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Role of initial and follow-up IL-6 (Interleukin-6) titre in COVID-19 pneumonia: A single center experience

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ABSTRACT

Background: Robust data of IL-6 is available in bacterial infection, and now it can be utilized in currently ongoing COVID-19 (corona virus disease-19) pneumonia pandemic to guide treatment strategy as marker of inflammation.

Methods: Prospective, observational study included 1,000 COVID-19 cases confirmed with RT PCR (reverse transcription polymerase chain reaction). All cases were undergone categorized after clinical details, HRCT (high resolution computerized tomography) thorax, oxygen saturation, IL-6 (interleukin 6) at entry point and follow up. Age, gender, comorbidity and use BIPAP/NIV (bilevel positive airway pressure/non-invasive ventilation), and outcome as with or without lung fibrosis as per HRCT severity were key observations. Statistical analysis is done by using Chi-square test.

Results: In study of 1,000 COVID-19 pneumonia cases, age (<50 and >50 years) and gender has significant association with IL-6. HRCT severity score at entry point has significant correlation with IL-6 level ($p<0.00001$). IL-6 level has significant association with duration of illness ($p<0.00001$). Comorbidities has significant association with IL-6 level ($p<0.00001$). IL-6 level has significant association with oxygen saturation ($p<0.00001$). BIPAP/NIV requirement has significant association with IL-6 level ($p<0.00001$). Timing of BIPAP/NIV requirement during course of hospitalization has significant association with IL-6 level ($p<0.00001$). Follow-up IL-6 titer during hospitalization as compared to entry point normal and abnormal IL-6 has significant association with post-COVID-19 lung fibrosis, respectively ($p<0.00001$).

Conclusion: IL-6 has very crucial role in COVID-19 pneumonia in predicting severity of illness, progression of illness including 'cytokine storm' and assessing response to treatment during hospitalization and follow-up titers in analyzing post-COVID-19 lung fibrosis.

Keywords: COVID-19 pneumonia, IL-6, oxygen saturation, inflammatory marker

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 (IFCC) 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].

Although lung is the primary target organ involvement in corona virus disease-19 (COVID-19), many patients were having pulmonary and extrapulmonary manifestations of diseases variably as a resultant pathophysiological effects of immune activation pathway and direct virus induced lung damage. In COVID-19 pneumonia, pathophysiology constitutes different pathways like immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues.

IL-6 was found in 1973 as a soluble factor that is secreted by T cells and is important for antibody production by B cells [4]. Since its discovery, role of IL-6 in immune regulation and dysregulation in many diseases has been studied in last 50 years. Before COVID-19, this molecule has been studied in rheumatoid arthritis, Crohn's disease, ulcerative colitis, multiple myeloma, systemic juvenile idiopathic arthritis, Castleman's disease, ankylosing spondylitis, psoriatic arthritis, and other immune dysregulated diseases. Robust data is available regarding its abnormally elevated levels of IL-6 in local tissue and serum of these cases due to dysregulated immune function and targeted therapy against novel molecule is now considered as best disease modifying approach rather than conventional steroids in these cases [5-7].

Role of IL-6 as marker of dysregulated immune system is earliest reports from China in initial period of COVID-19 pandemic [8], the researchers also mentioned that IL-6 is can be used with other inflammatory markers like CRP and Ferritin. In [9], the reseaerchers documented that IL-6 is raised in COVID-19, but its level not as high as documented in sepsis. The authors in [10] documented that, 1,000-fold increase in IL-6 level in COVID-19 pneumonia cases requiring intensive care unit hospitalization. US FDA [11] had approved IL-6 analysis during workup of COVID-19 pneumonia in June 2020, since then many laboratory companies came up with their methodology of IL-6 assay in COVID-19 pandemic. Hypercytokinaemic immune dysregulation in COVID-19 is known as cytokine storm syndrome. Interleukin-6 levels ≥80 pg/mL predict an increased risk of respiratory failure and death, and immunomodulatory therapy is an area of urgent investigation [12].

In present study, we have utilized IL-6 as basic marker in laboratory panel workup in all COVID-19 patients and analyzed as core marker during follow up in all admitted patients to assess progression illness and its role in assessing final outcome.

METHODS

Data Source

Prospective, observational study, conducted during July 2020 to May 2021, in MIMSR Medical College and Venkatesh Hospital Latur India, included 1,000 COVID-19 cases confirmed with RT PCR, to find out role of IL-6 in predicting severity of illness, assessing response to therapy and outcome as post-COVID-19 fibrosis in diagnosed COVID-19 pneumonia cases admitted in critical care unit. Total 1,000 cases were enrolled in study after written & informed consent was obtained from all individual participants admitted in indoor units after assessing overall status to give consent and whenever required taken from attendants of critically ill admitted cases.

Inclusion & exclusion 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.

Those not willing to give consent, not able to perform IL-6 and not willing to remain in follow-up were excluded.

Study Design

Figure 1 shows the flow of the study. All study cases were undergone following assessment before enrolling in study:

1. COVID-19 RT PCR test performed in all cases, if first test results were negative and radiological features clearly documenting pneumonia, we have repeated RT PCR test and enrolled all cases with positive COVID-19 RT-PCR test.
2. HRCT thorax to assess severity of lung involvement, and categorized as mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25.

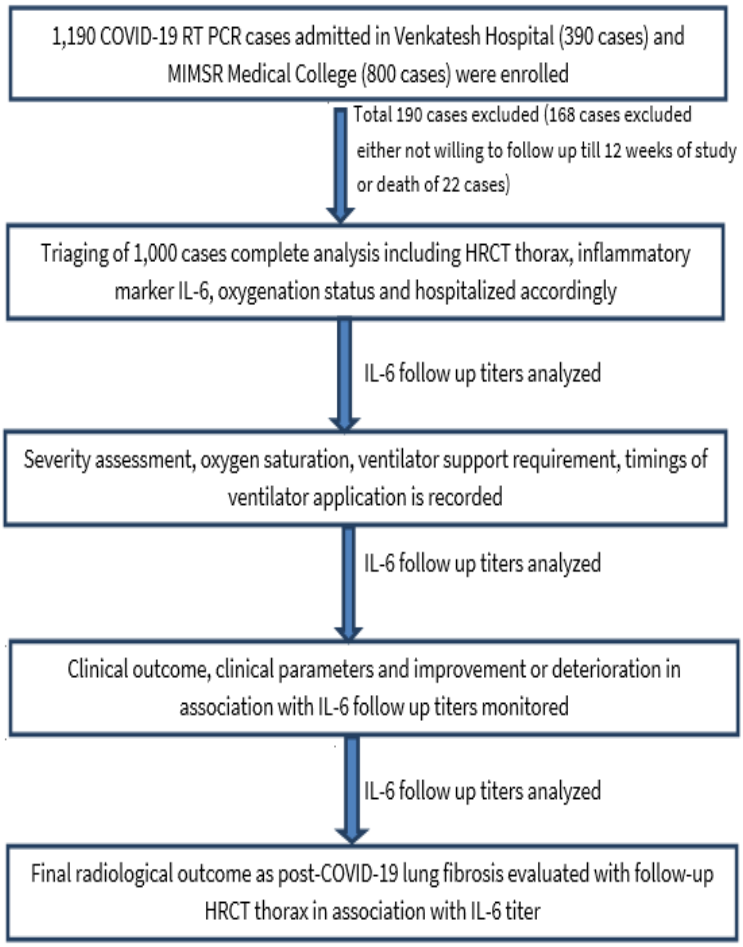

Figure 1. Flow of the study

Table 1. Other variables and IL-6 level in COVID-19 pneumonia cases (n=1,000)

COVID-19 RT PCR positive (n=1,000)	IL-6 level normal (n=320)	IL-6 level abnormal (n=680)	Chi 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

Table 2. Correlation of HRCT severity (at entry point) and IL-6 in COVID-19 cases (n=1,000)

HRCT severity	Normal IL-6 (n=320)	Abnormal IL-6 level (n=680)	Analysis
<8 score (n=300)	190	110	χ^2=224.87 p<0.00001
9-15 (n=300)	90	210	
>15 (n=400)	40	360	

3. Clinical assessment as vital parameters like heart rate, oxygen saturation, respiratory rate, blood pressure and documentation of respiratory adventitious sounds.
4. Laboratory parameters like hemoglobin, renal functions, blood sugar level, liver functions, ECG (electrocardiogram).
5. Viral inflammatory markers like IL-6, CRP (C-reactive protein), and ferritin assessed at entry point and repeated whenever required during course of illness. Normal and abnormal parameter readings were considered as per pathological laboratory standard.
6. Entry point IL-6 titer was utilized as assessment tool of severity of illness with clinical parameters.
7. If IL-6 analysis was normal at entry point, then IL-6 titer was repeated on day of discharge from hospital or done during hospitalization if clinical course deteriorates.
8. If IL-6 analysis was abnormal at entry point, we repeated on every 72 hours as follow up to assess severity, progression of illness and also titer level utilized to assess response to medical treatment.
9. Follow-up HRCT thorax was done after 12 weeks or 3 months of discharge from hospital for analysis of post-COVID-19 lung fibrosis in selected cases with abnormal IL-6 level at discharge and required BIPAP/NIV during hospitalization and cases required oxygen supplementation at home.

Methodology of IL-6 Titer Assessment-Immunoturbidimetry [13]

Normal values

Normal values up to <7 pg/mL.

Interpretation of results

1. Negative: value up to <7 pg/mL.
2. Positive: value above <7 pg/mL.
3. Significant: 4-fold raised IL-6 vale i.e., >28 pg/mL.
4. Highly significant: 16-fold raised values i.e., 98 pg/mL i.e., level considered as required for labeled as cytokine storm.
5. Follow up significance: values raised or decreased in two-to-four-fold change.

Statistical analysis

The statistical analysis was done using chi 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 less than 0.001.

Covariates

Significant association in IL-6 and COVID-19 pneumonia has been documented with variables like age, gender, diabetes mellitus, IHD, hypertension, COPD, and obesity (p<0.00001) shown in **Table 1**.

Observations and Analysis

In present study, 1,000 COVID-19 pneumonia cases confirmed by COVID-19 RT PCR, males were 650/1,000 and females were 350/1,000, age >50 were 600 cases and age <50 were 400 cases. HRCT severity score at entry point with IL-6 level has significant correlation in COVID-19 pneumonia cases (p<0.00001) (**Table 2**).

IL-6 level has significant association with duration of illness in COVID-19 pneumonia cases (p<0.00001) (**Table 3**).

IL-6 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 IL-6 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 IL-6 level (p<0.00001) (**Table 6**).

Table 3. Duration of illness at entry point during hospitalization and IL-6 level in COVID-19 pneumonia cases (n=1,000)

Duration of illness	Normal IL-6 (n=320)	Abnormal IL-6 level (n=680)	Analysis
<7 days (n=340)	30	310	χ^2=185.65 p<0.00001
8-15 days (n=460)	160	300	
>15 days (n=200)	130	70	

Table 4. Oxygen saturation at entry point and IL-6 level in COVID-19 pneumonia cases (n=1,000)

Oxygen saturation	Normal IL-6 (n=320)	Abnormal IL-6 level (n=680)	Analysis
>90% (n=210)	110	100	χ^2=60.37 p<0.00001
75-90% (n=490)	150	340	
<75% (n=300)	60	240	

Table 5. Correlation of BIPAP use with IL-6 level in COVID-19 pneumonia cases (n=1,000)

BIPAP/NIV	Normal IL-6 (n=320)	Abnormal IL-6 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	

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

BIPAP used (n=600) with duration of illness	Abnormal IL-6 level (n=290)	Four-fold raised IL-6 level (n=310)	Analysis
Entry point <1days (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 IL-6 level at entry point (n=680) and follow up and its correlation with post-COVID-19 lung fibrosis

Post-COVID-19 COVID-19 pneumonia fibrosis	IL-6 titer increased/abnormal at entry point (n=400)	IL-6 titer fourfold 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 IL-6 level (n=320) at entry point and follow up and its correlation with post-COVID-19 lung fibrosis

Post-COVID-19 COVID-19 pneumonia fibrosis	IL-6 normal at entry point & remained less than 4-fold (n=120)	IL-6 titer fourfold 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	

Table 9. Normal IL-6 level (n=320) & abnormal IL-6 level at entry point (n=680) and its correlation with follow up titer with cytokine storm (n=190)

Cytokine storm	Normal IL-6 titer at entry point (n=320)	Abnormal IL-6 at entry point (n=680)	Analysis
Cytokine storm present (n=196)	40	156	χ^2=15.05 p<0.0001
Cytokine storm absent (n=804)	280	524	

Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in post-COVID-19 lung fibrosis (p<0.00001) (**Table 7**).

Follow-up IL-6 titer during hospitalization as compared to entry point normal IL-6 has significant association in post-COVID-19 lung fibrosis (p<0.00001) (**Table 8**).

Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in predicting cytokine storm irrespective normal or abnormal of IL-6 at entry point (p<0.0001) (**Table 9**).

DISCUSSION

Correlation of CT Severity (at Entry Point) and IL-6 in COVID-19 Cases

In present study, CT severity score at entry point and IL-6 level has significant correlation i.e., score <8, 8-15, and >15 documented normal and abnormal IL-6 level as in 190/110, 90/210, and 40/360, respectively of total 1,000 study cases (p<0.00001). We have documented CT severity as the best visual marker of severity of COVID-19 pneumonia which can be correlated with inflammatory markers as IL-6, ferritin, CRP, LDH, D-dimer and lymphopenia, 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. In [8, 14-27], the authors documented that IL-6 and other inflammatory markers like, CRP and LDH has been raised with CT severity score and mild, moderate and severe pneumonia were having increasing trends of inflammatory markers.

Duration of Illness at Entry Point during Hospitalization and IL-6 Level in COVID-19 Pneumonia Cases (n=1,000)

In present study, IL-6 level has significant association with duration of illness i.e., cases duration of illness (doi) <7 days, 8-15 days, and >15 days of onset of symptoms documented normal and abnormal IL-6 levels in 30/310, 160/300 and 130/70

cases, respectively (p<0.00001). Although IL-6 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 with normal IL-6 level, while cases between 7-14 days of doi with abnormal or raised IL-6 level. Rational for observation is not known, may be inflammatory pattern is different, and we have correlated IL-6 pattern with other inflammatory markers like CRP and LDH and documented that these two markers raised parallel to IL-6. Raised IL-6 after second week of illness may indicate worsening of COVID-19 pneumonia or secondary bacterial infection which will help intensivist to formulate antibiotics policy accordingly, thus follow-up titers indirectly guiding in protocolized management of these cases.

Correlation of BIPAP/NIV Use with IL-6 Level in COVID-19 Pneumonia Cases (n=1,000)

In present study, BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with IL-6 level i.e., cases received BIPAP/NIV with normal and abnormal IL-6 level in 155/445, 165/235 cases, respectively (p<0.00001). IL-6 level has very well correlation with requirement of BIPAP/NIV, high flow nasal canula oxygen supplementation and invasive mechanical ventilation in critical care setting. Studies in [8, 19, 22, 28] documented, high IL-6 is predictor of critical illness requiring intensive care unit treatment including mechanical ventilatory support as compared to cases with normal IL-6 level.

Correlation of Oxygen Saturation at Entry Point and IL-6 Level in COVID-19 Pneumonia Cases (n=1,000)

In present study, IL-6 level has significant association with oxygen saturation i.e., cases with oxygen saturation >90%, 75-90%, and <75% observed as normal and abnormal IL-6 level in 110/100, 150/340 and 60/240 cases, respectively (p<0.00001). We have documented positive correlation with hypoxia at entry point during hospitalization and abnormal IL-6 level. Studies by various authors [8, 14-16, 18, 23-29] documented that higher IL-6 level is associated with hypoxemia, and observed that higher IL-6 level may be indicator of advanced pneumonia process resulting into failure of oxygenation due to more lung parenchymal damage or necrosis.

Correlation of BIPAP/NIV Initiation Time at Entry Point and IL-6 level COVID-19 Pneumonia Cases (n=600)

In present study, timing of BIPAP/NIV requirement during hospitalization in critical care setting has significant association with IL-6 level i.e., cases received BIPAP/NIV at entry point <1 day, 3-7 days, and after 7 days of hospitalization were documented significance in four-fold raised IL-6 level in 110/70, 150/160, and 30/80 cases respectively (p<0.00001). We observed that early initiation of BIPAP/NIV those meeting criteria of oxygenation, i.e., oxygen saturation less than 89% at room air during hospitalization were having beneficial effect in controlling systemic immune inflammatory syndrome which can be measured by IL-6 level in follow up; may be because of improvement in oxygenation and lung compliance after use of BIPAP/NIV; as hypoxia is important trigger for rise in inflammatory markers by means of hypoxia inducible transcription factor. Studies like [20, 21] documented similar observation in their study.

Normal IL-6 Level (n=320) & Abnormal IL-6 Level at Entry Point (n=680) and Its Correlation with Follow up Titer with Cytokine Storm (n=190)

Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in predicting cytokine storm, also its occurrence is irrespective normal or abnormal of IL-6 at entry point (p<0.0001). Cytokine storm is independent predictor of poor outcome and many of these cases represent rapidly evolving COVID-19 pneumonia progressing to ARDS and required ventilatory support and proportionately majority required high flow oxygen supplementation during hospitalization and few cases require oxygen backup at home after discharge form critical care setting. Authors in [15, 30-35] documented similar observation. We have documented significant role of tocilizumab in curtailing cytokine storm with severe COVID-19 pneumonia cases requiring ventilatory support and it will show improvement in oxygenation, inflammatory markers, and ventilatory requirement in majority of cases and mortality benefit in few cases. Thus, timely IL-6 inhibitor or tocilizumab has outcome modifying role in intensive care units in cases with ALI/ARDS with IL-6 level above 98 pg/ml. Various authors like [16, 29, 36-39] documented similar findings in their studies.

Other Important Observation in This Study:

Correlation of abnormal IL-6 level at entry point (n=680) and follow up and its correlation with post-COVID-19 lung fibrosis

In present study, follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in post-COVID-19 lung fibrosis (p<0.00001), i.e., IL-6 at entry point to four-fold raised cases in presence or absence of pulmonary fibrosis were 40/170 and 360/110 cases, respectively. We have documented that serial measurement of IL-6 during hospitalization irrespective of entry point level has very well correlation with requirement of interventions as high flow nasal canula, BIPAP/NIV, ECMO, invasive mechanical ventilation irrespective of IL-6 level reaching to cytokine storm. IL-6 will indirectly help in predicting future risk of development of post-COVID-19 lung fibrosis. Authors in [36, 37, 40-42] observed similar findings in their studies.

Correlation of normal IL-6 level (n=320) at entry point and follow up and its correlation with post-COVID-19 lung fibrosis

In present study, follow-up IL-6 titer during hospitalization as compared to entry point normal IL-6 has significant association in post-COVID-19 lung fibrosis (p<0.00001), i.e., IL-6 at entry point to four-fold raised cases in presence or absence of pulmonary fibrosis were 5/35 and 115/165 cases, respectively. We have documented that, normal IL-6 is predictor of good clinical and radiological outcome and serial measurement of IL-6 during hospitalization irrespective of entry point level has very well correlation with underlying lung pathology and rising trends will help in defining underlying lung parenchymal damage secondary to cytokine induced lung necrosis and cytokine induced ALI/ARDS. These may be considered as early marker of future lung fibrosis. Authors in [22, 40-42] documented similar observation and mentioned correlation of follow-up titers with post-COVID-19 lung fibrosis.

Correlation of other variables and IL-6 level in COVID-19 pneumonia cases

In present study, age of patient i.e., <50 years and >50 years has significant association in COVID-19 cases with normal and abnormal IL-6 level (p<0.00001). We have also documented gender of included cases has significant association in COVID-19 cases with normal and abnormal IL-6 level (p<0.010). Studies by various authors in [8, 14, 15, 17, 18, 25, 28, 40] also documented similar observations. In present study, comorbidity as diabetes mellitus, COPD, hypertension, IHD, and obesity has significant association in COVID-19 cases with normal and abnormal D-dimer level (p<0.00001). Studies by various authors [8, 14, 15, 17, 18, 25, 28, 40] also documented similar observations in IL-6 level and its correlation with underlying comorbidities.

CONCLUSION

IL-6 is easily available, sensitive, reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pneumonia. IL-6 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 IL-6 with variables as duration of illness, oxygenation status and timing of BIPAP/NIV has important role in predicting outcome.

IL-6 titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial IL-6 has progressed to critical course and we have documented follow up titers has played crucial role with other inflammatory markers, and many times in second week of illness rising titers indicates nosocomial bacterial infection and targeting treatment accordingly. IL-6 follow-up titer can help in predicting progression of COVID pneumonia, and assessing risk of post-COVID-19 lung fibrosis.

Research Quality and Ethics Statement

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/39-2020-2021; approval date 16/07/2020). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the observational studies, STROBE Guidelines, during the conduct of this research project.

Author contributions: All authors have sufficiently contributed to the study, and agreed with the results and conclusions.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. WHO. Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update. 2021. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (Accessed: 24 December 2021).
2. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020;58(7):1063-9. https://doi.org/10.1515/cclm-2020-0240 PMid:32191623
3. Bohn MK, Lippi G, Horvath A, et al. Molecular, serological, and biochemical diagnosis and monitoring of COVID-19: IFCC taskforce evaluation of the latest evidence. Clin Chem Lab Med. 2020;58:1037-52. https://doi.org/10.1515/cclm-2020-0722 PMid:32459192
4. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Respir J. 2020;56(4):2003006. https://doi.org/10.1183/13993003.03006-2020 PMid:32883678 PMCid:PMC7474149
5. Lau CS, Hoo SP, Koh JMJ, Phua SK, Aw TC. Performance of the Roche IL-6 chemiluminescent immunoassay in patients with COVID-like respiratory symptoms. J Virol Methods. 2021;296:114224. https://doi.org/10.1016/j.jviromet.2021.114224 PMid:34214571 PMCid:PMC8240448
6. Kishimoto T, Ishizaka K. Regulation of antibody response in vitro. VII. Enhancing soluble factors for IgG and IgE antibody response. J Immunol. 1973;111:1194-205.
7. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol. 2020;16(6):335-45. https://doi.org/10.1038/s41584-020-0419-z PMid:32327746 PMCid:PMC7178926
8. Hashizume M, Tan SL, Takano J, et al. A humanized anti-IL-6R antibody, as an emerging therapeutic option for rheumatoid arthritis: Molecular and cellular mechanistic insights. Int Rev Immunol. 2015;34(3):265-79. https://doi.org/10.3109/08830185.2014.938325 PMid:25099958
9. Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: Designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov. 2018;17(6):395-412. https://doi.org/10.1038/nrd.2018.45 PMid:29725131
10. Huang CL, Wang YM, Li XW, Ren LL, Zhao JP, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
11. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS. Cytokine elevation in severe and critical COVID-19: A rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020;8:1233-44. https://doi.org/10.1016/S2213-2600(20)30404-5
12. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Respir J. 2020;56. https://doi.org/10.1183/13993003.03006-2020 PMid:32883678 PMCid:PMC7474149
13. US Food and Drug Administration. FDA emergency use authorization elecsys IL-6. 2021. Available at: https://www.fda.gov/media/138596/download (Accessed: 27 December 2021).
14. Zhang J, Hao Y, Ou W, et al. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: A cohort study. J Transl Med. 2020;18:406. https://doi.org/10.1186/s12967-020-02571-x PMid:33121497 PMCid:PMC7594951

15. Chen LD, Zhang ZY, Wei XJ, et al. Association between cytokine profiles and lung injury in COVID-19 pneumonia. Respir Res. 2020;21:201. https://doi.org/10.1186/s12931-020-01465-2 PMid:32727465 PMCid:PMC7389162
16. Gubernatorova EO, Gorshkova EA, Polinova AI, Drutskaya, MS. IL-6: Relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 2020;53:13-24. https://doi.org/10.1016/j.cytogfr.2020.05.009 PMid: 32475759 PMCid:PMC7237916
17. Santa Cruz A, Mendes-Frias A, Oliveira AI, et al. Interleukin-6 is a biomarker for the development of fatal severe acute respiratory syndrome coronavirus 2 pneumonia. Front Immunol. 2021;12:613422. https://doi.org/10.3389/fimmu.2021.613422 PMid:33679753 PMCid:PMC7930905
18. Iannaccone G, Scacciavillani R, Del Buono MG, et al. Weathering the cytokine storm in COVID-19: Therapeutic implications. Cardio Renal Med. 2020;10:277-87. https://doi.org/10.1159/000509483 PMid:32599589 PMCid: PMC7360507
19. Han H, Ma Q, Li C, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020;9:1123-30. https://doi.org/10.1080/22221751.2020.1770129 PMid: 32475230 PMCid:PMC7473317
20. Rocio LG, Alberto UR, Paloma T, et al. Interleukin-6-based mortality risk model for hospitalised COVID-19 patients. J Allergy Clin Immunol. 2020;146:799-807. https://doi.org/10.1016/j.jaci.2020.07.009 PMid:32710975 PMCid: PMC7375283
21. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146:128-36. https://doi.org/10.1016/j.jaci.2020.05.008 PMid: 32425269 PMCid:PMC7233239
22. Yuan J, Zou R, Zeng L, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm Res. 2020;69:599-606. https://doi.org/10.1007/s00011-020-01342-0 PMid: 32227274 PMCid:PMC7103893
23. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76(1):16-32. https://doi.org/10.1128/MMBR.05015-11 PMid:22390970 PMCid:PMC3294426
24. Sun X, Wang T, Cai D, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev. 2020;53:38-42. https://doi.org/10.1016/j.cytogfr.2020.04.002 PMid:32360420 PMCid:PMC7182527
25. Zeng, Z, Yu, H, Chen, H, et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. Crit Care. 2020;24:1-12. https://doi.org/10.1186/s13054-020-03255-0 PMid:32854750 PMCid: PMC7450961
26. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: A retrospective cohort study. Lancet Rheumatol. 2020;2:e474-84. https://doi.org/10.1016/S2665-9913(20)30173-9
27. Atal S, Fatima Z. IL-6 inhibitors in the treatment of serious COVID-19: a promising therapy? Pharmaceut Med. 2020;34:223-31.https://doi.org/10.1007/s40290-020-0342-z PMid:32535732 PMCid:PMC7292936
28. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370. https://doi.org/10.1016/j.jcv.2020.104370 PMid:32344321 PMCid:PMC7194648
29. Chen X, Zhao B, Qu Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. Clin Infect Dis. 2020;71(8):1937-42. https://doi.org/10.1093/cid/ciaa449 PMid:32301997 PMCid:PMC7184354
30. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791-6. https://doi.org/10.1002/jmv.25770 PMid:32181911 PMCid:PMC7228247
31. Huang KJ, Su IJ, Theron M, et al. An interferon-gamma-related cytokine storm in SARS patients. J Med Virol. 2005;75(2):185-94. https://doi.org/10.1002/jmv.20255 PMid:15602737 PMCid:PMC7166886
32. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-39. https://doi.org/10.1007/s00281-017-0629-x PMid:28466096 PMCid:PMC7079893
33. Kim ES, Choe PG, Park WB, et al. Clinical progression and cytokine profiles of Middle East respiratory syndrome coronavirus infection. J Korean Med Sci. 2016;31(11):1717-25. https://doi.org/10.3346/jkms.2016.31.11.1717 PMid: 27709848 PMCid:PMC5056202
34. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136(1):95-103. https://doi.org/10.1111/j.1365-2249.2004.02415.x PMid: 15030519 PMCid:PMC1808997
35. Hou H, Zhang B, Huang H, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. Clin Exp Immunol. 2020;201(1):76-84. https://doi.org/10.1111/cei.13450 PMid:32365221 PMCid: PMC7267633
36. Bhandari S, Rankawat G, Singh A, Wadhwani D, Patel B. Evaluation of interleukin-6 and its association with the severity of disease in COVID-19 patients. Indian J Med Spec. 2020;11:132-6. https://doi.org/10.4103/INJMS.INJMS_63_20
37. Aykal G, Esen, H, Seyman, D, Caliskan T. Could IL-6 predict the clinical severity of COVID-19? Turkish J Biochem. 2021;46(5):499-507. https://doi.org/10.1515/tjb-2021-0020
38. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol. 2020;92(11):2283-5. https://doi.org/10.1002/jmv.25948 PMid:32343429 PMCid:PMC7267383
39. Grifoni E, Valoriani A, Cei F, et al. Interleukin-6 as prognosticator in patients with COVID-19. J Infect. 2020;81:452-82. https://doi.org/10.1016/j.jinf.2020.06.008 PMid:32526326 PMCid:PMC7278637
40. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci. 2020;;117(20):10970-5. https://doi.org/10.1073/pnas.2005615117 PMid:32350134 PMCid:PMC7245089
41. Conrozier T, Lohse A, Balblanc J-C, et al. Biomarker variation in patients successfully treated with tocilizumab for severe coronavirus disease 2019 (COVID-19): Results of a multidisciplinary collaboration. Clin Exp Rheumatol. 2020;38(4):742-7.

42. Montesarchio V, Parrela R, Iommelli C, et al. Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. J Immunother Cancer. 2020;8(2):e001089. https://doi.org/10.1136/jitc-2020-001089 PMid:32784217 PMCid:PMC7418768