ejpmr, 2021,8(8), 197-203.

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A GLIMPSE OF THE INFLAMMATORY BIOMARKERS OF COVID-19

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Article Received on 28/05/2021 **Article Revised on 18/06/2021** **Article Accepted on 08/07/2021**

ABSTRACT

Coronavirus disease 2019 is a clinical syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Patients can be asymptomatic or present respiratory and gastrointestinal symptoms, and those with multiple-organ failure which can lead to death. A life-threatening hyperinflammatory syndrome occurs after primary SARS-CoV-2 infection. Inflammation markers can appear elevated in infected individuals with SARS-CoV-2. Several research studies throughout the world suggested that the magnitude of the elevation of IL-6, CRP, PCT, HLA, Ferritin, D dimer, IL-6 and many others may relate to the severity of the resulting COVID-19. Monitoring levels of inflammatory markers may help identify progression to severity of the disease. Total lymphocyte count and levels of CD3+ and CD4+ T cells were decreased in severe and critical cases. The patients with acute respiratory distress syndrome expressed an elevated level of neutrophiles. Interleukin-6 was high in mild and severe patients. The D-dimer level was high in diabetic patients and patients who developed ARDS. Procalcitonin levels were elevated to varying degrees in severe and critical patients. Evidence shows that severe COVID-19 cases exhibit features of systemic inflammatory reactions, including hyperferritinemia. The severe patients had higher levels of serum ferritin than the nonsevere patients. The levels of serum ferritin positively correlate with levels of CRP. Azurophilic granules and similar molecules are elevated in the blood as they are liberated into the circulation. The elevated calprotectin level indicates the probability of the gastrointestinal involvement as a result of the COVID-19 disease.

KEYWORDS: COVID-19, Inflammation, IL-6, IFN, HLA, TNF, D-dimer, PCT, Ferritin.

INTRODUCTION

The biomarkers or biological markers or molecular markers, also called signature molecules are measurable indicators of severity or presence of some disease, levels of which are objectively measured, analysed and evaluated during normal physiological processes, pathophysiological processes or when any pharmacological drugs are administered to evaluate how accurately the body responds to it indicating biochemical or physiological interactions at the cellular or molecular level.[1] In the context of SARS-CoV-2 infection, the common biomarkers are CRP, serum ferritin, serum creatinine, ALT, AST, cardiac troponin-I, IL-6, neutrophils, platelets which can be categorized into haematological, inflammatory, cardiac, metabolic, renal and other parameters.[2] Like any other biomarkers, those of the COVID-19 disease must be rechecked and re-evaluated to clearly understand the prognosis of the disease.

Inflammatory Biomarkers

Interleukin-6

The cytokine storm is considered to be a vivid manifestation of COVID-19 disease which is intimately related with increased production of IL-6 whose increased release leads to the severity of the infection. The respiratory system -which is one of the most affected physiological system, often used by the virus as an invasive means, gets deteriorated sometimes solely due to the action of IL-6 causing respiratory distress and damage to the lungs.[3] The release of cytokines is always due to immune-mediated negatively feedbacked inflammatory responses and the increased effects of IL-6 produced by T-lymphocytes and macrophage activation are more pronounced than any other biomarkers in patients of SARS-CoV-2 infection and bilateral pneumonia. The IL-6 levels vary according to the stage of the coronavirus infection, i.e. the level of IL6 in Stage 1 is significantly lower than that of Stage 3 but this does not hold good when hypoxemia occurs during the infection, a condition expressed by fall in levels of IL-6. The value of IL-6 increases and reaches a peak during the initial infection, which does not last long and this biomarker is very useful in differentiating between the groups of survivors (lower IL-6 levels than non-survivors) and non-survivors[4] but the levels of IL-6 are more in severe cases than non-severe cases. IL-6 is produced by T & B lymphocytes, as part of defensive modulatory processes, where innate immune system is the first line of defence. The IL-6 along with other

cytokinesis help migrate immune cells to the place of viral infection, for instance, the damaged lung tissue from the circulation.[5] IL-6 acts through a signalling cascade pathway blockage of which may result in reduction of the fatality of cytokinesis storm. IL-6 is known to exert its effect through CD 4 & CD 8 T cells differentiation and consequent cytotoxic impact on the virus. Thus, the medications and therapies against IL6 hampers the preventive measures against viral replication.[6] However, CAR T cells can now respond to such blockades as a positive outcome. The increase in IL 6 in case of COVID-19 disease is sometimes more than 1000 times the normal and may even rise beyond hyper-IL6 syndrome cases.[7] The analysis of IL6 should be performed in combination with other biomarkers like CRP, albumin, etc. and IL 6 is regarded as the indicator of the acute phase.[8] The use of antagonists of IL-6 receptors are thought to be fruitful in addition to basal glucocorticoid treatment and these reduced activities of IL-6 may cause marked improvement in those patients who have survived the ill-effects of COVID-19.[9] IL 6 associated with severity and mortality of the COVID-19 infection serves as a protection against acute lung injury and triggers release of other pro-inflammatory cytokines.[10]

C-Reactive Protein (CRP)

The CRP is found to be elevated during the beginning of the onset of SARS-CoV-2 infection[11] and is thought to be upregulated during various instances of the severe acute respiratory syndrome. The study of CRP level can be utilised as a confirmatory test for the detection of the most acute stage when the rate of phagocytosis is increased and complement system is activated to do away with the pathogenic virus as is evident by its increased levels causing malfunction of various organs. Thus, an increase in levels of this protein can be accounted for by pulmonary injury, cardiac damage and renal damage.[12] The titre of CRP was high in those patients with increased severity of the disease as compared to the moderate or milder cases. The level of CRP can be used to infer the extent of inflammation as a result of COVID-19 infection and can be considered in one of those biomarkers, which are used to assess as to what the upcoming pathway of the disease be improving or deleterious and /or whether any chances of mortality exist.[13] Although the CRP level must be used in combination with other test reported values in order to ensure proper decisions, one can rely only on the CRP values in order to deduce what the next turn of the disease might be; thus, making this biomarker a unique one, since other immune-related pathological tests are time-consuming so far reporting is concerned. This early diagnosis plays a vital role since it may act as a preventive measure against life-threatening issues like respiratory failure.[14] CRP gets elevated in the majority of the patients who are suffering a COVID-19 attack but restoration to normal occurs, if any, within a short span of time after which other parameters continue to remain elevated, thus indicating a more conspicuous role of CRP in analysing the progression route of the infection first, and then the severity of the infection.[15] The study of CRP quantity in patients suffering from COVID-19-induced pneumonia, is quite useful as CRP levels are distinctively too high in patients suffering from a moderate-to-severe pneumonia than patients who have a milder stage of infection and the extremely high CRP levels are hand -in-hand with the poor lung test reports which is evident from chest CT analysis.[16] The patients who have been affected by the SARS-CoV-2 virus severely has increased CRP accompanied by elevated serum albumin level, giving rise to a high CRP: Albumin ratio which is helpful in detecting the mortality and malignancy during the infection, thus throwing some light on the adverse aspect though CRP alone is good enough to indicate inflammation, infection and any damage to the tissues leading to mortality.[8] The CRP reports, if studied in hospitalized COVID-19 affected patients, may assist the professionals to understand the risk factors and stage of the infection. Instead of the rate of change of CRP levels, the peak value of CRP which is observed within seven days of hospitalization may suggest the likeliness of an ICU admission, extent of systemic inflammation and worsening parameter of the disease. The low cost of CRP test is another advantage in de-escalating the seriousness and prognosis of the disease.[17]

Procalcitonin

Procalcitonin is a precursor of glycoprotein hormone calcitonin, secreted by para follicular cells of the thyroid gland; can be considered a potent biomarker during the COVID -19 disease which can be utilised to categorize patients into groups of high and low risk and evaluate the consequences of the risk involved. During the COVID-19 infection, the serum PCT level is markedly increased as it is the “endotoxin” category of molecules which triggers all parenchymal cells of the body to produce PCT. However, whether PCT can be tagged as effective analytic tool for COVID -19 is still debatable due to the preconceived notion that ‘PCT is a biomarker of bacterial infection'. In severely affected COVID-19 patients, PCT levels can rise as much as five times the normal and any such rise is symbolising critical stage of SARS-CoV-2 infection. The measurement of PCT might show a fall in severe infection owing to its inhibition caused by elevated levels of gamma-interferon but no role of PCT in prediction of mortality is reported yet.[18] PCT is a commonly used biomarker previously known in analysing bacterial infection accompanied by sepsis and septic shock due to the virtue of which PCT can assist in recognising those patients who are at a lower risk of developing bacterial infection during the COVID-19 infection which may even be fatal. The low PCT values show that there is no manifestation of bacterial infection and no administration of antibiotic medication is required and on the other hand increased PCT levels is used to analyse the risk of bacterial infection and consequent downfall of health involved during SARS-CoV-2 attack ---a condition that demands antibiotics, failure of which

may even cause death. PCT is also a parameter that can differentiate between pneumonia caused by bacteria which is severe; and that caused by virus, which is milder.[20] A common feature during COVID-19 is hypoxia which when aggravated, may require varied degrees of ventilation (mechanical ventilation, extra-corporeal membrane ventilation, for instance) which might lead to ventilator-associated pneumonia (VAP) that can be diagnosed using PCT levels much before the critical stages, this enabling cure.[20] Sometimes, bacterial influence may add to the severity of the SARS-CoV-2 infection by worsening the lower respiratory tract infection which can be assessed by the PCT reports and approached accordingly in the context of antibiotic administration. Patients suffering from COVID-19 with no secondary infectious manifestations have otherwise normal PCT levels.[21]

C3, C4, C5 – Components of Complement Pathway

The natural immunity is in-built and mediated through different mechanisms, like complement-cascade pathway of which C4a-C4b heterodimer is a subset which helps in fighting infections caused by virus. Any alterations in the structure of C4a, which is reported in schizophrenic patients, leads to changes in the expression of C4a ultimately impairing the synaptic pruning process. The adoption of secondary complement pathways, classical pathways or lectin signifies the severity of COVID-19 disease which may prevail in addition to vascular diseases like thrombosis and any inhibitor of C5 can be an effective therapy for COVID-19, which blocks the terminal products but not the CE inhibitors which eventually blocks all the complement activation pathways. The components of the complement pathway which include C3, C4, mannose-binding lectin (a C-type lectin) and terminal membrane attack complex pathways are present in excessive quantities during the COVID-19 infection as is evident from the staining techniques. The T cell response and humoral immune response are increased with the involvement of active components like C3a, C4a, C3b & C4b which leads to phagocytosis and lysis of cells using marked antigens (opsonization).[22] The tendency of immune-related complement pathways to be activated undergoes another inhibition and consequently reduced inflammation due to the use of CR1 or similar molecules (receptor of C3b/C4b) which are used as medications. The concentration of the CR1 receptor molecules on the membranes of the erythrocytes decrease while C4d gets deposited within the erythrocytes and blood capillaries of organs with the seriousness, aggravation and even death due to the disease.[23] The activation of complement pathway utilises convertase enzyme and breaks down large glycoprotein molecules like C3, C4 and C5 into smaller polypeptides which are related to altered genetic expression (pleiotropic defects) in processes like immune-mediation, programmed cell death (apoptosis), lipid metabolism and fibrosis.

Human Leucocyte Antigen (HLA)

One of the components of the immunological system is Class II Histocompatibility Antigens which is a subdivision of Human Leukocyte Antigen (HLA) system and DQ in it indicates an alpha or beta chain protein coded for by the specific HLA-DQ genes.

The risk of developing SARS-CoV-2 infection depends on which combination of HLA genes and what varieties of T cells are present, that is a certain type-specific ratio of the HLA genes to T cells makes an individual more prone to the COVID-19 infection while the other ratios may even serve as an over-protective role with respect to the disease manifestation. In patients suffering from the viral infection, one-tenth reports increase in both HLA I and HLA II. The patients who have higher percentage of alleles for HLA II are mostly females and are at a greater risk for hospitalization, while those having alleles for HLA II are mostly of the age group of below 65 years and those more than 65 years are at a greater risk of ICU admission. Hence, HLA is a significant biomarker that can be used to monitor the onset and severity of the infection.[24] In severely affected SARS-CoV-2 patients, genes for molecules like HLA-DRB5 and HLA-DQA2 are easily stimulated by the interferons, which in turn, have increased expression due to Antigen-Presenting cells (APCs), a process that indicates a reduction in antigen-presentation sequence.[25] The molecules of class II HLA proteins are thought to be inhibited in severely affected COVID-19 patients who are on ventilatory support which is why this virus can impair the process of inflammatory response regulation. HLA-DQA2 may even function in presenting the antigens to the T lymphocytes and differentiate between the self and foreign components, failure of which could have otherwise led to the development of autoimmune disorders.[26] HLA classes which are accompanied by other chains which include DR beta1 & DQ beta 1 might possibly play a role in serving as a drug-target during COVID-19 infection as is evident from the regulatory effects of the genes; thus increasing its concentration as a biomarker.[27]

Azurophilic Granules & Other Immune-related Proteins

As a part of the innate immunity, neutrophils release viral lytic enzymes and other toxins reserved in their granules which will lead to phagocytosis of the virus or any microbial cell and their subsequent degradation by the virtue of azurophilic granules but this process is impaired and turns futile as all these activities are negatively influenced by the inflammation (which is bound to occur as a manifestation of COVID-19) – thus disrupting the immune-response process. Out of the above mentioned azurophilic proteins, MPO has a function of employing greater number of neutrophils at the infectious site, vasoconstriction, oxidative stress, cell death, PRTN3 acts in increasing cell divisional process of granulocytes, CTSG is associated with maintenance of tissue protection, ELANE aims at activating the spike

proteins thus making the viral entry comparably difficult. Hence, all of these work in a synchrony to compensate the immune-compromised situation during the COVID-19 disease.[28] In addition to these proteins, the neutrophil cells can be fragmented into pieces during the COVID-19 disease by utilizing the matrix metalloproteinase-9 (MMP-9). The biomarkers found more commonly in tracheal extract, bronchiolar tissue and bronchoalveolar lavage fluid (BALF) samples as compared to plasma. The elevation of all these protein markers increase the likeliness of ICU requirement.[29]

Tumour Necrosis Factors (TNF) and Interferons (IFN)

Among all the pro-inflammatory cytokines produced during the passage of SARS-CoV-2 infection, TNF-alpha and IFN-gamma are found to perform a hand-in-hand action to cause death of inflammatory cells. This increased rate of programmed cell death caused by a TNF-alpha/IFN-gamma combo becomes effective with the help of different pathways in COVID-affected patients. For instance, pyroptosis is one such process where the cellular membranes become porous when Gasdermin D (GSDMD) gets fragmented, whose otherwise normal function is to release an active portion of P30 with the help of caspase-1 and/or inhibition of caspase-11. Again, the TNF-alpha/ IFN-gamma combo, when stimulated by Bone marrow-derived macrophage exhibits a massive scale in disintegration of GSDME, another pyroptotic agents. Another similar fragment called P20 is occasionally produced when caspase 3 gets stimulated subsequently inhibiting GSDMD. The alternately adopted path can be necroptosis in which MLKL gets phosphorylated leading to lesser activation of protein kinases namely, RIPK3 and RIPK1, which are regulators of apoptotic and necroptotic pathways. Lastly PANoptosis, is caused by this same combination, which requires NO and caspase 8 /FADD complex and activation of JAK-STAT1- IRF1 axis.[30] Now assessment of the concentration of TNF-alpha within the serum, without any other biomarkers, can alone dictate the understanding of severity of SARS-CoV-2 infection and the possibility of death. During the COVID-19 infection, out of all the biomarkers, TNF-alpha is one the most-altered parameters after IL-6 and IL-8. The degree to which TNF-alpha would get affected in a patient depends on the racial differences and whether he or she is a smoker. Patients who have developed chronic kidney disease (CKD), diabetic hypertension, or congestive heart failure as a manifestation of COVID-19 disease, have markedly elevated levels of TNF-alpha, though, of these, CKD is the manifested condition which affects TNF-alpha levels the most. Patients who suffer from associated respiratory failure and systemic inflammation during the infection, if treated with, any anti-IL-6 antibody, then levels of TNF-alpha eventually decline and sustain long but elevation in IL-6 occurs which is short-lived. The increase in concentration of TNF-alpha along with CXCL8/IL-8, IL6 and IL-1beta may be accounted for by the involvement of these biomarkers in employing a greater number of neutrophils as a remedy against inflammation and organ damage. In highly severe cases when other combinations or independent use of biomarkers fail in detecting the stage of infection or degree of comorbidities, TNF-alpha and IL-6 are the two exclusives those can be relied upon.[31] The levels of TNF-alpha are found to be greater in groups of ICU-admitted and severe patients than non-ICU and non-severe ones. The serum levels of IFN-gamma increase to a large extent when lungs are affected severely while IL-6 rise if pulmonary neutrophilic infiltration is persistent. If chloroquine and hydroxychloroquine are administered during COVID-19 infection, then TNF-alpha, IFN-gamma, IL- 2/6/18, CCL2, CXCL 10, cytotoxic C cells and other chemokines get inhibited while expression of INF-alpha increases, thus conferring protection.[32] To combat viral infections, IFN I, II and III are required as a part of innate immunity while IFN I and III are required after the infection has occurred, and IFN- gamma triggers CD 8-T to initiate cytotoxic processes. TNF-alpha increases the production of some soluble factors which are obtained from macrophages which deal with the lung epithelial cells and mucosal tissue, all these cause the cytokine storm to occur more effectively at a larger level.[33] If diabetes co-exists in a COVID-19 patient as an extension of pre-viral attack condition or caused due to the infection, then the level of TNF-alpha and IFN- gamma increase prominently in those patients as compared to those who do not suffer from diabetes. This is immensely useful in suspecting the chances chronic inflammation which results more in type 2 diabetes mellitus depending on insulin-sensitivity.[34] Thus, any significant increase in concentration of all these above mentioned inflammatory and associated molecules can be considered to be a deviation of the biomarker from the disease-free conditions and can be used to detect any deteriorating changes early.

Ferritin

The immuno-regulatory mechanisms are an integral part during the COVID-19 infection and this phase is characterized by increased levels of ferritin mostly in previously-affected diabetes mellitus patients. This is because ferritin is capable of implementing the required compensatory immunological effects, hence, ferritin has an important role in affecting the prognosis of the disease. In the hospital- admitted COVID-19 patients, the ferritin concentration increases beyond normal from the sixteenth day of admission and continue to increase if the infection worsens.[35] In addition to these, H chain of ferritin has important roles in macrophage and other immune cell-activation processes during the cytokinesis storm.[36] The increase in ferritin concentration may initiate programmed cell death (ferroptosis), a major reason that leads to respiratory distress syndrome. Whatsoever the cause may be, significant increase in the levels can tag ferritin as a biomarker of the SARS-CoV-2 infection.[37] The patients of COVID-19 who are administered with Vitamin C (ICU patients) and dexamethasone (patients on ventilatory support) may

recover, but too high ferritin levels may indicate a bacterial infectious manifestation along with the SARS-CoV-2 infection.[38] If COVID-19 disease is present in the company of diabetes mellitus, heart failure, coronary heart disease, hypertension and dyspnoea, then ferritin itself can serve as the most effective biomarker in monitoring disease severity.[39] One can rely more upon ferritin to discriminate between the novelty of the risk factors involved, suspect probability of death and differentiate between the various causes of death, instead of analysing the severity of the disease.[40]

D-dimer

The D-dimer concentration is increased in hospitalized COVID-19 patients which serves as a significant indicator to severity, prognosis and mortality for patients with COVID-19. The infected patients who have normal D-dimer values, mostly survive and recover while patients with higher than normal D-dimer values are prone to death. However, patients whose D-dimer level is normal at the time of admission may also have increased D-dimer values if the COVID-19 infection intensifies. The increased level of D-dimer is co-existent with an increase in fibrinolysin content suggesting an immunomodulatory load during the cytokine storm of COVID-19.[41] The D-dimer levels are increased till four months after the confirmation of presence of SARS-CoV-2 infection, but during the healing phase which awaits a complete restoration to the disease-free condition, D-dimer level may shoot up to greater than twice the normal threshold maxima. The patients who suffered from chronic acquired pneumonia only are found to exhibit higher levels of high sensitivity CRP and lower levels of D-dimer which is just the opposite in case of COVID-19 infection, so any change in D-dimeric values is the determining factor of disease profession in case of COVID-19 disease.[42] The results of D-dimer reports can distinguish between the groups of COVID-19 patients suffering from pulmonary embolism and those who lack such condition.

Calprotectin

Calprotectin is a protein released by a type of white blood cell called a neutrophil. When there is inflammation in the gastrointestinal (GI) tract, neutrophils move to the area and release calprotectin, resulting in an increased level in the stool. Calprotectin is highly expressed in pulmonary tissue of COVID-19 affected patients forming a heterodimer complex found dominantly in the neutrophilic cytoplasm and monocytic cellular membrane. The concentration of this protein in the serum is elevated in response to the COVID-19 infection-induced inflammation. The calprotectin levels rise in the faeces during COVID-19 infection which suggests inflammation of the intestine.[43] Since the effect of neutrophilic calprotectin predominates over that of monocytic calprotectin, the net effective plasma reading rises as a result of SARS-CoV-2 infection. If patients on ventilatory support are classified as deteriorating, constant and improving, then calprotectin levels are higher in the first group while the last two groups exhibit no alterations. This biomarker is also a scale which one can stick to for assessing the risk of seriousness of the disease.[44] The analysis of faecal calprotectin is another avenue for early detection of the COVID-19 disease in those patients who suffers from gastrointestinal complications in addition to the SARS-CoV-2 infection.[45] A patient who has manifested ulcerative colitis and Crohn's disease may also have increased levels of calprotectin in addition to bowel disease.[46]

CONCLUSION

The concentration of biomarkers gets elevated or reduced in comparison to the normal conditions which denote the likeliness or sometimes even confirm the presence of the disease. IL-6 and CRP are those biomarkers which are used in initiating immune responses during autoimmune and immunological consequences. These infer the seriousness of the subsequent conditions of the disease which is helpful for designing treatment strategies. The prevalence of increased procalcitonin levels can decide if bacterial infections coexist with the SARSCoV-2 infections. The components of complement pathway (C3, C4, C5) along with human leukocyte antigen triggers the classical and complement pathways through cell mediated and humoral immune processes as and when required. Azurophilic granules and similar molecules which are supposed to be intracellular parts of the normal physiological systems, get elevated in the blood as they are liberated into the circulation as an important symptom of this infection. The different ways by which the body wants to do away with the infection include programmed cell death processes which is brought about by the coordinated action of TNF alpha and interferons. The deviation in ferritin concentration has also been observed though it is not a promising test for the COVID-19 diagnosis. D dimer, as a biomarker, rises and suggests the relative chances between recovery and worsening of the disease. The calprotectin titre increases in the ECF and can indicate the probability of the gastrointestinal involvement as a result of the COVID-19 disease. These inflammatory biomarkers can provide an idea of the severity of the disease and monitor the disease prognosis. Sometimes these are also studied to understand if the disease is present at all and hence act as predictors. Hence biomarkers are immensely significant as these may allow early diagnosis and treatment plans for a patient which otherwise would cause unnecessary deterioration of the health conditions.

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