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Biosensors based detection of novel biomarkers associated with COVID-19: Current progress and future promise

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ABSTRACT

The pandemic situation of COVID-19 has caused global alarm in health care, devastating loss of lives, strangled economy, and paralysis of normal livelihood. The high inter-individual transmission rate created havoc in the global community. Although tremendous efforts are pitching in from across the globe to understand this disease, the clinical features seemed to have a wide range including fever, cough, and fatigue are the prominent features. Congestion, rhinorrhea, sore throat, and diarrhea are other less common features observed. The challenge of this disease lies in the difficulty in maneuvering the clinical course causing severe complications. One of the major causative factors for multi-organ failure in patients with severe COVID-19 complications is systemic vasculitis and cytokine-mediated coagulation disorders. Hence, effective markers trailing the disease severity and disease prognosis are urgently required for prompt medical treatment. In this review article, we have emphasized currently identified inflammatory, hematological, immunological, and biochemical biomarkers of COVID-19. We also discussed currently available biosensors for the detection of COVID-19-associated biomarkers & risk factors and the detection methods as well as their performances. These could be effective tools for rapid and more promising diagnoses in the current pandemic situation. Effective biomarkers and their rapid, scalable, & sensitive detection might be beneficial for the prevention of serious complications and the clinical management of the disease.

1. Introduction

SARS-CoV-2 associated novel coronavirus, COVID-19, is a huge global health concern. Since the time of the WHO declaration of this disease as a Public Health Emergency of International Concern, the number has risen to 10,662,536 active cases and 516,209 deaths as per the WHO statistics till July 3, 2020 (https://covid19.who.int/) and the count surge on daily basis. The first report of the outbreak of highly contagious COVID-19 (coronavirus disease-19) happened in the Hubei province of China on December 8, 2019. The disease was declared a pandemic by the World Health Organisation on March 11, 2020, and by the end of the month, the disease had already affected over 5 million people across the globe AD (Long et al., 2020). The Imperial College London has reported the age-adjusted mortality ratio among COVID-19 patients to be 0.66% in China. By August 2020, COVID-19 was responsible for confirmed infections of over 20 million and over 700,000 mortality (Coronavirus disease (COVID-19) Situation Report – 205, 2020). Several mild cases of COVID-19 did not possibly report for medical diagnosis for which, treatment and an exact number of fatal cases may be difficult to estimate. However, the overall mortality could be suggested to come between 2.3 and 12.8% (https://coronavirus.jhu.edu/map.html (Wu and McGoogan, 2020). COVID-19 is caused by the infection of a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Z. Li et al., 2020). The new coronavirus shared high genome sequence similarity with other members of the coronavirus family such as those causing severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (Lu

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Abbreviations

COVID-19	Corona virus disease-19
CoVs	Coronaviruses
SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome
CDC	Centers for disease control and Prevention
CRF	Case fatality rate
RT-PCR	Real-time reverse transcription polymerase chain reaction
PaO2	Arterial oxygen partial pressure
FiO2	Fractional inspired oxygen
ORFs	Open-reading frames
NSPs	Non-structural proteins
ACE	Angiotensin converting enzyme
TMPRSS2	Transmembrane cellular serine protease 2
RdRp	RNA-dependent RNA polymerase
IL	Interleukin
ICAM-1	Intercellular Adhesion Molecule 1
Hel	Helicase
HE	Hemagglutinin-esterase
IFNs	Interferons
NK cells	Natural Killer cells
NRL	Neutrophils-lymphocyte
ARDS	Acute respiratory distress syndrome
TNF-α	Tumor necrosis factor-α
CRP	C reactive protein
CT	Computed tomography
ESR	Erythrocyte sedimentation rate
LDH	Lactate dehydrogenase
DIC	Disseminated intravascular coagulation
FDP	Fibrin degradation product
PT	Prothrombin time
APTT	Activated partial thromoboplastin time
PCT	Procalcitonin
cTnI	Cardiac troponin I
BUN	Blood urine nitrogen
SCr	Serum creatinine
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
SpO2	Oxygen saturation
CK	Creatinine kinase

et al., 2020). However, it is different from these coronaviruses and has caused huge global concern (Hua et al., 2020; Z. Li et al., 2020). Coronaviruses comprise broad family members causing disease in animals and humans, of which, around seven of these are responsible for respiratory infections in humans. The Centers for Disease Control and Prevention (CDC) China has performed the largest epidemiology study on COVID-19 and presented that among 44,672 infected patients, 86.6% fall in the age group of 30–79 years, 80.9% showed mild or common pneumonia, while severe and critical cases comprise of 13.8% and 4.7% respectively. Even though the disease is highly contagious, the percentage of disease leading to severe infection may be likely less. More than 20% needed intensive care, 32.8% had acute respiratory distress syndrome and about 14% of hospitalized patients succumbed to the disease. Individuals above 85 years of age, and those with comorbid medical illnesses such as pre-existing respiratory and cardiovascular disease, immunocompromised status, and diabetes mellitus are identified as at risk for severe medical attention caused by this disease. The critical patient demonstrated a case-fatality rate for critical patients of 49%. Comorbid patients presented a higher risk for COVID-19 and they were estimated to show a higher case fatality rate (CRF) with health problems relating to cardiovascular disease associated with 10.5%, diabetes 7.3%, chronic respiratory disease 6.5%, hypertension 6.0%, and cancers 5.6% of the CFR in comparison to the CFR of 0.9% for patients without comorbidities (Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention). The potential discrepancies in calculating the mortality rate due to factors involving avoidance of testing, insufficient post-mortem testing, limitation of healthcare facilities, and other possible factors could suggest the need for caution while recording the accurate numbers of mortality rate. Despite the epidemiological suggestions of the disease routing its origin to the seafood market of Wuhan in China, this could not be proven forth, thereby making it difficult to understand completely the cause of this pandemic. However, human to human contagion has surged leading to medical, psychological, social, and economic burdens across the world.

2. Risk factors

Although SARS-CoV-2 infection has affected millions across the globe, most of the cases are mild, and only around 15% progress to develop into severe pneumonia that later complicates into acute respiratory distress syndrome accompanied by the impaired immune response, systemic inflammation, and cytokine storm (Elhabyan et al., 2020). Severe cases of COVID-19 are prominent among the elderly group of populations especially those with comorbid conditions (Chen et al., 2020). Almost a quarter of the fatal cases are under the age of 70–79 years and another two third of death from this disease comes under the age group of 80 years onwards (Calderón-Larrañaga et al., 2020). The plasma level of SARS-CoV-2 binding target receptor ACE2 is reportedly higher in men than in women (Sama et al., 2020). In addition, the gene expressing ACE2 is X-linked and the expression is higher, particularly in testes which can possibly explain the higher infection and mortality in males than in female individuals (Chakravarty et al., 2020; Shastri et al., 2020). An individual who smokes cigarette and those with chronic obstructive pulmonary disease are at increased risk of infection because of the higher levels of ACE2 (Leung et al., 2020). However, there is also a contradictory observation of current smokers as at higher risk of infection (Rossato et al., 2020). COVID-19 patients with comorbid conditions particularly cardiovascular-associated hypertension demonstrated maximum morbidity followed closely by those with diabetes, lung disease, and obesity (Garg et al., 2020). Whereas, other studies reported that severely affected patients without significant comorbidities make up over 50% of patients (Zhou et al., 2020, Guan et al., 2020a). Human genetic variants particularly those related to immune deficiency and activation of cytokine storm (inflammasome) attributed to severe cases of the disease (Elhabyan et al., 2020). Different studies have contributed to suggesting that blood type O has seemed to be at a lesser risk of infection than other blood types (Gérard et al., 2020). Whereas, some hematologists have suggested that particularly it is the serum anti-A antibody, that is, the IgG anti-A present in blood group O that is more significant in protecting from COVID-19 than the blood type itself. In addition, socially and economically weaker sections of society are more likely under the brunt of the pandemic as they are less likely to be covered with respiratory rehabilitation and monitoring (Liu et al., 2020). Moreover, recent studies have reported the risk factors for severe disease courses from different public authorities, such as Johns Hopkins University (one of the world's leading facilities for COVID-19 updates), the Disease Control and Prevention Center in USA, and the National Health Service of the United Kingdom as shown in Table 1.

Table 1
Overview of risk factors reported by leading institutions (Wolff et al., 2021).

US CDC	Johns Hopkins Medicine	NHS UK
Higher age (≥65 years)	Higher age (≥65 years)	Higher age (≥70 years)
Long-term care facility	Diabetes	Organ transplant recipients
Chronic lung disease	Male candidates	Lung diseases
Asthma	USA: obesity (BMI≥30)	Blood or bone marrow cancer
Heart diseases	USA: African American ethnicity	Heart diseases
Immunosuppression	Comorbidities	Pregnancy
Severe obesity (BMI≥40)	-	Severe obesity (BMI≥40)
Diabetes	-	Chronic kidney diseases
Chronic kidney disease undergoing dialysis	-	Conditions affecting the brain or nerves
Liver disease	-	Liver disease

3. Mode of transmission

Individuals who are diagnosed with COVID-19 through RT-PCR test may be asymptomatic at the time of testing; however, they can be the carrier for spreading the disease effectively. These asymptomatic or mildly symptomatic individuals have been infected with high loads of virus and caused many difficulties in the containment of the disease (Bai et al., 2020; Holshue et al., 2020; Hu et al., 2020). The National Health Commission of China issued guidelines for the diagnosis and treatment of the disease, which stated that disease transmission occurs primarily from person to person through respiratory droplets, aspirates, contacts, and feces, and transmission through aerosols is highly probable. During the beginning of the outbreak, a large number of transmissions occur through contact between asymptomatic or mildly symptomatic clinicians and visitors. In addition, public gatherings or familial meetings added much to the transmission of the disease (Rocklöv et al., 2020; Tong et al., 2020). The small respiratory droplets from an infected person can travel as far as 3–6 feet. In addition, the virus can transmit through a fomite medium as it can remain on surfaces for as long as 4 h on copper, a day on cardboard, and up to three days on plastic and stainless steel (van Doremalen et al., 2020). Once infected, the mean incubation period of the virus is estimated at 5.2 days (with a confidence interval of 95%, 4.1–7.0 days), but the 95th percentile of the distribution is at 12.5 days (Chan et al., 2020c; Z. Li et al., 2020). Some other studies reported the estimated incubation period range between 2 and 14 days (Backer et al., 2020). The RO of SARS-Cov2 falls in between the value of 2 and 3, referring that an infected person can pass on its infection to 2 to 3 other people in a susceptible population (Flahault, 2020; Li et al., 2020).

4. Clinical features of COVID-19

There is a varied form of clinical presentation for COVID-19 ranging from asymptomatic form to severe form associated with clinical features of which fever (88.7%) and cough (67.8%) were the most common primary clinical symptoms. This is followed by fatigue (38.1%), sputum production (33.7%), shortness of breath (18.7%), sore throat (13.9%), and headache (13.6%) (Guan et al., 2020b). Gastrointestinal-associated symptoms such as diarrhea and vomiting are also seen in a few of the COVID-19 patients (Guan et al., 2020a). In contrast to what is commonly observed, in some of the severe cases of COVID-19, fever is mild or not manifested at all (Wang et al., 2020). While it is a challenge to make the diagnosis and treatment of asymptomatic individuals, pneumonia (79.1%), acute respiratory distress syndrome (3.37%), and shock (1.00%) are the complicated features of the symptomatic patients (Guan et al., 2020b). Therefore, COVID-19 may be presented at different levels of severity identifiable as mild, moderate, severe, to critical cases. Mild symptoms do not exhibit radiographic characteristics. In moderate symptoms, fever occurs concomitantly with cough, and the radiographic features showed several patchy shadows and variations in the interstitia. Severe cases exhibit shortness of breath with a respiratory rate of more than 30 times per minute, oxygen saturation draws lower than 93% in ambient air and less than 300 mg Hg of PaO2/FiO2 is found. Critical cases appearances respiratory failure, septic shock, and multiple organ failure. In severe cases, pneumomediastinum and pneumothorax are indicated (Sun et al., 2018; Zhou et al., 2020). The lungs of those who succumbed to the disease show bronchial and bronchiole blockage with mucus plugs and damaged epithelial cells of bronchi (http://kjfy.meetingchina.org/msite/news/show/cn/3337. html%202020). The alveolar septal spaces are infiltrated by lymphocyte and mononuclear cells, while the alveolar cavities are occupied with exudates of fibrin and fibrinogen and hyaline-enriched membranes. Alveolar epithelial cells proliferate abundantly. The presence of polynuclear giant cells is evident. However, the occurrence of this kind of severe case is less in number. Severely affected COVID-19 patients are subjected to mechanical ventilation, nevertheless, not all of these patients responded well to this therapeutic approach (Guan et al., 2020a). Although clinical features of COVID-19 are chiefly respiratory involving severe pneumonia, several other organs are involved directly or indirectly in the disease (Guzik et al., 2020). The primary symptoms and other clinical features of COVID-19 are presented in Fig. 1.

Although much research has been done on this disease, much remained to be understood in the field of pathological physiology and clinical implications to develop the effective treatment strategies.

5. SARS-CoV-2: genetics and basic pathology

Coronaviruses (CoVs) comprise of large and enveloped viruses and consist of positive-sense, single-stranded RNA genomes (Lu and Liu, 2012). The term coronavirus refers to crown-like spikes (or corona) on the surface of the virus. This structure is thought to be due to a richly packed protein that covers the viral membrane and enables receptor binding on the host target membrane (Atri et al., 2020). The major structural protein components of coronaviruses are (i) the spike (S) required for binding to the target receptor, (ii) the nucleocapsid (N), (iii) the membrane (M), and (iv) the envelope (E) proteins (Fehr and Perlman, 2015; Khan et al., 2021) as shown in Fig. 2a. Coronaviruses comes under *Coronavirinae* subfamily (Zhang et al., 2018) and SARS-CoV-2 belong to coronaviruses (CoVs) of the genus *β-coronavirus* (Walls et al., 2020). SARS-CoV-2 consists of 30-kb genome size encoding up to 14 open-reading frames (ORFs). In particular, ORF1a and ORF1ab encode the 16 non-structural proteins (NSP1-NSP2) that constitute the replicase-transcriptase complex. The 3′ end of the genome has up to 13 ORFs that express the proteins including the major structural proteins like the spike, envelope, membrane, and nucleocapsid (Fehr and Perlman, 2015; Yu et al., 2020) as shown in Fig. 2b. The genome of SARS-CoV-2 and SARS-CoV are closely similar except that ORF3b and ORF10 are found in SARS-CoV-2 but this homology in SARS-CoV is limited in detection (Chan et al., 2020a; Wu and McGoogan, 2020).

SARS-CoV-2 infects the host when its spike protein binds to the membrane-bound glycoprotein receptor named the angiotensin-converting enzyme 2 (ACE2), of the host cells (Zhou et al., 2020). In humans, ACE2 protein is expressed in a broad range of tissues such as the lung epithelium mostly the type II pneumocyte, the endothelium, the myocardium, the spleen, kidneys, the gastrointestinal tract, bone marrow among other tissues, indicating the possible effect on multi-organ (Hamming et al., 2004). The X-chromosome also encodes ACE2 which may possibly relate to variation in the occurrence of COVID-19 among the two sexes (Wang et al., 2020). Upon infection, the virus internalized inside the host cells through endocytosis however without getting access to the intracellular compartment of the cell. After internalization, at least, the transmembrane cellular serine protease 2

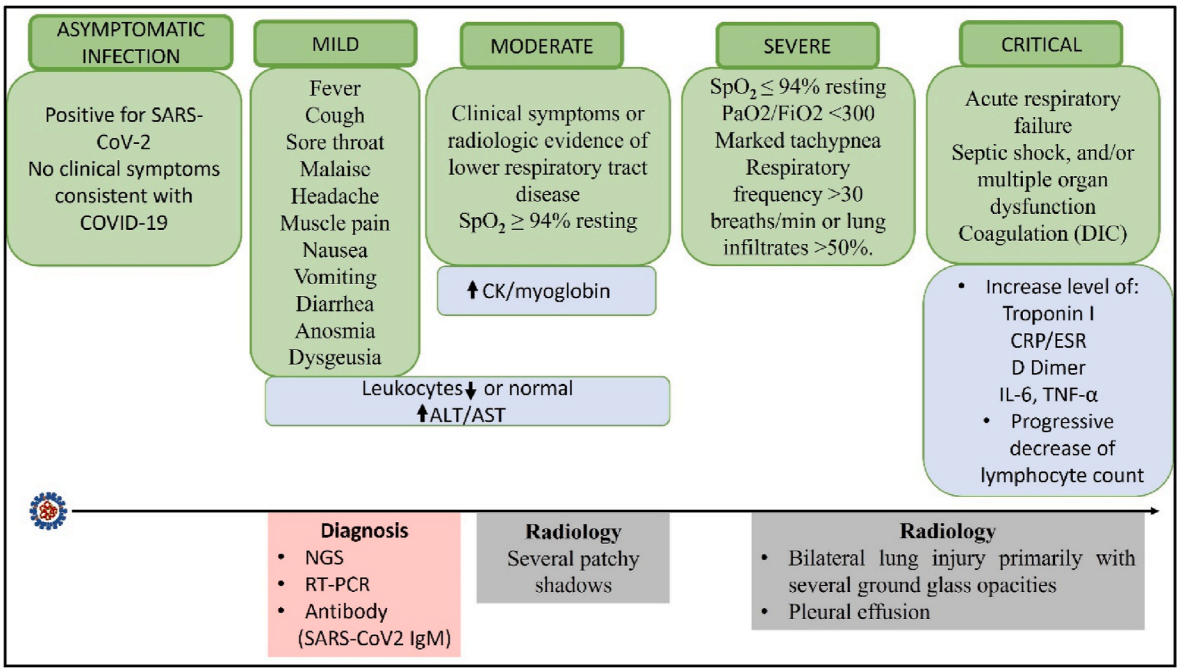


Fig. 1. Symptoms and characteristic features of COVID-19.

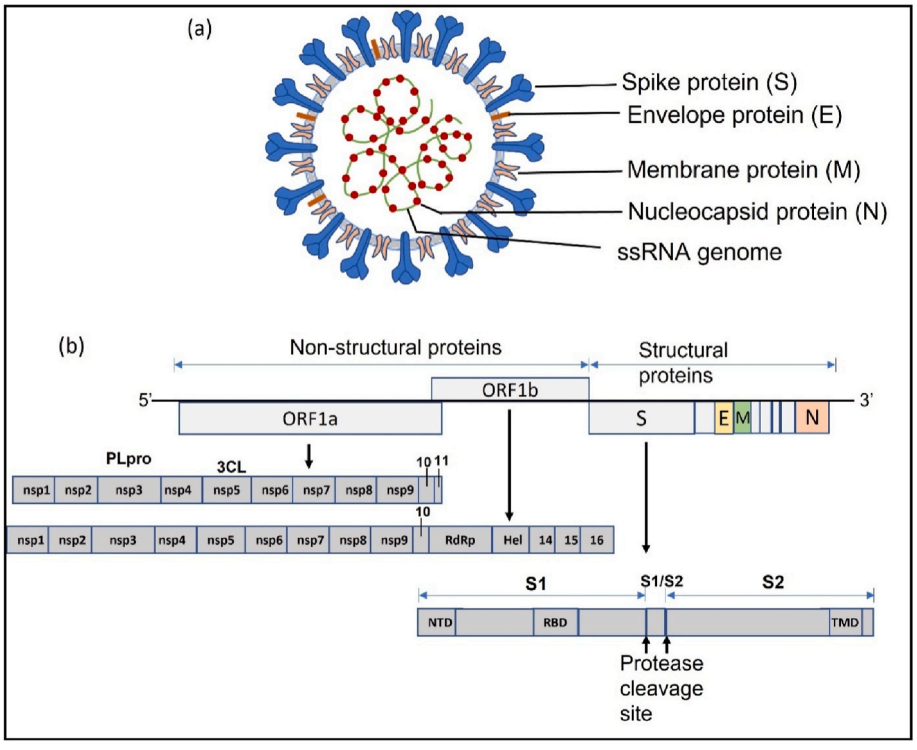


Fig. 2. Structure of SARS-CoV-2. (a) Spherical crown structure of SARS-CoV-2 consisting of four structural proteins and a positive-sense, single-stranded RNA (ssRNA) genome of 30 kb in length. (b) Genomic structure of SARS-CoV-2. ORF1a and ORF1b towards 5′-terminal encode 16 different non-structural proteins. The genome towards 3′-terminal end encodes the structural proteins - S, spike protein; E, envelope protein; M, membrane protein; N, nucleocapsid protein. The S1 subunit of the S protein contains a receptor-binding domain (RBD) that binds to the receptor of host angiotensin-converting enzyme 2; the S2 subunit mediates binding between the membranes of the host cells and the virus.

(TMPRSS2) as a protein primer, induced the cleavage of S protein into S1 and S2 protein subunits which is necessary for activation of the membrane fusion domain (Hoffmann et al., 2020). This is followed by membrane fusion that made access for the viral RNA genome to enter the intracellular compartment of the host cell where the viral genome encodes its structural and non-structural components leading to the amplification of the viral genome inside the host cells. One non-structural protein of the virus, a replicase, is an RNA-dependent RNA polymerase (RdRp) required for viral RNA replication and amplification (Cheng et al., 2005). Whereas, the viral structural proteins are transported to the endoplasmic reticulum and golgi bodies before they are finally budded and released outside via exocytosis (Du et al., 2009; Fehr and Perlman, 2015; Siu et al., 2008). It is important to identify clinical markers to enable tracing the progression of the disease toward critical cases such that timely interventions can be ensured to prevent the disease from becoming fatally severe. In addition, the identification of biomarkers would help in the discovery of new drugs to treat this novel disease, or even as a prognostic indicator in treatment

strategy. For instance, commonly identified respiratory disease biomarkers such as IL-6, and ICAM-1 are responsible for high mortality while of nitric oxide biomarkers are associated with increased survival (Jain, 2017).

6. Biomarkers associated with COVID-19

Timely detection, diagnosis, prognosis, and effective treatment strategies require a specific and sensitive molecular biomarker (Parihar et al., 2020, 2022a, 2022c, 2022d). The current biomarkers associated with COVID-19 are from the understanding of the mechanism of the viral pathogenicity, from the cells affected and organs damaged. The list of biomarkers related to COVID-19 is listed in Table 2.

6.1. Nucleic acid and proteins of SARS-CoV-2 as biomarkers

When detecting COVID-19-associated biomarkers in a symptomatic individual would mean either detecting the coronavirus or diagnosing the disease and in the latter aiming to differentiate from other viral pneumonia, or other pneumonia associated with mycoplasma, bacteria, and others, even from non-infectious diseases. Meanwhile, the detection of biomarkers in asymptomatic individuals would mean the identification of the virus itself. The genome of the SARS-CoV-2 itself served as a primary biomarker in identifying the presence of the virus in the patient. Helicase (Hel), nucleocapsid (N), transmembrane (M), envelope (E) and glycoproteins spike (S) of the virus is the candidate molecular targets. In addition, Hemagglutinin-esterase (HE), ORF1a and ORF1b, and RNA-dependent RNA polymerase (RdRp) encode the structural proteins that can be useful in the diagnosis of the disease (Tang et al., 2020). WHO recommended identifying E gene followed by RdRp gene assay to confirm the initial screening of the disease (Corman et al., 2020). While countries like United States use the nucleocapsid protein targets N1 and N2 in the assays (Holshue et al., 2020). Among the three RT-PCR assays that target the RdRp/Hel, S, and N genes as a biomarker to detect the virus SARS-CoV-2, RdRp/Hel assay is the most sensitive and specific with the lower limit of detection (Chan et al., 2020b). In others, antibodies against S protein are used in detecting and diagnosing the presence of viruses (Hoffmann et al., 2020; Li et al., 2003). Proteins encoded by the virus could serve as a biomarker in detecting the virus, however, in this, large amounts of samples are needed apart from the complexities faced in detecting the proteins. The proteins would rather be useful as a target in designing drugs against this virus (Udugama et al., 2020).

6.2. Haematologic and inflammatory biomarkers

Typically, viral infection is actively cleared through an innate immune response, followed by an adaptive immune response if required. Innate immune components include Type I interferons (IFNs), and activation of macrophages and neutrophils to produce pro-inflammatory cytokine and NK cells. Whereas adaptive immune responses lead to organize attacks by antigen-specific $CD8^+$ cytotoxic T cells, the Th1 subset of $CD4^+$ T helper cells coordinates immune response against pathogens. Commonly, a patient succumbed to COVID-19 due to the strong inflammation caused by SARS-CoV-2 associated with increased inflammatory biological markers and cytokines, often termed the cytokine storm. This is prominent in individuals at high risk for COVID-19 including male and elderly patients (Petrilli et al., 2020; Zeng et al., 2020a). Biomarkers associated with haematologic and inflammatory biomarkers are discussed here.

6.2.1. Leukocytes

Disproportionate numbers of white blood cells or leukocytes are frequent indicators of individuals affected with COVID-19. The granulocytes and agranulocytes are the two groups of white blood cells of which eosinophils, basophils, and neutrophils are the granulocytes while lymphocytes and monocytes comprise the latter group. An

Table 2
Biomarkers associated with COVID-19.

Biomarker	Description	References
Haematologic		
Leukocytes, Lymphocytes and Platelets	Patients (N = 274) requiring the intensive care unit (ICU) present showed an increase in leukocytes and neutrophils (+3.1 × 109/L and +6.4 × 109/L, respectively), a lymphocyte decrease and a platelet rise (−1.6 × 109/L and +60.8 × 109/L, respectively).	(Urbano et al., 2022)
Biochemical		
Alanine transaminase (ALT)	Liver biomarkers, significantly increased the Average ALT value 31.14 U/L in Covid Patients (N = 279).	Safari et al. (2020)
Aspartate aminotransferase (AST)	Liver biomarker, the average AST value 44.03 U/L in all patients (N = 279).	Safari et al. (2020)
Total bilirubin	During hospitalization within 2 weeks, 24 (11.5%) patients (N = 417) had total bilirubin levels elevated to more than 3 × the upper limit of normal.	Cai et al. (2020)
Alanine aminotransferase	During hospitalization within 2 weeks, 49 (23.4%) (patients (N = 417) had Alanine aminotransferase levels elevated to more than 3 × the upper limit of normal.	Cai et al. (2020)
Aspartate aminotransferase	31 (14.8%) patients (N = 417) having Aspartate aminotransferase levels elevated to more than 3 × the upper limit of normal, during hospitalization within 2 weeks.	Cai et al. (2020)
Gamma-glutamyl transferase	51 (24.4%) patients (N = 417) having Gamma-glutamyl transferase levels elevated to more than 3 × the upper limit of normal, during hospitalization within 2 weeks.	Cai et al. (2020)
Creatine kinase-MB (CK-MB)	Higher CK-MB concentrations were significantly associated with severe disease and mortality in COVID-19 patients (N = 11,791). Biomarkers of myocardial injury might be useful for the risk stratification group.	Zinellu et al. (2021)
Lactate dehydrogenase (LDH)	Elevated LDH was present in 44% (34%–53%) of the patients (N = 10399)	Martha et al. (2021)
Myoglobin	In COVID-19 patients (N = 357) elevated myoglobin and CK-MB on admission may be effective predictors for adverse outcomes, and combined use of myoglobin and CK-MB had a better performance for prediction.	Yang et al. (2021)
Creatine kinase (CK)	Level of CK associated with viral mRNA elimination, suggesting that a constitutive decrease of CK levels probably predicts a favourable recovery response for COVID-19 patients	Yuan et al. (2020)
Cardiac troponin I	Elevated cardiac biomarkers cardiac troponin I in patients with both severe and fatal COVID-19 (N = 3377)	Ali et al. (2021)

(continued on next page)

Table 2 (*continued*)

Biomarker	Description	References
Coagulation		
Procalcitonin (PCT)	Meta-analysis showed an elevated serum PCT, associated with a poor outcome in COVID-19 (N = 5350).	Huang et al. (2020)
D-dimer	Meta-analysis showed an elevated serum D-dimer associated with a poor outcome in COVID-19 (N = 5350).	Huang et al. (2020)
Inflammatory		
Erythrocyte sedimentation rate (ESR)	ESR has been reported to be significantly associated with the high risks of the development of severe COVID-19.	Qin et al. (2020b)
C reactive protein	Sensing of C-Reactive Protein Using an Extended-Gate Field-Effect Transistor with a Tungsten Disulfide-Doped Peptide-Imprinted Conductive Polymer Coated Biosensor. Sensing range from 1.0 pg/mL to 1.0 ng/mL.	Herold et al. (2020)
Serum Ferritin	Serum ferritin is considered both a prognostic and stratifying biomarker that can also contribute to therapeutic decision-making concerning patients with COVID-19.	(Dhar et al., 2021; Kappert et al., 2020)
13 cytokines (IL-1β, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-17, TNF-α and IFN-γ)	Out of the 13 cytokines, IL-6 and IL-10 showed statistically significant standardized mean differences across studies. Classifiers with mean values of both IL-6 and IL-10 as covariates performed well with an accuracy of ~92% which was significantly higher than the accuracy reported in the literature with IL-6 and IL-10 as individual covariates.	Dhar et al. (2021)

individual with severe cases of COVID-19 had remarkably high white blood corpuscles although lymphocytes and platelet counts are reduced compared to normal individuals or those affected mildly (Henry et al., 2020). The use of white blood cells as markers of COVID-19 however requires better understanding.

Lymphopenia or a decrease in lymphocyte count is the most common observation in patients with severe COVID-19 (Yang et al., 2020). This decrease is typical of the different cases reported. Lymphopenia is defined as an absolute lymphocyte count of $<1.0 \times 10^9$/L. While this decrease is consistent in severe cases of COVID-19 patients, the same may not be always true in the case of milder symptoms where both increased and decreased levels are found (Chen et al., 2020; Zeng et al., 2020b).

Lymphocytes response are among the initial action against the viral attack such as those of the current SARS-CoV-2, thereby low lymphocyte count perhaps indicates a defect in the immune response against the viral attack. Helper T cells or supporter T cells were decreased in severe cases of COVID-19. Although naïve helper T cells showed an increase in number, memory helper T cells were reduced in counts. In addition, decrease in cytotoxic T cells in COVID-19 indicates the disease progression to a severe state (Cossarizza et al., 2020; Qin et al., 2020a). Low lymphocyte components including lymphocyte, $CD3^+$, $CD4^+$, $CD8^+$ T cells, and B cells correspond to an escalation in disease progression and a higher risk of the disease (Cossarizza et al., 2020). High neutrophils-lymphocyte (NRL) ratio and low eosinophils, basophils and monocytes are evident in severe cases (Qin et al., 2020a; Wang et al., 2020), 75.8% of COVID-19-affected individuals expressed as high as 2.973 NLR during admission in the hospital due to progression of the disease (Xia et al., 2020). The NLR is an important marker of inflammation indicating the severity of the disease (Liu et al., 2020) which is commonly observed among patients above 50 years of age (Zeng et al., 2020b). The increase in neutrophils generally occurs before the reactive lymphocytes (Zini et al., 2020). An increase in neutrophils may also relate to superimposed infection from bacteria (Lippi et al., 2020b). Overall, failure in the proportionate regulation of inflammatory cytokines, an increase in the pathway leading to the destruction of lymphocytes due to the coronavirus attack, or the pathological increase in the neutrophils itself may contribute to the high NLR (Bai et al., 2020). While, low eosinophils corresponded to a decrease in lymphocyte count, and in a report of 140 patients with COVID-19, around half of the patients showed low eosinophils correlating with the lower lymphocytes in both the mild and the severe cases (Zhang et al., 2020). The importance of low eosinophils in COVID-19 requires further studies to confirm its sensitivity as a marker for COVID-19 prognosis.

6.2.2. Platelets

Low platelet count is a marker found in those associated with severe COVID-19. Platelet counts are generally considered as an indicator for scoring multiorgan dysfunction or chronic health evaluation, and thereby thrombocytopenia or a low platelet count is used as a reference for the severity of the disease (Lippi and Plebani, 2020a). Moreover, the progression of COVID-19 disease can be monitored by the level of platelets whereby, a progressive decrease in the count can be an effective prognostic factor (Zhang et al., 2020). Thrombocytopenia can be evident in 5–41% of COVID-19 patients, generally among severe to critical individuals (Tang et al., 2020). There is a significant correlation between patients with thrombocytopenia and those that died from the COVID-19 disease in comparison to those without thrombocytopenia. Thereby, thrombocytopenia acts as an independent risk factor for patients that died in hospitals due to COVID-19. Patients with a raised platelet count of 50×10^9/L are at a lower risk to succumb to the disease (Liu et al., 2020).

6.2.3. Interleukins

Cytokine storms involve the excessive release of proinflammatory molecules. The major cause of death from COVID-19 is due to acute respiratory distress syndrome (ARDS) causing failure in the respiratory system. IL-6 is a common cytokine released by activated macrophages and correlates with severe COVID-19 cases. An increase in IL-6 is associated with intensive care in hospitals and with ARDS. Those who succumbed to ARDS exhibited a sustained increase in IL-6 and IL-1 (McGonagle et al., 2020). IL-2, IL-6, IL-8, IL-10, TNF-α are important cytokines and chemokines associated with disease severity as per the study conducted in Wuhan (Qin et al., 2020a). In view of the importance of inflammatory cytokines in SARS, and disease severity, several drugs targeting inflammatory markers are in clinical trials (Vincent et al., 2005).

6.2.4. C-reactive protein

C reactive protein (CRP) level is elevated in COVID-19 patients and is associated with fatal cases of the disease (Sahu et al., 2020). Two independent studies reported CRP levels of 57.9 mg/L ($P < 0.001$) (Qin et al., 2020a) and >41.8 mg/L (Liu et al., 2020) in severe cases of COVID-19 patients. In a study conducted in China, computed tomography scores were not very efficient in differentiating mild diseases from severe ones. The increase in CRP in the early period of the infection before the CT findings can be an important indicator of the disease infection which can be useful as a potential marker for disease detection (Tan et al., 2020). This observation seemed to be more effective in evaluating the disease progression in comparison to the erythrocyte sedimentation rate (ESR). The elevation in the level of IL-6 followed by CRP may refer to the severity of lung lesions (Wang et al., 2020) that

need attention for a mechanical ventilator (Herold et al., 2020). In others, an increase in CRP with IL-6 or an increase in CRP, IL-6, and lactate dehydrogenase (LDH) had been correlated with poor prognosis associated with respiratory risk (Liu et al., 2021; Poggiali et al., 2020). CRP as a biomarker can be best obtained at sensitivity and specificity of 83% and 91% respectively (Tan et al., 2020).

6.3. Markers associated with disseminated intravascular coagulation

Severe and critical cases of COVID-19 demonstrate coagulation disorder and disseminated intravascular coagulation (DIC) which remained a major cause of the patient's mortality. Multi-organ failure can result from diffused and impaired microvascular systems leading to the mortality of patients from COVID-19 (Tang et al., 2020). The process of coagulation activation rises at its peak when it is in DIC state. When the disease is at DIC state, the patients exhibit sepsis. On injury, activated monocytes and endothelial cells produce cytokines. Free thrombins began to circulate, and without regulated anticoagulants, platelets are activated to induce fibrinolysis. Later, fibrin-associated markers such as D-dimer and fibrin degradation product (FDP) are raised in level significantly, which as a result activates coagulation associated with the demise of the patients (Lippi and Favaloro, 2020). Elevated D-dimer is commonly observed in 36–43% of COVID-19 individuals (Lippi and Favaloro, 2020). D-dimer along with the prothrombin time (PT) assay is a useful reference for the prognosis of COVID-19 (Perlman, 2020). In one report 58% of COVID-19 patients showed extended PT (Lupia et al., 2020). In another case study of patients (n = 183) with coronavirus-associated pneumonia, D-dimer, PT, activated partial thromboplastin time (APTT), antithrombin, fibrinogen, and FDP were measured. The patients that expired showed more D-dimer and FDP and longer time for APTT and PT assays in comparison to those that survived at the time of admission, whereas, reduced antithrombin and fibrinogen levels were associated with mortality among the groups studied (Tang et al., 2020). The study indicates the dysregulation of active coagulation and damage in anticoagulants. Timely evaluation of the platelet count and coagulation function will be significant in the strategic treatment of the patient infected with SARS-CoV-2. Mechanical ventilation in ARDS may not be relevant always where more damage to the lungs can be found. Rather, prompt treatment with anticoagulation would be beneficial (Lippi and Plebani, 2020b).

6.4. Procalcitonin

Procalcitonin (PCT) is produced in the C-cells of the thyroid gland as a precursor peptide of calcitonin. Its level is however undetectable in a normal state but increased as a consequence of infection from bacteria, fungus, or parasites. It rises from the normal level of <0.1 ng/ml to more than 100 ng/ml, primarily produced by extrathyroidal tissues (Karzai et al., 1997) such as the liver, kidney, pancreas, intestine, lung, and leukocytes. An important differentiation between viral infections to previously mention other infections is the decrease in the release of PCT because of its suppression by cytokines like interferon-γ released from viral infection (Cleland and Eranki, 2021). PCT level is either mildly or not affected by non-infectious stimuli. Among the COVID-19-affected individuals, comparatively, the level of PCT is higher in severe patients than that in moderately affected patients (Zhang et al., 2020; Zhang et al., 2020). An increase in serum PCT is more than four folds in severe patients and over eight folds higher in critically affected patients relative to that of the control individuals without COVID-19 (Hu et al., 2020). A slight increase in PCT level but less than 0.5 ng/ml differentiate the patients from COVID-19 from other COVID-19-negative patients (Chen et al., 2020), and the increase in level is correlated with a higher risk of infection. PCT level may remain within a reference value in milder COVID-19 patients however, a significant increase in the value may indicate a complication from other infections such as bacteria, and the severity of COVID-19 disease (Lippi and Plebani, 2020a). Therefore, the PCT level may be more helpful in the initial state of disease (Ponti et al., 2020) and serial-level analysis of PCT would be meaningful for prognostic use (Hu et al., 2020).

6.5. Lactate dehydrogenase

When cell membranes become necrotic lactate dehydrogenase induces pyruvate of the glucose metabolism pathway to produce lactate. In view of SARS-CoV-2 infection, damage and pneumonitis of the lungs may affect lactate dehydrogenase to induce the production of lactate. An increase in tissue damage can relate to higher levels of lactate dehydrogenase and a link between lactate dehydrogenase and SARS-CoV-2 infection has been made (Guan et al., 2020a). On serial evaluation, the level of lactate dehydrogenase was significantly higher in severe COVID-19 patients admitted to the intensive care unit in contrast to those who do not require admission to the intensive care unit (Fan et al., 2020). Hence, lactate dehydrogenase can be an important marker for examining the disease progression.

6.6. Cardiac troponin I

Cardiac injury is observed in severe and critical patients infected with SARS-CoV2 infection. Patients with severe COVID-19 exhibit high levels of cardiac troponin I (cTnI), which refers to cardiac injury, compared to the milder form of the disease (Lippi et al., 2020a). An elevated level is associated with the severity of the disease and a higher risk of mortality ("Cardiac Troponin-I may be a predictor of complications and mortality in COVID-19 patients," 2020). Cardiac troponin levels could be due to myocarditis due to SARS-CoV-2 infections (Vrsalovic and Presecki, 2020). Myocarditis in COVID-19 patients was reported in causing a remarkable increase in the concentration of high-sensitivity cardiac troponin I to as high as 9002 ng/L whereas, the normal concentration is less than 40 ng/L (Doyen et al., 2020). Old-age patients mostly come with elevated cTnI and are predominantly male patients (Shah et al., 2020). Acute cardiac injury is commonly seen in as much as one-fifth of the patient and the survival rate associated with this is 50%. It thereby indicates the importance of measuring the level of troponin routinely in COVID-19 patients to rule out the possibility of myocarditis (Doyen et al., 2020).

6.7. The renal markers

COVID-19 is multifaceted because of several tissues affected and biological markers involved at presentation. Some studies suggest the relation of SARS-COV2 infection with renal damage presented as acute kidney injury, haematuria, proteinuria, and blood urine nitrogen (BUN) (Cheng et al., 2020; Martinez-Rojas et al., 2020; Ronco and Reis, 2020). Renal dysfunction in COVID-19 is proposed as the consequence of SARS-CoV2 infection, cytokine storm, immune-associated impairment, and hypercoagulation (Hirsch et al., 2020; Pei et al., 2020; Su et al., 2020). In addition, renal impairment is manifested as an increase in the level of serum creatinine (SCr) clinically (https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf). A case study report a marked increase in the level of SCr from 53 μmol/L to 270 μmol/L until it reached 1147 μmol/L (Faqeeh and Madkhali, 2020). Severe and critically ill patients are associated with an elevated level of creatinine than that of a milder form of the disease, and the combined increase in blood urine nitrogen and creatinine impact negatively on the outcome of the patient (Lippi and Plebani, 2020b). In another study, the increase in renal biomarkers in association with proteinuria and haematuria is accompanied by critical COVID-19 patients (Pei et al., 2020; Petrilli et al., 2020), and the higher creatinine irrespective of age is related to higher mortality risk (Chen et al., 2020; Cheng et al., 2020; Pei et al., 2020).

6.8. The liver markers

There is increasing evidence about the association between COVID-19 and liver dysfunction (Gao et al., 2021). The ACE2 receptors, the target for SARS-CoV-2, are found in intestinal cells, cholangiocytes, and hepatocytes (Agarwal et al., 2020). In the analysis of the liver function in COVID-19 patients, 76.9% of the patient exhibited liver injury without any statistical difference between male and female patients (Kumar et al., 2020). In another study review, 2–11% of COVID-19 patients presented underlying chronic liver disease while 14–53% reportedly developed hepatic impairment (Zhang et al., 2020) frequently associated with severe cases. Several studies reported an increase in the level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). An increase in these enzymes indicates the need for intensive care and is associated with a statistically significant risk for mortality ($p = 0.001$). Moreover, the ratio of AST/AST is a good marker for a higher risk of mortality as per the ROC analysis (AUC = 0.713: p = 0.001) (Medetalibeyoglu et al., 2020). Hepatocytes infected with SARS-CoV-2 demonstrated noticeable mitochondrial swelling dilated endoplasmic reticulum and decreased glycogen granule (Wang et al., 2020). Increase in hyperbilirubinemia (OR = 1.7, 95% CI:1.2–2.5, I2 = 0%) and hypoalbuminemia (OR = 7.1, 95% CI: 2.1–24.1, I2 = 71%) were also reported in COVID-19 patients (Wong et al., 2020). Although marker of indirect liver injury like hypoalbuminemia level is significantly increased in severe COVID-19 patients, factors including systemic inflammation, malnutrition, and the timing of presentation to the hospital could contribute to the rising level (Mantovani et al., 2020).

7. Biosensors for the detection of COVID-19 biomarkers

The biomarkers and risk factors associated with COVID-19 should be monitored carefully in order to assess the disease pathophysiology, and severity and to assess therapeutic response. Post-COVID-19 complications can also be assessed by analyzing inflammatory biomarkers in patients' blood. Most conventional serological tests take a long time to provide results which could cost the patient lives. Recent advances in the field of biomedical sciences have provided a cost-effective assessment of various biomarkers in a faster and more user-friendly manner. In this context biosensor-based detection of various biomarkers has gained considerable attention due to added advantage of high specificity, high selectivity, and cost-effectiveness(Kumar et al., 2022; Parihar et al., 2020, 2021, 2022b, n.d.; Sadique et al., 2022; Singhal et al., 2022). Currently, biosensors are crucial tools in environmental monitoring, food processing, and clinical diagnostics to identify a variety of analytes, including particular proteins, viruses, bacteria, cancer biomarkers, nucleic acids, and toxins. Besides this, advances in nanotechnology plays a crucial role in the development of biosensors by combining nanomaterials with biosensors based on their unique properties. This improves the detection capabilities of biosensors by maximizing their surface area in contact with analytes and enhancing their electrical or optical capabilities. There are several recent reviews that explain the importance of nanomaterial-based biosensors for the diagnosis of COVID-19 (Dave et al., 2020; Naikoo et al., 2022; Narita et al., 2021; Pandey, 2020), and the role of wearable sensors for remote monitoring of COVID-19 symptoms (Liu et al., 2021; Mirjalali et al., 2022). A biosensor's selectivity refers to its capacity to only detect the analyte while other similar analytes and pollutants are present. With a nucleic acid genome, a protein capsid that surrounds the genome, and occasionally a lipid covering the genome and a protein coat, viruses typically exhibit structural similarities. The protein covering the virus sets it apart from bacteria. It might be possible to selectively identify some proteins on the capsid and then target them with other proteins through protein-protein interactions. The best immobilization of the monolayer of probes that target the selected biomarkers on the analyte on the sensor surface is typically how good selectivity is attained. Developing probes that are particular to the target typically requires a committed team and 6–12 months of effort in this area of research. This is unquestionably a barrier to the rapid development of a biosensor during pandemics like COVID-19. However, the progress in nanotechnology and the speed at which new materials are discovered and created offer researchers a strong chance to create chemical probes that are exclusively applicable to the target being detected. In this section, we overview currently available biosensors for the detection of COVID-19-associated biomarkers and risk factors which includes IL3, CK-MB, C-reactive protein, LDH, AST, APT, cTnI etc. A summary of biosensors available to detect these biomarkers has been presented in Table 3. One of the important biomarkers IL-3 is also involved in sepsis a disorder that results from a bodily reaction to severe microbial infection and can be deadly or life-threatening. When the immune system releases chemicals into the bloodstream to combat an infection, this results in inflammation and a medical emergency known as sepsis. Recently, the surface characteristics of a capacitance biosensor that is used to detect IL-3 were improved using a complexed longitudinal zeolite and iron oxide nanocomposite made from coal mine fly ash. Through the use of an amine linker, this anti-interleukin-3 (anti-IL-3) antibody was conjugated to the surface of the zeolite and iron oxide-complexed capacitance electrode. FESEM, FETEM, and EDX investigations were used to analyze the nanocomplex's morphological and chemical components. With a regression coefficient (R2) of 0.9673 [$y = 1.638 \times 1.1847$] the longitudinal zeolite and iron oxide nanocomposites at about 30 nm helped to achieve the linear limit of detection of 3 pg/mL. The improved surface current and higher antibody immobilization on the sensor surface brought about a lower detection limit in the dose-dependent range (3–100 pg/mL). Additionally, control experiments using pertinent biomolecules failed to show changes in capacitance; however, when IL-3 levels were increased in human blood, capacitance increased, demonstrating the specificity and selectivity of IL-3 detection (Chen et al., 2021).

Another very sensitive MIPs-based biosensor was developed to detect C-reactive protein (CRP) an inflammatory biomarker. This sensor produces a very sensitive and focused detection of CRP using conductive and biocompatible graphdiyne (GDY) nanosheets, antifouling, and customized MIPs. Dopamine was used because of its simple polymerization process and the verified low fouling property of polydopamine as the functional monomer to create a stable complex with the template molecule via hydrogen bonding and multipoint electrostatic attraction. To increase electrochemical responsiveness and create a favourable environment for the bioactive protein molecules, GDY with good biocompatibility and conductivity was first synthesized independently before being incorporated into C-reactive protein imprinted polymers (C-MIPs). With a LOD of 0.41,105 ng/mL, this specially constructed C-MIPs biosensor showed a larger linear detection range of 105 to 103 ng/mL. The C-MIPs biosensor also showed good selectivity, reversibility, and reusability in addition to a brief rebinding time and long-term stability. Notably, the C-MIPs biosensor's great sensitivity and selectivity as well as good antifouling characteristics were demonstrated by the fact that it worked well even in complex serum samples with no discernible signal suppression. The created C-MIPs biosensor functioned effectively in samples of human blood, demonstrating its potential for use in real-world applications. (Cui et al., 2022). The concentrations of common blood biomarkers (such as CRP and interleukin as reported for COVID-19) frequently serve as the signature of the infection at the early stages of the infection when there is less knowledge of the characteristics of the viral strain. A multiplexed system that enables the detection of numerous biomarkers is desirable for a quick, accurate, and early identification of the disease because, as previously mentioned, the detection of COVID-19 currently involves the combination of more than two biomarkers. By physically isolating several sections of the sensor surface, multiplexing can be accomplished, with each isolated area functioning as a separate sensor.

For the purpose of detecting bilirubin, the fluorescent platform (2,2′-((1E,1′E)-((6-bromopyridine-2,3-diyl) bis(azanylylidene)) bis(- methanylylidene diphenol) or BAMD was created. A green and

Table 3
Biosensors available for detection of biomarkers associated with COVID-19 mediated complications.

Sn no.	Biomarker	Detection technique	Limit of Detection (LOD)	Linear range	Sample	Ref.
1	Alanine aminotransferase (ALT)	Cyclic voltammetry (CV)	55.3 μA mM	1 to 500 μM^{-1} cm^{-2}	real human serum and whole blood samples	Li et al. (2006)
2	Alanine aminotransferase (ALT)	Amperometry	8.48 U/L	10–900 units/L	spiked ALT samples	Thuy and Tseng (2016)
3	Aspartate aminotransferase (AST)	Amperometry	10 U/L	25–1000 units/L	QC Serum	Guo et al. (2008)
4	Aspartate transaminase (AST) and Alanine transaminase (ALT)	Electroanalysis	20 units/L for AST and 25 units/L for ALT	30–240 units/L for AST and 43–480 units/L for ALT	Human plasma sample	Han et al. (2011)
5	Bilirubin	Colorimetric and Fluorimetric techniques	2.8 and 3.3 pM at pH = 7.4 and 9.0, respectively	1 pM–500 μM	human blood and urine sample	Ellairaja et al. (2017)
6	Cardiac troponin I (cTnI)	Differential pulse voltammetry (DPV)	0.42 pg/mL	–	serum samples	Han et al. (2021)
7	Creatine Kinase (CK-MB)	Surface Plasmon Surface (SPR)	0.209 ng m/L	5.0 ng m/L −100.0 ng m/L	urine and saliva samples	Ferreira et al. (2021)
8	Lactate dehydrogenase (LDH)	Chronoamperometry	0.41 mM	0.5–20 mM	artificial sweat	Hiraka et al. (2021)
9	Lactate dehydrogenase (LDH)	Chronoamperometry	1 μM	0.5–3 mM	real samples of yogurt and wine.	Istrate et al. (2021)
10	Myoglobin (Mb)	Cyclic voltammetry and Electrochemical impedance spectroscopy,	1.0–30.0 mmol/L & 0.05–0.55 mmol/L for TCA and NaNO2	0.33 mmol/L and 0.01 mmol/L for TCA and NaNO2	–	Shao et al. (2021)
11	Procalcitonin (PCT)	Photoelectrochemical (PEC)	0.03 pg m/L is	0.1 pg m/L- 50 ng m/L	Serum samples	Li et al. (2021)
12	D-dimer (DD)	Electrochemical impedance spectroscopy (EIS)	8.92 ng m/L	10–500 ng m/L	unfiltered blood samples	Tasić et al. (2021)
13	Interleukin-3 (IL-3)	Capacitance method	3 pg/mL	3–100 pg/mL	human serum	Chen et al. (2021)
14	Interleukin-6 (IL-6)	Differential pulse voltammetry (DPV)	5.1 pg/mL	10–500 pg/mL	Spiked PBS	Tan et al. (2021)
15	C reactive protein	Electrochemical impedance spectroscopy (EIS)	0.41 × 10−5 ng/mL	10^{-5} to 10^{3} ng/mL	human serum samples	Cui et al. (2022)
16	Ferritin	Anchored mAb to graphene field-effect transistors	0.23 nM	2–100 ng cm−2	Human serum	Esteban et al. (2022)

straightforward imine-based fluorescent compound called BAMD was synthesized and then examined using NMR and ESI mass spectrometry. With an 870 ps lifespan and a quantum yield of 0.85, BAMD showed a strong fluorescence intensity. As a result, it was employed to quantify bilirubin utilizing colorimetric and fluorimetric methods at physiological and basic pH. Under ideal experimental circumstances, the probe preferentially detects bilirubin in the presence of other interfering biomolecules and metal ions. At a pH of 7.4, the reported linear range of detection is 1 pM–500 μM, and at a pH of 7.4 and 9.0, the LOD is 2.8 and 3.3 pM, respectively. The probe uses the FRET principle to find the bilirubin. Human blood and urine samples were successfully used to assess the probe's usefulness. This fundamental idea may be used to develop a straightforward clinical diagnostic tool for jaundice based on the advantages mentioned above. Additionally, using the standard addition method, the biosensor was used to identify direct bilirubin in samples of human blood and urine. From bilirubin, a very good recovery was made. (Ellairaja et al., 2017). The sensor's reaction time is crucial if a diagnosis tool is to be actively used in a pandemic. When a biomolecule interacts with the sensor surface, the majority of transducers in the sensor react instantly (within 1 s). However, for a proper interpretation of the observed quantity, many of these signals occasionally need to be post-processed using cutting-edge electronics and computing systems. Additionally, there are a number of biosensors have been developed for biomarkers associated with Covid-19 as shown in the Supplemental file.

8. Conclusion

This review presented a general overview of several novel inflammatory, hematological, immunological, and biochemical biomarkers of COVID-19. The potential risk factors and clinical characteristics of patients have also been described that undoubtedly will help to reduce the mortality of COVID-19 patients. Moreover, the recent advancements in the development of biosensors and medical devices have great potential for rapid detection of various infectious diseases including COVID-19 and could be an effective complementary method with other diagnostic tests.

9. Future perspectives

There are various challenges have surfaced in the context of understanding the mechanisms of the pathogenesis of COVID-19 infection, effective diagnosis, and treatment strategies to combat COVID-19. Following are a few of the potential areas that could be worked upon in the near future.

- Extensive understanding of the structure and function of SARS-CoV-2 is needed to recognize the pathogenic mechanism of the virus.
- Moreover, structural studies of SARS-CoV-2 will help an added advantage in the determination of the presence of any mutations of the viral genome.
- Understanding the structure is necessary for designing and discovering of antiviral vaccines against SARS-CoV-2 infection. For this, the expression of ACE2 receptor binding region of S protein can be targeted as a focal point.
- Knowing the potential role of ACE2 inhibitors in managing COVID-19, it needs improvisation or advancement to avert any conflicting outcome. Other areas include the development of inhibitors for SARS-CoV-2 protease pathway to prevent the cleavage of the viral non-structural proteins.
- Attenuated or inactivated virus, viral vectors, DNA or RNA-based viral vaccine can be adopted as potential vaccines approach.

- Designing combinations of antibodies targeting different epitopes will be effective in neutralizing SARS-CoV-2 including those which have possibly mutated.
- Designing a drug aiming at inhibiting the membrane fusion reaction between the virus and endosomal membrane is an important area.
- Multiplex integrated electrochemical point of care device requires advancement in portable, rapid sensing, lost cost, and easy to use for specific and sensitive diagnosis of COVID-19.

Author contributions

Mintu Pal: Conceptualization, Supervision; **Thingreila Muinao**: Writing - Original Draft; **Arpana Parihar:** Writing - Original Draft; **Dilip Kumar Roy**: Writing - Review & Editing; **Hari Prasanna Deka Boruah**: Writing - Review & Editing; **Neeraj Mahindroo:** Writing - Review & Editing; **Raju Khan:** Conceptualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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