Review Paper:

Technological tools and Biosensors for detection and diagnosis of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a novel coronavirus. There is a constant increase in number of positive cases for COVID-19. The objective of this review is to study technology tools and sensors available for detection and diagnosis of COVID-19. COVID -19 pandamic has created surge demand for essential health care instrumentation, medicines along with technology and tools for proper control and management of corona virus. Diagnosing and screening of COVID-19 is possible using nucleic acid testing and CT scans.

In this study, we have described Field-effect transistor-based graphene sensor and Plasmonic Photothermal(PPT) biosensor for highly accurate SARS-CoV-2 detection. A dual-functional localized surface plasmon resonance (LSPR) biosensor combining the photothermal effect and plasmonic sensing transduction is used for SARS-CoV-2 viral nucleic acid detection. FET based sensor for COVID-19 used a graphene channel coupled to the SARS-CoV-2 spike antibody with the efficient gating effect of the FET through phosphate -buffered saline (PBS; pH 7.4) buffer as the electrolyte covering. The aqueous solution-gated FET system detects SARS-CoV-2 based on electrical signal due to changes in channel surface potential. Industry 4.0 technologies such as Artificial Intelligence (AI), Internet of things(IOT) have helped in early detection and diagnosis. AI can build an intellegent platform with neural network for automatic monitoring and prediction of the spread of virus.IOT can assist in diagnosis and treatment of COVID-19 patients and can help in setting in advanced clinical work. Industry 4.0 technologies improve the working efficiency of the health care professional and provide better solution.

Keywords: SARS-CoV-2, Biosensor, Nucleic acids, COVID-19, Industry 4.0.

Introduction

COVID-19 first detected in Hubei Province, China in December 2019 has spread globally. By 10 January 2020, samples from patients' bronchoalveolar lavage (BAL) fluid were analyzed to reveal a pathogen with a similar genetic sequence to the betacoronavirus B lineage.[3] It was discovered that this new pathogen had ~80%, ~50% and ~96% similarity to the genome of the severe acute respiratory syndrome virus (SARS-CoV), Middle East respiratory syndrome virus (MERSCoV) and bat coronavirus RaTG13, respectively.[20,40]

Because of the rapidly increasing rate of human infection, the World Health Organization (WHO) has classified the COVID-19 outbreak as pandemic.[34] Because of non-availability of specific drugs or vaccines for COVID-19 till date, early diagnosis and management play a crucial role for containing the outbreak. As per the World Health Organization (WHO), COVID-19 has so far affected 217 countries or territories or areas and has infected over 4 million people globally.

Globally, as of 6:45pm CEST, 28 May 2020, there have been 5,596,550 confirmed cases of COVID-19, including 353,373 deaths reported to WHO[34]. SARS-CoV-2-infected person will infect approximately new three people and hence the reproductive number is averaged to be 3.28.[19]

COVID-19 is the third large-scale pandemic which is caused by coronavirus. In the last two decades, Middle East Respiratory Syndrome (MERS) in 2012 and Severe Acute Respiratory Syndrome (SARS) in 2003 have been caused by coronavirus.[6,7] These two coronaviruses have caused about 10,000 cumulative cases with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.[12]

Regarding the SARS-CoV-2, the laboratory-confirmed COVID-19 cases have already been more than 90 times higher than the total confirmed cases of SARS and MERS.[21] A recent study conducted on aerosol and surface stability of SARS-CoV-2 showed that the virus may be found in aerosols (<5 μm) for at least up to 3 h and may be more stable on plastic and stainless steel than on copper and cardboard.[31]

SARS-CoV-2 is transmitted from human to human and is not airborne. SARS-CoV-2 symptoms can vary with some patients remaining asymptomatic, while the most common symptoms of this viral infection are fever, cold, cough, bone pain and breathing problems and ultimately leading to pneumonia.

The symptoms stated by COVID-19 patients are not particular and cannot be used accurately for diagnosis as many of these symptoms could be very closely associated with other respiratory infections. Diagnostics can play an

important function in the containment of COVID-19 that can enable the rapid implementation of control measures. These can help in limiting the spread through identification of cases, quarantine and contact tracing which means identifying a person who has come in contact with an infected patient.

With the symptom onset the patient has to visit the community health care centre. There the samples will be collected which will be transported to the clinical laboratories for testing. Testing will be performed on the samples which will indicate if tested positive or negative. The routinely used reverse transcription polymerase chain reaction (RT-PCR) test is currently the used reference method for COVID-19 diagnosis.[12] According to the WHO, the immediate priority for COVID-19 diagnostics research lays is the development of nucleic acid and protein tests and detection at the point of care.[28] Serological tests using proteins are needed in addition to nucleic acid tests to improve surveillance efforts. Biosensors are perfect for providing an alternate and reliable solution to real-time detection, clinical diagnosis and continuous monitoring.[22,29]

Technological Tools

There are different biosensing techniques but localized surface plasmon resonance (LSPR) biosensing systems are applicable to different classes of analytes of clinical interests.[13] Thus, LSPR is an ideal method for real-time and label-free detection of micro- and nanoscale analytes.[25,26] Recently in research, SPR is utilized to test the biophysical properties of SARS-CoV-2 spike protein and it was found that the SARS-CoV-2 spike glycoprotein bound angiotensin-converting enzyme 2 (ACE2) was having much higher affinity than SARS-CoV spike protein.[35]

Thus, the LSPR technique for genetic testing and nucleic acid detection in clinical practices could be an interesting alternative for SARS-CoV-2 detection and COVID-19 diagnosis.[8] The plasmonic chip is designed with the two dimensional distribution of nanoabsorbers (AuNIs) which is capable to generate the local PPT heat and transduce the *in situ* hybridization for highly accurate and sensitive SARS-CoV-2 detection.[12]

Nucleic acid tests using isothermal amplification are currently in development for detection of SARS-CoV-2. The techniques Isothermal amplification are conducted at a single temperature and do not need specialized laboratory equipment to provide similar analytical sensitivities to PCR.[9]

Emerging technologies like RPA Recombinase Polymerase Amplification, TR-RPA Reverse Transcription Recombinase Polymerase Amplification, Barcode, Loop Mediated Isothermal Amplification LAMP are some of types of technologies with biomarker used as nucleic acid and Magnetic Biosensor, DNA-assisted Immunoassay, lateral flow use protien as biomarker which provides a more extensive list that can be adapted for detection of SARS-CoV-2.[3]

Fast and accurate identification of a novel virus can play a great contribution in the control of an emerging pandemic. Industry 4.0 is also known as the fourth industrial revolution, which consists of advance manufacturing and information technologies supported by wireless connectivity and sensors to fulfil the customised requirement of different areas of the human being in lesser time.

Industry 4.0 is a smart system used as a flexible production line for almost entire production processes of real-time information provided by Artificial intelligence (AI), Internet of Things (IoT) and other digital technologies.[24] Industry 4.0 technologies have the capability of providing better digital solutions for our daily lives during this crisis for detection of the symptoms of COVID-19[1,4,11]. Hence it helps to predict the chances of acquiring the disease and to track potential health problems and expected chances of recovery.

AI and IOT technologies can track and forecast the nature of the virus, its risks of the infection and its likely spread and help collect data with help of IOT from mobile phones, social media and media platforms etc.

Real-time data available with IOT can assist to provide updated information which is helpful to predict the probable infected sites, the spread of the virus, need for beds and healthcare professionals during this crisis. Digital approaches help in early diagnosis and providing treatment at an early stage .AI-based video surveillance has a high capability to reduce the workload of doctors and hospital managers during this crisis. This is useful to observe the activities of the patient affected by this virus.

Standard testing is time consuming and hence AI helps to speed this process significantly which may not be possible by a human[1,14] Drug identification useful for the treatment of COVID-19 patients is possible with AI. It has become a powerful tool for diagnostic test designs and development of vaccination[27]. AI saves time as it helps in developing vaccines and treatments at much faster rate than usual. It is also effective tool for clinical trials during the development of the vaccine.

During COVID-19 pandemic, there is a sudden and massive increase in the numbers of patients and as a consequence healthcare professionals have a very high workload. Here, AI is used to effectively reduce the workload of healthcare workers[27]. Previously mentored data over data prevalent at different time help in AI analysis which can identify traits, causes and reasons for the spread of virus infection in future.

SARS-CoV-2 encodes four structural proteins: nucleocapsid, spike, matrix and envelope.[10] Among all the structural proteins, the spike protein is best suited to be used as a diagnostic antigen. It is because a major transmembrane

protein of the virus is highly immunogenic. Additionally, the spike protein displays amino acid sequence diversity among corona viruses, thus enabling the specific detection of SARS-CoV-2.[10]

COVID-19 FET sensor is aqueous solution-gated FET transducing an electrical signal to the SARS-CoV-2 spike antibody. The structure of the COVID-19 FET sensor utilised a graphene channel coupled to the SARS-CoV-2 spike antibody. Aqueous solution-gated FET sensor was covered with phosphate-buffered saline (PBS; pH 7.4) buffer as the electrolyte to maintain an efficient gating effect.[10]

The aqueous solution-gated FET sensing system could detect SARS-CoV-2 based channel surface potential changes and hence the corresponding effects on the electrical response.[10] COVID-19 FET sensor as a function of gate voltage showed that drain source current negatively increased as gate voltage negatively increased corresponding to the action of a p-type semiconductor.[5,30]

Sensors and technological tools for detection have the potential to play significant roles in the intensity of the infection and its clinical outcomes. In the current situation, they can be used for the following objectives:

- Early detection and diagnosis of the infection and initiate treatment, quarantine or stabilize the patient.
- Allowing for a close follow-up and contact tracing, citizens can stay monitored at home, avoiding over saturation of medical facilities, preventing the movement of people (reduction in travel time), reducing the risk of intra hospital infection and identifying people in contact with an infected person.
- Coordinating the medical resources used in distant locations.
- Projection of cases of mortality
- Development of drugs and vaccines
- Reducing the workload of healthcare workers
- Preventing the risk of contagion, especially via professionals, who are key assets that need to be taken care of in this context, avoiding direct physical contact, reducing the risk of exposure to respiratory secretions.
- Making citizens aware.
- Saving costs on antiseptic material (gloves, disposable robes, disinfecting of visitor spaces etc.)

Applications

There are few prominent and significant applications of the sensors and tool for detection for SARS-CoV-2. Several useful sensors and tools for detection of COVID-19 pandamic have been discussed such that there proper usage can lead to proper control and management of COVID-19 pandemic. The sensors technology and the tools for detection can fulfill the requirement for proper controlling and treating the COVID-19 patients. Proper implementation of these sensors and tools for detection for SARS-CoV-2 can help in fast diagnostic, can enhance information and communication regarding the public health. There are still lot of innovative ideas and solution yet to be explored for fighting local and global medical emergencies.

The biosensor exhibits characteristics as highly sensitive, fast and reliable. These characteristics were successfully used for reliable diagnostic for detection of SARS-CoV-2. This dual-functional plasmonic concept of biosensing united the PPT effect and the LSPR sensing transduction on a single AuNI chip which was cost effective.

Single AuNI chip is used for transduction of dual function plasmonic sensor and hence it is cost effective. Under the outbreak background of COVID-19, this proposed dual-functional plasmonic biosensor provided a diagnosis platform for COVID-19 which was reliable and easy-to-implement. This biosensor can improve the diagnostic accuracy in clinical tests and will provide an alternate solution for PCR-based tests.

IOT can be used for surveillance through drones to ensure quarantine of patient, contact tracing, mask wearing etc. Remote monitoring of the patient in-home is possible by the medical professional. AI can be a useful tool for the development of drugs, clinical trials for drugs and vaccines against this virus.AI can predict the outbreak and forecast the spread of virus and future of the virus with the previous mentored data and decision is made with the help of algorithms. AI technology can be used to produce CT scans and perform an online medical examination of the people for detecting pneumonia caused by a virus. AI can help in monitoring infected patients and developing proper treatment regimens and prevention strategies.

Industry 4.0 technology is beneficial to manufacture the equipment required for the health care system. Highly sensitive biosensing device is COVID-19 FET sensor in which the sensing area is SARS-CoV-2 spike antibody conjugated to a graphene sheet. This functionalized graphene-based sensor platform was used for the detection of the SARS-CoV-2 virus in clinical samples. The COVID-19 FET graphene sensor provides highly responsive, simple and rapid detection. Moreover, this technology can be easily adapted for emerging viral diseases diagnosis. The applications of these technologies are used to learn about COVID-19 and help in diagnostic and detection.

Conclusion

The established diagnostic technologies as shown in table 1 have enabled researchers and medical professionals in the design of COVID-19 diagnostics. Diagnostic technologies play an important role in the pandemic to identify and manage the spread of COVID-19. SARS 2002 outbreak has given us a guiding path from the experiences learnt.

To identify the morphological structure of the virus, transmission electron microscopy was used. Similarly, through genome sequencing, the identity of the virus was

confirmed. The sequence data were used to design Polymerase Chain Reaction (PCR) primers and probes for SARS-CoV-2. SARS-CoV virus took 5 months to be identified. The same techniques were used to identify SARS-CoV-2 virus in only 3 weeks.[30]

As a first line of defence against COVID-19, nucleic acid test was rapidly developed after the identification and sequencing of SARS-CoV-2. There is now a call for development of diagnostic technologies to be used to diagnose patients without laboratory infrastructure. To detect the infected patient, the samples need not be sent to the centralised facility. There are some diagnostic technologies that have shown clinical feasibility and broad list of emerging technologies that can be adapted to detect SARS-CoV-2.

In academic laboratories there are many platforms being developed such as elctrochemical sensors, biosensors, paper based system etc. Isothermal amplification, barcoding and microfluidic technologies are in conception phases. There is a need for clinical testing and clinical trials are to be further developed so that they can become plug-and-play systems and can be rapidly implemented in pandamic situation.

The integration of diagnostics and industry 4.0 technologies should provide greater communication and surveillance. Industry 4.0 technology can be used for tracing the origin of an outbreak and is very helpful in the fight against COVID-19. AI can help in proper health monitoring, in treating COVID-19 infected patients and tracking the situation of COVID-19 at different scales such as molecular, medical and epidemiological. AI can facilitate in developing proper prevention strategies for the virus, treating regimens for the patients and helping in drug and vaccine development. Diagnostics is an important part of the World Health Organisation (WHO) toolbox for dealing with outbreaks related to spread of pandemic and facilitate the care of those affected.

Future Scope

Exposure due to connectivity goes beyond the spread of the disease to the spread of misinformation, inaccurate medical advice and conspiracy theories. Disease and misinformation are destructive and hence proper technology is required to target both equally. Uncertainty is a fundamental characteristic of the pandemic prediction and no forecast of COVID -19 is complete without information. We are facing the massive threat of the new pandemic and trying hard to control the spread of the SARS-CoV-2 virus.

Table 1
Diagnostic and detection tools for COVID-19 outbreak

S.N.	Biosensor /Technological Tool	Description	How it can help in diagnostic and detection of COVID-19
1.	A dual-functional plasmonic biosensor combining the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) for COVID-19.	A dual-functional LSPR biosensor through combining the photothermal effect and plasmonic sensing transduction is used for SARS-CoV-2 viral nucleic acid detection.LSPR sensing transduction unit, uses the excitation laser with sensing beam generation at 532 nm peak wavelength and 40 mW maximum optical power was applied to the AuNI chip.Laser beam is incident at normal incident angle and it is in attenuated total reflection(ATR) mode at the interface between the glass substrate and liquid environment. Highly sensitive detection of the selected sequences from SARS-CoV-2 through nucleic acid hybridization is performed through two-dimensional gold nanoislands (AuNIs) functionalized with complementary DNA receptors. On the AuNIs chip thermoplasmonic heat is generated when illuminated at the plasmonic resonance frequency. Localized PPT heat helps the sensing performance and is capable to elevate the two similar gene sequences with the in situ hybridization temperature and thus facilitate the accurate discrimination. The dual-functional LSPR biosensor is highly sensitivity toward the selected SARS-CoV-2 sequences and the concentration of 0.22 pM and allows precise detection of the specific target in a multigene mixture.	Dual-functional plasmonic biosensor provides an alternative and promising solution for the clinical COVID-19 diagnosis. This Biosensor provides real time detection and continuous monitoring of micro and nanoscale anlytes. This bisensor gains perception into the thermo plasmonic improvement and its applicability in the nucleic acid tests for COVID-19 and viral disease diagnosis. The dual-functional plasmonic biosensor can provide a easy-to-implement and reliable diagnosis platform for COVID-19 and improve the diagnostic accuracy in clinical tests and provide an alternate solution for PCR-based tests.It is a lab free, highly sensitive, fast, real time and reliable diagnostic solution.

2.	To diagnose COVID-19 at the early stage and to improve its treatment by applying medical technology, using Industry 4.0 technologies based on the Internet of Things (IOT).	Industry 4.0 technologies based on the Internet of Things (IOT) can be used as follows: Online monitoring and location tracking: Can be used for online monitoring, identifying and locating patient diagnosed with COVID-19 and guide treatment when problem found in consultation with patient Planning and management: Help in diagnosis and treatment of patients with COVID-19. A plan can be set in advance in stratified direction for timely treatment of suspected, confirmed and suspicious cases and proper management regarding the same to be carried out. IOT can be used in investigation or expansion of the treatment and diagnosis functions based on the massive information and data collected will help in guiding how to better control and prevent COVID-19. Experts can perform statistical analysis based on the data of graded diagnosis and treatment of patients with COVID-19. IOT can help to analyze the stage of infection by this virus, identifying the clusters that are safe, infected and 'hot spots' and can successfully do the contact tracing of the individuals and also to monitor them. This technology can track the infected patients and forecast the nature of the virus. It can help collect data from media platforms and inform about the risks of the infection and its likely spread through social media IOT can provide updated information with the help of real-time data available, which is helpful to predict the probable places of infection and inflow of the virus. On this information healthcare professionals can schedule the need for beds and required diagnosis during this crisis.	The COVID-19 Diagnosis based on the Internet of Things (IoT) medical Technology aimed to conduct clinical work during the COVID-19 epidemic. especially for outpatients and It can provide quality control (QC) to assist the diagnosis and treatment for outpatient and achieve early identification, isolation and treatment of patients with COVID-19. It can summarize experiences, identifies problems and proposes solutions with the data available through location tracking. The functions of online monitoring, alarm linkage and follow-up scheduling can contribute to management and planning treatment assistance for COVID-19. Statistical analysis can expand the massive information mining of COVID-19 and help in complete management and timely treatment of COVID-19 patients. Digital approaches helps in early diagnosis and treatment thus reducing the workload of doctors and health care professionals.
3.	Early detection and diagnosis of the infection of COVID-19 using Industry 4.0 technologies based on Artificial Intelligence (AI)	Patients with symptom detected and are diagnosis with AI Based approach 1.Physician identify Possible match of COVID-19 Symptom with AI support 2. Samples taken to confirm infection and decide further therapy 3.Patients get quarantined /admitted 4. Start AI based treatment and monitoring 5.Recovery phase 6.Retest for COVID-19 i) Test Positive -isolation Or ii) Test Negative- cured In Conventional approach for Patients detected with symptom the Physician will analyse symptoms and if multiple matches found of Test samples taken Patients get quarantined /admitted and Symptomatic diagnosis will be started which is time consuming and can increase the intensity of the virus.	It helps to provide faster decision making. Algorithms developed can help in building a new diagnosis and management system for the COVID 19 cases. In the diagnosis of the infected cases AI can be used with the help of medical imaging Technologies. For COVID-19, coronavirus AI is an upcoming and useful tool to identify early infections and also helps in monitoring the condition of the infected patients. Developing useful algorithms can significantly improve treatment consistency and decision making. Through AI prediction of the number of positive cases and death in a region is possible from the data available and hence proper measures and planning can be possible. It can also predict the future course of the pandemic and its likely reappearance. It

		AI build intelligent platform can enable automatic monitoring and can predict the spread of this virus. A neural network can be designed to forecast and visualise the disease. This would help in proper medication and care of the patient. Day-to-day updates of the patients can be furnished which can help in providing diagnosis to be followed by the patient in COVID-19 pandemic. AI is used for drug research, drug delivery design and development by analyzing the available data on COVID-19.	can be used in speeding up drug testing in real-time. It is a cost-effective solution for diagnosis with AI Based approach.
4.	Field-effect transistor (FET)-based biosensing device for detecting SARS-CoV-2 spike protein.	The sensor is designed using graphene sheets of the FET coated with a specific antibody against SARS-CoV-2 spike protein. The performance of the sensor was observed using cultured virus, antigen protein and nasopharyngeal swab specimens from COVID-19 patients. The FET device could successfully detect the SARS-CoV-2 spike protein at concentrations of 1 fg/mL in phosphate-buffered saline and 100 fg/mL clinical transport medium. The FET sensor could also detected SARS-CoV-2 in culture medium and clinical samples. For transduction of electrical signal with the COVID-19 FET sensor, an aqueous solution-gated FET was prepared. COVID-19 FET sensor was designed using a graphene channel coupled to the SARS-CoV-2 spike antibody. The COVID-19 FET sensor was covered with phosphate-buffered saline buffer as the electrolyte to maintain an efficient gating effect. The aqueous solution-gated FET sensor could detect SARS-CoV-2 spike protein based on changes in channel surface potential and the corresponding effects on the electrical characteristic. The FET graphene based biosensor was tested for target analytes namely SARS-CoV-2 antigen protein, cultured SARS-CoV-2 virus, or SARS-CoV-2 virus from clinical samples and a reliable electrical signal was detected.	Thus, the successfully fabricated FET biosensor for SARS-CoV-2 is a promising and highly sensitive with immunological diagnostic method for COVID-19 that requires no sample pretreatment or labeling. Real-Time Detection of SARS-CoV-2 Antigen Protein is possible with FET sensor designed using a graphene channel coupled to the SARS-CoV-2 spike antibody.

Data-driven technologies could help understand the concern of the disease or the distribution of care, hence data should be communicated with all the uncertainty and complexity. AI in future will become an important technology to fight against the other pandemics. It can provide a solution for preventive measure and fight against many other diseases. AI will thus play a vital role in providing more preventive health care against the virus and help in predicting status of the virus.

The medical education to treat the current pandemic lags in many considerable ways and medical professionals are not trained to treat patients and save lives. The current pandemic has highlighted the need to extend medical education to emphasize current world issues at larger scales beyond the scale of individual patients. Doctors need to study disease modeling, big data, simulation and forecasting health problems. There is a gap evident between doctors and epidemiologists who are struggling to save lives and who are trying to save societies respectively. Telemedicines and similiar technologies should provide medical education to prepare doctors to deliver remote assistance to patients.

To sum up, the world needs to investment seriously in research and development to understand the current epidemics as well as to prepare for the possible future ones. There is a need to prepare proper health-care infrastructure, to develop new diagnostic and detection solutions, to conduct research on vaccines as well as to fund research infrastructure and pandemic predictability. Extensive research needs to be done into social sciences to help understand the social aspects of the pandemic, to help adoptive engagement, to trust in our communities, to improve our education to be more adaptive and to target misinformation.

References

1. Ahmed S.F., Quadeer A.A. and McKay M.R., Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS CoV immunological studies, *Viruses*, **12(3)**, 254 **(2020)**

2 Anker J.N., Hall W.P., Lyandres O., Shah N.C., Zhao J. and Van Duyne R.P., Biosensing with Plasmonic Nanosensors, *Nat. Mater*., **7**, 442−453 **(2008)**

3. Buddhisha Udugama, Pranav Kadhiresan, Kozlowski Hannah N., Ayden Malekjahani, Matthew Osborne, Li Vanessa Y.C., Hongmin Chen, Samira Mubareka, Gubbay Jonathan B. and Chan Warren C.W., Diagnosing COVID-19: The Disease and Tools for Detection, *ACS Nano*, **14**, 3822−3835 **(2020)**

4. Cheng G.J., Liu L.T., Qiang X.J. and Liu Y., Industry 4.0 development and application of intelligent manufacturing, In 2016 international conference on information system and artificial intelligence (ISAI), IEEE, 407-410 **(2016)**

5. Choi Y., Kang J., Jariwala D., Kang M.S., Marks T.J., Hersam M.C. and Cho J.H., Low-Voltage Complementary Electronics from Ion-Gel-Gated Vertical van der Waals Heterostructures, *Adv. Mater*., **28**, 3742−3748 **(2016)**

6. Corman V.M., Landt O., Kaiser M., Molenkamp R., Meijer A., Chu D.K., Bleicker T., Brunink S., Schneider J. and Schmidt M.L., Detection of 2019 Novel Coronavirus (2019-nCoV) by Real-Time RT-PCR, *Euro Surveill.*, **25(3)**, 2000045 **(2020)**

7. Coronavirus Disease (COVID-19), Centers for Disease Control and Prevention, https://www.cdc.gov/coronavirus/2019ncov/ about/transmission.html **(2019)**

8. Coronavirus Disease (COVID-19), U.S. Food and Drug Administration. http://www.fda.gov/emergency-preparedness-andresponse/mcm-issues/coronavirus-disease-2019-covid-19 (accessed 2020/03/03) **(2019)**

9. Craw P. and Balachandran W., Isothermal Nucleic Acid Amplification Technologies for Point-of-Care Diagnostics: A Critical Review, *Lab Chip*, **12**, 2469 **(2012)**

10. Giwan Seo, Geonhee Lee, Mi Jeong Kim, Seung-Hwa Baek, Minsuk Choi, Keun Bon Ku, Chang-Seop Lee, Sangmi Jun, Daeui Park, Hong Gi Kim, Seong-Jun Kim, Jeong-O Lee, Bum Tae Kim, Edmond Changkyun Park* and Seung Il Kim*, Rapid Detection of COVID-19 Causative Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor Based Biosensor, *ACS Nano*, **14**, 5135−5142 **(2020)**

11. Grasselli G., Pesenti A. and Cecconi M., Critical care utilisation for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response, *JAMA*, **323(16)**, 1545-1546 **(2020)**

12. Guangyu Qiu, Zhibo Gai, Yile Tao, Jean Schmitt, Kullak-Ublick Gerd A. and Jing Wang, Dual-Functional Plasmonic Photothermal Biosensors for Highly Accurate Severe Acute Respiratory Syndrome Coronavirus 2 Detection, /acsnano.0c02439, April 8 **(2020)**

13. Haes A.J., Chang L., Klein W.L. and Van Duyne R.P., Detection of a Biomarker for Alzheimer's Disease from Synthetic and Clinical Samples Using a Nanoscale Optical Biosensor, *J. Am. Chem. Soc.*, **127**, 2264−2271 **(2005)**

14. Haleem A., Javaid M. and Vaishya R., Industry 4.0 and its applications in orthopaedics, *J Clin Orthop Trauma*, **10(3)**, 615e6 **(2019)**

15. Kobayashi T., Jung S.M., Linton N.M., Kinoshita R., Hayashi K., Miyama T., Anzai A., Yang Y., Yuan B. and Akhmetzhanov A.R., Communicating the Risk of Death from Novel Coronavirus Disease (COVID-19), *J. Clin. Med*., **9(2)**, 580 **(2020)**

16. Ksiazek T.G. et al, A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome, *N. Engl. J. Med*., **348**, 1953−1966 **(2003)**

17. Li X., Zai J., Wang X. and Li Y., Potential of Large "first Generation" Human-to-human Transmission of 2019-nCoV, *J. Med. Virol*., **92**, 448−454 **(2020)**

18. Liu C. et al, Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases, *ACS Cent. Sci*., **6**, 315-331 **(2020)**

19. Liu Y., Gayle A.A., Wilder-Smith A. and Rocklov J., The Reproductive Number of COVID-19 Is Higher Compared to SARS Coronavirus, *J. Travel Med*., **27(2)**, taaa021 **(2020)**

20. Lu R. et al, Genomic Characterisation and Epidemiology of 2019 Novel Coronavirus: Implications for Virus Origins and Receptor Binding, *Lancet*, **395(10224)**, 565−574 **(2020)**

21. Mahase E., Coronavirus: COVID-19 Has Killed More People Than SARS and MERS Combined, Despite Lower Case Fatality Rate, *Br. Med. J*., **368**, m641, doi: 10.1136/bmj.m641 **(2020)**

22. Masson J.F., Surface Plasmon Resonance Clinical Biosensors for Medical Diagnostics, *ACS Sens*, **2**, 16−30 **(2017)**

23. Mizumoto K., Kagaya K., Zarebski A. and Chowell G., Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases on Board the Diamond Princess Cruise Ship, Yokohama, Japan, 2020, *Euro Surveill*, **25(10)**, 25 **(2020)**

24. Mohd Javaid, Abid Haleem, Raju Vaishya, Shashi Bahl, Rajiv Suman and Abhishek Vaish, Industry 4.0 technologies and their applications in fighting COVID-19 pandemic Diabetes & Metabolic Syndrome: *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **14**, 419-422 **(2020)**

25. Qiu G.Y., Ng S.P. and Wu C.M.L., Bimetallic Au-Ag Alloy Nanoislands for Highly Sensitive Localized Surface Plasmon Resonance Biosensing, *Sens. Actuators B*, **265**, 459−467 **(2018)**

26. Qiu G., Thakur A., Xu C., Ng S.P., Lee Y. and Wu C.M.L., Detection of Glioma-Derived Exosomes with the Biotinylated Antibody-Functionalized Titanium Nitride Plasmonic Biosensor, *Adv. Funct. Mater*., **29**, 1806761 **(2019)**

27. Raju Vaishya, Mohd Javaid, Ibrahim Haleem Khan and Abid Haleem, Artificial Intelligence (AI) applications for COVID-19 pandemic, *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, **14,** 337e339 **(2020)**

28. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), WHO: Geneva, Switzerland **(2020)**

29. Soler M., Huertas C.S. and Lechuga L.M., Label-Free Plasmonic Biosensors for Point-of-Care Diagnostics: A Review, *Expert Rev. Mol. Diagn*., **19,** 71−81 **(2019)**

30. Teng F., Hu K., Ouyang W. and Fang X., Photoelectric Detectors Based on Inorganic p-Type Semiconductor Materials, *Adv. Mater*., **30**, 1706262 **(2018)**

31. Van Doremalen N. et al, Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1, *N. Engl. J. Med.*, DOI: 10.1056/NEJMc2004973 **(2020)**

32. Wang L.F. and Anderson D.E., Viruses in Bats and Potential Spillover to Animals and Humans, *Curr. Opin. Virol*., **34,** 79−89 **(2019)**

33. Willets K.A. and Van Duyne R.P., Localized Surface Plasmon Resonance Spectroscopy and Sensing, *Annu. Rev. Phys. Chem*., **58**, 267−297 **(2007)**

34. World Health Organization, Laboratory Testing for Coronavirus Disease 2019 (Covid-19) in Suspected Human Cases: Interim Guidance, WHO/COVID-19/laboratory/2020.4; World Health Organization: Geneva, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratoryguidance (accessed May 29, 2020) **(2020)**

35. Wrapp D., Wang N., Corbett K.S., Goldsmith J.A., Hsieh C.L., Abiona O., Graham B.S. and McLellan J.S., Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation, *Science*, **367**, 1260−1263 **(2020)**

36. Wu Z. and McGoogan J.M., Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention, *J. Am. Med. Assoc*., DOI: 10.1001/jama.2020.2648 **(2020)**

37. Xie X., Zhong Z., Zhao W., Zheng C., Wang F. and Liu J., Chest CT for Typical 2019- nCoV Pneumonia: Relationship to Negative RT-PCR Testing, *Radiology*, **296**, E41–E45 **(2020)**

38. Ye Z., Zhang Y., Wang Y., Huang Z. and Song B., Chest CT Manifestations of New Coronavirus Disease 2019 (COVID-19): A Pictorial Review, *Eur. Radiol*., **19**, 1–9 **(2020)**

39. Zhang Q. and Zhao Q., Inactivating Porcine Coronavirus before Nucleic Acid Isolation with the Temperature Higher Than 56 °C Damages Its Genome Integrity Seriously, *BioRxiv*, https://doi.org/10.1101/2020.02.20.958785 **(2020)**

40. Zhou P. et al, A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin, *Nature*, **579**, 270 **(2020)**.

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