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Review: Functions and Mechanism of Biochemical Markers in The Monitoring of Covid-19 Patients

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Abstract

COVID-19 is an infectious disease caused by the SARSCoV-2 virus, which has given rise to a global sanitary emergency. The clinical characteristics of COVID-19 are varied and can range from an asymptomatic infection to a mild to severe pneumonia. Recent studies have shown that different laboratory parameters become altered in these patients, and as such are useful as biomarkers to assess the progression of the disease and categorize patients that may present a severe and/or fatal clinical condition. This review analyzes biochemical and immunological markers that become altered in COVID-19 patients and their impact on different organs at a hepatic, cardiac, renal and pancreatic level, as well as markers of inflammation, analyzing their implications in the evolution of the disease.

Keywords: Functions, Mechanism, Biochemical, Markers, Monitoring, Covid-19, Patients

INTRODUCTION

In December 2019, the city of Wuhan in China became the epicenter of unexplainable cases of pneumonia, which in January 2020 were identified as a new coronavirus, turning rapidly into a major problem of public health worldwide (Abuelgasim et al.,2020) . This pathogen, corresponding to a beta (β) coronavirus, is made up of single chains of positive RNA belonging to the large coronaviridae subfamily and has the ability to infect mammals and other animals (Gorbalenya et al.,2020). The 2019 coronavirus disease (COVID-19) is caused by the corona virus 2 of the severe acute respiratory syndrome (SARS-CoV-2) (Lai et al.,2020), which spread rapidly all over the world and was declared by the world Health Organization (WHO) as a pandemic on 11 march 2020 (Estevão et al.,2020). The entry of SARS coronavirus into the host cells has been associated fundamentally with the angiotensin II-converting enzyme (ACE2) that, when is located in the membrane of the cell, can function as a receptor for certain proteins expressed by this virus. The tissue location of ACE2 would be related to how the disease affects different tissues or organs (Hamming et al.,2004). This protein is expressed predominantly in different cell types such as epithelial, pulmonary alveolar, small intestine epithelial, vascular endothelial and smooth muscle cells (Hamming et al.,2004) . ACE2 regulates the angiotensinrenin system, counteracting the activity of the angiotensin-converting enzyme (ACE) and having a protective effect on acute respiratory distress syndrome (ARDS). ACE2 is a type I transmembrane glycoprotein consisting of 805 amino acids and a single extra-cellular catalytic domain with a molecular weight of approximately 120 kDa, whereas the ACE2 coding gene is located in chromosome X (Penninger et al.,2010). similar to ACE, ACE2 has two domains: the amino-terminal catalytic domain. The catalytic domain exhibits 41.8% sequence identity with the amino domain of ACE (Penninger et al.,2010). The coronavirus family contains seven viruses that can cause severe infections in human beings: HCoV-229E, HCoV-HKU1, HCoV-NL63, HCoV-OC43, SARS-CoV, MERS-CoV and SAR-CoV-2. These are zoonotic viruses with single-stranded enveloped RNA, spherical in shape with pronounced protrusions of spike glycoproteins, called protein S, on the surface of the envelope, in addition to structural proteins including the envelope (protein E), the matrix (protein M), and the nucleocapsid (protein N) (Andersen et al.,2020) (Loeffelholz et al.,2020). The spikes (S) glycoprotein of the virus act as binding proteins and are thus highly important because they allow the entry of this virus into the target cell. Protein S is trimeric, equipped with subunits S1 and S2, where S1 carries the receptor-binding domain

(RBD) that interacts with the target cell and binds with an ACE2 domain (Yan et al.,2020). When interacting it produces a greater concentration of angiotensin II and can unleash local vasoconstriction. It also binds with pulmonary and blood vessel cell receptors, which in severe cases leads to pulmonary compromise and diffuse alveolar damage, coating them with a membrane and causing respiratory distress and fibrosis (Xu et al.,2020). COVID-19 is diagnosed through laboratory tests in patients with epidemiological history and clinical symptoms, together with radiological examinations (Ahn et al.,2020) (Chan et al.,2020). The COVID-19 disease has different clinical presentations, ranging from asymptomatic to mild, moderate or severe symptoms, with or without the presence of pneumonia (Dong et al.,2020). Fever and coughing are the most common symptoms at a global level (Lian et al.,2020). The accumulated evidence has shown that many biochemical parameters become altered in COVID-19 patients, and this has been correlated with the severity of the disease and in some cases associated with the prognosis of the patients. The laboratory parameters together with other demographic and clinical data of patients could allow them to be categorized in the initial stages, thus identifying people who will become critically ill and making it possible to improve their clinical care and seek adequate therapeutic strategies.

Global Prevalence of Coronavirus Disease 2019 (COVID-19)

COVID-19 has affected 85403 patients in 57 countries/ territories and has caused 2924 deaths in 9 countries. However, epidemiological data differ between countries. Although china had higher morbidity and mortality than other sites, the of new daily cases in china has been lower than outside of china since 26 February 2020. The incidence ranged from 61.44 per 1 000 000 people in the Republic of Korea to 0.002 per 1 000 000 in India. The daily cumulative index (DCI) of COVID-19 (Cumulative cases/no. of days between the first reported case and 29 February 2020) was greatest in china (1320.85), followed by the Republic of Korea (78.78), Iran (43.11) and Italy (30.62). However, the DCIs in other countries/ territories were < 10 per day. Several effective measures including restricting travel from China, controlling the distribution of masks, extensive investigation of COVID-19 spread, and once-daily press conferences by the government to inform and educate people were aggressively conducted in Taiwan, which is much lower than that of nearby countries such as the Republic of Korea and Japan.

Prevalence of Coronavirus Disease 19 (COVID-19) in Africa

The coronavirus disease 2019 (COVID-19) pandemic has spread to all 55 countries in Africa. The prevalence is highly heterogeneous, and the majority of cases are asymptomatic. Several factors are thought to explain heterogeneity of COVID-19 in Africa, including the level of containment measures, demographic aspects, climate and environmental factors, host genetics and immune factors. Here, we discuss the prevalence of COVID-19 in Africa, the status of serological studies, COVID-19 and comorbidities, as well as the spread of SARS-CoV-2 variants and the status of vaccine roll-outs in Africa. Since the first case of coronavirus disease 2019 (COVID-19) in Africa was reported on 14th February 2020, more than 5.1 million cases and 136,000 deaths have been reported (as of June 2021), representing 3% of global cases. Contrary to initial models and forecasts, the reported data reflect a markedly less severe epidemiological picture of COVID-19 in Africa. Current data suggest a low proportion of patients with severe outcomes and death, and more than 80% of cases appear to be asymptomatic in some countries. Of the reported cases, 43% and 30% are from Southern and Northern Africa regions, respectively, and 5 of the 55 African countries — South Africa, Morocco, Tunisia, Ethiopia and Egypt — account for more than half of the total cases of confirmed COVID-19 in Africa. South Africa, Egypt and Tunisia account for more than two-thirds of all reported deaths from COVID-19 in Africa (Africacdc 2020). The underlying cause for the significant epidemiological heterogeneity of COVID-19 amongst different countries in Africa remains unknown. Several explanations have been proposed, including the timing of introduction of the SARS-CoV-2 virus, different preparedness and response measures, experience with previous pandemics, differences in the capacity of the health systems for testing and contact tracing, demographic factors, climate and environmental factors, host genetics and social factors that determine adherence to public policies.

Prevalence of Coronavirus Disease 19 (COVID-19) in Nigeria

The first case of COVID-19 in Nigeria was confirmed on 27 February 2020. The case was a 44-year old Italian citizen who arrived Nigeria through the Murtala Mohammed International Airport, Lagos, on a flight via Milan, Italy (Nigeria Centre For Disease Control 2020. pp.1-3). This index case led to the activation of COVID-19 Public Health Emergency Operation Centers (PHEOC) at national and sub-national levels, with associated active case finding via contact tracing. By 9 March 2020, 217 contacts were

linked to this index case (Nigeria Centre For Disease Control 2020. pp.1-3), out of which 136 (63.0%) were under follow-up, with one contact confirmed positive (Ebenso et al.,2020). The 14-day follow-up for contacts of the index case ended on 12 March 2020. During this period, two additional unlinked cases were reported in Nigeria. In addition, 42 suspected cases were identified across seven states in Nigeria namely the Federal Capital Territory (FCT), Edo, Kano, Lagos, Ogun, Rivers and Yobe (Nigeria Centre For Disease Control 2020. pp.1-3). Since the confirmation of the first COVID-19 case in Nigeria, cases and deaths have risen steadily in the country, although the government has implemented public health interventions – e.g. advocacy for physical distancing, complete and partial lockdown, and ban on large public gatherings including at churches and mosques – to contain or mitigate spread. As of 6 June 2020, 35 (out of 36) states, plus the FCT, have reported at least one confirmed COVID-19 case. A descriptive analysis of the clinical characteristics, treatment modalities and outcomes of the first 32 COVID-19 patients admitted to Mainland Hospital in Lagos State, Nigeria, found that two-thirds of patients were male, and the mean age was 38.1 years (Bowale et al.,2020). This early analysis however is insufficient to provide a national overview of COVID-19 epidemiology in Nigeria. The Nigeria Centre for Disease Control (NCDC) coordinates the public health response to COVID-19 in the country. Through NCDC's surveillance and laboratory network as well as coordination of state PHEOCs, epidemiological information on COVID-19 cases are captured into a real-time networked platform called Surveillance Outbreak Response Management and Analysis System (SORMAS). This forms the basis for the release of daily situation reports for COVID-19 on NCDC COVID-19 microsite (Nigeria Centre For Disease Control 2020. pp.1-3). By 6 June, thousands of individual records with laboratory diagnosis contained on SORMAS offered opportunities to expand and explore country-specific epidemiologic and clinical characteristics of COVID-19 from the onset of the outbreak. This study aims to provide the initial descriptive epidemiology of COVID-19 in Nigeria, with emphasis on the disease magnitude and patterns in terms of person, place and time.

History of Coronavirus Disease 19 (COVID-19)

When an acute respiratory infection of farmed hens first appeared in North America in the late 1920s, there were the first reports of a coronavirus infection in the animal. The first comprehensive study describing a novel respiratory infection in chickens in North Dakota was written in 1931 by Arthur Schalk and M.C. Hawn. With significant death rates of 40–

90%, the infection of newborn chicks was characterized by gasping and listlessness. The virus that caused the sickness was identified by Leland David Bushnell and Carl Alfred Brandly in 1933. At the time, the virus was called the infectious bronchitis virus (IBV). "In 1937, Charles D. Hudson and Fred Robert Beaudette successfully produced the virus. The Beaudette strain was given to the specimen. The mouse hepatitis virus (MHV), which causes hepatitis in mice and JHM which causes brain disease (murine encephalitis) were discovered in the late 1940s. The connection between these three distinct viruses was not known at the time" (Decaro et al.,2015). In the 1960s, two special techniques were used in the US and UK to identify human coronaviruses. A distinct common cold virus known as B814 was discovered in 1961 by E.C. Kendall, Malcolm Bynoe, and David Tyrrell when they were working at the British Medical Research Council's Common Cold Unit. Standard methods that had been successful in growing known common cold viruses like adenoviruses and rhinoviruses could not be used to grow the virus (de Groot et al.,2015). Tyrrell and Bynoe were able to successfully cultivate the new virus in 1965 by serially exposing it to a cultured human embryonic trachea organ. Bertil Hoorn introduced the novel cultivation technique to the laboratory. The isolated virus cold produced was administered intranasally to volunteers, and it was rendered inactive by ether, indicating it's possession of a lipid envelope. In 1962, John Procknow and Dorothy Hamre of the University of Chicago isolated a brand-new cold from medical students. The virus was identified as 229E after it was isolated and grown in kidney tissue culture. Like B814, the novel virus gave volunteers a cold and was destroyed by ether. In 1967, Tyrrell and Scottish virologist June Almeida at St. Thomas Hospital in London investigated the structural differences between IBV, B814 and 229E. The three viruses were demonstrated to be morphologically related via electron microscopy thanks to their characteristic club-like spikes and general shape. The same year, a team of researchers at the National Institutes of Health used organ culture to successfully isolate another member of this new group of viruses. One of the samples was given the designation OC43 (Geller et al.,2012) . "The novel cold virus OC43 displayed unique club-like spikes under the electron microscope, similar to B814, 229E, and IBV. The novel cold viruses that resemble IBV were quickly discovered to share morphological similarities with the mouse hepatitis virus. Coronaviruses is the term given to this new class of viruses because of their unique physical characteristics. In the decades that followed, research on human coronavirus 229E and human coronavirus OC43 proceeded. Loss of the coronavirus strain B814 which was a

human coronavirus. Since then, several human coronaviruses have been discovered, such as the SARS-CoV in 2003, the HCoV NL63 in 2003, the HCoV HKU1 in 2004, the MERS-CoV in 2013, and the SARS-CoV-2 in 2019. Since the 1960s, a significant number of animal coronaviruses have also been discovered" (Geller et al.,2012).

Coronavirus Found in Human

A wide family of respiratory viruses with positivestranded RNA is known as coronaviruses (C0V). The crown-shaped tips that are found on their surface are what give them their name. There are four different genera of coronaviruses (CoV), including:

1. The first is alpha-coronaviruses (α-CoV).
2. Beta Coronaviruses (β-CoV)
3. Gamma Coronaviruses (γ-CoV)
4. Delta Coronaviruses (δ-CoV)

While α-CoV and β-CoV can infect mammals, γCoV and δ-CoV typically infect birds. Six CoVs have previously been found to be humansusceptible, including the low pathogenic HCoVs HKU1 and HCoV-OC43, HCoV-229E and HCoVNL63, and HCoV-229E, which cause mild respiratory symptoms in addition to the common cold (Hui et al.,2020) . "SARS-CoV (Severe Acute Respiratory Syndrome-Coronaviruses) and MERS-CoV (Middle East Respiratory Syndrome-Coronavirus) are the other two –CoVs that causes potentially lethal respiratory tract infections that are severe" (Yin et al.,2018) . Unaccounted-for pneumonia, later known as the coronavirus disease 2019, or COVID-19, first appeared in Wuhan, China, in December 2019 (Li et al.,2020) .

Table 1. List of viruses belonging to human coronavirus type, divided by lethality

Less lethal known coronaviruses	Most lethal known coronaviruses
229E (the alpha coronavirus)	MERS-CoV (the beta coronavirus that causes the Middle East Respiratory Syndrome)
NL63 (the alpha coronavirus)	SARS-CoV (the beta coronavirus that causes the Severe Acute Respiratory Syndrome)
OC43 (the beta coronavirus) HKU1 (the beta coronavirus)	2019 new coronavirus (SARS-CoV-2)

The first case was associated with a wholesale seafood business in Wuhan. Human respiratory epithelial cells have produced a brand-new coronavirus that is a member of the sabevirus subgenus and the Coronavirus subfamily (Harding et al.,2020) . "This virus, known as SARS-CoV-2, is the recent coronavirus strand that can infect people and it's different from the earlier isolated MERS-CoV and SARS-CoV" (Guo et al.,2020) . The coronaviruses found in bats, pangolins, and other species are thought to serve as a "gene bank" for the creation of novel recombinants. "Frequent human-animal interactions have been theorized to be the very source of viral interspecies transmission, due to the usage of pangolins in traditional medicine and as food. Bat and pangolin-origin, coronavirus recombination events were expected to occur, according to the similarity analysis of SARSCoV-2 and the animal-origin of coronaviruses" (Zhang et al., 2020). The similarity between SARS-CoV-2 and the closest bat relative is very high: all proteins in the coronavirus proteome (apart from ORF10) have identities of above 85%, and the genome length (30 kb) has been fully conserved (Ceraolo et al.,2020). Seven coronaviruses that harm individuals have been identified so far as being widespread throughout the world. MERS-CoV, which frequently progresses to severe pneumonia with an estimated mortality rate between 30 and 40 percent, is the most dangerous of the known coronaviruses. "SARS-CoV, which causes fever chills, and body aches and frequently progresses to pneumonia, a serious condition in which the lungs become inflamed and fill with pus, has an estimated mortality rate of 9.6%. The most recent coronavirus, SARS-CoV-2, has an estimated mortality rate" (Harding et al.,2020) . Angiotensin converting enzyme II (ACE2), the same cell entry receptor used by SARS-CoV, is used by SARS-CoV-2 to infect cells. This infection can either be completely asymptomatic or can cause flu-like symptoms like fever, coughing, and breathing problems (Guo et al.,2020) . This later symptomatology, which is more prevalent and severe in elderly subjects who can also exhibit concurrent pathologies, is thought to occur in young subjects as well. Particularly, those with a weakened immune system such as, those receiving acute or chronic immunosuppressive therapy, those who are epigenetically predisposed, or those who are exposed to an excessive amount of environmental stress (Cannizzaro et al.,2019) . These include individuals who engage in extreme or physically demanding activities, those who have a particulate allergy. In severe circumstances, COVID-19 can eventually present as pneumonia; patients may quickly experience acute respiratory distress syndrome and pass away from multiple organ failure. Given these presumptions and the lack of understanding

regarding the protocols to be implemented in order to manage important events like the one we are currently experiencing. The goal of this review is to present a protocol designed to stop the spread of the SARS-CoV-2 infection. Additionally, we wish to provide an overview of SARS-CoV-2 and the approaches employed to combat this virus (Zhang et al.,2020).

Viral Structure and Gemone Organization

SARS-CoV-2 is an enveloped, single-stranded positive-sense RNA virus with a diameter of 60–140 nm and spikes of 9 – 12 nm in length (Figure 1). It is part of the betacoronavirus genus, which includes MERS-CoV and SARS-CoV (24). The virus particle is made of structural viral proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) protein (Figure 1). The 419 amino acid-long N protein is the only structural protein inside the virion, associated with the viral genomic RNA via electrostatic interactions driven by positively charged amino acid residues and modulates RNA unwinding after entry into the cell (33). Other structural proteins are inserted into the lipidic viral envelope. The E protein forms an ion channel and participates in viral assembly, while the M protein is critical for incorporating essential viral components into new virions during morphogenesis. The S protein binds the receptor expressed by host cells and promotes fusion of the viral and cellular membrane [see (34) for a review]. The SARSCoV-2 genome is ∼30 kb and encodes 14 ORFs. The genome is flanked by 5' and 3' untranslated regions (UTRs) that contain cis-acting secondary RNA structures essential for RNA synthesis. At the 5' end, the genomic RNA features two large open reading frames (ORF1a and ORF1b) that occupy twothirds of the capped and polyadenylated genome and encode 16 non-structural proteins (Nsps 1–16) that make up the replicase complex . Nine accessory proteins—termed ORF3a, 3 b, 6, 7a, 7b, 8, 9a, 9b, and 10—are encoded by homonymous orfs and, although deemed as non-essential for the virus replication in vitro, are thought to exert important functions in modulating the host cell metabolism and antiviral immunity [see (78) for a review].

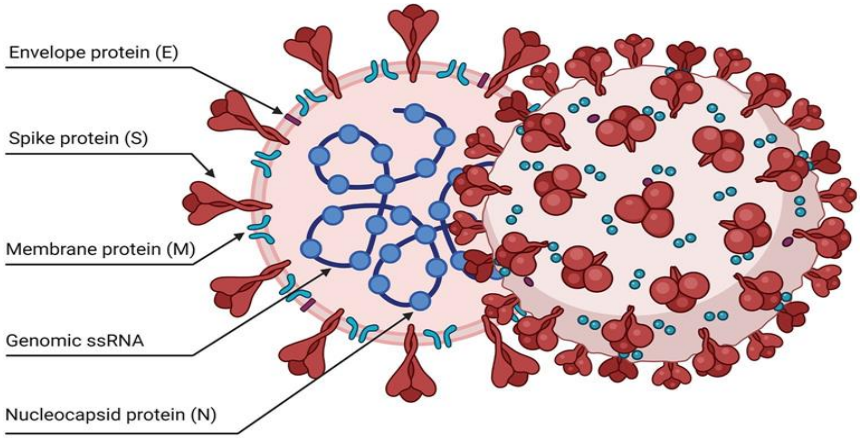


Figure 1. schematic representation of SARS-COV-2 viral particles.

Viral Entry and Replication

Coronaviruses are spheroidal, single-stranded RNA viruses with a diameter of 80–220 nm. Transmission of SARS-CoV-2 occurs either through exposure to micro-droplets from infected individuals or by contact transmission through contaminated fomites. The virus reaches the smaller airways and alveoli, and targets the bronchial and alveolar epithelial cells. The spike surface glycoprotein S on the virus binds to angiotensin-converting enzyme 2 (ACE-2), a membrane carboxypeptidase present in distal airways and alveoli, especially type 2 pneumocytes which have the highest expression of ACE-2, along with alveolar macrophages and dendritic cells. ACE-2 is also expressed on the vascular endothelium, nasal, oral, nasopharyngeal, and oropharyngeal epithelia, gut epithelia, cardiac pericytes, renal proximal tubular cells and in the skin, reticuloendothelial and the central nervous system (11). ACE-2 expression depends on age, gender, genetic factors, and presence of comorbid conditions such as obesity, chronic cardiopulmonary disease, cancer, and use of immunosuppressive drugs. Renin cleaves angiotensinogen to produce angiotensin I which is further cleaved by ACE to produce angiotensin II having a dual role. Action through AT1R (angiotensin II type 1 receptor), facilitates vasoconstriction, fibrotic remodeling, and inflammation, while that through AT2R (angiotensin II type 2 receptor) leads to vasodilation and growth inhibition. Angiotensin II is cleaved by ACE2 to Ang 1–7 which counteracts the harmful effects of the ACE/Ang II/AT1 axis. Thus ACE2 primarily plays a key role to physiologically counterbalance ACE and regulate angiotensin II. Internalization of the ACE-2 after viral interaction leads to its downregulation, and consequent upregulation of angiotensin II. The latter acting through AT1R, activates the downstream inflammatory pathways, leading to the "cytokine storm" that adversely affects

multiple organs (12). The alveolar epithelial cells, lymphocytes, and vascular endothelial cells are the primary targets of the virions. The virus inhibits the production of interferons which are part of cellular defense mechanisms. Viral replication releases a large number of virions leading to infection of neighboring target cells and viremia, which then cause an exaggerated pulmonary and systemic inflammatory response respectively. This explains the clinical presentation of severe COVID-19 which is predominated by ARDS, shock, and coagulopathy. Many acute phase reactants can serve as inflammatory protein biomarkers of COVID-19 infection exhibiting significant changes in serum levels, as discussed in the following sections (Fig. 2).

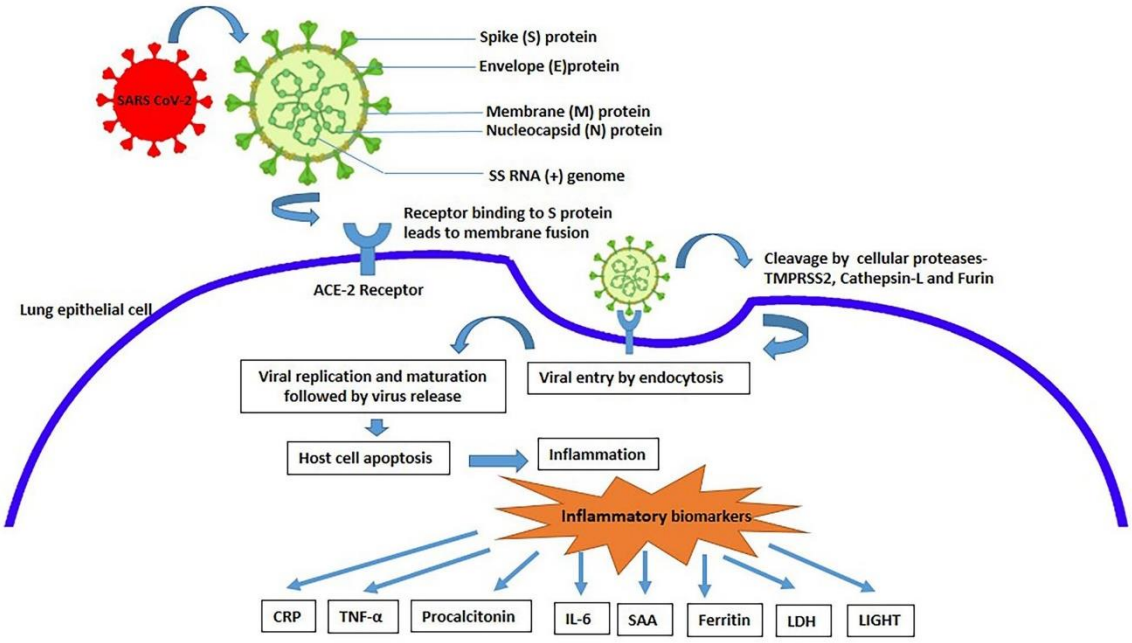
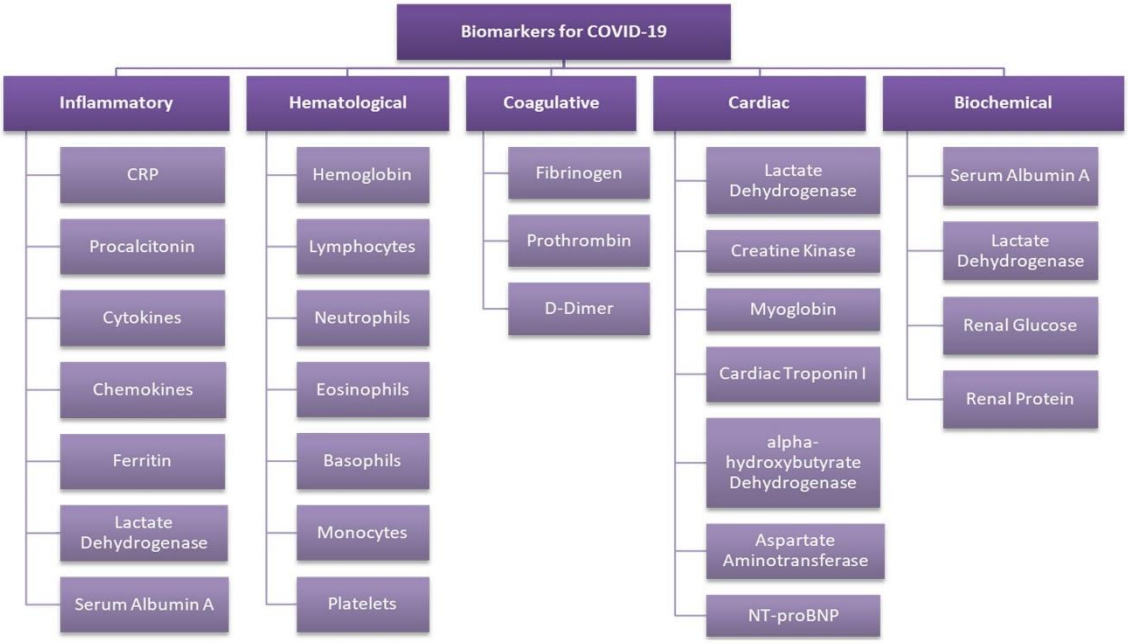


Figure 2. Pathogenesis of COVID-19 and polypeptide inflammatory biomarkers

BIOCHEMICAL MARKERS IN COVID-19

Rapid and accurate diagnosis of COVID-19 for prompt therapeutic intervention and efficacious treatment serves as a first line of defense in this far ending rift between SARSCoV-2 and humans. Diagnosis of COVID-19 in the initial stages of the disease is largely based on standard clinical case definitions, molecular testing using RT-PCR and immunological tests. Effective biomarkers would greatly aid the screening, diagnosis, management and timely intervention to avoid life-threatening complications (Ponti et al. 2020). Furthermore, identification of novel biomarkers associated with disease progression is undoubtedly related to understanding of the mechanism of viral pathogenesis along with

tissue and organ damage. Acute phase response (APR) aids to establish homeostasis following perturbations as a consequence of inflammation, infection, malignancy, trauma or stress. It acts as a dynamic systemic early defense mechanism being non-specific in nature. There are various characteristics of APR like fever, hormonal changes, and metabolic alterations. Furthermore, there are remarkable alterations in the serum protein levels known as the acute phase proteins (Cray et al. 2009). Proteins being one the most versatile and significant biomolecules, find varied applications in healthcare sector as therapeutic agents, analytical reagents, diagnostic and prognostic tools, biopharmaceuticals, digestive aids, research, etc. (Sinha and Shukla 2019; Vachher et al. 2021). Such protein biomarkers can be used to diagnose and monitor the progress of COVID-19 infection. The body's response to COVID-19 infection is closely interrelated in terms of immunological, inflammatory and clotting pathways. Numerous biomarkers are being employed for COVID-19 monitoring explicitly explaining the dynamic nature of the disease (Samprathi and Jayashree 2021) (Fig. 1). Keeping in view the significance of these biomarkers this review attempts to highlight and report current state of knowledge of research on the important protein inflammatory biomarkers including C-reactive protein (CRP), ferritin, procalcitonin (PCT), lactate dehydrogenase (LDH), serum amyloid A (SAA), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and LIGHT. Biomarkers in COVID-19 is useful for early diagnosis of disease, confirming and classifying disease severity, framing admission criteria for hospitalization, identifying high risk strata, deciding admission criteria for ICU requirement, rationalizing therapeutic advances, assessing the response to various therapies, predicting disease outcome, and framing criteria for discharge (Samprathi and Jayashree 2021).



C-Reactive Protein (CRP)

CRP is a homopentameric protein consisting of five identical non-glycosylated 23 kDa polypeptide monomers each having 206 amino acid residues, which are non-covalently associated symmetrically around a central pore. Each subunit possesses an intra-subunit disulphide bond with a phosphocholine binding site located on the same face of each monomer in the pentamer. The name CRP was coined as it binds to pneumococcal somatic C-polysaccharide. This acute-phase protein belongs to the family of related calcium dependent ligand binding plasma proteins known as the "pentraxins". Each protomer is folded into two anti-parallel beta-sheets having a flattened jelly like topology characteristic of a "lectin fold". It is a ring-shaped protein of hepatic origin found in blood plasma synthesized in response to certain pro-inflammatory cytokines such as Interleukin-6 (IL-6) (Pepys and Hirschfield 2003; Black et al. 2004). It recognizes and clears various foreign pathogens and damaged cells upon binding to phosphocholine, phospholipids, histones, chromatin and fibronectin. It is widely known that its concentration rises in the blood plasma in response to inflammation and infection, long before COVID-19 manifested itself as a global pandemic. Therefore, it is employed as a common biomarker for numerous inflammatory disorders despite being non-specific in nature. However, due to the inadequate prognostic and prophylactic measures to control the viral disease, CRP got

importance as one of the very first pattern recognition receptor biomarkers to indicate COVID-19 and its severity (Kermali et al. 2020; Sahu et al. 2020).

CRP is a vital component of the human innate immune system which protects us from any invading foreign organisms (Pepys and Hirschfield 2003). The human body in response to a microbial pathogen or other inflammatory conditions, such as tissue injury, malignancy, necrosis or chronic inflammatory rheumatic diseases, produces cytokines which further trigger the release of CRP from the liver, along with fibrinogen (Bray et al. 2016). CRP then binds to the various intrinsic and extrinsic ligands on the surface of the dead cells or pathogens, leading to activation of classical complement pathway, phagocytosis and opsonization. Activation of complement and interaction with the Fc gamma receptors provides a link between adaptive and innate immune response. CRP levels in the serum are indicative of the inflammatory status of the body. In COVID-19, when the SARS-CoV2 infects our lungs, it triggers a cytokine storm, cytokines like IL-6 and TNF-α stimulate hepatocytes to produce CRP which leads to activation of complement system and amplification of inflammatory insults. Heightened viral load might result in severe macrophage infiltration associated with high CRP levels aggravating acute lung injury (Luan et al. 2021). Since detection of the virus is difficult, and diagnostic tests like RT-PCR often produce false positive and false negative results, estimation of the serum levels of various inflammatory biomarkers such as CRP is of great aid to clinicians (Stringer et al. 2021). Two different tests are mainly used to measure CRP levels in the blood, namely the standard CRP test and the high sensitivity (hs)-CRP test. These vary in sensitivity. The standard CRP test can measure higher CRP levels ranging from 10 to 1000 mg/L, and thus can detect only severe forms of inflammation. The hs-CRP test on the other hand, can detect smaller quantities of CRP, ranging from 0.3 to 10 mg/L (Knight 2015). The CRP test is based on immunoassays of latex agglutination, immunoturbidimetry, ELISA and laser nephelometry (Nehring et al. 2021). Serum levels of CRP are dependent on many intrinsic as well as extrinsic parameters, which may cause two different healthy individuals to have different CRP concentrations. Some such factors are age, gender, pregnancy, gene polymorphisms etc. Usually, for healthy young individuals the median concentration of CRP is 0.8 mg/L, with 90th centile as 3.0 mg/L and 99th centile as 10 mg/L. But following an acute phase response, the values might rapidly rise 10,000-fold to 500 mg/L. No seasonal variations have so far been reported in serum concentrations of CRP. In blood, the halflife of CRP is 19 h (Pepys and Hirschfield 2003).

Inflammatory serum levels differ based on whether inflammation is acute or chronic. Acute inflammation caused by bacterial infection, necrosis, trauma, malignancy or allergy can cause CRP levels to reach 50–100 mg/L within first six hours, and peak at 500 mg/L within 50 h following inflammation. Due to the short half-life, CRP levels quickly fall once inflammation subsides. Chronic or metabolic inflammation which results from conditions such as type II diabetes mellitus and arteriosclerosis can result in CRP levels ranging from 2 to 10 mg/L (Bray et al. 2016). Recent studies, systematic literature reviews and meta-analyses have clearly established the role of inflammatory protein markers including CRP with the severity and outcome of COVID-19 (Zeng et al. 2020). CRP levels have been significantly associated with the greater risks of developing severe COVID19 (Kermali et al. 2020). Critically ill and severe cases had significantly higher serum CRP levels as compared to mild cases (Li et al. 2020; Zhao et al. 2021). Furthermore, patients with underlying comorbidities or cardiometabolic diseases have an elevated risk of mortality (Tian et al. 2020). In a recent study by Smilowitz et al. 2021, COVID-19 patients with high CRP levels indicating systemic inflammation had greater risk of critical illness and adverse outcomes. CRP levels in various COVID-19 patients based on several studies and meta-analyses by different groups of researchers have been summarized in Table 1, emphasizing the role of CRP as an essential biomarker for COVID-19.

Apart from COVID-19, increased CRP levels are used to clinically detect many other inflammatory conditions such as cardiovascular disease, coronary heart disease, fibrosis, cancer and rheumatoid arthritis (Pepys and Hirschfield 2003). CRP being a non-specific indicator of solely inflammation cannot be used as the only test to confirm COVID-19. It only indicates the extent of inflammatory response in the body, without confirming the cause. The test in conjunction with signs and symptoms, and other diagnostic tests and physical examinations can confirm the cause of inflammation to be COVID-19. Moreover, agglutination efficiency is not related to the concentration of serum CRP. Furthermore, antigen excess may also result in false negative results (Orr et al. 2018). Once confirmed, the healthcare workers might follow further necessary tests and treatment protocols. Monitoring dynamic CRP serum levels along with imaging techniques and computed tomography can be a vital strategy in the early identification and management of progressive and severe COVID-19 (Tan et al. 2020). Measurement of CRP levels is one of most practical tools to monitor prognosis of COVID19 being cost effective and easy to

interpret. It could be utilized clinically to predict COVID-19 outcomes and severity even before disease progression and manifestation of clinical symptoms (Fazal 2021).

Procalcitonin (PCT)

Procalcitonin (PCT) is a polypeptide which is the precursor of the functional protein calcitonin. Calcitonin is a hormone which is responsible for maintaining calcium homeostasis in the human body. Under normal conditions, pre-procalcitonin is transformed into PCT by endopeptidase cleavage of a 25 amino acid signal sequence. The 116 amino acid long proprotein PCT having molecular weight of 14 kD is processed by prohormone convertase into the 32 amino acid long hormone calcitonin, katacalcin and an N-terminal residue. PCT belongs to the calcitonin gene related peptide-amylin procalcitonin-adrenomedullin family (Floriańczyk 2003). Procalcitonin in healthy individuals is produced by parafollicular cells or C cells of the thyroid gland. It can also be produced by the lungs and intestine, via the neuroendocrine cells. The main function of PCT is to produce its daughter peptide calcitonin. Calcitonin reduces calcium absorption by the osteoclasts, thereby increasing the levels of circulating calcium.

It is an acute phase reactant, which is indicative of bacterial sepsis in the body (Lee 2013). PCT has a half-life of 20–24 h. In the current scenario, several assays including sandwich immunoluminometric assays are being employed to detect PCT (Schuetz et al. 2017). One of the earliest assays is immunochromatographic assay in which monoclonal antibodies against PCT are immobilized on a nitrocellulose membrane. It is a preliminary semi-quantitative test. Any PCT in the sample will bind the anti-PCT antibodies and form a visible conjugate. The conjugate usually appears as a pink line which indicates a positive result when compared to no color formation for a negative control sample. The color intensity is proportional to the PCT concentration and is compared to a reference strip. A homogenous immunoassay using time–resolved amplified cryptate emission (TRACE) technology composed of sheep polyclonal anticalcitonin (CT) antibody and monoclonal anti-katacalcin antibody binding to CT and katacalcin sequences respectively of PCT is employed nowadays (Cleland and Eranki 2020). The assay is rapid with a detection time of 19 min. The normal PCT levels in a healthy individual are usually below levels that can be detected by clinical assays. Very highly sensitive assays were needed to determine PCT levels in healthy people, and it was seen to be lower than 0.01 ng/ ml (Aloisio et al. 2019). On receiving a pro-inflammatory stimulus, especially of bacterial origin, PCT levels can

shoot up to several folds of the normal levels within four to twelve hours post infection. Higher magnitudes of increase in serum PCT levels correlate with more severe disease (Rowland et al. 2015). However, it has been observed that increase in PCT levels do not result in a subsequent rise in calcitonin or fall in calcium levels in the serum.

Upon infection or inflammation, the body responds with increased PCT levels within the first four hours, reaching a peak of around 1 ng/ml at the sixth hour, although the concentration at this stage varies with the severity of inflammation. The plateau is reached around the eighth hour, and the levels slowly subside and reach the baseline within 3 days (Póvoa and Salluh 2012). However, lower PCT levels do not exclude the chances of inflammation. They may indicate localized as opposed to a systemic infection. Many studies have been performed correlating the PCT levels with the severity and progression of COVID-19. One such study showed that serum PCT levels were more than four times greater in severe patients than the moderate ones, and over eight times greater in critical patients (Hu et al. 2020). PCT levels decreased with recovery and progressed with disease severity in case of patients who died. A recent meta-analysis reported PCT values associated with nearly five-fold higher severe COVID-19 risk, which might be a result of heightened levels of other inflammatory markers like IL-6 (Lippi and Plebani 2020).

The PCT Test is not an exclusive test for COVID-19 detection and monitoring. Rather, it is most commonly used to detect bacterial systemic sepsis, bacterial meningitis, kidney infection, bronchitis, pneumonia, post-operative infections, chronic obstructive pulmonary disease (COPD) exacerbation etc. (Stolz et al. 2007; Schuetz et al. 2009; Long et al. 2014). The polypeptide has also been seen to be associated with organ rejection (Yu et al. 2014), cardiovascular diseases (Schuetz et al. 2016), hepatitis (Chirapongsathorn et al. 2018) and thyroid cancer (Trimboli and Giovanella 2018). It is also used to monitor the efficacy of any antibiotic treatment (Schuetz et al. 2011; Pepper et al. 2019). Furthermore, PCT levels can increase non-specifically in absence of infection, such as in severe stress after a major trauma, surgery, or cardiac shock (Aabenhus and Jensen 2011). Thus PCT is not a very ideal biomarker for surgical patients. Elevated levels of PCT are also associated with autoimmune disorders such as the Kawasaki disease and birth stress in newborns (Reinhart et al. 2012). Heat shock, graft rejection, immunotherapies, cytokine therapies and transfusions can also result in increased PCT levels (Becker et al. 2008). It has been reported that serum PCT concentrations remain within normal range in uncomplicated cases of COVID-19 and enhanced values indicate bacterial coinfection in severe cases.

Bacterial infections lead to elevated levels IL-6, IL-1β and TNF-α resulting in increased synthesis of extra thyroidal PCT, while viral infections might hinder PCT production due to production of interferon γ (Schuetz et al. 2011).While it is still controversial whether PCT can discriminate between bacterial and viral pneumonia, it has been observed that PCT-guided therapy in acute respiratory infections reduces antibiotic exposure as well as side effects and leads to an upgraded disease outcome (Schuetz et al. 2018; Kamat et al. 2020). Thus it can serve as a disease prognosticator for severe COVID-19 patients. As PCT monitors bacterial infections and inflammation, it warrants the requirement of a combination of several blood tests to confirm COVID-19. Also monitoring symptoms along with CT- SCANs, RT-PCR and chest X-Rays are essential. Moreover, immunochromatographic assays are affected by climatic variations such as humidity and temperature. Interfering substances in the serum samples may sometimes lead to false results. Thus it is not possible to conclude that a person has COVID-19 based on a single PCT test without evaluating other parameters.

Ferritin

Ferritin is an intracellular cytosolic protein that regulates iron metabolism in the body. It is a protein complex that consists of twenty-four subunits. There are two types of subunits in vertebrates, namely heavy (21 kDa) and light (19 kDa). They form a hollow nanocage in the metalloprotein. Apoferritin is ferritin without iron bound to it (Wang et al. 2010). The globular protein has a molecular mass of 474 kDa (Theil 2012). It is involved in the storage and controlled release of iron in both prokaryotes and eukaryotes. It is mostly responsible for keeping iron soluble and thus nontoxic. In humans, it prevents both iron deficiency and iron overload. Very less amounts of ferritin are also secreted into the serum for performing the role of an iron carrier. Ferritin levels in the plasma also indicate the total amount of stored iron in the body, and thus it can be used to diagnose anemia (Wang et al. 2010). Ferritin also has a ferroxidase activity; wherein ferrous ions are converted to ferric ions and this limits the highly damaging Fenton reaction which generates deleterious hydroxyl ions (Honarmand Ebrahimi et al. 2015). It is an acute phase protein that increases in concentration in response to stress conditions such as anoxia (Larade and Storey 2004). It represents a paradox as it not synthesized in the serum but it is found in serum due to cellular damage (Kell and Pretorius 2014). Elevated ferritin levels indicate a consequence of cell damage and oxidative stress.

Various assays and commercial ELISA kits are available to measure serum ferritin levels (Koehler et al. 2020). A method of choice to measure serum ferritin levels is immune-turbidimetry. In this, the serum sample is added to ferritin antibodies which are latex-bound. An agglutination reaction takes place and the antigen–antibody complex is measured turbidimetrically at 700 nm. The turbidity of the sample is proportional to the concentration of ferritin in the sample. Calculation of ferritin levels in the serum is then done using various software (Amin et al. 2019). Typically, ferritin in normal healthy individuals ranges from 30 to 160 ng/ml for females and 30–300 ng/ml for males. Ferritin mediates immune dysregulation and contributes to a cytokine storm via direct pro-inflammatory and immunesuppressive activities. The cytokine storm worsens COVID19 in patients, and thus high levels of ferritin in the serum are correlated to disease severity (Vargas-Vargas and CortésRojo 2020). The relationship between iron metabolism and IL-6 is well-established. Hepcidin is a key regulator of iron homeostasis. It binds and internalizes and degrades the iron exporter ferroportin on macrophages and other cells leading to hypoferremia. IL-6 controls erythropoiesis by stimulating hepatic release of hepcidin. Reduced plasma iron levels serve as body's defense against pathogens as iron is unavailable for pathogens to thrive. But at the same time it can result in anemia in chronic inflammation as iron becomes unavailable for erythropoiesis. (Narazaki and Kishimoto 2018). In a recent study involving ICU patients, higher hepcidin levels were directly related to mortality (Jiang et al. 2019). Also serum ferritin levels act as direct indicators of cellular damage as they arise from damaged cells, with values rising to 600 ng/ml indicating association of ferritin levels and organ damage (Kell and Pretorius 2014).

Higher serum ferritin levels were observed in severe and critical COVID-19 patients (Vargas-Vargas and CortésRojo 2020). Serum ferritin was directly associated with increased risk of ARDS in COVID-19 patients in an Italian study (Gandini et al. 2020). Carubbi et al. (2021) reported that serum ferritin levels are associated with the severity of lung involvement. Hyperferritinemia as a result of excessive inflammation due to viral infection is a feature of hemophagocytic lympho-histiocytosis and is associated with cytokine storm, ICU admission and mortality, representative of an indication to identify high risk patients guiding therapeutic interventions. Serum ferritin was found to be a good discriminator of combined outcome of either death or ICU admission (Gandini and Lubrano 2021). Correlation of higher ferritin levels were reported with in-hospital mortality and invasive ventilator dependence in COVID-19 patients (Qeadan et al. 2021). Burugu et al. (2020),

reported mean serum ferritin levels of 1410 ng/ml and 478.81 ng/ml among expired and recovered COVID-19 patients indicating higher serum activities of ferritin in non-survivors. Many studies reveal high ferritin in patients who succumbed to COVID-19, and established the role of ferritin as a prognostic biomarker of COVID-19 inflammation

Ferritin levels are associated with many other medical conditions. Very low levels point towards iron deficiency which may eventually lead to anemia (Guyatt et al. 1990). Ferritin levels less than normal may also indicate a deficiency of Vitamin C, hypothyroidism, or Celiac disease. It may also be involved in restless leg syndrome (Schulte et al. 2014). High ferritin levels apart from indicating inflammation can also indicate a possible iron overload in the body, which may lead to disorders such as hemosiderosis or hemochromatosis. Hyperferritinemia is correlated with four major pathologies of adult-onset Still's disease, macrophage activation syndrome, catastrophic antiphospholipid syndrome and septic shock all sharing very severe disease course and high mortality (Rosário et al. 2013). Anorexia also increases the levels of ferritin in the serum (Kennedy et al. 2004). Abnormally high or low ferritin levels can also be associated with chronic liver diseases (Gkamprela et al. 2017).

Higher ferritin levels alongside lymphopenia, altered liver function tests, coagulopathy and reduced NK cells, had researchers agreeing that COVID-19 might be the latest member in the group of hyperferritinemic syndromes encompassing life-threatening hyperinflammation and multiorgan failure (Mahroum et al. 2021). Ferritin alone cannot predict COVID-19 severity unless coupled with other diagnostic procedures. Reports that suggest the role of ferritin in COVID-19 prognosis have certain limitations, such as they are not inclusive of all ethnicities, the sample size was not large enough, and only hospitalized cases were studied. Nonetheless an early analysis of serum ferritin levels might help to predict disease severity in COVID-19 patients (Bozkurt et al. 2021). A possible approach to lower serum ferritin levels is the use of iron chelators. Also decreasing dietary iron intake might be a useful strategy to lower serum ferritin (Vargas-Vargas and Cortés-Rojo 2020). Thus iron-depletion could be a potential therapeutic approach for COVID-19.

Lactate Dehydrogenase (LDH)

LDH (EC number 1.1.1.27) is an oxidoreductase enzyme produced by nearly all living cells. It catalyzes the reversible transformation of lactate to pyruvate with the reduction of NAD + to NADH and vice-versa, playing an indispensable role in pathways of anaerobic

metabolism. In humans, it exists as five isozymes and it is produced ubiquitously by all tissues including heart, liver, pancreas, kidneys, lymph, skeletal muscles and blood (Farhana and Lappin 2021).

The enzyme is a tetramer composed of two major subunits, namely A and B subunits. The various combinations of the lactate dehydrogenase subunit A (a polypeptide of 332 amino acids) and lactate dehydrogenase subunit B (a polypeptide of 334 amino acids) make up the five isoforms. The isozymes from LDH-1 to LDH-5 each have differential expression in different tissues which forms the basis of LDH as an important clinical diagnostic biomarker (Read et al. 2001). It is predominantly a cytoplasmic enzyme, though few studies also demonstrate its mitochondrial presence. Mitochondrial LDH has been shown to accelerate oxidative phosphorylation (Passarella and Schurr 2018). It plays an indispensable role in glucose metabolism and energy homeostasis. During hypoxic conditions as in muscles, it converts pyruvate to lactate leading to a stuck end in metabolism. The lactate thus formed is released in the blood and the reverse reaction is catalyzed by LDH in the liver via Cori cycle. Thus it plays an essential role in energy generation for the body via cellular respiration (Holmes and Goldberg 2009). Also during hypoxia, ATP production by oxidative phosphorylation is hindered. Thus LDH provides an alternative metabolic pathway for ATP generation. LDH can also dehydrogenate 2-hydroxybutyrate when lactate is absent. It is also involved in regulation of gluconeogenesis and metabolism. Cancer cells overexpress LDH as they display enhanced glucose uptake capacities and preferential generation of lactate even in the presence of oxygen as aerobic glycolysis, known as the Warburg effect (Liberti and Locasale 2016). Besides, LDH is produced in abundance on tissue damage, and thus is a biomarker of inflammation and injury (Henry et al. 2020).

Upon cellular damage, the plasma membrane lyses, releasing the LDH into serum. Thus LDH serum levels are indicative of tissue injury and inflammation. The reduced extracellular pH as a result of enhanced lactate levels from infection or inflammation triggers the activation of metalloprotease and increases macrophage mediated angiogenesis (Martinez-Outschoorn et al. 2011). The catalytic function of LDH is utilized as a basis of its qualitative and quantitative measurements in a clinical laboratory. The reduction of NAD + to NADH causes a change in absorbance that is measured spectrophotometrically at 340 nm. The activity of LDH in the sample is directly proportional to the rate of change of absorbance at 340 nm (Kumar et al. 2018). LDH isozyme test can further aid in the identification of damaged tissues and organs. Levels of LDH are measured in units per

Liter (U/L). Typically, normal levels of LDH vary from 140 to 280 U/L. LDH levels are dependent on various factors including age and certain medicine intakes. Infants have much higher normal levels than adults. Normal range for newborns, children below 1 year and above 18 years is 135–750 U/L, 180–435 U/L and 122–222 U/L, respectively (Farhana and Lappin 2021). Severe infections lead to inflammatory processes in the host immune system resulting in apoptosis of infected cells and tissue damage which further lead to LDH release (Martinez-Outschoorn et al. 2011). In high risk patients, such immune activities lead to a hyperactive inflammatory response and cytokine storm which further release LDH from multiple organs. Furthermore, oxygen imbalance and hypoxia also is observed in COVID-19 patients. This can also lead to accumulation of lactate via glycolysis. LDH can balance lactate secretion via pyruvate fermentation to maintain cellular homeostasis. Activated nuclear factor kappaB and Hypoxia inducible factor could also contribute to an over activated inflammatory response (Yan et al. 2021). As LDH is present in lungs (isozyme 3), patients with severe COVID-19 infections exhibiting interstitial pneumonia often developing into acute respiratory distress syndrome (ARDS), display greater amounts of LDH in circulation. However, contributions of various LDH isoforms leading to LDH elevation during COVID-19 infections hasn't been explored (Henry et al. 2020). It has been reported that to predict the incidence of COVID-19, the best threshold of serum LDH is 273 U/L (Zhou et al. 2020b). Some studies reported that elevated LDH levels were associated with a six fold increase in the odds of the severity of COVID-19, and greater than a 16- fold increase in the odds of COVID-19 mortality (Henry et al. 2020). In a recent study, LDH emerged as an independent risk factor for deterioration of the health of COVID-19 patients (Shi et al. 2020). Some studied that reported the association of high serum LDH levels with COVID-19 severity have been summarized in Table 1.

Since LDH is associated with so many cell types, high levels of LDH in the serum can be indicative of many conditions, such as anemia, stroke, heart attack, some cancers, sepsis, tissue injury, hepatitis, pancreatitis, and muscular dystrophy. Elevation in more than one isoenzyme of LDH can indicate multiple problems, such as a person with pneumonia having a heart attack. Very high serum levels can also indicate multiple organ failure and poor outcomes of hepatocellular carcinoma and pancreatic cancer (Faloppi et al. 2015). Low LDH levels in a person are very rare. It may be due to consumption of high amounts of Vitamin C. It may also be caused due to two genetic mutations. In the first mutation, people feel muscle pain and fatigue during exercising. In the second, patients are usually

asymptomatic. Patients with leiomyoma and ovarian cysts may also exhibit low levels of LDH in the serum (Koukourakis et al. 2009). Again, LDH is not exclusively indicative of COVID-19. More tests are required to confirm COVID-19 severity, although serum LDH levels are potentially useful prognosticator which can assist in stratification of high-risk patients (Wu et al. 2020).

Serum Amyloid A (SAA)

SAA belongs to a closely related conserved family of small proteins of 103–104 amino acids, which share high levels of sequence homology and are preserved in vertebrate evolution. Humans have four SAA genes of which SAA1 and SAA2 are inducible acute phase reactants with SAA1 accounting for 70% of the total protein content. SAA3 is a pseudogene while SAA4 is constitutively expressed. Liver is the primary site of SAA synthesis, while adipose tissue, macrophages and smooth muscle cells are also reported for extra-hepatic synthesis of SAA (Shridas and Tannock 2019). Amino terminal fragments of SAA form highly organized insoluble fibrils, which have been found to accumulate in secondary amyloid disease (Sack 2018). SAA is a prominent constituent of APR arising from various stimuli like inflammation and infection. SAA functions like a cytokine playing an important role in cell to cell communication as well as inflammatory and immunologic pathways. It modulates various biological processes like platelet activation, monocyte mobilization, fever, chemotaxis of different immune cells, and attraction and modulation of inflammatory cells in tissues. It exhibits lipophilicity being poorly soluble in aqueous solutions like blood, and thus it is partitioned into high density lipoproteins (HDL) (Gulhar et al. 2021). In this way it functions as an apolipoprotein.

Serum SAA levels could be measured using immunofluorescence chromatography using auto-analyzers (Fu et al. 2020) and ELISA (Targońska-Stępniak and Majdan 2014). SAA is typically quite low in the serum of healthy individuals, nearly 0.0–10.0 mg/L. Nonetheless its level rises rapidly and shows as much as a 1000-fold increase within 24 h of an acute phase response indicating its hepatic de novo synthesis. Also, the levels of SAA fall quickly following resolution of acute phase response (Sack 2018). SAA levels have been reported to be related with the severity of inflammation. Using protein chip array profiling analysis, it was proposed that SAA could potentially monitor the degree of pneumonia in SARS in 2005 (Yip et al. 2005).

In a cohort study of 35 patients, the severity and recovery of COVID-19 could be predicted with a cut-off value of 157.9 mg/L and 27.7 mg/L respectively for SAA with high sensitivity and specificity. It was reported that SAA is an efficient biomarker in predicting COVID-19 disease severity and recovery of patients (Fu et al. 2020). Another study in 118 patients found statistically 0significant higher mean elevated levels of SAA in severe cases of COVID-19 as compared to ordinary cases (198.32 vs 40.42 mg/L). It also showed greater diagnostic value of SAA for the prediction of disease progression (Mo et al. 2020). Furthermore, various systematic reviews and meta-analyses have been conducted to study the role of SAA in COVID-19 severity. Few such reports are mentioned in Table 1. SAA plays a significant role in COVID-19 pathogenesis for its potential role in cytokine storm. Also SAA might exhibit pro-coagulant effects because of increased fibrinogen and associated platelet activation leading to a prothrombic state (Page et al. 2019). There are reports of a complex interplay between COVID-19 inflammation and thrombosis, adding to life threatening complications of COVID-19 (Al-Samkari et al. 2020). Thus, SAA can serve as a reliable marker for monitoring clinical conditions of COVID-19 patients.

Besides, SAA has been implicated as having a causal relationship with atherosclerosis and cardiovascular diseases exhibiting pro-inflammatory and pro-atherogenic activities (Shridas and Tannock 2019). SAA has also been associated with chronic infection, rheumatoid arthritis, lung disorders, chronic obstructive pulmonary disease, inflammatory bowel syndrome and cancer (Husebekk et al. 1985; O'Hara et al.2000; Moshkovskii 2012; Vietri et al. 2020).

Interleukin-6 (IL-6)

IL-6 is a circulating, multifunctional cytokine protein that is produced as a part of the body's inflammatory response to an infection. The human IL-6 is a 26 kDa protein consisting of 212 amino acids. It is a single chain phosphorylated glycoprotein consisting of mainly four helix bundles (A-D). It is a soluble protein whose expression is strictly under transcriptional and post transcriptional control. Its deregulated expression results in pathological effects hence it acts as a mediator of chronic inflammation and autoimmunity (Tanaka et al. 2014; Shekhawat et al. 2021). Normally, IL-6 is a pleiotropic protein that plays a role in inflammation, hematopoiesis and immune response. It stimulates the production of acute phase proteins, acts as a maturing agent for B-lymphocytes, stimulates the synthesis of immunoglobulins, induces proliferation of T-cells and activates Natural

killer cells (Kaur et al. 2020). When a foreign body enters the human body, Toll-Like Receptors (TLRs), which are a part of the innate immunity and are located on the host cell surface, recognize and bind pathogen-associated molecular patterns (PAMPs) on the surface of the pathogen. This interaction triggers a cascade of intracellular signaling mechanisms which eventually result in the production of cytokines like IL-6 by the macrophages (Tanaka et al. 2014).

Besides, IL-6 also has some metabolic functions. It can initiate the synthesis of Prostaglandin E2 from the hypothalamus by crossing the blood–brain barrier. Thus it can regulate body temperature (Banks et al. 1994). In muscles and adipose tissues, it stimulates mobilization of energy, thus increasing body temperature (Wernstedt et al. 2006).

Besides, IL-6 triggers B cell differentiation, and plays a role in bone maintenance and brain function. It also plays antagonistic functions, such as it can promote growth in some cells while inhibiting growth in others. It has also been seen that externally administered IL-6 improves sleep-associated memory consolidation (Benedict et al. 2009). IL-6 can also act as an anti-inflammatory myokine (Febbraio and Pedersen 2005).

Among many ways to measure IL-6 levels is the serum, the most used is an electrochemiluminescence immunoassay. In this, the sample is incubated with a biotinylated monoclonal antibody specific against IL-6. Next, IL-6 specific monoclonal antibody labeled with a ruthenium complex is added, followed by microparticles coated with streptavidin. If the sample contains IL-6, it forms a sandwich complex between the antibodies. When the mixture is added to a measuring cell, the microparticles are attracted to the magnetic electrode, and on application of a voltage, chemiluminescent emissions are generated, which are measured using a photomultiplier. Results are then determined using a calibration curve (Zhang et al. 2020). IL-6 can also be quantified using ELISA and CSA (Cytometric Bead Assay) along with lateral flow cytometry analysis (Martinez-Urbistondo et al. 2020). It has been seen that a healthy individual has a normal IL-6 level in the serum ranging up to 5 pg/ml (Alecu et al. 1998). It has also been observed that IL-6 levels are indicative of the severity of COVID-19. Many researchers have reported positive correlations between IL-6 and disease severity of COVID-19 patients, proving the potential of IL-6 as a biomarker for detection of the viral disease (Chen et al. 2020b). It was observed that patients having mild to moderate disease had IL-6 levels between 1.5 and 2.5 pg/ ml. Severe patients had more than 5 pg/ml, whereas critical patients who eventually

died had greater than 37.65 pg/ml of IL-6 in their serum (Zhang et al. 2020). IL-6 increase is dramatic in COVID-19 patients, and more than half the hospitalized patients had elevated levels (Chen et al. 2020c). IL-6 increased with infection and decreased with the treatment significantly (Liu et al. 2020). Also a statistically significant association was found between IL-6 levels and ICU admission (Martinez-Urbistondo et al. 2020). Lymphocytopenia and pro-inflammatory cytokine storm resulting in an uncontrolled inflammation within tissues is correlated with severity of COVID-19 infections. Such cytokine storms including production of IL-6, IL-1 and TNF-α can be lifethreatening and are associated with multi/single organ failures. Studies report that the tremendous increase in IL-6 levels in all probability released from inflammatory monocytes and involving bilateral interstitial lung, results in heightened lung inflammation and depressed pulmonary function. IL-6 is being recognized as an essential pro-inflammatory molecule that mediates activation of JAK-STAT pathway leading to oxidative stress, cell division and a virus removing default "second wave in cytokine storm"(Pearce et al. 2020). Understanding these mechanisms are vital in reviewing the clinical algorithms and progression of COVID-19 patients. Various systematic reviews and meta-analyses have identified IL-6 as a prognosticator of COVID-19 and have been summarized in Table 1. Various other cytokines also have pro-inflammatory roles in the progression of COVID-19. Some of them are TNFα, IP-10, IL-1b, IL-8, IL-2, IL-17, CCL3, G-CSF, MCP-1 and GMCSF (Zheng et al. 2020; Chen et al. 2021).

Elevated IL-6 levels are also indicative of other acute and chronic conditions, such as autoimmune diseases, like rheumatoid arthritis and systemic lupus erythematous. Bacterial infections and sepsis also elevate cytokine levels in serum. High IL-6 levels can also indicate diabetes, stroke, cardiovascular diseases etc. Some cancers also can increase IL-6 levels in serum (Kaur et al. 2020). This test is not exclusively diagnostic of COVID-19, as high levels can also indicate other bacterial infections or sepsis. Thus, it can only indicate the severity of COVID-19 once the viral disease has been confirmed in a patient by other nucleic acid-based or molecular assays (Bhandari et al. 2020).

Tumor Necrosis Factor-Alpha (TNF-α)

Tumor necrosis factor–alpha (TNF-α) exists as either membrane bound or as a soluble form. Mature human TNF-α consists of 157 amino acid residues, preceded by 76 residue presequence which is highly conserved and anchors the precursor polypeptide in the

membrane. Proteolytic processing releases a 17 kDa active polypeptide and it exists as a homotrimer of total molecular mass of approximately 52 kDa. Human TNF-α exhibits pleotropic effects by binding to its receptors TNFR-1 and TNFR-2 belonging to TNF Receptor superfamily (Idriss and Naismith 2000). It is largely produced by activated macrophages, monocytes, T-lymphocytes and Natural killer cells (Atzeni and Sarzi-Puttini 2013). It plays essential role in cellular homeostasis as well as disease pathogenesis (Kalliolias and Ivashkiv 2016). It acts as a key mediator and regulator in the development of immune system, proliferation, cell survival signaling, metabolic processes as well as apoptosis (Varfolomeev and Vucic 2018). It is a pro-inflammatory cytokine produced during acute inflammation leading to diverse signaling events that lead to necrosis or apoptosis. It exerts its pathogenic effects via induction of inflammatory cytokine and lipid mediators, recruitment of inflammatory cells, necroptosis, tissue degeneration, endothelial cell activation, hypernociception and induction of tumorigenesis via tumor cell proliferation and metastasis (Kalliolias and Ivashkiv 2016).

TNF-α can be estimated using various cytokine assay kits based on various methods including flow-cytometry, ELISA, chemiluminescence (CLIA) as well as microfluidics available as ELLA microfluidics platform (Del Valle et al. 2020; Udomsinprasert et al. 2021). Serum levels of TNF-α have been found to be elevated in SARS-CoV2 infected patients and the levels were higher in ICU and more severe patients (Huang et al. 2020a). Higher level of TNF-α were reported in patients with poor clinical outcome of COVID19 (23.00 pg/ml vs 7.60 pg/ml) (Huang et al. 2020b). An inflammatory cytokine signature of TNF-α and IL-6 were found to be significant predictors of COVID-19 severity and mortality (Del Valle et al. 2020). In another study by Mortaz et al. 2021, serum levels of TNF-α were significantly higher in ICU patients as well as non-ICU patients compared to healthy controls (7.18 pg/ml and 5.73 pg/ml vs. 0.200 pg/ ml). In several retrospective studies significantly higher levels of various inflammatory cytokines including TNF- α and IL-6 were reported in severe patients (Chen et al. 2020a; Qin et al. 2020). In a literature review by Pedersen and Ho 2020, increased levels of TNF-α in severe patients was evidenced. Few important meta-analysis studies have been reported in Table 1. Cytokine storm might act as a key inducer of apoptosis of alveolar epithelial cells which leads to deterioration of condition and rapid progression of the disease in severe patients. Overproduction of inflammatory cytokines including TNF-α results in systemic inflammation and multiple organ failure. Azevedo et al. 2021, suggested important

correlation of inflammatory hyperactivity triggered with viral infection with myocardial injury and cardiovascular dysfunctions leading to worst prognosis in COVID-19 patients. A recent study reported synergism of TNF-α and IFN-γ triggering inflammation, cell death, tissue injury and even death in SARS-CoV2 infection as well as cytokine shock syndromes (Karki et al. 2021) Furthermore, Feldmann et al. (2020), suggested the potential role of anti TNF therapy leading to reversal of TNF-induced immunopathology for better prognosis of COVID-19 patients. Besides aberrant TNF-α signaling has been implicated in the pathogenesis of several disorders including rheumatoid disease, Crohn's disease, atherosclerosis, psoriasis, sepsis, obesity as well as diabetes. It is suggested to be a master regulator of inflammatory cytokine production and has been recommended as a therapeutic target for numerous pathologies (Parameswaran and Patial 2010).

Light

A novel and important inflammatory cytokine Tumor necrosis factor superfamily 14 (TNFSF14) (LIGHT) encoded by TNFSF14 gene plays vital role in the regulation of immune responses in several organs including lung, gut and skin as well as viral pneumonia (Zhang and Guo 2020). LIGHT levels were found to be significantly increased in serum samples of hospitalized COVID-19

Authors	Prognostic biomarker	Normal range	Mean/median serum levels in non-severe patients	Mean/median serum levels in severe patients	Conclusion
Blood count (× 10^9/L)					
Qin et al. (2020)	White cell count	4.5–11.0	4.9*	5.6*	Increased levels in severe disease
	Lymphocyte count	0.8–5.0	1.0*	0.8*	Decreased levels in severe disease
Wang et al. (2020)	Neutrophil count	1.5–8.1	2.7*	4.6*	Increased levels in severe disease
Guan et al. (2020)	Platelet count	150–450	172*	137.5*	Decreased levels in severe

					Disease
Other parameters					
Gao et al. (2020)	Erythrocyte sedimentation rate (ESR)	0–20 mm/h (females); 0–15 mm/h (males)	43.32 mm/h (females); 21.64 mm/h (males)	94.43 mm/h (females); 67.85 mm/h (males)	Increased levels in severe Disease
Yang et al. (2020)	Neutrophil to lymphocyte ratio (NLR)	1–3	4.8	20.7	Increased levels in severe Disease
Karampitsakos et al. (2020)	Red cell distribution width (RDW)	12–16%	< 14.5%	> 14.5%	Increased levels in severe Disease
Zhao et al. (2021)	Lymphocyte to monocyte ratio (LMR)	3.46–26.67	3.13*	1.88*	Decreased levels in severe Disease
	Platelet to lymphocyte ratio (PLR)	36–173	229*	237*	Increased levels in severe Disease

*Median

patients as compared to healthy controls (Perlin et al. 2020). LIGHT levels were also correlated with severity and mortality in SARS CoV2 infected patients in a recent ARDS COVID-19 biomarker study. This cytokine is postulated to be a potential carter of cytokine storm that results in ARDS and fatality. This cytokine fuels T-cell and B-cell response and induces release of other cytokines like IL-6, IL-1, IL-8, IL-10, TNF and GM-CSF. Amelioration of cytokine storm by inhibiting LIGHT is hypothesized. FDA has given Investigational New Drug status to CERC-002, an anti-LIGHT monoclonal antibody for clinical trials in patients exhibiting cytokine storm induced ARDS for assessing the efficacy and safety of this potential therapeutic target (Perlin et al. 2021).

Inflammation is a key element in the pathological process of organ disorder and acts as a key immune response to pathogens and damaged cells. Apart from the above mentioned protein inflammatory biomarkers for COVID19, 2, IL-8, IL-10, TGF-β, MCP-1 but their role in COVID-19 disease progression needs to be yet established. Cytokines are a diverse cohort of polypeptide signaling biomolecules regulating numerous biological processes including adaptive immunity, inflammation, stress and infections. Since the emergence and

evolution of the pandemic, numerous studies have described abnormal levels of various cytokines and chemokines in COVID19 patients including IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, TNF-α, IP-10, IFN-γ, MCP-1, MIP 1-α, M-CSF, G-CSF, GM-CSF, HGF (hepatocyte growth factor) and VEGF (vascular endothelial growth factor). A key feature of SARS-CoV2 infection is the heightened production of various inflammatory cytokines. Various studies have elaborated the role of cytokine storms in COVID-19 pathogenesis (Mangalmurti and Hunter 2020). Costela-Ruiz et al. (2020), have extensively reviewed the published data on the alterations in the expression patterns of different cytokines in COVID-19 patients. Herein we have reviewed the role of IL-6, TNF-α and LIGHT as biomarkers for COVID-19 in the former sections.

FUNCTION OF BIOMARKERS IN TREATMENT

Low molecular weight heparin (LMWH) has been identified as a potential treatment for severe COVID-19 infections through its actions in reducing the levels of IL-6 and mitigating the cytokine storm. One cohort study found that treatment with LMWH had multiple effects on biomarkers in patients with COVID-19, including a significant reduction in IL-6 levels and d-dimer and FDP levels. (Huag et al.,2021) Furthermore, these results illustrate the role of medications such as LMWH in mitigating the effects of IL-6 involved in the cytokine storm.

Cytokine inhibitors

Early treatment with anti-inflammatory agents has improved respiratory functions for COVID-19 patients. A retrospective cohort study with SARS-CoV-2 RNA-positive patients revealed that anti-cytokine agents such as tocilizumab and anakinra were effective in treating COVID-19 patients when provided early in the cytokine storm. The study showed that 42.3% of patients treated with tocilizumab and 63.4% of patients treated with anakinra responded favorably to the treatment by being extubated or never intubated. Also, accounting for differences in disease severity at treatment initiation showed that the advantage of using anakinra over tocilizumab was not statistically significant. Furthermore, the study revealed that concomitant treatment with corticosteroids may have resulted in a better response with anakinra treatment. (Martins-Filho et al.,2020) These findings illustrate the value of using medications based on biomarkers such as the anti-cytokine tocilizumab and anakinra to improve outcomes for patients with COVID-19. Clinicians can measure

the levels of cytokines such as IL-6 to identify the early stages of the cytokine storm and administer anti-cytokine medications to improve patient outcomes.

Cytokine inhibitors have decreased mortality in patients with severe COVID-19, highlighting their role in preventing COVID-19 deaths. (Martins-Filho et al.,2020) An observational study was conducted to confirm the optimal timing of IL-6 receptor inhibitor (IL-6ri) administration for 255 COVID-19 patients. During the IL-6ri administration, patients were divided into 2 groups; the stage IIB group required less than 45% of inspired oxygen (FiO2), and the stage III group required more than 45% of FiO2. (Shi et al.,2020) The findings from the study revealed that patients in stage IIB treated with IL-6ri had lower mortality, were more likely to be discharged and were less likely to be intubated. (Langer-Gould et al.,2020) These results highlight the role of biomarkers in the design of pharmaceutical interventions for treating COVID-19 infections. Furthermore, the lower mortality, reduced likelihood of intubation, and increased likelihood of discharge in patients with COVID-19 in the stage IIB group underscore the importance of early treatment with IL-6ri. Early and serial measurements of biomarkers such as IL-6 will enable clinicians to provide early treatment. Although immunomodulatory agents have shown promise for treating severe COVID-19, other clinical trials have demonstrated that tocilizumab administration did not significantly reduce ICU admission or mortality rate in a cohort of randomized patients with COVID-19 pneumonia. (Sinha et al.,2020) Investigators have proposed that IL-6 blockade can disrupt the immune response against SARS-CoV-2 infection, suggesting that clinicians should be aware of the potential risks of using immunomodulatory agents such as tocilizumab. (Colaneri et al.,2020) Immunomodulatory agents such as hydroxychloroquine and interferon were studied, and hydroxychloroquine showed statistically non-significant differences in multiple clinical trials for treating COVID-19, which suggests the need for further research into targeting the severe inflammatory response and cytokine storm caused by SARS-CoV-2. (Tsai et al.,2020) A diagnostic workup must be completed to evaluate the severity of COVID-19 in patients before initiating immunomodulatory therapy. Nevertheless, with so many biomarkers identified for multisystemic involvement in COVID-19, future medications can be designed to target the different organ dysfunctions associated with COVID-19 to decrease morbidity and mortality.

Medical Management of Covid-19

Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and this infectious disease is termed COVID-19 in short. The disease was first officially reported in December 2019 in Wuhan, China, and has spread globally since then, leading to the current COVID-19 pandemic. As of June 1, 2020, the Centers for Disease Control and Prevention (CDC) reported that a total of 1,787,680 people was found COVID-19 positive in the USA, and there were totally 104,396 individuals lost their lives to COVID-19 so far (CDC. 2020). On a global scale, as of the same date, the World Health Organization (WHO) published statistics of 6,057,853 infected patients and 371,166 deaths (WHO. 2020). The symptoms of infected people with this novel coronavirus can range from being asymptomatic or minimal respiratory symptoms to febrile illness, as well as severe respiratory failure needing ventilator support. Despite reported observational data about the experimental use of certain drugs, there is no proven curative therapy for COVID-19 as of now; however, remdesivir received emergency use authorization (EUA) by the Food and Drug Administration (FDA) recently for use in patients hospitalized with COVID-19. Most interventions and guidelines for the management of the COVID-19 pandemic are related to prevention, isolation, and supportive treatment strategies. There are several ongoing clinical trials related to the pharmacological choices of therapy for COVID-19 patients; however, drug trials related to observational studies so far have yielded mixed results and therefore have created a sense of confusion among healthcare professionals (HCPs). In this review article, we seek to collate and provide a summary of treatment strategies for COVID-19 patients with a variable degree of illness, and discuss pharmacologic and other therapies intended to be used either as experimental medicine/therapy or as part of supportive care in complicated cases of COVID-19. General Issues around Medical Management of COVID-19 are;

Use of Non-Steroidal Anti-Inflammatory Drug (NSAID)

Some anecdotal reports suggested association of NSAID use early during COVID-19 and progression to severe disease in young adults (BMJ.2020) . However, there has been no population-based research showing the direct relationship of NSAID use and severe COVID-19. WHO and the United States National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel do not recommend NSAIDs being avoided when clinically indicated (WHO.2020) . Acetaminophen should be used as the preferred antipyretic agent

for fever associated with COVID-19; NSAID, if used, should be administered in the lowest effective dose; this approach is consistent with an established general approach to fever reduction in adults. It is also not recommended to discontinue NSAIDs in patients who are on them chronically for other conditions, unless there are clinical rationale to stop them (e.g., acute renal injury, gastrointestinal (GI) bleeding).

Function of Glucocorticoids

In the past, glucocorticoids have been associated with an increased risk for mortality in patients with influenza and delayed viral clearance in patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Although they were widely used in the management of severe acute respiratory syndrome (SARS), there was no good evidence for benefit, and there was persuasive evidence of adverse short- and long-term harm (Russell et al.,2020) . Therefore, CDC recommended against the use of systemic glucocorticoids in patients with COVID-19, unless there are other indications such as asthma or chronic obstructive lung disease exacerbation, refractory septic shock, and adrenal insufficiency. However, their administration in critically ill patients with COVID-19-related adult respiratory distress syndrome (ARDS) is controversial. Based on data suggesting the potential benefit of glucocorticoids in patients with all-cause ARDS, the Society of Critical Care Medicine (SCCM) provided a conditional, weak recommendation in favor of glucocorticoids in patients with COVID-19 who have severe ARDS. If clinicians choose to administer glucocorticoids, the SCCM suggests that they should begin within the first 14 days, doses should be low, and courses should be short (e.g., intravenous (IV) dexamethasone 20 mg once daily for 5 days, then 10 mg once daily for 5 days). Data from retrospective Chinese cohort (Wu et al.,2020) regarding this topic were not without flaws, and hence large-scale prospective data will be required to settle this dilemma.

Venous Thromboembolism Prophylaxis

Patients with COVID-19 may carry an increased risk for systemic thrombosis. This is suggested by published case reports of pulmonary embolism in patients with COVID-19, and several cohorts reported to have elevated D-dimer levels and other markers of dysregulated coagulation (Tang et al.,2020) . Moreover, many patients hospitalized with COVID-19 have a higher risk of thromboembolism anyways because of advanced age and existing comorbidities. Additionally, markers of dysregulated coagulation and evidence of disseminated intravascular coagulation (DIC) have been seen to be associated with more

severe disease and death in patients with COVID-19 (Tang et al.,2020) . However, the impact of anticoagulation (prophylactic or therapeutic) on the outcome of COVID-19 remains unknown. As with all hospitalized patients, pharmacologic prophylaxis of venous thromboembolism is recommended even in COVID-19 patients, typically using low-molecular-weight heparin, unless there are clinical contraindications such as active bleeding or severe thrombocytopenia.

Use of Nebulized Medications

sInhaled medications should be administered by metered-dose inhaler and not through a nebulizer. This is to avoid the risk of aerosolization and transmission of SARS-CoV-2. If nebulized therapy must be used, patients should be in an airborne infection isolation room (preferably negative pressure room), and any healthcare worker who needs to be in that room should use the contact and airborne precautions with appropriate personal protection equipment (PPE) including N95 mask with goggles and face shield or equivalent. It is also recommended not to re-enter the room for 2 -3 h following nebulizer treatment for risk of aerosolized transmission of the virus.

Empiric Use of Antibiotics for Superimposed Bacterial Pneumonia

Clinical features of COVID-19 are challenging to distinguish from bacterial pneumonia. Empiric treatment for bacterial pneumonia may also be reasonable in patients with documented COVID-19 if there is clinical suspicion. Empiric antibiotic therapy, if initiated, should be guided by microbial diagnosis (e.g., sputum Gram stain and culture) and reevaluate the need to continue antibiotic therapy daily. A low procalcitonin level usually is helpful to suggest against bacterial pneumonia; however, elevated procalcitonin has been described in the late stage of COVID-19 and does not necessarily indicate bacterial pneumonia (Zhou et al.,2020) .

Angiotensin-Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs)

It was suspected that COVID-19 patients who are receiving these agents might be at increased risk for adverse outcomes, but there is no clinical evidence that supports such speculation. Conversely, ARBs were proposed to have potential protective effects based on their mechanism of action (CDC.2020) , but there is no conclusive evidence to support this hypothesis. Multiple experts and guidelines recommended that patients who are already on ACEI or ARB should continue treatment with these agents if there is no other reason for

discontinuation (e.g., hypotension, acute kidney injury (AKI)) (American Heart Association).

Statins

Concern has been raised regarding potential hepatotoxicity from statins in COVID-19 patients who commonly demonstrate elevated transaminase levels. However, most evidence indicates that liver injury from statins is uncommon. On the other hand, statins are known inhibitors of the myeloid differentiation primary response 88 (MYD88) pathway, which results in marked inflammation, and have been reported to stabilize MYD88 levels in the setting of external stress in vitro and animal studies. Dysregulation of MYD88 has been noted and associated with poor outcomes in SARS-CoV and MERS-CoV infections, but this has not been described with SARS-CoV-2 (Yuan S.2015) .

Immunomodulatory Agents

Initiation of immunosuppressive agents has been associated with increased risk for severe disease with respiratory viruses. However, no evidence routinely discontinuing treatment is of any benefit. Therefore, the plan to discontinue prednisone, biologics, or other immunosuppressive drugs in the setting of COVID-19 must be determined on a case-by-case basis. COVID-19-negative patients with underlying conditions requiring treatment with these agents should not be taken off suddenly, as discontinuing of these medications may result in loss of response when the agent is reintroduced. Statements from different medical societies support the approach of continuing immunomodulatory therapy in patients without infection (American Academy of Dermatology) .

Symptomatic Management

Fever is the most common symptom and was noted in 88.7% of the COVID-19 patients in a study in China (Guan et al.,2020) . Acetaminophen is the recommended antipyretic in COVID-19. It can also be used in headache and myalgias. NSAIDs could be used, at the lowest effective dose, as an alternative antipyretic or pain reliever despite some report of NSAID use and worsening of COVID-19 severity (BMJ.2020) . Aspirin causes Reye syndrome, and should be avoided in children. Cough (often dry cough) is another prominent and common symptom of COVID-19. Cough medications may contain antihistamines and decongestants, and so must be used with caution. It is recommended that metered-dose inhalers are used, and nebulizers are avoided as much as possible due to the increased risk of aerosolization and the spread of the virus (CDC.2020) . Hypotension

and shock are potential complications of COVID-19. Vasopressors are preferred to aggressive fluid resuscitation in patients with shock to avoid volume overload due to concern for the development of ARDS in these patients (Alhazzani et al.,2020). The use of empiric antibiotics and glucocorticoid therapy is controversial and has been discussed earlier in this article.

Management of Respiratory Failure

Viral infection causes inflammatory cytokine release and thereby edema in various vascular beds, usually subpleural in the early stages and alveolar edema in later stages (Gattinoni et al.,2020) . Vascular endothelial damage in COVID-19 disrupts pulmonary vascular autoregulation in response to hypoxia and contributes to ventilation-perfusion (VQ) mismatch (Marini et al.,2020) . Moreover, inflammation of the alveolar lining, as well as decreased fluid clearance, leads to alveolar collapse and edema. The respiratory mechanics, pathology, and clinical features change with disease progression in COVID-19. With the worsening of the disease process, alveolar edema leads to increased right heart pressure, which in turn causes more tissue hypoxia and multi-organ failure (Luks et al.,2020) . Gattinoni et al conceptualized two distinct phenotypes: the "L" and "H" types (later stages/ARDS) at the ends of the clinical spectrum with possible intermediate cases with overlapping features (Gattinoni et al.,2020 and Marini et al.,2020) . The "L" type is seen early on with low elastance/high compliance, low lung weight, low VQ mismatch, and low recruitability. The lungs at this stage are compliant, can hold a good amount of air, are not affected by much edema; VQ ratio is due to defects in vasoregulation and perfusion, and since most of the lung is already aerated, there is not much scope for recruitability (Gattinoni et al.,2020) . These patients have mild dyspnea, limited ground glass infiltrates on computed tomography (CT) scans, and they can withstand the distress. The "H" type is found later in the COVID-19 disease process with more resemblance to ARDS. It is the exact opposite of the "L" type with high elastance/low compliance, high lung weight, high VQ mismatch, and high recruitability (Gattinoni et al.,2020). These explain the resemblance to ARDS (non-cardiogenic pulmonary edema, shunting, and decreased lung size for gas exchange). These patients are symptomatic and with extensive infiltrates on CT suggestive of alveolar edema, and increased risk of ending up on the ventilator support device. Based on these concepts, respiratory support in COVID-19 should focus on optimizing oxygenation, reducing pulmonary and vascular stress, preventing edema and lung injury, and recruitment of functional lung units (Marini et al.,2020).

For acute hypoxemic respiratory failure, the recommended goal is to provide supplemental oxygen aiming for oxygen saturation (SpO2) 90-96% (Alhazzani et al.,2020) . Oxygen supplementation could be increased to considerably safer limits of 6 L/min through a nasal cannula and 10 L/min through a non-rebreathing mask. If conventional oxygen therapy fails, high flow nasal cannula (HFNC) is preferable to non-invasive ventilation (NIV) due to an increased risk of aerosolization with NIV. Early intubation is preferred, but the approach is controversial. During intubation, bag-valve-mask ventilation should be avoided, and the two-person technique is preferred (Alhazzani et al.,2020) . Overall, the decision to initiate NIV, HFNC or intubation, should be made by balancing the risks and benefits to the patient, the risk of exposure to healthcare workers, and best use of local resources; this approach should be reassessed as new research data and resources become available. In a systematic review of 10 retrospective cohort studies which evaluated transmission of SARS-CoV to healthcare workers, endotracheal intubation had the highest risk (odds ratio (OR): 6.6; 95% confidence interval (CI): 2.3 - 18.9), followed by non-invasive ventilation (OR: 3.1; 95% CI: 1.4 - 6.8), tracheostomy (OR: 4.2; 95% CI: 1.5 - 11.5), and bag-mask ventilation (Tran et al.,2020) . In general, indications for intubation include clinically worsening respiratory distress, rapidly progressive disease, SpO2 less than 90% despite maximal supplemental oxygen, acidosis with pH less than 7.3, and partial pressure of carbon dioxide (PaCO2) more than 50 mm Hg, multi-organ failure and hemodynamic instability.l The general guideline to initial ventilator settings includes the assist control (AC) mode with a tidal volume 4 - 8 mL/kg ideal predicted body weight; respiratory rate 25 - 30 breaths/min; positive end expiratory pressure (PEEP) 10 - 15 cm H2O; target SpO2 90-96%; plateau pressure less than 30 cm H2O. The L type patients tolerate lower PEEP (< 10 cm H2O) and higher tidal volume (7 - 9 mL/kg). In these patients, higher PEEP redirects blood flow and creates dead space, while higher tidal volumes for hypercapnia are well tolerated due to high compliance. The H type patients, with low lung compliance, need higher PEEP (< 15 cm H2O) and lower tidal volumes (5 - 7 mL/kg) (Marini et al.,2020) .

Prone positioning is an option when patients on ventilators have worsening oxygenation with mechanical ventilation (e.g., PaO2/fraction of inspired oxygen (FiO2) less than 150 mm Hg for 12 h). Patients must be maintained in a prone position for 12 - 16 h a day (Alhazzani et al.,2020) . Contraindications to prone positioning include shock, active bleeding, recent tracheal surgery, multiple fractures, and spine instability (Alhazzani et

al.,2020) . Recruitment maneuvers, high PEEP strategies, and trial of inhaled pulmonary vasodilators are probable options for patients that failed prone positioning (Alhazzani et al.,2020 and Pan et al.,2020). Neuromuscular blockade can be employed for patients with refractory hypoxemia on ventilator dyssynchrony (intermittent boluses are preferred unless persistent dyssynchrony) (Alhazzani et al.,2020) .

In general, extracorporeal membrane oxygenation (ECMO) is used in patients with refractory cardiac and respiratory failure in whom usually the venous blood is removed from the body and pumped through an artificial membrane lung, and is essentially a modified cardiopulmonary bypass. This oxygenation is needed for circulatory support and organ function. The role of ECMO in COVID-19 is unclear but may be used in patients with refractory hypoxemic respiratory failure. Venovenous ECMO has been used as a last resort for patients that have failed all other means; however, the mortality of COVID-19 patients who lands up on ECMO is extremely high and > 90% in one analysis (Henry et al.,2020) .

Pharmacological Therapy

Multiple pharmacotherapies have been tried on an experimental basis on COVID-19 patients across the globe. Some studies claimed faster clearance of virus from the patient, and some demonstrated decreased mortality. No large randomized scale-controlled trial has settled the argument of the true effectiveness of any medicine against COVID-19. In this section, we will briefly present the proposed mechanism of action of individual medications that have been most commonly tried and trialed in recent times against COVID-19, and also discuss possible pros and cons of experimental use of such medications in these vulnerable patients. We have also provided an updated list of ongoing trials of most major medications that are being investigated as a possible effective pharmacological therapy against COVID-19 as a supplement to this article (Supplementary Material 1, www.jocmr.org).

Hydroxychloroquine/Chloroquine and Azithromycin

Mechanism of action (MOA) Hydroxychloroquine and chloroquine block entry of the virus into human cells by proteolytic processing, inhibiting glycosylation of host receptors, and acidification inside endosomes. These agents may have immunomodulatory effects through blockage of autophagy and lysosomal activity in host cells, along with dissipating cytokine production and inhibition. Azithromycin is an antibacterial macrolide and works through

binding to 50s ribosomal subunit and inhibition of messenger RNA directed polypeptide synthesis. Antiviral mechanism of macrolides is scarce and was hypothesized to inhibit respiratory syncytial virus through the reduced expression of fusion protein receptor, activated isoform A of the Ras homologous (Rho) family, and the inhibition of subsequent Rho-kinase activation in human airway epithelial cells (Asada et al.,2009) . Azithromycin was shown to inhibit replication in Zika and Ebola viruses (Retallack et al.,2016 and Madrid et al.,2015)

Pros and cons Chloroquine and hydroxychloroquine are relatively well tolerated and has been used for ages in patients with systemic lupus erythematosus (SLE) and malaria. However, both agents can cause serious adverse effects (< 10%), like hypoglycemia, retinopathy, psychiatric effects, QTc prolongation. Azithromycin is a commonly used macrolide for respiratory bacterial infections. Gautret et al concluded that combination therapy with azithromycin and hydroxychloroquine cured 100% of patients virologically on day 6 compared to 57.1% in patients treated with hydroxychloroquine only, and 12.5% in the control group (P = 0.001) (Gautret et al.,2020) . However, the risk of QT prolongation from these two drugs should be considered, and caution should be taken, especially in cardiac patients, while administering this combination (Simpson et al.,2020) . Moreover, a study among 368 USA veterans found no benefit, rather touted hydroxychloroquine to be more harmful due to its side effect profile (Magagnoli et al.,2020) . Proposed dose for COVID-19 Hydroxychloroquine dose most used is 400 mg twice daily orally for two doses, then 400 mg daily orally for a total of 5 days. Chloroquine dose suggested by FDA is 1 g on day 1, then 500 mg daily for 4 - 7 days total.

Remdesivir

MOA Remdesivir, or GS-5734, is an adenosine monophosphate prodrug that metabolizes to an active C-adenosine nucleoside triphosphate analog, thereby interfering with the action of viral RNA-dependent RNA polymerase.

Pros and cons The agent was first discovered in 2015 in the process of finding antimicrobials with activity against RNA viruses. Initially, it was used for Ebola treatment. It has shown promising results in animals' studies with MERS and SARS caused by a coronavirus.

Remdesivir received EUA by FDA last week for use in patients hospitalized with COVID-19 based on a clinical trial, which showed remdesivir, accelerated the recovery time by 31%,

from 15 days to 11 days in patients who received treatment with it. It reduced the mortality from 11% to 8%, but it was not statistically significant (FDA) . Few case reports and series suggesting its effectiveness in the novel COVID-19 has been published (Sanders et al.,2020) . Notable side effects are nausea, vomiting, and reversible rise in aspartate aminotransferase and alanine transaminase. Proposed dose for COVID-19 The current dose under investigation is a single 200 mg loading dose, followed by 100 mg daily infusion (Sanders et al.,2020) . Under this EUA, the recommended dosing duration for patients requiring invasive mechanical ventilation and/or ECMO, and for patients not requiring invasive mechanical ventilation and/or ECMO is 10 days and 5 days, respectively (FDA) . Therapy is not recommended in patients with an estimated glomerular filtration rate less than 30 mL/min (Sanders et al.,2020) .

Favipiravir

MOA Favipiravir inhibits influenza viral replications by targeting RNA polymerase, and this mechanism is also being applied to the novel coronavirus, which is a single-stranded RNA virus and requires RNA polymerase for replication (Sanders et al.,2020) .

Pros and cons Favipiravir is not available commercially in the USA. The safety and efficacy of the drug is not established as of now. Favipiravir is a generic version of brand Avigan used for treating novel influenza infections in Japan. Notable side effects include decreased neutrophil count, diarrhea, increased uric acid levels, elevated transaminases (Sanders et al.,2020).

Proposed dose for COVID-19 Recommended dosing is 2,400 to 3,000 mg loading dose every 12 h for two doses, followed by 1,200 to 1,800 mg twice a day as maintenance dose (Sanders et al.,2020).

Interleukin (IL)-6 pathway inhibitor

MOA Elevated levels of the inflammatory marker, including IL-6, were found in the blood of COVID-19 patients, and were reported to have a bad prognosis in patients. IL-6 is a proinflammatory cytokine and binds to both soluble IL-6 receptor (sIL-6R) and membrane-bound IL-6R (mIL-6R). The resulting complex activates an inflammatory response through interaction with transducing component glycoprotein 130 (gp130), which can result in a cytokine storm (Tanaka et al.,2016) . Sarilumab and tocilizumab are the two IL-6 inhibitors widely available in the markets, and they bind specifically to sIL-6R and mIL-6R, and block signal transduction.

Pros and cons Cytokine storm in response to COVID-19 has been found to have devastating consequences in critically ill patients and may facilitate shock and multi-organ failure. IL-6 inhibitors can be helpful by diminishing the effect of an overactive cytokine system. New-onset abdominal symptoms should be monitored as there were reported cases of GI perforation, specifically in patients with a history of diverticulosis. Baseline lipid panel and liver function testing should also be done as these drugs might elevate these parameters significantly. Proposed dose for COVID-19 Standard dosing for these medications has been used for experimental purposes.

Lopinavir/Ritonavir

MOA The lopinavir component binds to the site of viral protease activity and inhibits the cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins required for infectious human immunodeficiency virus (HIV). This results in the formation of immature, noninfectious viral particles. The ritonavir component inhibits the cytochrome P450 3A (CYP3A) metabolism of lopinavir, allowing increased plasma levels of lopinavir.

Pros and cons Widely and successfully used in HIV management, this combination has been tried in the management of 2019 novel coronavirus (2019-nCoV). This drug has shown some effect in the in vitro model for MERS and SARS treatment (Chu et al.,2004 and de Wilde et al.,2014) .

Clinical trials so far have not managed to show any benefit of this combination in the treatment. In a recently published article from a study in China, this combination has not shown any effective benefit. No significant differences in viral clearance or 28-day mortality rates were observed in 199 studied patients (Cao et al.,2020) . Adverse reactions should be kept in mind. The most frequently reported reactions in patients receiving lopinavir therapy are asthenia, diarrhea, and nausea. Elevated total bilirubin, hepatic enzyme levels, and triglycerides have also been reported (Hurst et al.,2000) .

Proposed dose for COVID-19 Commonly studied lopinavir/ritonavir dosing in COVID-19 patients is 400 mg/100 mg twice daily for up to 14 days.

Histamine 2 Receptor Antagonist (H2RA)

MOA Histamine has pleiotropic effects on the immune system from different natures of its receptors. One of its effects being immunomodulation resulting in sepsis was noticed in

diabetic mice. This happens through decreased neutrophil recruitment and impaired oxidative burst from elevated histamine levels (Carlos et al.,2013 and Ciz et al.,2013). H2RAs block these immunosuppressive effects of histamine and stimulate the functions of T and B white cells (Jafarzadeh et al.,2019) . The antiviral effects of this H2RA were demonstrated in patients with herpes zoster infection, herpes simplex virus (HSV), and human papillomavirus (HPV) (Kapinska-Mrowiecka et al.,1996) (Kurzrock et al.,1987) (Harcourt et al.,1999) . It was also shown that cimetidine, an H2RA, increased immunogenicity when given as an adjuvant along with HBV viral vaccines (Zhang et al.,2011) . It also decreased HIV replication in vitro (Bourinbaiar et al.,1996) . Pros and cons Although H2RA is a very commonly used medication that is even available over the counter, no conclusive data are supporting how H2RA helps against COVID-19. This thought originated from Michael Callahan, an infectious disease doctor at Massachusetts General Hospital. He observed that many of the COVID-19 survivors had chronic heartburn and took famotidine rather than omeprazole, which is more expensive when he was working in Wuhan during the coronavirus epidemic began. It was later investigated in more than 6,000 patients who recovered and found a slightly higher number in the famotidine group, but was not high enough to be statistically significant. Proposed dose for COVID-19 Standard dose to treat gastroesophageal reflux disease.

Interferon (IFN) beta

MOA IFN-beta is a subtype of type I IFN secreted by many cell types, mostly by plasmacytoid dendritic cells upon recognition of viral components by pattern recognition receptors (PRR). IFN-stimulated genes (ISG) are involved in inflammation and immunomodulation. ISGs interfere with viral replication and viral spread through different pathways like cytokine secretion or slowdown of cell metabolism (Liu et al.,2005) .

Pros and cons Data obtained from the experiments involving treatment of SARS-CoV and MERS-CoV and ISG's ability to disrupt the IFN signaling pathway would be valuable for selecting IFN-beta as a potential treatment option against SARS-CoV-2 (Chan et al.,2015 and Stockman et al.,2006) .

Type I (IFN-alpha and beta) IFNs were efficient in vitro and also in specific animal models but failed to control the disease in humans (Chan et al.,2015) . It was hypothesized that SARS-CoV-2 induces an IFN-I mediated antiviral response, leading to tissue damage. Proposed dose for COVID-19 IFN-beta is the most relevant IFN-I that should be given as

early as possible to optimize antiviral therapy and avoid complications from the virus (Channappanavar et al.,2019) . No specific dose has been validated, especially for COVID-19. The general dosing guideline is being followed.

Convalescent Plasma (CP)

CP or immune plasma, is the plasma collected from donors who have successfully survived an infectious disease by generating antibodies. CP has been in use for over 100 years to treat a variety illness starting with measles, polio, chickenpox to recent epidemics as SARS-CoV-1 epidemic (SARS) in 2003, H1N1 influenza pandemic (H1N1) in 2009 - 2010, avian influenza A (H5N1), Ebola and MERS-CoV epidemic in 2012 (Luke et al.,2006) (Zhang et al.,2020) (Dodd et al.,2015) (Hung et al.,2011) (Mair-Jenkins et al.,2015) (Roback et al.,2020) . MOA The antibodies in the CP could potentially limit the viral replication, can mediate cellular toxicity and/or phagocytosis, and the plasma components can exert vital clinical effects such as replacing the coagulation factors, complement activation. Also, CP may potentially offer the only short-term strategy to confer immediate immunity to infection susceptible patients (Bloch et al.,2020) . In the absence of an effective specific treatment for COVID-19, clinicians across the globe have used the CP with varying success (Shen et al.,2020 , Duan et al.,2020) .

Pros and cons During the 2005 SARS outbreak in Hong Kong, Cheng et al (Cheng et al.,2005) , have published the most extensive study on the outcomes of 1,775 patients with the infection, of whom, 80 patients received CP had a lower mortality rate (12.5%) compared to overall SARS-related mortality. The study was not a randomized trial, and no adverse events reported (Cheng et al.,2005). Shen et al (2020) have published a preliminary study of five patients with COVID-19 who were severely ill and treated with CP from China. All five patients were mechanically ventilated, and one needed ECMO. The donor CP, an apheresis product, had demonstrable immunoglobulin G (IgG) and IgM anti-SARS-CoV-19 antibodies and in vitro virus-neutralizing properties. The authors concluded that the CP might have contributed to the recovery, although the patients were also on lopinavir/ritonavir antiviral therapy and IFN (Chen et al.,2020) .

Despite the numerous case series and emerging evidence with CP is compelling and well documented, it has several limitations as it is not evaluated in a randomized clinical trial, to determine the actual clinical benefit when compared to those who have not received it (Bloch et al.,2020 , Casadevall et al.,2003). In almost all the case series and studies

published so far, the patients received numerous other therapies, including various antivirals, steroids, etc. It is also interesting to note that the timing of administration of the CP was different in multiple studies. Prior studies have shown that passive antibody therapy is most effective if given prophylactically or used early in the disease course.

Proposed dose for COVID-19 Even though there is no compelling evidence from large scale randomized trials, the FDA has begun allowing CP to be used in patients with severe or immediately life-threatening COVID-19 infections starting March 24, 2020. The treatment with CP is considered experimental. It is important to note that effective formulations such as a convalescent plasma or H-Ig or immunoglobulins, is still unknown. A person who has tested positive for COVID-19 and recovered with no symptoms for 14 days could be a potential donor in the presence of high enough antibody levels in the plasma and negative for possible infections such as HIV, hepatitis C, etc. The donor and the recipient should have compatible blood groups.

Though been in use for over 100 years for various infectious diseases, there is a severe lack of cooperative global efforts to use CP as initial therapies against the new and emerging epidemics and pandemics. More than 4.5 million global infections and growing, COVID-19 provides an opportunity to perform large-scale rigorous clinical studies on CP against the viral agents to establish clinical efficacy. This pandemic could provide a strategic pathway for future viral pandemic management with CP.

Plasma Adsorption and Exchange

Emerging evidence suggests that managing cytokine storm in critically ill COVID-19 patients by using steroid or IL-6R blocking antibodies may be beneficial (Tanaka et al.,2016 , Xu et al.,2020) . In the case of fulminant systemic infection, patients may develop sepsis, ARDS, and multi-organ failure, which are not unique to coronavirus. Treatment with effective antiviral therapy is being sought; however, treatment of the systemic response to this viral infection is likely to be equally or more important. Overzealous host response to infection has been well described and involves a complex interaction of cytokine storm, inflammation, endothelial dysfunction, and pathologic coagulation (Chang et al.,2019, Hou et al.,2017, Johansson et al.,2017, Nguyen et al.,2006). The utilization of blood purification therapy in the form of plasma adsorption or therapeutic plasma exchange (TPE) has been proven in the setting of sepsis (Busund et al.,2002, Monard et al.,2019), but the same has not been adequately proven in critically ill COVID-19 patients. Knowledge of optimum

management of critically ill COVID-19 patients in the late phase is quite limited. The presence of cytokine storm or pathogenic antibodies in critically ill COVID-19 patients has a strong correlation with the disease severities. Monitoring inflammation and antibodies is significant, especially in patients infected by the virus with persistent fever or abnormal coagulopathy. Expeditious control of the cytokine storm utilizing plasma adsorption or TPE might be beneficial to selective patients with COVID-19 (Ma et al.,2020). These therapies are well tolerated if performed with the close guidance of specialists, and risks of infection or bleeding are minimized. So far, randomized trial data are not available regarding this in COVID-19, but such clinical trials should be done to utilize blood purification therapy to appropriate patients.

CONCLUSION

clinical laboratories perform a pivotal function in the SARS-CoV-2 pandemic, not only from a diagnostic point of view but also in terms of the prognosis of COVID-19 patients, determining the degree of metabolic disorder of the patients and favoring the development of support tools for clinical decision making in order to adjust the therapy to the biological changes experienced by the subjects. Likewise, the laboratory work allows optimizing the hospital environment resources of the critical units of the health systems, resulting in the enhancement of the response time and efficiency of this response (Lippi et al.,2020) . However, these approaches should be constantly reassessed based on new and reliable evidence published around the world, besides the incorporation of new technologies into the clinical laboratory work to obtain greater precision in the search for biochemical markers.

Recommendation

Although COVIDD-19 has taken so many lifes and affected many people, preventive measures can be taken to safeguard yourself and others from COVID-19. One of this many measure is being immunized, because COVID-19 can result in severe sickness and death in certain people, protection from it crucial. The greatest defense against is a combination of COVID-19 immunization and adhering to the CDC's instructions for protecting both you and others. COVID-19 patients should adhere strictly to treatment strategies provided by healthcare professionals.

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