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Prognostic Values of Interleukin-6, C-Reactive Protein and Procalcitonin in COVID-19 Patients

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ABSTRACT

Coronavirus disease 2019 Or Covid 19 is an infection which is caused due to severe acute respiratory syndrome Coronavirus 2 is an ongoing pandemic in our world. A study was undertaken which revealed that pro calcitonin levels were elevated in patients who were suffering from moderate to severe coronavirus disease or acute respiratory distress due to the coronavirus. These levels decreased and gradually returned to normal with recovery as seen in discharged patients. But these levels rocketed in patients who had succumbed to this disease. Thus, we could predict that Procalcitonin levels could be used to grade the severity of COVID-19 pandemic.

Hence this disease which was earlier thought to be a pure respiratory illness has been associated with multisystem organ dysfunction and heterogenous illness. Covid 19 affected patients can present with variable number of symptoms and can present with either and hyper inflammatory state or an endothelium dysfunction or maybe a thromboembolic phenomenon.

C-Reactive protein and interleukin six also been elevated along with pro calcitonin levels in the hyperinflammatory stage of this disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first isolated in Wuhan from people with pneumonia who were indeed connected to the cases of acute respiratory illness. The disease began in Huanan seafood market in Wuhan and now it has been declared as a public health emergency worldwide. Till date, total of seven human infecting CoVs (HCoV) have been identified and they have been classified into two major groups namely, SARS-CoV, MERS-CoV, and SARS-CoV-2 which are considered to be highly pathogenic and another group consisting of HCoV 229E, NL63, OC43, and HKU1 which are considered to be low on their pathogenicity.

Key words: SARS CoV 2, MERS, Procalcitonin, C-Reactive protein, IL-6, Coronavirus

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OBJECTIVE

To prove that interleukin 6, pro calcitonin and CRP can be used as prognostic markers to differentiate between mild moderate and severe Covid 19 cases.

INTRODUCTION

Coronavirus disease can be divided into four broad categories first the asymptomatic stage or the viral entry and replication stage which which has shown to be more common in children and younger adults as seen by the nuclear acid amplification tests.

The stage although been asymptomatic has been shown to be associated with increased risk of infectivity and hence repeat testing of people at this stage should be done. Reverse transcriptase polymerase chain reaction commonly known as RT PCR is used for detecting high viral load infected positive coronavirus patients. Quantitative loop mediated isothermal amplification is yet another rapid diagnostic test which is under development and can be used for testing of high viral load coronavirus patients within an hour of time [1]. The gold standard being the Nucleic Acid Amplification Tests as they are highly sensitive and specific. The US Centre for Disease control and prevention has stated that at least 2 molecular targets to be included. Other than RT-PCR, RT-qPCR which stands for Reverse Transcriptase quantitative polymerase chain reaction which brings into quantitative analysis along with simultaneous amplification in real time.

This technique makes the use of fluorescent dyes such as Sybr green [2]. Due to its expensive infrastructure and requirement of highly skilled manpower along with

high turnaround time this technique is limited to only centralised labs and is not easily accessible [3].

Tests include gene Expert assays which are nothing, but cartridge based nucleic acid amplification tests which are nothing else but quantitative reverse transcriptase polymerase chain reaction.

Some inexpensive and cheap methods detection of viral load include rapid antigen tests like immunofluorescence Assay, lateral flow assays or immunochromatographic tests, enzyme linked immunosorbent assay commonly known as ELISA and chemiluminescence assay [4].

These tests have high specificity but are not very sensitive.

The samples are usually taken from the upper respiratory tract and those of the lower respiratory tract are discouraged due to the production of the aerosols. Those of upper respiratory tract include oropharyngeal swabs, nasopharyngeal swabs, anterior nare swabs and nasal mid terminate swabs [5]. The lower respiratory tract samples being bronchoalveolar lavage, sputum, and bronchial washings with the most sensitive being the Bronchoalveolar lavage followed by the sputum nasopharyngeal and oropharangeal swabs and the least being the blood. The sample can also be stool, saliva and whole blood [6]. The second being the mild or moderate also known as viral dissemination phase which has a variable number of presentations such as anosmia throat congestion sore throat runny nose nausea or vomiting myalgia shortness of breath cough and fever which could be accompanied by chills. The infectivity of this stage is very high and hence requires early testing and confirmation of the disease followed by isolation and measures for prevention of infections such as self-isolation [7].

Some poor prognostic factors associated with this stage include presence of comorbidities like coronary artery disease diabetes mellitus, hypertension and others include male gender prominence increasing age and high viral load. This is the stage where elevated C-reactive protein procalcitonin interleukins and by products of coagulation pathway such as D-Dimer can be seen [8].

This stage requires adequate monitoring as the disease can progress and may lead to cardiac neurological and pulmonary complications. Anti-viral drugs and steroids have been found to be useful and have been included in the treatment protocols. Monoclonal antibody therapies along with covalent and hyper immune serum along with anti-thrombotics can be used as an adjuvant therapy [9].

The third stage which is a severe stage is characterised by multisystem inflammation which is characterized by worsening dyspnea and hypoxia in patients who have been associated with symptoms in the past 1 to 2 weeks. Investigations that indicate organ damage and coagulation biomarkers have been found to be elevated in this stage [7].

Instead of convalescent serum therapy oxygen supplementation along with anti-inflammatory and immuno modulator drugs have been found to be more beneficial and many experimental therapies such as mesenchymal stem cells have been developed and found to be more efficacious [10].

The last stage being the most critical stage is stage four which is characterized by endothelial damage multiorgan dysfunction and thrombosis. Endothelial dysfunction as seen by the elevated levels of one Willebrand's factor and endotheliosis's can be seen [7].

The biogenetic Markers have revealed the similarity between SARS Cov2 to be a RNA virus with 79%, homology to SARS CoV and 50% homology to middle east respiratory syndrome virus (MERS CoV) but the infectivity rate is greater than both of these [11].

Coronavirus belonging to the family Coronaviridae of the order Nidovirales and the subfamily being Torovirinae and Orthocoronavirinae. The subfamily Orthocoronavirinae has 4 genera included under it and those being alpha,beta,gamma and delta. These four genera are responsible for a wide variety of gastrointestinal, respiratory, and central nervous system disorders in humans' animals as well as birds. Out of these four genera only two of them that is alpha, and beta are known to cause diseases in humans while the rest two that is gamma and Delta are known to cause infections in even species [12].

Bats are the major reservoirs other than being the primary hosts of thousands of Corona viruses strains that infect the humans. The intermediate host of SARS Cov2 has been found to be civet and that of MERS has been found to be camels and since the hygiene of these wet-markets from where it has been acknowledged that virus may have taken its origin is very poor and only because of these poor practices there was an increase in transmission and infectivity [13].

Severe acute respiratory syndrome Coronavirus 2 has a unique property that is it can undergo recombination leading to formation of new serotypes just like the influenza virus and making the host susceptible to a new serotype once again that is this virus mutates very easily and thus increasing its transmission.

Recently there are reports of breakthrough infections of coronavirus which are nothing but due to the new Delta variant because of its property of immune evasion and increase transmission due to enhanced mutations(L452R) [14].

These are known to cause common cold, pneumonia, bronchiolitis in children and acute exacerbation of chronic obstructive pulmonary disease or AECOPD [15].

These single stranded positive sense RNA particles along with a nucleoprotein with a spherical or pleomorphic envelope and a capsid made of matrix proteins are responsible for a simple yet complicated respiratory tract infection. The benefit of this virus is being enveloped is that lipid solvents such as alcohol chloroform and ether are beneficial in rendering the surface aseptic and free of

these viruses [16].

Also, the genome of these viruses are the largest of all in comparison to other pathogenic RNA viruses. There are a total of four structural proteins out of which one is nuclear protein which includes is the single-stranded RNA of the viral genome and the other three structural proteins are a part of the lipid sensitive envelop. These three other proteins been small, enveloped proteins or E protein and membrane protein or M protein along with spike glycoprotein or S protein which none other than helps in binding of the virus to the host cell [17]. There has been development of some pharmacological drug possibilities for the treatment of corona virus infection. Since we have to a much greater extent have understood the viral genomic entry into the host cell, we have developed some therapeutics like blocking of S protein, ACE 2 receptor along with inhibition of type two serine proteases TMPRSS2.

Some investigational therapies have also been developed against RNA dependent RNA polymerases which include Remdesivir, Favipiravir and Ribavarin [18]. Another reason to produce new strains is due to the sloppy nature of RNA dependent RNA polymerase which is very much prone to error. To some extent these errors can be corrected by A special type of Exonuclease known as 3'-5' exonuclease and this process is known as proof reading. When this Exonuclease is not capable of proofreading at its best then new mutant strains arise. Since these mutations are linked to the RNA dependent RNA polymerase it can be concluded that more is the virus transmission more is it replication in the host more is its activity and more at the chances for action of RNA dependent RNA polymerase leading to production of new mutant strains. Thus, if we stop this viral transmission, we could to a much larger extent prevent the development of new mutants. These mutations are responsible for the immune evasion and inturn cause vaccine failures [19].

The receptors for severe acute respiratory syndrome (SARS) virus and severe acute respiratory syndrome coronavirus (SARS-CoV) virus are none other but the ACE-2 receptors which are ubiquitous enzymes and present on the epithelial surfaces of alveoli including type one and type two alveolar cells CVS, kidney, testis salivary glance and many more. Thus, some people who have high expression of these receptors are more susceptible to be infected from SARS-CoV 2.

While the Middle East Respiratory Syndrome coronavirus (MERS CoV) is Dipeptidyl Peptidase 4 (DPP-4) [20].

The binding of the SARS CoV 2 virus is executed by the receptor binding domain (RBD) which consist of two subunits S1 and S2. The S protein thus has a major role in facilitating the whole pathogenesis of Coronavirus [17]. There is a transmembrane protein in the host cell which binds to and proteolytically activates it and leads to the fusion of viral cell wall with the host cell and incorporation of the viral RNA into the host cell. Since the main mechanism of attachment and entry f virus into the cell involves S1 and ACE2 receptor; it can be concluded that pharmacological disruption of S1 from ACE2 can be an effective mechanism that can be used against SARS-Cov2 as a treatment modality [20].

Incidence of this infection which takes the form of local epidemics usually peaks in winter season and the same serotype may return and re-infect the same area years later.

Coronavirus being extremely fastidious organisms and hence they grow only in the differentiated respiratory epithelial cells. The exact pathogenic mechanism being disruption of cell membrane leading to release of inflammatory mediators that in turn lead to increase in nasal secretions and inflammation along with the swelling.

These are attributed to the sneezing, airway obstruction and increased in temperature of the localized area [21]. Infection usually passes through the community in the winter months and is responsible for outbreaks in small communities like schools. Transmission of this virus through via the nasal route through airborne droplet infection is responsible for its high infectivity. The transcription and translation of the uncoated genome after the entry of virus into the host and formation of a nested set mRNA that shares a common 3' end and this whole process of multiplication is brought about by the budding of virions from the host cell membrane. The classification of the coronavirus is based on the appearance of envelope glycoproteins which are usually crown or halo like in appearance. The serotypes in which most of the coronavirus's fall are OC43-like and 223E-like [19].

These two can be differentiated based on antigenic determinants and different cultural requirement for them to be grown [11]. Interleukin six is a cytokine that is elevated in inflammation and is responsible for B-cell maturation. Other than being a b-cell maturation Factor it is also a pyrogen and is elevated in autoimmune diseases infectious and non-infectious diseases.

It is elevated in both chronic and acute inflammation such as burns trauma cancers and infection. It is also involved in initiation of acute face reactants which keep the infection at bay.

T cell and natural killer or NK cell differentiation at early stages is yet another mechanism of action of interleukin 6. Indirectly by increasing the plasma cell production from the B cells it increases the blood levels of IgA and IgG antibodies. Endotoxin being an important initiator of pro calcitonin is responsible for its elevated levels in Corona virus disease. Not only pro calcitonin which is produced by the endotoxin which in turn is found in the lipopolysaccharide of gram negative but pro-inflammatory cytokines such as interleukin 6 interleukin 1B and Tumor necrosis factor alpha (TNF alpha). Does it can be estimated that the secondary bacterial infections in pre-existing Covid patients can be estimated by pro calcitonin levels.

The progression of disease of COVID-19 from the very viremic stage to the hyper inflammatory stage is characterized by the onset of respiratory symptoms and interstitial pulmonary infiltrates on chest radiograph and haematological can be estimated by the massive elevation of these markers which is commonly known as the cytokine storm.

In very severe cases of covid infection the virus induces a whole lot of cytokines which is sensed by the T helper 1 cell receptor and is inturn responsible for elevated levels of interleukins and tumor necrosis factor which reflects the ongoing inflammation or viremia [22].

The Level of the cytokines which are a direct consequence of the viral pathogenetic mechanisms that are occurring in the host is due to the crucial balance between the host immune response and the coronavirus load. Many studies have been conducted that have proven that the immuno deficient or depleted status of the host makes the person more prone to development of severe hypoxemic state. Does the viral sepsis syndrome can be considered as a direct consequence of the elevated levels of pro calcitonin? Chromosome 1 is where this CRP gene is present and is responsible for its expression. There is a small pentraxins family to which this CRP belong to. In a person without medical illness elevated CRP could be a consequence of genetic polymorphism of interleukin 1, interleukin 6 and polymorphic GT of CRP gene. CRP protein which is a Pentameric Structure of 206 amino acids is produced from its precursor CRP gene which has 224 amino acids [23]. Interleukin 1 interleukin 6 and glucocorticoids are the major producer of this acute phase reactant manufactured by the hepatocytes. The prime role of CRP is to bind to phosphocholine in dead and dying cells to activate the compliment system. Thus, it is involved in clearing of a apoptotic and necrotic cells [22].

Studies have proven that in lean and thin patients with elevated CRP levels have been found to be at a greater risk for atherosclerosis and type two diabetes mellitus and hence to underlying cardiovascular abnormalities. CRP levels peak at 48 hours and they start to rise after six hours and a half-life of 19 hours. CRP can be measured with the help of ELISA, nephelometry, immunoturbidimetry and radial immuno diffusion [23]. A new type of test also known as high sensitivity C reactive protein test is used to detect even small and minor quantities of C-reactive protein in the body.

High normal levels could be associated with ageing and pregnancy. In comorbidities such as malaria, malnutrition and HIV The CRP cut-off levels differentiating bacterial from non-bacterial illness can vary. Out of ESR and CRP The best prognostic marker is CRP and is highly sensitive because its level falls earlier as compared to ESR on resolution of infection and hence is a better marker of acute phase reactant elevation [24].

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