Role of Biomarkers in the Stratification of COVID-19 Disease Severity – A Review

Mohammed Nuruzzaman Bhuiyan1, Susane Giti2, Mahbuba Akhter3, Mohammad Shameem Montasil Hossen1, Md. Moshiur Rahman1

1Classified Specialist in Pathology, AFIP, Dhaka Cantt.
2Classified Specialist in Pathology, Commandant, AFIP, Dhaka Cantt.
3Associate Professor of Gynae and Obs, Marks Medical College & Hospital, Dhaka.

ABSTRACT

Background: There have been a wide variety of clinical publications on coronavirus disease 19 (COVID-19) focused on specific biomarkers. Acute-phase reactants, such as C-reactive protein (CRP), ferritin, serum amyloid A (SAA), and procalcitonin, have been identified as sensitive markers of acute COVID-19 illness, even though they are nonspecific markers. Objective: The purpose of this study is to summarize the role of several biomarkers in the stratification of COVID-19 disease severity. Methods: This study followed a systematic literature review method. The systematic review followed the review process as it was well developed and planned to reduce biases and eliminate irrelevant and low-quality studies. The steps for implementing a systematic review include correctly formulating the COVID-19 question to answer, developing a protocol based on inclusion and exclusion criteria, performing a detailed and broad literature search and screening the abstracts of the studies identified in the search and subsequently of the selected complete texts. After selecting the study, the next steps were synthesis of the evidence like extracting the necessary data into a form designed in the protocol to summarise the included studies, assessing the biases of each study, identifying the quality of the available evidence, and developing tables and text that synthesise the evidence. The secondary sources of data for this study included different published topics from national & international journals. Good number of Journal articles were taken regarding “Role of Biomarkers in the Stratification of COVID-19”. Published articles were collected from renowned indexing data sources like PubMed, Medline, and Scopus. Etc. Conclusion: Significantly increased white blood cell count, lymphopenia, decreased CD3, CD4, or CD8 T-lymphocyte counts, high neutrophil count, thrombocytopenia, and dramatically elevated inflammatory biomarkers were all linked to severe disease and the probability of developing sepsis as the disease progressed. Progressive decreases with lymphopenia, thrombocytopenia, elevated CRP, procalcitonin, increased liver enzymes, impaired renal function, and coagulation derangements were more common in critically sick patients and were linked to a higher rate of clinical sequelae. In seriously and critically ill patients, elevated interleukin levels and significantly increased SAA were most frequently reported. The neutrophil to lymphocyte ratio, the systemic immune inflammation index, and the COVID-19 Severity Score are all indicators of systemic inflammation that can be used to predict disease severity, outcome and death.

Keywords: Biomarkers, COVID-19, Disease Severity, IL- Interleukin, RT-PCR- Reverse transcription polymerase chain reaction, Stratification.
Introduction

After an outbreak of pneumonia with no evident reason, a novel Coronavirus SARS-CoV-2 was discovered in December 2019 in Wuhan, a city in China's Hubei province. The virus has spread to over 200 countries and territories worldwide, and the World Health Organization has declared it a pandemic (WHO). The number of COVID-19 patients is rapidly rising worldwide, making treatment in intensive care units (ICU) significant. The ability to predict the infection's final result at an early stage of the disease and provide appropriate treatment for individuals who may develop into a more severe state could lower the fatality rate. It's crucial to find reliable indicators of disease severity and, more importantly, reliable markers of a prospective unfavourable progression. In the early stages of the illness, most severely ill and dying patients did not show any significant clinical symptoms. In the later phases of the disease, these participants' clinical situations deteriorated suddenly. Clinical and wet biomarkers may help with illness stratification and the efficient use of limited expert resources by allowing early detection of high-risk cases.

To stratify high-risk individuals, scientists urgently require validated biomarkers related to COVID-19 disease progression. To ensure optimal resource allocation, patients must be immediately classified into risk groups following diagnosis due to the rapid spread of the disease. New biomarkers are required to identify individuals who would have rapid disease progression, significant complications, and death. Understanding viral pathogenetic pathways and cellular and organ damage are critical to the discovery of new biomarkers. Screening, clinical care, and the prevention of significant consequences could all benefit from effective biomarkers. Inflammatory cascades, complement activation, and proinflammatory cytokines are all implicated in organ destruction of seriously ill patients.1-2 Though laboratory medicine has traditionally aided clinical decision-making in various infectious diseases, it's critical to evaluate the ability of laboratory-derived biomarkers to aid COVID-19 disease risk classification. This review article comprehensively explored the role of biomarkers in the stratification of COVID-19 disease and its complications to address their association with disease severity, respiratory intervention, and outcome.

Methodology

This systematic review involves a critical and reproducible summary of the results of the available publications on COVID-19. To improve scientific writing, the methodology is shown in a structured manner to implement a systematic review. This study followed a systematic literature review method. The systematic review followed the review process was well developed and planned to reduce biases and eliminate irrelevant and low-quality studies. The steps for implementing a systematic review include correctly formulating the COVID-19 question to answer, developing a protocol based on inclusion and exclusion criteria, performing a detailed and broad literature search and screening the abstracts of the studies identified in the search and subsequently of the selected complete texts. After selecting the study, the next steps were synthesis of the evidence like extracting the necessary data into a form designed in the protocol to summarise the included studies, assessing the biases of each study, identifying the quality of the available evidence, and developing tables and text that synthesise the evidence. The secondary sources of data for this study included different published topics from national & international journals. Good number of Journals and articles were taken regarding “Role of Biomarkers in the Stratification of COVID-19”. Published articles were collected from renowned indexing data sources like PubMed, Medline, and Scopus etc.

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Results

Severe progression and markers of COVID-19 infection

Individuals with severe disease have a pattern of haematologic, biochemical, inflammatory, and immunological biomarker abnormalities that warrant inclusion in risk stratification models compared to patients with mild systemic disease.

Biochemical Parameters and Inflammatory Biomarkers, Including CRP, Ferritin, SAA, Procalcitonin, Albumin/ Prealbumin, and Proinflammatory Cytokines

The activation of acute-phase reactants, such as CRP, ferritin, serum amyloid A (SAA), albumin/prealbumin, procalcitonin, erythrocyte sedimentation rate (ESR), and proinflammatory cytokines, is one of the first host responses to viral or bacterial infection. CRP, a member of the short pentraxins family, is a 25-kDa protein produced in the liver that interacts with complement factor C1q to activate the complement cascade. Cytokines are released primarily by haematopoietic cells such as lymphocytes and macrophages, and they may play a role in the clinical course and outcome of the disease. During the acute period of sickness, a dysregulation of the inflammatory response can occur, resulting in enormous cytokine release and organ damage. IL-2/2R, IL-6, IL-10, tumour necrosis factor-a (TNF-a), and interferon-c are the most commonly measured cytokines in individuals with SARS-CoV-2 infection.

IL-6 is found to be the most responsive cytokine in several investigations and may be employed as a biomarker for determining prognosis. A high level of IL-6 has been suggested as a significant driving force behind the cytokine storm and as a factor in the multi-organ failure seen in advanced patients. The occurrence of identifiable blood virus particles by RT-PCR was closely linked with an extraordinarily high IL-6 level. In severe cases, other inflammatory markers such as interferon-c inducible protein (IP-10) and human monocyte chemotactic protein (hMCP) were also significantly elevated. The levels of IL-6, IL-8, and IL-10 in the CSF fluid were shown to be significantly higher in a case series of three patients with respiratory and neurologic problems. In a study comparing survivors and non-survivors, acute-phase proteins such as CRP, ferritin, SAA, procalcitonin, and the cytokine IL-6 revealed an increasing trend in non-survivors a constant or decrease trend in survivors. The relationship between inflammatory indicators and illness progression in moderate, severe, and critically sick patients was investigated. SAA levels were higher in individuals with mild and severe illness in several investigations. As the condition progressed from mild to severe, SAA levels gradually increased. Serial measures of SAA may help monitor the severity of pneumonia, and the levels were found to correlate well with the dynamic changes seen on serial computed tomography scans. Presepsin (PSP), also known as soluble cluster of differentiation CD14-subtype (sCD14-ST), is a regulatory factor that interacts with T and B cells to influence immunological responses. It is a better diagnostic for early sepsis identification in non-COVID-19 patients than other sepsis indicators. A high PSP level was associated with a more extended ICU stay, but it did not correlate well with CRP, lactate dehydrogenase (LDH), or procalcitonin levels assessed on the same day. PSP could be utilized to risk stratify SARS-CoV-2 patients and detect disease severity and lengthen hospitalization stays.

Other Biomarkers, Including LDH, Creatine Kinase, AST, ALT, Blood Urea Nitrogen, and Creatinine

In severe and critically ill patients, significant elevations of LDH, creatine kinase (CK), liver
enzymes (AST and ALT), total bilirubin, blood urea nitrogen (BUN), and creatinine were regularly documented. In COVID-19 patients with varying disease severity, the liver biochemistry and its relationship with other indicators were investigated. The dynamics of AST levels were related to LDH, CK, and ferritin levels but not to CRP. A significant increase in AST was seen in critically ill and intubated patients. There was no evident link between pre-existing liver illness and COVID-19 participants' clinical outcomes. According to another research of liver enzymes, higher levels of bilirubin, AST, and glutamyl transferase were largely detected in fatal cases. In a study, the clinical characteristics and outcomes of patients with high brain natriuretic peptide (BNP) levels were studied, and the results were compared to those of a control group of patients with normal BNP levels. CRP, AST, and c-Tn-I levels were more significant in the high BNP group, and they were more likely to develop pneumonia necessitating ICU hospitalization. Higher levels of serum LDH, CRP, direct bilirubin, BUN, and lower levels of albumin were related to a higher risk of severe disease and disease progression.

**Significant Biomarkers as Predictors of Disease Severity in Mild, Severe, and Critically Ill Cases**

Several studies evaluated haematologic, biochemical, inflammatory, and coagulation parameters in patients with mild, severe, and critical illness and found similar results. However, statistical analysis in several studies was limited due to the lack of serial test specimens in many patients, resulting in reduced total sample size. CRP, ferritin, LDH, and ALT levels were considerably higher in severe cases than in moderate instances, according to Chen et al. Lymphocytes, prealbumin, and albumin levels decreased as the condition advanced from mild to severe or critical, although WBC count, neutrophil count, CRP, and LDH levels increased. Increased SAA, neutrophil to lymphocyte ratio (NLR), PT, D-dimer, FDP, and inflammatory cytokines IL-2R, TNF-a, and IL-10 were among the other notable findings. Patients in the poor recovery group had longer viral shedding (up to 57 days), as evidenced by serial RT-PCR assays and anti–SARS-CoV-2 immunoglobulin M (IgM), as well as higher levels of ESR, CRP, ferritin, and IL-6.

Other laboratory characteristics of critically ill patients requiring ICU admission included a progressive decrease in lymphocyte count with worsening lymphopenia, decreased eosinophil count, thrombocytopenia, elevated CRP, elevated procalcitonin, increased IL-6 and IL-10, increased liver enzymes, increased total bilirubin, decreased renal function, and hypercoagulable state. In contrast to earlier findings, another study revealed no significant link between viral load, ICU admission, and prognosis. A progressive worsening of laboratory markers was noted as the condition proceeded, including decreasing lymphocyte count and elevated NLR, CRP, ferritin, IL-6, IL-10, some coagulation parameters, and serum viral load. The most critical determinants of illness severity, however, appeared to be lymphocytopenia and age.

**Significant Biomarkers as Predictors of Case Mortality**

The median patient age ranged from 71 to 72.5 years in retrospective analyses of non-survivor/fatal cases. Male patients and those with underlying medical disorders such as diabetes mellitus, hypertension, and heart illness were found to have a poor prognosis. The majority of the patients had lymphopenia, thrombocytopenia, extended PT, raised D-dimer, high lactate level, reduced oxygen saturation, high NLR (5.0), and systemic immune inflammation index (500) at the time of admission. A significant subset of patients...
exhibited elevated LDH, D-dimer, procalcitonin, and cTn-I levels, and all had high initial CRP and IL-6 (10 pg/mL) levels. Serum AST, ALT, CK-MB, myoglobin, BUN, and creatinine levels were raised in the 24 hours leading up to death. In addition, McRae et al. looked at the COVID-19 severity score and clinical decision support systems to see if they could predict mortality. The COVID-19 severity values for those who died were significantly greater than those who were discharged, with median (interquartile range) scores of 59 (40–83) and 9 (6–17), respectively. These promising findings have the potential to enable healthcare providers to save lives by prioritizing critical care for patients who are at risk of negative consequences.

Discussion

With over a million verified COVID-19 cases globally, studying the disease's pathogenesis, stratification, and management has become a top priority. Clinical evaluation of COVID-19 issues is still essential for decision-making, but laboratory biomarkers might help refine this information while also providing data on underlying biological processes. This review article has thoroughly examined the breadth of COVID-19 biomarkers for their utility in illness stratification. We've shown that IL-6, CRP, IL-10, LDH, and TNF- are all indicators of COVID-19 severity in various ways. IL-6 is a potent proinflammatory cytokine that raises CRP and has been linked to poor outcomes. It has been identified as a trigger of the COVID-19 cytokine storm. Herold et al. recently discovered that an IL-6 cut-off value of 80 pg/ml in their assay highly suggests respiratory failure, with only one patient requiring intubation misclassified. This backs up the argument for using anti-IL-6 monoclonals as one of the COVID-19 treatments in a clinical trial.

Anti-interleukin immunotherapy could be justified, and unnecessary consequences avoided by pre-selecting individuals with the worst prognosis and most severe disease based on immensely raised IL-6 levels. IL-10 is an immunoregulatory cytokine produced by macrophages that inhibits the development of Th1 cytokines while increasing B cell activation. Elevated levels are most likely due to the proinflammatory cytokine milieu found in severe disease, and they represent a healthy immune system. Some studies have found that IL-1 levels are higher in COVID-19 infection than in healthy controls. Despite this, early trials with Anakinra, an IL-1 antagonist, appear to minimize the need for mechanical ventilation and mortality in severe instances. However, no studies have looked at the drug's effect on IL1 levels before and after therapy or the impact of stratified Anakinra entry on IL-1 levels. Our findings suggest that non-IL-1 indicators may be more useful in the real world. The link between TNF-,-, CRP, and IL-10 with the need for dialysis, but not with IL-6, suggests that sepsis may play a role in renal failure. Patients admitted for neurological disease with concurrent, less severe COVID-19 infection had lower levels of COVID-19 disease severity markers, which could be explained in part by selection bias, as patients admitted for neurological disease with concurrent, less severe COVID-19 infection had lower levels of COVID-19 disease severity markers than those admitted primarily for COVID-19 respiratory failure. Rapid synthesis and release of cytokines and chemokines occur after respiratory cells are infected. Macrophages and other critical components of the innate immune system, such as dendritic cells, are activated, resulting in a more widespread immune response and the cytokine storm. To more conclusively explain such findings, more study is needed to understand the neurological symptoms of COVID-19 and the related cytokine response.

During the progression from mild to severe/critical condition, especially in non-survivors, an upward trend of CRP, ferritin, SAA, procalcitonin, and the
most prominent cytokine, IL-6, and a decreasing trend of albumin and/or prealbumin were frequently seen. These markers can be measured over time to predict disease progression, severity, and mortality.13,19 SARS-CoV-2 may target alveolar macrophages via the angiotensin-converting enzyme 2 receptor, causing a rise in cytokine secretion and, as a result, a surge in several Amyloid Precursor Proteins (APPs) such CRP, SAA, and complement factor, which are markedly elevated in the very ill group. In severe illness and non-survivors, changes in coagulation markers, such as extended PT, raised D-dimer, and high fibrinogen, were common observations.26 Additional biomarkers for the pathogenesis and prognosis of COVID-19 disease may be discovered using proteomic techniques and atypical samples such as cerebrospinal fluid.27 Changes in biomarker levels over time may help predict illness progression, prognosis, and outcome. Systemic inflammation indicators such as the NLR, Systemic-Immune Inflammation (SHI) index and coagulopathy screening utilizing a DIC score system could be utilized to predict disease severity, complications and outcome. Finally, the COVID-19 severity score and clinical decision support systems can be utilized to predict mortality by combining several biomarker measures.

**Conclusion**

COVID-19 is a systemic infection that affects the haematopoietic system and haemostasis. In addition to a thorough clinical examination of COVID-19 patients, a careful review of laboratory data and biomarker analysis of CRP, LDH, and the cytokines IL-6, IL-10, and TNF allows for more precise segmentation of high from low-risk cases and the requirement for intensive care support. Such categorization improves treatment for individual patients and resource management, hospital flow and staffing, and in the most severe cases, the launch of novel medications.

**References**


