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Perspective

Biosensors for Managing the COVID-19 Cytokine Storm: Challenges Ahead

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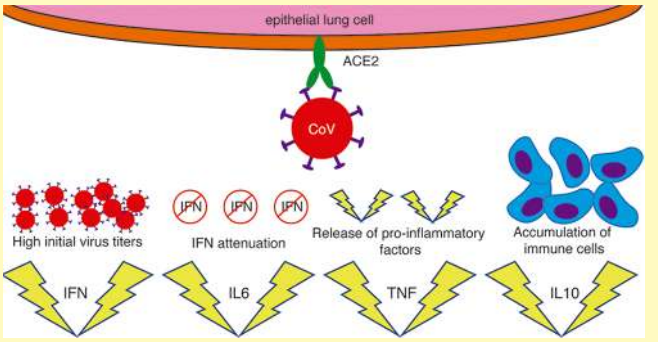
ABSTRACT: The global COVID-19 pandemic has oversaturated many intensive care units to the point of collapse, leading to enormous spikes in death counts. Before critical care becomes a necessity, identifying patients who are likely to become critically ill and providing prompt treatment is a strategy to avoid ICU oversaturation. There is a consensus that a hyperinflammatory syndrome or a "cytokine storm" is responsible for poor outcomes in COVID-19. Measuring cytokine levels at the point of care is required in order to better understand this process. In this Perspective, we summarize the main events behind the cytokine storm in COVID-19 as well as current experimental treatments. We advocate for a new biosensor-enabled paradigm to personalize the management of COVID-19 and stratify patients. Biosensor-guided dosing and timing of immunomodulatory therapies could maximize the benefits of these anti-inflammatory treatments while minimizing deleterious effects. Biosensors will also be essential in order to detect complications such as coinfections and sepsis, which are common in immunosuppressed patients. Finally, we propose the ideal features of these biosensors using some prototypes from the recent literature as examples. Multisensors, lateral flow tests, mobile biosensors, and wearable biosensors are seen as key players for precision medicine in COVID-19.



KEYWORDS: *SARS-CoV-2, IL-6, immunosensor, rapid diagnostic test, sepsis, inflammation, precision medicine*

The SARS-CoV-2 outbreak that originated in the province of Wuhan in December 2019 has rapidly evolved into a worldwide pandemic.[1] Although many patients remain asymptomatic, others develop severe pneumonia and even acute respiratory distress syndrome (ARDS). ARDS patients require mechanical ventilation, and due to the sudden spike in infections, some healthcare providers have been forced to make dire decisions about whom they connect to ventilators.[2] Currently, there is a common consensus that a hyperinflammatory syndrome or "cytokine storm" is indicative of a poor prognosis for critical COVID-19 cases, and that cytokines are useful prognosis biomarkers.[3−6] This has spurred an overuse of immunomodulator drugs with the hope of halting disease progression and improving outcomes.[7] The effectiveness and side effects of these treatments are still being analyzed, although preliminary reports suggest that timing and dosage will be keys for their success.[8] Thus, there is an urgent need to develop methods for monitoring cytokine levels in COVID-19 patients. Such methods would enable detecting COVID-19 patients that are worsening and to treat them before they become critically ill. This would not only improve outcomes, but also avoid oversaturation of the ICU. Measuring cytokine levels could also be useful for personalizing anti-inflammatory treatments and monitoring their efficacy.

Designing and prototyping biosensors for cytokine detection in the context of COVID-19 has unique technological and translational challenges. First of all, cytokines such as IL-6 are intrinsically difficult to detect because they are found at low levels in serum (typically below 10 pg mL^{-1} in healthy individuals).[9] Second, in order for point-of-care tests to be useful, rapid detection in whole blood is preferred so that information can be obtained at the bedside. The oversaturation of hospitals caused by COVID-19 has forced healthcare providers in especially hard-hit areas to decentralize COVID-19 care, including emergency field hospitals and home-based quarantine. Patients may worsen and require urgent care in these situations where centralized facilities for biochemical testing are not available. Similarly, economic factors may limit

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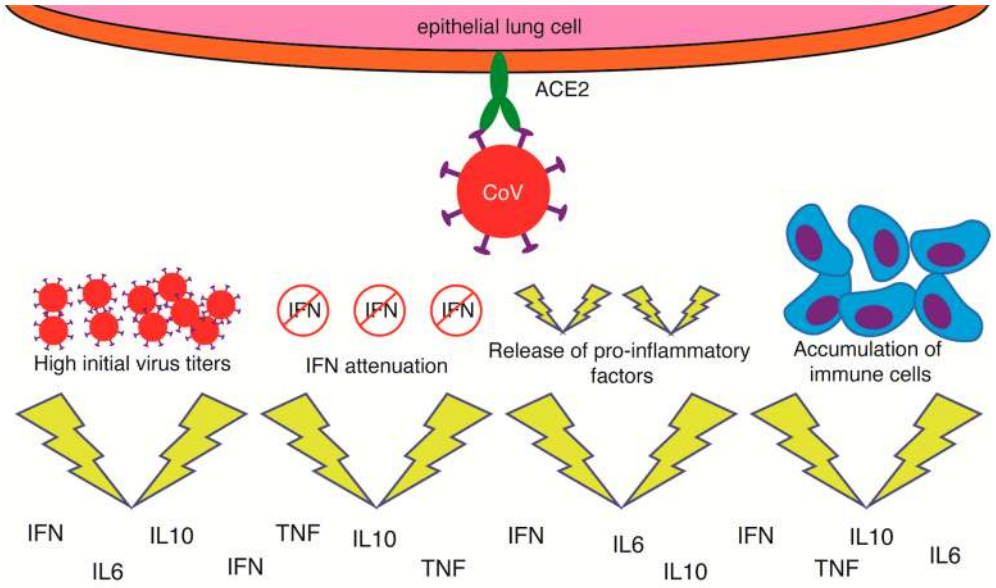

Figure 1. Schematic representation of main events leading to the hyperinflammation known as "cytokine storm" in COVID-19.

intensive care in some regions, where well equipped laboratories may not be available. Thus, in order to have significant impact against this pandemic, biosensors for COVID-19 management must be rapid, sufficiently sensitive to detect cytokines in whole blood, and independent of centralized equipment.

Below we summarize the trajectory of the COVID-19 cytokine storm, including the main inflammation biomarkers linked to this syndrome. We also summarize the current therapies and identify key points where biosensors are required to manage recovery. Finally, we critically review the recent literature for cytokine detection and propose future directions in the field.

MONITORING THE CYTOKINE STORM

SARS-CoV-2 infects epithelial lung cells via specific interactions with the angiotensin converting enzyme 2 (ACE2).[10] While efforts are being made worldwide to better understand the cytokine storm that characterizes the progression to severe pneumonia or ARDS, previous information from SARS-CoV and MERS-CoV infections, shown in Figure 1, indicates the main factors.[11−13] It is known that the virus replicates very quickly in the early stages of infection. This means that high levels of viral proteins known to antagonize interferon (IFN) responses are generated, which results in a strong yet delayed proinflammatory response at the site of infection. These pro-inflammatory cytokines and chemokines attract macrophages and neutrophils that also release pro-inflammatory agents. This amplifies the inflammation, giving rise to ARDS, sepsis, or multiorgan dysfunction syndrome (MODS), all of which are associated with poor outcomes.[14] A comprehensive review of the cytokines and chemokines involved in the COVID-19 cytokine storm is already available, although studies performed in large cohorts of patients have not been performed.[12] These are required in order to determine cutoff values for diagnosis and prognosis purposes.

Pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) have been found elevated in the sera of severely and critically ill COVID-19 patients.[15−24] This indicates that these cytokines could be good prognosis biomarkers; that is, they could indicate the progression to severe or critical COVID-19. Many recent cytokine profiling studies, however, have only been performed in small populations, and therefore cannot be broadly generalized.[17,22] Larger studies are required to establish cutoff values as well as to determine the intricate relationships between pro- and anti-inflammatory factors in COVID-19 progression. Based on other hyperinflammatory syndromes such as sepsis, the levels of these biomarkers will likely fluctuate rapidly. This means that patients with inflammation biomarkers below a certain threshold value may evolve quickly and require anti-inflammatory treatments even though their initial biomarker measurements indicated otherwise. A solution to this problem could be to perform periodic measurements of biomarkers in order to evaluate their kinetics.[23] This would require biosensors that are inexpensive and easy to use at the point of care in order to not overburden healthcare workers. It should also be noted that, although cytokines are also present in saliva, urine, and sputum,[24] no information is currently available about their function and usefulness as biomarkers for cytokine storm monitoring in COVID-19. Measuring cytokines in sputum could be particularly valuable because it would reveal information about local inflammation. However, only 30−40% of COVID-19 patients produce sputum.[16]

Anti-inflammatory cytokines such as IL-10 have also been found in the sera of COVID-19 patients.[22−25] It is known from other hyperinflammatory syndromes that dysregulated inflammation is often followed by immune suppression,[26] putting these patients at high risk of opportunistic infections from bacteria, fungi, or even latent viruses such as human cytomegalovirus (CMV).[27−29] This is particularly problematic in the context of the ICU, since nosocomial infections by multiresistant pathogens can be lethal if not promptly detected. Because of this, we anticipate that biosensors aimed at detecting coinfections will also be required in order to manage critical COVID-19 patients. For example, biosensors that detect procalcitonin (PCT) could be useful to detect opportunistic bacterial infections.[30−32] Procalcitonin is produced in parenchymal cells in response to bacterial toxins. In

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healthy individuals, PCT is considered undetectable (below 0.05 ng mL^{-1}). PCT levels above 1−2 ng mL^{-1} are usually considered as a warning of potential bacterial sepsis.[33] Since PCT levels do not rise to such a large extent in viral infections, biosensors for this biomarker could indicate the onset of bacterial infections in COVID-19 patients.

POTENTIAL BIOSENSOR-GUIDED THERAPIES

Table 1 summarizes some anti-inflammatory treatments proposed so far for ameliorating the cytokine storm in COVID-19 patients. It should be noted that the evidence supporting these treatments is weak. In other words, randomized clinical trials for these drugs in the context of COVID-19 care have not yet been completed. Their use is not recommended in official protocols by WHO, only for clinical trials or compassionate motives. Many are repurposed drugs already in use for other diseases and syndromes, but not for infections.[34] It is important to highlight this as many of these pharmaceuticals are immunosuppressive. Since COVID-19 patients are already immunosuppressed due to IFN attenuation and anti-inflammatory responses, the administration of these immunomodulators may exacerbate the risk of an opportunistic infection or reduce the effect of antiviral drugs.

Table 1. Main Immunomodulators Proposed So Far for Managing Inflammation in COVID-19

Immunomodulator	Target	Mechanism
Corticosteroids	Nonspecific	Binding to receptor enhances or represses the transcription of inflammation genes
(Hydroxy) chloroquine	Nonspecific	Suppressing the activation of T cells
Convalescent plasma	Nonspecific	Unknown
Immunoglobulins	Nonspecific	Binding to Fc receptors
Azithromycin	Nonspecific	Decreasing the pro-inflammatory response
Baricitinib	JAK	Inhibitor of Janus kinase (JAK)
Anankinra	IL-1	Antagonist of the IL-1 receptor
Tocilizumab/ Sarilumab	IL-6	Binding to IL-6 receptor thus blocking the interaction with gp130

A good example of the polemic surrounding these anti-inflammatory treatments is the use of corticosteroids. Corticosteroids such as methylprednisolone are inexpensive and globally available. They are not routinely recommended for sepsis care except in cases of septic shock. Previous evidence from SARS-CoV-1 and MERS patients treated with corticosteroids yielded widely disparate outcomes,[11] and the WHO and IDSA have discouraged the use of corticosteroids for COVID-19 care. Nevertheless, several authors report good outcomes when administering these drugs at cautious doses.[8,35,36] Of those reporting good outcomes, dosing and timing have been highlighted as the key factors for successful corticosteroid therapy in the context of SARS-CoV infections. Kinetic profiles of pro-inflammatory cytokines such as IL-6 could provide crucial data to guide the onset of corticosteroid treatment and adjust doses in order to reduce inflammation while minimizing side effects.[37] Other nonspecific anti-inflammatory treatments that could benefit from biosensor-guided administration are (hydroxy)chloroquine,[7] immunoglobulins, azithromycin,[38] and convalescent plasma therapies.[39]

Drugs based on monoclonal antibodies and recombinant proteins such as Tocilizumab[40] or Anakinra[41] have also been proposed for reducing hyperinflammation caused by COVID-19. These treatments block specific pro-inflammatory signal pathways. These drugs could benefit from a "companion diagnostics" approach similar to that which is used in cancer care. That is, the administration of these drugs would be guided by measurements of the specific pro-inflammatory factors they modulate. For example, Tocilizumab binds receptors of IL-6 (both soluble and membrane-bound). This blocks the interaction with membrane-bound gp130, which in turn prevents the activation of a downstream Janus kinase responsible for signal cascading.[42] It has been proposed that blockers of the IL6-mediated inflammatory response such as Tocilizumab and Sarilumab should be guided by IL-6 measurements with a threshold value around 20 pg mL^{-1}.[43,44] These antibodies have proven to be useful to treat unwanted cytokine release syndromes in immune anticancer therapies. Some early reports on the benefits of using Tocilizumab are encouraging, although a clinical trial for Sarilumab has recently been discontinued due to a lack of clear positive outcomes. Interestingly, serial IL-6 measurements have shown that after the administration of Tocilizumab there is a slight increase in IL-6 followed by sharp decrease over time.[43] These early reports highlight the relevance of performing kinetic measurements of biomarkers for monitoring the progress of inflammatory diseases.

CURRENT BIOSENSOR CANDIDATES FOR MANAGING THE CYTOKINE STORM

Table S1 summarizes the main features of recent biosensor prototypes for cytokine detection. As highlighted above, time-dependent pro- and anti-inflammatory responses are involved in COVID-19 progression. A multisensor system capable of detecting several of these biomarkers simultaneously would provide evidence to determine disease stage and guide personalized therapies. For example, it has been reported that plasmonic nanosensor arrays can detect 6 cytokines simultaneously (IL-2, IL-6, IL-4, IL-10, IFN-γ, and TNF-α, Figure 2a).[45] These multisensors require a minute sample size (1 μL) and show an impressive dynamic range for quantification (between 10 and 10 000 pg mL^{-1}). The signal transduction mechanism consists of measuring changes in the localized surface plasmon resonance (LSPR) of gold nanorods with dark-field microscopy. This provides information about cytokine binding to antibodies in real time, which is more informative than traditional end-point ELISA. The total time required to run the whole chip is only 40 min. The rapid analysis time makes this detection platform suitable for aiding clinical decision-making in emergency situations. Another interesting multisensor platform using electrochemical transducers is shown in Figure 2B. It contains 32 individually addressable electrodes, each one multiplexed with an 8-port manifold to provide 256 measurements in less than 1 h.[46] However, it also requires an off-line protein capture step on magnetic nanobeads. Electrochemical immunoassays for IL-6 with these devices reported a wide dynamic range between 0.1 and 10^4 pg mL^{-1}. Multiplexed cytokine measurements with electrochemical biosensors have also been reported using graphene oxide to fabricate nanoprobes.[47] This platform detects IL-6, IL-1β, and TNF-α spiked into the same mouse serum sample. The multiplexed detection was achieved by using antibodies bound to three different signal reporters (nile blue (NB), methyl blue (MB), and ferrocene (Fc)).

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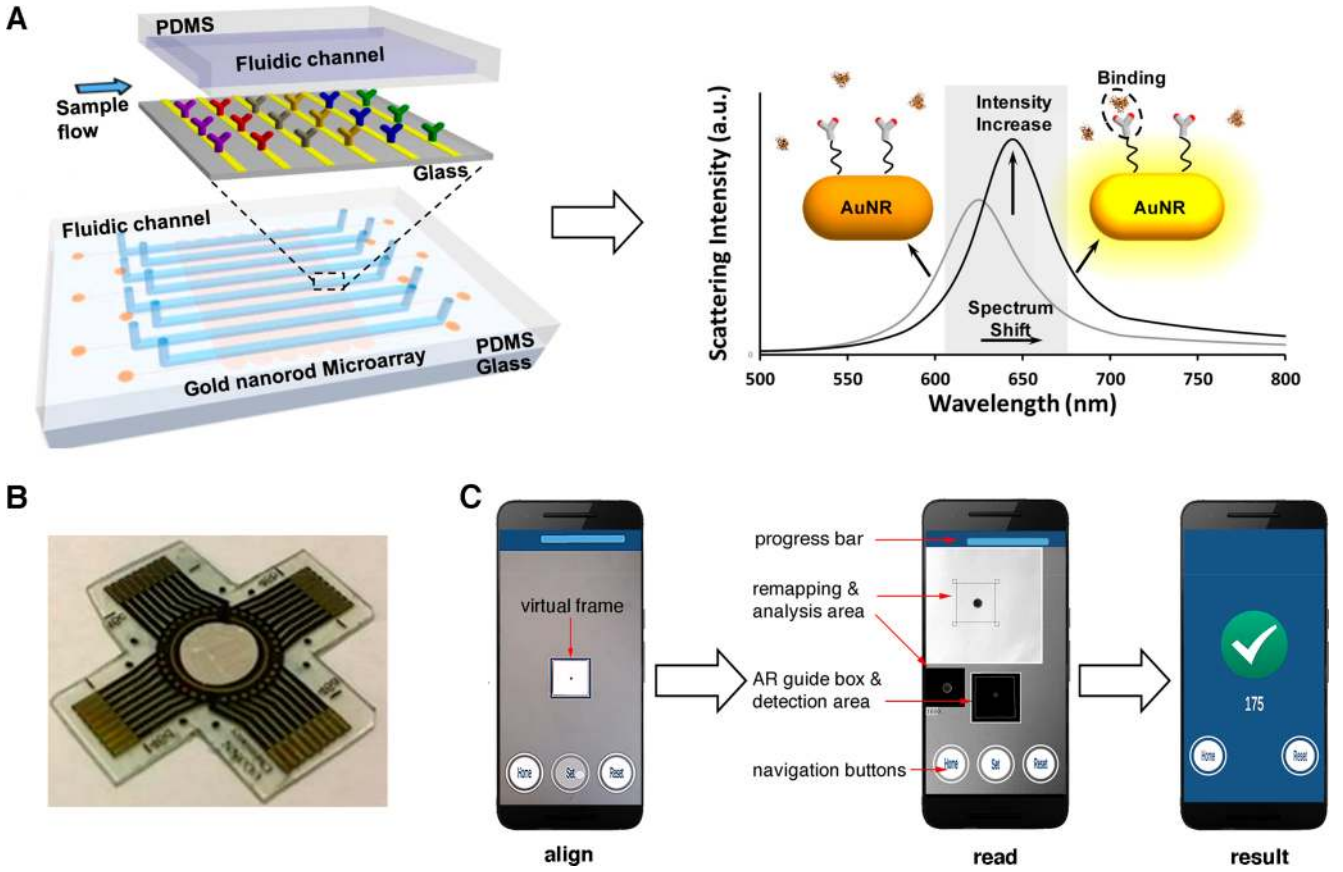

Figure 2. Potential biosensor candidates for managing the COVID-19 cytokine storm. (A) Simultaneous detection of multiple cytokines with arrays of plasmonic nanosensors showing the detection platform and microfluidics (left) and the transduction mechanism (right). Reprinted with permission from ref 45. Copyright (2015) American Chemical Society. (B) Electrochemical multisensor with 32 detection sites and 256 measurements can be performed in less than 1 h using an 8-port manifold. Reprinted with permission from ref 46. Copyright (2016) American Chemical Society. (C) Mobile immunosensors for IL-6, antibody-decorated gold nanoparticles generate colored spots that are quantified with a smartphone. A virtual frame or augmented reality box ensures a consistent distance and angle between the phone and the assay. Reprinted with permission from ref 52. Copyright (2019) The Royal Society of Chemistry.

COVID-19 is a global challenge and requires technologies that are easy to implement in many different scenarios. The oversaturation of hospitals during the peak of the infection has forced some governments to decentralize COVID-19 care and manage patients in temporary field hospitals and in-home quarantine. In these scenarios, detection systems that are not bound by centralized infrastructure play a key role. For instance, a lateral flow immunoassay has been proposed for detecting IL-6 in unprocessed blood with high sensitivity.[48] The ability to detect cytokines directly from blood is extremely useful in decentralized healthcare scenarios, since purifying serum or plasma requires a centrifugation step that is difficult to perform at the bedside. However, blood contains cells like erythrocytes, which can interfere with colorimetric detection schemes. The lateral flow test used antibody-decorated nanoparticles as probes and surface-enhanced Raman spectroscopy (SERS) as the signal transduction mechanism. It showed a limit of detection of 5 pg mL^{-1} in whole blood. This limit of detection, however, was achieved with a DXR Raman microscope, which is not suitable for point-of-care use. Over the past decade, a growing trend in biosensors has been to interface them with mobile devices such as smartphones.[49−51] This is an appealing option because smartphones already have a high global market penetration and therefore do not require the purchase of additional readers. Mobile biosensors for IL-6 have been recently proposed.[52] The devices consist of a paper immunosensor for colorimetric detection using gold nanoprobes (Figure 2C). The gold nanoprobes generate colored spots that are detected in real time with a smartphone app. Instead of external attachments, the app uses an augmented reality system in order to control photographic conditions. This system also compensates for variable light conditions, allowing the user to quantify colorimetric signals using only an unmodified smartphone. The biosensor was able to detect variations in IL-6 levels as small as 12.5 pg mL^{-1} in whole blood and with a rapid assay time of only 18 min. Furthermore, the paper substrate makes it particularly useful for monitoring infectious diseases because it can be easily disposed of by incineration.

Biosensors capable of continuously monitoring cytokine levels would be ideal for detecting COVID-19 patients progressing to severe or critical stages as well as to check the success of anti-inflammatory therapies. While to the best of our knowledge immunosensors for continuous detection of biomarkers in blood have not yet been proposed, some prototypes with the potential to achieve this feature can be found in the recent literature. For example, needle-shaped microelectrodes have been proposed for detecting alterations in IL-6 levels in real time (Figure 3A).[53] In this design, the interaction between the cytokine and antibodies bound to the

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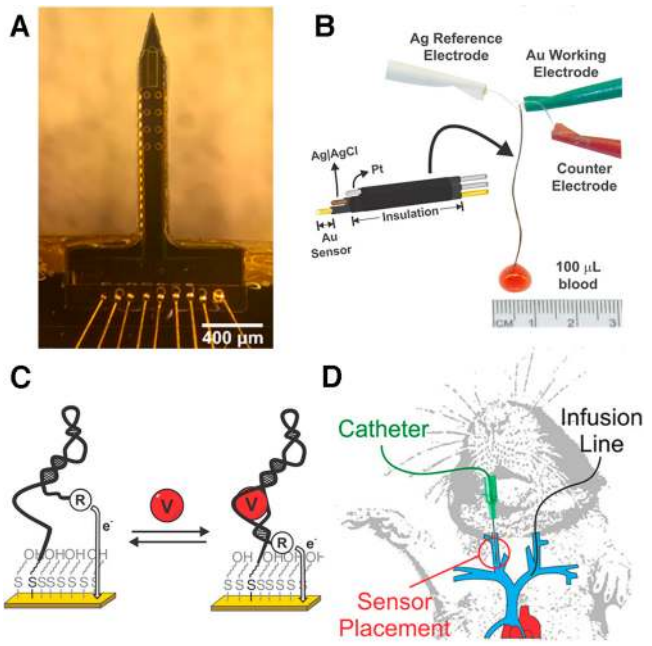

Figure 3. Potential wearable biosensors for inflammation monitoring. (A) Needle-shaped microelectrodes for IL-6 detection could be inserted into the bloodstream for continuous cytokine monitoring. Reprinted with permission from ref 53. Copyright (2019) Elsevier. (B) Electrode configuration, (C) aptamer conformational change, and (D) *in vivo* implementation of electrochemical sensors. Reprinted with permission from ref 54. Copyright (2019) The American Chemical Society.

electrode changes the impedance of the system without the need for detection antibodies or labels. The authors suggest that integrating the sensors with a cannula within the bloodstream could enable the real-time monitoring of IL-6 levels, although the initial prototype was only tested in surrogate serum samples. Recently, an electrochemical biosensor capable of continuous monitoring in blood samples has been proposed. It consists of a wire electrode modified with aptamers that change their configuration upon binding their target (Figure 3B).[54] This changes the position of a redox active molecule (methylene blue) with respect to the electrode, which can be followed with square-wave voltammetry (Figure 3c). The authors demonstrated that the sensors implanted in a rat could detect vancomycin as a target molecule in real time (Figure 3D). Adapting this technology for detecting cytokines could enable a precise profiling of the COVID-19 inflammation.[55] Finally, a wearable detection platform has also been proposed that could be a game-changer in inflammation monitoring.[56] It is based on the intradermal delivery of biocompatible near-infrared (NIR) quantum dots. An array of these nanosensors is delivered using dissolvable microneedles. The fluorescence emission of the quantum dots was fine-tuned so that they would be invisible to the naked eye, but detectable upon illumination with NIR light. The pattern of emitted light generated by the array can be detected with a modified smartphone and evaluated with a machine learning algorithm. While this technology has initially been demonstrated as a way to keep vaccination records, adaptation for continuous monitoring of biomarkers could revolutionize the field of personalized medicine.

FINAL THOUGHTS

To date, there have been more than 264 000 deaths due to COVID-19 worldwide. Social distancing measures have flattened the virus propagation curve, and many countries are relaxing confinement measures. At the same time, there is also a consensus view that the virus will not be eradicated until a vaccine is developed and deployed. Until then, new tools are required in order to reduce the burden of COVID-19. It is imperative to avoid the progression from severe pneumonia to critical ARDS. Measuring prognosis biomarkers and combining this knowledge with clinical observations and risk factors is a winning strategy for stratifying patients according to disease severity. Biosensors have the potential to play a central role in this process by providing rapid information at the point of care. They could also provide guidance for the administration of immunomodulators, which can have deleterious effects if they are not dosed carefully.

For this to happen, several translational challenges need to be met from a technological perspective. To ensure rapid measurements at the point of care, devices must be easy to use by a frontline healthcare worker. This means that analytical platforms should enable the detection of cytokines in one simple step. Also, biosensors need to be inexpensive enough to enable multiple measurements. This is important because inflammatory processes evolve rapidly, and therefore it would be ideal to obtain a personalized biomarker profile for each patient. Implanted biosensors could enable a continuous monitoring of patients. However, this technology still needs further development and regulatory aspects for future commercialization will be much tougher than nonimplanted biosensors. Multisensors are also seen as key players in precision medicine for COVID-19 because they provide information about the relative levels of different pro- and anti-inflammatory processes, which is important to design personalized therapies.

All in all, we propose that the ideal device for managing the cytokine storm responsible for severe and critical COVID-19 cases should encompass all the features of current biosensors; that is, they should monitor the levels of several cytokines simultaneously in raw blood samples, have a rapid turnaround time, be easy to dispose of, and use portable readers. Paper biosensors can be destroyed by incineration which is important to meet biosafety regulations. Readers should also be easily disinfected, especially for decentralized testing. Wearable biosensors would enable the continuous monitoring of patients, a much-desired feature; however, the technology still needs further development to be ready for clinical translation. The information provided by these devices should then be combined with patient data (age, comorbidities, treatments, microbiology results) in order to assess the risk of a poor prognosis. Using the information from these biosensors to train a neural network has the potential to achieve this goal.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssensors.0c00979.

Examples of biosensors for cytokine detection proposed in the last 5 years (Table S1) (PDF)

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Author Contributions

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ABBREVIATIONS

IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; SARS, sever acute respiratory syndrome; MERS, Middle East respiratory syndrome; WHO, World Health Organization; IDSA, Infectious Diseases Society of America

REFERENCES

(1) Wu, F.; Zhao, S.; Yu, B.; Chen, Y.-M.; Wang, W.; Song, Z.-G.; Hu, Y.; Tao, Z.-W.; Tian, J.-H.; Pei, Y.-Y.; et al. A New Coronavirus Associated with Human Respiratory Disease in China. *Nature* **2020**, *579*, 265−269.

(2) Villar, J.; Confalonieri, M.; Pastores, S. M.; Meduri, G. U. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. *Crit. Care Explor.* **2020**, *2*, e0111.

(3) Mehta, P.; Mcauley, D. F.; Brown, M.; Sanchez, E.; Tattersall, R. S.; Manson, J. J. COVID-19 : Consider Cytokine Storm Syndromes and Immunosuppression. *Lancet* **2020**, *395*, 1033−1034.

(4) Pedersen, S. F.; Ho, Y.-C. SARS-CoV-2: A Storm Is Raging. *J. Clin. Invest.* **2020**, *130*, 2202−2205.

(5) Wu, D.; Yang, X. O. TH17 Responses in Cytokine Storm of COVID-19: An Emerging Target of JAK2 Inhibitor Fedratinib. *J. Microbiol. Immunol. Infect.* **2020**, *53*, 368.

(6) Henderson, L. A.; Canna, S. W.; Schulert, G. S.; Volpi, S.; Lee, P. Y.; Kernan, K. F.; Caricchio, R.; Mahmud, S.; Hazen, M. M.; Halyabar, O.; et al. On the Alert for Cytokine Storm: Immunopathology in COVID-19. *Arthritis Rheumatol.* **2020**, DOI: 10.1002/art.41285.

(7) Zhao, M. Cytokine Storm and Immunomodulatory Therapy in COVID-19: Role of Chloroquine and Anti-IL-6 Monoclonal Antibodies. *Int. J. Antimicrob. Agents* **2020**, 105982.

(8) Shang, L.; Zhao, J.; Hu, Y.; Du, R.; Cao, B. On the Use of Corticosteroids for 2019-NCoV Pneumonia. *Lancet* **2020**, *395*, 683−684.

(9) Fabbri, E.; An, Y.; Zoli, M.; Simonsick, E. M.; Guralnik, J. M.; Bandinelli, S.; Boyd, C. M.; Ferrucci, L. Aging and the Burden of Multimorbidity: Associations with Inflammatory and Anabolic Hormonal Biomarkers. *J. Gerontol., Ser. A* **2015**, *70*, 63−70.

(10) Udugama, B.; Kadhiresan, P.; Kozlowski, H. N.; Malekjahani, A.; Osborne, M.; Li, V. Y. C.; Chen, H.; Mubareka, S.; Gubbay, J.; Chan, W. C. W. Diagnosing COVID-19: The Disease and Tools for Detection. *ACS Nano* **2020**, *14*, 3822−3835.

(11) Channappanavar, R.; Perlman, S. Pathogenic Human Coronavirus Infections: Causes and Consequences of Cytokine Storm and Immunopathology. *Semin. Immunopathol.* **2017**, *39*, 529−539.

(12) de la Rica, R.; Borges, M.; Gonzalez-Freire, M. COVID-19: In the Eye of the Cytokine Storm. *Preprints* **2020**, DOI: 10.20944/preprints202005.0157.v1.

(13) Coperchini, F.; Chiovato, L.; Croce, L.; Magri, F.; Rotondi, M. The Cytokine Storm in COVID-19: An Overview of the Involvement of the Chemokine/Chemokine-Receptor System. *Cytokine Growth Factor Rev.* **2020**, DOI: 10.1016/j.cytogfr.2020.05.003.

(14) Theron, M.; Huang, K. J.; Chen, Y. W.; Liu, C. C.; Lei, H. Y. A Probable Role for IFN-γ in the Development of a Lung Immunopathology in SARS. *Cytokine+* **2005**, *32*, 30−38.

(15) Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Xie, C.; Ma, K.; Shang, K.; Wang, W.; et al. Dysregulation of Immune Response in Patients with COVID-19 in Wuhan, China. *Clin. Infect. Dis.* **2020**, DOI: 10.1093/cid/ciaa248.

(16) Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497−506.

(17) Wong, C. K.; Lam, C. W. K.; Wu, A. K. L.; Ip, W. K.; Lee, N. L. S.; Chan, I. H. S.; Lit, L. C. W.; Hui, D. S. C.; Chan, M. H. M.; Chung, S. S. C.; et al. Plasma Inflammatory Cytokines and Chemokines in Severe Acute Respiratory Syndrome. *Clin. Exp. Immunol.* **2004**, *136*, 95−103.

(18) Kim, E. S.; Choe, P. G.; Park, W. B.; Oh, H. S.; Kim, E. J.; Nam, E. Y.; Na, S. H.; Kim, M.; Song, K. H.; Bang, J. H.; et al. Clinical Progression and Cytokine Profiles of Middle East Respiratory Syndrome Coronavirus Infection. *J. Korean Med. Sci.* **2016**, *31*, 1717−1725.

(19) Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**, *323*, 1061−1069.

(20) Chen, G.; Wu, D.; Guo, W.; Cao, Y.; Huang, D.; Wang, H.; Wang, T.; Zhang, X.; Chen, H.; Yu, H.; et al. Clinical and

Immunological Features of Severe and Moderate Coronavirus Disease 2019. *J. Clin. Invest.* **2020**, *130*, 2620−2629.
(21) Yuan, J.; Zou, R.; Zeng, L.; Kou, S.; Lan, J.; Li, X.; Liang, Y.; Ding, X.; Tan, G.; Tang, S.; et al. The Correlation between Viral Clearance and Biochemical Outcomes of 94 COVID-19 Infected Discharged Patients. *Inflammation Res.* **2020**, *69*, 599−606.
(22) Yang, Y.; Shen, C.; Li, J.; Yuan, J.; Yang, M.; Wang, F.; Li, G.; Li, Y.; Xing, L.; Peng, L. Exuberant Elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 Infection Is Associated with Disease Severity and Fatal Outcome. *medRxiv* **2020**, 1 DOI: 10.1101/2020.03.02.20029975.
(23) Chen, X.; Zhao, B.; Qu, Y.; Chen, Y.; Xiong, J.; Feng, Y.; Men, D.; Huang, Q.; Liu, Y.; Yang, B.; et al. Detectable Serum SARS-CoV-2 Viral Load (RNAaemia) Is Closely Correlated with Drastically Elevated Interleukin 6 (IL-6) Level in Critically Ill COVID-19 Patients. *Clin. Infect. Dis.* **2020**, DOI: 10.1093/cid/ciaa449.
(24) Dong, T.; Santos, S.; Yang, Z.; Yang, S.; Kirkhus, N. E. Sputum and Salivary Protein Biomarkers and Point-of-Care Biosensors for the Management of COPD. *Analyst* **2020**, *145*, 1583−1604.
(25) Wang, W.; He, J.; Lie, P.; Huang, L.; Wu, S.; Lin, Y.; Liu, X. The Definition and Risks of Cytokine Release Syndrome-like in 11 COVID-19-Infected Pneumonia Critically Ill Patients: Disease Characteristics and Retrospective Analysis. *medRxiv* **2020**, 1 DOI: 10.1101/2020.02.26.20026989.
(26) Patricio, P.; Paiva, J. A.; Borrego, L. M. Immune Response in Bacterial and Candida Sepsis. *Eur. J. Microbiol. Immunol.* **2019**, *9*, 105−113.
(27) Alba-Patiño, A.; Adrover-Jaume, C.; de la Rica, R. Nanoparticle Reservoirs for Paper-Only Immunosensors. *ACS Sensors* **2020**, *5*, 147−153.
(28) Mansfield, S.; Grießl, M.; Gutknecht, M.; Cook, C. H. Sepsis and Cytomegalovirus: Foes or Conspirators? *Med. Microbiol. Immunol.* **2015**, *204*, 431−437.
(29) Monneret, G.; Venet, F.; Kullberg, B. J.; Netea, M. G. ICU-Acquired Immunosuppression and the Risk for Secondary Fungal Infections. *Med. Mycol.* **2011**, *49*, S17−S23.
(30) Molinero-Fernández, Á.; Moreno-Guzmán, M.; Arruza, L.; López, M. Á.; Escarpa, A. Toward Early Diagnosis of Late-Onset Sepsis in Preterm Neonates: Dual Magnetoimmunosensor for Simultaneous Procalcitonin and C-Reactive Protein Determination in Diagnosed Clinical Samples. *ACS Sensors* **2019**, *4*, 2117−2123.
(31) Russell, S. M.; Alba-Patiño, A.; Borges, M.; de la Rica, R. Multifunctional Motion-to-Color Janus Transducers for the Rapid Detection of Sepsis Biomarkers in Whole Blood. *Biosens. Bioelectron.* **2019**, *140*, 111346.
(32) Jing, W.; Wang, Y.; Yang, Y.; Wang, Y.; Ma, G.; Wang, S.; Tao, N. Time-Resolved Digital Immunoassay for Rapid and Sensitive Quantitation of Procalcitonin with Plasmonic Imaging. *ACS Nano* **2019**, *13*, 8609−8617.
(33) Meynaar, I. A.; Droog, W.; Batstra, M.; Vreede, R.; Herbrink, P. In Critically Ill Patients, Serum Procalcitonin Is More Useful in Differentiating between Sepsis and SIRS than CRP, Il-6, or LBP. *Crit. Care Res. Pract.* **2011**, *2011*, 594645.
(34) McKee, D. L.; Sternberg, A.; Stange, U.; Laufer, S.; Naujokat, C. Candidate Drugs against SARS-CoV-2 and COVID-19. *Pharmacol. Res.* **2020**, *157*, 104859.
(35) Zha, L.; Li, S.; Pan, L.; Tefsen, B.; Li, Y.; French, N.; Chen, L.; Yang, G.; Villanueva, E. V. Corticosteroid Treatment of Patients with Coronavirus Disease 2019 (COVID-19). *Med. J. Aust.* **2020**, *212*, 416.
(36) Yang, Z.; Liu, J.; Zhou, Y.; Zhao, X.; Zhao, Q.; Liu, J. The Effect of Corticosteroid Treatment on Patients with Coronavirus Infection: A Systematic Review and Meta-Analysis. *J. Infect.* **2020**, DOI: 10.1016/j.jinf.2020.03.062.
(37) Zheng, C.; Wang, J.; Guo, H.; Lu, Z.; Ma, Y.; Zhu, Y.; Xia, D.; Wang, Y.; He, H.; Zhou, J.; et al. Risk-Adapted Treatment Strategy For COVID-19 Patients. *Int. J. Infect. Dis.* **2020**, *94*, 74−77.
(38) Gautret, P.; Lagier, J.-C.; Parola, P.; Hoang, V. T.; Meddeb, L.; Mailhe, M.; Doudier, B.; Courjon, J.; Giordanengo, V.; Vieira, V. E.; et al. Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial. *Int. J. Antimicrob. Agents* **2020**, 105949.
(39) Duan, K.; Liu, B.; Li, C.; Zhang, H.; Yu, T.; Qu, J.; Zhou, M.; Chen, L.; Meng, S.; Hu, Y.; et al. Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 9490−9496.
(40) Zhang, C.; Wu, Z.; Li, J.-W.; Zhao, H.; Wang, G.-Q. The Cytokine Release Syndrome (CRS) of Severe COVID-19 and Interleukin-6 Receptor (IL-6R) Antagonist Tocilizumab May Be the Key to Reduce the Mortality. *Int. J. Antimicrob. Agents* **2020**, *55*, 105954.
(41) Monteagudo, L. A.; Boothby, A.; Gertner, E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. *ACR open Rheumatol.* **2020**, *2*, 276.
(42) Liu, B.; Li, M.; Zhou, Z.; Guan, X.; Xiang, Y. Can We Use Interleukin-6 (IL-6) Blockade for Coronavirus Disease 2019 (COVID-19)-Induced Cytokine Release Syndrome (CRS)? *J. Autoimmun.* **2020**, *111*, 102452.
(43) Luo, P.; Liu, Y.; Qiu, L.; Liu, X.; Liu, D.; Li, J. Tocilizumab Treatment in COVID-19: A Single Center Experience. *J. Med. Virol.* **2020**, 1−5.
(44) Fu, B.; Xu, X.; Wei, H. Why Tocilizumab Could Be an Effective Treatment for Severe COVID-19? *J. Transl. Med.* **2020**, *18*, 164.
(45) Chen, P.; Chung, M. T.; McHugh, W.; Nidetz, R.; Li, Y.; Fu, J.; Cornell, T. T.; Shanley, T. P.; Kurabayashi, K. Multiplex Serum Cytokine Immunoassay Using Nanoplasmonic Biosensor Microarrays. *ACS Nano* **2015**, *9*, 4173−4181.
(46) Tang, C. K.; Vaze, A.; Shen, M.; Rusling, J. F. High-Throughput Electrochemical Microfluidic Immunoarray for Multiplexed Detection of Cancer Biomarker Proteins. *ACS Sensors* **2016**, *1*, 1036−1043.
(47) Wei, H.; Ni, S.; Cao, C.; Yang, G.; Liu, G. Graphene Oxide Signal Reporter Based Multifunctional Immunosensing Platform for Amperometric Profiling of Multiple Cytokines in Serum. *ACS Sensors* **2018**, *3*, 1553−1561.
(48) Wang, Y.; Sun, J.; Hou, Y.; Zhang, C.; Li, D.; Li, H.; Yang, M.; Fan, C.; Sun, B. A SERS-Based Lateral Flow Assay Biosensor for Quantitative and Ultrasensitive Detection of Interleukin-6 in Unprocessed Whole Blood. *Biosens. Bioelectron.* **2019**, *141*, 111432.
(49) Russell, S. M.; de la Rica, R. Policy Considerations for Mobile Biosensors. *ACS Sensors* **2018**, *3*, 1059−1068.
(50) Draz, M. S.; Lakshminaraasimulu, N. K.; Krishnakumar, S.; Battalapalli, D.; Vasan, A.; Kanakasabapathy, M. K.; Sreeram, A.; Kallakuri, S.; Thirumalaraju, P.; Li, Y.; et al. Motion-Based Immunological Detection of Zika Virus Using Pt-Nanomotors and a Cellphone. *ACS Nano* **2018**, *12*, 5709−5718.
(51) Quesada-González, D.; Merkoçi, A. Mobile Phone-Based Biosensing: An Emerging "Diagnostic and Communication" Technology. *Biosens. Bioelectron.* **2017**, *92*, 549−562.
(52) Alba-Patiño, A.; Russell, S. M.; Borges, M.; Pazos-Perez, N.; Alvarez-Puebla, R. A.; de la Rica, R. Nanoparticle-Based Mobile Biosensors for the Rapid Detection of Sepsis Biomarkers in Whole Blood. *Nanoscale Adv.* **2020**, *2*, 1253−1260.
(53) Russell, C.; Ward, A. C.; Vezza, V.; Hoskisson, P.; Alcorn, D.; Steenson, D. P.; Corrigan, D. K. Development of a Needle Shaped Microelectrode for Electrochemical Detection of the Sepsis Biomarker Interleukin-6 (IL-6) in Real Time. *Biosens. Bioelectron.* **2019**, *126*, 806−814.
(54) Dauphin-Ducharme, P.; Yang, K.; Arroyo-Curras, N.; Ploense, K. L.; Zhang, Y.; Gerson, J.; Kurnik, M.; Kippin, T. E.; Stojanovic, M. N.; Plaxco, K. W. Electrochemical Aptamer-Based Sensors for Improved Therapeutic Drug Monitoring and High-Precision, Feedback-Controlled Drug Delivery. *ACS Sensors* **2019**, *4*, 2832−2837.
(55) Cao, C.; Zhang, F.; Goldys, E. M.; Gao, F.; Liu, G. Advances in Structure-Switching Aptasensing towards Real Time Detection of Cytokines. *TrAC, Trends Anal. Chem.* **2018**, *102*, 379−396.
(56) McHugh, K. J.; Jing, L.; Severt, S. Y.; Cruz, M.; Sarmadi, M.; Jayawardena, H. S. N.; Perkinson, C. F.; Larusson, F.; Rose, S.;

https://dx.doi.org/10.1021/acssensors.0c00979
ACS Sens. XXXX, XXX, XXX−XXX

Tomasic, S.; et al. Biocompatible Near-Infrared Quantum Dots Delivered to the Skin by Microneedle Patches Record Vaccination. *Sci. Transl. Med.* **2019**, *11*, eaay7162.

https://dx.doi.org/10.1021/acssensors.0c00979
ACS Sens. XXXX, XXX, XXX−XXX