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COVID-19: Diagnosis, Evaluation and Treatment Strategies

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Mini Review

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ABSTRACT

In December 2019, a serious viral respiratory disease, named COVID-19, emerged in Wuhan, Hubei province in China. Subsequently, the infectious disease has spread to other parts of the world and was recognized as a global thread. Since the outbreak of COVID-19 tremendous amount of research has been published discussing various features of this pandemic. This review article summarizes main clinical aspects regarding COVID-19 diagnosis, pathology, evaluation of disease severity and treatment trials providing readers with concise information regarding this novel disease. Real-time reverse transcription polymerase chain reaction (RT-PCR) is the gold standard technique for confirming COVID-19 infection while non-contrast chest computed tomography(CT) images may be considered for early diagnosis purposes. In addition, several laboratory biomarkers can be utilized to evaluate disease status and prognosis such as C-reactive protein, lymphocyte count, platelet count and coagulation profile indicators. Unfortunately, to date there is no approved cure for COVID-19 infection; however, a variety of agents and treatment strategies such as convalescent plasma infusion and monoclonal antibodies are under investigation. Vigorously, health care professionals and the scientific research communityare craving to identify effective antiviral medications and protective vaccine.

INTRODUCTION

With In December 2019, a serious viral respiratory disease emerged in Wuhan, Hubei province in China [1,2]. The acute respiratory illness has subsequently spread to other provinces in China and other countries. Early in January a novel corona virus, now named the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was isolated and identified by deep sequencing analysis of samples from throatand lower respiratory tract specimens. The world health organization (WHO) has named the novel epidemic as coronavirus disease 2019 (COVID-19). On March 2020 WHO has declared its assessment of COVID-19 as a global pandemic [3]. According to real-time WHO statistics, the total number of confirmed COVID-19 cases worldwide as of August, 2020 has exceeded 17.9 million with more than 680 thousands deaths.

SARS-CoV-2 virus belongs to the family of betacorona viruses. It is an enveloped non-segmented positive stranded RNA virus [4]. COVID-19 has comparable characteristics to other betacorona viruses such as the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Virus (MERS-CoV) [5]. SARS-CoV and MERS-CoVcaused infections with variable clinical severity presenting respiratory and extra-respiratory manifestations [6]. Symptomatic COVID-19 patients are presented with fever, dry cough, bilateral lung ground glass opacity, dyspnea and diarrhea. In severe cases, especially in older patients with co-morbidities, COVID-19 causes pneumonia leads to acute respiratory distress syndrome (ARDS), multiple organ failure and even death [7]. This review summarizes important aspects and achievements in diagnosis, pathology, monitoring and treatment of SARS-CoV-2 infection.

DIAGNOSIS OF COVID-19 INFECTION

Although viral nucleic acid detection using real-time reverse transcription polymerase chain reaction (RT-PCR) is the gold standard technique for confirming COVID-19 infection, non-contrast chest computed tomography (CT) images may be considered for early

diagnosis of the viral disease [8]. A number of studies analyzed the sensitivity of RT-PCR testing and chest CT scan in COVID-19 diagnosis. Investigators from Tongji Medical College and Huazhong University of Science and Technology Wuhan, Hubei, Chinaclaimed that chest CT achieved higher diagnosis sensitivity for COVID-19 as compared with initial RT-PCR from pharyngeal swab samples(8). Another research group from Shanghai, China found that the sensitivity of CT for COVID-19 was 98% compared to RT-PCR sensitivity of 71% [9]. On the other hand a systematic review published in the investigative radiology journal stated that the difference in sensitivity between CT scan and RT-PCR for severe acute respiratory syndrome is lower than expected, as after stratifying 641 studies, the true sensitivity for CT based on the unbiased studies is limited [10]. Moreover, researchers suggested that testing specimens from multiple sites such as bronchoalveolar lavage fluid, fibrobronchoscope brush biopsy and pharyngeal swabs may improve the sensitivity and reduce false-negative test of RT-PCR results [11]. Furthermore, number of biochemist have designed several RT-PCR assays with improved sensitivity for detecting SARS-CoV-2 genome in clinical samples [12-14]. These assays provide rapid and specific tests with very low detection limits; however, false-negative and false-positive results are still reported.

Serological testing may be suitable for the diagnosis of suspected patients with negative RT-PCR results and for the identification of asymptomatic cases. It was reported that a 100% of patients tested positive for antiviral immunoglobulin-G (IgG) within 19 days after symptom onset [15]. Another group proposed a point-of-care lateral flow immunoassay that can detect IgM and IgG antibodies against SARS-CoV-2 virus in blood samples within 15 minutes with an overall test sensitivity of 88.66% and specificity of 90.63% [16].

In fact, the limited availability of the nucleic acid test in some countries in addition to the time wasted waiting for both test results and radiographic examination reports illustrate the need for time and cost effective triage and diagnosis protocols. A group of investigators conducted an electronic search comparing laboratory findings of COVID-19 confirmed cases to those of patients with COVID-19-like symptoms but had negative RT-PCR results [17]. According to their results, elevated high sensitivity C-reactive protein (hs-CRP) and eosinopenia (<0.02×109/L) were the most encountered changes (72.8%) among COVID-19 patients at an early days of the infection;thus eosinopenia in conjunction with elevated hs-CRP could be used to facilitate rapid triage and identification of highly suspectedCOVID-19 cases from other falsely-suspected patients attending fever clinics [17].

IMMUNE RESPONSE IN COVID-19

Although most of the infected individuals, around 90%, are asymptomatic or presented with mild self-recovering symptoms, most critically ill patients are presented with life threatening manifestations [18]. This variation in the disease severity among patients is linked to different immune responses. Several studies have focused on understanding changes in immune response induced by SARS-CoV-2. In vitro, in vivo and post-mortem sample analysis strongly suggest that SARS-CoV-2 is capable to replicate within the pulmonary tissue, evade the antiviral effects of interferon I and III, activate innate responses, and induce cytokines production which is required for the recruitment of adaptive immunity cells [19]. In particular, protective T cell with CD4 helping B cells, produce specific neutralizing antibodies, and cytotoxic CD8 cells responsible for eliminating infected cells [20]. Failure to achieve an effective adaptive response along with the exacerbated pulmonary inflammatory response lead to worse morbidity manifested in ARDS.

Moreover, uncontrolled proliferation and activation of macrophages and T cells lead to development of macrophage activation syndrome (MAS), also known as secondary hemophagocyticlymphohistiocytosis (sHLH) [21]. There are evidence of exacerbated pulmonary and systemic inflammatory responses in severely ill COVID-19 patients. The immunological profile of such patients involve very high serum levels of C-reactive protein (CRP), lactic dehydrogenase (LDH), Interleukin-6 (IL-6), D-dimer levels and ferritin, as well as a tendency for monocytosis, rather than lymphocytosis [22]. Also, a low number of natural killer cells (NK) and cytotoxic T cells, and finally tendency for disseminated intravascular coagulation (DIC) [22,23]. The above abnormalities are associated with MAS serology profile indicating that MAS and cytokine storm could be the main causes of poor outcomes; however several studies have revealed that COVID-19 settings exhibit some crucial differences compared to typical MAS manifestation such as absence of hepatosplenomegaly [22,24]. A number of researchers point toward ARDS as the reason behind the above listed serum indicators; in general, patients with ARDS with elevated IL-6 plasma baseline levels had poor survival rate. Furthermore, higher bronchoalveolar (BAL) fluid levels in ARDS pathology indicating a pulmonary, rather than systemic origin for these cytokines [24]. Undoubtedly, elucidation of the exact pathological behavior of COVID-19 is complicated due to the limited post mortem studies and immunological studies of asymptomatic patients.

LABORATORY BIOMARKERS FOR PREDICTING DISEASE PROGNOSIS

There is an urgent need for reliable clinical biomarkers in order to optimize patient care and resources management. Routine examinations for active COVID-19 cases include complete blood count (CBC), coagulation profile, and serum biochemical tests mainly include renal and liver function, creatine kinase (CK), lactate dehydrogenase (LDH), and electrolytes [25]. CBC is certainly the most available, efficient and cost effective examination, therefore clinician and researchers analyze the time courses of complete blood count of COVID-19 patients, an a way to obtain predictors for disease progression and treatment outcomes. In particular, WBC count, lymphocytes count (LYM%) and platelet count, Interleukin6 (IL-6) and serum ferritin were suggested as potential markers for disease progression [26].

Lymphopenia, defined as lymphocyte count≤1100 cells/μL, has been proposed as a good predictor to assess the severity of COVID-19 disease [25,27,28]. Lymphocyte reduction at early stages is independently associated with poor survival especially in young

patients [28]. Many studies have revealed that individuals who died of COVID-19 have had desperately lower lymphocyte levels than those of survivors [28-30]. Poor results of chest CT scan score, cardiac biomarkers, liver enzymes and renal function tests were associated with the increase in LYM% reduction which indicates higher degree of multi-organ failure [27,31]. Researchers speculated several mechanisms contributed to lymphocyte deficiency in COVID-19 disease [25]. On a molecular level, since lymphocytes express the coronavirus receptor angiotensin converting enzyme 2 (ACE2) they might be a direct target for the virus; thus it can invade lymphocytes and destroy them. The second hypotheses focus on the fact that the virus might directly attack lymphatic organs, such as thymus and spleen, causing rapid decline in LYM%. Another proposed mechanism considers the accumulation of inflammatory cytokines particularly tumour necrosis factor (TNF) α and IL-6 which could induce lymphocyte apoptosis. In addition, metabolic disorders observed in sever COVID-19 cases such as hyperlacticacidemia might suppress lymphocyte proliferation [25].

Moreover, platelet count and coagulation profile are significant predictors of health deterioration during hospitalization. Hematological changes include thrombocytopenia with normal white blood cell count, prolonged activated partial thromboplastin time, normal prothrombin time (PT) in addition to lymphopenia are the predominant changes in COVID-19 patients [32]. Thrombocytopenia was observed in 72.5% of hospitalized patients in Beijing; in fact, compared to survivors, most non-survivors had thrombocytopenia, and lower nadir platelet counts [33]. Although the mechanisms by which corona virus affect the hematopoietic system are not clear many hypotheses have been postulated. Based on the fact that corona viruses are able to directly infect bone marrow and inhibit hematopoiesis, SARS-CoV-2 was also expected to have similar effects on bone marrow function. Therefore it causes a decline in platelet production [32]. However, knowing that the rest ofblood counts,particularly WBC and hemoglobin, were not significantly affected disproves this mechanism [33]. Researchers also suggested that corona viruses, like HIV viruses, increases platelet destruction through immune-mediated thrombocytopenia; since such viral infections were proven to be associated with immune complexes contain platelet membrane immune components. These immune complexes might deposit on the platelet surface and stimulate platelets destruction by the reticulo endothelial cells [32,34]. Most patients recover normal platelet counts after steroid treatment which further proves the previous mechanism [34].

Furthermore, the SARS-CoV-2 induced pulmonarymicrothrombi, which result in platelet consumption,is also presented as a cause for thrombocytopenia [32]. Most hospitalized COVID-19 patients had elevated D-dimer levels whichindicates high fibrinolytic activity; these findings coincide with the above hypothesis [35]. Apparently, all presented factors are collectively responsible for thrombocytopenia development in COVID-19 patients. Another recommended indicator for evaluating severity of the infectious pneumonia is the serum CRP. CRP levels were positively associated with pulmonary lesions reflecting disease severity [36,37]. Similarly, CRP, erythrocyte sedimentation rate and granulocyte/lymphocyte ratio showed significant correlation to the CT severity scores in severe COVID-19 patients at initial stages [38].

CURRENT CLINICAL TREATMENTSTRATIGIES

Presently, there is no approved treatment for COVID-19 infections, nevertheless since the emergence of the virus many agents with possible efficacy against COVID-19 have been proposed. Supportive care is the key measurement applied to all patients; active vital signs monitoring and routine laboratory tests forcritical biomarkers listed in the above sections are recommended to facilitate disease state assessment and to provide rescue interventions as soon as needed. Potential antiviral used in clinical practice include protease inhibitors such as lopinavir and ritonavir, nucleoside analogues as favipiravir, remdesivir and ribavirin, in addition to umifenovir acting as fusion inhibitor. Unfortunately, to date few treatment options are available for COVID-19; however the antiviral medications listed above can be used as off-label therapy for patients with COVID-19 [39]. Furthermore, combination of some antiviral medications and interferon-α is another potential treatment strategy for this disease; such combination exhibited viral load reduction effect in MERS-CoV patients and could also benefits COVID-19 patients [40].

Chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial drugswith potentials againstviral infections. CQ exhibited in vitro growth inhibition effect against many viruses such as MERS, Ebola, and HIV [41]. Although CQ failed to reduce viral replication in SARS-CoV model, yet its anti-inflammatory effect contributes to the suppression of cytokine storm and consequently prevents ARDS development [42]. Moreover, recent study presented the FDA-approved anti-parasitic ivermectin as an inhibitor of SARS-CoV-2. Single addition of ivermectin to a SARS-CoV-2 infected cell line induced 5000 fold reduction in viral RNA in 48 hours [43]. A newer study suggests that HCQ and ivermectin could act synergistically to inhibit viral replications in COVID-19 patients [44].

Convalescent plasma and hyper immune immunoglobulin are currently being investigated as a potential therapy for COVID-19. A published case study report claimed that a high dose intravenous immunoglobulin (IVIG) at 0.3–0.5 g per kg weight per day for five days was effectively used as a potent and safe immune modulator [45]. The investigatorsillustrated that patients receiving IVIG at the stated ratio had normalization of temperature within two days of treatment, and alleviation of respiratory symptoms within five days [45]. Furthermore, adescriptive study indicated that a transfusion of ABO-compatible convalescent plasma to six COVID-19 patients resulted in alleviation of their symptoms and improvement in radiologic abnormalities as well as laboratory tests [46]. Another study suggested that convalescent plasma in addition to supportive care measures is potentially effective in treating critically ill COVID-19 patients [47]. In contrast, recent review on the use of convalescent plasma as a treatment for COVID-19 warned that most of the published studies are at a high risk of bias due to several factors such as; limited number of participants, co-administration of other treatments and the person's own immunity [48]. In addition, convalescent plasma administration is associated with number of limitation including difficulty in collection, variability of binding and neutralizing antibody titers, risk of contamination with infectious agents, possibility of transfusion reactions, and circulatory overload associated with administration [49].

Numerous research groups have focused on neutralizing antibodies with therapeutic and prophylactic potentials. Monoclonal antibodies of interest typically target a surface spike (S) glycoprotein responsible for binding the SARS-CoV-2 to the host cells, particularly to the ACE2 receptors found on several cell types [49,50]. Tocilizumab (TCZ) has received tremendous attention around the world. In Italy, a study involved 100 COVID-19 patients who received TCZ. Researchers reported oxygenation improvement in 74% of patients who were on invasive ventilation and 65% of patients who were on noninvasive ventilation [51]. Moreover, in a cohort study conducted in Cleveland, Ohio quicker recovery rates and around 81% improvement in oxygen support was reported in patients who required invasive and noninvasive oxygen support and were treated with single infusion of TCZ [52]. Another study included 15 COVID-19 patients whose disease ranges from moderate to critical conditions; the study illustrated that the use of a single dose of TCZ might benefit both moderately ill patients with 90 times of normal elevated IL-6 and seriously ill patients with 10 times of normal elevated IL-6 but not the critically ill group. Nonetheless, repeating TCZ dose at a frequency of daily, every other day, or every 3 days with a total of 2-3 doses would be beneficial for critically ill patients or patients with an extremely high level of IL-6 [53]. On the other hand, a published case report indicated that the use of TCZ was not effective in two cases of COVID-19 confirmed patients complicated by cytokine release syndrome (54). Authors reported that both patients progressed to sHLH despite treatment with TCZ, and one developed viral myocarditis; therefore more clinical trials focusing on determining optimal patient selection and timing for TCZ treatment during disease course are anticipated [54]. At this point of time, the demand for a specific antiviral agent and/or effective vaccine is vital therefore research community efforts should continue until their efforts are crowned with success.

CONCLUSION

COVID-19 is continuing to spread worldwide at a rapid pace. Healthcare professionals and the scientific community worldwide share the responsibility of stopping the pandemic and its global consequences. Providing available and cost effective diagnosis and patient care protocols as well as identifying effective treatment or prophylactic agents are crucial measures. Although most of the potential therapies may provide clinical benefits, various side effects could result in undesirable outcomes thus healthcare providers should be extremely cautious during practice.

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