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Original Research Paper

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ROLE AND USEFULNESS OF BIOCHEMICAL MARKERS IN COVID-19 CASES: A SYSTEMATIC REVIEWS

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ABSTRACT **Background:** Coronavirus disease 2019 (COVID-19) is a highly contagious viral illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It has a catastrophic effect on the world resulting in more than 25 million deaths worldwide. In India on 30th January 2020 first positive case in a student from Kerala of the SARS-CoV-2 infection. The SARS-CoV-2 can cause serious clinical complications, especially in elderly patients and in those with co-morbidities, especially diabetes obesity; cancer and digestive, endocrine, nervous and respiratory systems pathologies. The elevated biomarkers level was noticed in severe COVID 19 cases compared to non-covid 19 patients, revealing that D-dimer, CRP, ferritin, LDH, are significantly correlated to COVID-19 severity. This review study aims to identify the most effective biomarker among C-reactive protein, IF6, D-dimer and ferritin to predict disease severity. This review intends to outline the biochemical laboratory tests that are useful in disease monitoring and assessment of severity in confirmed cases of COVID-19.

KEYWORDS : COVID-19,RT-PCR,IL-6, ferriten, CRP

INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is a highly contagious viral illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It has a catastrophic effect on the world resulting in more than 25 million deaths worldwide. After the first cases of covid 19 were first reported in Wuhan, Hubei Province, China, in late December 2019, SARS-CoV-2 rapidly disseminated across the world in a short span of time. This compelled the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020 [1]. The SARS-CoV-2 virus is similar to Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), which have their origins in bats. and the covid-19 virus spread worldwide within 2 months later [2].

In India on 30th January 2020 first positive case in a student from Kerala of the SARS-CoV-2 infection, who was studying in Wuhan University and had travelled to India, tested positive by reverse transcriptase polymerase chain reaction (RT-PCR). Soon after this, it became a global concern [3].

This outbreak has been a challenge for clinicians and researchers. COVID-19 infection has a variable clinical presentation from asymptomatic to milder symptoms, including fever, dry cough, dyspnoea, myalgia, sore throat and headache, to more severe and emergent manifestation including confusion, chest pain, hypoxemia, pneumonia and other complications requiring intensive care unit (ICU) admission and mechanical ventilation [4]. Diarrhoea, anosmia and ageusia have also been reported in a few studies [5].

The SARS-CoV-2 can cause serious clinical complications, especially in elderly patients and in those with co-morbidities, especially diabetes [6].Cardio and cerebrovascular diseases [7,8].Obesity, cancer and digestive, endocrine, nervous and respiratory systems pathologies [9]. Constituting 50% to 75% of deaths [10]. pertaining to COVID-19 infection.

Upon examination, these subjective clinical symptoms can be interpreted more confidently with the use of biological markers (biomarkers). These provide objective values throughout the progression of the disease [11].

Diagnosis of COVID-19 is confirmed by direct detection of SARS-CoV-2 nucleic acids in respiratory tract specimens with a polymerase chain reaction (PCR) (9). A rapid and accurate diagnosis has wide implications for the patient, healthcare institution, and the public health and administrative personnel. In the current pandemic, healthcare systems are struggling to meet the increasing demands of the rapidly rising infected population. Effective utilization of available resources is paramount to saving the maximum number of lives. Clinical assessment is indispensable, but laboratory markers, or biomarkers, can provide additional, objective information which can significantly impact many components of patient care [12].

Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2, many countries continue to have outbreaks of this viral illness that are attributed to the emergence of mutant variants of this virus.

This review article aims to comprehensively describe the ethology, biomedical markers, clinical features, and the latest novel therapeutics in the management of COVID-19. This review also briefly provides an overview of effect of biomarker in SARS-CoV-2 and the efficacy of different available vaccines for prevention against COVID-19 and its variants.

CLINICAL CHARACTERISTICS OF COVID-19 CASES:

The symptoms of COVID-19 remain very similar to those of the other respiratory epidemics in the past, which include SARS and MERS, but here wide range of symptoms includes mild fever to septic shock. Some intestinal disturbances were reported with the other epidemics, but COVID-19 was devoid of such symptoms. When examined, unilateral or bilateral involvement compatible with viral pneumonia is observed in the patients, and bilateral multiple lobular and sub-segmental consolidation areas were observed in patients hospitalised in the intensive care unit. The co-morbid patients showed a more severe clinical course than predicted from previous epidemic [3]. In patients with COVID-19, the most common clinical symptoms are fever and cough, shortness of breath, and other breathing difficulties in addition to other nonspecific symptoms, including headache, dyspnea, fatigue, and muscle pain[13].Moreover, some patients also report digestive symptoms such as diarrhea and vomiting [14].Fever occurred in 98-100% of patients with SARS or MERS, compared to 81.3% of patients with COVID-19 [11].Approximately 18.7% of patients had no fever at admission, suggesting that the absence of fever could not rule out the possibility of COVID-19[15]. Although patients initially have fever with or without respiratory symptoms, various

degrees of lung abnormalities develop later in all patients, and these can be seen on chest CT (CT). Although diarrhea is present in approximately 20-25% of patients infected with MERS-CoV or SARS-CoV- 2, intestinal symptoms have rarely been reported in patients with COVID-19 [16].

Morphology of SARS-CoV-2 19 virus:

Coronaviruses are enveloped, positive single-stranded RNAs with the largest known RNA genome ranging from 26 to 32 kilobases in length. They are spherical virions with a core shell and a surface that resembles a solar corona based on its surface protein projections, hence their name .There are four main subfamilies; alpha-, beta-, gamma- and delta-coronaviruses [17].Alpha- and beta-coronaviruses originate from mammals, mainly bats, and are thought to cause more severe and fatal diseases in humans, while gamma- and delta-viruses mainly originate from birds and pigs and are thought to cause asymptomatic or mild disease in humans [17].SARS-CoV-2 belongs to the beta-coronavirus group, which also includes MERS-CoV and SARS-CoV. The latter shares ~75–80% of its viral genome with SARS-CoV-2 [18]. Beta-coronaviruses have three important envelope proteins: Spike (S) protein, Membrane (M) protein, and Envelope (E) protein. S protein mediates viral attachment to the cell membrane receptor, membrane fusion, and ultimately viral entry into the host cell. M protein, the most abundant membrane protein, together with E protein is responsible for the coronavirus membrane structure. Another component of the beta-coronavirus is the N protein, which is the protein component of the helical nucleocapsid that includes the genome RNA [19].

Laboratory Findings of SARS-CoV:

Various biochemical abnormalities were seen in COVID-19 infected patient, including elevated serum C-reactive protein (increased in >60% of patients), lactate dehydrogenase (increased in approximately 50%-60% of patient), alanine aminotransferase (elevated in approximately 25%), and aspartate aminotransferase (approximately 33%) [20]. Approximately 75% of patients had low albumin. The most common hematological abnormality is lymphopenia (absolute lymphocyte count $<1.0 \times 109/L$), which is present in up to 83% of hospitalized patients with COVID-19 case [21]. In conjunction with coagulopathy, modest prolongation of prothrombin times (prolonged in >5% of patients), mild thrombocytopenia (present in approximately 30% of patients) and elevated D-dimer values (present in 43%-60% of patients) are common [22]. However, most of these laboratory characteristics are nonspecific and are common in pneumonia. More severe laboratory abnormalities have been associated with more severe infection. D-dimer and, to a lesser extent, lymphopenia seem to have the largest prognostic associations [23].

Biomarkers for COVID-19 Disease:

IL-6: The commonly reported cytokine implicated in COVID-19 is IL-6. Elevated levels of IL-6 are directly associated with higher mortality [24].Moreover, tocilizumab is a candidate drug to be used in managing the CS accompanying COVID-19. Encouraging results have been reported in China where tocilizumab was used in the treatment of patients with severe and critical COVID-19 [25]. Increased IL-6 has been seen in respiratory dysfunction, which implicates a mechanism that might be shared with cytokine-mediated lung damage caused by COVID-19 infection[26].In addition, the extremely pathogenic SARS-CoV-2 is associated with rapid viral replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6-induced severe respiratory distress.Thus, studies have recommended that it is plausible for immediate initial evaluation of IL-6 levels upon hospital admission of COVID-19 patients. This attributes to its implication in the assessment of deterioration of the clinical presentation and severity of the disease in COVID-19 [27]. IL-6 is assayed using immunoassay techniques, preferably electrochemiluminescence immunoassay (ECLIA). An assay-dependent cut off value of the reference range up to 7 pg/mL has been determined in normal individuals. Various cohort studies demonstrated that at presentation, an IL-6 level greater than 35 pg/mL showed high rates of sensitivity to detect patients at risk for respiratory failure (84% and 95% of patient) with moderate specificity (63%). Laboratory finding also suggested that calculated the cut off value for IL-6 was slightly lower, that is, 60pg/mL than the suggested cut off of 80 pg/mL in covid-19 patient [28].

CRP:

C-reactive protein is a pentameric acute-phase protein and acute pneumococcal pneumonia. CRP shows raised expression during inflammatory diseases such as some cardiovascular diseases, rheumatoid arthritis and some how involved in their pathogenesis. C-reactive protein is synthesized predominantly in hepatocytes but also by other cell types such as adipocytes, lymphocytes, endothelial cells, macrophages, and smooth muscle cells. CRP levels can rise up to 1000 folds in any bacterial infection and decline abruptly as soon as infection resolves. CRP plays a critical role in the recognition of self and foreign molecules. This interaction leads to an activation of the adaptive immune system in inflammatory or infectious diseases. CRP has an affinity towards phosphatidylcholine ligands present on damaged cell membranes; exposed and denatured chromatin and small nuclear ribonucleo proteins. CRP plays a significant role in the clearance of these molecules through interaction with the complement system and Fc receptors on phagocytic cells [29].Therefore, it has been suggested that CRP acts as a scavenger which is significant in clearing damaged membranes, decayed nuclear material, and autoantigens. CRP acts as an opsonin and helps to eradicate pathogens by phago-cytosis through opsonization and activation of the classical complement pathway by which it protects organisms from infections.

Elevated CRP is clearly recognized in the major acute-phase response following ischemic or hemorrhagic stroke, and it is related to the development of vascular complications [30]. From clinical observations, it was noted elevated concentration of D- dimer, fibrinogen, and CRP in COVID-19 patients with acute ischemic stroke, suggesting systemic hyper inflammatory and hypercoagulable state. In a retrospective, observational cohort study, CRP was found to be correlated between stroke onset and the peak of acute phase reactants in COVID-19. Furthermore, CRP was the mortality predictor, and its expression might be correlated with the formation of ischemia in COVID-19 associated strokes [31] . Various researches suggest that CRP levels are a strong indicator to reflect the presence and severity of COVID-19 infection.

Ferritin:

Human ferritin is composed of two subunits, namely ferritin heavy chain (FTH) and ferritin light chain (FTL) [32]. The FTH chain has ferroxidase activity and oxidizes $Fe2+$ to $Fe3+$. $Fe3+$ then moves towards the nucleation site on the FTL chain and thus by acting in a synchronizing way, iron oxidation and core formation is carried out [33]. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome. Many individuals with diabetes exhibit elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from COVID-19. On this basis, we briefly review evidence supporting the hypothesis that ferritin levels might be a crucial

factor influencing the severity of COVID-19 [34] .

High serum ferritin level was found to be associated with more severe disease and negative/poor outcome in COVID-19. Thus serum ferritin level can serve as an important predictive biomarker in COVID-19 management and in triage. However, in presence of other co-morbid conditions/disease, serum ferritin level needs to be interpreted cautiously [35] .

D-Dimer:

D-dimer is a protein fragment formed after fibrinolysis. Each fibrinogen molecule comprises two sets of α, β, and γ polypeptide chains that combine to produce a protein with two distal D regions joined by a cross-link to a central E region. After the clot finally dissolves, the D-dimer protein is all that is left floating in the blood.

D-dimer is a fibrin degradation product, widely used as a biomarker for thrombotic disorders. A D-dimer value less than 0.5 g/mL is usually considered normal, and values increase with increasing age and in pregnancy. The level of D-dimer rises with increased severity of community-acquired pneumonia [36]. Following the outbreak of the COVID-19 pandemic, D-dimer has been identified as a potential indicator for its prognosis in COVID-19 patients. Admission day D-dimer has shown promise for predicting the disease severity in multiple studies [37]. COVID-19 patients have been shown to present with D-dimers twice as high on admission than patients with community acquired pneumonia [38]. Various other researchers identified that the degree of variation in D-dimer values from those on admission were associated with outcomes in COVID- 19 patients [39]. And also found an admission D-dimer of >2.0 g/mL was associated with an increased risk of mortality. As an indirect measure of thrombotic burden, D-dimer values may have the potential to help guide treatment of covid-19. D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and are a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19.

FUTURE PERSPECTIVES AND BARRIERS OF COVID -19:

Currently, nucleic acid-based molecular tests are still considered the gold standard for the diagnosis of COVID19 disease. The detection time has been reduced to 30 min. It is a highly sensitive specific technique in the diagnosis of infected COVID-19 patients. RT-PCR is the most used test among molecular techniques. The requirement of reliable control for confirmation, the necessity for expensive equipment and trained person, certificated reagents, and laboratory facilities are known disadvantages of molecular methods. In future applications, alternatives such as LAMP and CRISPR-Cas methods may become more common as they are a less costly, simple procedure. The biosensor-based virus detection systems that utilize nanotechnology and microfluidics and instrumental advances are predicted to be among the most promising technologies in pandemic situations like COVID-19 [40]. In the future, it is thought that easier and more mature biosensor platforms will replace RT-PCR. Further studies are needed to compare existing methods in terms of robustness, reproducibility, reliability, and sensitivity [41].

To summarize, current analysis methods are not sufficient to distinguish infected persons, especially in public places. There is a need to produce POC devices that can detect infections on the site without the need for professionally trained personnel. In future applications, POC diagnostic devices and tests are increasing in popularity, especially in the case of a worldwide pandemic such as COVID-19 [42].

CONCLUSION :

In conclusion, several laboratory parameters could be associated with the severity and mortality of COVID-19 pandemic since The continuous research and measurement required to understand the progression of the infection, its pathophysiology and for the discovery of an effective antiviral drug therapy and a vaccine. Therefore, the search for biochemical or other suggestive laboratory parameters are extremely necessary in this scenario to evaluate and establish early clinical diagnosis of SARS-CoV-2 infection. These parameters included ,CRP, D-dimer , IF6 and S. ferritin could be helpful to monitor the severity of the disease and symptomatic treatment because of the lengthy procedure and large numbers of suspected individual samples are awaiting diagnosis through RT-PCR.

CONFLICT OF INTERESTS:

Authors have no conflict of interests.

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