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Review Article



Effect of COVID-19 on c-reactive protein and d-dimer

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Abstract

Since December 2019, the International Committee on Taxonomy of Viruses (ICTV) has formally designated a novel human coronavirus found in Wuhan, China, as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new RNA virus strain that belongs to the beta-coronavirus 2b families in the evolutionary tree. COVID-19 had a reported overall case-fatality rate (CFR) of 2.3 percent by this time, while cases in those aged 70 to 79 years had an 8.0 percent CFR and cases in those aged 80 and above had a 14.8 percent CFR. Severe pulmonary and extrapulmonary problems can result in respiratory failure and life-threatening events in certain individuals. D-dimer levels were found to be elevated in nearly half of the patients, and aberrant D-dimer levels are linked to a bad prognosis. As a result, in some stable individuals who die suddenly, acute organ failure, embolism, and infarction should be considered. Although the incidence of thrombosis in COVID-19 patients has not been identified, deep vein thrombosis (DVT) and pulmonary embolism (PE) were found to be 20.5 percent and 11.4 percent in SARS cases, respectively.

Keywords COVID-19, C- reactive protein, D-dimer, Coronavirus, Respiratory Disease.

Introduction

Since December 2019, the International Committee on Taxonomy of Viruses (ICTV) has formally designated a novel human coronavirus found in Wuhan, China, as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020). SARS-CoV-2 is a new RNA virus strain that belongs to the beta-coronavirus 2b families in the evolutionary tree (Tan et al., 2020; Ranjan et al., 2020). SARS-CoV-2 has just been dubbed COVID-19 (coronavirus disease 2019) by the World Health Organization (WHO). Globally, the number of infected patients is quickly increasing and has now surpassed 100,000.

The clinical features of COVID-19 patients have been examined in earlier publications (Wang et al., 2020). COVID-19 is characterized by lower respiratory symptoms such as fever, dry cough, and dyspnea, which are comparable to the symptoms of two other coronavirus illnesses, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (Tsang et al., 2003; Assiri et al., 2013). COVID-19 had a reported overall case-fatality rate (CFR) of

2.3 percent by this time, while cases in those aged 70 to 79 years had an 8.0 percent CFR and cases in those aged 80 and above had a 14.8 percent CFR (Wu & McGogon, 2020). Severe pulmonary and extrapulmonary problems can result in respiratory failure and life-threatening events in certain individuals. D-dimer levels were found to be elevated in nearly half of the patients, and aberrant D-dimer levels are linked to a bad prognosis (Guan et al., 2020; Tang et al., 2020). As a result, in some stable individuals who die suddenly, acute organ failure, embolism, and infarction should be considered. Although the incidence of thrombosis in COVID-19 patients has not been identified, deep vein thrombosis (DVT) and pulmonary embolism (PE) were found to be 20.5 percent and 11.4 percent in SARS cases, respectively (Chong et al., 2004). In addition, pathologic investigations based on autopsies or biopsies revealed the development of thromboembolisms, which closely resembled the symptoms of SARS and MERS coronavirus infection (Xu et al., 2020; Lang et al., 2003). Traditional anticoagulation, on the other hand, may need to be carefully evaluated because individuals with COVID-19 have a higher risk of bleeding (Mao et al., 2020). As a result of our expertise, biomarkers that may detect thrombus development at an earlier stage

might be utilized to assess thrombus formation and therapy response.

D-dimers are fibrin degradation products that have been demonstrated to be useful in a clinical decision rule for excluding pulmonary embolism (Van Belle et al., 2006), emphasizing their potential as a valuable biomarker. However, the connection between D-dimer and COVID-19, as well as variations in level throughout illness progression, has not been extensively explored. In this study, we compared COVID-19 patients' D-dimer levels to those of patients with bacterial pneumonia, evaluated the use of successive D-dimer levels after admission to the hospital, and looked at the relationship between inflammatory markers and D-dimer levels.

Coronavirus disease-19 (COVID-19)

Coronaviruses are spheroidal, single-stranded RNA viruses with a diameter of 80–220 nm. Transmission of SARS-CoV-2 occurs either through exposure to micro-droplets from infected individuals or by contact transmission through contaminated fomites. The virus reaches the smaller airways and alveoli and targets the bronchial and alveolar epithelial cells.

The spike surface glycoprotein (S) of the virus binds to angiotensin-converting enzyme 2 (ACE-2), a membrane carboxypeptidase present in distal airways and alveoli, especially type 2 pneumocytes which have the highest expression of ACE-2, along with alveolar macrophages and dendritic cells. ACE-2 is also expressed on the vascular endothelium, nasal, oral, nasopharyngeal, and oropharyngeal epithelia, gut epithelia, cardiac pericytes, renal proximal tubular cells, and in the skin, reticuloendothelial, and the central nervous system (Bal et al., 2020). ACE-2 expression depends on age, gender, genetic factors, and presence of comorbid conditions such as obesity, chronic cardiopulmonary disease, cancer, and use of immunosuppressive drugs.

Renin cleaves angiotensinogen to produce angiotensin I which is further cleaved by ACE to produce angiotensin II having a dual role. Action through AT1R (angiotensin II type 1 receptor), facilitates vasoconstriction, fibrotic remodeling, and inflammation, while that through AT2R (angiotensin II type 2 receptor) leads to vasodilation and growth inhibition. Angiotensin II is cleaved by ACE2 to Ang 1–7 which counteracts the harmful effects of the ACE/Ang II/AT1 axis. Thus ACE2 primarily plays the main role to physiologically counterbalance ACE and regulate angiotensin II. Internalization of the ACE-2 after viral interaction leads to its downregulation and consequent upregulation of angiotensin II. The latter acting through AT1R, activates the downstream inflammatory pathways, leading to the "cytokine storm" that adversely affects multiple organs (D'ardes et al., 2020).

The alveolar epithelial cells, lymphocytes, and vascular endothelial cells are the primary targets of the virions. The virus inhibits the production of interferons that are part of cellular defense mechanisms. Viral replication releases a large number of virions leading to infection of neighboring target cells and viremia, which then cause an exaggerated pulmonary

and systemic inflammatory response respectively. This explains the clinical presentation of severe COVID-19 which is predominated by ARDS, shock, and coagulopathy.

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 (WHO, 2020). It was declared a pandemic on March 11, 2020. As of December 9, 2020, there are more than 67 million cases worldwide with more than 1.5 million deaths (WHO, 2020).

In adults, though SARS-CoV-2 typically causes pneumonia and acute respiratory distress syndrome (ARDS), it is now being recognized as a multisystem disease. In contrast, most children are asymptomatic or have mild to moderate illness. Severe or critical illness is rare (Ding et al., 2020; Cui et al., 2021). A novel illness, termed multisystem inflammatory syndrome in children (MIS-C) is being increasingly reported in children. Children with MIS-C are sicker, may have multiorgan dysfunction, and often require intensive care (Singh-Garewal et al., 2020; Feldstein et al., 2020; Davies et al., 2020; Dhanalakshmi et al., 2020).

Direct identification of SARS-CoV-2 nucleic acids in respiratory tract specimens with a polymerase chain reaction (PCR) confirms the diagnosis of COVID-19 (Hanson et al., 2020). The patient, the healthcare facility, and public health and administrative employees all benefit from a quick and correct diagnosis. 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.

Despite the burgeoning COVID-19 literature database, the treating clinician must be effectively updated to offer the best care at the bedside. This review attempts to provide updated and practical information to clinicians on the role of biomarkers in COVID-19.

Novel biomarkers of COVID-19

Hematological parameters

Hemoglobin

In a retrospective study, anemia and altered iron homeostasis were common in hospitalized COVID-19 patients. Initial anemia was associated with increased mortality, and a higher ferritin/transferrin ratio predicted the need for ICU admission and mechanical ventilation (Bellmann et al., 2020).

Lymphocytes

Peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced in early disease when symptoms tend to be non-specific (Terpos et al., 2020). Approximately 7 to 14 days from the onset of symptoms, the appearance of significant lymphopenia coincides with worsening clinical status, increase in inflammatory mediators, and "cytokine storm."

Lymphocytopenia is directly correlated with disease severity and death. Lymphopenia on admission (defined as lymphocyte count $\leq 1,100$ cells/ μ l) is associated with a three-fold risk of poor outcomes, in younger as compared to older patients (Terpos et al., 2020). Lymphocyte counts were lower in patients with ARDS, severe disease requiring ICU care, and in non-survivors (Huang & Pranta, 2020). A temporal model based on lymphocyte counts at two-time points showed that patients with $<20\%$ and $<5\%$ lymphocytes at days 10–12 and 17–19 from the onset of symptoms respectively had the worst prognosis (Tan et al., 2020).

Severe disease was also characterized by a marked reduction in the absolute number of circulating CD4+ cells, CD8+ cells, B cells, and natural killers (NK) cells.; plasma cells are remarkably increased (Catanzaro et al., 2020; Liu et al., 2020). The highest values of inflammatory parameters firmly correlated with the decrease in CD8 T-cells, an effect that was not seen with CD4 cells (Urta et al., 2020).

Neutrophils

Patients who require admission to the ICU had a higher percentage and an absolute number of neutrophils (Urta et al., 2020).

Eosinophils

A low percentage of eosinophils and airway and serum eosinophil-derived neurotoxin (EDN-1) can be a potential biomarker of COVID pneumonia (Yang et al., 2020; Dosanjh, 2020). However further studies are required to correlate EDN-1 with clinical, radiographic, and physiological parameters (Dosanjh, 2020).

Monocytes and basophils

Monocytes and basophils are also decreased akin to lymphocytes and eosinophils.

Platelets

Both thrombocytopenia and thrombocytosis have been observed. However severe thrombocytopenia and bleeding are uncommon (Amgalan & Othman, 2020). Thrombocytopenia was found to correlate with other coagulation parameters and increased risk of mortality (Bao et al., 2020).

Composite hematological markers

Putting it all together it is clear that severe COVID-19 disease is associated with significantly increased leukocytes,

neutrophils, infection biomarkers (such as CRP, PCT and ferritin) and cytokine levels (IL-2R, IL-6, IL-8, IL-10 and tumor necrosis factor (TNF)- α) and decreased lymphocyte counts (Dosanjh, 2020).

IL-2R levels correlated positively with the other cytokines and negatively with lymphocyte number. An elevated IL-2R to lymphocytes ratio was discriminative of severe and critical condition. In fact this ratio was superior to other markers for differentiation of critical illness. The ratio was significantly decreased in recovered patients, but further increased in patients who deteriorated, thus correlating with the outcome (Hou et al., 2020).

Zheng et al. devised a score based on the neutrophil, lymphocyte and platelet counts, with an "NLP score" of >6 , predicting progression to severe disease (Zheng et al., 2020). A high neutrophil-to-lymphocyte ratio (NLR) at admission can be a good surrogate marker for diagnosis of COVID-19. A rising NLR can also be used as a prognostic marker for predicting poor outcomes (Yan et al., 2019; Ma et al., 2020). Another prognostic marker the lymphocyte-to-CRP ratio (LCR), used in several types of cancers, may also be helpful. A meta-analysis on six studies concluded that a rise in the NLR and decline in LCR correlates with the severity of COVID-19 (Layuanas-Rangel, 2020). Specifically, a low LCR at presentation was seen to predict ICU admission and need for invasive ventilation.

Inflammatory parameters

CRP and procalcitonin

In a study, CRP was elevated in 60.7% of patients, procalcitonin (PCT) in 5.5%, and lactate dehydrogenase (LDH) in 41% of patients (Guan et al., 2020). A cut-off of >10 mg/L and >0.5 ng/ml for CRP and PCT respectively are predictors of poor outcomes (Huang et al., 2020). A retrospective study showed that a CRP level of 26 mg/L could serve as a cut-off to predict progression to severe disease (Wang et al., 2020). A meta-analysis showed that elevated PCT values were associated with a nearly 5-fold higher risk of severe infection (Lippi & Plebani, 2020).

Cytokines

IL-6 is dramatically increased in COVID-19 patients. More than half of admitted patients were found to have elevated IL-6 levels (Chen et al., 2020). Higher baseline IL-6 correlated with severity, bilateral interstitial lung involvement, and other acute inflammatory markers (Liu et al., 2020). Furthermore, IL 6 is good to monitor therapeutic response. Other pro-inflammatory cytokines (IL-1 β , IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP-10, MCP-1, CCL3, and TNF α) are significantly increased in patients with severe disease (Catanzaro et al., 2020).

Biochemical parameters

Serum albumin

Hypoalbuminemia in critically ill patients is multifactorial and is attributed to increased capillary permeability, decreased protein synthesis, increased turnover, decreased serum albumin total mass, increased volume of distribution, and increased expression of vascular endothelial growth factor. Although common, the exact temporal association of hypoalbuminemia is yet to be studied (Aziz et al., 2020).

In COVID 19 disease a similar trend was found; a meta-analysis of 11 studies showed that the mean serum albumin on admission was 3.50 g/dl and 4.05 g/dl in severe and non-severe COVID-19, respectively (Aziz et al., 2020).

LDH

About 40% of patients presented with increased LDH levels. Elevated LDH has been associated with a higher risk of ARDS, need for intensive care, and mortality (Terpos et al. 2020).

Urine biochemical parameters

Urine biochemical parameters have been studied to predict the severity of the disease. The positive rates of urine glucose and protein were higher in the severe and critical groups compared to those in the moderate group. Urine occult blood and specific gravity were not associated with the severity (Liu et al., 2020).

D- dimer as a parameter for COVID-19

D-dimer levels were shown to be elevated in a small number of investigations including SARS and CAP patients (Hui et al., 2003; Snijders et al., 2012; Salluh et al., 2011; Agapakis et al., 2010). COVID-19 patients' D-dimer levels were likewise high in our research, as they were in SARS and CAP patients. Only a portion of the reasons for the increased D-dimer levels has been elucidated. D-dimers are generated during the breakdown of fibrin and are used as a marker of fibrinolytic activity. In critical patients or patients with sepsis, a link between proinflammatory cytokines and indicators of coagulation cascade activation, such as D-dimer, has been discovered (Shorr et al., 2002; Pettila et al., 2002). There is additional evidence that in inflammatory circumstances, the alveolar hemostatic balance shifts toward a prothrombotic activity preponderance (Gunther et al., 2000). In individuals with severe sepsis, pro-inflammatory cytokines may also have a role in endothelial damage, as well as activating coagulation and inhibiting fibrinolysis (Bone et al., 1997).

One issue that must be overlooked is that patients with COVID-19 have greater D-dimer levels when their CRP levels are lower than CAP patients. This strongly implies that additional variables, other than inflammation, are involved in the activation of the coagulation system in COVID-19 individuals. In a prior investigation (Gralinsk et al., 2013), Gralinski *et al.* looked into viral pathogenesis and discovered a new host route that plays a role in SARS development.

Their findings show that during SARS-coronavirus infection, deregulation of the urokinase pathway contributes to more severe lung disease and significant changes in the systemic haemostatic balance.

The prevention and management of thrombus should be considered while treating COVID-19 patients. Reactive thrombocytosis was found in 4% of patients, which might be linked to an increased risk of thrombus formation (Dhanalakshmi, et al., 2020). Furthermore, patients with COVID-19 may have increased blood viscosity due to high fever and excessive sweating, as well as a hypercoagulable state due to coagulation system activation (Hanson et al., 2020), which, when combined with risk factors such as long-term bed rest, obesity, and old age, increases the risk of thrombus. The diagnostic relevance of D-dimer levels in COVID-19 patients for thrombus development is unknown. It's worth debating whether greater D-dimer levels in COVID-19 patients indicate the necessity for more severe anticoagulant treatment.

Previous research found elevated D-dimer levels in patients with CAP, which were comparable to those found in patients with pulmonary embolism, lowering the test's reliability in the differential diagnosis of CAP and pulmonary embolism (Bellmann-Weiler et al., 2020).

Polymerase chain reaction (PCR) for COVID-19

There has been a lack of guidance for practicing physicians in interpreting published evidence and limitations of emerging lab tests for coronavirus disease 2019 (COVID-19). Current diagnosis requires a combination of symptoms/signs of respiratory infection and a positive reverse-transcriptase polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) (Huang et al., 2020; Li et al., 2020; Zhou et al., 2020; Corman et al., 2020). The Chinese Centers for Disease Control and Prevention (China CDC) first submitted the SARS-CoV-2 genome to Global Initiative on Sharing All Influenza Data. The CDC in the United States (U.S.) then obtained emergency use authorization (EUA) from the Food and Drug Administration (FDA) for the first RT-PCR (Mustafa et al., 2020). Tests were limited to the CDC, but later extended to other agencies and Clinical Laboratory Improvement Amendments (CLIA) certified labs for rapid diagnosis to interrupt the transmission cycle via quick isolation (Patel & Jernigan, 2020) With increasing EUAs, careful considerations are necessary to interpret test results (Caliendo et al., 2013; Petherick, 2020)

While RT-PCR is the current gold standard for the laboratory diagnosis of COVID-19, potential pre-analytical (ineffective symptom screening, sampling errors, prolonged transportation time, sample contamination, etc.) and analytical errors (insufficient sample, non-validated tests, instrument malfunction, testing out of the diagnostic window, viral RNA recombination, etc.) that compromise the results should be kept in mind (Tang et al., 2020; Lippi et al., 2020).

While a false positive result may result in wasteful use of health care and public health resources, a false negative could lead to failure of isolation and foster community spread (Lippi et al., 2020). If SARS CoV-2 RNA quantity is below the threshold of RT-PCR analytical sensitivity (very early symptomatic or post-symptomatic/recovery), then results will be reported as negative, emphasizing the importance of appropriate sample collection technique and transport. The CDC has published clear guidelines for appropriate collection. In contrast to SARS CoV infection (SARS 2002–2003) where RT-PCR sensitivity was low during the early symptomatic period, early shedding (pre- or early symptomatic phase of illness) of SARS CoV-2 virions is remarkable in COVID-19, accounting for its rapid spread in pandemic proportions (Walfel et al., 2020; He et al., 2020). Like other viral illnesses, the shedding of infectious SARS CoV-2 virions is also suspected to drop over time from the onset of illness, but data is insufficient at this time (To et al., 2020). Wolfel et al. evaluated SARS CoV-2 replication by assessing sub-genomic RNA (a marker of replication) from the serial throat, sputum, blood, and fecal samples in nine mildly symptomatic COVID-19 patients (Walfel et al., 2020). They noticed early viral replication in throat and sputum samples that lasted for almost two weeks beyond the symptomatic period. Hence, RTPCR from naso- or oropharyngeal samples will continue to remain as the reference standard for diagnosis during the acute phase of COVID-19.

Conclusion

Direct identification of SARS-CoV-2 nucleic acids in respiratory tract specimens with a polymerase chain reaction (PCR) confirms the diagnosis of COVID-19 (Hanson et al., 2020). The patient, the healthcare facility, and public health and administrative employees all benefit from a quick and correct diagnosis. 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.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that they have consent for publication.

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