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A Review on Inflammatory and Coagulative Biomarkers for Diagnosis and Prognosis Prediction of COVID-19

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Abstract

As of December 14th, 2021, WHO had received reports of 270,031,622 confirmed cases of COVID-19 globally, with 5,310,502 mortalities, the COVID-19 epidemic had entered over 200 nations and afflicted over three million confirmed victims. Emerging Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) variants, particularly those of concern, may affect the virus's transmissibility and pathogenicity, as well as the performance of diagnostic equipment and vaccination efficacy. Despite the fact that the SARS-CoV-2 Delta variation (B.1.617.2) appeared during India's second wave of illnesses, Delta variants have become prominent globally and are continually developing. The World Health Organization designated the variation B.1.1.529 as a variant of concern on November 26th, 2021, calling it Omicron, based on information that Omicron has multiple mutations that may alter its behavior. However, the route of transmission and severity of the Omicron variant remains unknown.

To save as many lives as possible clinical assessment is vital, but laboratory indicators, or biomarkers, can provide additional, objective information that can have a significant impact on patient therapy. COVID-19 is a multisystem illness characterized by a diffuse systemic process that involves a complicated interaction of the immunological, inflammatory, and coagulative cascades. Studying what the virus causes to the body and how the body reacts to it has led to the discovery of many possible biomarkers. Biomarkers will play an important role in early identification, diagnosis, monitoring, and detection of issues, as well as patient treatment and disposal. Each of these aspects might have major implications for the healthcare system and administrative machinery, directly influencing patient care. We have studied several biomarkers to see if they predict clinical outcomes and correspond with the severity of COVID-19 infection. This review examines different groups of biomarkers - immunological, inflammatory, and coagulation - in terms of their pathophysiology, followed by the most recent evidence. The association of biomarkers with clinical and radiological characteristics, as well as viral load, temporal evolution, and therapeutic impact has to be evaluated in-depth.

We discussed the following biomarkers in this article: The immunological inflammatory indicators include C-reactive protein, Erythrocyte sedimentation rate, Procalcitonin, Serum ferritin, Cytokine (interleukin-6), and lactate dehydrogenase. D-dimer, von Willebrand Factor (vWF), type 1 Plasminogen Activator Inhibitor 1 (PAI-1) and Tissue-activating Plasminogen (tPA), prolonged Prothrombin Time (PT) and Activated Partial Thromboplastin (aPTT), and platelet activation all these contribute to coagulative markers. All of these biomarkers were shown to be significantly greater in individuals with severe COVID-19 infection sequelae when compared to their non-severe counterparts. Of these all, except platelets exhibited a consistent decline in level.

Keywords: COVID-19; Biomarkers; Immunological; Inflammatory; Coagulative biomarkers

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Introduction

Coronavirus is an outbreak that began on December 8th, 2019, in the Chinese city of Wuhan and quickly spread among individuals, infecting people worldwide. The World Health Organization (WHO) declared COVID-19 as a pandemic in February 2020. Globally, as of December 17th, 2021, WHO had received reports of 271,963,258 confirmed cases of COVID-19, with 5,331,019 deaths. Coronaviruses are classified into four genera in the *Nidovirales* order: Alpha, beta, delta, and gamma. Coronaviruses are spherical single-stranded RNA viruses with a diameter of 80 nm to 220

nm. Coronavirus structural proteins include the Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N) [1]. Coronaviruses cause the common cold, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). Coronavirus Disease 2019 (COVID-19) is caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome) a novel viral respiratory disease, by a member of the beta-corona virus family [2]. SARS-CoV-2 has a sequence similarity of 88% to 96% to three bat-derived SARS-like coronaviruses (bat-SL-CoVZC45, bat-SLCoVZXC21, RaTG13) and a coronavirus strain isolated in pangolins [3].

On November 26th, 2021, WHO recognized the COVID-19 Omicron variant as a variant of concern. The viral sequence was discovered after the first Omicron case was detected in Botswana, in Southern Africa, due to evidence that it contains various mutations that may change how it behaves. There is consistent evidence that Omicron is spreading substantially quicker than Delta in nations, with a doubling period of 2 to 3 days. The overall risk associated with this new variant remains extremely significant [4].

The SAMRC (South African Medical Research Council) researchers examined case rates and mortality rates over four COVID-19 waves. When case rates reached 18 percent per 100,000 of population at the peak of the first Alpha wave (July 2020), mortality rates neared two per million. During the Beta wave (January 2021), case rates reached 15 percent per 100,000, with a fatality rate peaking at slightly more than two per million of population. The Delta wave (July 2021) had the greatest peak of 35 percent cases per 100,000 of population, with a fatality rate of roughly four per million [5]. The case rate in the continuing fourth or Omicron wave has exceeded 30 percent per 100,000 of population - though the peak is yet to arrive - however the mortality rate per million is little more than zero or even less than the Alpha wave.

SARS-CoV-2 variations have been classified as variants of interest, variants of concern, and variants of high importance by the Centers for Disease Control and Prevention (CDC). Several SARS-CoV-2 variations have been found, raising the potential of long-term infection in immunocompromised people [6]. SARS-CoV-2 is transmitted by infected people's microdroplets or through contact transmission *via* contaminated fomites [7]. COVID-19 is a multisystem illness produced by a diffuse systemic process involving the immunological, inflammatory, and coagulative cascades. This study investigates the pathophysiological basis of several biomarker categories – Immunological inflammatory and Coagulative biomarkers.

Search Strategy and Selection Criteria

A broad literature search was performed on SCOPUS, PubMed, Web of Science, Embase, Google Scholar and Sci-Hub to find articles reviewing biomarkers and its clinical implications on COVID-19 from commencement to December 2021. Key words used were 'C-reactive protein, Procalcitonin, Erythrocyte Sedimentation Rate (ESR), Cytokines, Serum Ferritin, D-Dimer, lactate dehydrogenase, platelet count in relation to COVID-19. Finally, all the relevant studies were identified and summarized separately, excluding the studies from which we could not obtain data on the existence of mean and standard deviation of the biomarker described in non-severe and severe cases of COVID-19. However, there was a limit on language of the article. Articles other than English were not selected for the study.

Results

In total 3,560 articles were retrieved based on the search terms. Out of which 97 articles were retained finally for this review. However, it was not possible to conduct an appropriate meta-analysis because there were not enough research data among the studies on this subject.

Risk Factors

Host related

Everyone, regardless of age, is susceptible to infection [8]. Men are more vulnerable to SARS-CoV-2 when compared to women, since women have higher levels of estradiol, thereby enhancing the expression and activity of ADAM17 (A disintegrin and metalloprotease 17) in their bodies. Diabetic individuals respond less to therapy and are at a higher risk of mortality due to weakened immune systems [9]. High blood pressure appears to increase mortality because it decreases lung function and oxygen supply. The sensitivity to COVID-19 is greater in individuals with cardiovascular disorders. The root cause behind the inflation might be connected to (Angiotensin Converting Enzyme-2) ACE2 expression in myocytes and vascular fibroblasts [10]. Cardiovascular cells harboring the COVID-19 can cause damage and inflate the infiltration of mononuclear inflammatory cells into the heart tissue, causing the condition to worsen [11]. Cancer patients are more susceptible to infection than non-cancerous individuals are, since malignancy and chemotherapy impair immune cell development and proliferation, resulting in an immunosuppressive state in the body.

Environmental related

The virus travels from bats to humans through an intermediary host [12], is found in human feces, and may infect other species [13]. The presence of an infected individual on public transportation will be a risk factor for contamination while maintaining social distance can reduce the transmission of the disease. Furthermore, In India, the SARS-CoV-2 virus was isolated and identified from urban effluent, polluted water, and rivers [14]. The virus may be present due to viral excretion in human feces or droplets from the human sputum [10]. There is insufficient data to support viral transmission *via* water and wastewater [15]. Although there is a considerable risk of transmission *via* waste or polluted water, further research is required to back up the conclusions [16]. Close contact with an infected individual, however, is the predominant method of transmission *via* respiratory droplets generated when talking, singing, sneezing, or coughing.

Pathophysiology

COVID-19 indicates a wide range of clinical severity, from asymptomatic to serious pneumonia, Acute Respiratory Distress Syndrome (ARDS), and even mortality [17]. The incubation phase might last anywhere from two to fourteen days. The average time for the onset of symptoms is five days. The symptoms' intensity might range from moderate to severe. In asymptomatic individuals, Computerized Tomography (CT) scans revealed the distinctive pulmonary ground-glass opacification [18]. Omicron symptoms include a low to moderate temperature, intense fatigue, dizziness, and nausea that lasts for 3 to 5 days. So far, no cases of pneumonia or lung injury have been reported. Yet Omicron is still a swifter, with an incubation period of roughly three days. However, the spread rate of Omicron variant is faster than prior variants. Vaccination and taking precautions, on the other hand, are crucial in helping to avoid

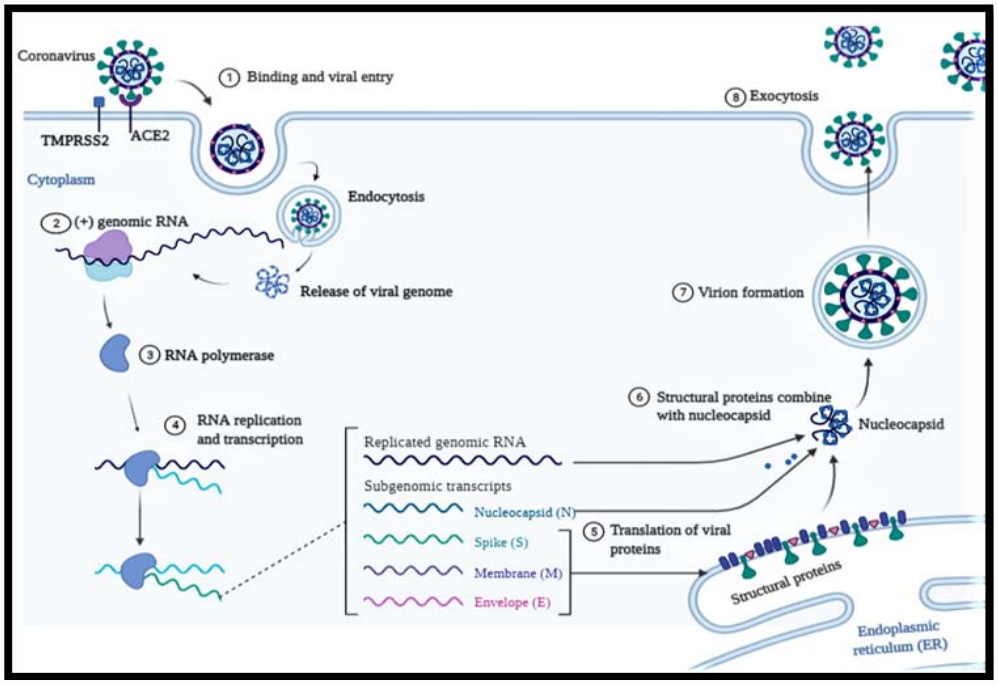

Figure 1: Life cycle of virus and Invasion into the host cell.

the spread of COVID-19, and we know these measures have been successful against other variants. There is no evidence that Omicron produces distinct COVID-19 symptoms than other COVID-19 variants.

The virus life cycle and invasion of host cell

The life cycle of the virus within the host consists of five stages: Attachment, Penetration, Biosynthesis, Maturation, and Release (Figure 1). Viruses enter host cells by Endocytosis or membrane fusion after binding to host receptors (Attachment and Penetration). The primary receptor for both SARS-CoV-2 and SARS-CoV is ACE2 (Angiotensin Converting Enzyme) [19]. According to Hoffman et al. TMPRSS2 (Transmembrane Serine Protease 2) is required for SARS-CoV-2 entry into host cells, although Cathepsin B/L can be employed as a replacement [20].

A two-step protease cleavage at subunits S1 and S2 activates S protein during attachment. The first cleavage stabilizes the S2 subunit at the attachment site, while the second activates the S protein, triggering conformational changes that lead to membrane fusion between the virus and the host cell. The virus penetrates pulmonary alveolar epithelial cells after membrane fusion and releases its contents within the host cell. The virus then replicates *via* RNA polymerase activity (transcription). In the cell cytoplasm, this newly generated RNA produces new viral proteins (translation). These newly produced viral proteins are wrapped in the endoplasmic reticulum membrane and carried to the lumen, where they are transported to the cell membrane through Golgi vesicles and exocytosed to the extracellular environment. These new viral particles are now ready to infect neighboring epithelial cells and provide new infectious material for community transmission *via* respiratory droplets [21]. Because of a considerable number of mutations in the SARS-CoV-2 Receptor-Binding Domain (RBD), the Omicron variation displayed a greater affinity for human Angiotensin-Converting Enzyme 2 (ACE2) than the Delta variant, indicating a higher potential for transmission. Docking studies have found that the Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K mutations substantially contribute to high binding affinity with human ACE2 [22].

Both the entire spike protein and the RBD in Omicron have a significant amount of hydrophobic amino acids such as leucine and phenylalanine as compared to the Delta variant. These amino acids are found in the core of the protein and are necessary for structural stability. The presence of several mutations in the spike protein's receptor-binding domain in Omicron compared to the Delta version implies that the Omicron variant may be immunologically resistant to antibody-mediated protection [23].

Host response to SARS-CoV-2

The SARS-CoV-2 infection causes airway epithelial cell death and damage in a variety of ways, including Pyroptosis. When viral-mediated cell death occurs, pattern recognition receptors on alveolar macrophages and endothelial cells; identify Damage Associated Molecular Patterns (DAMPs) and Pathogen Associated Molecular Patterns (PAMPs).

Epithelial cells, Alveolar macrophages, and Dendritic Cells (DCs) are three essential components of innate immunity in the airway [24]. Antigen presentation of dendritic cells and macrophages initiates T cell responses. Dendritic Cells (DCs) and macrophages can phagocytize virus-infected apoptotic cells.

Now, antigen-presenting cells migrate to draining lymph nodes where they present viral antigens to T cells. CD4+ T cells stimulate B cells to produce virus-specific antibodies, whereas CD8+ T cells can kill virally infected cells. Patients with severe COVID-19 had lymphopenia, namely a decrease in peripheral blood T lymphocytes [25]. Furthermore, elevated plasma concentrations of pro-inflammatory cytokines such as interleukin IL-6, IL-10, Granulocyte-Macrophage Colony Stimulating Factor (G-CSF), Monocyte Chemoattractant Protein-1 (MCP1), Macrophage Inflammatory

Protein (MIP) 1, and Tumor Necrosis Factor (TNF) -α are seen [26]. The higher the IL-6 levels, the more serious the patients' illness [27]. Another intriguing discovery was the presence of abnormal pathogenic CD4+ T cells co-expressing Interferon (IFN) -γ and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) in COVID-19 patients with severe illness. SARS-CoV research revealed that virus-infected lung epithelial cells generate IL-8, which is a strong well-known neutrophil and T cell chemoattractant in addition to IL-6. Inflammatory cells represent a mix of innate and adaptive immune cells [28,29]. The majority of infected immune cells are likely to be T cells because of the significant reduction of circulating T-cells [30]. Neutrophils can promote lung injury, and act as a double-edged sword. The primary cytotoxic T cells are CD8+ T cells. The pathogenic cytotoxic T cells from CD4+ T cells are also reported in severe patient therapy. These cytotoxic T cells can destroy viruses but also help to damage the lung. CD14+, CD16+ inflammatory monocytes displayed a high expression of IL-6, which probably speeds up systemic inflammatory responses [31].

The levels of certain traditional biochemical markers of acute infection, such as C-Reactive Protein (CRP) and ferritin (both positive acute phase reactants) have increased, on the other hand, persistent decrease in lymphocytes and a significant increase in neutrophils, apart from these, the release of dysfunctional cytokines was observed. As a result, the neutrophil-to-lymphocyte ratio can be useful in predicting illness prognosis and therapy. Critical COVID-19 individuals suffer Acute Respiratory Distress Syndrome (ARDS), Venous Thromboembolism (VTE), and multiple organ failure as a result of cytokine storm and coagulation hyperactivity in later stages.

This study aims to investigate the involvement of immunological inflammatory and coagulative biomarkers in the development of COVID-19 disease and to examine how their changing levels are associated with the severity of the sickness. This provides clinicians with a complete picture of their patients and anticipates diagnosis, treatment, and death. Furthermore, reducing the length of hospital stay and the high expense of therapy to the patient. This early prognosis will provide a great opportunity for the scientific community to conduct additional research.

Inflammatory Biomarkers

The main inflammatory biochemical and immunological biomarkers correlated with COVID-19 disease summarized are C-Reactive Protein (CRP), ESR (Erythrocyte Sedimentation Rate), serum Ferritin, PCT (Procalcitonin), Lactate Dehydrogenase (LDH), cytokines (IL-2, IL-6, IL-8, IL-10).

Cytokine Release Syndrome (CRS), an inflammatory immunological response that leads to organ failure, is characterized as extreme in COVID-19 [32]. COVID-19 and CRS are related to excessive interleukin IL-6 levels [33], which promotes the liver to stimulate both C-Reactive Protein (CRP) and the fibrinogen [34]. Lactate Dehydrogenase (LDH) and ferritin correlate with plasma levels of IL-6 in addition to CRP and fibrinogen. Serum LDH correlates in extreme and continual lung infections with IL-8 production with the aid of using lively macrophages and improved CD8+ cytotoxic T-cells [35]. The death of lymphocytes or direct tissue damage caused by pathogens, infections, or ischemia can cause elevated LDH levels. Studies found that an increase in risk and seriousness can be related to excessive baseline infection markers and higher CRS (Cytokine Release Strom) risk.

Cytokines (IL-2, IL-6, IL-8, IL-10)

Cytokines are polypeptide signaling molecules that regulate several biological processes *via* cell surface receptors. These cytokines include adaptive immunity participants (for example IL-2 and IL-4) and proinflammatory cytokines (ILs). Host cells produce cytokines with a highly significant function in cell metabolic reprogramming for defense mechanisms in response to internal stress-generating events (e.g., carcinoma or microbial infections) [36].

In the most severe situations, the prognosis of most pro-inflammatory cytokines, such IL-1, IL-6, IL-12, IFN-μ, and TNF-α, that selectively target lung tissue will be significantly exacerbated by hyperproduction. Several cohort researches found markedly multiplied levels of circulating proinflammatory cytokines and chemokines, considerably correlating to disease severity and mortality.

Cytokine Release Syndrome (CRS) is an immoderate immune response characterized by an overabundance use of pro-inflammatory mediators. This pathway roots several clinical disorders, including Acute Respiratory Distress Syndrome (ARDS) [37]. Understanding their function in COVID-19 can contribute to the event of new immunotherapies. Studies have shown that IL-6, the most prevalent cytokine produced by activated macrophages, is significantly increased in severe COVID-19 conditions [38]. A meta-analysis conducted by EA Coomes et al. had shown that mean IL-6 concentration was 2.9-fold higher in patients with complicated COVID-19 compared to those with the non-complicated condition [39]. Numerous investigations on patients with COVID-19 have reported aberrant levels of the Cytokine and Chemokines: IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, M-CSF, CGSF, G M-CSF, IP-10, IFN-μ, MCP-1, MIP 1-α, HFC (HGF), TNF-α and VEGF [40]. SARS-CoV-2, which in itself enhances proinflammatory cytokines, such as IL-6 and TNF-α appears to work upon activation and maturation of IL-1β, a constituent of the cytokine storm caused by infections with coronavirus [41]. Most COVID-19 patients have high IL-1β levels, with related SARS, hypercoagulation, and intravascular coagulation. Liu et al. also identified higher IL-1 α in severe COVID-19 patients, and this significantly leads to lung lesions [42]. Huang et al. in their studies found higher IL-2 and their IL-2R receptor levels in COVID-19 patients and this increase was claimed to be directly proportionate to the disease severity. Studies conducted by Wan et al. showed elevated IL-6 levels in 1/3 mild-symptomatic patients and 3/2 severely symptomatic patients, suggesting that, additionally to IL-10, IL-6 might be prognostic in COVID-19 patients [43]. High levels of IL-6 have also been shown to exacerbate the inflammatory process in COVID-19 patients, resulting in a cytokine storm, and deterioration of prognosis. In these individuals, cytokine storms and high levels of IL-6 are also associated with cardiac failure. Like other cytokines, levels of IL-10 were greater for COVID-19 patients than for SARS-CoV or MERS patients [44]. Elevated IL-4, IL-7, IL-12, IL-13, and IL-17 levels were associated with viral load and illness severity in patients with SARS-CoV-2 as part of the cytokine storm.

PCT (Procalcitonin)

PCT, a glycoprotein, is the calcitonin pro-peptide without hormonal action. They are generated in the thyroid gland C cells in normal conditions. PCT levels in healthy persons (<0.1 ng/mL) cannot be detected. The PCT levels primarily caused by extra-thyroid tissues may increase by more than 100 ng/ml during severe infections with systematic manifestations (bacterial) [45]. Although

the pharmacological activity of PCT is mostly unknown, sequences of PCT are consistent homologies with other human cytokines, such as TNF-α families, IL-6 families, etc. which supports the assumption that PCT is an inflammatory biomarker [46].

For COVID-19 patients, a significant rise of PCT in comparison with non-severe instances was observed with more severe cases. An important indicator to distinguish between SARS-CoV-2 positive and negative patients is a minor increase (with a significantly lower level of 0.5 ng/mL) in PCT levels [47] and approximately five times the risk of severe SARS-CoV-2 infection has been associated with the increase in PCT values.

PCT levels in patients with uncomplicated SARS-CoV-2 infection remain within reference limits, but any significant rise is indicative of bacterial co-infection and the development of a severe and more complex disease form [48]. Although the original PCT value can be beneficial to determine the severity of the disease, a predictive indication cannot always be appropriate. Existing co-morbid conditions, such as CKD (Chronic Kidney Disease) and congestive heart failure, might influence PCT levels, resulting in a high baseline value. PCT measurements can be employed to aid customize therapy, offer antibiotic prescriptions, and reduce drug exposure in patients with acute respiratory infections [49]. However, if examined within the therapeutic context, PCT can give useful information [50].

ESR (Erythrocyte Sedimentation Rate)

An ESR (Erythrocyte Sedimentation Rate) measures how fast the erythrocytes (red blood cells) sediment in the blood sample. Red blood cells usually settle down quite slowly. Inflammation in the body is possible by speeding up the usual sedimentation rate. ESR is a possible measure that indirectly analyses plasma protein levels, which are influenced by a range of illness circumstances. Because ESR is reliant on multiple proteins, the rate increases and decreases slowly as CRP concentrations rise and fall [51].

In addition, typical ESR levels are age- and sex-specific; the rate progressively increases with age and is higher in women than in males. While CRP measures show a significant benefit from ESR levels [52]. ESR has a negative influence on red blood cell size, form, concentration, and plasma features. The precise cause of the increased ESR remained unclear. Previous studies have hypothesized that COVID-19 may trigger a change in the form of erythrocytes or plasma properties, including the immune system, through an unknown ESR mechanism. The continuous high levels of ESR may harm the prognosis for COVID-19 patients, because high ESRs might damage the joints, leading to joint conditions such as arthritis [53]. Strangely, recent investigations have shown a substantial increase of ESR levels by around two weeks following diagnosis with COVID-19, with explanatory laboratory evidence. Therefore, COVID-19 can affect patients' long-term prognostic, but the long-term prognostics of COVID-19 patients are difficult to forecast based on ESR only. To resolve this situation, further diagnostic evaluations are required.

CRP (C Reactive Protein)

CRP (C Reactive Protein) is a liver-produced plasma protein that gets activated by different inflammatory mediators, such as IL-6. This acute phase reagent, while not specific, is clinically recognized as a biomarker for several inflammatory diseases; elevated CRP levels are linked to increased illness severity [54].

In other retrospective cohort studies, the probability of progression to severe COVID-19 disease increased by CRP>41.8 mg/L. Both studies demonstrate that CRP levels are a significant indicator of the presence and severity of COVID-19. Retrospective research by Chen et al. found that CRP levels were considerably greater in COVID-19 patients than in surviving patients [54].

Wang's additional analysis revealed that the increase in CRP is strongly related to the intensity and severity of COVID-19 [38]. Fang Liu's retrospective study of cohorts indicated a rise of about 65% in hospitalized COVID-19 patients and about 93.9% in severe COVID-19 patients. All three investigations indicated that the level of CRPs represents the severity of COVID-19 infection with robust biological indications. CRP becomes one of the first biomarkers of COVID-19 patients to demonstrate physiological complications.

Serum Amyloid A (SAA) is an acute-phase protein that increases in virus and bacterial infections along with CRP (C Reactive Protein). Although CRP and serum Amyloid A is employed to screen inflammatory diseases simultaneously, Serum Amyloid A should be further examined when used as a biomarker in COVID-19 patients [55].

CRP levels, on the other hand, were significantly higher in early phases of chronic cases when compared to Erythrocyte Sedimentation Rate (ESR), indicating that they were more sensitive biomarkers in reflecting illness progression [56]. As a result, CRP levels for early case severity diagnosis are more accurate in comparison with the CT scans alone.

Lactate Dehydrogenase (LDH)

The LDH (Lactate Dehydrogenase) enzyme turns pyruvate into lactate in glucose metabolism. The necrosis of the cell membrane, suggesting viral infection or lung injury, such as SARS-CoV-2 pneumonia, triggers LDH release [57]. There is considerable evidence that LDH is associated with COVID-19 disease [58].

Drent M et al. studies have consistently demonstrated that SARS-CoV-2 patients with high levels of LDH are more vulnerable to Acute Respiratory Distress Syndrome (ARDS) during their admissions. Yuan et al. reported a very high association of LDH levels with COVID-19-mRNA clearance [59]. As an inherently positive RNA virus, SARS-CoV-2 has been linked to inflammasome, cell pyroptosis, and aggressive symptoms, according to research. The association of LDH with ARDS (Acute Respiratory Disorder Syndrome) in COVID-19 patients can be explained in part. However, researchers discovered that 273 U/L was the best threshold for predicting ARDS. LDH was found to be significantly associated with ARDS, and the occurrence of ARDS was highly predictable [60]. A multicenter analysis of 1,099 patients confirmed the evidence of association of tissue damage and inflammation to increase in LDH levels [61]. Thus, the use of LDH as a biomarker to evaluate the severity of COVID-19 infection is more acceptable. A further investigation revealed that the LDH levels of persistent COVID-19 patients had significantly increased.

Serum Ferritin

Ferritin is an intracellular iron-blood protein, and its presence of multiple viruses or bacteria in the human body is associated with high levels of iron accumulation. Ferritin is a major modulator of dysregulation of immune systems, especially under severe hyper-ferritinemia, through the pro-immune and immunosuppressive actions of the cytokine storm. When ferritin levels begin to increase, there is likely to be a time bomb of inflammation. Many people with diabetes are experiencing high levels of serum ferritin, making them more vulnerable to COVID-19 complications [62]. Research has

shown that high levels of ferritin are associated with COVID-19 since 50% of the individuals with COVID-19 having particularly high levels of ferritin are deceased. According to this hypothesis, ferritin levels may be a significant biomarker influencing the severity of COVID-19. In another study of 20 individuals experiencing COVID-19, the serum ferritin levels were substantially greater in the extremely severe COVID-19 group than in the severe COVID-19 group, with a higher level of serum ferritin (1006.16 ng/ml *vs.* 291.13 ng/ml respectively). This has been supported by a recent study indicating that in patients admitted into the hospital and in patients who died of COVID-19 during the whole hospital stay, ferritin levels were high. Chen et al. examined 99 individuals with 63 folds serum ferritin much above from baseline, including clinical characteristics [63]. 12 autopsy patients who died of SARS-CoV-2 infection showed higher levels of serum ferritin [38]. The severity of COVID-19 was therefore closely connected to serum ferritin levels [64]. Laboratory results revealed that cytokine storms with high inflammatory signs, especially ferritin, comply with critical and life-threatening conditions, in patients with severe COVID-19 [65].

Coagulative Biomarkers

Coagulation is triggered when a serious infection occurs [66]. Several studies have discovered abnormal intravascular coagulation in COVID-19 patients' clinical and biochemical observations [67]. COVID-19 coagulopathy is characterized by an increase in D-dimer and fibrin/fibrinogen-degradation products, von Willebrand Factor (vWF), and prothrombin time prolongations [68-70], as well as an increase in some coagulation regulators like type 1 Plasminogen Activator Inhibitor 1 (PAI-1) and tissue-activating Plasminogen (tPA) [71]. Late presentations, show signs of a prolonged Prothrombin Time (PT) and activated Partial Thromboplastin (aPTT), as well as increased platelet and fibrinogen levels.

Because of the close association between cytokines and procoagulant biomarkers, a hypercoagulable state is produced, which has been linked to an increased risk of thrombotic events and mortality [72].

D-dimer

D-dimer is a fibrin degradation product, a minute protein fragment seen in the blood when a blood clot is broken down by fibrinolysis. It gets its name from the fact that it consists of two D fragments of the fibrin protein linked together by a cross-link. In the acute stage of COVID-19 patients, D-DIMER levels rise, which is associated with an increase in mortality. Among COVID-19 patients who died, Ning et al. observed higher levels of d-dimer [72]. Similarly, in a study of 1,099 COVID-19 patients, Guan et al. discovered that the d-dimer levels were substantially higher in non-survivors than in survivors [73]. Fei et al. discovered a greater amount of d-dimer (1 g/mL on admission) in 191 COVID-19 patients, which was linked to a high death rate [18]. According to Huang et al., COVID-19 patients with d-dimer values of 0.5 g/mL or above on arrival require critical care assistance. Huang et al. also reported that D-dimer levels on admission may be used to categorize patients into critical care. The researchers discovered that median D-dimer levels in ICU patients were higher than in non-ICU patients (2.4 mg/L *vs.* 0.5 mg/L). This study, along with the preceding one, shows that D-dimer levels can be used as a prognostic biomarker, allowing doctors to identify patients with the worse condition.

Partial Thromboplastin Time (PTT) and Prothrombin Time (PT)

PT (Prothrombin Time) and PTT (Partial Prothrombin Time) are coagulating factors that define blood coagulation and these variables can also be used to make an early diagnosis of DIC (Disseminated Intravascular Coagulation) [74]. Prothrombin, which is proteolytically broken to generate thrombin, functions as a serine protease, converting fibrinogen to fibrin. Prothrombin overexpression is linked to increased plasma thrombin, which causes coagulation activation and thrombosis. These factors are used to track bleeding issues [75].

Long et al. discovered that hypercoagulation is more common in COVID-19 patients in the early stages and has been linked to disease progression and poor clinical outcomes [76].

In COVID-19 patients, the coagulation mechanism is disrupted, resulting in a prolonged PT test time, which is related to illness outcome.

The Partial Thromboplastin Time (PTT) also called activated Partial Thromboplastin Time (aPTT) is a screening test that assesses an individual's capability to produce blood clots. It quantifies the time taken for a clot to develop in a blood sample. The PTT measures the quantity and performance of coagulation or clotting factors, which are proteins found within the blood.

PTT is employed to assess coagulation factors XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen), as well as Prekallikrein (PK) and high molecular weight kininogen (HK). The coagulation factors VII, X, V, II, and I are all evaluated by a PT test. These variables may also be used to make an early Diagnosis of DIC [75,77]. Coagulation dysfunction is one of the major reasons for mortality in COVID-19 patients [76] and has been linked to higher cardiac damage and death rates, according to research. As a result, coagulation-related indicators should be investigated (PT, aPTT) [78].

Long et al. demonstrated that hypercoagulation is possibly seen in COVID-19 patients in the initial stages. Hypercoagulation has been linked to disease progression and poor clinical outcomes [73]. Chen's research of 99 COVID-19 patients revealed that coagulation markers like aPTT and Prothrombin (PT) were increased by 6% and 5%, respectively [75].

In COVID-19 patients, the coagulation mechanism is disrupted, resulting in a prolonged PT test time that is related to disease severity [38].

D – Dimer and Prothrombin Time

D-dimer and PT levels were measured in COVID-19 patients to see whether they might predict a poorer outcome, which was defined as the development of ARDS, ICU hospitalization, and mortality [79]. In a study of 201 patients, Wu et al. discovered that PT and D-dimer levels were strongly related to the development of ARDS. Patients who got ARDS and died had considerably greater coagulation indices than those who survived. Perlman et al. and Han et al. both found that D-dimer and fibrin/fibrinogen breakdown products were substantially greater in moderate illness than in severe disease [80]. Han et al. discovered no evidence of a link between PT and illness severity, reporting no differences in PT, aPTT, and PT-International Normalized Ratio (INR) levels between the mild, severe, and control groups [81]. Zhang et al. discovered that a D-dimer level of 2.0 g/mL on admission was the diagnostic cut-off for predicting COVID-19

in nosocomial mortality [70]. Huang et al. observed that D-dimer levels on admission were greater in ICU patients than in non-ICU patients, leading them to infer that D-dimer might be used to triage patients into critical care [74]. Although a few studies have shown that D-dimer has poorer predictive accuracy than CRP assessment of coagulation indices in the prognosis of COVID-19 patients have shown that PT and D-dimer are the best biomarkers of a severe disease course.

vWF Factor (Von Willebrand Factor)

vWF is a multimeric glycoprotein molecule that has a role in inflammation as well as primary and secondary hemostasis. The virus entering into the endothelium cell may contribute to inflammation and damage by triggering the release of prothrombotic mediators such as vWF, which is stored in the Weibel-Palade storage bodies, as well as exposing underlying collagen to which vWF binds [82]. According to studies, high levels of vWF antigen and activity have been clinically linked to poor outcomes. The severity of a COVID-19 infection appears to decrease molecules that control vWF levels and activity, such as ADAMT-13 (A Disintegrin and Metalloproteinase with Thrombospondin type I motif, member 13) and High-Density Lipoproteins (HDL) [83]. More research is needed, however, to fully understand the significance of vWF. High circulating vWF levels have been reported in patients with severe COVID-19 infection. The high levels of vWF enhance its interaction with circulating platelets and damaged endothelium leading to a prothrombotic state. Accumulation of neutrophils in the lung vasculature contributes to the damage. VWF and Fibrin interactions with NETs (Norepinephrine Transporters) are key mechanisms in the intricate relation between the coagulation system and the innate immune system called immunothrombosis [84].

VWF plasma concentrations were substantially greater in the severe COVID-19 group (153.5 24.3 UI/dL) and Death group (149.8 17 UI/dL) as compared to non-severe COVID-19 (133.9 20.18 UI/dL) and healthy donors (98.9 20.7 UI/dL), with concentrations increasing with disease severity [85].

Fibrinolysis and Pai-1

Reduced fibrinolysis has been seen in individuals with severe COVID-19, and high VTE (Venous thromboembolism) occurs in patients with more severe clot dissolution abnormalities [86]. The combination of high D-dimer (a fibrinolytic marker) with hypo-fibrinolysis has been attributed to changes in systemic and local effects or the fibrinolytic system being overburdened [87,88]. The fibrinolytic inhibitor Plasminogen Activator Inhibitor 1 (PAI-1) is elevated in COVID-19, SARS-CoV-1 infection, and other causes of ARDS with hypo-fibrinolysis and fibrin deposition. Inflammation causes endothelial cells to produce PAI-1, which prevents urokinase-plasminogen activator and tissue-type Plasminogen Activator (tPA) from converting plasminogen to plasmin, resulting in decreased fibrin breakdown [89]. PAI-I levels are elevated in both ICU and non-ICU COVID-19 patients, indicating a role in disease pathophysiology and development that is not limited to acute respiratory distress syndrome [90].

During sepsis, tissue factor is upregulated, which causes anti-thrombin to be downregulated, increasing plasma thrombin. At the same time, endothelial injury promotes the production of anti-fibrinolytic mediators such as PAI-1 and inhibits fibrinolysis further, resulting in fibrin accumulation in the intra-alveolar region. All of these alterations, when combined, result in a hypercoagulable condition, which is also observed in COVID-19 [85].

Platelets

According to research, severe hematological alterations have been linked to thrombocytopenia in COVID-19 patients. A meta-analysis of 2361 patients found that 13% to 61% of individuals with severe COVID-19 infections had thrombocytopenia and thrombocytosis [91]. Another meta-analysis of 1,799 individuals found that patients with severe COVID-19 had substantially lower platelet counts [92]. A retrospective cohort study of 52 COVID-19 patients discovered that increased platelet levels were the most common indicator of infection in the severe group [93]. Platelet counts, however, have not been proven to be a predictor of COVID-19 mortality in all investigations [94]. According to Yin et al., individuals with COVID-19 disease had higher platelet counts than those with severe pneumonia but no COVID-19 illness [95]. A consistent decline in platelet counts in COVID-19 patients might indicate a deteriorating thrombotic condition [96,97].

Conclusion

COVID-19 is causing a pandemic that is impacting people all over the nation. Current management is to prevent the viral spread and offer supportive care for ill individuals in the absence of basic therapeutic approaches. There is a critical need for the development of focused medicines. Understanding the responses of biomarkers such as inflammatory and coagulative responses may aid in targeting the immune-based treatments.

According to research, increased CRP levels in COVID conditions cause an overproduction of cytokines, resulting in a cytokine storm (IL's) and serious COVID condition. PCT levels, on the other hand, were eight times higher in severe patients and moderate in mild patients. Patients with SARS-CoV-2 who have high ferritin and LDH levels are more likely to die and are more sensitive to Acute Respiratory Distress Syndrome, whereas a PTT and Prothrombin (PT) levels were raised by 6% and 5% respectively coupled with higher ESR values. COVID-19 patients had greater levels of d-dimer, which is connected to a high mortality rate. Individuals with COVID-19 exhibited significantly increased Vwf and PAI-I levels. Only a consistent decline in platelet count is observed in COVID-19 individuals among all of them. Therefore, biomarkers play an important role in understanding the severity of the patients, which will therefore help us in categorizing patients into ICU and non-ICU/ critical or non-critical patients.

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