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Biosensors for Rapid SARS CoV-2 Diagnosis: A review

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Coronavirus disease 2019 (COVID-19), is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with symptoms similar to that of influenza. The disease was attributed toa zoonotic origin, but the transmission has been taking place from human to human thus resulting in an unprecedented global public health emergency. The virulence of the disease is high and the rate of transmission is rapid, reaching pandemic proportion with the fatality rate ranging from 2 to 4% in different countries. The incubation time for the virus in humans ranges from 2 to 14 days. Day by day, the world is facing a negative impact of COVID-19 on economy, productivity, social interactions, and public health. The diagnosis of the COVID-19 currently includes molecularlevel viral gene (RNA) detection in respiratory secretions using polymerase chain reaction, detection of viral antigen or viral protein, human antibody detection, and chest CT scan. Current prevention strategies include vaccination, surface disinfection, wearing of a mask, and social distancing. Treatment strategies include the use of antiviral therapeutic agents [1]. Reverse Transcript Polymerase Chain Reaction (RT-PCR) is regarded as a gold standard diagnostic test for the detection of viral genes (RNA) in the samples. However, the method can be prone to an error resulting in either false positives or negatives and can potentially hinder disease management. Quantitative real-time polymerase chain reaction (QRT-PCR) is time-consuming, labor-intensive, and may not be readily deployable in remote or resource-limited settings. However, in the context of the rapid transmission rate of the virus, there is a need for a fast, simple but yet sensitive, selective, and affordable testing method. Such an instant diagnosis has several advantages under pandemic conditions such as the following:

- Rapid mass scale screening for determining the actual number of infected people
- Deriving the realistic disease transmission rate
- Provision of directed and precise medical aid
- Decision making on lockdowns and travel advisory
- Early detection of the viral infection since the incubation time varies upto 14 days.
- Accurate determination of infection rate including asymptomatic carriers
- Efficient diagnosis in rural settings with limited medical infrastructure and resources
- Long term monitoring and tracking of viral transmission and community spread
- Ruling out re-occurrence of infection

[2] Reviewed and provided a comparative account of RT PCR detection versus other detection techniquesincluding biosensor based detection of viral antigens, colorimetric or fluorescent detection, CRISPR-Cas 13 and Cas-9 based kits, next generation sequencing or microarray based kits, and have emphasized that though these methods can be used for emergency point of care purpose they must be followed with RT PCR test to confirm the viral infection. Yüce et al. (2020) reported SARS CoV-2 detection kits authorized by US FDA for emergency use.Serological antibody presence testing is generally used for immune screening but it does not conclusively determine the presence of the virus, especially since the virus is undergoing constant mutation in its genetic makeup. Development of diagnostic tests for direct detection of the viral antigen might take some time to cover all the mutant strains.The probability of false-negative rate in RT-PCR necessitates a combination assay protocol for reliability [3].

Accurate, and on the spot detection of SARS CoV-2 virus in the early stages of infection is critical for effective control of disease and restricting its transmission, as there are several asymptomatic carriers(approximately 30% of the overall positive cases were asymptomatic) with varying incubation time [4]. Recent technologies and techniques available for COVID-19 diagnosis include NAAT, serological tests including LFAs, paper-based techniques, microfluidic modules, and piezoelectric with different advantages and disadvantages.These techniques are important for small healthcare facilities with limited resources for easier, faster, and more accurate diagnoses of COVID-19 [4].

Biosensor-based diagnostic methods were used effectively for detecting viral respiratory diseases. They are portable and enable instant and realistic tracking and tracing of the disease transmission. These sensors were designed to detect the surface proteins of the virus or the internal genetic material. Some of the examples of biosensors used for the detection of the RNA viruses in the sample include CRISPR-Cas9 paper strip, nucleic-acid sensor, aptamer-based bio-naogate, nucleic acid hybridization, DhITACT-TR chip-based, graphene-FET, antigen-Au/Ag nanoparticles-based electrochemical biosensor, optical biosensors, as well as Surface Plasmon Resonance based sensors[5,6] demonstrated a rapid assay for SARS-CoV-2 antigen detection with comparable sensitivity and specificity to the real-time RT-PCR assay based on 454 nasopharyngeal and throat swab samples and recommended it for screening of infections in high prevalence areas.

G-quadruplex is a nucleic acid structure formed by the folding of guanine-rich DNA or RNA. G-quadruplex-based biosensors can detect metal ions, organic macromolecules, proteins, and nucleic acids with improved ligand binding affinity and specificity compared to standard biosensors. [7] suggested the development of G-quadruplex based optical, fluorescent, colorimetric, and electrochemical biosensors for potential application in SARS-CoV-2 detection since the surface protein of SARS-CoV-2 can act as a potential target for the detection and treatment of this virus and can be recognized by the unique spatial structure of G-quadruplex modulated by the number and polarity of nucleotide strands and type of cations. [8] Evaluated a CE-approved POCT, the STANDARD Q COVID-19 Ag (SD-Biosensor, RELAB, I), for the detection of SARS CoV-2 nucleoprotein in nasopharyngeal swabs from 330 patients in terms of sensitivity, specificity, and accuracy and suggested that POCTs based mass screening testing and surveillance could decrease the burden on virology laboratories and address the shortage of PCR reagent. [9] Have developed a specific and sensitive immunosensor for the detection of immunoglobulin produced against SARS-CoV-2 infection. The method was based on a label-free paper-based electrochemical

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platform targeting SARS-CoV-2 antibodies in the clinical sera of the patients without the specific requirement of an antibody.SARS-CoV-2 antibodies will interpose the redox conversion of the indicator thus producing decreased current response. This electrochemical sensor was proven effective in real clinical sera from patients with satisfactory results. This method was also applied to the detection of the spike protein on SARS-CoV-2. The detection could be completed in 30 minutes and was more sensitive (detection limit of 1 ng/m)when compared to the colorimetric LFA. [10] Havedeveloped a specific lateral flow immunoassay (LFIA)-based biosensor for detection of COVID-19. The fusion antibodies could bind specifically to the SARS-CoV-2 nucleocapsid protein antigen with high affinity, but not to other coronaviruses. This COVID-19 biosensor could detect the SARS-CoV-2 virus within 20 min and distinguished SARS-CoV-2 from other similar CoVs, such as SARS-CoV and MERS-CoV.

[11] Reported the development of a rapid, low-cost, quantitative paper-based electrochemical sensor chip to detect SARS-CoV-2 genetic material in less than 5 min. The electrochemical response generated from the graphene-ssDNA-AuNP surface was used for precise digital monitoring. The biosensor targets the viral nucleocapsid phosphoprotein gene. The sensor was found to distinguish the positive COVID-19 samples from the negative ones with good accuracy, sensitivity, and specificity. Since the ssDNA-conjugated AuNPs simultaneously target two separate regions of the same SARS-CoV-2 N-gen, the sensor is feasible even during the genomic mutation of the virus [12,13].

Conclusion

Quantitative RT PCR remains the gold standard method for confirming the positive infection of the SARS CoV-2 virus. Eventhough biosensors were developed they need to be used in combination with RT PCR for the final confirmation of the infection. Several biosensors are in the evaluation stage with limited sample numbers and therefore they can be used for point of care and rapid screening for estimation purposes rather than clinical correlation. Moreover, the virus undergoes mutations and therefore there is a need to studythe flexibility of the biosensors to detect the mutated strains. Biosensor based data can nevertheless be used to formulate health policies and advisories.

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