Biomarkers in Serum that Correlate to Disease Severity and Prognosis Within COVID-19 Patients – A Retrospective Analysis

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Abstract

The Covid-19 pandemic shocked the world to its core as it quickly swept the globe ravaging both healthcare systems and infected individuals alike. Our overwhelming lack of knowledge placed scientists and medical providers at an enormous disadvantage when faced with combating this newly discovered SARS-CoV virus. Nevertheless, as we progress further into the pandemic our knowledge and resources have been maximally directed towards uncovering how to stop SARS-CoV-2 or Covid-19. However, our focus on the creation of a vaccination for the novel Covid-19 virus has overcast the discovery of many biological markers which could directly help medical providers predict disease severity and patient outcome. Various studies around the world have communicated commonalities in concentration levels of ferritin, C-reactive proteins, hemoglobin, lymphocytes, red blood cell count and the cytokine interleukin-6 which all serve as biological markers in serum within afflicted Covid-19 patients. This study analyzes various lines of research which identified the presence of these biomarkers to then establish a connection between their concentrations and how they relate to each other and disease progression. By following the virus's intricate path of infection and breaking down the various mechanisms which are known to us, we were able to provide an exemplar list of biomarkers which could serve as a primitive system towards monitoring patients. The overall goal is to use the correlations between these biological markers and disease severity to help enable risk stratification, guide interventional studies to target patients at enhanced risk of developing severe cases and to optimize the allocation of limited human and technical resources during the ongoing pandemic.

Introduction

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) commonly termed Covid-19 has ravaged the world for over a year infecting well over 151 million individuals worldwide, with over 33 million cases belonging solely to the United States (CDC, 2021). The coronavirus was first published within scientific literature near the end of the 1960's as scientists described this novel virus within infants suffering from acute lower respiratory-tract disease (McIntosh, 2004). Currently, only three known coronaviruses have the capability to cause severe human disease: severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), the Middle East respiratory syndrome coronavirus (MERS-CoV), and the reason for our current pandemic severe acute respiratory syndrome coronavirus 2 (Ehsani, 2020). A total of four genera of coronavirus' have been identified and each one is comparatively composed of four main structural proteins: a spike protein, membrane proteins, envelope proteins, and nucleocapsid proteins (Seah et al., 2020). Moreover, previous works were able to determine that the receptor binding domain of the virus is not only housed within the spike protein component but also the most mutable segment of the coronavirus (Andersen et al., 2020).

Generally, the Covid-19 virus is notoriously known for its exceptional ability to spread and infect human hosts. This is principally due to six critical amino acids which are located on the receptor binding domain of the virus which is used when converging and entering a human

host in cells with angiotensin converting enzyme 2 (ACE2) (Kang et al., 2020). Within humans, ACE2 is primarily produced in club cells of distal bronchioles and type 2 pneumocytes of the alveolar epithelium (Bombardini & Picano, 2020). Both cells normally play a vital role in preventing the onset of acute respiratory distress syndrome (ARDS) however, when the enzyme is bound by the spike proteins of the virus it is downregulated in function leading to detrimental lung damage triggered by the unregulated actions of angiotensin I and II (Bombardini & Picano, 2020). Consequently, if the development of ARDS occurs, it is characterized by an atypical retainment of lung gas volume which in turn leads to low treatment efficacy of mechanical ventilation or extracorporeal membrane oxygenation within afflicted patients (Taneri et al., 2020).

Unsurprisingly, as seen in other maladies, the elderly along with those that have preexisting chronic conditions like cardiovascular disease, diabetes mellitus and hypertension are disproportionately threatened by the virus (Taneri et al., 2020). Upon infection, patients typically develop fever, myalgia or fatigue, dry cough, and in more severe cases dyspnea and hypoxemia which if left unaddressed, give rise to more fatal complications such as end-organ failure or ARDS (Wu et al., 2020). The internal workings and responses of our body to the infection of the Covid-19 virus however hold much more complex processes. Once infected, individuals undergo a viral-induced hyperinflammatory condition with multiorgan involvement due to a cytokine cascade known as a "cytokine storm" (Herold et al., 2020). When discovered, this hyperinflammatory state served as a landmark development in the progression of the virus infecting its host. Typically associated with the cytokine storm are increased concentrations of inflammatory factors such as interleukin-6 (IL-6), C-reactive protein (CRP), and ferritin whose concentrations in serum have shown to correlate to disease severity (Bellmann-Weiler et al., 2020).

Previous lines of work have also shown that during this hyperinflammatory state, an alteration of iron regulation within the human body occurs, which is normally hallmarked by increased iron acquisition and retention within macrophages along with reduced intestinal iron absorption (Bellmann-Weiler et al., 2020). This deprivation of iron in turn causes reduced metal availability for erythropoiesis where it is needed for the production of our next two monitorable markers, red blood cells (RBC) and hemoglobin (Hgb) (Bellmann-Weiler et al., 2020). Furthermore, the development of lymphopenia, or reduced levels of lymphocytes, were readily seen across varying cases of Covid-19 patients but even more astonishing their concentrations in serum also help us predict case progression (Kang et al., 2020). A wide range of dispersed studies identified all of these biological markers or biomarkers, which have been shown to remarkably predict patient prognosis and outcome. However, no study has gone beyond identifying their presence, leaving a void in how it is all these biomarkers are associated with each other as well as how their concentrations fluctuating could help us predict patient case severity. Thus, the relationships between case severity and the concentrations of the cytokine IL-6, ferritin, C-reactive proteins, Hgb, RBC count, and lymphocytes may hold the key to do just that.

Indeed, the development of multiple successful vaccinations marks a great advancement in our understandment of Covid-19. However, our knowledge of how the virus will progress, mutate, and continue to engulf the world is relatively unknown. Therefore, this study was conducted to retrospectively review and analyze the data attained from various lines of research to identify and develop an exemplar concept of tracking disease progression and prognosis to better enable risk stratification as well as the allocation of limited resources appropriately.

Methods

The protocol for this study and protocol was not reported through PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) or PROSPERO. However, alike guidelines to those of PRISMA were used when working in conjunction with the Department of Integrative Biology at Oklahoma State University.

Data Sources and Strategy

We conducted a systematic review on factors related to SARS-CoV-2, Coronavirus pandemic, or Covid-19 by using EBSCO databases, Medline, Google Scholar, PubMed, and Science Direct. Search terms used in our search related to Covid-19, SARS-CoV-2, ferratin, anemia, iron homeostasis, iron dysregulation, iron metabolism, cytokine, interleukin-6 (IL-6), C-reactive protein (CRP), biomarkers, hemoglobin (Hgb), red blood cell (RBC), lymphopenia, lymphocytes, death, mechanical ventilation, disease severity, and disease prognosis. While searching, we also included terminology which described a relation between factors and the Covid-19 virus by adding language like associated, predictors, predicting, forecasters, and prognosticators. The literature looked at for analysis within these databases spanned from inception until April 4th 2021. The studies analyzed were limited and restricted to those written in English, as well as to those without follow up literature that refuted or contradicted their findings to assure our information obtained was as well-grounded as possible.

Selection and Criteria

Meta-analysis, retrospective, cohort, cross-sectional and case-control studies were all used and included if deemed satisfactory. Prospective studies, case reports, and case series were all excluded from our search since our focus was not centered around diagnosis, treatment, or response to treatment. Previous lines of work which reported biomarker concentrations of the cytokine IL-6, ferritin, C-reactive proteins, Hgb, RBC count, and lymphocytes were included into our selection criteria. Outcomes of interest in studies were those concentrated on correlations, or predictive conclusions which found biomarkers to dictate disease severity, prognosis, or outcome of patients who suffered from Covid-19. As we know SARS-CoV-2 has been extant for a very short amount of time consequently studies involving patients were not limited only to American patients but instead included data collected from patients in other areas of the world such as Wuhan, the epicenter of the pandemic.

Data Collection and Extraction

A sole reviewer underwent three phases of assortment and screening for article selection. First, the titles were initially screened according to the criteria provided above. This allowed for quick interpretation of the focus and emphasis of a study to quickly be deemed unsatisfactory or potentially useful towards our work. Studies found suitable would then begin the second process of screening which involved reading the selected journal to collect the following information: author names, date of inception, location of study, population sampled, results of the study, outcomes of data extraction or laboratory examinations, demographics, and clinical characteristics, and finally relations between biomarkers and Covid-19 disease severity or prognosis. Finally, the third aspect of screening selected studies required ensuring that no follow up study refuted the information presented as studies on this virus are relatively new and at times hold incorrect material. Articles that passed both the screening and met the selection criteria

were then used for this study. ARDS as well as Covid-19 was defined according to the criteria provided by the World Health Organization.

Results

Infection

The Covid-19 virus created a shockwave pandemic due to how astonishingly fast and well transmission was occurring between human hosts. Previous SARS-associated coronavirus (SARS-CoV) infections such as the 2003 outbreak had a miniscule 8,093 individuals infected in comparison to the current count of individuals who have been infected by Covid-19 (Shereen et al., 2020). As aforementioned, the spike glycoprotein has been identified as the key component responsible for the attachment and entry of the SARS-CoV virus into human hosts through ACE2 (Ehsani, 2020). Additionally, a study analyzing the genome of SARS-CoV-2 showed that homologous recombination was found to be involved at the spike protein which assorted the receptor binding domain of a bat SARS-CoV to a receptor binding domain of a not yet known Beta-CoV (Shereen et al., 2020). This alteration of the receptor binding domain causes the N501Y domain within it to considerably enhance the overall binding affinity for ACE2 giving rise to the rapid infectious spread seen (Tian et al., 2021).

Moreover, ACE2 is prevalent throughout the human body and has astonishingly been found throughout various parts such as in arterial and venous endothelial cells, arterial smooth muscle cells, enterocytes of the small intestine, and as stated earlier on lung alveolar epithelial cells (Hamming et al., 2004). Club cells and type 2 pneumocytes are normally responsible for preventing ARDS but most importantly are the primary source of ACE2 which is where the Covid-19 virus seeks to attack (Bombardini & Picano, 2020). Normally, club cells secrete a solution similar to surfactant plus protective proteins against airway inflammation and oxidative stress while type 2 pneumocytes synthesize, secrete, and recycle all components of the surfactant which regulate alveolar surface tension in the lungs (Bombardini & Picano, 2020). ACE2 on the other hand is responsible for the degradation of Angiotensin II which if left unregulated causes lung tissue damage, triggers vasoconstriction, inflammation, apoptosis, and fibrosis (Bombardini & Picano, 2020). This cascade triggered by the infection of Covid-19 is further supported by previous lines of research which found elevated circulating levels of angiotensin II in severe cases of Covid-19 when compared to healthy control individuals (Gheblawi et al., 2020). Therefore, when SARS-CoV-2 infects humans, the downregulation of this enzyme is detrimental to lung functionality giving rise to the virus's characteristic attack on the respiratory system.

Cytokine Storm & IL-6

After entering respiratory epithelial cells, SARS-CoV-2 provokes an immune response with inflammatory cytokine production accompanied by a weak interferon response (Hu et al., 2021). Additionally, the virus rapidly activates pathogenic Th1 cells to secrete proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor, which can further activate $CD14^+$ and $CD16^+$ inflammatory monocytes, tumor necrosis factor-α, IL-6, and other cytokines (Hu et al., 2021). Findings have proposed a potential mechanism of the cytokine storm caused by the angiotensin II pathway (Hu et al., 2021). In particular multiple lines of research have showed that the presence of raised circulating levels of IL-6 appear to closely connect to disease severity not only in Covid-19 but also in various other forms of avian and common seasonal influenza (Herold et al., 2020). This is due to the role IL-6 plays in inducing the hyperinflammatory state

that is seen associated to the cytokine storm. Once SARS-CoV-2 has downregulated ACE2 and increased angiotensin II levels, the AngII-angiotensin receptor type 1 axis activates nuclear factor-κB and releases tumor necrosis factor-α and the soluble form of IL-6Ra (sIL-6R) via disintegrin and metalloprotease 17 (Hu et al., 2021). IL-6 then binds to sIL-6R through gp130 to form the IL-6-sIL-6R complex, which activates the signal transducer and activator of transcription 3 (STAT3) (Hu et al., 2021). Nuclear factor-κB and STAT3 are then both capable of activating the IL-6 amplifier to induce various proinflammatory cytokines and chemokines, including vascular endothelial growth factor, monocyte chemoattractant protein, IL-8, and more IL-6 (Hu et al., 2021).

The role of IL-6 is very pronounced, and studies have shown that maximal levels of IL-6, prior to intubation, are capable of predicting respiratory failure and the need for mechanical ventilation with great accuracy (Herold et al., 2020). This finding could be a transformative discovery as studies have shown that up to 20% of infected patients need to be hospitalized, at times with ensuing admission to the intensive care unit and requiring the need for mechanically assisted ventilation (Bellmann-Weiler et al., 2020). Furthermore, previous lines of research that looked at infected non-survivors vs. survivors, showed that a significantly greater increase in IL-6 release was seen in the non-survivor group when comparing the two groups of infected individuals (Henry et al., 2020). Therefore, monitoring levels of IL-6 could help predict disease progression in addition to case severity as patients progress through infection. Lastly, IL-6 and toll-like-receptor-4 dependent pathways induce an increase in the levels of the liver-derived iron hormone hepcidin (Taneri et al., 2020). As a master regulator of iron homeostasis, increased levels of hepcidin block the activity of the transporter ferroportin therefore, decreasing the amount of iron absorbed from diet causing cellular sequestration of iron which plays a pivotal role in the next step of disease progression (Taneri et al., 2020).

Ferritin & Anemia

The hyperinflammatory state of SARS-CoV-2, is also characterized by the presence of ferritin, the major iron storage protein linked to a variety of processes that occur after infection (Bellmann-Weiler et al., 2020). The expression of ferritin is typically induced by inflammation as the innate immune system orchestrates control over iron metabolism as a response to the viral infection (Taneri et al., 2020). As the virus tries to replicate, enhanced cellular metabolism and optimal iron levels within host cells are necessary for it to do so thus, the innate immune system will react by decreasing the bioavailability of iron to limit the replication of the virus during the acute phase of infection (Taneri et al., 2020). For the increased intracellular iron sequestration to occur an upregulation in cytosolic ferritin must first occur. The release of ferritin will then increase retention and storage of iron within macrophages which contributes to the characteristic fall in serum iron concentrations (Taneri et al., 2020). A study on patients in New York City and China confirms the importance of ferritin in iron regulation, as hospitalized patients suffering from Covid-19 encompassed pathologically high levels of ferritin (Taneri et al., 2020). Various studies also found that mean difference in serum ferritin was higher in severe cases of Covid-19 when compared to moderate cases, as well as higher mean ferritin levels in non-survivors as compared to survivors suggesting that these elevated ferritin levels within patients can help serve as a crucial biomarker to allow medical providers the ability to screen for severity of the hyperinflammatory state within infected patients (Taneri et al., 2020).

Hyperferritinemia, or an excess of ferritin, gives rise to ferroptosis which increases mitophagy with accelerated cell apoptosis or necrosis subsequently triggering some of the

associated clinical symptoms highlighted during Covid-19 (Cavezzi et al., 2020). However, increased levels of circulating ferritin may not only reflect an acute phase response but may also play a critical role in inflammation by contributing to the development of the cytokine storm (Taneri et al., 2020). Ferritin is composed of an H-chain whose role activates macrophages to increase the secretion of inflammatory cytokines (Shoenfeld, 2020). Overall, the result of iron sequestering leads to diminished iron availability for erythropoiesis and as a result the development or further aggravation of anemia occurs (Taneri et al., 2020). In fact, serum iron levels in patients with severe Covid-19 cases were significantly lower than those in patients with mild Covid-19 (Kang et al., 2020). Some studies even reported up to 90% of Covid-19 patients were afflicted with abnormally low serum iron levels (Kang et al., 2020).

The importance of serum iron levels must not be disregarded because various types of pulmonary diseases have been associated with iron deficiencies including chronic cough which is a chief symptom of Covid-19 patients (Kang et al., 2020). Indeed, some reports have shown that the oral intake of iron attenuated ACE inhibitor therapy benefits chronic cough through its effect on nitric oxide generation consequently iron therapy could be a key treatment for afflicted patients (Kang et al., 2020). More importantly, as above-mentioned, a restriction in iron can lead to anemia which if present upon admission to the hospital tends to correlate with longer stays and significantly higher rates of mortality within Covid-19 patients (Bellmann-Weiler et al., 2020). The increase in hepcidin and the cytokine mediated inhibition of erythropoiesis shortens erythrocyte half-life and reduces biological activity of the red cell hormone erythropoietin, which results in the development of anemia of inflammation within patients (Bellmann-Weiler et al., 2020). Research indicates that about 24% of infected individuals have some level of anemia upon admission, which over the span of 7 days increases to 68% of the originally admitted patients developing anemia (Bellmann-Weiler et al., 2020). Overall, anemia reduces oxygen delivery to tissues and may thus play an important role in the development of multi-organ failure and progression of disease severity (Taneri et al., 2020). Therefore, early monitoring of these key indicators for anemia development such as iron and ferritin levels could prove to be an advantage when combating this disease and tracking patient prognosis.

Hemoglobin and RBC Count

As previously mentioned, the vital process of erythropoiesis is impaired by the inflammatory response of iron sequestering which in turn diminishes the production of hemoglobin. With hemoglobin being a primary carrier of oxygen within the body, it can provide us an insight as to what the oxygen carrying capacity of the blood is like as peripheral tissues combat the disease. A study on SARS-CoV-2 infected individuals in Singapore reported that during the course of patients being admitted into an intensive care unit, patients developed more profound and significantly lower hemoglobin levels when compared to patients not admitted to intensive care unit (Fan, 2020). Similarly, hemoglobin levels in relation to survivorship exhibited the same pattern as the association between case severity and hemoglobin levels, with non-surviving patients having lower hemoglobin levels than survivors (Cavezzi et al., 2020). Throughout early studies on SAR-CoV-2, the GRP78 receptor has been considered another possible entry point or facilitator of the virus, which also happens to be located within bone marrow stem cells (Cavezzi et al., 2020). This additional receptor could facilitate anti-hemoglobin viral actions on hematopoietic stem cells which would confirm previous studies that indicated SARS-associated coronavirus illnesses interfere with hemoglobin synthesis at the erythrocyte and bone marrow level (Cavezzi et al., 2020). Regardless, patients with COVID-19

tend to present decreased hemoglobin levels as case progression worsens establishing yet another biomarker for us to monitor.

As mentioned previously, the atypical combination of a hypoxemic hypoxia with relatively normal lung compliance and normocapnia is seen in up to 80% of intensive care unit patients with Covid-19 (Taneri et al., 2020; Cavezzi et al., 2020). This phenomenon astonishes scientists as gas exchange problems don't appear to be the main cause of progressing case severity until the most critical stages. Uniquely, hemoglobinopathy, hyperferritinemia, and iron dysmetabolism may induce a cascade of events which seriously compromise the capacity of erythrocytes to perform oxygen transportation as well as progressively affect alveolar-capillaries, cell membrane integrity, and permeability thus forming the kind of silent hypoxia that is described in Covid-19 patients (Taneri et al., 2020; Cavezzi et al., 2020). If procured for long, progressively decreased hemoglobin levels may lead to a sideroblastic-like anemia pattern, with myelodysplastic features, as studies reveal that severe patients encompass lower RBC count and higher red cell distribution width - a reliable marker of myelodysplasias- when compared to moderate cases. (Taneri et al., 2020; Cavezzi et al., 2020). Although scientist still remain slightly obscured about the full extent by which SARS-CoV-2 attacks erythropoiesis one thing remains certain, using both parameters to help monitor patient prognosis and predict outcome could help save countless lives.

Lymphocytes and C-Reactive Proteins

Lymphopenia, at times referred to as lymphocytopenia, was a common development that occurred within SARS-CoV-2 afflicted patients. Preliminary studies on SARS-CoV had already determined that peripheral T lymphocytes, both CD4+ and CD8+, are rapidly reduced due to lymphocyte sequestration in specific target organs (Huang & Pranata, 2020). However, follow up studies throughout the initial stage of the pandemic further supported this idea as they discovered that lymphocyte count and percentage of lymphocytes in blood were of great value in predicting the transition of COVID-19 from mild to severe and critical illness (Kang et al., 2020). Nevertheless, case severity is not the only thing that has been associated with decreased lymphocyte count as additional studies revealed that mortality, the onset of ARDS, and the need for ICU care increase in probability as lymphocyte count decreases in infected patients (Huang & Pranata, 2020). The mechanism of significant lymphocyte reduction in severe COVID-19 patients remains unclear, but the release of IL-6 could downregulate lymphocyte count and the expression of ACE2 receptors on lymphocytes may cause SARS-CoV-2 to directly target lymphocytes which would only further reduces their availability (Huang & Pranata, 2020).

CRP on the other hand, is a protein produced by the liver and its release is correlated with levels of inflammation. The concentration levels of CRP are not affected by factors such as age, sex, and physical condition making it a great biomarker to monitor (Wang, 2020). Pulmonary diseases with inflammatory features typically raise serum CRP levels in response to inflammatory cytokines such as the previously mentioned IL-6 (Luo, et al., 2020). Furthermore, CRP has already been used as an important index for the diagnosis and assessment of severe pulmonary infectious diseases such as pneumonia which makes its transition as a trackable biomarker for Covid-19 that much easier (Wang, 2020). Typically, the role of CRP in disease pathology is to serve as the first line of innate host defense by promoting the elimination of pathogens using phagocytic cells which is why its concentrations are also raised (Luo, et al., 2020). Unsurprisingly, previous studies confirmed that severe cases of Covid-19 encompassed significantly higher levels of CRP than non-severe cases prior to disease progression and patient deterioration (Guyi et al., 2020). Raised levels of CRP are so prevalent that a study of 194

patients, exposed that 166 or 85% of them demonstrated increased CRP concentrations in serum (Wu et al., 2020). Another line of research unveiled that when CRP levels were greater than 32.5 mg/L, the ability to detect patients at risk for respiratory failure is as high as 95% (Herold et al., 2020). Therefore, with CRP concentrations able to predict patient prognosis prior to deterioration with such great acuity, it serves as a suitable serum marker of disease aggravation which gives physicians an already established basis to guide treatment strategies as well as assess case severity.

Discussion

Our understandment of the virus has grown since its inception yet, as we learn more about this biological jigsaw puzzle in hopes of minimizing the lives lost to this pandemic, it seemingly becomes more intricate to battle. This comprehensive analysis on various lines of research identifies biomarkers in serum which possibly holds the key towards better patient care by allowing medical providers the ability to understand disease progression, enable risk stratification, and allow for the the allocation of limited resources. The ability for SARS-CoV-2 to infect human hosts astonished scientists as previous strains of SARS-CoV failed to reproduce and spread as rapidly. Upon entry, infection of the SARS-CoV-2 is characterized by a cytokine storm which studies have shown is induced by the important monitorable biomarker, IL-6. (Henry et al., 2020; Hu et al., 2021). The role of IL-6 goes beyond inducing the cytokine storm however, as it also begins the first step of iron dysregulation within the body which occurs in infected individuals. As the homeostatic regulation of iron within the body innately changes to sequester iron from the virus, ferritin plays a vital role in enabling such sequestration. However, studies have also shown that the role of ferritin goes beyond the acute response of iron storage and instead also helps in inducing the cytokine storm (Taneri et al., 2020). As iron acquisition and retention occurs it leaves a reduced availability of the metal for erythropoiesis to occur where it is needed for the production of hemoglobin. Another important biomarker, hemoglobin allows us to understand the oxygen carrying capacity of the blood. SAR-CoV-2 may use the GRP78 receptor to induce anti-hemoglobin viral actions on hematopoietic stem cells allowing us to track disease severity by monitoring hemoglobin levels (Cavezzi et al., 2020). The reduction in hemoglobin levels seen in severe cases gives rise to a sideroblastic-like anemia pattern, with myelodysplastic features, which reduces RBC as patient deterioration occurs. Therefore, RBC serves as another key indicator of disease progression alongside hemoglobin levels. Furthermore, lymphopenia was prevalent in infected individuals since IL-6 release downregulates their production. Therefore, when IL-6 concentrations increase during infection, lymphocyte concentrations drop causing further deterioration of patients. Additionally, SARS-CoV-2 possibly uses ACE2 receptors located on certain lymphocytes as a point of entry which only further decreases their count. Likewise, IL-6 raises serum concentrations of CRP as its release is correlated with levels of inflammation. CRP monitoring is an already established system for other various pulmonary diseases making its transition alongside the monitoring of lymphocytes stress-free. Ultimately, enabling risk stratification by monitoring these biomarkers allows medical providers the ability to guide treatment plans, properly allocate resources such as mechanical ventilators- which became a crisis during the early stages of the pandemic, and reduce the amounts of lives lost by combating the disease in its earlier stages.

Conflicts of Interest & Acknowledgements

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