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Original Article

Biochemistry Section

Interleukin-6: A Versatile Biomarker in the Clinical Chemistry Laboratory in the COVID-19 Era

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ABSTRACT

Introduction: Interleukin-6 (IL-6) is a proinflammatory cytokine released during the cytokine storm of sepsis and Coronavirus Disease-2019 (COVID-19). IL-6 has been extensively used as a biomarker in Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) and in the emerging novel paediatric disease called Paediatric Inflammatory Multisystem Syndrome-temporarily associated with SARS-CoV-2 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C). Additionally, IL-6 measurement is necessary to decide for several cytokine-blocking and cytokine-removal therapies and to determine treatment adequacy.

Aim: Evaluation of the performance of IL-6 in COVID-19, PIMS-TS/MIS-C and in CytoSorb cytokine removal therapy in sepsis as a versatile biomarker in clinical chemistry laboratory.

Materials and Methods: The study was an exploratory descriptive study carried out between March 2019 and February 2021 for a period of 24 months. IL-6 (pg/mL) was measured on Roche e411 immunoassay platform using Electrochemiluminiscence Assays (ECLIA) in 15 adult patients. Biological reference interval of the parameter was <7 pg/mL.

Results: The results showed that IL-6 was increased significantly in non survivors compared to survivors with COVID-19 (p-value=0.0043). IL-6 levels (normal <7 pg/mL) were highly elevated in children with PIMS-TS {median 75.9 pg/mL (IQR: 47.3-223.4)} reflecting the intense inflammatory state of the novel paediatric condition. All PIMS-TS cases (n=13) survived. IL-6 levels were increased post CytoSorb therapy in sepsis patients who did not survive and declined in survivors. IL-6 serially measured during treatment helped to monitor therapeutic adequacy in prolonged sepsis case.

Conclusion: The various applications of automated IL-6 testing in the clinical chemistry laboratory reflects the versatility of the trending biomarker.

Keywords: Coronavirus disease-2019, Cytokine removal therapy, Diagnostic marker, Multisystem inflammatory syndrome, Sepsis

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) presents as an asymptomatic disease in some while in others it may range from mild symptomatic to moderate and severe, resulting in death in a few severe individuals [1,2]. The underlying pathophysiology of the disease spectrum reveals interplay of the viral infection and the host inflammatory response; host immune dysregulation being a prime cause of mortality due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [3]. The COVID-19 has been associated with a hyper immune condition; the hallmarks of which are T cell deficiencies, with early and progressive lymphopenia; systemic hyperinflammation often increasing at a later phase, associated with coagulopathy and fatal organ damage. Evidence suggests that this subgroup of severe COVID-19 patients may have Cytokine Storm Syndrome (CSS); leading to Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Dysfunction Syndrome (MODS) [4].

The cytokine storm is the massively elevated plasma levels of cytokines Interleukin-6 (IL-6), IL-1, and Tumour Necrosis Factor-alpha (TNF-α), as well as ferritin and other inflammatory biomarkers, released from dendritic cells and macrophages, very similar to Systemic Inflammatory Response Syndrome (SIRS) and secondary Haemophagocytic Lymphohistiocytosis (HLH) and Macrophage-Activation Syndrome (MAS) associated with viral triggers [4-6]. While the CSS of COVID-19 is reminiscent of cytokine storm in sepsis, it is unique in certain ways [4,7,8]. IL-6 has been one of the best studied inflammatory biomarker, possibly due to its role in monitoring response to anti-IL-6 therapy [9,10].

It has been quite evident now that to control the rising mortality, timely identification and treatment of hyperinflammation using several treatment strategies is necessary [11,12]. The laboratory plays a pivotal role in assessing disease severity, selecting appropriate therapeutic options, and monitoring treatment response [13]. Biochemical monitors of hyperinflammatory phase in COVID-19 have played a crucial role in this regard with special emphasis on the role of IL-6, both as a prognostic marker and in monitoring treatment response [14].

The immunotherapies used in COVID-19 and sepsis to control the cytokine storm rely on blockade of cytokines such as IL-1 (anakinra) and IL-6 (tocilizumab) [15]. Other treatment modalities that monitor reduction of cytokines for treatment responses include plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., that can remove inflammatory factors. Cytosorb, a haemoadsorption device, has been used for removing cytokines in sepsis and in COVID-19 successfully [16,17], and is monitored for adequacy with decline in IL-6 levels.

Another facet of COVID-19 disease in children is the emergence of a novel disease entity about 2-4 weeks postinfection termed MIS-C by WHO and CDC, also known as, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [18]. MIS-C is gradually emerging in the country as COVID-19 cases have peaked in metropolitan cities and paediatricians are reporting cases from Mumbai, Chennai and Kolkata [19]. It is associated with greatly increased inflammatory biomarkers, including IL-6. Biomarker profiling is crucial in differentiating it from other similar conditions in children such as Kawasaki Disease (KD) [20].

The aim of the present study was to address the performance of IL-6 in three different clinical settings: in severity detection and prognosis of COVID-19; assessing inflammatory status in PIMS-TS/MIS-C; and monitoring efficacy of blood purification therapies in sepsis. This study will thus attempt to bring forth the role of IL-6 as

a versatile biomarker in the clinical chemistry laboratory. This was also an effort to share the experiences of testing IL-6 since 2013; when automated testing was rarely used, and in performing early IL-6 biomarker testing in COVID-19 cases.

MATERIALS AND METHODS

The study was an exploratory descriptive study carried out between March 2019 and February 2021 for a period of 24 months. Since, it was an exploratory descriptive study design, sample size calculation was not applicable. Institutional Ethics Committee (No. IEC/219/2020 dated 31.07.2020) approved the study with a waiver of informed consent. Patients who were referred to Institute of Child Health, Kolkata, West Bengal, India, for IL-6 analyses between 3rd March 2019 and 15th October 2020 were studied.

Inclusion and Exclusion criteria: These included: a) patients on Cytosorb therapy (haemoadsorption column with beads to remove inflammatory mediators from blood); b) patients with COVID-19 disease; and c) children diagnosed with PIMS-TS/MIS-C. Patients with inadequate data were excluded from the study.

Demographic details, clinical history and outcome assessments of the cases were recorded for study purpose. IL-6 was measured by Electrochemiluminescence Assays (ECLIA) on the Roche e411 platform. The assay range is 1.5-5000 pg/mL; the biological reference interval is <7 pg/mL.

STATISTICAL ANALYSIS

D'Agostino and Pearson omnibus normality test was used to determine distribution of data. Median values with Inter Quartile Range (IQR) were reported for non normally distributed data. Mann-Whitney non parametric test was used to determine differences between non normal test variables. Correlation of IL-6 with other inflammatory markers was computed using Spearman test; r and two-tailed p-values have been reported. The p-value <0.05 was considered significant. Analysis of data was performed on Graph pad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

RESULTS

A. IL-6 trends in COVID-19 patients

Between 28th March 2020 and 4th July 2020, IL-6 was measured in 15 adult patients {median age, 57 years (IQR 52-68); males, 12/15, 80%} as a part of patient management in active SARS-CoV-2 cases; most of these cases had either moderate or severe COVID-19 [Table/Fig-1]. Majority of patients had fever (100%); cough, dyspnoea and hypoxia (80%), and features of Acute Respiratory Distress Syndrome (ARDS), requiring intensive care support (50%). IL-6 was measured around the 13th day following onset of fever. Indications were to gauge inflammatory status and decide for use of therapeutics, such as IL-6 receptor inhibitor, tocilizumab. The median length of hospital stay was 17 days (IQR, 15-20); one patient required 82 days of stay till discharge. There were 6 survivors, 4 non survivors; outcome in 5 could not be ascertained due to loss to follow-up.

Demography (adult)	Value
Total patients	n=15
Median age, (IQR, years)	57 (52-68)
Sex, males, %	12/15 (80%)
Median days of hospital stay, IQR	17 (15-20)
Outcome	
Recovered cases	6/15 (40%)
Non survivors	4/15 (27%)
Lost to follow-up	5/15 (33%)

[Table/Fig-1]: Demography of adult patients diagnosed with COVID-19 and tested for IL-6 (pg/mL).

COVID-19 is rare in infants. The present study reported the IL-6 level (at day 18) of a male infant with TGA/IVS, migrated from neighbouring state for Arterial Switch surgery and found to be positive for SARS-CoV-2 by Reverse Transcription-Polymerase Chain Reaction (RT-PCR). The patient required ventilator support and developed ARDS. The patient's serum C-reactive protein and procalcitonin concentrations were 200 mg/L and 2.9 ng/mL, respectively. His serum triglycerides (991 mg/dL), lactate dehydrogenase (1200 U/L), and ferritin (>2000 ng/mL), levels were elevated. IL-6 level was tested prior to therapeutic management consisting of steroid, Intravenous Immunoglobulin (IVIG) and tocilizumab and was found to be 284.8 pg/mL. The patient succumbed due to severe lung bleed.

B. IL-6 as an inflammatory marker in PIMS-TS/MIS-C in children

Between 7th July 7 2020 and 15th October 2020, thirteen children {median age 6 (IQR 4-10); males, 11/13, 85%} diagnosed with PIMS-TS/MIS-C were tested for IL-6 levels as a part of inflammatory panel. Common presenting symptoms were high grade fever, conjunctivitis, mucositis, oedema, irritability and vomiting and diarrhoea. The patients reported negative for SARS-CoV-2 active infection by RT-PCR but had high levels of Immunoglobulin G (IgG) antibodies indicating past infection. One child had history of contact as father was positive for SARS-CoV-2 infection and mother had anosmia. [Table/Fig-2] presents the demographic, and laboratory features of the group. All patients recovered; 6 required Paediatric Intensive Care Unit (PICU) support.

Demography (children)	Value	Normal values
Total patients	13	
Median age, years, (IQR)	6 (4-10)	
Sex, males, %	11/13 (85%)	
Laboratory features		
SARS-CoV-2 detected by RT PCR	0/13, none	
High SARS-CoV-2 IgG levels (positive cases)	12/13, one had contact history	
Inflammatory markers	**Median (IQR)**	
Median WBC count, per mm^3	9800 (8450-20100)	4500-13500
Median IL-6, pg/mL	75.9 (47.3-223.4)	<7
Median CRP, mg/L	223 (118.4-306)	<5
Median Ferritin, ng/mL	1023 (570.2-1172)	<120
Cardiac injury marker		
Median NT-Pro BNP, pg/mL	5340 (1586-26564)	<150
Chemistry parameters		
Median AST, U/L	33 (25-48)	<40
Median ALT, U/L	26 (16-41)	<35
Median Na+, mmol/L	129 (125-131)	135-145
Median K+, mmol/L	3.5 (3.3-4.1)	3.5 - 5.3
Median Creatinine, mg/dL	0.48 (0.395-0.65)	0.29-0.47 (Age specific, for 5-7 years child)
Outcome		
Median days of hospital stay	8 (6-10)	
Recovered cases	13/13 (100%)	

[Table/Fig-2]: Characteristics and outcome in children and adolescents diagnosed with PIMS-TS/MIS-C.
PIMS-TS/ MIS-C: Paediatric inflammatory multisystem syndrome temporally associated with COVID-19/Multisystem inflammatory syndrome in children; IQR: Inter quartile range; WBC: White blood corpuscles; IL-6: Interleukin-6; CRP: C-Reactive protein; NT-ProBNP: N-terminal pro brain natriuretic peptides; AST: Aspartate transaminase; ALT: Alanine transaminase; Na: Sodium; K: Potassium

Median IL-6 level was 75.9 (IQR 47.3-223.4) pg/mL. Correlation of IL-6 with other inflammatory markers, C-Reactive Protein (CRP) (r=-0.25, p=0.44), Ferritin (r=-0.06, p=0.85) or White Blood Corpuscles (WBC) count (r=-0.09, p=0.52) was not significant.

C. IL-6 as a biomarker of therapeutic response

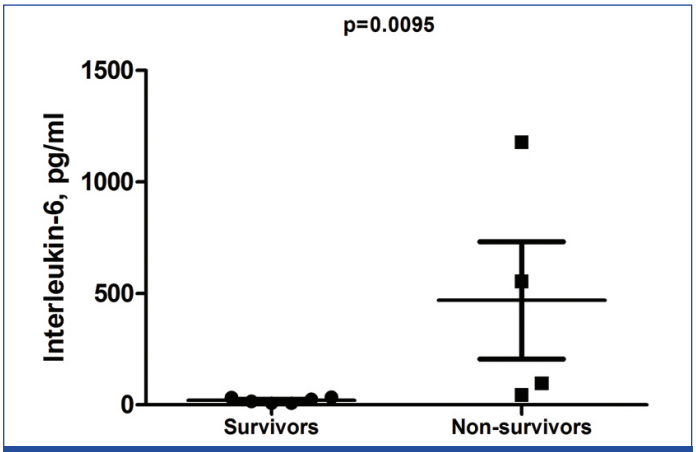
Between March 3 2019 and January 1, 2020; IL-6 was tested in 16 critically ill patients {9 children (mean age, 9 years 4 months;

5 males) and 7 adults (mean age was 52 years; 2 males)} scheduled for cytokine removal therapy using haemoadsorption device, CytoSorb. Out of these, four adult cases have been presented in [Table/Fig-3].

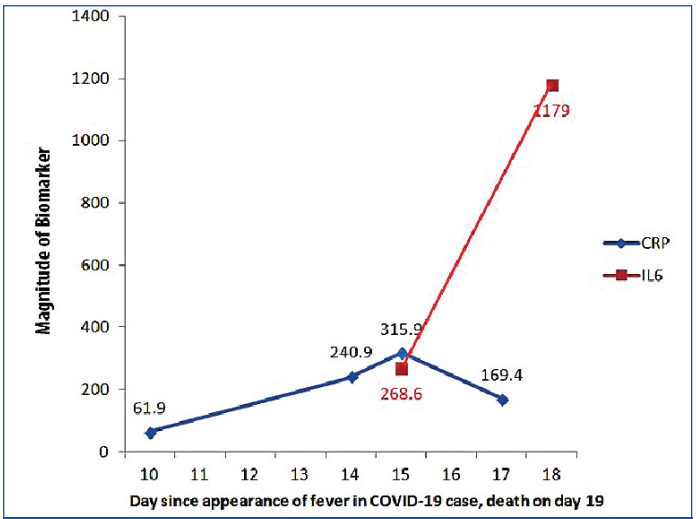
Case #	Patient diagnosed with:	Age (years)	Sex	Pretreatment IL-6 level pg/mL	Post-treatment IL-6 level pg/mL following the first assessment	Outcome
1	ARDS	53	F	792	3043 (day 4)	Death
2	Sepsis with Acute on CKD (III)	43	M	1225	5000 (day 4)	Death
3	Septic shock with onset of AKI	56	F	236.5	147.4 (same day)	Discharged
4	Septic shock with MODS	67	M	465.6	20.16 (day 47)	Discharged

[Table/Fig-3]: Summary of case profile of patients (n=4) who underwent cytokine removal therapy (CytoSorb); monitored by IL-6 levels.
ARDS: Acute respiratory distress syndrome; AKI: Acute kidney injury; CKD: Chronic kidney disease; MODS: Multiple organ dysfunction syndrome; M/F: Male/female

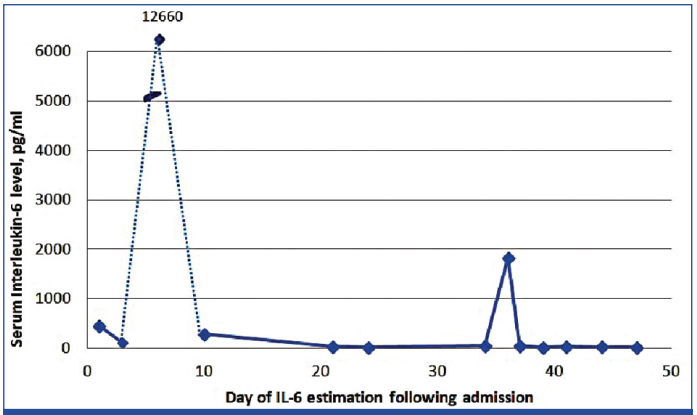
The median IL-6 (initial value) was 38 pg/mL (IQR, 25-181). IL-6 levels (near outcome) were significantly raised in non survivors {median 325.2 (IQR, 57.6-1023.0)} compared to survivors {median 20.7 (IQR, 7.1-32.4)} [Table/Fig-4]. Serial measurements of IL-6 showed an increasing trend in patients who died, achieving values of over 1000 pg/mL [Table/Fig-5]. While IL-6 levels decreased post-therapy in survivors, it remained significantly high in those who died. Non survivors also had high baseline IL-6 levels. Cases of septic shock recorded extremely high levels of serum IL-6; which were decreased significantly following therapy [Table/Fig-6].



[Table/Fig-4]: IL-6 levels (pg/mL) compared in COVID-19 survivors and non survivors.
Mann-Whitney statistical test; p-value <0.05 considered significantly different



[Table/Fig-5]: C-Reactive protein (CRP), mg/L (blue) and Interlekin-6 (IL-6), pg/mL (red) trends in a COVID-19 patient who succumbed in the ICU.



[Table/Fig-6]: Serial measurements of IL-6 in a case of septic shock with MODS, showing the rise and fall of IL-6 with cytokine removal therapy.
The last value of IL-6 recorded was 20.16 pg/mL, on day 47. Patient was discharged following successful therapy

DISCUSSION

This study emphasises the role of IL-6 as an important biomarker in the clinical chemistry setting. Till recently, IL-6 had minimal clinical application due to its surrogacy to CRP and its prohibitive cost. It was mainly restricted to the research arena in the field of cytokine studies]. Author's own laboratory had explored its role in neonatal sepsis with limited scope as an isolated biomarker [21]; and there was a far greater application scope in monitoring IL-6 concentrations to trace therapeutic modulation as in cytokine removal strategies in sepsis [16]. In this study, authors have demonstrated the usefulness of serial IL-6 measurements to determine therapeutic efficacy in sepsis patients. Cytosorb (Cytosorbents Corporation, New Jersey USA) is a haemoadsorption device containing porous polymeric beads capable of removing cytokines and other mid molecular weight toxins from blood by size exclusion and surface adsorption and is being used in patients with sepsis and septic shock including COVID-19 [17]. The rationale of bulk removal of cytokines during the cytokine storm (and therefore at the start of sepsis) is that there will be abundance of one component. Removal of same will be proportionately higher that can then help to regain the homeostatic balance. With respect to biomarkers, there is maximum data with IL-6, which has been used as a surrogate for cytokine removal. IL-6 is induced rapidly in sepsis and has a short half-life, which makes it an ideal marker for patient monitoring and adequacy of treatment [16].

The same principle for IL-6 measurements has been applied to COVID-19. The clinical presentation of COVID-19 is highly heterogeneous, ranging from asymptomatic to severe pneumonia. With the SARS-Cov2 infection, clinical (and radiological) progression of patients from mild to severe state is often corroborated with increasing trend of IL-6 concentrations [22,23]. Coomes EA and Haghbayan H have shown in patients with severe COVID-19, IL-6 levels are significantly elevated and associated with adverse clinical outcomes [13]. Zhang J et al., recorded values of over 5000 pg/mL in critical patients akin to sepsis and septic shock [23]. Thus, IL-6 is an important marker of inflammation and can guide the clinicians in recognising patients with severe COVID-19 early in the disease course. The present study showed that IL-6 levels were highly elevated in non survivors (median >200 pg/mL) compared to survivors and hence has an important role in understanding the disease progression in patients. IL-6 has been used to predict the need for mechanical ventilation in COVID-19, with levels >80 pg/mL predicting risk of respiratory failure [24,25]. A cut-off value of >25 pg/mL has been proposed a risk factor for progression to severe syndrome and in-hospital mortality [26].

Recently, a number of specific anti-cytokine approaches have proven effective in treating a variety of CSS, including those triggered by viruses. These include drugs which cause powerful immunosuppression such as tocilizumab (IL-6 receptor blocker)

and haemoadsorption for removal of circulating cytokines [17]. IL-6 measurement in the laboratory has assumed a critical role for the monitoring of anti-cytokine therapies, such as tocilizumab which were used apriori in many patients in the study.

The IL-6 has been equally effective in determining the inflammatory status of children and adolescents with PIMS-TS/MIS-C. Ahmed M et al., reviewed laboratory measures in PIMS-TS and reported a mean IL-6 of 184 pg/mL (SD 15.6) similar to high levels seen in our study [17]. Other inflammatory markers like CRP {mean 160 mg/L (SD 7)} and ferritin {mean 977 ng/mL (SD 55.8)} were comparable to our findings, depicting the intense inflammatory state of the disease. PIMS-TS has a very similar clinical presentation as KD [27]. The IL-6 levels of PIM-TS {median 75.9 pg/mL (IQR, 47.3-223.4)} was compared to levels in our prior study of IL-6 {median 33 pg/mL (IQR, 5-108)} on pre COVID-19 KD [28], and was found to be significantly higher (p-value <0.04). These distinct features of PIMS-TS may thus help to discern PIMS-TS from KD; also suggesting that they are two different entities even if they may have overlapping presentations and would therefore need different management protocols.

Currently, the measurement of IL-6 has become common place in clinical chemistry laboratories worldwide with the surge of the pandemic. Measurements options available are by several commercially available sandwich Enzyme-Linked Immuno-Sorbent Assay (ELISA)-based immunoassays, and bead based immunoassays especially Luminex bead based assays [29]. These have been largely replaced by the automated systems using chemiluminiscent methods in the clinical set ups for faster turn around times [30]. Reviews on IL-6 measurements in COVID-19 report heterogeneity in IL-6 levels between studies [14]. This may have arisen from multiple sources of variability; one of them could be attributed due to differences in testing methods largely due to choice of antibodies and different epitopes recognised by antibodies from different vendors. Another potential reason of variability is the time of testing after collection of sample. Gong Y et al., have elegantly demonstrated the effect of time on IL-6 levels in pre-centrifugal and post-centrifugal samples [30]. Serum should be separated ideally just after collection and preferably within 2 hours of collection at room temperature to avoid pre-analytical errors of falsely increased values. CytoSorb® is a product of CytoSorbents Corporation, USA as an extracorporeal cytokine adsorber designed to reduce the “cytokine storm” or “cytokine release syndrome” in common critical illnesses including COVID-19.

Limitation(s)

Most of the samples of patients of COVID-19 and of CytoSorb recipients were received after collection from external sources; hence there was no control on the time of separation of serum except for that they were collected as per manufacturers’ instruction. Therefore, there may be some variability in the true values of IL-6. The present study was limited by sample size, but on the whole a comprehensive picture of the versatile role of IL-6 in a clinical chemistry laboratory has been captured in the COVID-19 era.

Future large scale studies on performance of IL-6 in diagnosis, treatment choice and prognostication of clinical course in sepsis, and especially in COVID-19, can better elucidate its applicability and acceptance as a singular biomarker of choice.

CONCLUSION(S)

The IL-6, a cytokine, is now performed on automated systems in far greater number of laboratories than ever before because of its unsurpassed application in the prediction of severity, disease progression and mortality in COVID-19. Its levels were far higher in non survivors compared to survivors, measured roughly 2 weeks after onset of fever. The concentrations of serially measured IL-6 pretherapy and post-therapy help to gauge therapeutic adequacy of IL-6 receptor blockers, and cytokine removal therapy in sepsis and COVID-19 patients. In paediatrics, IL-6 was a valuable inflammatory marker of post-COVID-19 PIMS-TS/MIS-C disease and helps to differentiate it from other similar pathologies such as KD. Overall, IL-6 has earned the status of a versatile biomarker in the clinical chemistry setting given its multifaceted role in emerging diseases and therapy in the COVID-19 era. Biochemists should be aware of associated preanalytical and analytical errors for quality reporting.

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REFERENCES

[1] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-29.
[2] Li X, Geng M, Peng Y, Meng L, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-08.
[3] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. J Infect. 2020;80(6):607-13.
[4] Pedersen SF, Ho YC. SARS-CoV-2: A storm is raging. J Clin Invest. 2020;130:2202-05.
[5] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-34.
[6] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LSP. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-74. https://doi.org/10.1038/s41577-020-0311-8.
[7] Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol. 2020;11:01-04. https://doi.org/10.3389/fimmu.2020.01446.
[8] 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. Doi: 10.1016/j.cytogfr.2020.05.009.
[9] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for Coronavirus Disease 2019 (COVID-19)-induced Cytokine Release Syndrome (CRS)? J Autoimmun. 2020;111:102452. Doi: 10.1016/j.jaut.2020.102452.
[10] Miao Y, Fan L, Li JY. Potential treatments for COVID-19 related cytokine storm-beyond corticosteroids. Frontiers in Immunology. 2020;11:01-03. Doi: 10.3389/fimmu.2020.01445.
[11] Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine Growth Factor Rev. 2020;53:66-70. Doi: 10.1016/j.cytogfr.2020.05.002.
[12] 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):1063-69. Doi: 10.1515/cclm-2020-0240.
[13] Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: A systematic review and meta-analysis. Rev Med Virol. 2020;e2141. https://doi.org/10.1002/rmv.2141.
[14] Magro G. COVID-19: Review on latest available drugs and therapies against SARS-CoV-2. Coagulation and inflammation cross-talking. Virus Res. 2020;286:01-09. Doi: 10.1016/j.virusres.2020.198070.
[15] Schadler D, Pausch C, Heise D, MeierHellmann A, Brederlau J, Weiler N, et al. The effect of a novel extracorporeal cytokine haemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. PLoS ONE. 2017;12(10):e0187015. https://doi.org/10.1371/journal.pone.0187015.
[16] Al Shareef K, Bakouri M. Cytokine blood filtration responses in COVID-19. Blood Purif. 2020. Doi: 10.1159/000508278.
[17] Ahmed M, Advani S, Moreira A, Zoretic S, Martinex J, Chorath K, et al., Multisystem inflammatory syndrome in children: A systematic review. E Clinical Medicine. 2020;26:100527. https://doi.org/10.1016/j.eclinm.2020.100527.
[18] Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S, et al. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. Indian Pediatr. 2020;S097475591600230. Epub ahead of print. PMID: 32788432.
[19] Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: Prospective observational study. BMJ. 2020;369:m2094. Doi: https://doi.org/10.1136/bmj.m2094.
[20] Mondal P, Maity S, Ray J. Role of interleukin-6 and interleukin-10 in early diagnosis of neonatal sepsis, a prospective study in a tertiary care hospital. IJAR. 2020;10(8):59-62. Doi: 10.36106/ijar.
[21] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intens Care Med. 2020;46:846-48.
[22] Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol. 2020 Apr 28:10.1002/jmv.25948. Doi: 10.1002/jmv.25948. Epub ahead of print. PMID: 32343429; PMCID: PMC7267383.

[23] Zhang J, Hao Y, Ou W, Ming F, Liang G, Qian Y, 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(1):406-21. Doi: https://doi.org/10.21203/rs.3.rs-47937/v1.
[24] Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-36. Doi: 10.1016/j.jaci.2020.05.008.
[25] Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, et al. Interleukin-6 as prognosticator in patients with COVID-19. J Infect. 2020;81(3):452-82. Doi: 10.1016/j.jinf.2020.06.008.
[26] Cattalini M, Della Paolera S, Zunica F, Bracaglia C, Giangreco M, Verdoni L, et al. Defining Kawasaki disease and pediatric inflammatory multisystem syndrome-temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: Results from a national, multicenter survey. Pediatr Rheumatol. 2021;19(29):01-11. https://doi.org/10.1186/s12969-021-00511-7.
[27] Nandi A, Pal P, Basu S. A comparison of serum IL-6 and CRP levels with respect to coronary changes and treatment response in Kawasaki disease patients: A prospective study. Rheumatol Int. 2019;39(10):1797-801. Doi: 10.1007/s00296-019-04375-9.
[28] Thompson DK, Huffman KM, Kraus WE, Kraus VB. Critical appraisal of four IL-6 immunoassays. PloS ONE. 2012;7:e30659. https://doi.org/10.1371/journal.pone.0030659.
[29] Rao SA, Kunte AR. Interleukin-6: An early predictive marker for severity of acute pancreatitis. Indian J Crit Care Med. 2017;21(7):424-28.
[30] Gong Y, Liang S, Zeng L, Ni Y, Zhou S, Yuan X. Effects of blood sample handling procedures on measurable interleukin 6 in plasma and serum. J Clin Lab Anal. 2019;33:e22924. https://doi.org/10.1002/jcla.22924.

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