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Protein based biomarkers for Non-invasive Covid-19 detection

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Abstract

COVID-19 has become a substantial lethal disease worldwide, and early diagnosis is a significant concern for this virus. Currently, RT-PCR is being used worldwide for the detection of this virus with human to human transmission. Furthermore, the recent develop biosensor leading to others diagnosis approach but being invasive are painful and time taking. Another possibility can be protein-based biomarkers as an application of biosensors for detection and early diagnostics. Considering the other approach, that is, microfluidics-based biosensor, though being a non-invasive method, will be restricting virus transmission. This review commences with the recent develop biosensor for Covid-19 detection and listing down the available biomarkers with their secretion range comparison of normal to COVID-19 patients through clinical analysis in china and concludes with the future approach for the diagnosis.

Keywords: Covid-19, Biomarkers, Virus, Non-invasive, Biosensors, Microfluidics.

Introduction

COVID-19 is a recent outbreak occurred worldwide and created a colossal dysfunction of various activity all around the world [12]. COVID-19 stand for Coronavirus diseases 2019. The infection and spread of this virus were firstly observed in Wuhan city of China, has now affected nearly 200 countries worldwide [10]. Coronaviruses constitute the subfamily Orthocoronavirinae. These are enveloped viruses, positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry with genome size ranging from approximately 26 to 32 kilobases, one of the largest among RNA viruses [11]. They have characteristic club-shaped spikes that project from their surface. The primary concern related to this virus is early diagnosis, cost-effectiveness and reduce the chance of spread so that working professional also do not get affected while testing. Currently, RT-PCR is being used for testing the virus which is time taking and costly, moreover some of the research group has recently

develops biosensor for Covid-19 detection though different approach but they all are invasive and lead to virus particles exposure, to overcome this issue, a 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 biomarker isolation and sample preparation are much more comfortable in protein-based biomarker as compared to a nucleic acid or other biomarkers. In the current detection of COVID-19, which is RT-PCR required RNA isolation, purification and processing step, which increase the time of detection and cost of testing. We can locate out such biomarker through proteomics studies from COVID-19 infected patient and find out specific biomarker for COVID-19.

Recent develop Biosensor

All around the worldwide several research groups are indulged in developing a rapid diagnostic technique for Covid-19 detection, as the current method RT-PCR is time-consuming and costly. To begin, this scenario Qiu and his team develop a Dual-Functional Plasmonic Photothermal Biosensors, in this, they used plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) with the help of two-dimensional gold nanoislands (AuNIs) which they functionalized with complementary DNA receptors which can perform a sensitive detection of the selected sequences from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8]. Though this sensor is fast and more accurate as compared to RT-PCR result, still it does not remove the obstacle of virus particles exposure. To improve the detection limit et al, recently develop an immunosensor based on SARS-CoV-2 spike protein based on graphene sheet on FET based system, this sensor has a better limit of detection [9]. However, it lacks the specificity in longer terms if viral strain gets mutated and change its morphology. These are some of the recent development through different research group for the rapid detection of Covid-19 and their various parameters are listed in table 1. However, none of them approaches towards the development of non-invasive biosensor, which can be user friendly and cheaper.

Potential Biomarkers through clinical studies

Rapid and early diagnosis of any diseases is always a major concern for any country. Currently, the situation related to COVID-19 is enormous, as we do not have any rapid system for early and

fast detection of this virus. Several countries are trying to develop a rapid kit based on antibodies or gene for detection. There are other techniques which can resolve out this problem with a more manageable approach and detect the virus rapidly. One of these techniques is biomarker based on sensors, termed biosensors. There are several reported biosensors based on biomarkers which accurately detect particular diseases such as non-invasive biosensors developed by Kumar et al., for oral cancer detection which used CYFRA-21 as a specific biomarker for oral cancer [6], same like these specific biomarkers for COVID-19 can also be used, and biosensors can be made.

Furthermore, the other issue with this virus detection is human to human transmission while detecting. Professionals working for the diagnosis are 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, such as Singh et al., has tried to develop a microfluidics-based biosensor for influenza detection [7]. In this review article, we have listed out the significant biomarkers which were reported in various papers after the clinical studies in COVID-19 patients in China. Biomarkers such as Serum amyloid A (SAA) which secreted in a more substantial amount in COVID-19 patient as compared to a healthy patient, Serum ferritin is also a considerable biomarker 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, furthermore biosensors based on this approach will be non-invasive that can be user friendly in use so that the need of highly qualified professionals can be overcome, apart from these other biomarkers which can also be considered are listed in table 2 with the secretion range in healthy patients and COVID-19 infected patients [5]. Lastly, there are some more studies which report some more biomarkers such as IL-10, IL-6 and IL-1 β [4].

Future prospects and Conclusion

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 biosensor with microfluidics system.

Through clinical studies of COVID-19 patient biomarkers such as Serum ferritin, Interleukin-2R are found to show considerable difference in their secretion range of healthy patients and affected patients with COVID-19 diseases, further to develop biomarkers based biosensor such biomarkers can be used and to investigate more specific biomarkers further proteomics analysis can be done. We can also look forward with 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.

The schematic representation of this review is prepared in fig 1.

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Author's contribution

The authors contributed equally in reviewing the work and providing a unique solution to use the biomarkers in biosensors.

Conflict of interest

Authors declare none.

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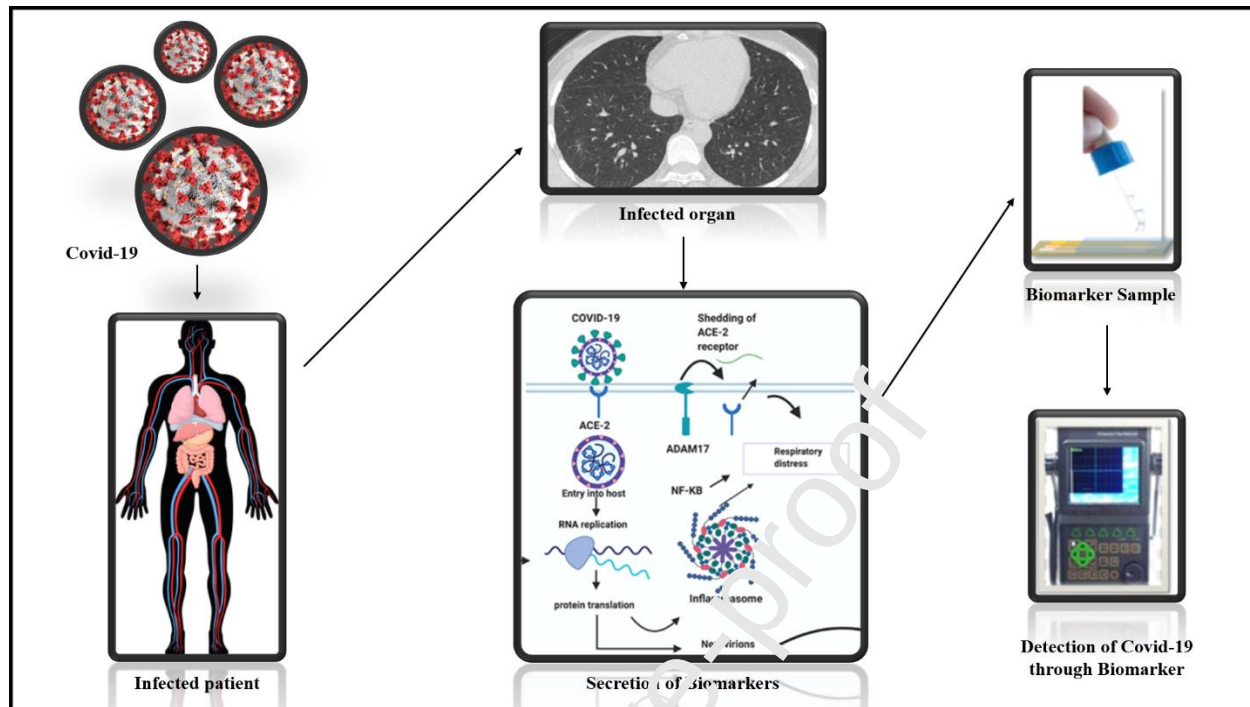
Table 1: Recently develop biosensor and their parameters

S. No	Techniques Used	Materials used	Limit of Detection	Analytes	Linear Detection Range (LDR)	Incubation Time	Advantage	Limitation	Ref.
1	Surface Plasmon Resonance	Gold nanoislands	0.22 pM	DNA	0.01 pM to 50 μ M	-	- Fast responsive - Low detection limit	-Sample isolation and purification are time consuming	8
2	Field-effect transistor	Graphene sheet	1.6×10^1 pfu/mL	Protein	1.6×10^1 pfu/ml to 1.6×10^4 pfu/ml	4 hours	- Low cost - Highly selective	- Incubation time is more	9

Table 2: List of considerable biomarkers for Covid-19

S.No.	Biomarker	Normal patient	Affected patient	Biological samples	Ref.
1	Serum ferritin, (ng/mL)	15.0–150.0	800.4 (452.9-1451.6)	Serum	1
2	C-reactive protein,(mg/L)	0.0–1.0	57.9 (20.9-103.2)	Plasma	1
3	Interleukin-2R, (U/mL)	223.0–710.0	757.0 (528.5-1136.3)	Serum	1
4	IL-6 (pg/mL)	0.0–7.0	7.9	Blood	2
5	D-Dimer (μ g/mL)	0-0.243	0.4	Plasma	3
6	Serum amyloid A (SAA) (mg/L)	0-10	108.4	Serum/Saliva	3

Figure 1: Schematic representation of biomarkers based biosensor



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Highlights

- Protein based biomarkers for Non-invasive Covid-19 detection
- Cost-effective
- Cheaper
- Integration of microfluidics system with this kind of biosensor, so that a minimal amount of sample will be used and the chance of virus transmission remains insignificant
- Non-invasive method of bio-sensing the biomarkers of COVID-19

Declaration of interests

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

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Author's contribution

The authors contributed equally in reviewing the work and providing a unique solution to use the biomarkers in biosensors.

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