Abstract

The direct and precise diagnosis of COVID-19 is vital. Symptoms alone are insufficient as various infections manifest comparable COVID-19 symptoms, such as swollen lymph nodes, cough, fever, and fatigue. Thus, health care personnel’s functional knowledge of SARS-CoV-2 infection biomarker levels is imperative in containing the spread of and managing the disease. The immediate detection and interpretation of SARS-CoV-2 infection biomarker levels aid medical personnel in better predicting the disease’s severity and allotting limited resources. Two important biomarkers regarding more severe prognoses of SARS-CoV-2 are inflammatory and blood coagulation biomarkers.

Most patients who have contracted a SARS-CoV-2 infection feel fatigued with fever and cough. Thus, physicians should examine biomarkers (e.g., hematological biomarkers, cytokines, liver enzymes, and coagulation parameters) in differential diagnosis and treatment. The virus employs its spike proteins to bind to ACE2 molecules and capture them as if they were a cell surface receptor, undergoing consequent endocytosis. In severe cases, the virus provokes an extensive inflammatory response, resulting in a cytokine storm. The heightened presence of thrombosis and D-dimer levels intimates the complement system’s involvement in response to a SARS-CoV-2 infection. The most critical biomarkers are a significant decrease in lymphocytes and increases in C-reactive protein, D-dimer, cardiac troponin, ferritin, and interleukin-6.

Keywords: Azithromycin; C-Reactive Protein; D-Dimer; Ferritin; Obesity; Respiratory Tract

Abbreviations

ACE2: Angiotensin-Converting Enzyme 2; ARDS: Acute Respiratory Distress Syndrome; CAD: Coronary Artery Disease; CFR: Case Fatality Rate; COPD: Chronic Obstructive Pulmonary Disease; Case Fatality Rate; CQ: Chloroquine; CRP: C-Reactive Protein; cTnI: Cardiac Troponin I; HCQ: Hydroxychloroquine; ICU: Intensive Care Unit; IL-6: Interleukin-6; IR: Incidence Rate; PCR: Polymerase Chain Reaction; RT-qPCR Quantitative Fluorescence-based Reverse Transcription Polymerase Chain Reaction; TTCR: Time to Clinical Recovery

Introduction

The early detection and analysis of biomarker levels allow medical personnel and hospitals to anticipate the potential severity of SARS-CoV-2 infections [1]. Inflammatory and blood coagulation biomarkers are two of the most significant biomarkers associated with severe...
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It is essential to study the most prevalent biomarkers for SARS-CoV-2 as its overall symptoms overlap with several other diseases [3]. The early detection and analysis of biomarker levels will allow medical and hospital personnel to anticipate the potential severity of the disease in considering the course of treatment and allotment of limited resources. Most COVID-19 biomarkers are upregulated, especially in severe cases, with white blood cell count being downregulated [4].

The exact cause and mechanism of lymphopenia in COVID-19 are not yet understood; however, they appear related to the increased inflammatory response and cytokine storm in severe COVID-19 infections. Lymphatic organs may be destroyed in the course of a SARS-CoV-2 infection, although that has not been found among the viral infection’s main effects thus far [5].

COVID-19 is an infection of distinct phases or stages: 1) the initial stage involves lung tissue infection and a vigorous inflammatory reaction; 2) if untreated, unsuccessfully treated, or in an inadequate host immune response, the initial stage progresses to the next stage, mainly occurring in individuals with comorbidities, such as advanced age or metabolic disorders. Moreover, during the inflammatory reaction, blood coagulation can often be observed [6]. (It is noteworthy to consider that not all treatment regimens for COVID-19 work equally well for all stages of the infection in all individuals [7]).

The more severe cases of COVID-19 are associated with infection and inflammation of the respiratory tract. C-reactive protein (CRP) is upregulated in more severe cases. Also, D-dimer is elevated in severe infections. These two elevated findings are consistent with an accumulation of blood clots in the lungs and other organs in severe COVID-19 cases [8].

Discussion

Biochemical sequelae of SARS-CoV-2 infection

Researchers have observed endothelial deposits of complement system components between alveoli, suggesting that the increase of thrombosis and D-dimers’ presence signifies complement systems is involved in response to a SARS-CoV-2 infection. The elevation of interleukin-6 (IL-6) in SARS-CoV-2 infections results from the induction of an inflammatory reaction [9].

As mentioned before, there are stages to SARS-CoV-2 infection. The initial stage resembles a typical viral infection, affecting the respiratory epithelium’s cells first and foremost. The virus uses its spike proteins to bind to angiotensin-converting enzyme 2 (ACE2) molecules and hijacks them as if they were a cell surface receptor, undergoing subsequent endocytosis [10]. A further stage of the infection regards the virus inducing a widespread inflammatory response, which in some cases results in a cytokine storm.

Notably, the virus infection also provokes thromboses within the lung’s blood vessels, as seen in several biomarkers discussed above. In autopsies of patients that died from a COVID-19 infection, researchers found local accumulations of megakaryocytes (cells that secrete platelets and therefore aid the coagulation process) in the lungs. The resulting local thromboses can lead to further destruction of lung tissue and ultimately cause death, as optimal blood circulation is not assured throughout the respiratory system [11].

COVID-19 biomarkers

Two of the most critical tasks for health care personnel are identifying the disease and correctly diagnosing a patient. Visible symptoms alone are insufficient since several infections present with similar symptoms, such as swollen lymph nodes, cough, fever, and fatigue. Even tropical diseases that may seem exotic to the Western world have many overlapping features. The immune system responds to pathogens, including protozoans, bacteria, fungi, parasites, and viruses—this interaction often resulting in an inflammatory response. Therefore, various infections may seem similar in presentation to SARS-CoV-2 infection [12]. The correct identification of a specific disease by combining characteristic symptoms is of paramount importance, especially since comorbidities in patients can obscure specific disease conditions.
In COVID-19, several specific biomarkers have been identified [13]. Most patients that have contracted a SARS-CoV-2 infection feel fatigued with fever and cough. Thus, physicians should consider several markers, e.g., hematological biomarkers, cytokines, liver enzymes, and coagulation parameters. Eventually, antibody tests and, more so, quantitative fluorescence-based reverse transcription-polymerase chain reaction (RT-qPCR) will reveal exactly if a patient has been infected with SARS-CoV-2 [13].

The early detection and analysis of biomarker levels allow medical personnel and hospitals to predict the potential severity of the disease. Thus, the lab workup should be done on all suspected cases of COVID-19. The most critical biomarkers determining the disease’s severity are a significant reduction in lymphocyte number, elevation in C-reactive protein (CRP), D-dimers, cardiac troponin, ferritin, and IL-6. Table 1 shows an overview of the most critical biomarkers as displayed in Velavan and Meyer (2020) [14], together with a change of concentration in infected patients and the SARS-CoV-2 case number with a percentage of severe cases [13].

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Concentration</th>
<th>CoV-2 infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count</td>
<td>Downregulated in most cases</td>
<td>n = 268 cases, 47.3% severe</td>
</tr>
<tr>
<td>CRP</td>
<td>Upregulated, esp. severe cases</td>
<td>n = 446 cases, 32.1% severe</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Upregulated, esp. severe cases</td>
<td>n = 198 cases, 50.5% severe</td>
</tr>
<tr>
<td>Cardiac troponin I</td>
<td>Upregulated in severe cases</td>
<td>n = 491 cases, 29.9% severe</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Upregulated in severe cases</td>
<td>n = 150 cases, 45.3% severe</td>
</tr>
<tr>
<td>IL-6</td>
<td>Upregulated in severe cases</td>
<td>n = 177 cases, 67.2% severe</td>
</tr>
</tbody>
</table>

Table 1: Biomarkers used in predicting the severity of COVID-19 disease progression. Adapted from Velavan and Meyer (2020) [14].

Lymphopenia

Tan., et al. (2020) found that the lymphocyte percentage in the blood decreases with the progression of the CoV-2 infection. Moreover, autopsies of COVID-19 patients revealed massive cell death of lymphocytes within the lymphatic system’s organs [13]. COVID-19 patients requiring relocation to the intensive care unit (ICU) frequently exhibit significantly reduced CD8 T cell count [15].

The exact causes and mechanisms of lymphopenia are not yet wholly understood; however, they are likely connected to the increased inflammatory response and cytokine storm in severe COVID-19 infections. Furthermore, lymphocytes carry the ACE2 cell surface molecule and could be actual targets of the virus, which might then kill. Lymphatic organs may be destroyed in the course of a SARS-CoV-2 infection, although that has not been found among the viral infection’s main effects so far. The inflammatory state and cytokine storm may also lead to the destruction of T-cells and other lymphocytes [13].

C-reactive protein (CRP)

CRP is a standard biomarker for inflammation, being upregulated at infection sites. CRP is produced as a homopentameric protein, which dissociates into monomeric units at its target sites. It takes part in regulating and modulating the immune response [16]. Since more severe cases of COVID-19 are associated with infection and inflammation of the respiratory tract, CRP can be found upregulated in the more severe cases of SARS-CoV-2 infections [17].

While CRP is not a biomarker that explicitly identifies a patient as carrying the coronavirus, its upregulation—together with flu-like symptoms in the patient—can give physicians an indication that a patient may harbor SARS-CoV-2. They can then employ other diagnostic tools to test for that specific infection and place the patient under more stringent care, as an elevated CRP concentration identifies the individual to be at risk for a more inimical progression of COVID-19 [18].

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D-dimer

D-dimer elevation in severe cases of the disease is an important observation as the molecule is a byproduct of thrombin blood clots. D-dimer; it consists of two cross-linked D-fragments from fibrin proteins [19]. As mentioned previously, such biomarkers indicating thrombosis formation are found in severe COVID-19 cases. This finding is consistent with an accumulation of blood clots in the lungs and other organs in severe COVID-19 cases. Moreover, researchers have observed endothelial deposits of complement system components between alveoli, suggesting that the increase of thrombosis and D-dimers’ presence signifies the complement system’s involvement in response to SARS-CoV-2 infection [20].

Ferritin

A similar inflammatory biomarker, ferritin, is elevated in severe cases of SARS-CoV-2 infections. This protein functions to sequester iron and thus mediate these ions’ homeostasis; free iron can generate reactive oxygen species that attack and destroy cells. Ferritin is also upregulated in infections, depriving bacterial metabolism of essential iron ions [21]. The upregulation of ferritin in severe SARS-CoV-2 infections may be a product of the inflammatory reaction.

Interleukin-6 (IL-6)

The elevation of IL-6 in SARS-CoV-2 infections results from the induction of an inflammatory reaction. IL-6 can be utilized to mitigate lung inflammation and cytokine storm. The IL-6 inhibitor tocilizumab can prevent progression mild COVID-19 into a more severe version of the disease [22].

Cardiac troponin I (cTnI)

Cardiac troponin I (cTnI) is a protein essential to cardiac function. As a regulator of actin-myosin contraction, it is crucial for translating electrical signals into the heartbeat and heart muscle contraction [23]. This mechanism is consistent with the possibility of SARS-CoV-2 infections spreading to the heart, leading to myocarditis. Thus, SARS-CoV-2 infections may not be limited to the lung and may manifest long-term complications in other vital body parts [24].

This view supports COVID-19 infections as consisting of distinct phases or processes: a viral infection that occurs predominantly in the lungs and a potentially severe inflammatory response, which can further develop into a cytokine storm that adversely affects multiple organs besides the respiratory tract [25]. As mentioned above, cytokine inhibition is a method to stop severe COVID-19 progression.

Biomarker summary

The elevated biomarkers that suggest the presence of a more severe SARS-CoV-2 infection are a lowered immune cell count, an increased level of inflammatory biomarkers, indicators of blood clot formation, and indicators of myocarditis or other heart damage. Thus, the types and numbers of biomarkers present support the hypothesis that SARS-CoV-2 affects several organ systems within the body and can induce a massive inflammatory reaction by the body’s immune system.

Stages of SARS-CoV-2 infection

There are distinct stages in SARS-CoV-2 infection. Initially, the infection resembles a typical viral infection, primarily affecting the respiratory epithelium’s cells. The virus generally spreads via aerosols and the oral route. (For example, an individual contacts virus particles from a surface by touching it with their hands, followed by touching their mouth.) Once within the respiratory epithelium, the virus...
binds to ACE2 proteins on cell surfaces. The subsequent complex is modified by TMPRSS2 surface protease, allowing the viral membrane to fuse with the cell membrane and release its RNA genome into the cell [26].

The subsequent stage involves the virus entering a host cell via an endocytic route and fuses once it is located in late endosomes or lysosomes [26]. The virus uses its spike proteins to bind to ACE2 molecules and hijack them as if they were a cell surface receptor. The virus RNA is then translated inside the cell, and itself replicated. After all parts have been synthesized using the cell’s translation and replication machinery, the new virus particles are assembled and released. After the virus particles are released, they spread throughout the body, entering more cells and infecting more tissues [26,27].

Furthermore, the subsequent stage of the infection sees the virus inducing a widespread inflammatory response, which in some cases leads to a cytokine storm. It is this step that makes a SARS-CoV-2 infection deadly for at-risk patients. The overabundance of cytokines leads to widespread recruitment and activation of fibroblasts and myofibroblasts, killing virus particles and depositing collagen molecules in the affected areas [28].

This process destroys alveolae, and the generation of cellular debris induces osmotic pressure, leading to an eventual accumulation of fluid in the lungs. Thus, the patient’s lungs cannot perform the regular and healthy exchange of oxygen and carbon dioxide. This event is referred to as acute respiratory distress syndrome (ARDS). Moreover, if a cytokine storm brings about ARDS, it will also affect other organs through oxygen deprivation, increasing immune reactivity and triggering the additional release of cytokines. Eventually, not just the lungs but the entire body succumbs to the disease [29].

Notably, the virus infection also induces thromboses within the blood vessels of the lung. In autopsies of patients who had died from a COVID, researchers found local accumulation of platelet-secreting megakaryocytes, exacerbating the coagulation process in the lungs [29]. This finding suggests that in SARS-CoV-2 infections, blood clots are not just the secondary results of the destruction of lung epithelium but also that their formation is actively pursued throughout the inflammation reaction. The resultant local thromboses can lead to further destruction of lung tissue and ultimately bring about death—adequate blood circulation is no longer available within the respiratory system [30]. Sometimes, thromboses can also be found in organs. However, it is unclear whether they originated in the lungs and were transported to other organs via the blood circulation, or whether they formed de novo. Blood clots are a characteristic feature of severe SARS-CoV-2 infections [30,31].

The physiological, cell biological, and pathological blood clot formation mechanisms in SARS-CoV-2 infections are not yet well understood. However, some infections by influenza viruses can also induce blood clots inside the lungs. Viral particles traversing the endothelial barrier between the surrounding tissue and the blood vessels make the endothelial layer more permeable. This passage, then, leads to the local leakage of plasma into the surrounding tissues. These local injuries then activate a coagulation cascade, resulting in the widespread formation of blood clots [32].

**Effect of comorbidities in SARS-CoV-2**

Individuals suffering from comorbidities, such as old age, obesity, or hypertension, may be more at risk of developing an aggressive inflammatory reaction [33]. As mentioned on several occasions previously, the virus infection also induces thromboses within the blood vessels of the lung [34]. In autopsies of patients who had died from a COVID-19, researchers found local accumulations of megakaryocytes in the lungs [35]. This finding suggests that in SARS-CoV-2 infections, blood clots are not just the secondary results of the destruction of lung epithelium, but that their formation is actively induced throughout the inflammation reaction.

The resulting local thromboses can lead to the further destruction of lung tissue and ultimately bring about death—sufficient blood circulation no longer occurs within the respiratory system [32]. Sometimes, thromboses can also be found in other organs. However, it is
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not known whether they originated in the lungs and were transported to the organs via the blood circulation, or whether they formed de novo. Again, as mentioned previously, clots are a characteristic feature of SARS-CoV-2 infections [36].

To date, most individuals who have succumbed to COVID-19 showed blood clots in the lungs and some degree of clotting in other organs. A specific group of autopsied patients suffered from hypertension, diabetes, obesity, or all three. These findings suggest that hypertension increases the risk for severe SARS-CoV-2 infection due to endothelial cells being weakened and thus primed for injury [37,38].

As people who suffer hypertension are more prone to embolism and blood clot formation, it is conceivable that they are also more at risk to succumb to an elevated formation of blood clots as part of a SARS-CoV-2 infection. However, it is essential to note that when comparing people that died from COVID-19 with people who died from non-COVID-related pulmonary inflammation, the latter did not necessarily show the same histopathology as COVID-19 cases, even if, in both cases, patients suffered from hypertension. Thus, SARS-CoV-2 infections may induce additional adverse effects on blood and endothelial cells [35].

It is not fully understood how age increases the mortality rate in SARS-CoV-2 infections. Age seems to be independent of other comorbidities, such as chronic obstructive pulmonary disease (COPD), asthma, metabolic syndrome, coronary artery disease (CAD), dementia or other cognitive impairments, and cancer, among others [39]. Remaining healthy does not necessarily decrease the increased risk that older age presents in individuals infected with SARS-CoV-2 [40,41].

It is plausible that with increasing age, the immune system becomes less efficient in combating viruses and other infections. Also, aging tissue in the body lose their ability to regenerate quickly, being less elastic and flexible. It is likely that older adults have less functional immune systems (termed immunosenescence), while younger people have a controlled immune response, which is suppressed in many older people. Also, older tissues become more easily inflamed, a phenomenon called inflammaging [42,43].

In older people, coagulopathies more easily manifest since tissues, especially blood vessels, are more easily damaged if they are aged than AS occurs in younger people [44]. Notably, the apical surface of endothelial cells, which faces the blood plasma, has a changed glycome, i.e., the glycocalyx structure is different in older blood vessels, making it potentially easier for them to become damaged [45]. It is possible that epigenetic biomarkers, such as histone acetylation and DNA methylation, are more likely to be dysregulated in aging people, especially if their biological age is older than their chronological age—which might explain the lower fatality rate of COVID-19 in individuals below the age of 45 [46]. A SARS-CoV-2 infection is taxing to the body’s tissues and immune system and will affect people with an unhealthy lifestyle more significantly than healthy-lifestyle individuals [47,48].

**Conclusion**

The early detection and analysis of SARS-CoV-2 infection biomarker levels aid medical personnel in better anticipating the severity of the condition and allocating limited resources. Two important biomarkers regarding the more severe prognoses of SARS-CoV-2 are inflammatory and blood coagulation biomarkers. Most patients who have contracted a SARS-CoV-2 infection feel fatigued with fever and cough, which are similar to symptoms in more common viral infections. Thus, physicians should consider biomarkers (e.g., hematological biomarkers, cytokines, liver enzymes, and coagulation parameters) in differential diagnosis and treatment.

The virus uses its spike proteins to bind to ACE2 molecules and react with them as if they were a cell surface receptor, undergoing subsequent endocytosis. In severe cases, the virus induces a widespread inflammatory response, resulting in a cytokine storm. The increased presence of thrombosis and D-dimer levels indicates the complement system’s involvement in response to a SARS-CoV-2 infection. The most notable biomarkers are a significant reduction in lymphocytes and elevations in C-reactive protein, D-dimer, cardiac troponin, ferritin, and interleukin-6.
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The early and accurate diagnosis of SARS-CoV-2 infection is crucial. Symptoms alone are insufficient as various infections manifest similar symptoms, such as swollen lymph nodes, cough, fever, and fatigue. Thus, health care personnel’s practical knowledge of SARS-CoV-2 infection biomarker levels is essential in containing the spread of and treating the disease.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note


References


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