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**Review**

# An Update on SARS-COV-2/COVID-19 with particular reference on its clinical pathology, pathogenesis, immunopathology and mitigation strategies – A Review

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**Abstract**

Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus named Severe Acute Respiratory Syndrome - Coronavirus-2 (SARS-CoV-2), emerged in early December 2019 in China and attained a pandemic situation worldwide by its rapid spread to nearly 167 countries with 287.239 confirmed cases and 11.921 human deaths with a case fatality rate (CFR) of around 4 per cent. Bats were considered as the reservoir host, and the search of a probable intermediate host is still going on. Animals have anticipated culprit of SARS-CoV-2 as of now. The disease is mainly manifested by pneumonia and related respiratory signs and symptoms, but the involvement of the gastrointestinal system and nervous system is also suggested. The severe form of the disease associated with death is mainly reported in older and immune-compromised patients with pre-existing disease history. Death in severe cases is attributed to respiratory failure associated with hyperinflammation. Cytokine storm syndrome associated with rampant inflammation in response to SARS-CoV-2 infection is considered as the leading killer of COVID-19 patients. COVID-19 patients were reported with higher levels of many pro-inflammatory cytokines and chemokines like IFN-γ, IL-1β, IP-10, and MCP-1. Furthermore, severe cases of COVID-19 revealed higher levels of TNF-α, G-CSF, and MIP-1A. Blood profile of the COVID-19 patients exhibits lymphopenia, leucopenia, thrombocytopenia and RNAaemia along with increased levels of aspartate aminotransferase. SARS-CoV-2 infection in pregnant women does not lead to fetus mortalities unlike other zoonotic coronaviruses like SARS-CoV and MERS-CoV, with no evidence of intrauterine transmission to neonates. Rapid and confirmatory diagnostics have been developed, and high efforts are being made to develop effective vaccines and therapeutics. In the absence of any virus-specific therapeutic, internationally health care authorities are recommending adoption of effective prevention and control measures to counter and contain this pandemic virus. This paper is an overview of this virus and the disease with a particular focus on SARS-COV-2 / COVID-19 clinical pathology, pathogenesis and immunopathology along with a few recent research developments.

**Keywords:** SARS-COV-2; COVID-19; clinical pathology; pathogenesis; immunopathology.

## Introduction

Severe Acute Respiratory Syndrome - Coronavirus-2 (SARS-CoV-2), causing the Coronavirus Disease 2019 (COVID-19), first reported with pneumonia-like symptoms in Wuhan city of China in late 2019 (Zhou et al., 2020a). The initial human-to-human spreading of the virus was noted in an epidemiological investigation on January 20, 2020, where two patients were detected COVID-19 positive in Guangdong Province and had no history of personal visits to Wuhan in the past (Chan et al., 2020a). Subsequently, the assumptions of human-to-human transmission strengthened by the report of COVID-19 in 14 hospital staff from patients (Wang et al., 2020a). Since then, SARS-CoV-2 has affected 287.239 persons and plagued more than 11.921 human patients. Although currently, the case fatality rate (CFR) in COVID-19 outbreaks is less than previous SARS and MERS outbreaks (Mahase, 2020), a sharp rise in CFR has been observed during last few weeks, reaching to 4 per cent, and consequently, COVID-19 entered the pandemic stage (Dhama et al., 2020a; WHO, 2020a; Yang et al., 2020). The most prominent clinical signs manifested by the COVID-19 patients are fever, coughing, pneumonia, chest pain with bilaterally consolidated lungs and ground glass appearance on computed tomography (CT) (Bassetti et al., 2020; Chan et al., 2020a; Huang et al., 2020; Hui et al., 2020). Deaths in the severe form of COVID-19 were reported mostly due to respiratory failure (Chen et al., 2020a; Huang et al., 2020) probably caused by hyper inflammation resulted in lethal pneumonia. COVID-19 associated fatalities were mainly reported in elderly patients with known comorbidities (Chen et al., 2020a; Huang et al., 2020) than young, healthy people and children probably due to their strong immunity. A retrospective study evaluated the susceptibility of COVID-19 in older and young patients where elderly patients showed higher PSI score compared to young patients and elderly patients also possess more chances of multiple lobe involvement ($P<0.001$) than young patients (Liu et al., 2020a). This paper presents an overview on this virus (SARS-CoV-2) and the disease (COVID-19) with a particular reference to clinical pathology, pathogenesis and immunopathology along with mitigation strategies to contain and restrain this pandemic virus.

**SARS-COV-2 / COVID-19; A brief overview**

SARS-CoV-2 has spread rapidly through travellers to 167 countries across the globe (Rodriguez-Morales et al., 2020a; WHO, 2020a; Wilson and Chen, 2020). Apart from China, the countries severely affected by this virus include Italy, Iran, South Korea, France, Spain, USA, Japan, Spain, and a few others (WHO, 2020a). Presently, SARS-CoV-2 has posed severe negative impacts on the economy of China and other countries besides social impacts, e.g. growth of China slowed down to 2.4 from expected 5.7 and that of India to 5.3 from expected 5.7 due to COVID-19 (Ayittey et al., 2020 Munster et al., 2020; WHO 2020b, https://www.bloombergquint.com/amp/opinion/coronavirus-the-economic-impact-of-covid-19-on-india).

Role of animals, zoonotic links and spillover of SARS-CoV-2 and transmission to humans have been implicated as reported with SARS and MERS (Ahmad et al., 2020; Ji et al., 2020; Li et al., 2020a; Malik et al., 2020a; Murdoch and French, 2020; Rodriguez-Morales et al., 2020b; Salata et al., 2020). Bats and pangolins have been suggested to have links with SARS-CoV-2 (Li et al., 2020b; Malik et al., 2020a; Xiao et al., 2020; Zhou et al., 2020b). A Pomeranian dog of COVID-19 infected owner was tested positive for SARS-CoV-2 by real-time PCR, two days after the quarantine ended, he died of the virus. Suggesting dogs' permissiveness for the virus as a result of reverse zoonosis (OIE, 2020a), although the dog showed an only mild form of infection. Taking into account the higher similarity between the spike glycoprotein of current virus (SARS-CoV-2) and previous coronaviruses, a study hypothesized the role of "unconventional" biological hosts. Notably, in their observations, mild infection of COVID-19 was seen outside the Wuhan, China with better recovery of patients and was suggestive of some past contact of patients with infected dogs that protected them against the current COVID-19 virus (Tilocca et al., 2020). SARS-CoV-2 origin of exposure to humans has been related to the seafood market in Wuhan, China, which is a wet-market selling various kinds of poultry, bats, snakes, and other wildlife animals, acting as a hotspot for human-animal interface to happen paving the emergence of novel pathogens such as SARS-CoV-2 (Hui et al., 2020; Jalava, 2020). Several essential preventive measures like stopping

people movements, avoiding mass gatherings, educational institutions closers, handling office work at home, have implemented to minimize and break the virus spread cycle (Li et al., 2020c).

Diagnostic tests for SARS-CoV-2/ COVID-19 have been developed such as reverse transcription-polymerase chain (RT-PCR), real-time PCR, real-time quantitative RT-PCR (rRT-qPCR), COVID-19-RdRp/Hel real-time RT-PCR assay, POCT/bedside testing, loop-mediated isothermal amplification (RT-LAMP), full genome analysis by next-generation sequencing (NGS), fluorescence-based quantitative PCR assay, enzyme-linked immunosorbent assay (ELISA), computed tomography technique (CT) imaging and X-Ray (Corman et al. 2012; Chan et al., 2020b; Dhama et al. 2020a; Xu et al. 2020a; Yu et al., 2020; Zhang et al. 2020a).

An effective treatment regimen and vaccine is urgently needed to halt the COVID-19 spread and death toll (Casadevall and Pirofski 2020; Dhama et al., 2020b; Jin et al. 2020; Shang et al. 2020; Rodriguez-Morales et al., 2020b). The lessons learned from earlier pandemics and epidemics of SARS, MERS, bird flu, swine flu, Ebola, Zika, Nipah along with exploring high advances in science and technology including research to their optimal potential would aid in discovering suitable vaccines and therapeutics/drugs to combat the current pandemic posed by COVID-19 (Dhama et al. 2012, 2013b, 2018a, 2018b, 2020b; Munjal et al. 2017; Singh et al. 2018, 2019; Peeri et al., 2020).

**Clinical Pathology**

COVID-19 clinical manifestations include respiratory (mainly pneumonia), digestive, and systematic affections (Chen, 2020; Chen et al., 2020b; Huang et al., 2020; Yang et al., 2020). The CFR is approximately 4% now, severely affected persons die owing to too much alveolar injury and progressive respiratory failure (Porcheddu et al., 2020). Asymptomatic carriers revealing no clinical signs (cold, fever, fatigue or chest/lung pathology) can be seen in few persons infected with SARS-CoV-2, and these can shed virus up to 21 days that can potentially infect persons coming in their contacts (Hu et al., 2020). The estimated incubation period is reported to vary from 3 to 6 days, with a mean value of 5.2 days (Huang et al., 2020; Li et al., 2020d). Additionally, Kritas et al.

(2020) reported the incubation period of COVID-19 from 1 to 14 days whereas the median incubation period of SARS-CoV-2 was reported to be four days in a study of 1099 COVID-19 cases in China (Guan et al., 2020). The clinical symptoms manifested by COVID-19 patients are reported to be milder than SARS and MERS epidemics (Hui et al., 2020). Moreover, the milder nature of the symptoms was reported to be the major hurdles in the identification of the transmission chains, followed by its subsequent tracing (Lee and Hsueh, 2020). The clinical symptoms of the COVID-19 were mainly observed in older and immune-compromised individuals with pre-existing conditions like cardiovascular disease, hypertension, asthma, and diabetes (Huang et al., 2020; Wang et al., 2020b).

COVID-19 symptoms start with fever, mild chills, pharyngalgia, dry cough, fatigue, shortness of breath, severe respiratory distress, pulmonary pneumonia, that could aggravate if goes undiagnosed and not medicated timely (Qian et al., 2020; Xu et al., 2020b). Additionally, fever and cough are reported to be the most common symptoms associated with COVID-19 patients (Sun et al., 2020). However, mild symptoms like nausea, headache, respiratory distress, sore throat, myalgia, vomition and sometimes diarrhoea are also shown in COVID-19 patients (Li et al., 2020e; Sun et al., 2020). The unique symptom reported in SARS-CoV-2 infection is the involvement of the gastrointestinal system, which was not found in the case of SARS and MERS. Additionally, the presence of viral RNA in the faecal samples of the COVID-19 patients suggests the probable transmission by the faecal-oral route (Holshue et al., 2020).

Moreover, a study reported mild infection of the upper respiratory tract associated with COVID -19. Additionally, shedding of the virus from nasopharynx for seven days or more with subsequent detection of the virus in blood and stool was reported, but the urine was found negative for the virus (Young et al., 2020). In a study, the SARS-CoV-2 RNA detected in stool was found accurate with the pharyngeal samples of COVID-19 patients. Moreover, the absence of gastrointestinal symptoms in the patients had no relation with the severity of pneumonia (Zhang et al., 2020b). Hypoxemia triggers while lung inflammation progresses, occasionally cardiac arrest happens for compensating shortness of breath, due to which patient sinks. AAs the symptoms of

dry cough and fever appear, a medical doctor needs to be consulted immediately to avoid further pathological complications (Chan et al., 2020a).

Histologically, biopsy tissues of lungs, liver, and heart tissue reveal desquamation of pneumocytes, the formation of hyaline membrane, bilateral diffused alveolar damages along with cellular fibromyxoid exudate. Multinucleated syncytial cells, atypical enlarged pneumocytes, interstitial mononuclear inflammatory infiltrates along with the presence of a majority of lymphocytes in the affected lungs constitute the significant cytopathic effects (Huang et al., 2020). Almost all the COVID-19 patients are reported with a variable degree of flaws in the lungs like other viral pneumonia on CT imaging. Additionally, the other finding includes bilateral multilobular subsegmental consolidation of lungs in early stages followed by multiple mottling and ground-glass opacity (Bassetti et al., 2020; Chan et al., 2020a; Chen et al., 2020a; Huang et al., 2020). Severe lung lesions were evident on around day $10^{th}$ after the beginning of symptoms in most patients who recovered from COVID-19 illness (Pan et al., 2020a, 2020b). Moreover, extensive lower respiratory tract involvement was reported in pneumonia associated with SARS-CoV-2 infection (Huang et al., 2020).

Adverse maternal and prenatal effects like miscarriage, fetal growth retardation, premature birth along with neonatal mortality has been reported in SARS-CoV and MERS-CoV (Wong et al., 2004a, Alfaraj et al., 2019). However, vertical transmission from mother to neonates is also suggested as a possible route of SARS-CoV-2 infection based on positively tested neonates in China (Wang et al., 2020c). In contrast to this, studies suggested SARS-CoV-2 infection during pregnancy does not lead to maternal mortalities unlike SARS-CoV and MERS-CoV infection with no evidence of intrauterine or transplacental transmission to neonates (Rothan and Byrareddy, 2020; Schwartz, 2020).

Blood profile of the COVID-19 patients revealed lymphopenia, leucopenia, thrombocytopenia and RNAaemia along with higher levels of aspartate aminotransferase and hypersensitive troponin I (Chan et al., 2020a; Huang et al., 2020). Initially, procalcitonin levels

were reported normal, but a little rise in the levels at the advanced stage was noted, indicating probable secondary infection (Huang et al., 2020).

The platelet count and procalcitonin levels were reported near to average in COVID-19 along with elevation in ESR and CRP levels. Additionally, severe COVID-19 might be associated with higher levels of AST, ALT, LDH, CPK, creatinine, and prothrombin time and maybe of high diagnostic value (Singhal, 2020).

As far as clinical features are concerned, SARS-CoV-2 associated pneumonia is different from other pneumonia is as liver damage was observed frequently with abnormal levels of ALT, AST, γ-GT, α-HBDH and LDH. Also, HBDH and LDH may be used as evaluation markers for diagnosis of the COVID-19 (Zhao et al., 2020).

**Pathogenesis**

The COVID-19 pathogenesis involves from mild to severe respiratory involvement (Chan et al. 2020a; Zhu et al. 2020a) with an incubation period of (Guan et al. 2020) ranging from 1 to 14 days (Kritas et al., 2020). Severe pneumonia mostly bilateral occasionally unilateral, leading to respiratory failure is the leading cause of mortality in SARS-CoV-2 infection (Sun et al., 2020). Respiratory failure in severe COVID-19 is generally associated with hyperinflammation. A cytokine storm syndrome probably may be the reason for hyper inflammation in severe SARS-CoV-2 disease (Huang et al. 2020; Mehta et al., 2020). Gross lesions include multiple mottling, ground-glass opacity, pneumothorax, bilateral multiple lobular and subsegmental areas of consolidation and multiple organ failure as having been reported in COVID-19 patients (Chan et al. 2020a; Chen et al. 2020a; Huang et al. 2020).

Further, in COVID-19 patients, the brightness of both lungs was diffusely decreased, showing a large area of patchy shadow with uneven density (Chen et al. 2020a). Massive lung involvement is further supported by histopathological findings like desquamation of pneumocytes, hyaline membrane formation, bilateral diffused alveolar damage and presence of cellular fibromyxoid exudates (Huang et al., 2020). Though it mainly affects lungs but multi-organ

dysfunctions affecting vessels, heart, liver, kidney and other organs were also recorded (Yao et al., 2020). Microscopically SARS-CoV-2 has shown to damage surface layers of human airway epithelial cells causing cytopathic effects and cessation of the cilium beating of the cells (Liu et al. 2020a). This can result in severe inflammatory cascade, earliest targets being macrophage, lymphocyte and pneumocytes (Liu et al. 2020a).

At a molecular level, both cellular and humoral immune mechanisms are believed to be responsible for this pathogenesis (Ahmed et al. 2020; Tetro 2020). In addition to direct macrophage and lymphocyte stimulated response, T cell and B cell-mediated immunological mechanisms are initiated against SARS-CoV-2 (Ahmed et al. 2020; Tetro 2020; Walls et al. 2020). That includes antigen detection and presentation and B cell activation (Ahmed et al. 2020; Liu et al. 2020a; Tetro 2020; Walls et al. 2020). Involvement of T-helper and T-cytotoxic cells is also possible. However, the role of cellular response needs to be evaluated, cytotoxic T cells may kill the virus directly, while helper T cells present it to B cells for immunoglobulin production and neutralization (Ahmed et al. 2020; Huang et al. 2020). SARS-CoV-2 attacks respiratory mucosal epithelial cells and spread to other cells, infects peripheral white blood cells and immune cells, particularly T lymphocytes (Chen et al. 2020a). Multilobular infiltration and lymphopenia observed in SARS-CoV-2 infection may suggest cellular response (Chen et al. 2020a). Cellular immune deficiency and lymphopenia reported in COVID-19 patients suggest cell-mediated immune response against SARS-CoV-2 (Chen et al. 2020a; Tetro 2020). Damage to lymphocytes, including T lymphocytes by coronavirus leads to lymphopenia, predisposing to secondary bacterial infections and exacerbating severity (Chen et al. 2020a). An increase in levels of proinflammatory cytokines and decrease in anti-inflammatory cytokines may indicate T cell-mediated response against SARS-CoV-2 resulting in cytokine storm that causes hyper inflammation leading to severe pneumonia in COVID-19 (Chen et al. 2020a; Huang et al. 2020; Liu et al. 2020a). Lymphopenia and sustained inflammation are characteristic findings in severe and fatal cases (Tetro 2020). Altered and elevated values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), D-dimer and lower values of serum albumin and haemoglobin in most of the cases significantly

indicates COVID-19 in the person. Most of the patients have shown increased white blood cell count, increased neutrophil number, decreased lymphocytes, reduced albumin concentration, enhanced levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, cardiac troponin, prothrombin time (PT) and high levels of procalcitonin (Lei et al., 2020; Lippi and Plebani, 2020; Liu et al., 2020b). A set of B cell and T cell epitopes have been identified in the immunogenic structural proteins of SARS-CoV-2 further indicating cellular response against the pathogen (Ahmed et al. 2020).

The humoral immune response may also have a role in the pathogenesis of COVID-19 (Ahmed et al. 2020; Giwa and Desai, 2020). As there is a decrease in levels of immunoglobulins in COVID-19, this may indicate effects on antibody-producing cells B lymphocytes (Chen et al. 2020a). Though antigens of SARS-CoV-2 have shown potential for stimulating antibody production, the impact of overall lymphopenia may have caused depletion of immunoglobulins (Chen et al. 2020a; Wrapp et al. 2020). Antibodies developed against SARS-CoV-2, especially anti-spike protein antibodies, may be responsible for the infection of immune cells (Tetro 2020). Antibody-dependent enhancement (ADE) requiring pre-exposure to similar antigenic epitopes of coronaviruses, may be responsible for the severity of the disease leading to acute respiratory injury, acute respiratory distress syndrome, and other observed inflammation-based sequelae including cellular immune deficiency, coagulation activation, myocardia injury, hepatic and kidney injury, and secondary bacterial infection (Tetro 2020).

Most of the molecular mechanisms of pathogenesis of SARS-CoV-2 infection are being elucidated with rapid pace to understand the disease and to develop countermeasures (Giwa and Desai, 2020; Tetro 2020; Walls et al. 2020; Wrapps et al. 2020). Though limited progress has been made on SARS-CoV-2 pathogenesis and most of the inferences are being drawn from other coronaviruses, especially the SARS-CoV and MERS-CoV (Chen 2020; Chen et al. 2020b). However, future explorations will enable a better understanding of pathogenesis mechanisms (Liu et al. 2020a; Tetro 2020; Walls et al. 2020; Wrapps et al. 2020). Initially, structural and non-structural proteins of the SARS-CoV-2 need to be elucidated for antigenic properties and initiation

of the immune response. Structural proteins of SARS-CoV-2 including envelope (E), membrane (M), nucleocapsid (N), and spike (S) are being explored as antigens (Chan et al. 2020c; Shang et al. 2020). Spike (S) and nucleocapsid (N) epitopes induce an immune response (Tian et al. 2020). Targeting S protein both cellular and humoral immunity can be developed by inducing neutralizing antibodies and by developing protective cellular immunity (Shang et al. 2020), this indirectly also reflects the role in pathogenesis as the severity of COVID-19 is correlated to the degree of immune response generated against SARS-CoV-2 (Chen et al. 2020a; Tetro 2020). Antibody-dependent enhancement (ADE) of SARS-CoV-2 is assumed to be a significant pathogenesis mechanism resulting in sustained inflammation, lymphopenia, and cytokine storm in severe cases (Tetro 2020).

The overall structure of SARS-CoV-2 ‘S’ protein resembles that of SARS-CoV ‘S’, with a root mean square deviation (RMSD) of 3.8 Å over 959 Cα atoms (Wrapp et al. 2020). Spike protein (S) helps SARS-CoV-2 in binding and entry into cells (Letko and Munster, 2020; Lu et al. 2020; Walls et al. 2020). S1 subunit of S glycoprotein enables strong binding to ACE2 receptor while as S2 subunit ensures fusion with the host cell (Coutard et al. 2020; Hoffmann et al. 2020; Wan et al. 2020). Within the host respiratory tract and gastrointestinal tract epithelial cells can be affected (Liu et al. 2020a; Rothan and Byrareddy 2020). In general, respiratory epithelial cells (pneumocytes) and enteric cells (enterocytes) are infected by CoVs, causing cytopathic changes (Habibzadeh and Stoneman 2020). Type 2 pneumocytes and unciliated bronchial epithelial cells are prime targets (Habibzadeh and Stoneman 2020; Walls et al. 2020). Cytopathic effects on respiratory epithelial cells and cessation of the cilium beating of the cells have been noted (Liu et al. 2020a; Zhu et al. 2020a). Though cytokine storm is believed to be responsible for this pathogenesis however actual pathogenic mechanisms are yet to be elucidated.

**Immunopathology**

In COVID-19, high leukocytes counts and neutrophil-lymphocyte-ratio was reported with low eosinophils, lymphocytes, monocytes, and basophils counts. Additionally, all lymphocytes subsets viz. T cells, B cells and NK cells were reported to be significantly decreased in severe cases

of COVID-19 (Qin et al., 2020). A decrease in helper T cells along with suppressor T cells has been reported in patients with less severe COVID-19, however, in severe COVID-19 lower helper T cells, regulatory T cells and memory T cells occur. Surprisingly, higher naïve population of helper T cells noted, thereby analysis of lymphocytes along with neutrophil-lymphocyte-ratio must be considered for initial screening of COVID-19 patients (Qin et al., 2020).

COVID-19 patients show higher plasma levels of pro-inflammatory cytokines along with chemokines like IFN-γ, IL-1β, IP-10, and MCP-1, whereas severe cases which required ICU admissions had higher concentrations of TNF-α, G-CSF, MCP-1, IP-10, IL-8, IL-10 and MIP-1A (Huang et al., 2020; Qin et al., 2020). Increased expression of IL-6 in serum and IL-2 receptor reported in severe cases might play a crucial role in determining the severity of COVID-19 (Chen et al., 2020c; Qin et al., 2020).

Upregulation of pro-inflammatory cytokines in serum was found associated with severe pulmonary damage and inflammation in SARS-CoV (Wong et al., 2004b) and MERS-CoV infections (Mahallawi et al., 2018), and also in COVID-19 (Huang et al., 2020). Surprisingly, in SARS-CoV-2 infection, elevated levels of both Th1 and Th2 cytokines were reported in comparison to SARS and MERS where only Th1 cytokines were upregulated (Wong et al., 2004b; Huang et al., 2020).

The binding of SARS-CoV-2 with Toll-like Receptors (TLR) triggers the release of pro-IL-1b and subsequent production of mature IL-1b, which mediates fever, pulmonary inflammation and fibrosis. Therefore, suppression of IL-1b and other members of pro-inflammatory IL-family by IL-37 and IL-38 may prove highly beneficial in COVID-19 patients to reduce pulmonary inflammation and might be considered as a relevant therapeutic agent (Conti et al., 2020). Miscellaneous HLA types and diverse epitope binding affinity give rise to an extensive array of immunopathological upshots of novel human coronavirus 2019-nCoV in humans (Ramaiah and Arumugaswami, 2020).

**Immunobiology**

The virus affects the immune system by altering the magnitude and type of biomolecule production from the immune cells in the body of patients as the disease progresses (Lippi and Plebani, 2020; Zhu et al., 2020b). Based upon bioinformatics profiling of the class I and class II MHC molecules researchers have analysed the binding potentials of the 2019-nCoV proteins and epitopes to MHC molecules within the host body cells and can also predict the probable mutational hotspots (https://qbrc.swmed.edu/projects/2019ncov_immuneviewer/). With the help of netMHCpan suite of software, it was elaborated that when proteins-peptides of 2019-nCoV binds with MHC class I and class II, it stimulates the CD8+ and CD4+ T cell responses and hence proposed that CD8+ and CD4+ T cell activity is capable of eliminating the virus from the body (Jensen et al., 2018).

Immune vulnerability maps of SARS, MERS and 2019-nCoV were compared for B and T cell epitope profile, and findings emphasized that there is variation in T-cell biology and response to 2019-nCoV while no significant difference was observed in B cell epitope profiling (Sanchez-Trincado et al., 2017).

An overview of COVID-19 clinical pathology, pathogenesis and immunopathology is presented in **Figure 1.**

**COVID-19 Mitigation measures**

Under the present pandemic situation, strict vigilance, enhanced screening, surveillance, and monitoring, implementation of effective prevention and control measures, isolation, and quarantine of suspected patients, strengthening medical facilities, adopting best health care and biosafety measures by health-care workers during handling COVID-19 patient, following good hygiene, sanitation and disinfectant usage practices, limiting tours and travels, cancellation of visas, issuing of different advisories from time to time for the mass population as large scale awareness programmes for the public with tips to avoid infection from this virus, personnel hygiene including hand hygiene and restricting touch of nose and face, closing of schools, colleges, malls, and offices

for a while, advising the public to stay at home in affected areas, are being followed to counter and restrain COVID-19 pandemic and challenges ahead (CDC, 2020; Lai et al. 2020; Gao 2020; Guo et al. 2020; Habibzadeh and Stoneman 2020; Hellewell et al. 2020; Malik et al., 2020b; Rodriguez-Morales et al., 2020c; WHO 2020b).

Considering it as the public health emergency of international concern (PHEIC) and the subsequent declaration of a pandemic, efforts are being directed against prevention and control at case, cluster, and community level with measures implementing at both national and international levels (Heymann and Shindo 2020; WHO 2020b). Focus on public health, prevention of community spread and detection of asymptomatic carriers especially among the travellers through surveillance, diagnosis, contact tracing quarantine; and isolation and management of affected patients can help in mitigation of the pandemic (Rothe et al. 2020; She et al. 2020; WHO 2020c). Many affected countries have shifted response from the containment to mitigation strategies like USA, India, and Saudi Arabia (CDC 2020; Ebrahim et al. 2020; WHO 2020d). Community sanitation, restriction of public movement and gatherings, cancellation of socio-religious activities, the imposition of curfews, locating and quarantine of affected or asymptomatic cases and close contacts, and therapy under quarantine of COVID-19 patients are being implemented (Ebrahim et al. 2020; https://www.thehindubusinessline.com/specials/pulse/time-to-implement-mitigation-strategies-not-just-react-to-health-threats/article30823430.ece). Besides, response strategies of most of the countries mainly focuses on the variable degree of contact tracing, self-isolation, quarantine, endorsement of public health measures like respiratory etiquette, personal protective hygiene and social distancing, the building of robust healthcare facilities with particular attention to nursing homes and cancellation or postponement of all the events requiring public gatherings. Moreover, lower-income and middle-income countries must be supported technically and financially in order to develop the capacity for PCR testing and management of COVID-19 successfully (Bedford et al., 2020).

Unprecedented and wartime strategies including increasing production of medical supplies, upgrading healthcare infrastructure, use of national security to restrict movement and manage

crowds, cancellation of visas, travels, suspension of exports, and ban on imports are applied by countries to minimize the risk of further entry and spread and to prevent future transmission, severity and loss of lives (Ebrahim et al. 2020). As the largest outbreak of COVID-19 outside China was reported on the Diamond Princess cruise ship with many asymptomatic infected individuals, cruise ships were considered as a potential source of sustained community spread in many other countries. In this context, a clear cross-national management treatment plans, strategies for isolation, quarantine and evacuation of global citizens must be developed to prevent such outbreaks in future (MacIntyre, 2020). Additionally, countries must increase their readiness, preparedness and response actions robustly and rapidly based on their risk assessment and four WHO transmission scenarios (4Cs: no cases; first cases; first clusters and community transmission and spread) (WHO, 2020d; Bedford et al., 2020). Seeing the proven zoonotic linkages, One health approach may play a crucial role in countering this virus (Bonilla-Aldana et al., 2020; Cohen and Kupferschmidt 2020; Dhama et al., 2013a; Mallapaty, 2020; OIE, 2020b).

**Conclusion and prospects**

The SARS-CoV-2 continues to expand in the form of pandemic and might be responsible for massive causalities besides leaving the world in a situation of significant economic loss. Although the virus originated in China but left only a few countries undisturbed as far as mortalities are concerned. Bats are reported to be the reservoir host with no solid proofs available on possible intermediate hosts. The main clinical signs associated with the COVID-19 like fever, coughing, sneezing, headache, respiratory distress, chest pain and fatigue are suggestive of the massive involvement of lungs as principal organ leading to severe pneumonia and subsequently death. Bilateral multilobular subsegmental consolidation, multiple mottling and ground-glass opacity with a variable degree of flaws in the lungs on CT imaging may suggest the degree of involvement. Besides, massive lung involvement is further supported by histopathological findings like desquamation of pneumocytes, hyaline membrane formation, bilateral diffused alveolar damage

and presence of cellular fibromyxoid exudate. However, the involvement of the brain leading to acute respiratory failure and gastro-intestinal tract resulting in diarrhoea is also reported.

Cytokine storm associated with the rampant inflammation resulted into the release of pro-inflammatory cytokines and chemokines like IFN-γ, IL-1β, IP-10, MCP-1, TNF-α, G-CSF, MCP-1, IP-10, and MIP-1A which severely damages pulmonary tissues leading to death in severe COVID-19 patients. Although, lymphopenia, leucopenia, thrombocytopenia, and RNAaemia occurs with a decrease in helper T cells, regulatory T cells, and memory T cells in severe COVID-19 cases notably the levels of Th1 and Th2 cytokines are found elevated. However, elevated levels of ALT, AST, LDH, CPK, creatinine, γ-GT and α-HBDH in a severe form of the disease suggests multi-organ involvement. Molecular mechanisms of the viral binding, entry, multiplication and pathogenesis are being elucidated with S1 subunit of viral spike protein (S) showing the early indication of binding to ACE2 as a receptor and S2 subunit helping infusion, however actual pathogenic mechanisms are yet to be explicated. As no approved treatment and vaccines are available against SARS-CoV-2, a thorough knowledge of clinical signs, pathogenesis, and pathology remains indispensable in order to safeguard the lives and reduce the mortalities. Also, while providing supportive therapy during clinical management of the patients using unapproved but probably beneficial drugs, utmost care must be taken to avoid untoward severe side effects produced by the immune system in response as pregnant women were found infected as well as their neonates, suggesting the potential spread of COVID-19 infection from mother to neonates. Hence, the inclusion of pregnant women in the clinical trials of vaccine is necessary.

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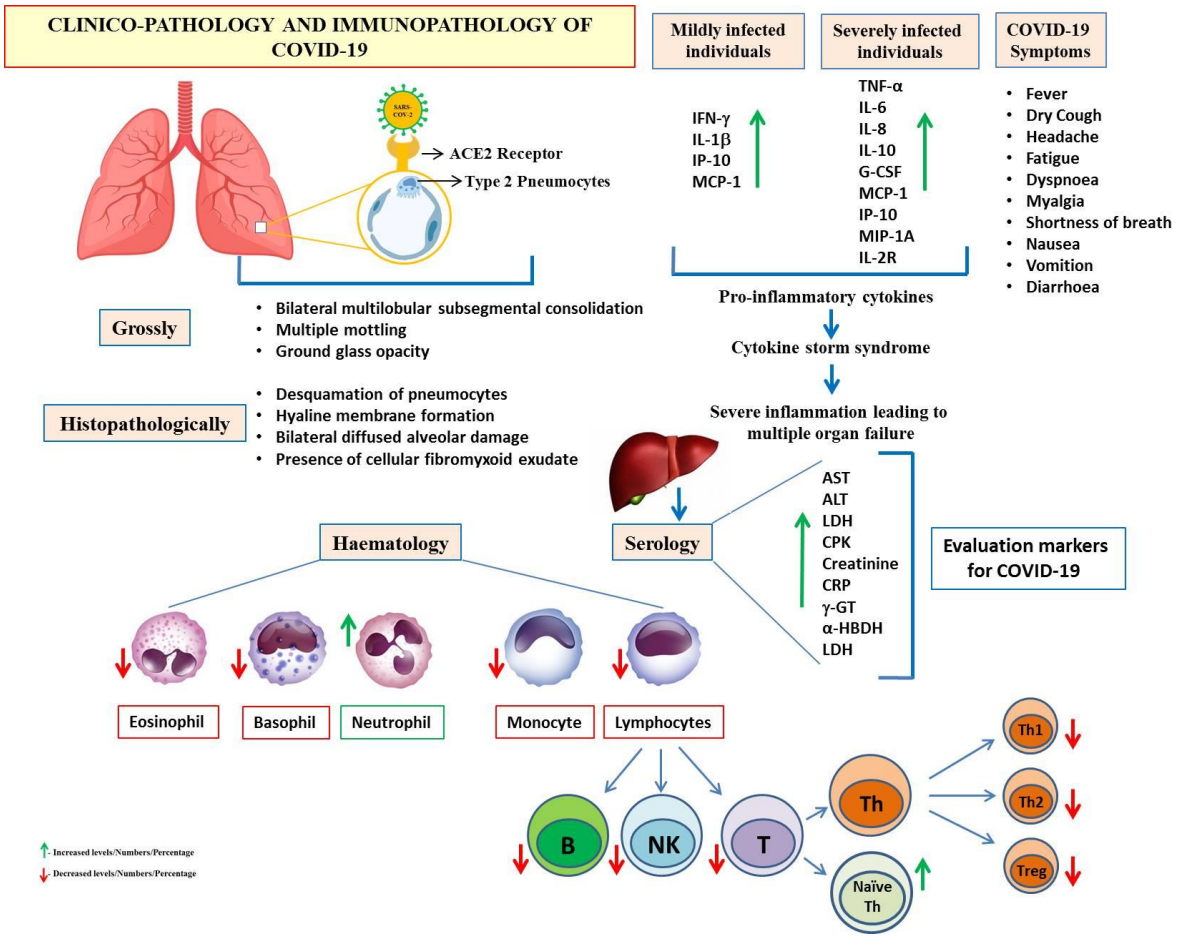


Figure 1: An overview of COVID-19 clinical pathology, pathogenesis and immunopathology