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Does IL-6 level help in assessment of severity in COVID-19 Pneumonia, and predicting radiological outcome? Tertiary care center experience of 1000 COVID-19 cases in India

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Abstract

Introduction: COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. **Materials and methods:** Multicentric, prospective, observational and interventional study conducted during July 2020 to May 2021, in MIMSR Medical College and Venkatesh Hospital Latur India, included 1000 COVID-19 cases confirmed with RT PCR. All cases were assessed with lung involvement documented and categorized on HRCT thorax, oxygen saturation, inflammatory marker as IL-6 at entry point and follow up. Age, gender, Comorbidity and use BIPAP/NIV and outcome as with or without lung fibrosis as per CT severity were key observations. CT severity scoring done as per universally accepted standard scoring tool as score <7 as mild, 7-14 as moderate and score >15 as severe affection of lung. Statistical analysis is done by using Chi square test. **Observations and analysis:** In study of 1000 covid-19 pneumonia cases, age (<50 and >50 years) and gender (male versus female) has significant association with IL-6 in predicting severity of covid 19 pneumonia [p<0.00001] & [p<0.010] respectively. CT severity score at entry point with IL-6 level has significant correlation in severity score <8, 8-15 and >15 documented normal and abnormal IL-6 level as in 190/110, 90/210 and 40/360 respectively. [p<0.00001] IL-6 level has significant association with duration of illness i.e., 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] Comorbidity as diabetes mellitus, hypertension, COPD, IHD & obesity has significant association in covid-19 cases with normal and abnormal IL-6 level respectively. [p<0.00001] IL-6 level has significant association with oxygen saturation in covid1-19 pneumonia cases; 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] BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with IL-6 level; cases received BIPAP/NIV during hospitalization were documented normal and abnormal IL-6 level in 155/445, 165/235 cases respectively [p<0.00001] Timing of BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with IL-6 level; 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] Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in post-covid lung fibrosis [p<0.00001] Follow-up IL-6 titer during hospitalization as compared to entry point normal IL-6 has significant association in post-covid lung fibrosis [p<0.00001] 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] **Conclusion**: IL-6 is sensitive, reliable, cost effective, and now universally acceptable inflammatory marker in COVID-19 pandemic. 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. Follow up IL-6 titer during hospitalization and at discharge can be used as early predictor of post-covid lung fibrosis.

Keywords: Covid-19 Pneumonia, Il-6, Cytokine Storm, Oxygen Saturation, Inflammatory Marker.

INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, originally emerged from China, but has since then confirmed cases 274,628,461 and deaths 5,358,978 worldwide, 34,752,164 confirmed cases 478,007 total deaths in the India alone [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].

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 corona virus disease-19 (COVID-19), many patients were shown pulmonary and extrapulmonary manifestations of diseases variably during first and second wave, which occurred as resultant pathophysiological effects of immune activation pathway and direct virus induced lung damage.

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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 [5]. 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 this novel molecule is now considered as best disease modifying approach rather than conventional steroids in these cases [6-8].

Role of IL-6 as marker of dysregulated immune system is earliest reports from China in initial period of COVID-19 pandemic by Huang C.L *et al* [9]. they also mentioned that IL-6 is can be used with other inflammatory markers like CRP and Ferritin. Leisman D.E et al [10] documented that IL-6 is raised in COVID-19, but its level not as high as documented in sepsis. Chen L.Y.C *et al* [11]. documented that, 1000-fold increase in IL-6 level in COVID-19 pneumonia cases requiring intensive care unit hospitalization. U.S. FDA [12]. 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 [13].

In present study, we have utilized IL-6 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 progression illness as cytokine storm and response to therapy by analyzing IL-6 level and its role as earliest predictor of post-covid fibrosis as resultant Pathophysiological effect of COVID-19 pneumonia in tertiary care setting.

MATERIALS AND METHODS

Multicentric, prospective, observational and interventional study, conducted during July 2020 to May 2021, in MIMSR Medical College and Venkatesh Hospital Latur India, included 1000 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 fibrosis in diagnosed covid-19 pneumonia cases admitted in critical care unit. Total 1000 cases were enrolled in study after IRB approval and written informed consent of patient.

Inclusion criteria

1. All COVID-19 pneumonia cases above 18-year age, admitted in indoor unit has been enrolled in study.
2. COVID-19 pneumonia irrespective of CT severity were enrolled in study.
3. COVID-19 pneumonia irrespective oxygen saturation was enrolled in study.
4. COVID-19 pneumonia with comorbidity like Diabetes Mellitus, IHD, CVD, CKD, COPD were enrolled in study.
5. COVID-19 pneumonia cases willing to undergo follow up IL-6 analysis during hospitalization were enrolled in study.

Exclusion criteria

1. Covid-19 pneumonia cases not willing to participate in study.
2. Covid-19 pneumonia cases not willing to undergo follow up IL-6 analysis.
3. Covid-19 pneumonia cases want discharge against medical advice before clinical recovery from hospital.
4. COVID-19 pneumonia below 18 years of age.

All study cases were undergone following assessment before enrolling in study

1. COVID-19 RT PCR test.
2. Covid-19 rapid antigen tests if positive, were included and; if antigen test negative then all tests subjected to COVID-19 RT PCR test.
3. 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.
4. Clinical assessment as- vital parameters like heart rate, oxygen saturation, respiratory rate, blood pressure and documentation of respiratory adventitious sounds.
5. Laboratory parameters- hemoglobin, renal functions, blood sugar level, kidney functions, ECG.
6. Hematological parameters like total white blood cell counts, platelet count and repeated whenever required if initial documentation is abnormal. Normal and abnormal parameter readings were considered as per pathological laboratory standard.
7. Viral inflammatory markers like IL-6, CRP, 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.
8. Entry point IL-6 titer was utilized as assessment tool of severity of illness with clinical parameters.
9. 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.
10. 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.

Methodology of IL-6 titer assessment: Immunoturbidimetry *[4]*

The Roche Elecsys IL6 assay is a non-competitive (sandwich) chemiluminescent immunoassay. 18 u L of sample undergoes a first incubation with IL6 specific antibodies, followed by a second incubation with IL6 specific antibodies labelled with ruthenium complexes to form a sandwich complex. Thereafter, complexes are magnetically captured, where a voltage then induces a chemiluminescent emission directly proportional to the IL6 concentration. The assay has a claimed measuring range of 1.5–5000 pg/mL, a limit of quantitation (LOQ) of 2.5 pg/mL, an inter-assay precision (CV) of 17.4 % (at 1.82 pg/mL) and 2.0 % (at 4461 pg/mL). The stated reference interval is <7 pg/mL.

Normal values: Normal values up to <7 pg/mL.

Interpretation

1. Negative: value up to <7 pg/mL.
2. Positive: value above <7 pg/mL.
3. Significant: four-fold raised IL-6 vale i.e.,>28 pg/mL
4. Highly significant: sixteen-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-squared test. Significant values of $\chi 2$ 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.

RESULTS

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

CT severity score at entry point with IL-6 level has significant correlation in COVID-19 pneumonia cases, 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 1000 study cases [p<0.00001] [Table 1].

Table 1: *Correlation of CT severity (at entry point) and IL-6 in covid-19 cases (n=1000)*

CT severity	Normal IL-6 (n=320)	Abnormal IL-6 level (n=680)	Analysis
<8 score (n=300)	190	110	Chi test value 224.87 p<0.00001
9-15 (n=300)	90	210	
>15 (n=400)	40	360	

IL-6 level has significant association with duration of illness in covid1-19 pneumonia cases, 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] [Table 2].

Table 2: Duration of illness (Doi) at entry point during hospitalization and IL-6 level in COVID-19 pneumonia cases (n=1000)

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

Significant association in IL-6 and COIVD-19 pneumonia has been documented with variables like age, gender, diabetes mellitus, IHD, Hypertension, COPD, Obesity [p<0.00001] [Table 3].

Table 3: Other variables and IL-6 level in Covid-19 Pneumonia cases (n=1000)

COVID-19 RT PCR positive (n=1000)	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	$\chi2$=51.77 p< 0.00001
Age <50 years (n=400)	180	220	
Male gender (n=650)	190	460	$\chi2$=6.5 p< 0.010
Female gender (n=350)	130	220	
Diabetes mellitus (n=600)	150	450	$\chi2$=33.77 p< 0.00001
Without diabetes (n=400)	170	230	
Hypertension (n=210)	160	50	$\chi2$=238.55 p< 0.00001
Without Hypertension (n=790)	160	630	
COPD (n=150)	100	50	$\chi2$=97.46 p< 0.00001
Without COPD (n=850)	220	630	
IHD (n=200)	110	90	$\chi2$=60.77 p< 0.00001
Without IHD (n=800)	210	590	
Obesity (n=160)	20	140	$\chi2$=33.28 p< 0.00001
Without obesity (n=840)	300	540	

IL-6 level has significant association with oxygen saturation in covid1-19 pneumonia cases; 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] [Table 4].

Table 4: Oxygen saturation at entry point and IL-6 level in Covid-19 pneumonia cases (n=1000)

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

BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with IL-6 level; cases received BIPAP/NIV during hospitalization were documented normal and abnormal IL-6 level in 155/445, 165/235 cases respectively [p<0.00001] [Table 5].

Table 5: Correlation of BIPAP use with IL-6 level in covid-19 pneumonia cases (n=1000)

BIPAP/NIV	Normal IL-6 (n=320)	Abnormal IL-6 level (n=680)	Analysis
BIPAP/NIV required (n=600)	155	445	Chi test value 26.21 p<0.00001
BIPAP/NIV not required (n=400)	165	235	

Timing of BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with IL-6 level; 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] [Table 6].

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	Chi test value 31.30 p<0.00001
3- 7 days (n=310)	150	160	
After 7 days (n=110)	30	80	

Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in post-covid 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 [Table 7].

Table 7: Abnormal IL-6 level at entry point (n=680) and follow up and its correlation with post-covid lung fibrosis

Post-covid Covid 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	Chi test value 198.45 p<0.00001
Pulmonary fibrosis absent (n=470)	360	110	

Follow-up IL-6 titer during hospitalization as compared to entry point normal IL-6 has significant association in post-covid 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 [Table 8].

Table 8: Normal IL-6 level (n=320) at entry point and follow up and its correlation with post-covid lung fibrosis

Post-covid Covid pneumonia fibrosis	IL-6 normal at entry point and remained less than fourfold (n=120)	IL-6 titer fourfold increased during follow up (n=200)	
Pulmonary fibrosis present (n=40)	5	35	Chi test value 12.19 p<0.00048
Pulmonary fibrosis absent (n=280)	115	165	

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].

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	Chi test value 15.05 p<0.0001
Cytokine storm absent (n=804)	280	524	

DISCUSSION

Correlation of CT severity (at entry point) and IL-6 in covid-19 cases

In present study, CT severity score at entry point with IL-6 level has significant correlation in COVID-19 pneumonia cases, 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 1000 study cases [p<0.00001] We observed that CT severity is best visual assessment and indirect marker of inflammation which can be collaborated with IL-6, a Classical marker of inflammation. Zhang, J. *et al* [14]. Huang *et al* [9]. documented important role of IL-6 in predicting inflammation and with additive role of CT severity score in targeting interventions in critically ill cases. Li-Da Chen *et al* [15]. documented that CT severity has very well correlated with IL-6 level in predicting severity of COVID-19 pneumonia with other inflammatory markers like CRP, chemokines, D-dimer and LDH. Bhandari S *et al* [23]. *et al* observed that as normal IL-6 level in low CT severity and higher IL-6 level as CT severity increases. Aykal Guzin et al [24]. *et al* 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. Santa Cruz A *et al* [31]. has documented that, IL-6 and CRP is significantly raised in advanced COVID-19 pneumonia as compared minimal lung involvement on chest radiology. Studies by Iannaccone G *et al* [32]. Han H *et al* [33]. Rocio LG *et al* [34]. and Herold T *et al* [35]. observed high IL-6 level in advanced COVID-19 pneumonia cases with high CT severity as compared to early or mild pneumonia with less CT severity, and they documented correlation of IL-6 with other inflammatory markers, oxygenation status and patients requiring mechanical ventilation in their respective studies. Authors Aziz M *et al* [36]. and Grifoni E *et al* [37]. documented as CT Severity or lung abnormality increases, IL-6 level and other inflammatory markers increased. Researchers Liu F *et al* [40]. Chen X *et al* [41]. and Gao Y *et al* [42]. observed that as severity of COVID-19 pneumonia increases, core inflammatory markers IL-6 and CRP increases and it has been correlated with percentage of lung involvement on HRCT thorax.

Duration of illness (Doi) at entry point during hospitalization and IL-6 level in COVID-19 pneumonia cases (n=1000)

In present study, IL-6 level has significant association with duration of illness in covid-19 pneumonia cases, 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 duration of illness < 1 week or 7 days and many cases with duration of illness > two weeks or 15 days were having normal IL-6 level, while pneumonia cases between 7-14 days of illness were having abnormal or raised IL-6 level. Rational for observation is not known, may be inflammatory response pattern is different, and we have correlated IL-6 pattern with other inflammatory markers like IL-6 and IL-6 and documented that these tow 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 clinician to formulate antibiotics policy accordingly and indirectly guiding in management of these cases by assessing follow-up titers.

Correlation of BIPAP/NIV use with IL-6 level in covid-19 pneumonia cases (n=1000)

In present study, BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with IL-6 level; cases received BIPAP/NIV during hospitalization were documented 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 COVID-19 pneumonia cases. studies by Huang *et al* [9]. and Hou H *et al* [22]. documented that high IL-6 is predictor of critical illness requiring intensive care unit treatment as compared to cases with normal IL-6 level those can be managed in indoor unit without critical care setting. Authors Iannaccone G *et al* [32]. and Herold T *et al* [35]. observed that IL-6 can be used as core marker of inflammation and in clinical scenario with worsened hypoxia and increased inflammatory markers like CRP and IL-6 will help guiding BIPAP/NIV therapy, additionally it will also help in assessing response to therapy by doing follow up titers with clinical assessment.

Correlation of Oxygen saturation at entry point and IL-6 level in Covid-19 pneumonia cases (n=1000)

In present study, IL-6 level has significant association with oxygen saturation in covid1-19 pneumonia cases; cases with oxygen saturation >90%, 75-90%, and <75% observed as normal.

We have documented positive correlation with hypoxia at entry point during hospitalization and abnormal IL-6 level. Studies by various authors Huang et al [9]. Zhang, J. et al [14]. Li-Da Chen et al [15]. and Hou H et al [22]. observed that IL-6 level was well correlated with the oxygenation status and concluded that IL-6 level could be an independent biomarker for poor outcome as with oxygenation status and need for aggressive ICU interventions. Bhandari S et al [23]. and Xu X et al [25]. documented strong association between elevated IL-6, measured at admission and during hospitalization, and critical illness and mortality after covariate adjustment. Santa Cruz A et al [31]. 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. Authors Aziz M et al [36]. and Grifoni E et al [37]. mentioned in their study, hypoxia itself is important trigger of inflammation and high IL-6 has been documented in patients presenting to intensive care unit with hypoxia as compared to near normal IL-6 in cases with normal oxygen saturation initially at entry point. Researchers Liu F et al [40]. Chen X et al [41]. and Gao Y et al [42]. observed low oxygen saturation in cases with high inflammatory burden documented with high IL-6 and CRP.

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 course of covid-19 pneumonia in critical care setting has significant association with IL-6 level; 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, as 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 burden by means of hypoxia inducible transcription factor. Studies by Han H et al [33]. documented that timely mechanical ventilation in COVID-19 pneumonia will improve oxygenation and overall outcome rather than conservative approach during management of COVID-19 pneumonia. Author Rocio LG et al [34]. documented early use of aggressive approach including NIV/BIPAP in COVID-19 pneumonia and utilizing this as protocol in cases with increase inflammatory markers like CRP, IL-6 and hypoxia or oxygen saturation less than 90% will have favorable treatment outcome.

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 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. Li-Da Chen et al [15]. observed that IL-6 level that approaching to 'cytokine storm' at entry point or during follow up indicates poor outcome in intensive care setting with dismal prognosis in COVID-19 pneumonia. Authors Tisoncik JR et al [16]. Sun X et al [17]. Huang KJ et al [18]. and Channappanavar R et al [19]. documented cytokine storm in infectious diseases and septicemia, COVID-19, SARS and MERS in their studies respectively and its correlation associated with poor prognosis. Channappanavar R et al [19]. and Kim ES et al [20]. documented cytokine storm is associated with ALI/ARDS in cases with MERS. Wong CK et al [21]. documented cytokine storm including IL-6 and other chemokines in SARS and is having poor outcome.

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, ventilatory requirement in majority of cases and mortality benefit in few cases. Thus, timely IL-6 inhibitor or Tocilizumab has outcome defining role in intensive care units in cases with ALI/ARDS with IL-6 level above 98 pg/ml. Bhandari S et al [23]. and Xu X et al [25]. documented positive role of Tocilizumab in severe COVID-19 pneumonia cases with cytokine storm. Conrozier T et al [26]. and Montesarchio V et al [27]. documented that modest role of IL-6 inhibitor or Tocilizumab in Severe COVID-19 pneumonia in intensive care unit with one third cases will have negative outcome in terms of mortality and they also mentioned that timely utilization will have more positive outcome. Researchers Guaraldi G et al [38]. and Atal S et al [39]. documented promising role of IL-6 inhibitors in COVID-19 pneumonia with cytokine storm and mentioned that it will have positive impact on clinical, radiological and biochemical markers and overall outcome in intensive care units.

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 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 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 outcome and requirement of interventions in intensive care setting, which will indirectly help in predicting future risk of development of post covid lung fibrosis in majority of cases required aggressive interventions like high flow nasal canula, BIPAP/NIV, ECMO, Invasive mechanical ventilation irrespective of IL-6 level reaching to cytokine storm. Authors Yuan J et al [28]. Zeng Z et al [29]. and Gubernatorova, EO et al [30]. documented that serial measurement during hospitalization has very well correlated with need of interventions required for satisfactory treatment outcome and it will guide intensivist for timely interventions by predicting early ALI/ARDS. Serial measurements also predict chances of lung fibrosis in these patients as cytokine induced lung damage resulted in lung necrosis and resultant lung fibrosis. Authors Guaraldi G et al [38]. and Atal S et al [39]. observed high IL-6 at entry point and subsequent follow up predicts ongoing inflammation and underlying lung necrosis and help in predicting poor radiological outcome, which may result in lung fibrosis.

Correlation of Normal IL-6 level (n=320) at entry point and follow up and its correlation with post-covid 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 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 in COVID-19 pneumonia. 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, being requirement of interventions required for satisfactory outcome of these patients including ventilatory support. Authors Yuan J et al [28]. Zeng Z et al [29]. and Gubernatorova, EO et al [30]. documented importance of serial measurement IL-6 in COVID-19 pneumonia during hospitalization in their study. Aziz M et al [35]. done meta-analysis and mentioned that normal IL-6 in initial phase of pneumonia needs strict follow up in indoor cases and subsequent IL-6 level will guide and predict outcome, if level is raised needs aggressive interventions and persistent high level is predictor of poor outcome and post covid lung sequalae as fibrosis.

Correlation of other variables and IL-6 level in Covid-19 Pneumonia cases

1. In present study, age of patient i.e., <50 years and >50 years has significant association in covid-19 cases with normal and abnormal D-Dimer level [p<0.00001]. we have also documented gender of included cases has significant association in covid-19 cases with normal and abnormal D-Dimer level [p<0.010] documented significant differences in age, gender, comorbidities, respiratory symptom, neutrophil count, lymphocyte count, eosinophil count, and IL-6 level. Studies by various authors Huang et al [9]. Zhang, J.et al [14]. Li-Da Chen et al [15]. Hou H et al [22]. Aykal Guzin et al [24]. Yuan J et al [28]. Santa Cruz A et al [31]. and Liu F et al [40]. also documented similar observations in IL-6 level and its correlation with associated factors like Age, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein (CRP) and ferritin.

2. 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 Huang et al [9], Zhang, J.et al [14]. Li-Da Chen et al [15]. Hou H et al [22]. Aykal Guzin et al [24]. Yuan J et al [28]. Santa Cruz A et al [31]. and Liu F et al [40]. also documented similar observations in IL-6 level and its correlation with underlying comorbidities like hypertension, diabetes mellitus, stroke/cerebrovascular disease and ischemic heart disease.

CONCLUSION

IL-6 is sensitive, reliable, cost effective, and now universally acceptable inflammatory marker in COVID-19 pandemic. Robust data of IL-6 is available in bacterial infection, and it can be utilized in this COVID-19 pneumonia pandemic for initial assessment before planning of treatment in indoor setting in comparison with other inflammatory markers and CT severity.

IL-6 has very crucial role in covid-19 pneumonia in predicting severity of illness, and 'cytokine storm', especially follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating IL-6 with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment 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 target therapy accordingly.

IL-6 titer can help in predicting progression of COVID pneumonia, and assessing risk of post covid lung fibrosis, also follow up titers in suspected lung fibrosis case can be monitored underlying lung inflammation with this easily available marker.

Conflict of Interest

None declared.

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