hospitalization as compared to entry point normal ferritin has significant association in post-COVID lung fibrosis ($P < 0.00001$), that

Table 1: Other variables and ferritin level in COVID-19 pneumonia cases (*n*=1000).

COVID-19 RT-PCR positive (*n*=1000)	Ferritin level normal (*n*=320)	Ferritin level abnormal (*n*=680)	Chi² test value and *P* value
Age>50 years (*n*=600)	140	460	χ^2=51.77
Age<50 years (*n*=400)	180	220	*P*<0.00001
Male gender (*n*=650)	190	460	χ^2=6.5
Female gender (*n*=350)	130	220	*P*<0.010
Diabetes mellitus (*n*=600)	150	450	χ^2=33.77
Without diabetes (*n*=400)	170	230	*P*<0.00001
Hypertension (*n*=210)	160	50	χ^2=238.55
Without hypertension (*n*=790)	160	630	*P*<0.00001
COPD (*n*=150)	100	50	χ^2=97.46
Without COPD (*n*=850)	220	630	*P*<0.00001
IHD (*n*=200)	110	90	χ^2=60.77
Without IHD (*n*=800)	210	590	*P*<0.00001
Obesity (*n*=160)	20	140	χ^2=33.28
Without obesity (*n*=840)	300	540	*P*<0.00001

IHD: Ischemic heart disease, COPD: Chronic obstructive pulmonary disease

Table 2: Correlation of CT severity (at entry point) and ferritin in COVID-19 cases (*n*=1000).

CT severity	Normal ferritin (*n*=320)	Abnormal ferritin level (*n*=680)	Analysis
<8 score (*n*=300)	190	110	χ^2=224.87,
9–15 (*n*=300)	90	210	*P*<0.00001
>15 (*n*=400)	40	360	

Table 3: Doi at entry point during hospitalization and ferritin level in COVID-19 pneumonia cases (*n*=1000).

Doi	Normal ferritin (*n*=320)	Abnormal ferritin (*n*=680)	Analysis
<7 days (*n*=340)	30	310	χ^2=185.65
8–15 days (*n*=460)	160	300	*P*<0.00001
>15 days (*n*=200)	130	70	

Doi: Duration of illness

Table 4: Oxygen saturation at entry point and ferritin level in COVID-19 pneumonia cases (*n*=1000).

Oxygen saturation	Normal ferritin level (*n*=320)	Abnormal ferritin level (*n*=680)	Analysis
>90% (*n*=210)	110	100	χ^2=60.37
75–90% (*n*=490)	150	340	*P*<0.00001
<75% (*n*=300)	60	240	

Table 5: Correlation of BIPAP use with ferritin level in COVID-19 pneumonia cases (*n*=1000).

BIPAP/NIV	Normal ferritin (*n*=320)	Abnormal ferritin level (*n*=680)	Analysis
BIPAP/NIV required (*n*=600)	155	445	χ^2=26.21, *P*<0.00001
BIPAP/NIV not required (*n*=400)	165	235	

is, ferritin at entry point to 4-fold raised cases in the presence or absence of pulmonary fibrosis was 5/35 and 115/165 cases, respectively ($P < 0.00001$) [Table 8].

DISCUSSION

Correlation of CT severity (at entry point) and ferritin in COVID-19 cases

In the present study, CT severity score at entry point with ferritin level has significant correlation in COVID-19 pneumonia cases, score <8, 8–15, and >15 documented normal and abnormal ferritin level as in 190/110, 90/210, and 40/360, respectively, of total 1000 study cases ($P < 0.00001$). We have documented that, as CT severity increases, inflammatory marker ferritin also increases, significant number of mild cases was also having abnormal ferritin level. Similarly, various authors[4,14-22] have analyzed role of ferritin as "severity predictor" in their study. We have observed CT severity as the best visual marker of severity of COVID-19 pneumonia which can be correlated with inflammatory markers such as ferritin, CRP, IL-6, LDH, D-dimer, lymphopenia, and lymphocyte-platelet ratio, and it will help in triaging cases in casualty and help in targeting interventions in indoor units accordingly to have successful treatment outcome. Fox *et al.*[23] documented in

Table 6: BIPAP/NIV initiation time at entry point and ferritin level COVID-19 pneumonia cases (*n*=600).

BIPAP used (*n*=600) with duration of illness	Abnormal ferritin level (*n*=290)	Four-fold raised ferritin level (*n*=310)	Analysis
Entry point<1 days (*n*=180)	110	70	χ^2=31.30, *P*<0.00001
3–7 days (*n*=310)	150	160	
After 7 days (*n*=110)	30	80	

Table 7: Abnormal ferritin level at entry point (*n*=680) and follow-up and its correlation with post-COVID lung fibrosis.

Post-COVID pneumonia fibrosis	Ferritin titer increased/ abnormal at entry point (*n*=400)	Ferritin titer 4-fold increased during follow-up (*n*=280)	Analysis
Pulmonary fibrosis present (*n*=210)	40	170	χ^2=198.45, *P*<0.00001
Pulmonary fibrosis absent (*n*=470)	360	110	

Table 8: Normal ferritin level (*n*=320) at entry point and follow-up and its correlation with post-COVID lung fibrosis.

Post-COVID pneumonia fibrosis	Ferritin normal at entry point and remained less than 4-fold (n=120)	Ferritin titer 4-fold increased during follow-up (n=200)	Analysis
Pulmonary fibrosis present (*n*=40)	5	35	χ^2=12.19, *P*<0.00048
Pulmonary fibrosis absent (*n*=280)	115	165	

autopsy series in New Orleans regarding high ferritin level in cases with advanced pneumonia showing necrosis and hyaline membrane formation on histopathology of lung specimens.

Doi at entry point during hospitalization and ferritin level in COVID-19 pneumonia cases (*n*=1000)

In the present study, ferritin level has significant association with Doi in COVID-19 pneumonia cases, Doi <7 days, 8–15 days, and >15 days of onset of symptoms documented normal and abnormal ferritin levels in 30/310, 160/300, and 130/70 cases, respectively ($P < 0.00001$). Although ferritin is raised in COVID-19 pneumonia, we have documented that proportionate number of cases with Doi <1 week or 7 days and many cases with Doi >2 weeks or 15 days were having normal ferritin level, while pneumonia cases between 7 and 14 days of illness were having abnormal or raised ferritin level. Rational for observation is not known, may be inflammatory response pattern is different, and we have correlated ferritin pattern with other inflammatory markers such as CRP, IL-6, and LDH and documented that these two markers raised parallel to ferritin. Various authors have mentioned similar observation in their studies.[4,17,21,22] Raised ferritin after the 2nd week of illness may indicate worsening of COVID-19 pneumonia or secondary bacterial infection which can be confirmed with procalcitonin and it will help clinician to formulate antibiotics policy accordingly and indirectly guiding in management of these cases by assessing follow-up titers. Authors[9,17,24] have mentioned similar observation in their studies.

Correlation of BIPAP use with ferritin level in COVID-19 pneumonia cases (*n*=1000)

In the present study, BIPAP/NIV requirement during the course of COVID-19 pneumonia in critical care setting has significant association with ferritin level; cases received BIPAP/NIV during hospitalization were documented normal and abnormal ferritin level in 155/445 and 165/235 cases, respectively ($P < 0.00001$). We have observed that ferritin level has very well correlation with requirement of BIPAP/NIV, high-flow nasal cannula oxygen supplementation, and invasive mechanical ventilation in ICU setting. Rational for this, high ferritin and its strong association with extreme inflammatory burden and these patients have propensity to land in to hyperkinetic cytokine stimulation syndrome. Numerous authors [4,16,17,18,22,25-27] have documented similar observation in their studies.

Correlation of oxygen saturation at entry point and ferritin level in COVID-19 pneumonia cases (*n*=1000)

In the present study, ferritin level has significant association with oxygen saturation in COVID-19 pneumonia cases; cases with oxygen saturation >90%, 75–90%, and <75% observed as normal and abnormal ferritin level in 110/100, 150/340, and 60/240 cases, respectively ($P < 0.00001$). We observed

that, as oxygen saturation drops at entry point, ferritin level increases in significant number of COVID-19 cases. Probable mechanism for correlation of hypoxia or low oxygen saturation and increase in inflammatory markers such as ferritin and CRP is underlying lung parenchymal inflammation secondary to pneumonia resulting into inflammatory burden and hypoxia go hand-in-hand in these cases. Authors[4,14,17,18,20,21,22,26,27] have mentioned similar findings collaborating with our study. We have also observed that raised ferritin level will help in predicting severity of illness as many of these cases are having low oxygen saturation requiring interventions in intensive care units.

Correlation of BIPAP/NIV initiation time at entry point and ferritin level COVID-19 pneumonia cases (*n*=600)

In the present study, timing of BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with ferritin level; cases received BIPAP/NIV at entry point <1 day, 3–7 days, and after 7 days of hospitalization were documented significance in 4-fold raised ferritin level in 110/70, 150/160, and 30/80 cases, respectively ($P < 0.00001$). We have observed that early initiation of BIPAP/NIV those meeting criteria of oxygenation, as oxygen saturation less than 89% at room air during hospitalization was having beneficial effect in controlling systemic immune inflammatory syndrome which can be measured by ferritin level in follow-up, may be because of improvement in oxygenation and lung compliance after the use of BIPAP/NIV; as hypoxia is important trigger for rise in inflammatory burden by means of hypoxia-inducible transcription factor. Similarly, authors [4,17,18,20,22,26] have mentioned similar observation in their study.

Other important observation in this study

Correlation of abnormal ferritin level at entry point (n=680) and follow-up and its correlation with post-COVID lung fibrosis

In the present study, follow-up ferritin titer during hospitalization as compared to entry point abnormal ferritin has significant association in post-COVID lung fibrosis ($P < 0.00001$). The elevated levels of ferritin might be linked to the overproduction of inflammatory cytokines in severe patients with COVID-19. Cytokines fight against the microbes but when the immune system becomes hyperactive, it can damage lung tissue. Thus, ferritin production is induced by inflammatory cytokines and by tissue destruction in patients with COVID-19 and resultant outcome is lung fibrosis. Various authors have documented similar observation in their studies[8,17,21,28-32] and mentioned that raised titers during hospitalization and follow-up were having ongoing lung inflammation and can predict future lung fibrosis. We have also observed that raised ferritin at entry point is indicator of poor radiological outcome and many of these cases were having lung fibrosis and radiological sequelae in post-COVID care setting recovered in intensive care units or history of mechanical ventilation during hospitalization, and findings are in correlation with studies by various authors.[4,8,33,34]

Correlation of normal ferritin level (n=320) at entry point and follow-up and its correlation with post-COVID lung fibrosis

In the present study, follow-up ferritin titer during hospitalization as compared to entry point normal ferritin has significant association in post-COVID lung fibrosis ($P < 0.00001$). In this study, a small fraction of non-severe patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality. We have documented role of LDH, ferritin, CRP, and lymphocytes count in COVID-19 cases for prognostic prediction, and persistent abnormality in these markers indicates state of unstoppable inflammation resulting in necrosis and resultant fibrosis due to increased fibromyxoid stroma and organized consolidations, which are ultimate sequelae of ARDS either due to COVID-19. Various authors have mentioned similar observation in their studies.[4,22,31,32,35-39]

Correlation of other variables and ferritin level in COVID-19 pneumonia cases

In the present study, age of patient, that is, <50 years and >50 years, has significant association in COVID-19 cases with normal and abnormal ferritin level ($P < 0.00001$). We have also documented that gender of included cases has significant association in COVID-19 cases with normal and abnormal ferritin level ($P < 0.010$). Similarly, various authors in their studies[4,12,15-19,21,23-27,32] have documented important role of ferritin in predicting severity in geriatric cases.

In the present study, comorbidity as diabetes mellitus, COPD, hypertension, IHD, and obesity has significant association in COVID-19 cases with normal and abnormal ferritin level ($P < 0.00001$). Numerous authors have documented similar observation.[4,12,15-19,21,23-27,32]

CONCLUSION

Ferritin is easily available, sensitive, reliable, cost-effective, and universally acceptable inflammatory marker in COVID-19 pneumonia. Ferritin has very crucial role in COVID-19 pneumonia in predicting severity of illness, especially follow-up titers have significant role in step-up or step-down interventions in critical care setting. Correlating ferritin with variables such as Doi, oxygenation status, and

timing of BIPAP/NIV has important role in predicting outcome.

Ferritin titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial ferritin has progressed to critical course and we have documented that follow-up titers have played crucial role with other inflammatory markers, and many times in the 2nd week of illness rising titers indicates nosocomial bacterial infection and targeting treatment accordingly. Ferritin titer can help in predicting final radiological outcome as post-COVID lung fibrosis, especially follow-up high titers in cases requiring aggressive interventions during hospitalization have higher chances of post-COVID lung fibrosis.

Limitations of the study

Our study is having enough sample size and analyzed role of ferritin at entry point and follow-up during 12 weeks period and association with post-COVID-19 lung fibrosis is documented. Limitations of this study are multivariate analysis which will help in finer details associated with ferritin level and oxygenations status, severity of illness, ventilatory support requirement, and post-COVID lung fibrosis are not done. The second limitation is other confounding factors leading to abnormal ferritin level and its effect on COVID-19 severity parameters were not possible. The third limitation is association of ferritin titer with other modes of intensive care treatments as high-flow nasal cannula and invasive mechanical ventilatory support is not assessed differently and cases predominantly on BIPAP/NIV were considered as ventilatory support, probably because majority of COVID-19 cases receiving high-flow nasal cannula were shifted to BIPAP/NIV and/or mechanical ventilation in intensive care units.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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