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Review

COVID-19: A Complex Immuno-Thrombo-Inflammatory Disease

S. K. Verma[1]* and Nita Sahi[2]

[1]*Department of Medicine and [2]Department of Biochemistry,
Pacific Medical College and Hospital, Udaipur. Rajasthan, India

*Corresponding author Email: skvermaster@gmail.com

ABSTRACT

Coronavirus disease-2019 (COVID-19) is caused by the infection of SARS-CoV-2. After an average incubation period of 5 days, the disease begins with dry cough and low grade fever often associated with decrease or absence of smell or taste sensation. The disease remains mild or moderate in majority of patients and the symptoms resolve within a week. Those who remain symptomatic for long have a higher risk of developing more severe disease requiring hospitalization and ventilator support. The outcome of COVID-19, however, is often unpredictable, especially in elderly subjects with co-morbidities. It is a complex disease where the clinical spectrum swings between completely asymptomatic to rapidly devastating courses, and pathologically there is abnormal immunologic, inflammatory and thrombotic interactions involving practically all the organs of the body. The treatment till date is symptomatic and supportive.

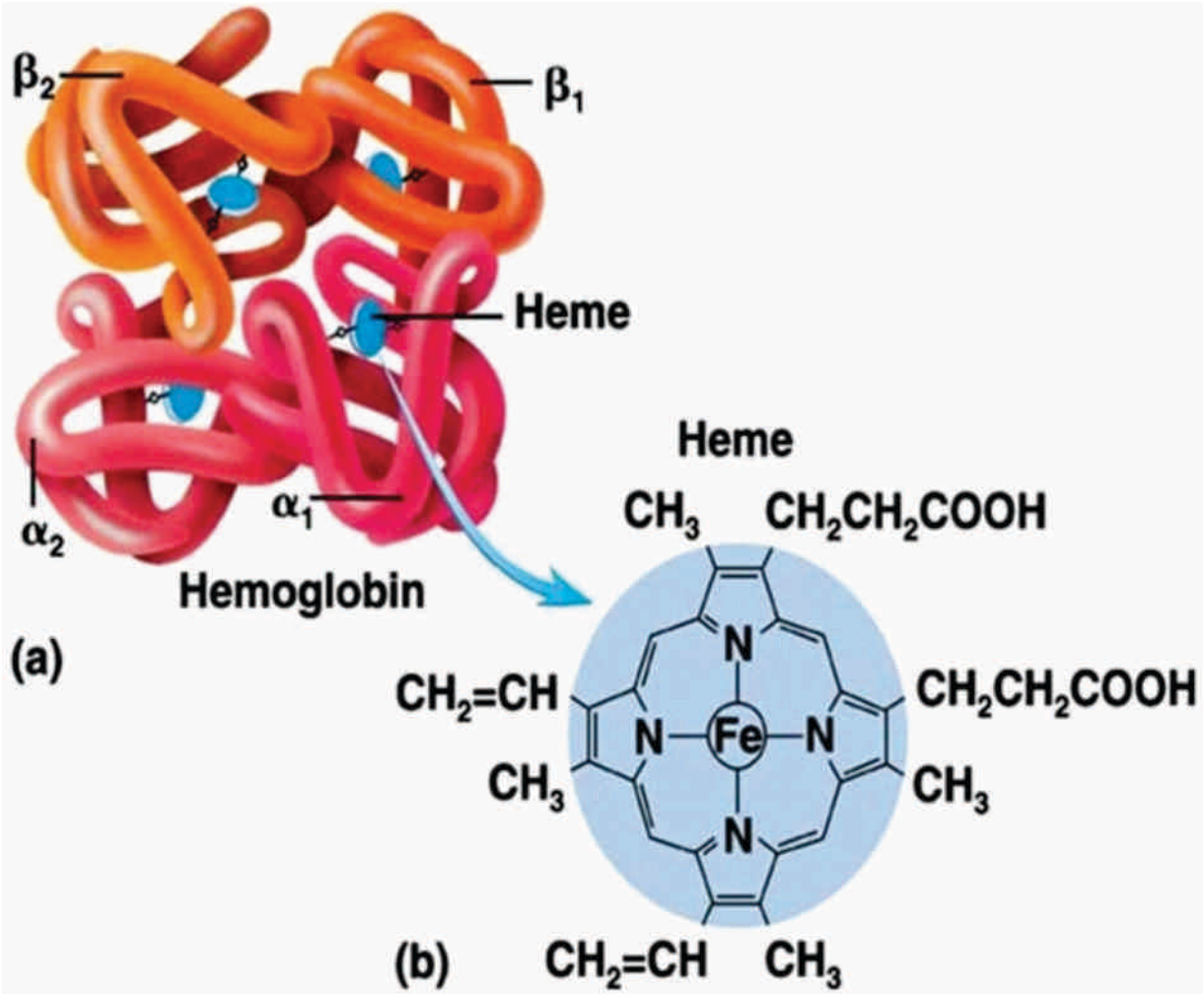
KEYWORDS: Cytokine storm, Interleukin-6, ORF 3a, Anosmia, Covid-toes

INTRODUCTION

COVID-19 started as an outbreak of pneumonia of unknown cause in Wuhan city; the capital of Hubei province in China in December 2019. The isolated virus was named as 2019-nCoV (2019 novel coronavirus) by WHO and later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses[1]. Initially the disease was named as 2019-nCoV' acute respiratory disease (2019-nCoV AR) which was subsequently reclassified as coronavirus disease 2019 (COVID-19) by WHO[2].

COVID-19 causes mild or atypical illness in 82%, moderate to severe illness in 15% and critical illness in 3% of infected patients. It affects all age groups, predominantly males, with an average incubation period of five days (range 2 to 14 days)[3]. The virus spreads from human to human via large and small droplets and also from surface to humans. Virus enters through the mucous membrane of eyes, nose or mouth and the spike protein gets attached to the ACE-2 (Angiotensin Converting Enzyme-2) receptors. ACE-2 receptors are found in organs throughout the body like lungs, heart, nervous tissue, kidney, liver, blood vessels etc. and therefore, the COVID-19 presents a complex pattern in many patients[4].

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 have caused human epidemics. Both had much higher fatality rates, 40% in MERS-CoV and 10% in SARS-CoV. Notably, the current SARS- CoV-2 shares 79% of its genome with SARS-CoV, it appears to be much more transmissible but has relatively less fatality rate (0.3-0.6%)[5].



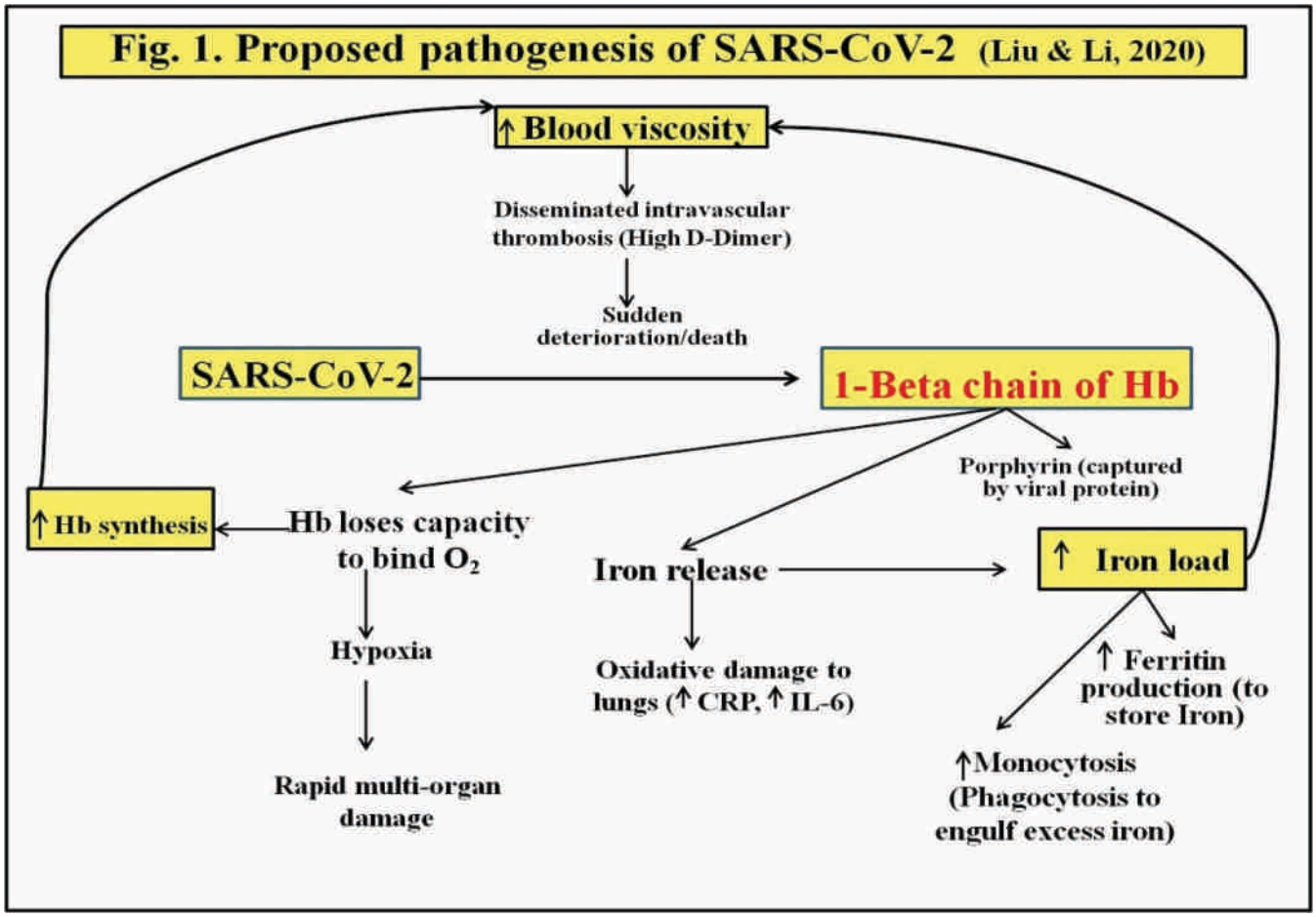
Pathogenesis

The SARS-CoV-2 first predominantly infects lower airways and binds to ACE-2 on alveolar epithelial cells[6]. Both SARS viruses are potent inducers of inflammatory cytokines. The 'cytokines storm' or 'cytokine cascade' is the postulated mechanism for organ damage. The virus activates immune cells and induces the secretion of inflammatory cytokines and chemokines into pulmonary vascular endothelial cells[7]. In-depth

analysis of host responses to SARS-CoV-2 revealed a unique and inappropriate inflammatory response to SARS-CoV-2

which is imbalanced with regard to controlling virus replication versus activation of the adaptive immune response. This phenomenon is defined by low levels of Type I and III interferons juxtaposed to elevated chemokines and higher expressions of IL-6. It has been proposed that reduced innate antiviral defenses coupled with exuberant inflammatory cytokines production are the defining and driving features of COVID-19[8]. However, the pathogenicity of SARS-CoV-2 is not so simple, it still remains mysterious. There is also a reflection of abnormal phenomenon of Hb-related biochemical indices in patients with SARS-CoV-2 pneumonia.

Liu and Li conducted a study in which conserved domain analysis, homology modeling and molecular docking techniques were used to analyze the functions of SARS-CoV-2 related proteins. The conserved domain analysis showed envelope protein (E), nucleocapsid phosphoprotein (N) and ORF3a had heme linked sites. ORF3a could dissociate the iron of heme to form porphyrin. Heme linked sites of E protein may be relevant to the high infectivity and heme linked sites of N protein may be related to the Virus replication. The docking results showed that Orf1ab, ORF 10 and ORF 3a proteins coordinated to attack the 1-beta chain of hemoglobin and



capture the porphyrin to inhibit heme metabolism. It would ultimately cause increasingly less hemoglobin that could carry oxygen and carbon dioxide, thereby producing symptoms of respiratory distress and coagulation reaction, damaging many organs and tissues[9] (Fig. 1).

Furthermore, COVID-19 virus that attacked hemoglobin would yield iron, carbon dioxide, and oxygen, which might put both lungs tissue is a toxic and inflammatory state. This will lead to formation of multiple ground glass images on both sides of the lungs. These ground glass images are often associated with rapid and noticeable hypnoxemia[10].

Risk factors for severe disease with fatal outcome

COVID-19 has presented an extremely variable course. On one hand, the disease is completely asymptomatic while on the other hand, it is fulminating fatal. There are many risk factors which govern the severity of the disease.

1.Age

Summary of a report of 72,314 cases from the Chinese Centre for Disease Control and Prevention (CDC) found that the overall death rate was 2.3 % among confirmed cases of COVID-19 while it was higher in older population (14.8% in case of 80 years and older)[11]. In almost all studies published throughout the world have reported that the age group of eighty years or older contributed to more than 90% of all death cases of COVID-19.

2.Sex specific difference

Data from world around show that there is lower mortality in female patients and even the presence of co-morbidities have less impact in females[12]. The presence of subclinical systemic inflammation blunted immune system, down-regulation of ACE-2 and accelerated biological aging are the speculations for higher vulnerability in older men[13].

3.Co-morbidities

Early studies from China also found that co-morbidities such as hypertension, cardiovascular disease and diabetes have been associated with severe disease and death[14]. Studies conducted outside China have found that obesity is also an important risk factor[15]. Chronic cardiac disease and chronic pulmonary disease have been independently associated with in-hospital mortality[16].

4.Genetic susceptibility

Interestingly, in some cases, COVID-19 affects young and apparently healthy people where disease severity is neither caused by age nor by any co-morbidity. This remarkable heterogeneity of COVID-19 disease has led to the speculation that the idiosyncratic response of individual patient may be to some extent related to underlying genetic variations[17]. Following are some interesting reports directing towards genetic susceptibility-

a) Case report from Iran of three brothers aged 54-66, all died of COVID-19 after less than two weeks of fulminating progress. Before COVID-19, all were healthy without any underlying illnesses[18].

b)In postmortem of 21 COVID-19 cases showed that 65% of the patients had blood group 'A'. The possible explanations of this correlation are (i) blood group 'A' may be associated with the failure of pulmonary microcirculation and coagulopathies and (ii) there might be direct interaction between antigen A and the viral S protein, thereby facilitating virus entry via ACE-2[19].

c)There is some association between Apo Ee4e4 allele and COVID-19 severity. The Apo Ee4e4 allele increased risk of severe COVID-19 infection independently of pre- existing diseases[20].

In addition to the genetic predisposition, other potential reasons for a severe course are the amount of viral exposure, the route by which the virus enters to the body, the virulence of the pathogen and possible immunity from previous viral disease[4].

Complex clinical spectrum

A plethora of symptoms have been described which suggest that coronavirus disease-19 is not a simple viral infection but a complex disease, not only limited to respiratory system but also involving musculoskeletal, enteric, cardiovascular, neurologic and uncommonly muco-cutaneous structures (Fig.2).

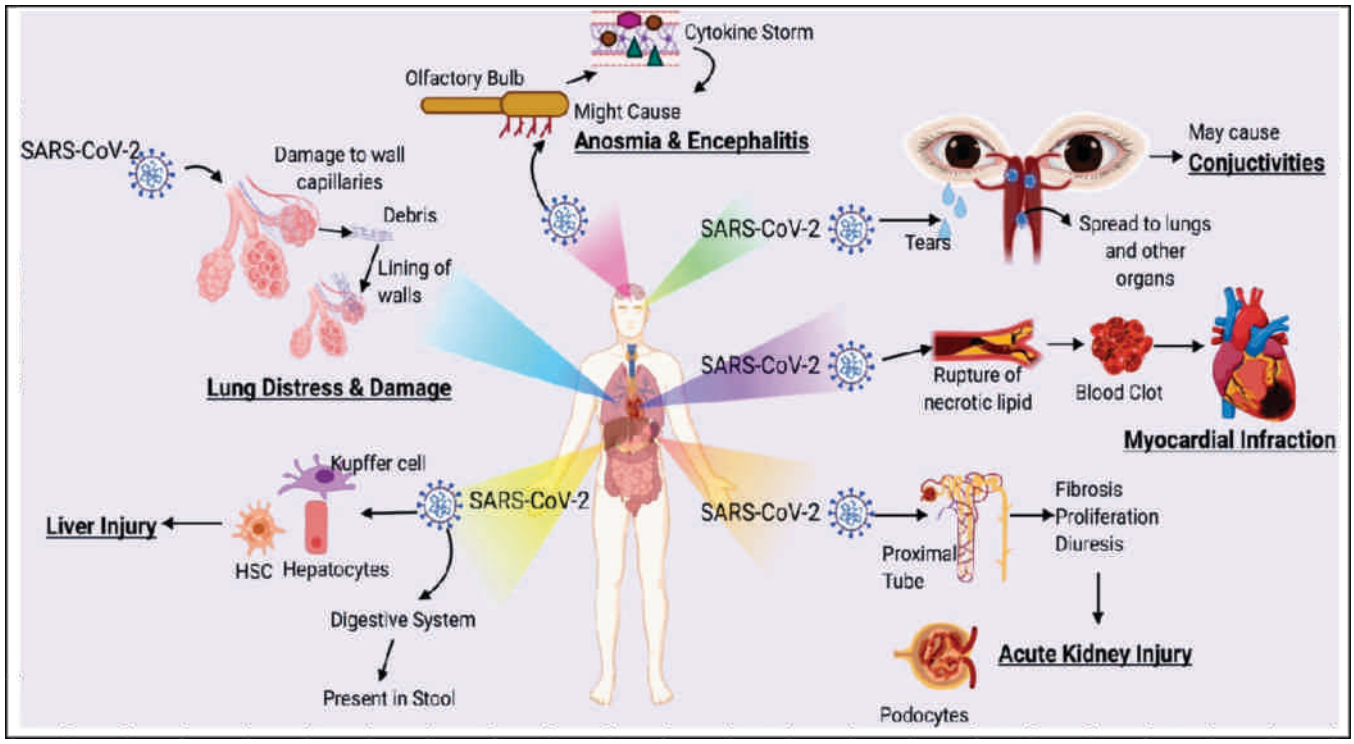


Figure 2: Effect of SARS-CoV-2 on human body (Source: Balachandar *et al.*, 2020; *Sci. Tot. Env.* 729, 10 August 2020, 139021)

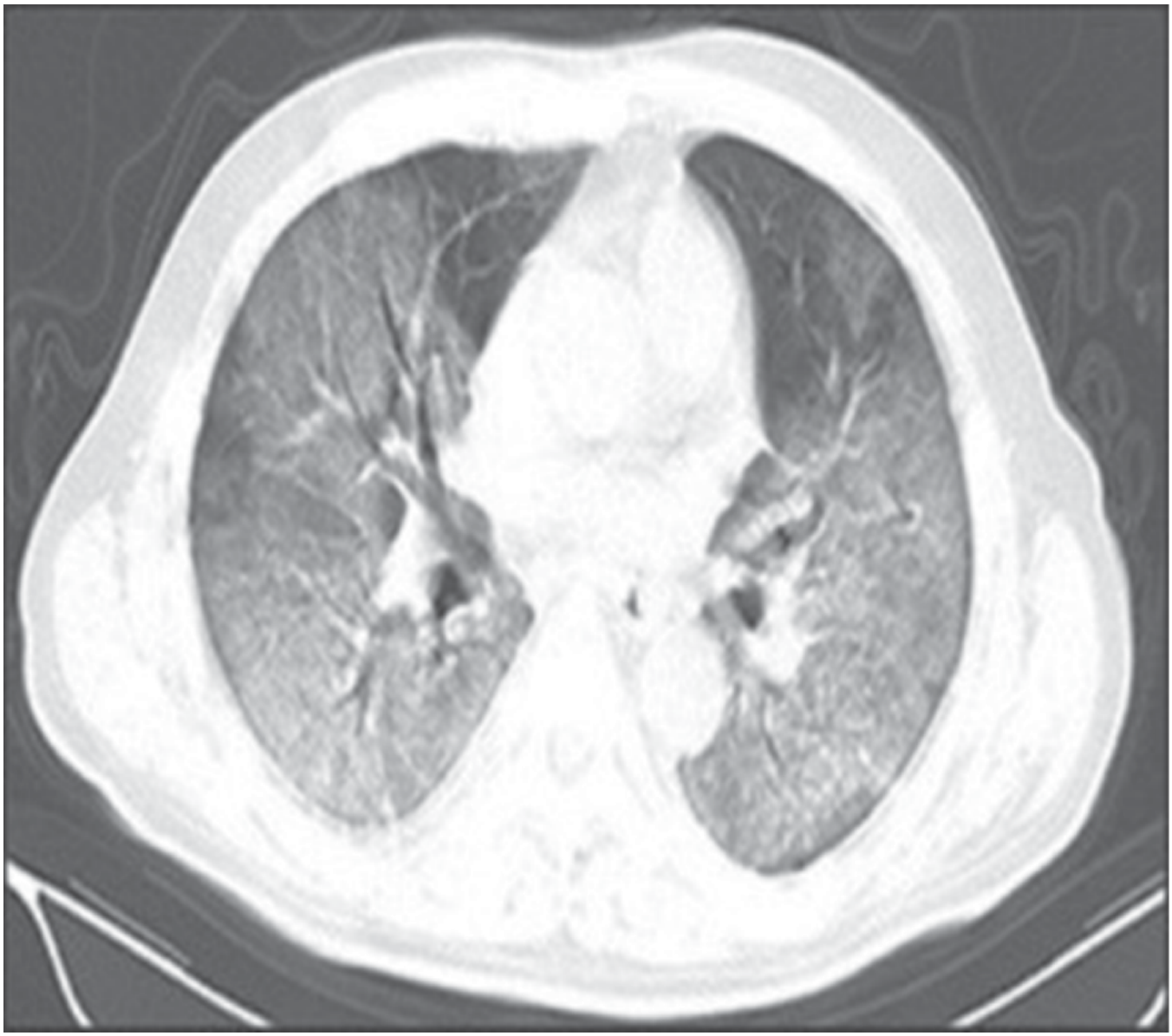


Figure 3: Lungs in COVID-19

Respiratory symptomatology

COVID-19 patients present clinically with fever, dry cough and dyspnea. Fever is the most common symptom with median maximum of 38.3°C and the median duration of 12 days (8 to 13 days). However, fever alone may not be sufficient to detect cases in public surveillance. Cough is the second most symptoms occurring in about two-third of all patients and usually persists for 19 days (Inter-quartile range 12-23 days).

In a meta-analysis of COVID-19 papers published until February 23, fever (88.7%), cough (57.6%) and dyspnea (45.6%) were the most prevalent clinical presentations[19]. Although fever and cough are the most common symptoms that do not differentiate between mild and severe cases nor do they predict the course of the disease. Dyspnea, however, has been identified as a strong predictor of severe disease[22]. CT chest shows bilateral ground glass appearance of lungs in patients having COVID-19 (Fig. 3).

Musculoskeletal symptoms

These include myalgia, joint pain, headache and fatigue in 15 to 40 % of patients[23]. These symptoms are disturbing but do not indicate the severity of disease. Headache has been observed in 11-34% of hospitalized COVID-19 patients and in 6-10% as a presenting symptom. It is moderate to severe, bilateral,

pulsating or pressing quality, located in temporo-parietal, forehead or periorbital regions. The most striking features are sudden to gradual onset and poor response to common analgesics[24].

Otorhinolaryngeal symptoms

Upper respiratory symptoms such as sneezing, nasal congestion, rhinorrhea and sore throat are relatively uncommon but ansomia and hyposmia are important signs of COVID-19[25]. These symptoms appear to be much more common in Europe than in Asia. In Europe, in one of the largest study, it was found that 87% patients reported loss of smell (anosmia) and 56% reported taste dysfunction[26]. The association of anosmia was so strong that it was said "Flu plus 'loss of smell' means COVID-19".

In another study on 263 patients presenting with flu like symptoms, loss of smell was found in 68% of COVID-19 patients compared to only 16% in negative patients. It has been concluded that smell and taste impairment were independently and strongly associated with COVID-19 positivity and the sore throat was independently associated with negativity[27]. Although these otorhinolaryngeal symptoms do not indicate severity of the disease yet are important indicators for SARS-CoV-2 infection.

Cardiovascular symptoms

Clinically, COVID-19 can manifest with an acute cardiovascular syndrome ("ACovCS") presenting not only with typical chest complaints, but also with very diverse cardiovascular manifestations where Troponin and D-dimer are important markers. The prevailing dictum during COVID-19 pandemic is that in patients a seemingly typical coronary heart syndrome, COVID-19 should also be considered in the differential diagnosis, even in the absence of fever or cough[28-29].

SARS-CoV-2 has the potential to infect cardiomyocytes, pericytes and fibroblasts via the ACE-2 receptor pathway leading to myocardial injury[30]. Moreover, myocardial injury may be related to cytokine excess and/or antibody mediated mechanisms[31]. It is also possible that there may be direct SARS-CoV-2 infection of the endothelium because ACE-2 receptor is widely expressed on these cells also leading to diffuse endothelial inflammation (endotheliitis). Post-mortem study does indicate a strong virus induced vascular dysfunction[19].

Whatever the mechanism may be, there is growing evidence that heart is directly or indirectly affected by SARS-CoV-2 infection especially in patients with pre-existing heart disease[32].

Coagulation abnormalities

Coagulation abnormalities occur frequently in patients with COVID-19. Incredibly higher number of venous thrombo-embolism especially in these with sever COVID-19 have been reported. The initial coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products (FDPs), while abnormalities in prothrombin time, partial thromboplastin time and platelet count are relatively uncommon. Measurements of D-dimer and fibrinogen levels are the suggested coagulation screening tests[33]. Exact mechanisms are not clear but there is possibility of de novo coagulopathy in these patients with COVID-194.

Gastrointestinal symptoms

Gastrointestinal symptoms were rarely observed in early Chinese studies. Among the first 393 consecutive patients admitted to two hospitals in New York City, diarrhoea (24%) and nausea and vomiting (19%) were relatively frequent15. Cell experiments have shown that SARS-CoV and SARS-CoV-2 are able to infect enterocytes and active replication has been shown in both bats and human intestinal organoids[34].

Neurologic symptoms

Human coronaviruses have neuro-invasive propensity. This viral neuro-invasion may be achieved by several routes such as trans-synaptic transfer, entry via the olfactory nerve, infection of vascular endothelium or leukocyte migration across the blood-brain barrier[35].

In a retrospective observational case series, neurological manifestations were observed in 36% of patients of COVID-19; ranging from fairly specific symptoms (loss of sense of smell or taste, myopathy, encephalopathy and stroke) to non specific symptoms (headache, low consciousness, dizziness or seizures)[36]. Besides these symptoms, there are several observational series of specific neurologic features such as Guillain-Barre syndrome[37] and Miller fisher syndrome and polyneuritis cranialis[38].

Cutaneous manifestations

There are several reports of dermatological involvement in SARS-CoV-2 infection. The most prominent phenomena "COVID toes" are chilblain like regions mainly at acral areas, can be painful and may represent the only symptom or late manifestations of COVID-19. The point of interest is that in most patients with "COVID toes" (Fig. 4), the disease is only mild-to-moderate. It is not yet clear whether 'COVID toes' represent a coagulation disorder or hypersensitive reaction[4].

Galvan and associates have described five clinical cutaneous lesions; acral areas of erythema with vesicles or pustules (pseudo chilblain)-19%, other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and

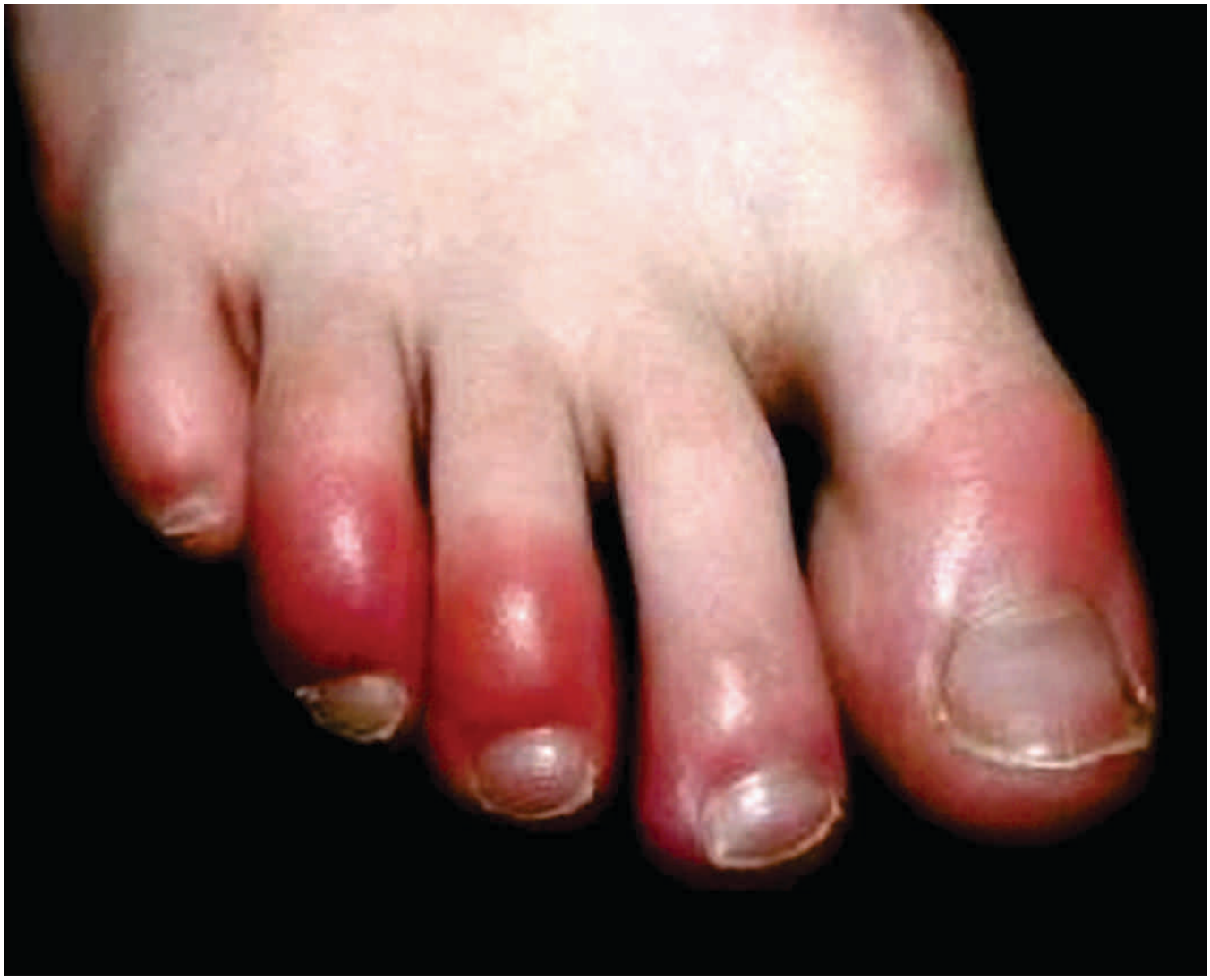


Figure 4: "COVID toes"

livedo or necrosis (6%)[39].

Hepato-renal involvement

SARS-CoV-2 has an organotropism beyond the respiratory tract and includes kidney and liver.

Renal tropism

SARS-CoV-2 viral load has been detected in all the compartments of kidney with preferential targeting of glomerular cells. Renal tropism is a potential explanation of commonly reported new clinical signs of kidney injury in COVID-19 patients even in patients with SARS-CoV-2 infection who are not critically ill[40].

Recent data indicate that renal involvement is more frequent than described in early studies. Argenziano and associates reported that in 236 patients who were admitted or transferred to Intensive Care units; 78% developed acute kidney injury and 35.2% needed dialysis[41].

Hepatic injury

Evaluation of liver injury in 2273 SARS-CoV-2 positive patients reveal that 45% had mild, 21% moderate and 6.4% severe liver injury. Severe acute liver injury was significantly associated with elevated inflammatory markers including ferritin and IL-6[42].

Ocular involvement

Ocular manifestations are common (32%) and more common in severe COVID-19 cases. These include conjunctival hyperemia, chemosis, epiphora, or increased secretions

consistent with conjunctivitis. Even two patients had positive PCR results from conjunctival swabs[43]. Optical Coherence Tomography (OCT) has shown the involvement of retina as well.

Laboratory reflection of severity

It is now clear that COVID-19 is a complex disease involving all the major systems of the body. Patients with severe disease, because of multisystem involvement have many prominent laboratory abnormalities than those with non-severe disease[4].

- The common laboratory risk parameters are:
- Elevated CRP, procalcitonin, interleukin-6 and ferritin
- Lymphocytopenia, CD4 T cell and CD8 T cell depletion, Leukocytosis
- Elevated D-dimer and troponin
- Elevated LDH

Clinical classification of severity of COVID-19

There is no well accepted or valid clinical classification to categorize the patients of COVID- 19 based on the severity of disease. The first large clinical study distinguished between severe and non-severe cases[14] according to the diagnosis and treatment guidelines for adults with community- acquired pneumonia published jointly by the American Thoracic Society and Infectious Diseases Society of America[44].

Severe cases include either one major criterion or three or more minor criteria.

Major criteria

- Septic shock with need for vasopressors
- Respiratory failure requiring mechanical ventilation

Minor criteria

- Respiratory Rate > 30/min
- PaO_2 / $F1O_2$ Ratio < 250
- Multi-lobar infiltrates
- Confusion / disorientation
- Uremia
- Leukopenia
- Thrombocytopenia
- Hypothermia
- Hypotension requiring aggressive fluid resuscitation Wang and associates[45] have used the following classification-

1. *Mild cases:* Clinical symptoms were mild without pneumonia manifesting through image results
2. *Ordinary cases:* Having fever and other respiratory symptoms with pneumonia manifesting through image results
3. *Severe cases:* Meeting any one of the following: respiratory distress, hypoxia (SpO2 <93%), abnormal gas analysis (PaO_2 < 60 mmHg, $PaCO_2$ > 50 mmHg)
4. *Critical cases:* Meeting any one of the following: respiratory failure which require mechanical ventilation, shock accompanied by other organ failure that needs ICU monitoring and treatment

Wu and McGoogan in the report of the Chinese CDC for the estimation of disease severity used almost the same categories as described by Wang and associates; although number 1 (mild cases) and number 2 (ordinary cases) were combined to mild cases category[9].

Mild - Non-pneumonia and mild pneumonic

Severe - Dyspnea respiratory frequency 30> min, blood oxygen saturation < 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 and/or lung infiltrates > 50% within 24 to 48 hrs.

Critical - Respiratory failure, septic shock and or multiple organ dysfunction or failure.

In a nutshell, COVID-19 is not just a respiratory tract infection of SARS-CoV-2 but it can involve all the organs of the body especially where the viral load is much more and the person is compromised because of age and other co-morbid conditions. It is in fact a complex disease process involving the abnormal immunogenic response leading to widespread inflammatory and thrombogenic process affecting the major organs of the body leading to multi-organ failure. The disease is new to humanity and the medical science is still in the process of learning about COVID-19 and searching the possibility of developing vaccine against SARS-CoV-2 infection.

CONFLICT OF INTEREST: None

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