A Viewpoint on Potential Biomarkers for Infectious COVID-19 Severity: An Updated Literature Survey

Suraj N. Mali1,*, Fatemeh Mohajer2, Ghodsi Mohammadi Ziarani2 and Amit P. Pratap3,*

1Department of Pharmaceutical Sciences, Institute of Chemical Technology, Matunga, Mumbai, India; 2Department of Chemistry, Alzahra University, Tehran, Iran; 3Department of Oils, Oleo chemicals and Surfactant Technology, Institute of Chemical Technology, Matunga, Mumbai, India

TO THE EDITOR,

1. BACKGROUND

Currently, the whole world is facing the pandemic situation of the novel coronavirus disease 2019 (COVID-19), which is caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-5]. This COVID-19 pandemic situation causes a colossal dysfunction of various activities all around the world. It has been reported to spread primarily through respiratory droplets from sneezing, talking and coughing leading to the human to human transmissions [1-6]. Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols (“aerosol generating procedures”) [5]. Recently, 239 scientists signed in support commentary in the Oxford Academic journal, Clinical Infectious Diseases. The commentary, “It is Time to Address Airborne Transmission of COVID-19”, pushes the medical community and World Health Organization (WHO) to recognize airborne transmission of COVID-19 [6]. The symptoms of COVID-19 include but may not be limited to shortness of breath, cough, primarily fever, etc. As per WHO situation report (184th, updated on 22nd July 2020, data as received by WHO from national authorities by 10:00 CEST), there are 14,765,256 confirmed cases of COVID-19; while 612,054 deaths have already occurred throughout the world [3].

The SARS-CoV-2 belongs to subfamily Betacoronaviruses like SARS-CoV and MERS–CoV [1]. This SARS-CoV-2 virus is an enveloped one having a positive-sense single-stranded RNA genome with 26 to 32 kilo-bases genome size [1]. They are known to have characteristic spikes, which are projecting from their surfaces. The recent genomic sequencing study showed that this virus has 79.5% sequence identity with SARS-CoV and 96% to a bat coronavirus [5].

With the increasing number of infected patients and mortality rate due to this virus, it has become essential to carry out early diagnosis, infection prevention and control.

A biomarker is an indicator of early warning systems for our health [7-12]. Many of them are derived from simple measurements; while some others rely on sophisticated laboratory tests like blood, urine tests, etc. Some other capturing at the molecular and cellular levels is also there.

We can use biomarkers for better understanding of disease prognosis and studying exposures. As these are specific in some clinical conditions, we can detect them by using biomarkers based biosensor approach, which may be invasive or non-invasive methods. As numbers of trials associated with COVID-19 are increasing day by day, most of them are using biomarkers to speed up the trials as well as to reduce the cost of drug developments. It has been also noted that biomarkers are helping to reduce trial times, verifying the drug’s mechanism of action, guiding the subject and minimising patient risks.

2. POTENTIAL BIOMARKERS AND CURRENT LITERATURE SURVEY

According to the one of database (GlobalData’s Biomarkers database, https://www.globaldata.com/), it has been found that two of them from 20 trials, top biomarkers utilised are the diagnostic markers. Out of two, one is SARS-CoV-2 (30.6% of trials) and another one is Coronavirus Nucleic Acid (7.3% of trials) [13]. As COVID-19 virus has a positive-sense, single-stranded ribonucleic acid (RNA), it has been initially used in earlier detection techniques using polymerase chain reaction (PCR) methods. Some of the diagnostic biomarkers are helping to adopt non-PCR methods, which include ISAA (iso-thermal nucleic acid amplification), LAMP (loop-mediated isothermal amplification) and NASBA (nucleic acid sequence-based amplification) [13]. Some of the notable biomarkers during Covid-19 trials included SARS-CoV-2 RNA, C-reactive protein, and lymphocytes.

Biomarkers are helping the researchers in earlier or severity assessments of COVID-19 cases. Biomarkers are also

*Address correspondence to these authors at the Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, P.O. Box: 400019, Mumbai, India; Tel/Fax: +91965730138; E-mail: mali.suraj1695@gmail.com and Department of Oils, Oleo chemicals and Surfactant Technology, Institute of Chemical Technology, Matunga, Mumbai, India; E-mail: ap.pratap@ictmumbai.edu.in
Fig. (1). Graphical representation of potential biomarkers for the development of Biosensors for rapid identifications of COVID-19.

able to give more insights into mechanisms of how drug re-
repurposing can be used to treat COVID-19 cases [14]. A re-
rospective cohort study, carried out on 191 patients in Jinyin-
tan Hospital and Wuhan Pulmonary Hospital (Wuhan,
China) showed that higher Sequential Organ Failure As-
assessment (SOFA) score, a D-dimer ≥1 μg/L, and advanced
age were capable of demonstrating higher mortality risk [15].
A recent research has demonstrated that IL-6, which can act
as a biomarker during increased immune response and in-
flammation, is more apparent in patients suffering from
pneumonia [16]. A recent editorial, published in a well re-
nowned journal, explains how biomarkers of biological age
could be able to tell the severity of COVID cases. Lauc and
Sinclair (2020), explained the importance of glycans as bio-
markers. Basically, glycans are key regulators involved in
structure, energy storage and system regulatory purposes
including of immune systems. Authors say that “Based on
these and other findings, we believe that glycans should be in
the focus of biomarker discovery in COVID-19 cases” [17].
An interesting study carried out by Moein et al., (2020), ex-
plains about smell dysfunction as a biomarker for COVID-19
[18]. They used a well-validated 40-odorant test. All 60 con-
firmed COVID-19 inpatients and 60 age- and sex-matched
controls were allowed to go through these tests for better
assessments of the magnitude and frequency of olfactory
dysfunction. They found that Fifty-nine (98%) of the 60 pa-
tients exhibited some smell dysfunction [mean (95% CI).
Finally, the authors concluded that “Quantitative smell test-
ning demonstrates that decreased smell function, but not al-
ways anosmia, is a major marker for SARS-CoV-2 infection
and suggests the possibility that smell testing may help”
[18]. In another meta-analysis by Lippi et al., 2020, it has
been shown that thrombocytopenia is associated with
COVID-19 severity [19]. For this study, authors included
nine studies of 1,779 COVID-19 patients-399 with severe
disease. They found that platelet count was significantly
lower in patients with more severe COVID-19 (WMD -31 ×
109/L; 95% CI, from −35 to −29 × 109/L). Finally, authors
concluded that there had been association of lower platelet
count and increased risk of severe disease and COVID-19
mortality rate. ACE-1 enzyme (the angiotensin-converting
enzyme) has been characterized by intron 16 genetic dele-
tion/insertion (D/I) polymorphism. This is responsible for
alterations in concentrations of ACE. Particularly, D allele is
responsible for decremented ACE2 expressions. In one of the
editorial published in Clinica Chimica Acta, there is an inter-
esting explanation of how host’s angiotensin-converting en-
yzme polymorphism relates with epidemiological findings in
COVID-19 [20]. Authors also wrote that ACE D/I genotype
could affect the COIVD-19 clinical course. In one of the
study published [21], it has been reported that there is an
association between the levels of procalcitonin (PCT) and
cardiovascular markers, and thrombocytopenia and COVID-
19 severity. Association of analyte such as D-dimer with a
higher mortality risk factor may be useful in understanding
the severity characteristics of the disease. In one of the letters
to the editor (Lippi and Plebani, 2020), it has been demonstrated using the meta-analysis of 4 articles that raised PCT levels has an association with higher risk of infection in COVID-19 patients. However, authors concluded that “additional studies are compellingly needed to verify the putative bacterial origin of procalcitonin increase in patients with severe COVID-19”. In one of the writings [22], it has been reported that hs-cTnI (cardiac troponin values) was observed abnormal in most patients, and hs-cTnI was found to be elevated in more than 50 % of COVID-19 patients who died. Authors also observed that there have been elevated levels of B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) in patients. One of the recent studies published in the Journal of Infectious Diseases, reports significant decrease in CD3+T, CD4+T, CD8+ T cells and NK cells in COVID-19 patients. This article also explains elevated levels of CD4/CD8 ratio in patients. Authors from this paper suggested counts of CD8+T and CD4+T cells as a diagnostic markers for disease severity [23]. A very recent retrospective study, carried out on 989 patient’s data reported a combination of cosinopenia and elevated hs-CRP for designing triage strategies in an epidemic region having higher number of COVID-19 patients [24]. In another study, authors explained the use of an analysis of initial Fibrinogen to Albumin Ratio and Platelet count in correlation with COVID-19 severity [25]. Furthermore, one study showed a positive correlation between COVID-19 CRP levels and lung lesions, which could reflect disease severity [26]. One study carried out on 93 patients reports neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR) and elevated age as biomarkers for indicating poor clinical outcomes [27]. A very recently published study in the Journal of Medical Virology, indicated the use of elevated levels of serum cancer biomarkers in estimations of the pathological progressions of COVID-19 [28]. A study analysing 48 cytokines in the plasma samples from 50 COVID-19 cases, reported important relationship between expression levels of IP-10, MCP-3, HGF, MIG and MIP-1α with disease severity during disease progression [29]. Various biomarkers, including Serum amyloid A (SAA), which is secreted in COVID-19 patients, could also be considered for rapid detection using biosensor based technologies. Furthermore, biomarker based biosensors could also act as non-invasive, eco-friendly and cheaper method of detection of SARS-Cov-2. Finally, Fig. (1) illustrates that potential biomarkers may be used during COVID-19 disease progression or identifications. Several studies also reported some additional biomarkers such as IL-10, IL-6 and IL-1beta [30, 31].

The study, published in “Cell systems” Journal, which was a collaborative effort between the Francis Crick Institute, UK, and Charité – Universitätsmedizin, Berlin, has unveiled 27 potential biomarkers present in different levels in patients with COVID-19, depending on the severity of their symptoms. This team has utilized higher end mass spectrometry platform to enable them to rapidly test for the presence and quantity of various proteins in the blood plasma [32]. Table 1 indicates a summary of recently reported potential biomarkers for estimations of COVID-19 severity [31-33].

### Table 1. List of Biomarkers involved in Severe COVID-19 Infection.

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Trend in COVID-19 Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAA</td>
<td>↑</td>
</tr>
<tr>
<td>LDH</td>
<td>↑</td>
</tr>
<tr>
<td>D-dimer, Prothrombin time</td>
<td>↑</td>
</tr>
<tr>
<td>WCC</td>
<td>NLR ↑</td>
</tr>
<tr>
<td>Platelet count, Albumin</td>
<td>↓</td>
</tr>
<tr>
<td>IL-6, IL-2, IL-8, IL-10</td>
<td>↑</td>
</tr>
<tr>
<td>CRP, Serum ferritin</td>
<td>↑</td>
</tr>
<tr>
<td>Renal biomarkers</td>
<td>↑ (Urea &amp; creatinine)</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac troponin I</td>
<td>↑</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>↓</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>↓</td>
</tr>
<tr>
<td>T cell count</td>
<td>↓</td>
</tr>
<tr>
<td>NK cell count</td>
<td>↓</td>
</tr>
<tr>
<td>ALT, AST, Total bilirubin</td>
<td>↑</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>↑</td>
</tr>
<tr>
<td>neutrophil–lymphocyte ratio</td>
<td>↑</td>
</tr>
<tr>
<td>monocyte–lymphocyte ratio</td>
<td>↑</td>
</tr>
<tr>
<td>Alamandine, Ang-(1-7), Ang-(1-9)</td>
<td>↓</td>
</tr>
</tbody>
</table>

CRP = C-Reactive Protein; SAA = Serum Amyloid A; IL-6 = Interleukin 6; LDH = Lactate Dehydrogenase; WCC = White Cell Count; NK: Natural Killer; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.

### CONCLUSION

By considering the current pandemic scenario, there is an urgent need to develop biomarkers based technologies for rapid detection of COVID-19. It may reduce the time of detection, amount of sample, will be cheap, and ultimately reduce exposure of virus transmission while diagnosis. Although various biomarkers have been investigated, there is still a need to investigate more in this regard in order to develop more accurate rapid identification techniques for COVID-19. For this, more data that is clinical needs to be analyzed.

### LIST OF ABBREVIATIONS

COVID-19 = Coronavirus disease 2019
WHO = World Health Organization
SARS-CoV 2 = The Severe Acute Respiratory Syndrome Human coronavirus 2

CONSENT FOR PUBLICATION
Not applicable.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS
Authors are thankful to GlobalData (Ms. Rebecca Panks) and Christine DeLong from CLN Stat (The American Association for Clinical Chemistry (AACC)) for sharing their kind words.

REFERENCES


[24] Li, Q.; Ding, X.; Xia, G.; Chen, H.G.; Chen, F.; Geng, Z.; Xu, L.; Lei, S.; Pan, A.; Wang, L.; Wang, Z. Eosinopenia and elevated C-


