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Role of Polypeptide Inflammatory Biomarkers in the Diagnosis and Monitoring of COVID-19

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Abstract

The COVID-19 (coronavirus disease 2019) pandemic that took over the world in December 2019 has had everlasting devastating impacts on the lives of people globally. It manifests a huge symptom spectrum ranging from asymptomatic to critically ill patients with an unpredictable outcome. Timely diagnosis and assessment of disease severity is imperative for effective treatment. Possibilities exist that by the time symptoms appear the viral load might increase beyond control. However, it is advisable to get adequately diagnosed as soon as the first symptom appears. There is an immediate requirement of reliable biomarkers of COVID-19 manifesting an early onset for effective clinical management, stratification of high risk patients and ensuring ideal resource allocation. In this review, we attempt to explore and describe important polypeptide inflammatory biomarkers, namely C-reactive protein, Procalcitonin, Ferritin, Lactate Dehydrogenase, Serum amyloid A, Interleukin-6, Tumor necrosis factor-alpha and LIGHT used in the detection and management of COVID-19. Viral pathogenesis and the role of these inflammatory biomarkers is highlighted, based on the evidences available till date. An integrative data monitoring along with their correlation with the natural disease progression is of utmost importance in the management of COVID-19. So further research and in-depth analysis of these biomarkers is warranted in the present scenario.

Keywords COVID-19 · Protein biomarkers · Inflammation · C- reactive protein · Procalcitonin · Ferritin · Interleukin-6 · Lactate dehydrogenase · Serum amyloid A · TNF-α · LIGHT

Introduction

Coronavirus disease 2019 (COVID-19) pandemic has emerged as one of the greatest healthcare challenges and is a threat to the entire humanity. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a novel coronavirus, initiated an outbreak of COVID-19 in December 2019, which rapidly spread across the globe from Wuhan in China. World Health Organization declared the viral disease as a Public Health Emergency of International Concern (PHEIC) on 30th January, 2020 (COVID-19 PHEIC Global reseach and innovation forum, http://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum). It rapidly turned into a catastrophic social, scientific and economic trial. The clinical features of COVID-19 vary from asymptomatic cases to mild non-specific symptoms like cough, headache, fever, sore throat, sneezing and nasal congestion, to severe cases like pneumonia, respiratory failure, multi-organ failure, sepsis and even death (Hu et al. 2021; Cascella et al. 2021). Patients with comorbidities including diabetes, hypertension, obesity and old age may also experience exacerbated symptoms (Zhou et al. 2020a). Furthermore, with the emergence of several new strains of SARS-CoV-2 as variants of concern/interest with enhanced transmission rates makes controlling this pandemic all the more challenging (Boehm et al. 2021). As on 23th December 2021, there were more than 276,436,619 confirmed cases and 5,374,744 deaths worldwide (WHO Coronavirus (COVID-19) Dashboard, http://covid19.who.int.)

The unpredictable clinical course of the disease that might quickly develop into lethal complications adds a great

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complexity and uncertainty to the clinical outcome of the disease. This is where biomarkers come into play. A biomarker is any measurable characteristic that can indicate whether the human body is under normal physiological or disease conditions (Mayeux 2004). Biomarkers offer advantages of being reliable, economical, easier to work and are capable of significantly extending our understanding of the underlying pathogenesis of a disease (Aronson and Ferner 2017). Biomarkers act as effective clinical assessment tools and help the clinicians to predict, diagnose and monitor the progress of a disease (Pierce et al. 2012). Greater insights into the pathobiology of the virus and identification of early as well as effective biomarkers based on a patient's risk to severe disease is imperious to provide immediate medical help to the patients who might progress towards severe form of the disease.

Potential Role of Protein Inflammatory Biomarkers 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 SARS-CoV-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).

COVID-19 Pathogenesis

It is vital to understand the molecular mechanism of viral action and damage upon human cells so as to find potential effective therapeutic strategies and recognize novel biomarkers predictive of severity of the disease. Coronaviruses primarily have four structural proteins, namely the spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins (Satarker and Nampoothiri 2020). The primary mode of SARS-CoV-2 infection is the binding of the virus to the angiotensin-converting enzyme 2 (ACE-2) receptor (Medina-Enríquez et al. 2020). It employs its homotrimer S glycoprotein to bind to ACE-2 receptor, present on the surface of various cells in the human body, and trigger a cascade of events that leads to fusion of viral and host cellular membranes for target cell entry. S protein has two functional subunits, namely S1 subunit, that engages the host cell receptor, and S2 subunit, that plays an important role in the fusion of membranes. This ACE-2 receptor has been found to be central for the virulence of virus as cells lacking the same are resistant to the SARS-CoV-2 infection (Ou et al. 2020b). ACE-2 is a glycoprotein and metalloprotease and exists in both membrane bound and soluble forms. The primary function of ACE-2 is to convert angiotensin-II (Ang-II) to angiotensin 1–7 (Ang1-7) in the renin-angiotensin system, which is a tissue protective protein (Touyz et al. 2020). ACE-2 receptors are expressed in the human upper and lower respiratory tracts, small intestine, pancreas, kidneys, heart, esophagus and brain, making these organs vulnerable to viral infection.

Upon interaction of SARS CoV-2 with the ACE-2 receptor, the S protein undergoes proteolytic activation via a two-step cleavage by host cell enzymes, one for priming at S1/S2 cleavage site and second for activation at a position adjacent to a fusion peptide within the S2 subunit. S protein is cleaved by cellular proteases including transmembrane serine protease 2 (TMPRSS2), cathepsin L and Furin, leading to viral

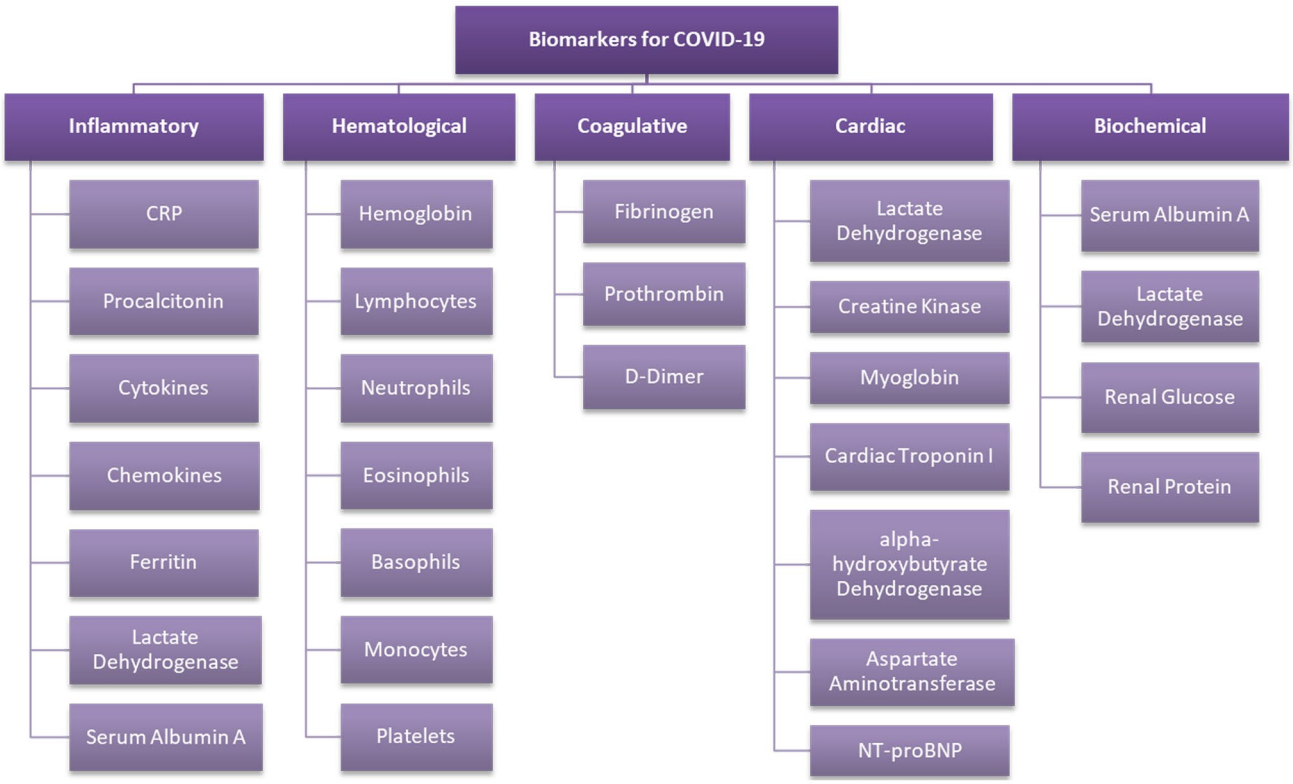

Fig. 1 Biomarkers in the diagnosis and monitoring the progress of COVID-19

entry through Clathrin facilitated endocytosis pathway (Yuki et al. 2020; Attaway et al. 2021; Shekhawat et al. 2021). The spike fusion peptide produced by the action of Furin leads to cell fusion, resulting in viral spread and persistence. Following membrane fusion, endosome having a lower pH favors the release of viral genetic material into the cytosol. SARS CoV-2 like other coronaviruses has single stranded RNA with positive polarity as its genome. Inside the host cytosol the virus undergoes replication leading to the formation of a negative strand RNA using its single strand positive RNA as a template for RNA polymerase. The freshly formed negative RNA serves as template for the synthesis of new positive RNA strands which then undergo the process of translation in the cytosol for protein synthesis. The viral N protein binds the new genomic RNA and the M protein helps integration to the cellular endoplasmic reticulum (ER). The newly formed nucleocapsids are enclosed in the ER membrane, transported to the lumen and via golgi they move to the plasma membrane followed by exocytosis. (Jiang et al. 2020). The newly formed viral elements are all set to invade neighboring epithelial cells and act as fresh infective agents for community transmission by means of respiratory droplets (Parasher 2021). This is followed by the necrosis or apoptosis of the infected cell, thus triggering an inflammatory response characterized by the production of pro-inflammatory cytokines and recruitment of macrophages and T-helper cells. This resultant exaggerated uncontrolled immune deregulation releases massive amounts of cytokines and chemokines known as the "cytokine storm" (Catanzaro et al. 2020). The latter acts as a driver for the development of systemic inflammatory response leading to Acute Respiratory Distress Syndrome (ARDS), lung and other progressing tissue damage that might lead to COVID-19 related coagulopathy, thromboinflammation and multi organ failure in critically ill patients (Masi et al. 2020). 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).

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

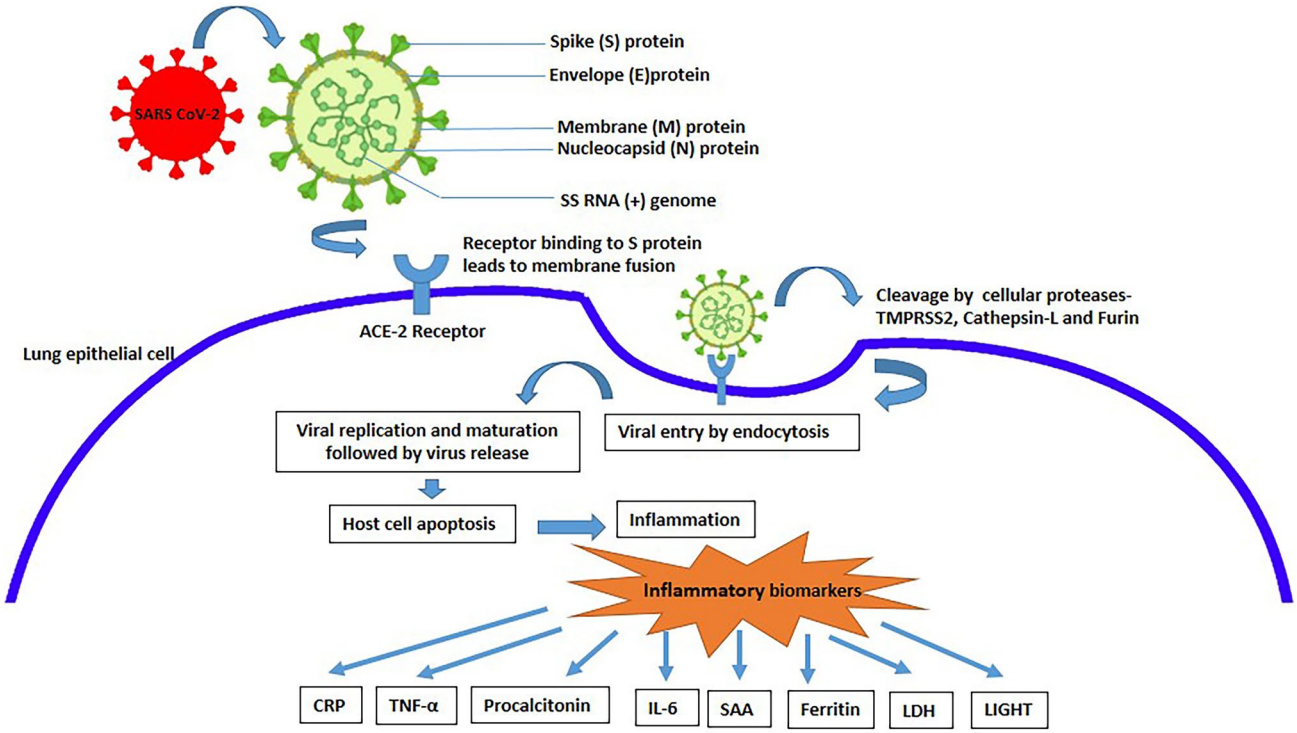

Fig. 2 Pathogenesis of COVID-19 and polypeptide inflammatory biomarkers

"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 half-life 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 COVID-19 (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 COVID-19 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 pro-protein 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 anti-calcitonin (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

Table 1 Various significant meta-analyses and systematic reviews assessing the role of polypeptide inflammatory biomarkers in COVID-19

Authors	Poly-peptide Biomarker	Number of studies included	Weighted mean difference/mean difference in serum of severe vs non-severe patients	Remarks
Zeng et al. (2020)	CRP	13	+41.78 mg/L	Patients in severe group had significantly higher serum levels of CRP, PCT, IL-6, Ferritin and SAA. Thus these can be used as biomarkers to predict disease severity
	PCT	9	+0.13 ng/ml	
	IL-6	7	+21.32 pg/ml	
	Ferritin	3	+398.80 mg/L	
	SAA	3	+43.35 mg/L	
Tian et al. (2020)	CRP	8	+66.3 mg/L	Non-survivors had higher levels of CRP and IL-6 than survivors; CRP and IL-6 along with other biomarkers could predict mortality in hospitalized patients
	IL-6	3	+4.6 ng/ml	
Kazemi et al. (2021)	CRP	38	+54.81 mg/L (Mean)	Significantly increased levels were observed in critically ill patients
Ou et al. (2020a)	CRP	24	+42.7 mg/L	Higher serum CRP and PCT levels in severe disease as compared to mild cases; can used to predict disease severity. Higher LDH are associated with disease severity and mortality
	PCT	23	0.07 ng/ml	
	LDH	17; 2	+137.4 U/L (severe); +139.3 U/L (non-survivors)	
Melo et al. (2021)	CRP	15; 14	+58.48 mg/L (fatality); +53.54 mg/L (Severity)	Higher CRP, IL-6, Ferritin, and LDH levels were observed in fatal versus non-fatal group; severe versus mild group. Thus these can be used as biomarkers for mortality and severity. For PCT higher levels were observed in fatal versus non-fatal group; only small effect size observed in severe versus mild group
	IL-6	19; 22	+70.82 pg/ml (fatality); +28.99 pg/ml (Severity)	
	Ferritin	9; 6	+853.43 ng/ml (fatality); +654.40 ng/ml (Severity)	
	LDH	10; 10	+230.99U/L (fatality); +153.58U/L (Severity)	
	PCT	11; 11	+0.24 ng/ml (fatality); +0.08 ng/ml (Severity)	
Alnor et al. (2020)	CRP	11	+49.2 mg/L	Severe disease was associated with elevated CRP and LDH levels, indicating their use as biomarkers for severity of the disease
	LDH	45	+196 U/L	
Di Minno et al. (2020)	CRP	60	Elevated levels	CRP levels were directly proportional to disease severity and mortality in meta regression analysis
Ghahramani et al. (2020)	CRP	18	+36.61 mg/L	Increase in CRP, PCT and LDH levels was observed in severe vs non-severe group
	PCT	12	+0.03 ng/ml	
	LDH	11	+102.15 U/L	
Kermali et al. (2020)	CRP	34	Significantly higher levels	CRP can be used as an indicator of disease severity
Ji et al. (2020)	CRP	34	+38.85 mg/L (severe), +74.18 mg/L (patients died)	Severe disease is associated with high CRP, PCT and IL-6 levels
	PCT	27	+0.08 ng/ml (severe vs mild); +0.26 ng/ml (non-survivors vs survivors)	
	IL-6	11	+23.87 pg/ml (severe vs mild); +59.88 pg/ml (non-survivors vs survivors)	
Huang et al. (2020c)	CRP	13	⩾10 mg/L	Higher CRP, PCT and Ferritin levels are significantly associated with composite poor outcome
	PCT	16	⩾0.5 ng/ml	
	Ferritin	10	0.90 (SMD)	

Table 1 (continued)

Authors	Poly-peptide Biomarker	Number of studies included	Weighted mean difference/mean difference in serum of severe vs non-severe patients	Remarks
Panda et al. (2021)	CRP	13	+31.45 mg/L	Severe disease is associated with high levels of CRP, PCT, Ferritin and IL-6
	PCT	8	+0.12 ng/ml	
	IL-6	9	+13.75 pg/ml	
	Ferritin	4	+425.94 ng/ml	
Hariyanto et al. (2021)	CRP	19	+36.88 mg/L	Elevated CRP, PCT and LDH levels can predict severe outcomes of COVID-19
	PCT	16	+0.07 ng/ml	
	LDH	16	+102.79 U/L	
Mahat et al. (2021)	CRP	44; 19	1.14 (severe); 1.18 (non-survivors) (SMD)	Increased serum levels of CRP, IL-6, PCT and Ferritin indicative of severe disease and mortality. Increased SAA levels indicate disease severity
	IL-6	18; 8	16.94 pg/ml (severe); 15.62 pg/ml (non-survivors)	
	PCT	30; 12	0.88 (SMD) (severe); 0.26 ng/ml (non-survivors)	
	Ferritin	9; 11	0.71 (severe); 0.95(non-survivors) (SMD)	
	SAA	9	1.16 (SMD)	
Hoang et al. (2020)	PCT	29	0.25 ng/ml (Mean)	PCT was elevated in pediatric COVID-19 patients
Cheng et al. (2020)	Ferritin	17; 18	+397.77 ng/ml (severe); +677.17 ng/ml (non-survivors)	Serum ferritin levels are higher severe versus non-severe patients; non-survivors versus survivors
Izcovich et al. (2020)	PCT	10; 28	OR = 12.42 (non- survivors); OR = 5.13 (severe)	High serum PCT, LDH, Ferritin, IL-6 and CRP levels in non-survivors; severe cases
	LDH	6; 26	OR = 4.09 (non-survivors); OR = 4.48 (severe)	
	Ferritin	4; 5	OR = 5.71 (non-survivors); OR = 3.81 (severe)	
	IL-6	4; 7	OR = 1.31 (non-survivors); OR = 7.36 (severe)	
	CRP	8; 37	OR = 6.6 (non-survivors); OR = 4.5 (severe)	
Martha et al. (2021)	LDH	21	OR = 5.33 (composite poor outcome); OR = 4.22 (non-survivor)	LDH was significantly associated with severity and mortality
Zinellu et al. (2021)	SAA	19	1.20 (SMD)	SAA concentrations were significantly higher in severe patients and non-survivors
Udomsinprasert et al. (2021)	IL-6	24(17; 7)	+18.63 pg/ml in severe patients; +57.83 pg/ml in non-survivors	Higher systemic levels of IL-6 were observed in severe as well as non-survivors; Significantly elevated levels of TNF- α were observed in non-survivors
	TNF-α	3	+5.6 pg/ml in non-survivors	
Zhang et al. (2021)	IL-6	7	+13.07 pg/ml	Significantly elevated levels were observed in severe patients compared to mild cases
	TNF-α	6	+0.34 pg/ml	
Lippi and Plebani (2020)	PCT	4	OR = 4.76	Increased PCT levels are associated with nearly fivefold risk of severe disease

Table 1 (continued)

Authors	Poly-peptide Biomarker	Number of studies included	Weighted mean difference/mean difference in serum of severe vs non-severe patients	Remarks
Akbari et al. (2020)	CRP	37	+41.07 mg/L	SAA, CRP, TNF- α, PCT, IL-6 and ferritin concentrations were significantly higher in severe patients as compared to non-severe. These could be used as biomarkers to predict disease severity
	TNF- α	17	+0.24 pg/ml	
	PCT	29	+0.07 ng/ml	
	IL-6	23	+17.79 pg/ml	
	Ferritin	8	+594.25 ug/L	
	SAA	5	+90.45 mg/L	

SMD standard mean difference, *OR* odd's ratio, *MD* mean difference

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 serum PCT values and several studies associated with COVID 19 infections of different severities have been summarized in Table 1.

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 co-infection 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 non-toxic. 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 immune-suppressive activities. The cytokine storm worsens COVID-19 in patients, and thus high levels of ferritin in the serum are correlated to disease severity (Vargas-Vargas and Cortés-Rojo 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 Cortés-Rojo 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. Few have been summarized in Table1.

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 significant 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 life-threatening 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 COVID-19 (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

Table 2 Few non-polypeptide biomarkers of 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 ($\times 10^9$/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 COVID-19, other protein biomarkers can indicate inflammation like IL-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 COVID-19 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.

Non-peptide Biomarkers of Inflammation in COVID-19

Certain biomarkers that have evolved as essential prognosticators of COVID-19 are not proteinaceous in nature. COVID-19 severity may also be indicated by biomarkers such as erythrocyte sedimentation rate, neutrophil-to-lymphocyte ratio, platelet count, lymphocyte count etc. (Kermali

et al. 2020). Some such non-peptide biomarkers have been summarized in Table 2.

Limitations

To date, for the diagnosis of SARS-CoV2 infection molecular testing identifying viral particles by RT-PCR using nasopharyngeal samples remains the gold standard. The above mentioned inflammatory polypeptide biomarkers can act as important biomarkers for predicting disease severity. An increased levels of CRP, ferritin, SAA, procalcitonin and IL-6 were frequently observed during progression from mild to severe and critical conditions as well as in non-survivors (Tjendra et al. 2020). However these biomarkers being nonspecific acute phase reactants might also predict underlying comorbid pathologies as well as other inflammatory conditions. Also several other coagulation, hematological, cardiac, renal and biochemical biomarkers are known to play essential role and are altered during the course of SARS-CoV2 infection. Thus a combined battery of several biomarkers is required for the diagnosis and predicting the severity of the disease. Serial trends of the biomarkers instead of single assessments along with clinical and radiological evaluation are considered as the best indicators while deciding treatment modalities. Routine blood tests along with CRP and LDH levels may also be used as early predictors of molecular tests as they have detection rates comparable to those of molecular tests (Ferrari et al. 2020). Several developing countries are experiencing a shortage of funds, RT-PCR reagents and specialized labs. However early recognition of severe disease is also mandatory for well-timed triage of patients. Several retrospective comparison studies between survivors and non-survivors show an upward trend of inflammatory biomarkers can serve to indicate severe disease and adverse outcomes while a downward trend can help to indicate recovery and favorable prognosis of COVID-19 patients (Chen et al. 2020c). But these tests have to be employed in conjunction with other biomarkers as well as molecular and radiological tests. The correspondence of inflammatory biomarker levels with clinical and radiological characteristics as well as viral load still needs to be ascertained in more detail. Besides, interpretation of the above mentioned inflammatory biomarkers data reviewed here has several variations in study design, inadequate sample size and absence of well-defined clinical benchmarks. Thus, assessments of levels of inflammatory biomarkers and the benefits of their monitoring along with antiviral and anti-inflammatory therapies needs to be categorically established.

Summary and Conclusions

COVID-19 harbors a heterogeneous presentation spectrum with unpredictable manifestations differing among individuals of different age, immunological state and presence of comorbidities. There is an immediate requirement of reliable biomarkers for COVID-19 for effective medical support, stratification of high risk patients and safeguarding optimum resource allocation (Tabassum et al. 2021). Biomarkers play a significant role in diagnosis, management of complications, prognosis and discharge of patients from hospital settings. Along with clinical assessment, biomarkers need to be meaningfully integrated into therapeutic decision making and clinical algorithms. The above mentioned protein biomarkers including CRP, PCT, LDH, Ferritin, SAA, TNF-α and IL-6 which are established markers of inflammation can be employed for detection and monitoring the disease course of COVID-19. A combination of biomarkers rather than a sole biomarker provides more meaningful information to the clinicians. Besides it is also vital to consider the timings of biomarker testing to extract useful information regarding a patient health status and stratify into high risk group.

Future Perspectives

Biomarkers for COVID-19 diagnosis and monitoring remains a prime area of research that might help us to overcome the pandemic along with better insights into disease pathogenesis and progression. An integrated clinical, biochemical, pathological, molecular and ultrasound approach is significant for the diagnosis, triage, monitoring and prognosis of COVID-19 patients. Panel of proteins along with other biomolecules acting as inflammatory biomarkers can certainly help in the management and control of pandemic. Future studies are warranted to decipher novel biomarkers and to study the role of existing ones in the disease progression.

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Declarations

Conflict of interest All authors declare absence of any commercial relationships that could emerge as a potential conflict of interest.

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