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'Composite index' in COVID-19 related 'Dragon' Pandemic: Novel approach to predict outcome

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Abstract

COVID-19 related 'Dragon pandemic' caused significant mortality and its lingering effects as long covid with huge impact on morbidity and quality of life. As pandemic has waned off, still rescue breath is in doubt due to evolving mutants and variants of great concern. COVID-19 infection involves a complex interplay of the immunological and inflammatory responses. Inflammatory parameters are closely linked to the COVID-19 severity and mortality. Inflammatory parameters could be used to predict the transition from mild to severe/critical infection in patients of COVID-19. Numerous Inflammatory markers were analyzed and used as point of care test to predict severity of illness, monitoring of illness, treatment planning and predicting final outcomes such as CRP, LDH, IL-6, D-dimer and ferritin. Robust data of these inflammatory markers is available and proved crucial in predicting pathophysiological trends such as cytokine storm, coagulation abnormalities, oxygenation status and response to therapy. Isolated assessment of inflammatory markers in absence of clinical and radiological parameters were observed as 'double edged weapon' due to overestimation and its impact on health burden and underprediction resulting into progression of illness and resultant poor outcome and increased health care cost. Composite index is combination clinical, radiological and laboratory inflammatory marker assessment. Combination of any two abnormalities were observed crucial role in early suspicion, diagnosis, monitoring, and recognition of complications, management and disposition of patients. Composite index rather than single biomarkers may provide more reliable information. Availability and cost issues cannot be ignored. It would be impossible for clinicians to consolidate and critically analyze the enormous data that is continuously added to the COVID-19 literature to extract practically useful information for the benefit of patients. Still, as of now Composite index is sensitive and effective tool to assess COVID-19 cases at entry point and to analyze exact status of illness which will have successful treatment outcome and thus considered as 'point of care test' in this 'Dragon Pandemic'.

Keywords: COVID-19; CRP; IL-6; LDH; Ferritin; D-Dimer; Long COVID; Post covid lung

1. Introduction

The ongoing pandemic of severe acute respiratory syndrome by coronavirus 2 (SARS-CoV-2) continues to pose several diagnostic and therapeutic challenges. First reported from Wuhan in China in December 2019, the World Health Organization on February 11, 2020 officially named this infection, coronavirus disease 2019 (COVID-19) and the virus as SARS-CoV-2 (1). It was declared as a pandemic on March 11, 2020 [1]. After the virus' genome was sequenced, the virus was given the name severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. It shared genetic ancestry with the coronavirus outbreak that caused the SARS epidemic of 2003 [2]. As of today, more than 500 million people have been infected and more than six million have died globally.

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Acute inflammation in the lungs is a complex pathophysiological mechanism involving inflammatory mediators such as cytokines and chemokines, which stimulate the macrophages in the alveoli, leading to poor regulation of the immune system. In humans, the clinical progression of the novel coronavirus-induced disease exists in a triphasic form. The clinical features in first phase include fever, dry cough, myalgia, and other systemic infections that are likely to be increased by the replication of the virus and cell necrosis. The associated feature of the second phase is the onset of IgG immunoglobulins conversion, correlated with the decrease in viral replication. During this phase, uncontrolled viral replication occurs causing severe worsening of symptoms. The exact hypothesis behind this might be the severe damage to alveoli caused by over exuberant immune response of the host. In nCOVID-19-infected patients, the major patient population recovered after two weeks, but one-third of the patients progressed to the third phase, which is characterized by severe lung inflammation leading to ARDS, i.e., acute respiratory distress syndrome [3,4].

The virus causing nCOVID-19 belongs to a family of viruses known as Coronaviridae. Coronaviruses can be classified in four genera: alpha, beta, gamma, and delta. Human CoV belong to either alpha or beta. Gamma and delta CoV tend to infect birds. The coronaviruses affecting humans are of seven types, as depicted in Table 1. Among them, the highly pathogenic corona viruses are SARS CoV, MERS CoV, and SARS CoV-2. They cause severe pneumonia in humans by infecting the lower respiratory tract, which causes diffuse alveolar damage, resulting in increased morbidity and mortality [3,5].

Table 1 Types of coronaviruses affecting human

S. No.	Type
1	229E (alpha coronavirus)
2	NL63 (alpha coronavirus)
3	OC43 (beta coronavirus)
4	HKU1 (beta coronavirus)
5	MERS-CoV (beta coronavirus)
6	SARS-CoV (beta coronavirus)
7	SARS CoV-2 (novel coronavirus)

The nCOVID-19 virus has a round, enveloped structure with a diameter of approximately 80 to 120 nm and contains a positive genome of single stranded RNA of 31 kb size [6]. Structure of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an enveloped virus with single-stranded positive-sense (+sense) RNA taking four principal proteins, including membrane (M) and spike (S) glycoproteins, in addition to nucleocapsid (N) and envelope (E) proteins forming peplomer on the surface of the virion giving the structure a crown-like appearance as shown in Figure 1 [7].

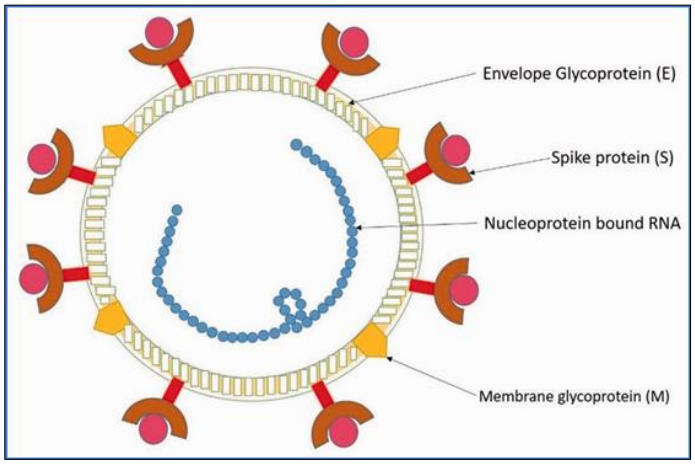

Figure 1 Structure of novel coronavirus, SARS-CoV-2

Spike proteins bind to the ACE-2 receptor, and after binding, conformational changes occur in the spike protein facilitating the fusion of the viral envelope with the host cell membrane. After entering the host cell, the virus releases its RNA into the cell, and the process of translation begins. Replicase polyproteins (pp1a and 1ab) of virus's form, which are then cleaved by proteinases into smaller products. The viral genome RNA and the proteins assembled in the endoplasmic reticulum and Golgi complex as virions are then carried out through the vesicles and released out from the cells [8].

- The interaction between the angiotensin-converting enzyme 2 (ACE2) receptor and S-protein leads to the attachment of the virus
- The entry of virus conducted by endocytosis and/or by
- Membrane fusion of virus
- Translation of virus RNA leads to produce proteins 1a & 1ab
- Proteolysis of proteins results in non-structural proteins and replicase-transcriptase complex (RTC)
- Synthesizing the new viral RNA (-sense) and the viral proteins
- The association of the viral particle
- Release of virus through exocytosis.

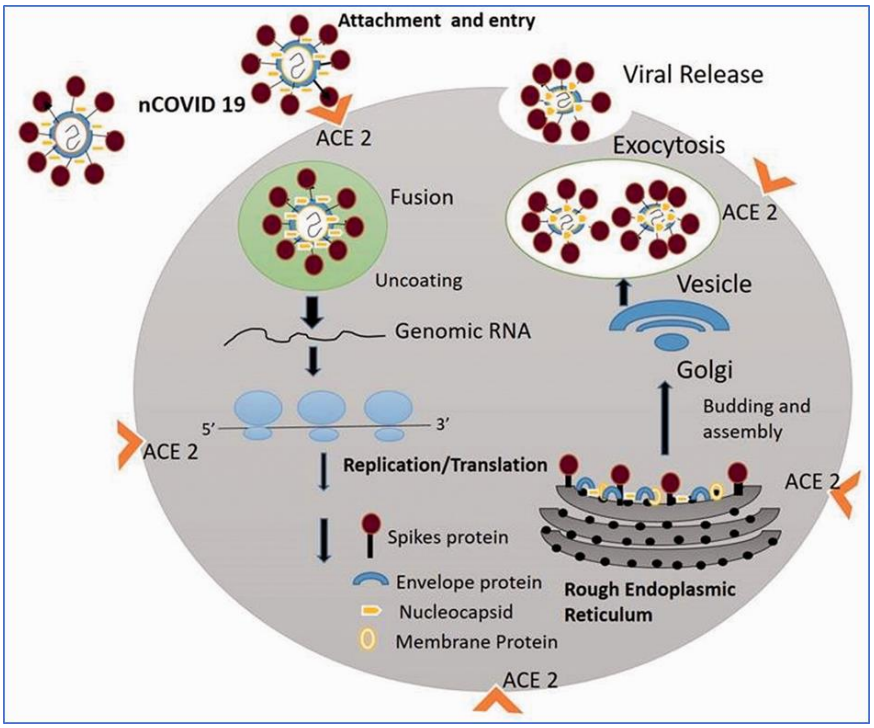

Figure 2 The life cycle of nCOVID-19 in human cells [3]

The heterogeneous course of COVID-19 disease is unpredictable, with most patients presenting with mild, self-limiting symptoms. The virus infection commonly starts with flu-like symptoms and can be asymptomatic or may have a minor to severe development. Despite this, up to 30% of patients require hospitalization, and up to 17% of them need intensive care support for acute respiratory distress syndrome (ARDS), hyper-inflammatory responses, and multiorgan failure [9-10].

1.1. The common features observed in critically ill nCOVID-19 patients are

- Respiratory failure
- Sudden worsening of disease around 1–2 weeks after onset
- High level of inflammatory mediators including CRP (C-reactive proteins) and pro-inflammatory cytokines like interleukins, tumor necrosis factor (TNFα), etc.
- Damaged immune system presented by the atrophy of lymph nodes and spleen, also reduction in the lymphocytes level
- Elevated levels of infiltrated immune cells like monocytes, macrophages found in lung lesions

- Hypercoagulation, vasculitis, and multiple organ damage

Genetic makeup of corona virus was determining factor for overall outcome in first and second wave, first was classical 'Wuhan variant virus' and second one was mutant 'Delta variant' corona virus; and as mutant in second wave was associated with increased morbidity and mortality. In both the waves, covid pathophysiology were same i.e., immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues. Covid-19 is corona virus related disease, its etiological agent discovered in middle of 20th century, its epidemics-pandemics has created health burden in early 21st century; but evidences are coming up with its correlation with "Russian or Asiatic flu" of late 19th century [11-15].

2. Available inflammatory markers in COVID-19 pneumonia

Now the robust data is available for role of various inflammatory markers in initial assessment of cases which are associated with direct or indirect virus-related lung injury. Apart from lung involvement, proportionate number of cases were shown systemic manifestations due to activation of inflammatory pathway and inflammatory surge resulting in to pulmonary and extrapulmonary effects which have significant impact on final outcome. All these effects can be easily picked up by timely analysis of inflammatory markers. Now these markers are also called as 'inflammatory biomarkers.' Various inflammatory markers such as CRP, Ferritin, LDH, D-dimer and IL-6 were exuberantly used during workup of COVID-19 cases worldwide and reported their valuable role in initial assessment, predicting severity, guiding or triaging hospitalization, predicting need of interventions during hospitalization, analyzing final outcome, predicting post recovery outcome and possibility of long covid manifestations. But more misinformation was reported regarding inflammatory markers in COVID-19 pneumonia and reported as Infodemic during this pandemic [16].

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions which occurred 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 presenting with pulmonary and extrapulmonary manifestations [17-19]. COVID-19 infection is accompanied by vigorous immune and inflammatory response that causes severe lung damage to limit the entry of oxygen to the bloodstream, resulting in long-term breathlessness and severe complications including renal failure. Inflammatory markers (ferritin/LDH) could be useful as a predictor for COVID-19 mortality and respiratory failure and could help the physicians to discern at-risk COVID-19 patients to facilitate early treatment. Elevated LDH increases the odds of severe COVID-19 disease and mortality among ICU-admitted patients.

3. Role of CRP in COVID-19 pneumonia

The laboratory of Oswald Avery first documented 'CRP' as inflammatory protein released in serum of patients with acute infections and later on labelled as 'acute phase reactant'. Robust data is available regarding its role in infections, inflammatory, ischemic, and traumatic tissue injuries, and malignancy, whilst the advent of sensitive quantitative immunoassays in the 1970s greatly enhanced its clinical utility. In 1974, Kaplan and Volanakis [20] and Siegel et al. [21] reported 'pro-inflammatory' role of CRP. CRP can be used as marker of inflammation in COVID-19 pneumonia's can be used as inflammatory marker and help in analyzing infective and non-infectious causes, surgical, post operative, inflammatory conditions as rheumatoid, gout and venous thromboembolism. Data of CRP in severe H1N1 viral pneumonia is available and a number of recent series have reported an association between CRP and COVID-19 disease severity [22-25].

CRP is easily available, sensitive, reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pneumonia. CRP has very crucial role in COVID-19 pneumonia in predicting severity of illness, especially 'follow up titters' have significant role in step-up or step-down interventions in critical care setting. Correlating CRP with variables as duration of illness, oxygenation status and timing of BIPAP/NIV has important role in predicting outcome. CRP titer has significant association in predicting progression of pneumonia and we have documented that proportionate number of COVID-19 cases with mild variety on CT thorax with normal initial CRP has progressed to critical course. Authors [22-25] have also documented that serial or follow up CRP titers has played crucial role along with other inflammatory markers. Authors have observed rising CRP titers, especially in second week of illness indicates nosocomial bacterial infection and guided in targeting antibiotic treatment accordingly. CRP follow-up titer can help in predicting progression of COVID pneumonia and assessing risk of post-COVID lung fibrosis [22-25].

3.1. LDH in COVID-19 pneumonia

In last few decades, LDH has been analyzed as prognostic marker in hematology and oncology, in hemolytic anemia, in megaloblastic anemias, Hodgkin disease and non-Hodgkin lymphoma and leukemias [26] Elevated LDH levels are the product of enhanced glycolytic activity of the tumor and tumor necrosis due to hypoxia, the latter being associated with high tumor burden. LDH has many subtypes, 1-5 released by erythrocytes, heart and skeletal muscles, its isolation usually done as major component and subtyping is not routinely required.[26] Severe infections including interstitial pneumonia or ARDS (acute respiratory distress syndrome) may cause tissue damage induced by cytokine production with subsequent release of LDH into the bloodstream [26-28]. As 5% of COVID-19 Pneumonia cases require intensive care unit treatment including mechanical ventilation and these patients are at high risk of death. Therefore, markers with high positive predictive value for early prediction of ARDS will help in decreasing mortality [28]. In inflammatory panel evaluation, LDH has very good association with direct lung damage and significantly raised in more widespread tissue injury [27-28]. In a recently published study on a large case-series of COVID-19 patients, documented high serum concentrations of LDH was associated with more chance of death due to pneumonia [29].

LDH is an easily available, sensitive & reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pandemic. Correlating LDH with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome. LDH titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial LDH has progressed to critical course which were documented with help of rising titers and we have documented follow-up rising titers has played crucial role with other inflammatory markers like LDH & ferritin [30-32]. LDH rising titers in the second week of illness indicates nosocomial bacterial infection and target therapy accordingly. Also decreasing LDH titers has been assessed and analyzed with improved oxygenation status and excellent response to treatment and decreased underlying inflammation. LDH titer can help in predicting progression of COVID-19 pneumonia, and assessing risk of post covid lung fibrosis if LDH titer is persistently high in these cases and proportionate number of cases with normal or abnormal LDH at entry point were predicted with underlying fibrosis or ongoing inflammation and necrosis of lung parenchyma if LDH is persistently high. LDH titer can guide antifibrotic treatment response in follow-up post covid care setting [30-32].

3.2. IL-6 in COVID-19 pneumonia

Various biomarkers, especially inflammatory markers like C-reactive protein (CRP), ferritin, fibrinogen, D-dimer and Interleukin 6 (IL-6) are associated with COVID-19 progression. According to known evidence, IL-6 is superior to CRP and other markers of inflammation in predicting respiratory failure in COVID-19. IL-6 appears to be the most important driver of immune dysregulation and ARDS in COVID-19 [33-34]. There is a substantial body of evidence linking the IL-6 concentration to the severity of disease and unfavorable outcome of COVID-19. Herold et al. examined the predictive value of various cytokines and concluded that IL-6 is the best predictor of severe COVID-19 [35]. Authors have documented that IL-6 > 80 pg/mL the predicts respiratory failure and need for mechanical ventilation [35]. Chen et al. found cut-off 80 pg/mL of IL-6 differentiates the survivors from the non-survivors [36]. The direct role of IL-6 in COVID-19 pathogenesis is further supported by findings that IL-6 inhibition improves the prognosis of severe COVID-19 [37].

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 [38-40]. 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 lung fibrosis [38-40].

3.3. D-Dimer in COVID-19 pneumonia

In COVID-19 pneumonia pathophysiology constitutes different pathways like immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues. COVID-19, the pandemic disease caused by infection with the novel virus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) can now be added to the already extensive list of conditions that may be associated with elevated D-dimer. The discovery that D-dimer may be elevated in COVID-19 was first reported by physicians in Wuhan, China where the epidemic started. A study of 191 patients with covid-19, who were hospitalized in Wuhan during January 2020 at the outset of the pandemic, revealed that D-dimer was elevated in many of these patients and the magnitude of the elevation was greatest in those who did

not survive [41]. Fibrin degradation products (FbDP) are a highly heterogeneous group of soluble fragments that appear in the circulation as a result of two simultaneous physiological processes: 1) Coagulation, resulting in the conversion of soluble fibrinogen into insoluble stabilized fibrin by the enzymes thrombin and factor XIIIa, 2) Fibrinolysis, resulting in the dissolution of the fibrin clot by the enzyme plasmin. The D-dimer fragment is the terminal product of this process [42]. A number of subsequent studies conducted around the world have confirmed that D-dimer is elevated in those with severe COVID-19 and highest in those who are most critically ill and those who do not survive. Much COVID-19 research over the past months has been directed at understanding the significance of D-dimer elevation and the COVID-19 related coagulopathy that is presumed responsible for the elevation [41]. D-dimer has been extensively investigated for the diagnosis, monitoring, and treatment of venous thromboembolism (VTE) for which it is used routinely [43]. D-dimer levels are also elevated in conditions of chronic inflammation, such as active malignancy, rheumatoid arthritis, sickle cell disease, and asthma [44]. In the setting of covid-19, D-dimer has been reported to be higher in subjects who are critically ill or those who expire [45-47]

D-Dimer is easily available, and universally acceptable inflammatory marker, which has documented very crucial role in COVID-19 pneumonia in predicting severity of illness, and assessing response to treatment during hospitalization. D-Dimer has important role during interventions in intensive care unit, as follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating D-dimer with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome [48-50]. D-Dimer titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial D-Dimer 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 ongoing coagulation abnormality, worsening of pneumonia, and increased inflammatory burden which will help to target therapy accordingly. D-Dimer follow-up titer can help in predicting progression of COVID pneumonia, and assessing risk of post covid lung fibrosis [48-50].

3.4. Ferritin in COVID-19 pneumonia

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 [51]. Ferritin is highly ubiquitous iron binding protein first isolated in 1937 from horse spleen, since then its isolation methodology and role as acute phase reactant and role as marker of inflammation has been evolved over decades. Various inflammatory markers like Ferritin, LDH, CRP, IL-6 and D-Dimer have been evaluated in this pandemic and now robust data is available regarding its usefulness in analyzing severity, decision making in critical cases, assessing response to interventions, predicting outcome.

Cytokine syndrome is defined as 'A group of conditions sharing same pathological mechanisms with different etiologies, causing massive release of pro-inflammatory cytokines resulting into aberrant activation of immune and coagulation systems' [52]. Cytokine storms have direct association with raised ferritin level and indirectly it will help in predicting ongoing inflammatory surge resulting in cytokine storm. cytokine storm is most dreadful event in pathophysiology of COVID-19 pneumonia and ultimately it will lead to either direct cytokine induced lung injury manifesting as ALI/ARDS or extrapulmonary systemic secondary haemophagocytic lymphohistiocytosis. [53] Studies have documented significantly raised ferritin with other inflammatory markers in COVID-19 pneumonia [54] and now COVID-19 has been included in conditions causing Hyperferritinemia [53]. Ferritin analysis found to be very crucial in this COVID-19 pneumonia, apart from routine inflammatory marker, its usefulness as marker of underlying immunosuppression [55]. Additionally, it is useful in predicting severity of illness in patients suffering with comorbidity as Diabetes mellitus and in geriatric cases and marker of increased morbidity in these cases [56-57].

Ferritin is easily available, sensitive & reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pandemic. Robust data of Ferritin 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. Ferritin has very crucial role in covid-19 pneumonia in predicting severity of illness, especially follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating Ferritin with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome [58-61].

Ferritin titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial Ferritin has progressed to critical course and we have documented 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. Ferritin 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 [58-61].

4. Inflammatory markers, antigenic mimicry and COVID-19 dengue overlap

COVID-19 pandemic is a big health concern in dengue endemic areas due to overlapping of clinical and laboratory features and its challenging job for critical care physicians for correct diagnosis and management of both the diseases [62-64] Many case reports and case series published the concurrent COVID-19 and dengue co-infections, which has been associated more mortality than isolated single infection [64-65]. Both viral diseases share may pathogenic and clinical features, as Antibody Dependent Enhancement phenomenon (ADE) has documented in both dengue and COVID-19 which is the reason for overlapping nature of both the disease and behaving like 'two sides of same coin.' Both are RNA viruses and shown similar pathologic pathways as cytokines and chemokine release, altering the integrity of the vascular endothelium leading to vasculopathy, coagulopathy and capillary leak [66].

Dengue-COVID-19 overlap is clinical syndrome with overlapping clinical and laboratory workup of both the illnesses. High index of suspicion is must in all covid cases in tropical setting where dengue is endemic; and all cases with leukopenia and thrombocytopenia with fever should be screened for dengue serology. False positive dengue serology or dengue antigen cross-reactivity is known to occur in underlying COVID-19 illness, and have impact on clinical outcome as it will result in delay in covid appropriate treatment initiation and many cases require intensive care unit treatment due to progressed covid pneumonia. Covid-dengue antigenic cross-reactivity has significant association with lung fibrosis as resultant pathophysiological effect of immune activation pathway; and these cases were required longer oxygen supplementation and anti-fibrotics in follow up. 'Dengue-COVID-19 overlap' is very frequently documented in tropical setting and disease of concern in critical care setting; as natural trend of this entity is different and having impact on clinical outcome if diagnosis is delayed. Both diseases may behave like 'two sides of same coin', and rational for coexistent pathology were still undetermined [67-69].

4.1. Inflammatory markers during initial assessment, monitoring, targeting interventions and predicting final outcome in COVID-19 pneumonia

Studies have documented that inflammatory marker titer has significant association with duration of illness (DOI) in COVID-19 pneumonia cases [22-25,30-32,38-40,48-50,58-61]. Authors have also documented that proportionate number of cases with duration of illness < 7 days and many cases with duration of illness >15 days were having normal inflammatory markers titer, while pneumonia cases between 7-14 days of illness were having abnormal or raised inflammatory markers titer. Rational for this observation is not known, may be inflammatory response pattern is different, and authors have correlated CRP pattern with other inflammatory markers like IL-6 and D-dimer and documented that these two markers raised parallel to CRP [22-25,30-32,38-40,48-50,58-61].

Studies have reported that BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with inflammatory marker titer. Authors have documented higher inflammatory marker titer in cases requiring ventilatory support than requiring high flow nasal canula or just oxygen supplementation, thus it will help in predicting severity timely to and help in analyzing disease severity [22-25,30-32,38-40,48-50,58-61].

Studies have reported that inflammatory marker titer has significant association with oxygen saturation in COVID-19 pneumonia cases [22-25,30-32,38-40,48-50,58-61]. Various authors have documented similar to our observation in their studies, mentioned that hypoxia and infection are best triggers of inflammation and synergistic effects of both lead to significant rise in CRP titer which indicates advanced disease [22-25,30-32,38-40,48-50,58-61].

Studies have documented that Timing of BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with inflammatory marker titer [22-25,30-32,38-40,48-50,58-61]. Numerous studies have observed positive correlation of inflammatory marker titer with ventilatory requirement and underlying pathophysiology of ARDS in these cases, and timely CRP titer analysis helped in predicting 'timings of ventilatory support' requirement [22-25,30-32,38-40,48-50,58-61].

Studies have documented that Follow-up inflammatory marker titer during hospitalization as compared to entry point abnormal inflammatory marker titer has significant association in post-covid lung fibrosis [22-25,30-32,38-40,48-50,58-61,70-72]. Rational for similar observation is exaggerated inflammatory response due to advanced lung inflammation and necrosis resulting in overproduction of inflammatory cytokines linked to elevated inflammatory

marker titer in severe patients with COVID-19. Cytokines has 'double edge sword effect' i.e., cytokines have protective role in controlling infection, while in hyperactive state, cytokines will cause exaggerated lung inflammation and lung parenchymal damage and resultant lung fibrosis and possible explanation for this is significantly raised inflammatory marker titer in cases with lung fibrosis than without lung fibrosis [22-25,30-32,38-40,48-50,58-61,70-72].

Studies have reported that Follow-up inflammatory marker titer during hospitalization as compared to entry point normal inflammatory marker titer has significant association in post-covid lung fibrosis [22-25,30-32,38-40,48-50,58-61,70-72]. Authors have documented progression of illness in few cases presented with nonsevere illness which were picked up by follow up inflammatory marker titer, hence authors recommended follow-up titer has crucial role in analyzing progression and preventing worsening in these cases. Importantly these cases have documented post covid lung fibrosis than those with normal follow up titers [22-25,30-32,38-40,48-50,58-61,70-72].

5. Inflammatory markers during follow-up in recovered COVID-19 cases presenting with Long COVID manifestations

Rheumatological syndrome is known to occur after COVID pneumonia and now data is available its association with illness irrespective of diseases severity and hospitalization. Inflammatory markers patterns during initial COVID-19 pneumonia have direct correlation with rheumatological symptoms and can be suspected during hospitalization in indoor patients by analyzing titers of these markers during evolution of pneumonia [73-76]. Inflammatory markers analysis such as IL-6, Ferritin, D-Dimer, CRP and LDH at discharge has helped in majority of cases. Higher the titer of these markers, there will be more chances of long COVID in these cases. Inflammatory markers such as CRP, Uric acid and LDH are 'best laboratory clues' during follow up to pick up rheumatological symptoms early [77-79]. Cases with history of antigenic mimicry and antigenic cross reactivity such as positive dengue serology were laboratory clue during hospitalization that these patients may develop rheumatological or autoimmune features in follow-up.

Although Rheumatological syndrome that occurs with COVID-19 pneumonia is showing reversible nature over duration of time and few cases are showing persistent nature. All cases with rheumatological symptoms need prompt workup due to Immunological nature of disease. All cases should undergo analysis of rheumatoid factor, anti CCP, ANA and other tests to confirm exact type of disease-causing symptoms. Although ANA test is not confirmatory and specific to rule out Rheumatological syndrome, its high titer signifies towards immune nature of disease. ANA blot panel is more specific to label in exact nature of autoimmune disease. Steroids are cornerstone of treatment of Rheumatological syndrome with or without lung involvement and shown excellent response to steroids with hydroxychloroquine. Echocardiography is must in all cases to rule out cardiac dysfunction before initiation of treatment. Rheumatological syndrome which is rare vaccine related adverse event, and importantly it is reversible and managed with routinely available medicines and is having excellent prognosis. Vaccines has shown positive impact on controlling chances of rheumatological symptoms and now data is available regarding protective role of vaccine in preventing rheumatological symptoms [80-87].

Long covid is more prevalent chronic health care issue in post covid care settings. We are in great piece of relief due to nearly end of this deadly pandemic which has caused significant change in routine of entire globe. Long covid is an unpredicted sequel of COVID-19 disease documented nearly in half cases globally. Long covid is multisystem syndrome with nonspecific symptoms and organic signs of unidentified pathology occurs after COVID-19 disease. Long covid symptoms has been documented in 'selected' cases irrespective of disease severity or hospitalization and possible link remains unknown. Long covid symptoms has significant impact on quality of life in those cases suffered from disease in recent past and lingering to almost two years since infection. Importantly, not all cases of COVID-19 were shown long covid symptoms. Most common long covid symptoms as joint pain, fatigability, chest discomfort, shortness of breath, hair loss, chest pain, weight gain, anxiety/depression & memory impairment. Pathophysiology resulting into long covid manifestations is still not completely validated. Researchers have reported 'immune dysregulation', 'autoimmunity', 'antigenic mimicry' & 'coagulation abnormalities' are probable pathophysiological mechanism for long covid. Some of the long covid effects shown complete reversibility including post covid lung fibrosis. Reboot system to restore immune dysregulation and recovery in long covid is real concern. Long covid symptoms cases are more health conscious and usually follows pattern of doctor shopping due to underestimation by family physicians either due to lack of suspicion or lack of knowledge regarding treatment protocol. Still, we are not having right answer for exact duration of long covid symptoms and when it will show complete reversibility. Further, it needs 'birds eye vision' to pick up and manage cases with long covid manifestations during routine care in rehabilitation unit [80-87].

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Spirometry is cost effective, non-invasive, easily available, sensitive tool for assessment lung function in post covid care setting and it will help management of these cases by assessing response

to treatment. Pulmonary functions abnormality in post-COVID-19 pneumonia cases has been documented and should be assessed cautiously to have successful treatment outcome. Restrictive lung disease is the predominant lung function impairment in post-COVID 19 recovered lung pneumonia cases. Age above 50 years, male gender, Diabetes mellitus, High CT severity, longer duration of illness, proper timing of initiation of BIPAP/NIV therapy, has documented significant impact on post covid lung functions at 12 weeks assessment. All post covid cases needs lung functions assessment by spirometry to predict course of underlying lung pathology and targeting interventions accordingly [88,89].

6. Inflammatory markers after COVID vaccination

However, as vaccination programmes are being rolled out globally, many COVID-19 vaccine-related side-effects have been recently reported [90-91], ranging from mild local symptoms (e.g. pain at the injection site) to systemic symptoms (e.g. fever and/or headache) [92]. Localized pain, fatigue, headache and muscle ache are the most prevalent adverse effects in patients with autoimmune and inflammatory rheumatic diseases following six COVID-19 vaccines [93]. Previous studies indicated that human papillomavirus, hepatitis B and influenza vaccines may trigger the onset or exacerbations of autoimmune diseases by molecular mimicry inducing autoimmunity [94,95]. Authors have reported reversible autoimmune features which has reported for short period and reverted with medical management [96-97].

Rheumatological syndrome is known to occur after COVID pneumonia and now data is available its association with COVID Vaccination [98-100]. Although Rheumatological syndrome that occurs with COVID-19 pneumonia is not totally reversible or many cases showing persistent nature, authors [94,95] have documented reversible nature as its association with COVID Vaccination in our case. Rheumatological syndrome which is rare vaccine related adverse event, and importantly it is reversible and managed with routinely available medicines and is having excellent prognosis. Minimal systemic adverse events known to occur with all viral vector vaccines, but its occurrence is rare and it should not impact on routine vaccinations; as vaccination is key step in this pandemic to protect mankind.

7. Inflammatory markers as a 'double edge sword' if not considered with clinical and radiological markers as a 'Composite Index':

Since the beginning of COVID-19 outbreak, the capacity of hematological, biochemical, inflammatory, and immunological factors to predict patients with severe or fatal forms of COVID-19 has been of great scientific importance. To predict the severity of the disease in the early stages, it is critical to obtain a full profile of the laboratory analysis. According to the published literature, hematological, inflammatory, and biochemical parameters are associated with severe prognosis in COVID-19 cases and can thus be used as predictive factors [22-25,30-32,38-40,48-50,58-61].

7.1. Composite index

Clinical, radiological and laboratory markers joint assessment of COVID-19 cases with inclusion of appropriate methods is called as composite index.

- Clinical criteria are vital parameters assessment which includes oxygen saturation, heart rate, respiratory rate, blood pressure, and sensorium. Oxygen saturation less than 93% at room air is highly significant and have impact on overall outcome. Saturation at room air is predictor of hospitalization and outcome. Respiratory rate and heart rate are good predictors of aggressive interventions in indoor units.
- Laboratory assessment criteria includes inflammatory markers such as ferritin, CRP, LDH, IL-6, D-Dimer. Surprisingly, these markers are having very unpredicted course in few cases and unable to predict course during hospitalization. Authors have also documented that proportionate number of cases with duration of illness < 7 days and many cases with duration of illness >15 days were having normal inflammatory markers titer, while pneumonia cases between 7-14 days of illness were having abnormal or raised CRP titer. Rational for this observation is not known, may be inflammatory response pattern is different, and we have correlated inflammatory markers pattern with other inflammatory markers like IL-6 and D-dimer and documented that these two markers raised parallel to CRP [22-25,30-32,38-40,48-50,58-61].
- Radiological assessment criteria include anatomical involvement of lung parenchyma by means of CT severity score. Authors have documented CT severity as best visual marker of COVID-19 Pneumonia severity, which can be correlated with inflammatory markers. Various authors have documented similar observation in their study [101-102]. Best 'visual marker' of severity of illness is CT thorax and authors have documented inflammatory markers as stronger inflammatory marker associated with it [22-25,30-32,38-40,48-50,58-61]. Authors have

documented usefulness of inflammatory markers and CT severity in Triaging the cases at entry point and proper use of interventions in indoor setting according to 'clinical, radiological and inflammatory marker panel' in their institute [22-25,30-32,38-40,48-50,58-61].

8. Importance of composite index as 'Point of care test'

Limitations of individual makers has been documented (Clinical, radiological and laboratory markers) when assessed independently. All these parameters of composite index should be assessed in parallel to avoid overestimation or underestimation of severity and to analyze exact nature of COVID-19 pneumonia. Discordance with Clinical, radiological and laboratory markers is possible, and more frequently reported during second and third wave of COVID-19 pneumonia with delta and omicron variant and less frequently reported in Wuhan variant of corona virus.

In first wave with 'Wuhan variant' caused corona virus related COVID-19 pandemic, many cases were having concordance and synchronous abnormalities in Clinical, radiological and laboratory markers. Risk stratification, triaging of cases, targeting interventions and overall planning of COVID-19 cases were quantified well due to proper correlation of these markers of composite index. Rational is clear virus-related pathophysiological like immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues presenting with pulmonary and extrapulmonary manifestations. During first wave, a greater number of cases were having balanced pulmonary and extrapulmonary manifestations. Cardio-vascular involvement were seen more often in first wave as compared to second wave, rational for same was not known, may be 'Wuhan variant virus has more thrombogenic activation syndrome' as compared to Delta variant corona virus. In first wave pseudo-acute coronary syndrome, pulmonary thromboembolism and stroke were documented in a greater number of cases as compared to second wave. Pulmonary and extrapulmonary manifestation of pandemic virus were balanced and mortality was minimal with first wave of COVID-19 [77-90].

In second wave with 'Delta' variant caused corona virus related COVID-19 pandemic, many cases were having discordance and asynchronous abnormalities in Clinical, radiological and laboratory markers. Risk stratification, triaging of cases, targeting interventions and overall planning of COVID-19 cases were observed difficult to quantify due to improper correlation of these markers of composite index. In second wave many patients were in advanced stage till they access treatment and required intensive care unit treatment including ventilatory support. Overall mortality is 'no significantly different' in first and second wave or slightly more in second wave, as we are dealing with Wuhan variant virus in first wave and mutant Delta variant corona virus in second wave. Shortage of oxygen and shortage of ventilators was big concern in second wave as compared to first wave in spite of increase in oxygen beds and increase in ventilator beds across the country, this might be faced because of 'exuberant case load' because of rapidly spreading nature of Delta variant corona virus as compared to less mutant first wave Wuhan variant corona virus. Although health system has prepared to tackle a greater number of covid cases till evolution of second wave, rapid resurgence of cases and rapidly evolving ARDS were determining factor for relatively more mortality in second wave as compared to first wave. Rational is similar i.e., virus-related pathophysiological like immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues presenting with pulmonary and extrapulmonary manifestations. Pulmonary and extrapulmonary manifestation of pandemic virus were balanced and mortality was minimal with first wave of COVID-19. Rapidly evolving pneumonia or 'accelerated acute respiratory distress syndrome' (a-ARDS) was more commonly documented in second wave and more number of patients were presenting with similar syndrome in second wave with time interval of less than a week, with rapidly deteriorating radiological and clinical-laboratory parameters like increased CT severity score, worsened oxygenation, increased inflammatory markers like CRP, IL-6, Ferritin, LDH, D-dimer, decreased leucocyte and platelet counts. Cytokine storm were documented very commonly with first and second wave, but duration of manifestation of cytokine storm was delayed till second week in first wave as compared to second wave in which cytokine storm presented too early i.e., documented in first 3 days to end of first week of illness may be due to delayed presentation to hospital admission. Clinical assessment may either overestimate or underestimate the exact severity of COVID-19 pneumonia in the absence of radiological and laboratory assessment inflammatory parameters. Clinical scenario where overestimation is possible are the cases with minimal radiological disease with raised inflammatory markers underestimation is possible with minimal disease with mild symptoms but high titers of laboratory markers. Underestimation was more frequently reported due to minimal lung involvement and mild symptoms on first few days of disease and these cases were rapidly evolved and developed advanced disease in short time and these were picked up with composite index. and advanced disease with Predominant Pulmonary involvement with minimal extrapulmonary involvement was 'typical and most common' presentation of second wave due to delta variant. Rational for these localized disease with minimal extrapulmonary disease is not known and requires further research. Composite index has documented very crucial role in second wave of COVID-19 pandemic [77-90].

In third wave with 'omicron variant' caused corona virus related COVID-19 pandemic, many cases were having discordance and asynchronous abnormalities in Clinical, radiological and laboratory markers. Risk stratification, triaging of cases, targeting interventions and overall planning of COVID-19 cases were observed difficult to quantify due to improper correlation of these markers of composite index. Rational is similar which is documented in previous two wave of COVID-19 i.e., virus-related pathophysiology's such as immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues presenting with pulmonary and extrapulmonary manifestations. During third wave, a greater number of cases were having extrapulmonary manifestations or involvement due to covid-19 as compared to pulmonary as compared to predominant pulmonary in second wave and balanced pulmonary-extrapulmonary in first wave. Rational for these localized and systemic disease is not known and requires further global research. Extrapulmonary manifestations such as Cardio-vascular and neurological involvement were seen more often in third wave as compared to first and second wave, rational for same was not known, may be 'omicron variant virus has more thrombogenic activation syndrome along with inflammatory pathway activation' as compared to Wuhan and Delta variant corona virus. As observed in first wave with Wuhan variant, in third wave with omicron variant associated pseudo-acute coronary syndrome, pulmonary thromboembolism and stroke were documented in a greater number of cases. Predominant extrapulmonary with minimal pulmonary manifestation is 'typical and most common 'in omicron variant associated disease in third wave and mortality was minimal with first and second wave of COVID-19 [77-90]. Rational for same virus-related disease with heterogeneous presentation needs more global data and further research.

8.1. Importance of composite index as 'point of care test' during course of COVID-19 pneumonia in outdoor and indoor settings:

Composite index has documented in assessment of COVID-19 cases during entry point setting in outdoor units and guided further in triaging & decision making of these cases before hospitalization. Thus, composite index has guided for treatment planning and decision to hospitalize were independently assessed by composite index rather than to depend on only clinical, laboratory or radiological markers. Still, data is available that many cases were underestimated during second wave due to 'Delta variant' in presence of discordance in individual Clinical, radiological and laboratory markers and observed crucial role of composite index. Thus, a greater number of cases were presented late due to individual parameters assessment and received treatment in advanced stage. Thus, composite index is best assessment tool for assessment of severity of COVID-19 pneumonia. Data is also available stating that many covid cases were overestimated if analyzed individual Clinical, radiological and laboratory markers which was observed in first and third wave due to 'Wuhan and omicron' variant respectively. Composite index is sensitive and effective tool to assess COVID-19 cases at entry point and to analyze exact status of illness which will have successful treatment outcome and thus considered as 'point of care test' in this COVID-19 pandemic.

9. Conclusion

COVID-19 infection involves a complex interplay of the immunological and inflammatory responses. Inflammatory parameters are closely linked to the COVID-19 severity and mortality. Inflammatory parameters could be used to predict the transition from mild to severe/critical infection in patients of COVID-19. Low blood-oxygen levels have been a hallmark in COVID-19 patients. The lung tissue damage infiltered by the viral-mediated inflammation decreases oxygen saturation to cause silent hypoxia and cell death. Inflammatory markers could effectively discriminate the risk of mortality in severe COVID-19 patients. As CRP, LDH, and ferritin levels determine the tissue oxygen availability, they seem to be valuable biomarkers in the prognosis of COVID-19.

CRP should be considered as basic, bed side test, sensitive, cost-effective inflammatory marker which is widely used and subsequent titer has documented crucial role in analyzing inflammatory status. Ferritin is most sensitive marker of inflammation in correlation with CRP and IL-6 and important marker of predictor of cytokine storm. LDH is best to assess oxygenation status and follow-up titer will guide chances of post covid lung sequel and high titer during hospitalization helps in predicting ongoing severe necrotic lung disease. D-dimer has documented role in predicting microvascular and microvascular complications of COVOID-19 and subsequent titers has documented role in predicting post covid complications. IL-6 hs documented very specific role in predicting inflammatory surge and best predictor of cytokine storm independently.

Composite index will play a crucial role in early suspicion, diagnosis, monitoring, and recognition of complications, management and disposition of patients. Each of these components in turn can have crucial implications on the healthcare system and the administrative machinery, directly impacting patient care. Needless to say, clinical evaluation will be paramount at every step and Composite index will need to be meaningfully integrated into bedside decision making. Composite index panels rather than single biomarkers may provide more reliable information which will

prevent overestimation and undervaluation to prevent detrimental outcomes. Availability and cost issues cannot be ignored. It would be impossible for clinicians to consolidate and critically analyze the enormous data that is continuously added to the COVID-19 literature to extract practically useful information for the benefit of patients. Composite index should be considered as 'point of care test' to honor successful treatment outcome and prevent mortality and morbidity due to this 'Dragon Pandemic'.

Compliance with ethical standards

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Venkatesh Hospital and Critical care center Latur Maharashtra India.

Disclosure of conflict of interest

No conflict of interest declared.

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