Review Study of Interleukin-6 and its Association with Coronavirus

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Abstract:

Backgrounds: Coronaviruses are a wide family of viruses that can infect birds and mammals, including humans, according to the World Health Organization**.** Corona viruses can cause severe inflammation of the lungs and damage the digestive tract and nervous system. Cytokines have been found that play major role in driving presence of these clinical features and are also at the center of the development of inflammation. Inflammatory cytokine storm coupled with an inflammatory cytokine storm characterized primarily by increased levels of IL-6.

الخلاصة:تعتبر فيروسات كورونا عائلة واسعة من الفيروسات التي يمكن أن تصيب الطيور والثدييات ، بما في ذلك البشر ، ووفقًا لمنظمة الصحة العالمية يمكن أن تسبب فيروسات كورونا التهابًا حادًا في الرئتين وتلف الجهاز الهضمي والجهاز العصبي.وقد تم العثور على ان السيتوكينات تلعب دورًا رئيسيًا في زيادة وجود هذه المظاهر السريرية وتعتبر أيضًا في مركز تطور الالتهاب. تتميز العاصفة الالتهابية القاتلة للخلايا المقترنة بعاصفة السيتوكينات الالتهابية في المقام الأول بزيادة مستويات الانترلوكين-6.

الهدف من ألدراسة : كان الغرض من هذه الدراسة هو مراجعة البيانات عن السيتوكينات التي تؤثرعلى تطورCOVID-19.

الاستنتاجات : تقدم هذه الدراسة رؤى ودراسة بحثية جديدة وتظهر أن المستوى المرتفع منIL-6 من المحتمل أن يكون عامل خطر كبير للوفيات داخل المستشفى للمرضى المصابين بـCOVID-19. كما تقدم هذه الدراسة أيضًا رؤى جديدة توجه التدخل العلاجي المبكر للمرضى المصابين بـCovid-19،مثل التدخلات الغذائية والأدوية التي تحتوي على مثبطات لمستقبلات الانترلوكين-6.مهمة جدًا لعلاج مرضى كوفيد -19.

Aim of The Study*:* The purpose of this study was to review data on cytokines influencing the progression of COVID-19.

Key Words:COVID-19, interlukin-6 IL-6, Cytokines

1.Introduction:

Coronaviruses are a wide family of viruses that can infect birds and mammals, including humans, according to the World Health Organization. At the end of 2019 in

the Chinese city of Wuhan, a new coronavirus, named 2019-nCoV, appeared [1]. Within two months, the disease had spread rapidly across the world, and in March 2020, a global pandemic was declared very dramatically. On 9 April, 1,436,198 cases were confirmed with a worldwide COVID-19 rate of almost 6% death. This recent infectious infection triggers respiratory disease that is normally mild or pneumonic in the upper respiratory tract [2].

Human corona viruses (HCoVs) constitute a very large group of corona viruses associated with many respiratory diseases of varying gravity, including the common cold, pneumonia and bronchiolitis [3]. Their genomes range from 26 to 32 kb base, and it is the largest known viral genome for viral RNA, and includes single coated, unfragmented, positive-sense RNA genomes [1,4,5].Corona viruses can cause severe inflammation of the lungs and damage the digestive tract and nervous system [6].Next the first cases in China of serious coronavirus 2 respiratory syndrome, the increase of hyper inflammatory syndrome similar in patients with either a macrophage-activation or cytokine-release syndrome combined with chimeric antigen receptor T-cell therapy was demonstrated in patients with extreme signs of the COVID-19 disease[7].

2.Corona Virus 2 Respiratory Syndrome and Cytokines:

Instantaneous immune response to infection by viruses , bacteria or other micro-organisms includes the mobilization of cells and molecules and the use of energy, enzymes and biosynthetic resources, i.e. metabolic resources[8].A host metabolism reprogramming is required to produce effective antiviral defence, in the case of metabolic disorders caused by viral infection. Data reported on interferences between virus and cytokine activity indicate the molecular mechanisms behind the inherent immune response to viral infections [9,10].Over 212 countries have been affected by SARS-CoV-2since about 25 May 2020.About 5,529,195 cases have been confirmed worldwide, 347,192 of them dead. Cytokine storm" is believed to be the cause for these deaths, also called “cytokine storm syndrome” (CSS) [11]."Cytokine storm syndrome" is a diverse range of

disorders associated with a clinically consistent phenotype of systemic inflammations, inter-organ dysfunction, hyperferritinemia, and, if left untreated, often death.[12]

Cytokines have been found that play major role in driving presence of these clinical features and are also at the center of the development of inflammation[13]. Inflammatory cytokine storm coupled with an inflammatory cytokine storm characterized primarily by increased levels of IL-6.

Interleukinin-6 is produced via almost all stromal and immune systems, like B, T, lymphocytes, macrophages, dendritic, monocyte and several othernon-lymphocytes like fibroblasts and endothelial cells.[14].IL-6 is a thin, four α-helices polypeptide. The IL-6 gene encoding is found on the chromosome 7p15-21, which includes four introns and five exponents [15]. It comprises 184 amino acid residues with isoelectrical point 5.0, glycosylation sites and two monomeric disulfide bonds[16].

3.Interleukin's -6 function in COVID-19 pathology:

Interleukin 1beta & tumor necrosis factor (TNF-alpha) are the key activators of Interleukin-6 (IL-6) expression, but several other variables can such as Toll-like receptors (TLRs), stress response, adipokines, prostaglandins, and other cytokines may contribute to its secretion [17]. Inter leukin-6 has a broad impact on immune system cells and non immune system cells , and also exhibits hormonelike features that influencehomeostatic processes. Interleukin6 has pro and antiinflammatory characteristics that are contextdependent andisnow considered a popular option for clinical intervention .IL-6 is responsible for the increases in acute phase reactant, such as C-reactive protein, serum amyloid A, hepcidin, and fibrinogen, and inhibition of synthesis of albumin [18].

Interlukin-6, achemokine, is an important markers of inflammation and has been shown in studies as an important predictor of intense COVID-19 [19, 20].The key point in infection with SARS-CoV-2 is the degradation of antiviral defenses

linked to innate immune response and the enhanced expression of inflammatory cytokines[21].

In the form of cytokine storm, IL-6 is one of the major proinflammatory factors, which significantly enhances vascular permeability and impairs organ function. [22]. Many COVID-19 patients undergo a fulminant and detrimental cytokine immune reaction that results in macrophages and monocytes infiltration in the alveolar environment [23].

SARS-CoV-2 predominantly reaches the human body through the nose, eyes, Via attachment to its receptors (ACE2, CD147, DC-SIGN, L-SIGN), it enters the host cell (primarily alveolar type 2 cells) and triggers inflammatory and antiviral responses through the synthesis and secretion of cytokines and inflammatory cytokines, such as IL-6. Often, a cytokine storm, ARDS, and multi-organ failure or even death may result from dysregulated inflammatory responses. It may be possible, on the other hand, 2 SARS-CoV-2,; One RNA strain, ss RNA ACE2; DC-SIGN; Angiotomin Converting Enzyme, 2 Dendritic Cell Converting Enzyme; Extreme acute respiratory reactant coronavirus Intercellular adhesion molecule-3-integrin seizure; Graphic-like receptors, TLR RIG-I; First gene triggering retinoic acid, MAVS; Antiviral mitochondrial signals Protein, MDA-5; Melanoma 5 differentiation-associated protein, NF-B; Kappa-light-chain enhanced nuclear agent for activated B-cells, PAF; Platelet activating factor, Lt; Leuka-5 differentiation-associated protein, NF-B. It is evident from the above-mentioned observations that IL-6 plays an important role in viral respiratory diseases such as CoVs or influenza and it can be identified as a useful biomarker for diagnosis and an effective the therapeutic target for the treatment of viral infections of these types (Fig .1.) [24]..

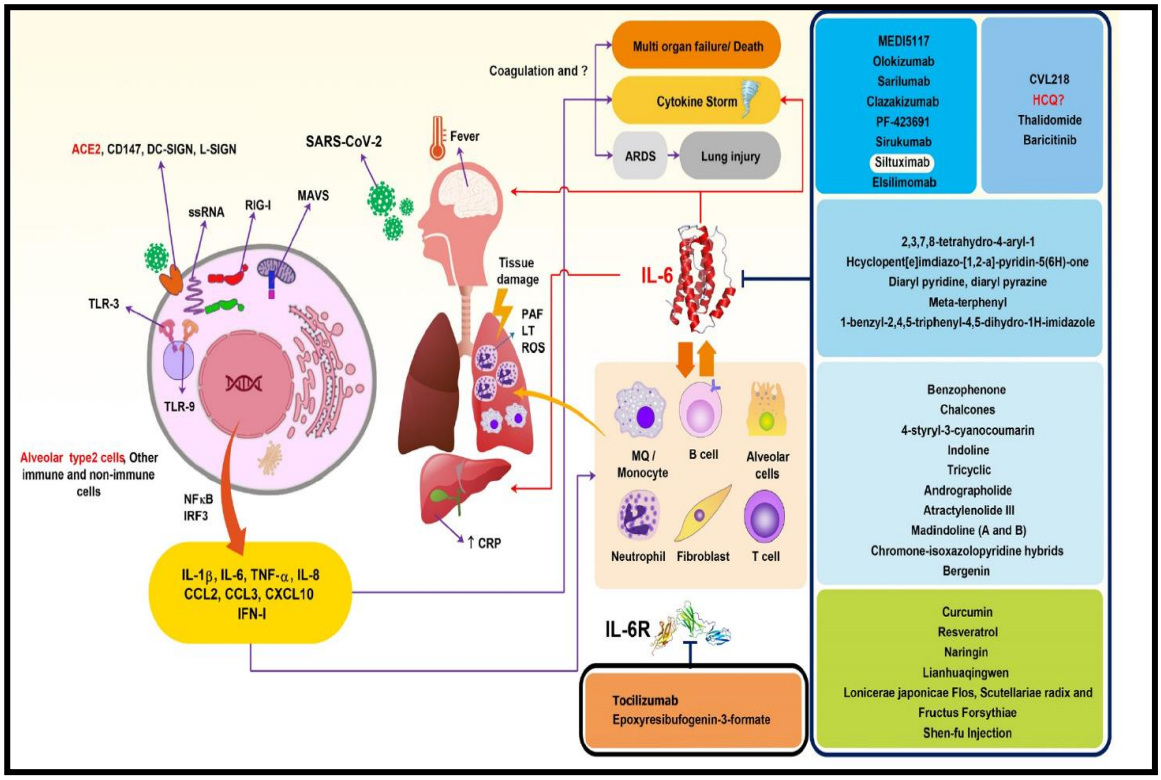

Fig 1.Role of IL-6 in the pathogenesis of COVID-19 and possible therapeutic approaches[24].

According to the various types of corona virus, IL-6 levels were found to increase in SARS cases and linked to the severity of symptoms [25,26] and in SARS-CoV, being implicated in possible T-cell dysfunctionality.

Wan *et al*. found that in one-third of moderately symptomatic and three-quarters of seriously symptomatic patients, IL-6- were increased, concluding that IL-6 may have a predictive value in COVID-19 patients[27].In patients killed with COVID-19, the levels of IL-6 were also substantially higher than those recovered.[28].

Inflammatory reaction, respiratorial failure, need for mechanical ventilation, appear to be correlated with IL-6. In order to understand the progression of COVID-19 and the reaction to therapy, complex observation of IL-6 is helpful[29].

Elevated of interleukin-6 was detected in the acute stage associated with lung lesions in patients of SARS-CoV-1. In particular IL-6 can stimulate the hyper-innate inflammatory response due to the SARS-CoV-1 invasion of the respiratory tract [30].

The increase of IL-6 levels in SARS-CoV-1 was also extreme as a result of serious inflammation in mice[31,32]. This occurs in the case of SARS-CoV-2 in COVID-19. Higher IL 6 and C-reactive protein have been shown to be correlated with mortality and serious disorder in contrast to mild disease by some meta-analyzes and retrospective studies[33]. A lot of evidence indicates, that critically ill groups have a macrophage activation Syndrome or an immune deficiency in patients with acute respiratory failure and SARS CoV-2 as both are taken into consideration. Inflammatory cytokines are characteristic the IL-6, not the interleukin-1beta (IL1beta), thus regulates the immune dysregulation.

Further, earlier studies have shown the main characteristics of such immune dysregulation are: overproduction of pro-inflammatory cytokines by monocytes and lymphocyte dysregulation with CD4 lymphopenia [34].

Related research demonstrates how Interleukin-6 actinga significant role in acute lung injury, evidence of that was observed in a murine model, where interleukin-6 loss indicated to reduce the severity of acute lung injury in response to acid respiration. Furthermore, it was demonstrated that SARS-CoV-1 has the capability of stimulate generation of compounds same oxidized phospholipid both in animals and humans. oxidized phospholipid in turn induce cytokine production and acute lung injury by Toll-Like Receptor 4 (TLR4) [35].This is proof of the capacity of SARS-CoV-1 to cause acute lung injury indirectly, and cytokine synthesis, such as that of interlukin-6 [36].

4.Conclusion:

In conclusion, IL-6 levels tend to be a strong indication of the progression of the typical endpoint towards serious illness and/or hospital mortality when hospitalized by a group of patients with COVID-19 illness and tend the best indication of negative results. Our study therefore supports the assumption that a cytokine storm aimed at SARS-CoV-2 with anti-drug and dietary interference from

IL-6, along with supportive treatment strategies, may provide a viable therapeutic alternative for improving outcomes for COVID-19.

Conclusions::This study provides insights and a new research study that shows that an elevated level of IL-6 is likely to be a very risk factor for in-hospital deaths for patients with COVID-19. This study also provides new insights that direct the early therapeutic intervention for patients with Covid-19, such as dietary interventions and drugs containing The IL-6 receptor blockers are very important for treating covid-19 patients

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