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REVIEW

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Biomarker based biosensors: An opportunity for diagnosis of COVID-19

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Abstract

Early diagnosis and treatment of diseases are crucial research areas of human health. For early diagnosis, one method that has proven efficient is the detection of biomarkers which can provide real-time and accurate biological information. Most biomarker detection is currently carried out at localised dedicated laboratories using large and automated analysers, increasing waiting time and costs. Smaller, faster, and cheaper devices could potentially replace these time-consuming laboratory analyses and make analytical results available as point-of-care diagnostics. Innovative biosensor-based strategies could allow biomarkers to be tested reliably in a decentralised setting. Early diagnosis of COVID-19 patients has a key role in order to use quarantine and treatment strategies in a timely manner. Raised levels of several biomarkers in COVID-19 patients are associated with respiratory infections or dysfunction of various organs. Through clinical studies of COVID-19 patient biomarkers such as ferritin, Interleukins, albumin and ...are found to reveals significant differences in their excretion ranges from healthy patients and patients with SARS-CoV-2, in addition to the development of biomarkers based biosensor such as stated biomarkers can be used and to investigate more specific biomarkers further proteomic analysis can be performed. This review presents several biomarker alterations in COVID-19 patients such as salivary, circulatory, coagulation, cardiovascular, renal, liver, C-reactive protein (CRP), immunological and inflammatory biomarkers. Also, biomarker sensors based on electrochemical, optical, and lateral flow characteristics which have potential applications for SARS-COV-2 in the recent COVID-19 pandemic, will be discussed.

KEYWORDS

biosensors, COVID-19, Corona virus, diagnosis

Abbreviations: ACE2, Angiotensin-converting enzyme 2; α-HBDH, Alpha-Hydroxybutyrate Dehydrogenase; ALT, Aminotransferase Alanine; AST, Aspartate aminotransferase; BNP, B-type natriuretic peptide; BNU, Blood Urine Nitrogen; CK, Creatine kinase; CK-MB, Creatinine kinase-muscle/brain activity; COVID-19, Coronavirus Disease 2019; CRP, C-Reactive Protein; CTn-I, Cardiac Troponin I; EIS, Electrochemical impedance spectroscopy; ELISA, Enzyme-Linked Immunosorbent Assay; ESR, Erythrocyte Sedimentation Rate; FGF, Fibroblast growth factors; G-CSF, Granulocyte Colony Stimulating Factor; GFR, Glomerular filtration rate; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamic Pyruvic Transaminase; Gr-FET, Graphene Field Effect Transistor; HBV, Hepatitis B virus; HEV, Hepatitis E virus; IgA, Immunoglobulin A; IL, Interleukin; INF, Interferon; IP, Interferon gamma-induced protein; LDH, Lactate Dehydrogenase; LFD, Lateral Flow Device; LSPCF, Localised Surface Plasmon Coupled Fluorescence; LSPR, Plasmonic Photothermal; Mb, Myoglobin; MCP, Monocyte chemoattractant protein; MIP, Macrophage Inflammatory Protein; NLR, Neutrophil/Lymphocyte Ratio; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; PDGF, Platelet-Derived Growth Factor; PLR, Platelet/Lymphocyte Ratio; PPT, Receptor Binding Domain; QDs, Quantum Dots; RBD, Receptor Binding Domain; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus; sHLH, Hemophagocytic Lymphohistiocytosis; TB, Total Bilirubin.

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1 | INTRODUCTION

A novel human coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the disease COVID-19 was identified in China in December 2019.[1] Severe acute respiratory syndrome coronavirus 2 has acquired the ability to establish sustained human to-human transmission. Its basic reproductive number, the number of secondary infections generated from one infected individual, is estimated to be between 1.4 and 6.49, with a mean of 3.28.[2] The recent emergence of SARS-CoV-2 in the human population has caused a dramatic and unprecedented impact of the economy and prompted mobilisation of public health authorities around the world to counter the rapid spread of the virus, and a wide variety of methods have been developed for the purpose of the rapid and accurate diagnosis of COVID-19 virus.[3] Several studies have reported haematologic and blood chemistry alterations in patients infected by SARS-CoV-2.[1] Major laboratory findings in COVID-19 patients identified by meta-analysis include leucopenia, leucocytosis, decreased albumin levels, increased levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), creatinine kinase, and bilirubin, and a high erythrocyte sedimentation rate (ESR).[4] A growing body of evidence suggests that SARS-CoV-2 infection can trigger the overproduction of cytokines in some patients, known as a cytokine storm, which is associated with poor outcomes.[5] As for other severe viral infections, the exacerbated production of proinflammatory cytokines may be involved in some of the pathophysiology of COVID-19, including pulmonary oedema, lung failure, and damage to the liver, heart, and kidneys. Compared to healthy adults, COVID-19 patients had higher levels of several biomarkers such as IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factors, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, IFN-γ, IP-10, MCP-1, MIP-1A, MIP-1B, platelet-derived growth factor, and VEGF.[5] Serum biomarkers associated with severe disease included IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α.[5] A recent retrospective study of 150 confirmed COVID-19 cases (68 fatal and 82 discharged cases) in Wuhan, China, identified several serological biomarkers that were more elevated in lethal cases than in survivors: elevated ferritin, IL-6, myoglobin, CRP, and cardiac troponin.[6] Together, these findings suggest that COVID-19 makes alterations in biomarkers compared to healthy individuals.

Since stricter requirements regarding human health have led to a rising number of clinical tests, there is an increasing need to develop highly sensitive, fast, and economic methods of analysis.[7] There are several reported biosensors based on biomarkers that accurately detect particular diseases such as non-invasive biosensor developed by Kumar et al.,[7] for oral cancer detection which used CYFRA-21 as a specific biomarker for oral cancer, same as these specific biomarkers for COVID-19 can also be used, and biosensor can be made.[8] The development of biosensors is probably one of the most promising ways to solve some of the problems concerning the increasing need to develop highly sensitive, fast, and economic methods of analysis in medical diagnostics.[7]

In this review, some consideration will be given to biomarkers levels in COVID-19 patients as well as biomarkers based-biosensors and their application in medical diagnostics, taking into account several crucial features. Researchers can break through bottlenecks of existing biomarker sensors by reviewing previous works and finally meet the various complex detection needs for the early diagnosis of COVID-19. The purpose of this review is to understand the present by reviewing the past.

1.1 | Types of biomarkers

Early identification and classification of COVID-19 patients is very important in order to use treatment strategies in a timely manner.[9]

According to research, several biomarkers have been identified to be increased in COVID-19 patients that are associated with respiratory infections and dysfunction of various organs. Prognostication of intense diseases such as COVID-19 can be possible by Prognostic biomarkers.[10] According to research, markers of the surface and sequence of the genome of the COVID-19 virus have been identified. This data is essential for identifying new biomarkers that can be used to diagnose and predict pandemics.[11]

1.1.1 | Salivary biomarkers

Saliva is a hypotonic fluid secreted by the salivary glands, including the parotid, submandibular, and sublingual glands. Since salivary glands have high permeability and molecular exchange and are also located in an environment rich in capillaries, blood, and acini, they can be an appropriate source for evaluating circulating biomarkers.[12]

Human salivary glands secrete 600 ml of serum and mucinous saliva daily containing mucins, minerals, growth factors, cytokines, buffers, electrolytes, enzymes and enzyme inhibitors, immunoglobulins, and glycoproteins.[13] Saliva is currently being considered as a potential diagnostic tool and as an alternative to other biological fluids such as serum or urine for diagnosis. Saliva assessment is a non-invasive, self-collecting method for detecting and monitoring COVID-19. Several salivary biomarkers, including salivary metabolism, have the ability to better detect COVID-19 and possibly identify a disease with the ability to classify the severity of the disease and even identify asymptomatic carriers.[14] It is competitive with nasopharyngeal swabs in terms of sensitivity and properties.

Human saliva is exuded about 600–1000 ml from the salivary glands every day. Saliva, like a serum, contains growth factors, IgA, cytokines, hormones, antibodies, enzymes, and microbes and has the diagnostic ability. Therefore, saliva can be used as a fluid to assess the physiological function of the body.[15] Although it is difficult to evaluate some analytics in saliva due to their low concentration compared to blood, highly sensitive molecular methods and nanotechnology have largely solved this problem. Saliva has been used to diagnose several diseases, including malignancies, autoimmune and hereditary diseases.[16] Saliva could be evaluated in terms of

proteomics, transcriptomics, metabolomics, microRNA, microbiome.[17] The viral infections are detectable by evaluating of presence viral RNA, DNA, microRNA, antigens, or antibodies in saliva, and some kind of viral infections may be detected up to 29 days after contamination.[18,19]

The potential use of saliva for the diagnosis of SARS-CoV-2 by expression of ACE2 as a SARS-CoV-2 major surface receptor[20] from the salivary gland has been scientifically proven.[21] In addition, recent studies by To et al. Have shown the presence of live SARS-CoV-2 in saliva.[22] The diagnostic use of saliva for several viral infections such as coronavirus has been shown >90% accordance between saliva and pharyngeal swabs.[23]

Recently, salivary biomarkers have been considered to use in advanced technologies like electro-mechanical systems, RNA-sequencing, fluorescent biosensors, photometric and electrochemical, and lab-on-chips.[24] Reduction or delayed generation of interferon (IFN) after coronavirus infection leads to high inflammatory reactions that lead to severe pulmonary disorders.[25]

The inflammatory cytokines production is depends on infection severity.[26] Increased expression of pro-inflammatory chemokines and cytokines, such as chemokine ligand (CC motifs; CCL) -2, CCL-3, Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), interleukin (IL) -2 and IL-8 have been shown during MERS-CoV infection.[26] According to recent studies in COVID-19 patients with increasing severity of infection, the amount of gamma-induced protein, interferon gamma 10 kDa, IL-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, macrophage chemotactic protein 1, macrophage inflammation of protein-1A, and tumour necrosis factor-α (TNFα) in serum were increased to inflammatory response induced of cytokine secretion.[5,25] Also, inflammatory markers like chemokines and cytokines are present in saliva and this source is available for diagnosis and prognosis of oral and systemic diseases such as COVID-19 infection.[16] Biomarkers such as lactate hydrogenase, CRP, malic acid, platelet degranulation, guanosine monophosphate, and macrophage-related proteins could be detected in saliva as well as in plasma.

Metabolism or the study of small molecules in cells, tissues, or fluids that identify a phenotype. Metabolomics are used to identify biomarkers and describe metabolic pathways in a variety of clinical conditions, including viral pathogens, especially those that affect the respiratory system, such as SARS and influenza.[27,28]

There are studies that suggest the specific regulation of microRNA is related to various infections, including respiratory virus infection.[29] The previous study has been demonstrated the effect of upregulation of miR-574-5p and miR214 expression and down-regulation of miR-223 and miR-98 expression on pro-inflammatory cytokines generation in coronavirus (SARS-CoV) infection.[30]

Recently, the expression potential of microRNAs has been considered as salivary biomarkers because microRNAs in extracellular vesicles are protected from degradation. Therefore, microRNAs in the biological fluid can be used to assess the condition of cell infection.[18] SARS-CoV-2 infects the host respiratory tract cells via ACE2 receptors.[31] Also previous studies the expression of ACE2 receptor in epithelial cells of salivary glands, oral and the tongue in humans.[32] So it can be an available source for the detection of SARS-CoV-2 infection.[33] Furthermore, the salivary glands may have hidden COVID-19 infection that may be activated.[34]

According to the information obtained, the study of salivary biomarkers is an opportunity to achieve a more complete molecular view of the clinical relationship and risk assessment of COVID-19, as well as the evaluation of new antiviral therapies.

1.1.2 | Blood biomarkers

Using of recovered COVID-19 patients serum has been approved as a safe and effective treatment in severe patients or to strengthen instant immunity of high-risk patients.[35,36] Boostels et al. have shown that a new class of inflammatory dendritic cells (inf-cDC 2) as a virus-specific antibody in serum can increase patient immunity.[37] In clinical trials, collecting enough volunteers for testing is one of the most important limitations.

In an interesting study, patients who recovered from acute respiratory syndrome induced by SARS-CoV were evaluated by metabolic assessment after 12 years. Phospholipids, organic acids, amino acids, carnitine, and inositol in the serum of these patients were different from healthy persons. Therefore, metabolism will be considered to evaluate long-term results.[28]

The existence of IgM and IgG blood antibodies in the serum versus COVID-19 proteins (e.g., S and N protein) can show a history of the previous infection regardless of any symptoms. Serum evaluation methods like lateral flow assays and ELISAs, to tracing of IgM/IgG antibodies or S and N proteins have been improved in human plasma (Figure 1).

Primitive SARS-COV-2 infection could be diagnosed by increases level of IgM antibodies 3–7 days after the viral attack and secondary SARS-COV-2 infection can be determined by enhancement of IgG level in serum that is mostly associated with increased IgM level. Generally, the presence of IgG or IgM/IgG in the serum shows active immunity.[38] According to research, the diagnosis of IgM was more variable than IgG and the results of both should be analysed to more precisely evaluate.[39]

White blood cells

Evaluation of immune response in 450 COVID-19 patients has been reported that severe cases compared with mild cases had lower lymphocyte counts, higher leucocyte, and lower percentages of eosinophils, basophils, and monocytes.[40] Henry et al., in another study of 3377 COVID-19 patients with a severe and fatal disease, reported that patients' WBCs increased significantly and the number of lymphocytes and platelets decreased compared with non-severe disease.[41] In COVID-19 patients with severe cases, the level of helper T cells, memory helper T cells, and T regulatory cells were less than normal levels while the percentage of naïve helper T cells and suppressor T cells were increased.[42]

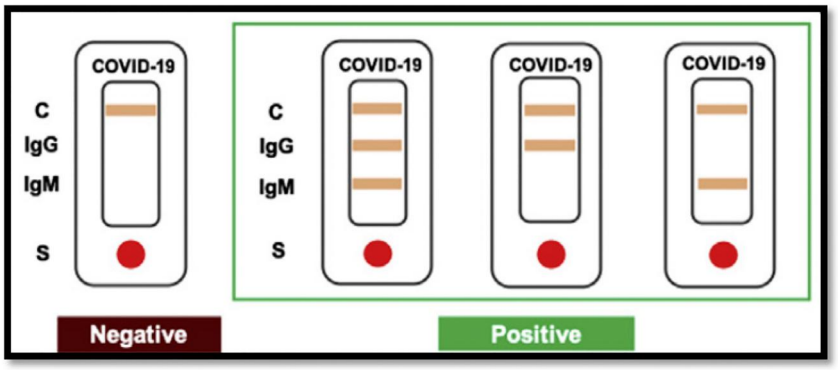

FIGURE 1 Schematic of serological antibody testing by a lateral flow assay for COVID-19. Reprinted from [11]

To control viral infection, the role of cytotoxic lymphocytes, like natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), are essential, and decreased cytotoxic lymphocytes potency is associated with exacerbation of the disease.[43]

In some studies demonstrated that SARS-CoV-2 patients had a lower amount of T cells, NK and, B cells.[44,45] According to the research decreased specific subtypes of T lymphocytes such as lymphocyte (<500/μL), B cell (<50/μL), $CD3^+$ T cell (<200/μL), $CD4^+$ T cell (<100/μL) and $CD8^+$ T cell (<100/μL) were observed in patients who died of COVID-19 infection in hospital.[46]

Analysis of eosinophil count in COVID-19 patients showed that although in most COVID-19 patients eosinopenia was seen at admission and returned to normal before discharge, in some cases eosinopenia was not reported, so eosinopenia could not be a potential predictor for COVID-19 progression.[47–49] Neutrophil/lymphocyte count ratio (NLR) is used as an inflammatory marker to predict mortality in cardiovascular disease[50,51] Also, NLR is known as a biomarker for severe diseases such as sepsis.[52] In studies in patients with severe COVID-19 infection have been shown that NLR amount was remarkably increased.[53]

Platelet

Platelet counts are used as available biomarkers to assess disease severity and mortality risk in intensive care units (ICUs).[54] In COVID-19 patients, platelet depletion has been reported to be significantly associated with disease severity and risk of death.[55,56] Previous studies have shown that COVID-19 patients with higher platelets and platelet/lymphocyte ratio (PLR) stayed longer in the hospital.[57]

C-reactive protein (CRP)

C-reactive protein is a serum protein generated by the liver through the stimulation of various inflammatory mediators such as IL-6. This biomarker is used to assess various inflammatory conditions and prediction of disease severity.[58] C-reactive protein is one of the first biomarkers in serum that indicates the physiological condition. According to the studies, severe COVID-19 patients had higher CRP (>41.8 mg/L) levels.[59] C-reactive protein levels were an important indicator of the presence and severity of COVID-19 infection. Although the same study showed that in some COVID-19 patients, serum amyloid (SAA) levels were changed significantly instead of CRP levels. However, with more evaluations, this biomarker can be used to predict the progression of COVID-19 infection.[60] This biomarker in the beginning period of infection is more sensitive versus ESR to indicate the severity of COVID-19 infection.[61,62]

D-dimer

D-dimer is derived from fibrin lysis and its increase indicates activation of coagulation and fibrinolysis.[63] Because COVID-19 is associated with haemostatic disorders, high levels of D-dimer were observed among patients.[64] D-dimer levels were increased in approximately 90% of patients admitted to pneumonia. It was directly related to the mortality rate.[65] It can be an appropriate marker for predicting severity and mortality in COVID-19 patients.[62]

1.1.3 | Cardiovascular biomarkers

The most common clinical complications of COVID-19 are acute respiratory distress syndrome and lung disturbance. Also, the cardiovascular disorder is another complication of this viral disease. Evidence suggests the prediction of COVID-19 severity and mortality by cardiac biomarkers.[10]

According to the researches, in COVID-19 patients the number of cardiac markers such as alpha-hydroxybutyrate dehydrogenase (α-HBDH), Lactate dehydrogenase (LDH), creatine kinase (CK), aspartate aminotransferase (AST), N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), creatinine kinase-muscle/brain activity (CK-MB), myoglobin (Mb) and cardiac troponin I (cTnI) were enhanced.[66] Increased in CTnI, NT-proBNP, CK-MB, and Mb biomarker indicate the heart injury (Table 1) but an increase of LDH, CK, α-HBDH, and AST as cardiac enzymes, may not necessarily indicate cardiac damage.[74]

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TABLE 1 A table of prognostic valuable cardiac biomarkers in the coronavirus patients (COVID-19)

Cardiac biomarker	Definition	Dependence with COVID-19	Prognostic potential	References
cTn	cTnI and cTnT are specific biomarkers of myocardial necrosis, regardless of injury mechanism[67]	Increased cTnI/cTnT is associated with - Acute myocardial damage - ICU admission - In hospital death - Severity COVID-19 infection	+++	5,68
BNP	BNP predicts the severity of acute myocardial injury. BNP levels rise immediately after myocardial injury, this level is directly related to the severity of the injury.[69]	BNP raised by - Acute myocardial damage - ICU admission - In hospital death	++	70,71
CK-MB	CK-MB is a biomarker of heart damage and blood flow. CK-MB level is directly related to the severity of the injury.[72,73]	Increased CK-MB is associated with - Acute myocardial damage - ICU admission - In-hospital death	+	74-76

aspartate aminotransferase (AST), N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), creatinine kinase-muscle/brain activity (CK-MB), myoglobin (Mb), and cardiac troponin I (cTnI) were enhanced.[66] Increased in CTnI, CK-MB, NT-proBNP and Mb biomarker indicate heart injury but an increase of LDH, CK, α-HBDH, and AST as cardiac enzymes, may not necessarily indicate cardiac damage.[74]

The lungs and heart express the angiotensin-converting enzyme 2 (ACE2).[74] Studies have shown that ACE2 receptor expression is directly associated with SARS virus attack,[77] and SARS-CoV infection can cause ACE2-dependent cardiomyocyte infection.[78] In addition, some studies have confirmed that due to cardiac expression, SARS-CoV-2 viruses easily attack cardiomyocytes and destroy cardiomyocytes, thereby altering cardiac markers.[79]

Troponin is a cardiac biomarker that can be used to predict and assess the severity of heart damage. According to the studies, COVID-19 patients who died had a higher amount of troponin than those who survive.[80]

Heart injury is a complication of COVID-19 patients, the severity of infection is associated with increase B-type natriuretic peptide (BNP) levels as well as high-sensitivity cardiac troponin I (hs-TnI). So the early detection and severity prediction of COVID-19 can be carried out by measuring Cardiac biomarkers BNP and hs-TnI.[80]

1.1.4 | Immunological and inflammatory biomarkers

The most of severe COVID-19 cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines. Virus particles spread through the respiratory mucosa, initially using the ACE2 receptor at ciliated bronchial epithelial cells, and infect other cells, induce a cytokine storm in the body, generate a series of immune responses, and cause changes in peripheral white blood cells and immune cells such as lymphocytes.[20,81,82] The total white cell count was less consistently elevated among COVID-19 patients who required ICU admission or died compared to patients who did not.[61,83,84] The neutrophil to lymphocyte ratio (NLR) is a well-known marker of inflammation and appears to reflect the severity of COVID-19, particularly among patients older than 50 years of age.[85,86] Higher serum levels of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6) and chemokines (IL-8) were found in patients with severe COVID-19. It demonstrated pronounced lymphopenia and low counts of CD3+ cells and CD4+ cells in COVID-19 cases.[87] The frequency of lymphopenia found suggests that COVID-19 might act on lymphocytes, especially T lymphocytes.[25] Secondary hemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, it is most commonly triggered by viral infections.[88] A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased Interleukin (IL2-IL7), Granulocyte colony stimulating factor, Interferon-γ, Inducible protein 10, Monocyte chemoattractant protein, macrophage inflammatory protein 1-α and tumour necrosis factor-α.[5] Immunoglobulin G and M (IgG and IgM) were detected from the human serum of COVID-19 patients using an enzyme-linked immunosorbent assay (ELISA).[89] Many properties of IgM make this immunoglobulin particularly well-suited to its role in microbial immunity. But IgM has a relatively short half-life in the serum, approximately 28 h, in normal mice in the absence of antigen. It is present in high concentrations in blood (in the range of 1.5 mg/ml), and is the first antibody elicited in immune response following immunisation or infection. IgG and IgM antibodies were detected in SARS-CoV-2 cases and increased to 81% and 100% at day five.[90] C-reactive proteins are another protein or cellular marker that can be used for detection. Studies showed that infected patients had elevated levels of CRP and D-dimer as well as low levels of lymphocytes, leucocytes, and blood platelets.[9]

1.1.5 | Renal biomarkers

There is also an indication that kidney injury is related to infection with COVID-19.[41] There are many biomarkers for kidney dysfunction diagnosis which can be divided into urinalysis and blood indicators related to kidney injury.[91] Biomarkers of renal impairment, including an increase in creatinine, blood urine nitrogen (BUN), and the presence of AKI have been reported in most studies.[77] Furthermore, independent of age and sex, a higher baseline creatinine, underlying proteinuria, and haematuria were associated with a higher risk of mortality.[62,92] In patients with severe disease, creatinine and BUN levels were consistently higher in men compared to women and older males were more likely to have a higher baseline creatinine and develop AKI,17.[92] Although studies have not investigated the effect of sex on renal biomarkers and COVID-19 severity. A woman's hormonal environment, however, is thought to have a protective effect against the development of AKI and females have been previously shown to be at lower risk of AKI compared to males.[93] Similarly, smaller studies of renal transplant patients have suggested that male sex may be a risk factor for AKI in COVID-19.[94] Table 2 lists the types of biomarkers in the diagnosis of Covid-19 related to renal impairment.

1.1.6 | Liver biomarker

Liver dysfunction caused by COVID-19 has also been identified in some cases, which may suggest a risk of liver damage caused by COVID-19.[95] Popular causes with different degrees of hepatic damage are viral agents such as hepatitis C virus (HCV), hepatitis B virus (HBV) and hepatitis E virus (HEV). In addition, some studies have indicated that SARS-infected patients and MERS-infected patients have elevated liver enzyme levels and differing degrees of liver damage.[96,97] In intense COVID-19, hepatic dysfunction is followed by relatively greater activation of coagulative and fibrinolytic pathways, depressed counts of platelets, climbing counts of neutrophils and neutrophils lymphocyte percentages, and elevated amounts of ferritin.[66] Therefore, it is necessary to pay attention to the level of liver tests in Covid-19 patients. Aminotransferase aspartate (AST) and aminotransferase alanine (ALT) are enzymes present in heart cells, muscle tissue, red blood cells, and other tissues, such as the pancreas and kidneys, are found primarily in the liver. AST and ALT were previously referred to as serum glutamic oxaloacetic transaminase (GOT) and serum glutamic pyruvic transaminase (GPT), respectively.[98] In COVID-19 patients, the prevalence of elevated ALT and AST levels ranged from 14% to 53%.[99] However, liver dysfunction tests have concentrated mostly on improvements in the levels of ALT, AST, and total bilirubin (TB). The role of prealbumin has been underestimated as an important biomarker for assessing the liver's protein synthesis function.[100] Increased TB and decreased albumin were seen in patients with Covid-19.[101]

TABLE 2 Biomarkers associated to blood test and urinalysis in renal injury

Urinalysis	Blood test
Proteinuria	Creatinine (cr)
Haematuria	Blood urea nitrogen (BUN)
Leukocyturia	Estimated glomerular filtration rate (GFR)
Urine glucose	Cystatin C

1.1.7 | Coagulation biomarkers

COVID-19 patients with thrombotic complications generally follow a course of disease that is more aggressive. Moreover, evidence consistently demonstrates the negative prognostic value of individual coagulation parameters, including elevated D-dimer[41,102] and reduced platelet counts.[76,77] The underlying mechanism of coagulopathy in COVID-19 patients is a disproportionate inflammatory response resulting in endothelial cell dysfunction and a prothrombotic state.[103] Due to ACE2 receptor expression on endothelial cells, the COVID-19 virus may cause endotheliitis, which could result in not only arterial and venous inflammation but also microcirculatory and lymphocytic endotheliitis. Patients with severe COVID-19 develop a hypercoagulable state.[78] Further demonstrated by increased levels of factor VIII and von Willibrand factor, marginally decreased anti-thrombin III activity,[104] and inactivation of the fibrinolytic system.[105] These derangements likely underlie venous thromboses; arterial thromboses that may present as ischaemic stroke, mesenteric ischaemia, and acute limb ischaemia, and the phenomenon of free-floating thrombi seen in COVID-19 infection-related thrombotic events.[106]

2 | BIOSENSORS

During the last decade, electrochemical biosensors have emerged as reliable analytical devices and represent a new promising tool for the detection of different pathogenic viruses. Future research also looks at the use of biosensors regarding a potential detection kit for the rapid identification of the COVID-19. Biosensors should offer quick and efficient detection of viral diseases with high levels of specificity and sensitivity.[107] These criteria are crucial in the success or failure of the detection technology. As such, the choice of the targets of any given pathogen can be a deciding factor. There are two strategies followed: viral nucleic acid or specific proteins or biomarkers. Nanotechnology-based biosensors are known for their promising results in addition to their advantage of being highly customisable through immobilisation, labelling, and biofunctionalisation. In order to find an efficient biomolecule immobilisation, a surface plasmon resonance (SPR) biosensor was developed for SARS-CoV based on the use of gold binding polypeptide (GBP).[108] GBP was fused to enhanced green fluorescent protein (GBP-E) and to SARS-CoV membrane envelope (SCVme), the latter that can bind to anti-SCVme antibodies.

Laboratory detection approaches for COVID-19 in biological samples demonstrate many pros and cons where the sequestration of the virus could be obtained via cell culture, quick antibody kits, blood samples, and other technologies such as CRISPR or biosensor-based methodologies. They are all assays actively utilised in epidemiological studies and point of care applications.[109,110]

2.1 | Types of biosensors

2.1.1 | Electrochemical biosensors

Electrochemical impedance spectroscopy (EIS) is considered as an efficient technique, which even detects any tiny changes that occur at the solution–electrode interface. However, considering highly sensitive and selective, cost-effective, simple, label-free detection, POC testing, antibody seroprevalence, nucleic acid amplification-free, and rapid diagnosis, electrochemical biosensors might be potential for the detection of COVID-19 (Figure 2).[112-115] The development of electrochemical biosensors for COVID-19 detection is now in the early stage. Therefore, thorough review of an electrochemical biosensor for virus detection will help biosensing communities as soon as to develop an effective electrochemical biosensor platform for COVID-19.

2.1.2 | Electrochemical immunosensors

The application of immunosensors in clinical diagnosis and monitoring of diseases has been reported for the detection of biomarkers,[114,116] and viruses.[117] In electrochemical immunosensors, the biological signal is converted into an electrical signal when the antigen-antibody complex is formed.[84] Recently, an electrochemical immunosensor has been developed for the detection of highly pathogenic coronavirus associated with the MERS-CoV.[77] Another immunosensor based on ELISA have revealed to detect total antibodies (Ab), IgM and IgG against COVID-19 from human serum. IgM and IgG detection methods were based on IgM μ-chain capture method (IgM-ELISA) and recombinant nucleoprotein respectively.[86] A biosensor device (eCovSens) has built and compared with a commercial potentiostat for the detection of nCovid-19 spike antigen (nCovid-19Ag) in spiked saliva samples. A potentiostat based sensor was fabricated using fluorine doped tin oxide electrode (FTO) with gold nanoparticle (AuNPs) and immobilised with nCovid-19 monoclonal antibody (nCovid-19Ab) to measure change in the electrical conductivity (Figure 3).[118] In order to facile and fast screening/diagnosis of novel coronavirus, a sensitive graphene field effect transistor (Gr-FET) is combined with highly selective antibody-antigen interaction to develop a coronavirus immunosensor. The Gr-FET immunosensors can rapidly identify (about 2 min) and accurately capture the COVID-19 spike protein S1 (which contains a receptor binding domain, RBD) at a limit of detection down to 0.2 pM, in a real-time and label-free manner.[25] This sensor was constructed by conjugating the graphene of the FET with an antibody against the spike protein of the COVID-19 via 1-pyrenebutyric acid N-hydroxysuccinimide ester. The platform was able to detect the S protein as low as 1.0 fg/ml in PBS while in clinical transport medium it reached 100 fg/mL.[119]

2.1.3 | Electrochemical nucleo-sensors

COVID-19 is an RNA virus and has single-strand RNA instead of ssDNA. By utilising the corresponding immobilisation of the single-stranded DNA probe nucleotide on to the biosensor, a specific viral RNA sequence of COVID-19 can be detected. A DNA probe is made with functionalised gold nanoparticles as the transducing elements (AuNP) chips to match specific viral RNA sequences through nucleic acid hybridisation. This plasmonic photothermal biosensor is proposed for highly sensitive and accurate COVID-19 detection by

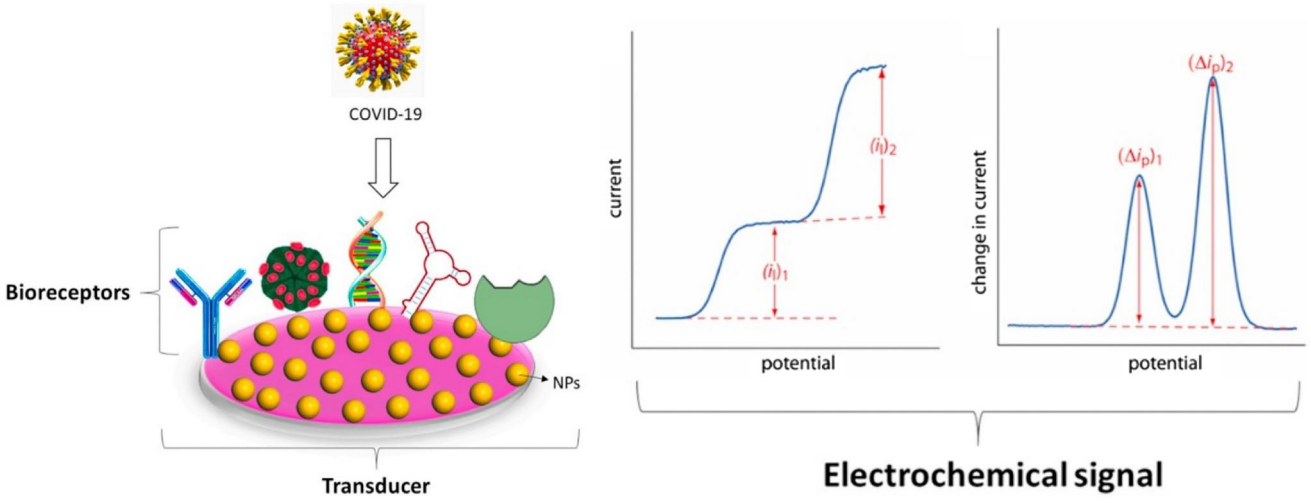


FIGURE 2 Coronavirus electrochemical biosensors arrangement[111]

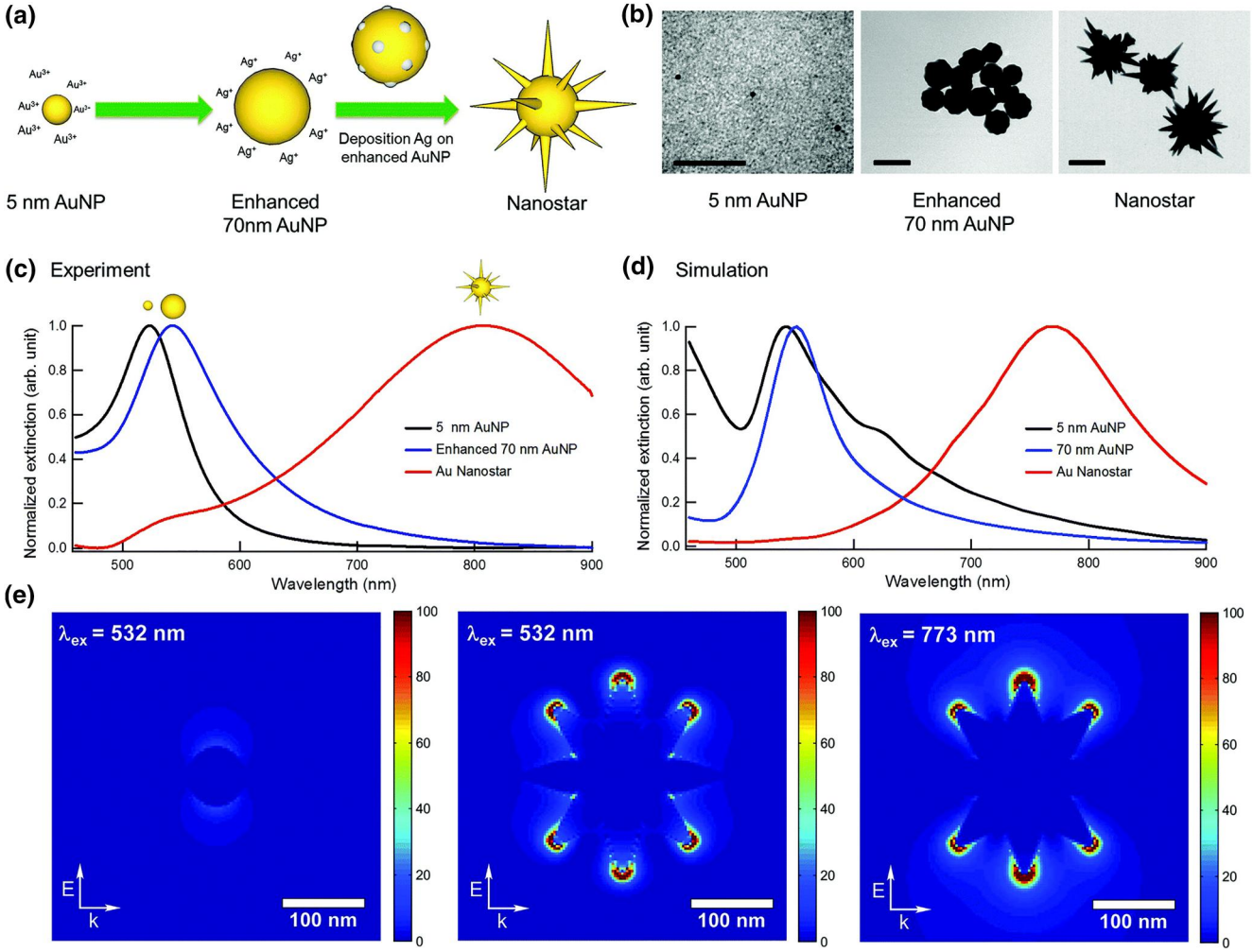


FIGURE 3 Plasmonic properties of Au nanoparticles in a potentiostat based sensor.[87] (a) A schematic diagram of nanostar synthesis. (b) TEM images of 5 nm AuNP, enhanced 70 nm AuNP, and nanostars (scale bar: 100 nm). (c) Extinction spectra of 5 nm AuNP (black), 70 nm AuNP (blue), and nanostars (red). The maximum absorbances of 5 nm AuNP, 70 nm AuNP, and nanostars occur at 519 nm, 543 nm, and 809 nm, respectively. (d) FDTD-simulated scattering spectra of the corresponding nanoparticles. (e) Simulated local field distribution around a 70-nm spherical AuNP at $\lambda = 532$ nm, a Au nanostar at $\lambda = 532$ nm, and a Au nanostar at $\lambda = 773$ nm

testing on SARS-CoV (Figure 4).[120] However, the DNA-hybridisation-based disease diagnosis requires the extraction of target DNA/RNA from the infected host and the subsequent sample preparation.

In another attempt, label-free electrochemical detection of DNA hybridisation has been presented as a potential approach for COVID-19 diagnosis by using complementary thiolated probes (Figure 5).[121] The methods of electrochemical analysis to be used for data acquisition and subsequent calibration, in relation to target analytic detection. DNA hybridisation can be considered as a portable electrochemical sensor for point mutation detection of COVID-19-specific viral RNA/cDNA.

2.1.4 | Electrochemical protein sensors

It is predicted that the whole virus SARS-CoV-2 have 28 proteins with particle size in the ranges of 50–200 nm,[122–124] and their structural proteins include the spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, nucleocapsid (N) protein, and also several accessory proteins can be used as antigens for COVID-19 diagnosis. For example, N protein from SARS-CoV is recognised by using quantum dots-conjugated RNA aptamer immobilised over a designed chip[125] or the spike (S) glycoprotein was detected by the Graphene FET technique (Figure 6).

The FET system has detected SARS-CoV-2 based on the changes in channel surface potential and its effect on the electrical response. The gate surface of FET is covered with a layer that can be modified with biomolecules for selective detection of targets (Figure 7).[127] Graphene FET was decorated with an antibody of SARS-CoV-2 spike S1 subunit protein (CSAb) or angiotensin-converting enzyme 2 (ACE2) to detect SARS-CoV-2 spike protein S1. The binding of the S1 protein that possesses a slightly positive charge with the CSAb/ACE2 receptors on the graphene surface changed the conductance/resistance in graphene-FET which was

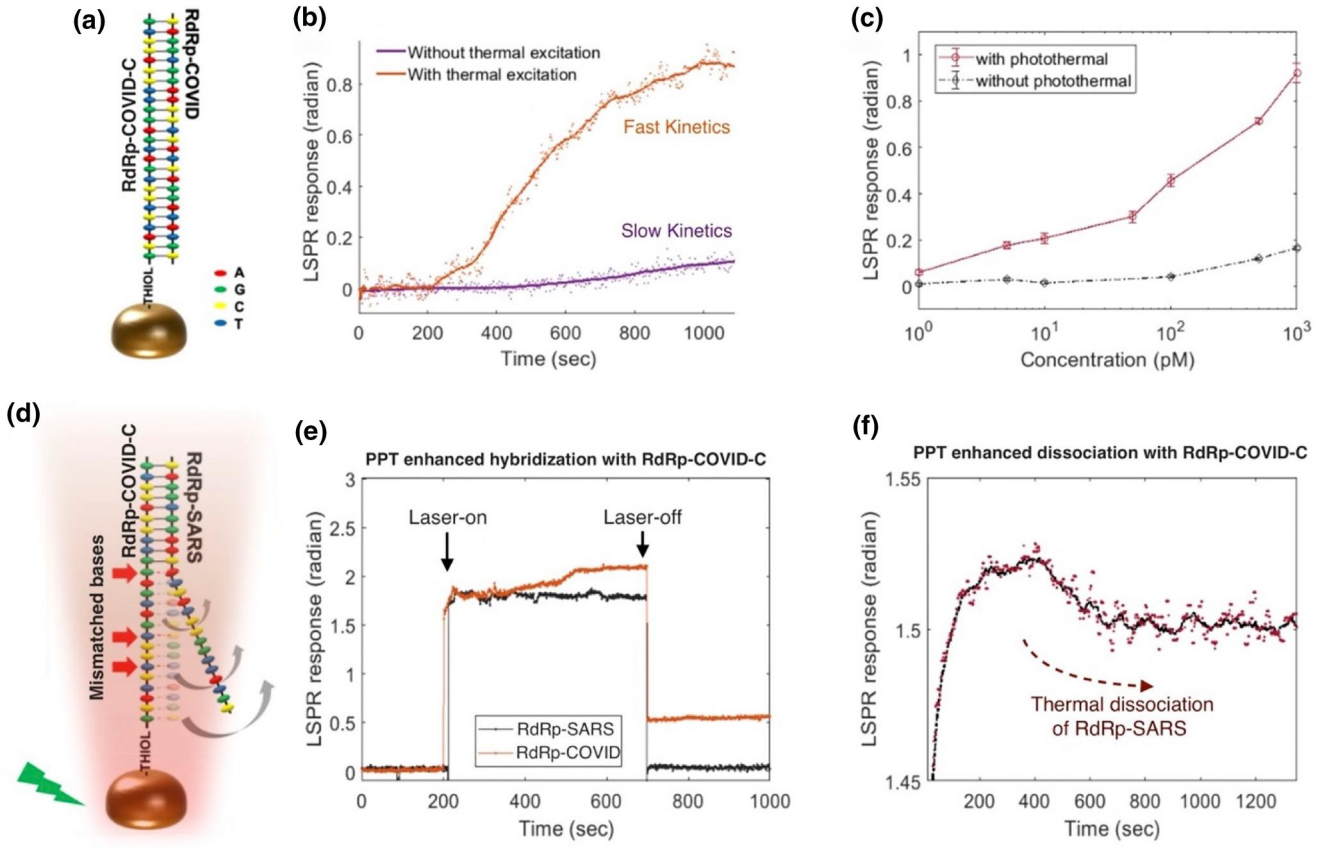


FIGURE 4 The surface-functionalised AuNI chips in the LSPR systems for specific viral sequence detection.[120] (a) Schematic illustration of the hybridisation of two complementary strands. (b) Realtime hybridisation of RdRp-COVID and its cDNA sequence (RdRp-COVID-C) with or without the thermoplasmonics enhancement. (c) PPT enhancement on RdRp-COVID sequence detection at different concentrations. The error bars refer to the standard deviations of LSPR responses after reaching the steady conditions following the buffer flushing. (d) Schematic illustration of inhibited hybridisation of two partially matched sequences. The red arrows indicated the mismatch bases of RdRp-SARS and functionalised cDNA of RdRp-COVID. (e) Discrimination of two similar sequences with PPT heat. The laser was applied at 200 s and switched off at 700 s. (f) RdRp-SARS sequence dissociation from the immobilised RdRp-COVID-C sequence. The original phase responses (red dots) and the corresponding smoothed means (black curve) are shown

considered the basis of the detection. CSAb modified graphene-FET exhibited better sensitivity due to the higher affinity of this antibody.[128]

2.2 | Optical biosensors

Optical biosensors focus on the measurement of a change in the optical characteristics of the transducer surface when the analyte and recognition element form a complex. These biosensors can be divided into two groups. For example, signal generation depends on the formation of a complex on the transducer surface in the direct optical biosensor. The indirect optical biosensors are mostly designed with various labels such as fluorophores or chromophores to detect the binding events and amplify the signal.[129] A dual-functional plasmonic biosensor combining the plasmonic photothermal (PPT) effect and localised surface plasmon resonance (LSPR) sensing transduction provides an alternative and promising solution for the clinical COVID-19 diagnosis. The two-dimensional gold nanoislands (AuNPs) functionalised with complementary DNA receptors can perform a sensitive detection of the selected sequences from SARS-CoV-2 through nucleic acid hybridisation. For better sensing performance, the thermoplasmonics heat is generated on the same AuNPs chip when illuminated at their plasmonic resonance frequency. The localised PPT heat is capable to elevate the in situ hybridisation temperature and facilitate the accurate discrimination of two similar gene sequences.[130,131] A tunable biosensor using the localised surface plasmon resonance (LSPR), controlling the distance between fluorescent CdZnSeS/ZnSeS quantum dots (QDs) and gold nanoparticles (AuNPs) has been developed for the detection of the virus. The distance between the AuNPs and QDs has been controlled by a linkage with a peptide chain of 18 amino acids. In the optimised condition, the fluorescent properties of the QDs have been enhanced due to the surface plasmon effect of the adjacent AuNPs.[132] Successive virus binding on the peptide chain induces steric hindrance on the LSPR behaviour and the fluorescence of QDs has been quenched (Figure 8).[132] The nucleocapsid (N) protein of the severe acute respiratory

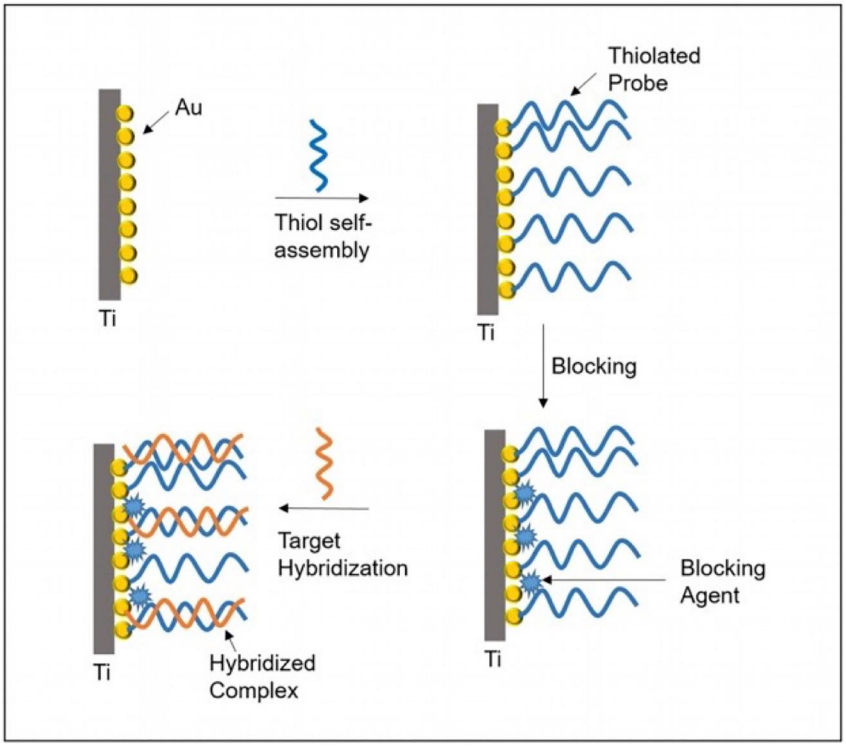


FIGURE 5 DNA immobilisation protocol on to the gold sensing electrodes[121]

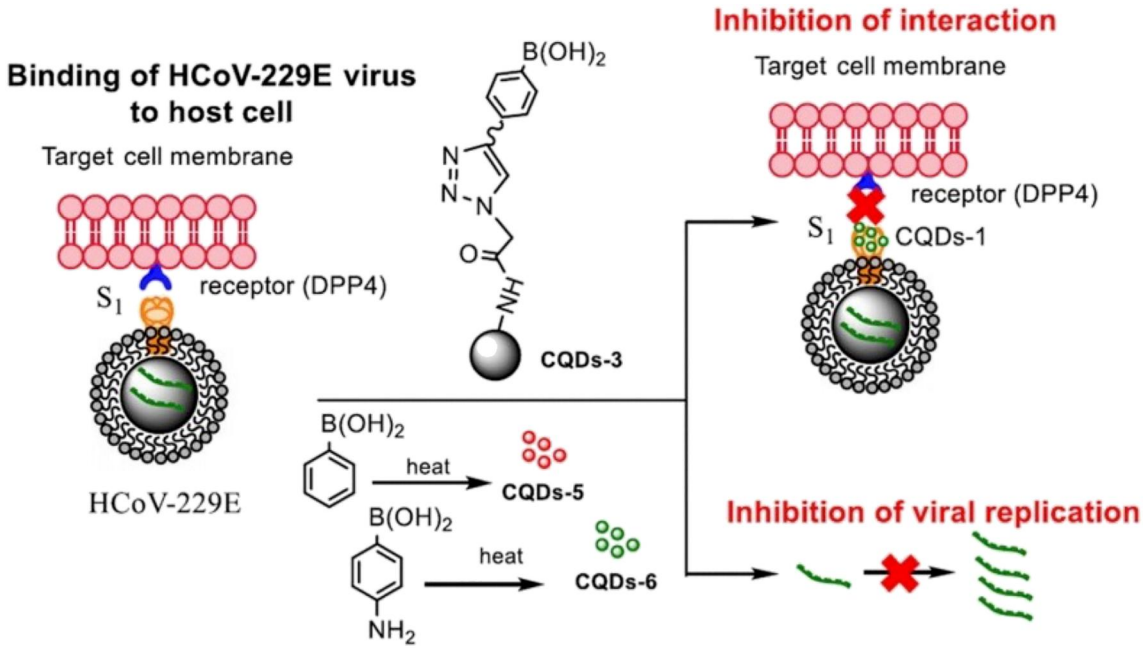


FIGURE 6 Carbon quantum dots inhibit human corona virus interaction with its host receptor[126]

syndrome (SARS)-associated coronavirus (SARS-CoV) is an important antigen for the early diagnosis of SARS and the detection of diseases.

Here, a new quantum dots (QDs)-conjugated RNA aptamer with high sensitivity and rapidity is proposed for the detection of SARS-CoV N protein using an on-chip system. It was demonstrated that the QDs-conjugated RNA aptamer could interact on a designed chip specifically and sensitively. This device could form a QDs-conjugated biosensor prototype chip for SARS-CoV N protein diagnosis.[125]

Based on the principle of localised surface plasmon resonance (LSPR), an opto-microfluidic sensing platform designed with gold

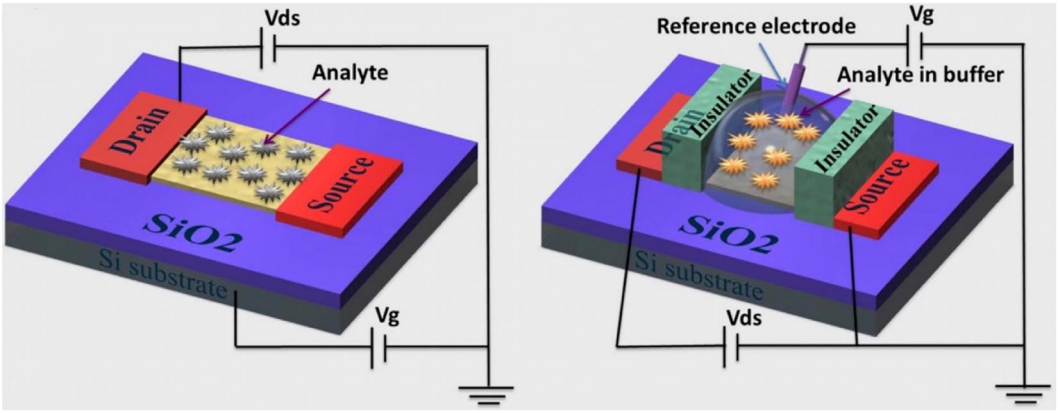
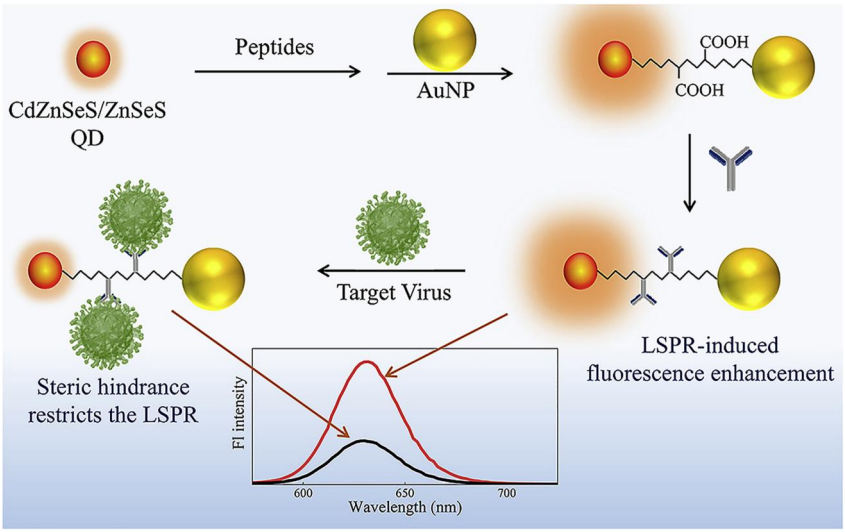


FIGURE 7 A typical back-gated (left) and solution-gated (right) FET biosensors used in chemical and biological sensing applications[127]

FIGURE 8 Preparation of CdZnSeS/ZnSeS QD-peptide-AuNP 218 nanocomposite and its detecting mechanism towards influenza virus[132]



nanospikes, fabricated by electrodeposition, to detect the presence and number of antibodies specific to the SARS-CoV-2 spike protein in 1 μL of human plasma diluted in 1 ml of buffer solution, within ~30 min. The target antibody concentration can be correlated with the LSPR wavelength peak shift of gold nanoparticles caused by the local refractive index change due to the antigen-antibody binding. This is performed in diluted human plasma without any labelling agents, reaching a LOD of ≈0.08 ng/ml (≈0.5 pM), which falls under the clinically relevant concentration range of specific antibodies against bacteria or viruses responsible for the infection. This platform shows great potential to complement the existing serological COVID-19 antibody tests.[133] Localised surface plasmon coupled fluorescence (LSPCF) is another combined method of sandwich immunoassay that a linear relationship between the fluorescence signal and the concentration of recombinant SARS-CoV N (GST-N) protein in buffer solution could be observed from 0.1 pg/ml to 1 ng/ml. This level is very suitable for application to the clinical diagnosis at the early stage of SARS patients.[134]

2.3 | Lateral flow biosensors

A lateral flow device (LFD) is a particular type of biosensor, in which the recognition layer is fabricated onto the surface of a porous membrane. The membrane creates and sustains the flow of samples and reagents by capillarity and holds specific recognition elements that are confined in spatially defined zones or detection sites.[135] A multiplex reverse transcription loop-mediated isothermal amplification (mRT-LAMP) is designed that coupled with a nanoparticle-based lateral flow biosensor (LFB) assay (mRT-LAMP-LFB) for diagnosing COVID-19.[136] Using two LAMP primer sets, the ORF1ab (opening reading frame 1a/b) and N (nucleoprotein) genes of SARS- CoV-2 were simultaneously amplified in a single-tube reaction and detected with the diagnosis results easily interpreted by LFB. In presence of FITC (fluorescein)-/digoxin- and biotin-labelled primers, mRT-LAMP produced numerous FITC/digoxin and biotin-attached duplex amplicons, which were determined by LFB through immunoreactions (FITC/digoxin on the duplex and anti-FITC/digoxin on the test line of

LFB) and biotin/streptavidin interaction (biotin on the duplex and streptavidin on the polymerase nanoparticle; Figure 9).[136]

3 | FUTURE PROSPECTS AND CONCLUSION

Biosensors have been demonstrated as effective tools for early diagnosis, on-site, rapid, and ultrasensitive detection of SARS-CoV-2. Clinical research on COVID-19 patients shows that in addition to the ability to assess the status of SARS-CoV-2 virus infection, some biomarkers in the body also change and can be used in diagnosis, treatment and disease monitoring. So, considering the urgent need for fast detection of COVID-19 the biomarkers-based biosensors can play an important role as it will decrease the detection time, will be save cost, and also reduce the chance of virus transmission while diagnosis.

COVID-19 is a recent outbreak that occurred worldwide and created an enormous dysfunction of various activities all around the world.[137] The infection and spread of SARS-CoV-2 were firstly observed in Wuhan city of China, has now affected nearly 200 countries worldwide.[138]

In this review article, we have reviewed the significant biomarkers which were reported in various papers after the clinical studies in COVID-19 patients. Biomarkers such as proinflammatory

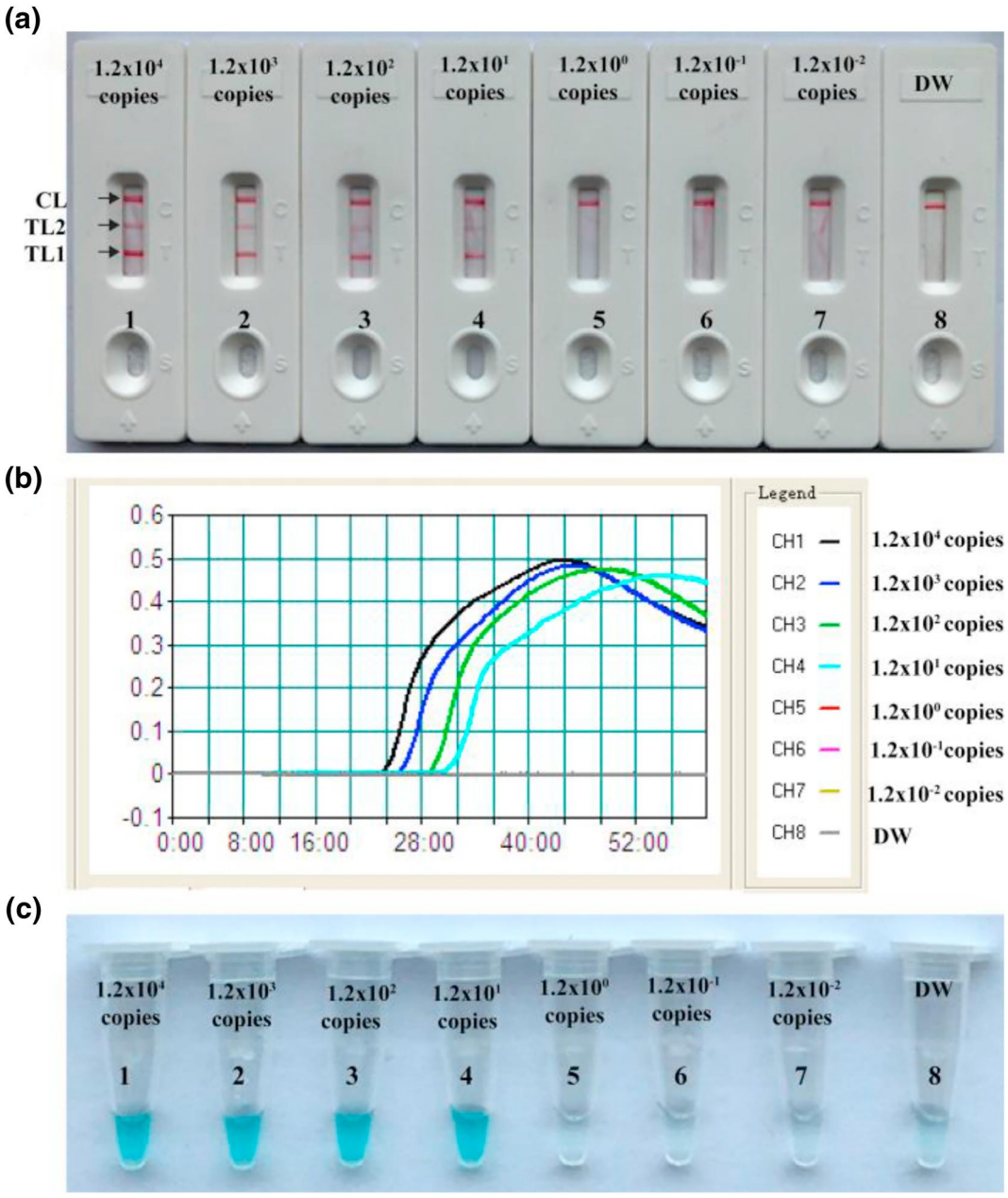


FIGURE 9 Sensitivity of COVID-19 mRT-LAMP-LFB assay. (a) LFB applied for reporting the results; (b) Real-time turbidity applied for reporting the results; (c) Visual detection reagent applied for reporting the results[136]

cytokines, ferritin, amyloid A and … are considerable biomarkers from these studies which also shows a potential to detect specifically COVID-19 as there is a difference between secretion range and cut off the range, and also haematological biomarkers which secreted in a more substantial amount in COVID-19 patient as compared to a healthy patient.[5,139–141]

COVID-19 has become a substantial lethal disease worldwide, and early diagnosis is a significant concern for this virus. Rapid and early diagnosis of any disease is always a major concern for all countries. Currently, the situation related to COVID-19 is enormous, as the globe does not have any rapid system for early and fast detection of this virus.[142] Currently, RT-PCR is being used for testing the virus which is time taking and costly, moreover, some of the research group has recently developed a biosensor for COVID-19 detection through different approach but they all are invasive and lead to virus particles exposers.

There are other techniques that can resolve this problem with a more manageable approach and detect the virus rapidly. One of these techniques is biomarker-based on sensors, terming biosensors.[142] The biomarker-based biosensor can play a pivotal role, as biomarkers are naturally occurring biomolecules specific to particular diseases, such as CYFRA-21 is a protein-based biomarker for oral cancer. Protein-based biomarkers are easy to isolate as compared to a nucleic acid (DNA/RNA) or cell-based biomarker. Moreover, the biomarkers isolation and sample preparation are much more comfortable in protein-based biomarker as compared to a nucleic acid or other biomarkers. The current detection of COVID-19, which is RT-PCR required RNA isolation, purification, and processing step, which increases the time of detection and cost of testing. It can locate out such biomarkers through proteomics studies from COVID-19 infected patients and find out specific biomarkers for COVID-19.

Furthermore, biosensors based on this approach will be non-invasive that can be user-friendly in use so that the need for highly qualified professional limits can be overcome, apart from these other biomarkers which can also be considered in healthy patients and COVID-19 infected patients.[143] As well, the primary concern related to this virus is early diagnosis, cost-effectiveness and, reducing the chance of spread so that working professionals also do not get affected by human-to-human transmission while testing. Professional working for the diagnosis is in a major threat to get into the contact of this virus and get affected and to subdue this approach this biomarkers based biosensor can be integrated with microfluidics system which will restrict the sample amount as well as the chance of virus transmission,[142] such as Singh et al., has tried to develop a microfluidics-based biosensor for influenza detection. Considering the urgent need for rapid detection of COVID-19 the biomarkers based sensor can play a pivotal role as it will reduce the time to detect, will be cost-effective, and also reduce the chance of virus transmission while diagnosis, we can look forward to the integration of microfluidics system with this biosensor so that a minimal amount of sample is used and the chance of virus transmission remains insignificant.[142]

In the other words, in recent years, the development of biosensors for biomarkers of diseases has received a lot of attention. However, the developments of biomarkers and the innovation of diagnostic tools for early detection of COVOD-19 are still in their early stages. For future works, the development of another problem is that owing to its low accuracy and reliability, few portable electrochemical instruments are in clinical usage. Therefore, robust biosensor-based POCT devices are required of ultrasensitive electrochemical label-free methods will be of great potential. Researchers must train the electrochemical biosensor to solve their reliability problems with a significant number of clinical samples. The development of wireless micro/nano electrochemical biosensors is an ideal option for infection detection, as they can work in contaminated environments. The approachable properties of electrochemical instruments improve the performance of infection diagnostics and therapy monitoring. With further advancement and funding, these handheld instruments are anticipated to improve COVID-19 diagnosis, rendering diagnostic findings accessible in a matter of minutes at the patient bedside or practitioner's office. Nonetheless, proposed detection approaches for biomarker detection of COVID-19 necessarily require a standardisation of pre- and post-analytical protocols such as sample preparation, storage, and optimisation of experimental conditions for true validity of assays and more genuine output of the biosensor produced. The production and progression of these advanced COVID-19 detection systems will aid in the early stages of accelerated clinical SARS-CoV-2 diagnoses.

However, several challenges and limitations remain, which need to be improved, in the design and application of biosensors for the appropriate interpretation of the identified and quantified biomarkers for COVID-19. Researchers are continuing to conquer the difficulties above and will eventually develop biomarker-based devices capable of clinical application.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Zhou H, Zhang Z, Fan H, et al. Urinalysis, but not blood biochemistry, detects the early renal-impairment in patients with COVID-19. *medRxiv*. 2020.

2. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Trav Med*, 27, (2), https://doi.org/10.1093/jtm/taaa021, . 2020.
3. da Silva SJR, Silva CTAd, Guarines KM, et al. Clinical and laboratory diagnosis of SARS-CoV-2, the virus causing COVID-19. *ACS Infect Dis*. 2020;6(9):2319-2336, https://doi.org/10.1021/acsinfecdis.0c00274
4. Hosseinzadeh Shirayeh B, Shojaie L, Maharatfard Jahromy M, et al. Comparison of clinical characteristics of hospitalized patients with and without Covid-19 in Mashhad, Iran: a retrospective, single-center experiences. *Int J Pediatr*. 2020;8(12):12619-12628.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506, https://doi.org/10.1016/s0140-6736(20)30183-5
6. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846-848, https://doi.org/10.1007/s00134-020-05991-x
7. Mascini M, Tombelli S. Biosensors for biomarkers in medical diagnostics. *Biomarkers*. 2008;13(7-8):637-657, https://doi.org/10.1080/13547500802645905
8. Kumar S, Sharma JG, Maji S, Malhotra BD. Nanostructured zirconia decorated reduced graphene oxide based efficient biosensing platform for non-invasive oral cancer detection. *Biosens Bioelectron*. 2016;78:497-504, https://doi.org/10.1016/j.bios.2015.11.084
9. Guan W-j, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720, https://doi.org/10.1056/nejmoa2002032
10. Dawson D, Dominic P, Sheth A, Modi M. Prognostic value of cardiac biomarkers in COVID-19 infection: a meta-analysis. *Research square*. 2020.
11. Zhang L, Guo H. Biomarkers of COVID-19 and technologies to combat SARS-CoV-2. *Adv Biomarker Sci Technol*. 2, 1, 23, https://doi.org/10.1016/j.abst.2020.08.001, 2020.
12. Santosh TS, Parmar R, Anand H, Srikanth K, Saritha M. A review of salivary diagnostics and its potential implication in detection of Covid-19. *Cureus*. 2020;12(4).https://doi.org/10.7759/cureus.7708
13. Lawrence HP. Salivary markers of systemic disease: noninvasive diagnosis of disease and monitoring of general health. *J Can Dent Assoc*. 2002;68(3):170-175.
14. Sapkota D, Søland TM, Galtung HK, et al. COVID-19 salivary signature: diagnostic and research opportunities. *J Clin Pathol*. 2020;74(6):344-349, https://doi.org/10.1136/jclinpath-2020-206834
15. Lima DP, Diniz DG, Moimaz SAS, Sumida DH, Okamoto AC. Saliva: reflection of the body. *Int J Infect Dis*. 2010;14(3):e184-e188, https://doi.org/10.1016/j.ijid.2009.04.022
16. Galhardo LF, Ruivo GF, deOliveira LD, et al. Inflammatory markers in saliva for diagnosis of sepsis of hospitalizes patients. *Eur J Clin Invest*. 2020;50(5):e13219, https://doi.org/10.1111/eci.13219
17. Kaczor-Urbanowicz KE, Martin Carreras-Presas C, Aro K, Tu M, Garcia-Godoy F, Wong DT. Saliva diagnostics–Current views and directions. *Exp Biol Med*. 2017;242(5):459-472, https://doi.org/10.1177/1535370216681550
18. Martelli F, Mencarini J, Rocca A, Malva ND, Bartolozzi D, Giannecchini S. Polyomavirus microRNA in saliva reveals persistent infectious status in the oral cavity. *Virus Res*. 2018;249:1-7, https://doi.org/10.1016/j.virusres.2018.03.002
19. Castro T, Sabalza M, Barber C, et al. Rapid diagnosis of Zika virus through saliva and urine by Loop-mediated isothermal amplification (LAMP). *J Oral Microbiol*. 2018;10(1):1510712, https://doi.org/10.1080/20002297.2018.1510712
20. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273, https://doi.org/10.1038/s41586-020-2012-7
21. Sapkota D, Thapa SB, Hasséus B, Jensen JL. Saliva testing for COVID-19? *Br Dent J*. 2020;228(9):658-659, https://doi.org/10.1038/s41415-020-1594-7
22. To KW, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis*. 2020;20(5):565-574, https://doi.org/10.1016/s1473-3099(20)30196-1
23. To KK-W, Yip CCY, Lai CYW, et al. Saliva as a diagnostic specimen for testing respiratory virus by a point-of-care molecular assay: a diagnostic validity study. *Clin Microbiol Infect*. 2019;25(3):372-378, https://doi.org/10.1016/j.cmi.2018.06.009
24. Aro K, Wei F, Wong DT, Tu M. Saliva liquid biopsy for point-of-care applications. *Public Health Front*. 2017;5:77, https://doi.org/10.3389/fpubh.2017.00077
25. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513, https://doi.org/10.1016/s0140-6736(20)30211-7
26. Fehr AR, Channappanavar R, Perlman S. Middle East respiratory syndrome: emergence of a pathogenic human coronavirus. *Annu Rev Med*. 2017;68(1), 387, 399, , https://doi.org/10.1146/annurev-med-051215-031152
27. Banoei MM, Vogel HJ, Weljie AM, et al. Plasma metabolomics for the diagnosis and prognosis of H1N1 influenza pneumonia. *Crit Care*. 2017;21(1):97, https://doi.org/10.1186/s13054-017-1672-7
28. Wu Q, Zhou L, Sun X, et al. Altered lipid metabolism in recovered SARS patients twelve years after infection. *Sci Rep*. 2017;7(1):1-12, https://doi.org/10.1038/s41598-017-09536-z
29. Leon-Icaza SA, Zeng M, Rosas-Taraco AG. microRNAs in viral acute respiratory infections: immune regulation, biomarkers, therapy, and vaccines. *ExRNA*. 2019;1(1):1-7, https://doi.org/10.1186/s41544-018-0004-7
30. Canatan D. The impact of MicroRNAs (miRNAs) on the genotype of coronaviruses. *Acta Biomed Atenei Parm*. 2020;91(2):195.
31. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367(6483):1260-1263, https://doi.org/10.1126/science.abb2507
32. Chen L, Zhao J, Peng J, et al. *Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Patients*; 2020. Available at SSRN 3556665.
33. Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary glands: potential reservoirs for COVID-19 asymptomatic infection. *J Dent Res*. 99(8), 2020: 0022034520918518, https://doi.org/10.1177/0022034520918518
34. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12(1):1-5, https://doi.org/10.1038/s41368-020-0074-x
35. Casadevall A, Pirofski L-a. The convalescent sera option for containing COVID-19. *J Clin Invest*. 2020;130(4):1545-1548, https://doi.org/10.1172/jci138003
36. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. In: *Mayo Clinic Proceedings*. Elsevier; 2020.
37. Bosteels C, Neyt K, Vanheerswynghels M, et al. Inflammatory type 2 cDCs acquire features of cDC1s and macrophages to orchestrate immunity to respiratory virus infection. *Immunity*. 2020;52(6):1039--1056, https://doi.org/10.1016/j.immuni.2020.04.005

38. Garcia-Basteiro AL, Moncunill G, Tortajada M, et al. Seroprevalence of antibodies against SARS-CoV-2 among health care workers in a large Spanish reference hospital. *medRxiv*. 2020.
39. Whitman JD, Hiatt J, Mowery CT, et al. Test performance evaluation of SARS-CoV-2 serological assays. *medRxiv*. 2020.
40. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2019;71(15):762-768. (February 17, 2020).
41. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med (CCLM)*. 2020;58(7):1021-1028, https://doi.org/10.1515/cclm-2020-0369
42. Cossarizza A, De Biasi S, Guaraldi G, Girardis M, Mussini C. SARS-CoV-2, the virus that causes COVID-19: cytometry and the new challenge for global health. *Cytometry*. 2020;97(4):340-343, https://doi.org/10.1002/cyto.a.24002
43. Zhang C, Wang XM, Li SR, et al. NKG2A is a NK cell exhaustion checkpoint for HCV persistence. *Nat Commun*. 2019;10(1):1-11, https://doi.org/10.1038/s41467-019-09212-y
44. Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol*. 2020;17(5):533-535, https://doi.org/10.1038/s41423-020-0402-2
45. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis*. 2020;221(11):1762-1769, https://doi.org/10.1093/infdis/jiaa150
46. Bo X, Fan Cy, Wang Al, et al. Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan, China. *J Infect*. 2020;81(1):e51-e60, https://doi.org/10.1016/j.jinf.2020.04.012
47. Yun H, Sun Z, Wu J, Tang A, Hu M, Xiang Z. Laboratory data analysis of novel coronavirus (COVID-19) screening in 2510 patients. *Clin Chim Acta*. 507, 94, 97, https://doi.org/10.1016/j.cca.2020.04.018, 2020.
48. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. *Int J Infect Dis*. 95, 183, 191, https://doi.org/10.1016/j.ijid.2020.03.013, 2020.
49. Lippi G, Henry BM. Eosinophil count in severe coronavirus disease 2019 (COVID-19). *QJM Int J Med*. 2020.
50. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expet Rev Cardiovasc Ther*. 2013;11(1):55-59, https://doi.org/10.1586/erc.12.159
51. Haybar H, Pezeshki SMS, Saki N. Evaluation of complete blood count parameters in cardiovascular diseases: an early indicator of prognosis? *Exp Mol Pathol*. 2019;110:104267, https://doi.org/10.1016/j.yexmp.2019.104267
52. Huang Z, Fu Z, Huang W, et al. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med*. 2019.
53. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *J Med Virol*. 2020.
54. Khurana D, Deoke SA. Thrombocytopenia in critically ill patients: clinical and laboratorial behavior and its correlation with short-term outcome during hospitalization. *Indian J Crit Care Med Peer-Reviewed, Off Publ Indian Soc Crit Care Med*. 2017;21(12):861-864, https://doi.org/10.4103/ijccm.ijccm_279_17
55. Ganji A, Farahani I, Khansarinejad B, Ghazavi A, Mosayebi G. Increased expression of CD8 marker on T-cells in COVID-19 patients. *Blood Cell Mol Dis*. 2020;83:102437, https://doi.org/10.1016/j.bcmd.2020.102437
56. Qu R, Ling Y, Zhang Y, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J Med Virol*, 92, (9), 1533, 1541, https://doi.org/10.1002/jmv.25767, . 2020.
57. Gong J, Dong H, Xia Q, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. *medRxiv*. 2020.
58. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol*. 2020;127:104370, https://doi.org/10.1016/j.jcv.2020.104370
59. Ji W, Bishnu G, Cai Z, Shen X. Analysis clinical features of COVID-19 infection in secondary epidemic area and report potential biomarkers in evaluation. *medRxiv*. 2020.
60. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. 92(7), , 856, 862, https://doi.org/10.1002/jmv.25871, 2020.
61. Kermali M, Khalsa RK, Pillai K. The role of biomarkers in diagnosis of COVID-19–A systematic review. *Life Sci*. 254, 2020:117788, https://doi.org/10.1016/j.lfs.2020.117788
62. Zhang L, Long Y, Xiao H, Yang J, Toulon P, Zhang Z. Use of D-dimer in oral anticoagulation therapy. *Int J Lab Hematol*. 2018;40(5):503-507, https://doi.org/10.1111/ijlh.12864
63. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemostasis*. 2020;18(4):844-847, https://doi.org/10.1111/jth.14768
64. Milbrandt EB, Reade MC, Lee M, et al. Prevalence and significance of coagulation abnormalities in community-acquired pneumonia. *Mol Med*. 2009;15(11-12):438-445, https://doi.org/10.2119/molmed.2009.00091
65. Li L, Zhou Q, Xu J. Changes of laboratory cardiac markers and mechanisms of cardiac injury in coronavirus disease 2019. *BioMed Res Int*. 2020;2020:7413673, 7, https://doi.org/10.1155/2020/7413673
66. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069, https://doi.org/10.1001/jama.2020.1585
67. Gohar A, Chong JPC, Liew OW, et al. The prognostic value of highly sensitive cardiac troponin assays for adverse events in men and women with stable heart failure and a preserved vs. reduced ejection fraction. *Eur J Heart Fail*. 2017;19(12):1638-1647, https://doi.org/10.1002/ejhf.911
68. Shi S, Qin M, Shen B, et al. Association of cardiac injury with motality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*, 5, (7), 802, https://doi.org/10.1001/jamacardio.2020.0950, . 2020.
69. Heeschen C, Hamm CW, Mitrovic V, Lantelme N-H, White HD. N-terminal pro–B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation*. 2004;110(20):3206-3212, https://doi.org/10.1161/01.cir.0000147611.92021.2b
70. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;2020a(7), 811, https://doi.org/10.1001/jamacardio.2020.1017, .
71. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 5(7), 819, https://doi.org/10.1001/jamacardio.2020.1096, 2020.
72. Mastro F, Guida P, Scrascia G, et al. Cardiac troponin I and creatine kinase-MB release after different cardiac surgeries. *J Cardiovasc Med*. 2015;16(6):456-464, https://doi.org/10.2459/jcm.0000000000000044
73. Lopes RD, Lokhnygina Y, Hasselblad V, et al. Methods of creatine kinase-MB analysis to predict mortality in patients with myocardial

infarction treated with reperfusion therapy. *Trials*. 2013;14(1):123, https://doi.org/10.1186/1745-6215-14-123
74. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*, 92, (7), 797, 806, https://doi.org/10.1002/jmv.25783, . 2020.
75. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 395(10229), 1054, 1062, https://doi.org/10.1016/s0140-6736(20)30566-3, 2020.
76. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. *Int J Infect Dis*. 2020;96:467-474, https://doi.org/10.1016/j.ijid.2020.05.055
77. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemostasis*. 2020;18(5):1094-1099, https://doi.org/10.1111/jth.14817
78. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemostasis*. 2020;120(6):998--1000, https://doi.org/10.1055/s-0040-1710018
79. Stefanini GG, Chiarito M, Ferrante G, et al. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. *Heart*. 2020;106(19):1512-1518, https://doi.org/10.1136/heartjnl-2020-317322
80. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034, https://doi.org/10.1016/s0140-6736(20)30628-0
81. Rodríguez-Morales AJ, MacGregor K, Kanagarajah S. Going global–Travel and the 2019 novel coronavirus. *Trav Med Infect Dis*. 2020;33:101578, https://doi.org/10.1016/j.tmaid.2020.101578
82. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020:368, https://doi.org/10.1136/bmj.m1091
83. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J Clin Med*. 2020;9(4):941, https://doi.org/10.3390/jcm9040941
84. Zeng F, Li L, Zeng J, et al. Can we predict the severity of coronavirus disease 2019 with a routine blood test? *Pol Arch Intern Med*. 2020;130(5).
85. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. *J Transl Med*. 2020;18:1-12, https://doi.org/10.1186/s12967-020-02374-0
86. Kim W, Kim N, Park JW, Kim ZH. Nanostar probes for tip-enhanced spectroscopy. *Nanoscale*. 2016;8(2):987-994, https://doi.org/10.1039/c5nr06657c
87. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516, https://doi.org/10.1016/s0140-6736(13)61048-x
88. Zhang W, Du R-H, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microb Infect*. 2020;9(1):386-389, https://doi.org/10.1080/22221751.2020.1729071
89. Xiang J, Yan M, Li H, et al. Evaluation of enzyme-linked immunoassay and colloidal gold-immunochromatographic assay kit for detection of novel coronavirus (SARS-Cov-2) causing an outbreak of pneumonia (COVID-19). *medRxiv*. 2020.
90. Lv Z, Cheng S, Le J, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Microb Infect*. 2020;22(4-5):195-199, https://doi.org/10.1016/j.micinf.2020.05.007
91. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020;506:145-148, https://doi.org/10.1016/j.cca.2020.03.022
92. Cheng Y, Luo R, Wang X, et al. The incidence, risk factors, and prognosis of acute kidney injury in adult patients with coronavirus disease 2019. *Clin J Am Soc Nephrol*. 2020;15(10):1394-1402, https://doi.org/10.2215/cjn.04650420
93. Neugarten J, Golestaneh L. Influence of sex on the progression of chronic kidney disease. In: *Mayo Clinic Proceedings*. Elsevier; 2019.
94. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int*. 2020;97(6):1083-1088, https://doi.org/10.1016/j.kint.2020.04.002
95. Gholizadeh P, Safari R, Marofi P, et al. Alteration of liver biomarkers in patients with SARS-CoV-2 (COVID-19). *J Inflamm Res*. 2020;13:285-292, https://doi.org/10.2147/jir.s257078
96. Tseng T-C, Liu C-J, Chang CT, et al. HEV superinfection accelerates disease progression in patients with chronic HBV infection and increases mortality in those with cirrhosis. *J Hepatol*. 2020;72(6):1105-1111, https://doi.org/10.1016/j.jhep.2020.01.012
97. Lee JY, Kim YJ, Chung EH, et al. The clinical and virological features of the first imported case causing MERS-CoV outbreak in South Korea, 2015. *BMC Infect Dis*. 2017;17(1):1-10, https://doi.org/10.1186/s12879-017-2576-5
98. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov*. 2020;10(6):783-791, https://doi.org/10.1158/2159-8290.cd-20-0422
99. Huang X-J, Choi Y-K, Im H-S, Yarimaga O, Yoon E, Kim H-S. Aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) detection techniques. *Sensors*. 2006;6(7):756-782, https://doi.org/10.3390/s6070756
100. Li T, Guo Y, Zhuang X, et al. Abnormal liver-related biomarkers in COVID-19 patients and the role of prealbumin. *Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc*. 2020;26(5):272, https://doi.org/10.4103/sjg.sjg_239_20
101. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci*. 2020;57(6):389-399, https://doi.org/10.1080/10408363.2020.1770685
102. Gu Y-z, Xue Q, Chen Y-j, et al. Different roles of PD-L1 and FasL in immunomodulation mediated by human placenta-derived mesenchymal stem cells. *Hum Immunol*. 2013;74(3):267-276, https://doi.org/10.1016/j.humimm.2012.12.011
103. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-1418, https://doi.org/10.1016/s0140-6736(20)30937-5
104. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemostasis*. 2020;18(7):1738-1742, https://doi.org/10.1111/jth.14850
105. Zátroch I, Smudla A, Babik B, et al. Procoagulation, hypercoagulation and fibrinolytic 'shut down' detected with ClotPro® viscoelastic tests in COVID-19 patients. *Orvosi Hetil*. 2020;161(22):899-907, https://doi.org/10.1556/650.2020.31870
106. Viguier A, Delamarre L, Duplantier J. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *J Neuroradiol*. 47(5), , 393, 394, https://doi.org/10.1016/j.neurad.2020.04.003, 2020.
107. Solanki PR, Patel MK, Kaushik A, Pandey MK, Kotnala RK, Malhotra BD. Sol-gel derived nanostructured metal oxide platform for

bacterial detection. *Electroanalysis*. 2011;23(11):2699-2708, https://doi.org/10.1002/elan.201100351
108. Park TJ, Hyun MS, Lee HJ, Lee SY, Ko S. A self-assembled fusion protein-based surface plasmon resonance biosensor for rapid diagnosis of severe acute respiratory syndrome. *Talanta*. 2009;79(2):295-301, https://doi.org/10.1016/j.talanta.2009.03.051
109. Loeffelholz MJ, Tang Y-W. Laboratory diagnosis of emerging human coronavirus infections–the state of the art. *Emerg Microb Infect*. 2020;9(1):747-756, https://doi.org/10.1080/22221751.2020.1745095
110. Yuen K-S, Ye ZW, Fung SY. SARS-CoV-2 and COVID-19: the most important research questions. *Cell Biosci*. 2020;10(1):1-5, https://doi.org/10.1186/s13578-020-00404-4
111. McArdle H, Spain E, Keyes TE, Stallings RL, Brennan-Fournet M, Forster RJ. Triangular silver nanoplates: properties and ultrasensitive detection of miRNA. *Electrochem Commun*. 2017;79:23-27, https://doi.org/10.1016/j.elecom.2017.04.010
112. Lai C, Liu S, Zhang C, et al. Electrochemical aptasensor based on sulfur–nitrogen codoped ordered mesoporous carbon and thymine–Hg2+–thymine mismatch structure for Hg2+ detection. *ACS Sens*. 2018;3(12):2566-2573, https://doi.org/10.1021/acssensors.8b00926
113. Christodouleas DC, Kaur B, Chorti P. From point-of-care testing to eHealth diagnostic devices (eDiagnostics). *ACS Cent Sci*. 2018;4(12):1600-1616, https://doi.org/10.1021/acscentsci.8b00625
114. Hajian R, Balderston S, Tran T, et al. Detection of unamplified target genes via CRISPR–Cas9 immobilized on a graphene field-effect transistor. *Nat Biomed Eng*. 2019;3(6):427-437, https://doi.org/10.1038/s41551-019-0371-x
115. Khan M, Hasan MR, Hossain SI, Ahommed MS, Daizy M. Ultrasensitive detection of pathogenic viruses with electrochemical biosensor: state of the art. *Biosens Bioelectron*. 2020;166:112431, https://doi.org/10.1016/j.bios.2020.112431
116. Sinawang PD, Rai V, Ionescu RE, Marks RS. Electrochemical lateral flow immunosensor for detection and quantification of dengue NS1 protein. *Biosens Bioelectron*. 2016;77:400-408, https://doi.org/10.1016/j.bios.2015.09.048
117. Layqah LA, Eissa S. An electrochemical immunosensor for the corona virus associated with the Middle East respiratory syndrome using an array of gold nanoparticle-modified carbon electrodes. *Microchim Acta*. 2019;186(4):1-10, https://doi.org/10.1007/s00604-019-3345-5
118. Qin C, Ziwei MP, Tao SY, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis Off Public Infect Dis Soc Am*. 2020.
119. Seo G, Lee G, Kim MJ, et al. Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor. *ACS Nano*. 2020;14(4):5135-5142, https://doi.org/10.1021/acsnano.0c02823
120. Qiu G, Gai Z, Tao Y, Schmitt J, Kullak-Ublick GA, Wang J. Dual-functional plasmonic photothermal biosensors for highly accurate severe acute respiratory syndrome coronavirus 2 detection. *ACS Nano*. 2020;14(5):5268-5277, https://doi.org/10.1021/acsnano.0c02439
121. Tripathy S, Singh SG. Label-free electrochemical detection of DNA hybridization: a method for COVID-19 diagnosis. *Transactions of the Indian National Academy of Engineering*. 2020;5(2), 205-209, https://doi.org/10.1007/s41403-020-00103-z
122. Kim J-M, Chung Y-S, Jo HJ, et al. Identification of coronavirus isolated from a patient in Korea with COVID-19. *Osong Public Health Res Perspect*. 2020;11(1):3-7, https://doi.org/10.24171/j.phrp.2020.11.1.02
123. Ramphul K, Mejias SG. Coronavirus disease: a review of a new threat to public health. *Cureus*. 2020;12(3).https://doi.org/10.7759/cureus.7276
124. Wu A, Peng Y, Huang B, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host Microbe*. 2020;27(3):325-328, https://doi.org/10.1016/j.chom.2020.02.001
125. Roh C, Jo SK. Quantitative and sensitive detection of SARS coronavirus nucleocapsid protein using quantum dots-conjugated RNA aptamer on chip. *J Chem Technol Biotechnol*. 2011;86(12):1475--1479, https://doi.org/10.1002/jctb.2721
126. Jindal S, Gopinath P. Nanotechnology based approaches for combatting COVID-19 viral infection. *Nano Express*. 1(2), 022003, https://doi.org/10.1088/2632-959x/abb714, 2020.
127. Ahmad R, Mahmoudi T, Ahn M-S, Hahn Y-B. Recent advances in nanowires-based field-effect transistors for biological sensor applications. *Biosens Bioelectron*. 2018;100:312-325, https://doi.org/10.1016/j.bios.2017.09.024
128. Zhang X, Qi Q, Jing Q, et al. *Electrical Probing of COVID-19 Spike Protein Receptor Binding Domain via a Graphene Field-Effect Transistor*; 2020. arXiv preprint arXiv:2003.12529.
129. Suri C. Immunosensors for pesticide monitoring. In: MalhotraAPF, TurnerBD, eds. *Advances in Biosensors: Perspectives in Biosensors*. 1st ed.; 2003:161-178.
130. Haes AJ, Chang L, Klein WL, Van Duyne RP. Detection of a biomarker for Alzheimer's disease from synthetic and clinical samples using a nanoscale optical biosensor. *J Am Chem Soc*. 2005;127(7):2264-2271, https://doi.org/10.1021/ja044087q
131. Zhang DY, Chen SX, Yin P. Optimizing the specificity of nucleic acid hybridization. *Nat Chem*. 2012;4(3):208-214, https://doi.org/10.1038/nchem.1246
132. Nasrin F, Chowdhury AD, Takemura K, et al. Fluorometric virus detection platform using quantum dots-gold nanocomposites optimizing the linker length variation. *Anal Chim Acta*. 2020;1109:148-157, https://doi.org/10.1016/j.aca.2020.02.039
133. Funari R, Chu K-Y, Shen AQ. Detection of antibodies against SARS-CoV-2 spike protein by gold nanospikes in an opto-microfluidic chip. *Biosens Bioelectron*. 2020;169:112578, https://doi.org/10.1016/j.bios.2020.112578
134. Huang JC, Chang Y-F, Chen K-H, et al. Detection of severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein in human serum using a localized surface plasmon coupled fluorescence fiber-optic biosensor. *Biosens Bioelectron*. 2009;25(2):320-325, https://doi.org/10.1016/j.bios.2009.07.012
135. Anfossi L, Di Nardo F, Cavalera S. Multiplex lateral flow immunoassay: an overview of strategies towards high-throughput point-of-need testing. *Biosensors*. 2019;9(1):2, https://doi.org/10.3390/bios9010002
136. Zhu X, Wang X, Han L, et al. Multiplex reverse transcription loop-mediated isothermal amplification combined with nanoparticle-based lateral flow biosensor for the diagnosis of COVID-19. *Biosens Bioelectron*. 2020;166:112437, https://doi.org/10.1016/j.bios.2020.112437
137. De Vrieze S, Van Camp T, Nelvig A, Hagström B, Westbroek P, De Clerck K. The effect of temperature and humidity on electrospinning. *J Mater Sci*. 2009;44(5):1357-1362, https://doi.org/10.1007/s10853-008-3010-6
138. Giri R, Bhardwaj T, Shegane M, et al. When darkness becomes a ray of light in the dark times: understanding the COVID-19 via the comparative analysis of the dark proteomes of SARS-CoV-2, human SARS and bat SARS-like coronaviruses. *bioRxiv*. 2020:2020.03.13.990598.
139. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect*. 2020;53(3):368-370, https://doi.org/10.1016/j.jmii.2020.03.005
140. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir*

Med. 2020;8(4):420-422, https://doi.org/10.1016/s2213-2600(20)30076-x

141. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med*. 2020;58(7):1131-1134, https://doi.org/10.1515/cclm-2020-0198
142. Kaur M, Tiwari S, Jain R. Protein based biomarkers for non-invasive Covid-19 detection. *Sens Bio-Sens Res*. 2020;29:100362, https://doi.org/10.1016/j.sbsr.2020.100362
143. Deshpande P, Ramachandran C, Sefat F, et al. Simplifying corneal surface regeneration using a biodegradable synthetic membrane and limbal tissue explants. *Biomaterials*. 2013;34(21):5088-5106, https://doi.org/10.1016/j.biomaterials.2013.03.064

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