Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies

Kuldeep Dhama[a,**], Shailesh Kumar Patel[a], Mamta Pathak[a], Mohd Iqbal Yatoo[b], Ruchi Tiwari[c], Yashpal Singh Malik[d], Rajendra Singh[a], Ranjit Sah[e], Ali A. Rabaan[f], D. Katterine Bonilla-Aldana[g,h], Alfonso J. Rodriguez-Morales[h,i,*]

[a] Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, 243 122, Bareilly, Uttar Pradesh, India
[b] Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, 190025, Srinagar, Jammu and Kashmir, India
[c] Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, UP Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishwavidyalay Evum Go-Anusandhan Sansthan (DUVASU), Mathura, 281001, India
[d] Division of Biological Standardization, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, 243 122, Uttar Pradesh, India
[e] Department of Microbiology, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal
[f] Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
[g] Semillero de Zoonosis, Grupo de Investigación BIOECOS, Fundación Universitaria Autónoma de las Américas, Sede Pereira, Pereira, Risaralda, Colombia
[h] Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Colombia
[i] Grupo de Investigacion Biomedicina, Faculty of Medicine, Fundacion Universitaria Autonoma de las Americas, Pereira, Risaralda, Colombia

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ABSTRACT

Coronavirus Disease 2019 (COVID-19), emerged in early December 2019 in China and became a pandemic situation worldwide by its rapid spread to more than 200 countries or territories. Bats are considered as the reservoir host, and the search of a probable intermediate host is still going on. The severe form of the infection is 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 inflammation in response to SARS-CoV-2 infection is considered as the leading cause of mortality in COVID-19 patients. COVID-19 patients have thus higher levels of many proinflammatory cytokines and chemokines. The blood laboratory profile of the COVID-19 patients exhibits lymphopenia, leukopenia, thrombocytopenia, and RNAaemia, along with increased levels of aspartate aminotransferase. SARS-CoV-2 infection in pregnant women does not lead to fetus mortality, unlike other zoonotic coronaviruses such as SARS-CoV and MERS-CoV, and there is, to date, no evidence of intrauterine transmission to neonates. Rapid diagnostics have been developed, and significant efforts are being made to develop effective vaccines and therapeutics. In the absence of any virus-specific therapy, internationally, health care authorities are recommending the adoption of effective community mitigation 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 recent research developments.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing the Coronavirus Disease 2019 (COVID-19), was first reported with pneumonia-like symptoms in Wuhan, China, in late 2019 [1]. The initial human-to-human spreading of the virus was noted in an epidemiological investigation on January 20, 2020, where two patients were detected SARS-CoV-2 positive in Guangdong Province and who had no travel history of personal visits to Wuhan in the past [2]. Subsequently, the assumptions of human-to-human transmission were strengthened by the report of COVID-19 in 14 hospital staff from patients [3]. Since then, SARS-CoV-2 has affected 6.22 million people and plagued more than 373,032 human patients (June 1, 2020). Although currently, the case fatality rate (CFR) in COVID-19 outbreaks is less than previous SARS and MERS outbreaks [4], a sharp rise in CFR has been observed during the last few weeks, reaching to more than six per cent. COVID-

* Corresponding author. Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Colombia.
** Corresponding author. Division of Pathology, ICAR –Indian Veterinary Research Institute, Izatnagar, Bareilly, India.
E-mail addresses: kdhama@rediffmail.com (K. Dhama), arodriguezm@utp.edu.co (A.J. Rodriguez-Morales).

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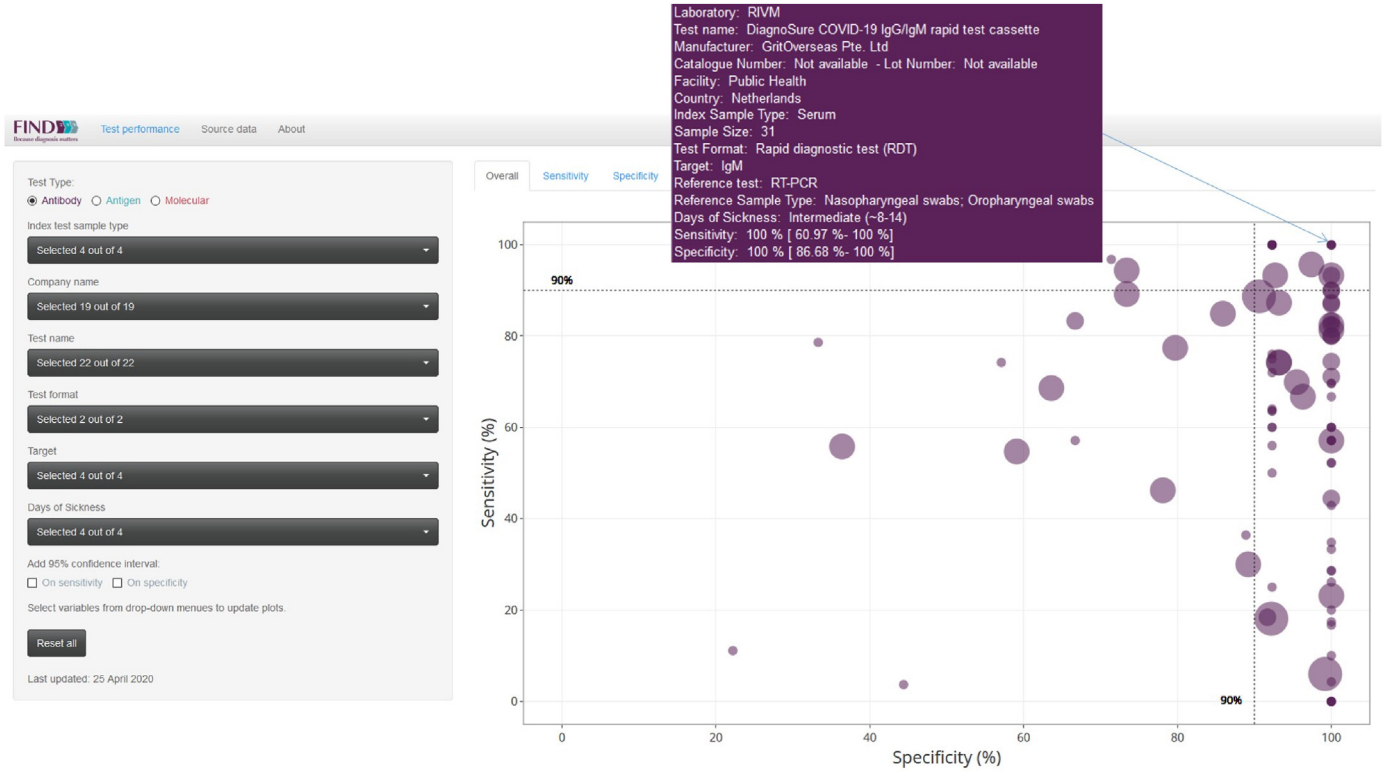

Fig. 1. FIND Diagnostic Performance Data Tool (https://www.finddx.org/covid-19/dx-data/) for assessment of serological, antigen and molecular tests for SARS-CoV-2 infection.

19 has been declared a pandemic [5–7]. 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) [2,8–10]. Deaths in the severe form of COVID-19 were reported mostly due to respiratory failure [2,9], probably caused by hyper inflammation resulting in lethal pneumonia. COVID-19 associated fatalities were mainly published in elderly patients with known comorbidities [2,9] rather than in 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 pneumonia severity index (PSI) score compared to young patients. Elderly patients also possess more chances of multiple lobe involvement ($P < 0.001$) than young patients [11]. This review article presents an overview of this virus (SARS-CoV-2) and the disease (COVID-19) with a particular reference to clinical pathology, pathogenesis, and reviewing multiple relevant references in the field [12–148].

2. Literature sources

For the current narrative review, we searched on the following scientific bibliographical databases: Web of Sciences, Scopus, PubMed/Index Medicus, ScienceDirect, SciELO, and LILACS, using the combined terms: “COVID-19,” “SARS-CoV-2,” “coronavirus,” “clinical pathology,” “pathogenesis."

2.1. SARS-CoV-2/COVID-19; A brief overview

SARS-CoV-2 has spread rapidly through travellers to more than 200 countries across the globe [6,94,120]. Apart from China, the countries severely affected by this virus include the USA, Brazil, Russia, United Kingdom, Italy, Spain, Iran, South Korea, France, India, Germany, Japan, Spain, Peru, Turkey, among many others [6]. Presently, SARS-CoV-2 has posed severe negative impacts on the economy of China and other countries besides social effects, 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 [15,78].

The zoonotic links and spillover of SARS-CoV-2 and transmission to humans have been implicated in this infection as also reported with SARS and MERS [12,53,64,71,79,93,100]. Bats and pangolins have been suggested to have links with SARS-CoV-2 [12,53,64,71,79,93,100,124,133]. Recently, some domestic animals, such as dogs and cats in different European and Asian countries, have been found infected as a consequence of their interaction with SARS-CoV-2 infected human owners [81,137–139]. Besides, a study performing experimental infections with SARS-CoV-2 found cats and ferrets to be susceptible to this virus [81,107]. Other felines, such as tigers and lions in New York, USA, have been found infected, also a consequence of their interaction with infected workers in one zoological park of the city [81,137–139]. These pieces of evidence suggest a potential anthropozoonotic transmission and animal receptivity and susceptibility for the virus as a result of reverse zoonosis. Taking into account the higher similarity between the spike glycoprotein of current virus (SARS-CoV-2) and previous coronaviruses, a study hypothesised 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 [111]. SARS-CoV-2 origin of exposure to humans has been related to the seafood market in Wuhan, China [63,80], which is a wet-market, selling various kinds of poultry, bats, snakes, and other wildlife animals, acting as a hotspot for the human-animal interface and likely to pave the way for the emergence of novel pathogens such as SARS-CoV-2 [10,51]. Several essential preventive measures, like curtailing population movements, avoiding mass gatherings, educational institutions closure, home office, have implemented to minimise and break the virus spread cycle [61].

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 [5,21,29,125,129,131]. Over time, new serological tests have appeared, in addition to molecular analyses [86]. However, their diagnostic performance remains to be validated. With the FIND diagnostic performance data tool (https://www.finddx.org/covid-19/dx-data/), it is possible to assess the current information regarding the diagnostic performance of available commercial tests assessing antibodies, antigens and molecular techniques (Fig. 1). Given the present scenario, the best option, especially during the first two weeks of disease, is the use of molecular tests. Before this point, the value of serological tests seems to be limited. After that, especially for epidemiological purposes, seroprevalence studies would be useful. In particular, the use of IgA appears to be of higher value than IgM [140,141].

An effective treatment regimen and vaccine is urgently needed to halt the COVID-19 spread and death toll [18,34,55,93,102]. The lessons learned from earlier pandemics and epidemics of SARS, MERS [142], bird flu, swine flu, Ebola, Zika, and Nipah along with exploring considerable advances in science and technology including research to repurpose drugs [75,99,143] and find new antivirals [144] would aid in discovering therapeutics/drugs and suitable vaccines to combat the current pandemic posed by COVID-19 [31–35,77,87,104,105].

2.2. Clinical pathology

COVID-19 clinical manifestations include respiratory (mainly pneumonia), digestive, and general symptoms [7,9,24,25]. The CFR is approximately 5.99% now (June 1, 2020), although in countries such as France can reach as high as 18.98% (28,802 deaths from 151,753 cases), severely affected persons die owing to too much alveolar injury and progressive respiratory failure [88]. Asymptomatic carriers revealing no clinical signs (such as cough, fever, fatigue or chest/lung pathology) can be seen in persons infected with SARS-CoV-2 [23], and these carriers can shed virus up to 21 days that can potentially affect persons coming in contact [50]. The estimated incubation period is reported to vary from 3 to 6 days, with a mean value of 5.2 days [9,62]. Additionally, Kritas et al. [56] reported the incubation period of COVID-19 from 1 to 14 days. In contrast, the median incubation period of SARS-CoV-2 was said to be four days in a study of 1099 COVID-19 cases in China [41]. The clinical symptoms manifested by COVID-19 patients are reported to be milder than in SARS and MERS infections [10,136,145]. Moreover, the milder nature of the symptoms was said to be the major hurdle in the identification of the transmission chains, followed by subsequent tracing [58]. The clinical manifestations of the COVID-19 were mainly observed in older and immune-compromised individuals with pre-existing conditions like cardiovascular disease, hypertension, asthma, and diabetes [9,115].

COVID-19 symptoms can include fever, mild chills, pharyngalgia, dry cough, fatigue, shortness of breath, severe respiratory distress, pulmonary pneumonia [42], that be aggravated if it goes undiagnosed and not treated timely [89,126]. Additionally, fever and cough are reported to be the most common symptoms associated with COVID-19 patients [108]. However, mild symptoms like nausea, headache [95], sore throat, myalgia, vomiting and sometimes diarrhoea have also been reported in COVID-19 patients [65,108]. Furthermore, emerging neurological manifestations, such as anosmia and ageusia, have been reported [82]. 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 [136]. Additionally, the presence of viral RNA in the faecal samples of the COVID-19 patients suggests probable transmission by the faecal-oral route [48]. Recent evidence indicates that even asymptomatic patients may be unaware of their SARS-CoV-2 infection status and can, therefore, transmit the virus from faeces to others unknowingly if they are not isolated for medical observation [54].

Previously evidence suggested that drugs such as chloroquine (or hydroxychloroquine) with or without azithromycin or clarithromycin, would be useful [75,99,143], nevertheless somes studies showed no significant benefit for patients and concerning risk of adverse effects [149,150]. Other drugs such as lopinavir/ritonavir, remdesivir, among others, may be used in mild to severe, under close medical observation given the frequency of adverse effects [43]. Potential adverse effects of chloroquine or hydroxychloroquine plus azithromycin include cardiac arrhythmias, hypoglycemia, neuropsychiatric effects, such as agitation, confusion, hallucinations and paranoia, interactions with other drugs, and metabolic variability, among others [146].

Additionally, shedding of the virus from nasopharynx for seven days or more with subsequent detection of the virus in blood and stool was reported. However, the urine was found negative for the virus [128]. In a study, the SARS-CoV-2 RNA detected in stools was found to accurately correlate with the pharyngeal samples of COVID-19 patients. Moreover, the absence of gastrointestinal symptoms in the patients had no relation to the severity of pneumonia [130].

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 [9]. CT imaging alterations in COVID-19 patients are common and should be considered by clinicians. Such changes would be highly variable. Additionally, the other finding includes bilateral multilobular subsegmental consolidation of lungs in early stages followed by multiple mottling and ground-glass opacity [8,9,22]. Severe lung lesions were evident on around day 10th after the beginning of symptoms in most patients who recovered from COVID-19 illness [84,85]. Moreover, extensive lower respiratory tract involvement was reported in pneumonia associated with SARS-CoV-2 infection [9].

Adverse maternal and prenatal effects like miscarriage [122], fetal growth retardation, premature birth along with neonatal mortality have been reported in SARS-CoV and MERS-CoV [14,124]. 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 [114,147,148]. In contrast to this, other studies suggest that SARS-CoV-2 infection during pregnancy does not lead to maternal mortalities unlike SARS-CoV and MERS-CoV disease with no evidence of intrauterine or transplacental transmission to neonates [96,101].

The blood laboratory profile of the COVID-19 patients revealed lymphopenia, leukopenia, thrombocytopenia and RNAaemia along with higher levels of aspartate aminotransferase and hypersensitive troponin I [8–15]. Initially, procalcitonin levels were reported normal, but a little rise in the levels at the advanced stage was noted, indicating probable secondary infections [9].

The platelet count and procalcitonin levels were reported to be close 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 [106].

As far as clinical features are concerned, SARS-CoV-2 associated pneumonia is different from other pneumonia in that 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 [132]. Recent studies suggest that lymphopenia (< 1000 cells/mL), neutrophilia (> 10,000 cells/mL), elevated LDH (> 350 IU/L), elevated C-reactive protein (> 10 mg/dl), D-dimer (> 1 mg/ml), elevation of total bilirubin, hepatic transaminases,

ferritin, and troponins, are prognostic markers [43].

2.3. Pathogenesis

The COVID-19 pathogenesis involves mild to severe respiratory involvement [2,134] with an incubation period ranging from 1 to 14 days [41,56]. Severe pneumonia mostly bilateral occasionally unilateral, leading to respiratory failure is the leading cause of mortality in SARS-CoV-2 infection [108]. Respiratory failure in severe COVID-19 disease is generally associated with hyperinflammation. A cytokine storm syndrome probably may be the reason for hyper inflammation in severe SARS-CoV-2 illness [9,74]. Interleukin 6, interleukin 8, E-cadherin, MCP-1, VEGF, among other molecules are involved in the cytokine release syndrome through trans signalling [76], consequently, immunomodulation with drugs such as tocilizumab [83], sarilumab, and related agents is under compassionate use and investigation [99]. At ClinicalTrials.gov there are more than 30 registered trials with tocilizumab for COVID-19, 8 for sarilumab, and 3 for eculizumab.

Main imaging findings 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 [8–15].

Further, in COVID-19 patients, the opacities of both lungs are usually diffuse, showing large areas of patchy shadow with uneven density [24]. 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 [9]. Though it mainly affects lungs, COVID-19 patients with multi-organ dysfunction, including blood vessels, heart, liver, kidney and other organs were also reported [127]. 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 [67]. That can result in the severe inflammatory cascade, especially by cytokines, earliest targets being macrophage, lymphocyte and pneumocytes [67].

At a molecular level, both cellular and humoral immune mechanisms are believed to be responsible for this pathogenesis [13,109]. In addition to direct macrophage and lymphocyte stimulated response, T cell and B cell-mediated immunological mechanisms are initiated against SARS-CoV-2 [13,109,112]. This process includes SARS-CoV-2 antigen presentation and activation of B cells [13,67,109,112]. Involvement of T-helper and T-cytotoxic cells also may occur. Besides that, the role of cellular response needs to be further evaluated. Cytotoxic T cells (CD8) may kill the virus directly, while helper T cells (CD4) presenting SARS-CoV-2 antigens to B cells. B cells will product immunoglobulin and contribute with the neutralisation [9,13]. SARS-CoV-2 attacks respiratory mucosal epithelial cells and spread to other cells, infects peripheral white blood cells and immune cells, particularly T lymphocytes. That explains, in part, the observed lymphopenia clinically found in COVID-19 patients [24]. Multilobular infiltration and lymphopenia found in SARS-CoV-2 infection may suggest cellular response [24]. Cellular immune deficiency and lymphopenia reported in COVID-19 patients suggest cell-mediated immune response against SARS-CoV-2 [24,109]. Damage to lymphocytes, including T lymphocytes by coronavirus leads to lymphopenia, predisposing to secondary bacterial infections and exacerbating severity [24]. 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 [9,24,67]. Lymphopenia and sustained inflammation are characteristic findings in severe and fatal cases [112]. 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 [11,59,66]. 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 [13].

The humoral immune response may also have a role in the pathogenesis of COVID-19 [13,40]. As there is a decrease in levels of immunoglobulins in COVID-19, this may indicate effects on antibody-producing cells B lymphocytes [24]. Though antigens of SARS-CoV-2 have shown potential for stimulating antibody production, the impact of overall lymphopenia may have caused depletion of immunoglobulins [24,123]. Antibodies developed against SARS-CoV-2, especially anti-spike protein antibodies, may be responsible for the infection of immune cells [112]. 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 [112].

Most of the molecular mechanisms of pathogenesis of SARS-CoV-2 infection are being elucidated at a rapid pace to understand the disease and to develop countermeasures [40,109,112,123]. 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 [24,25]. However, future explorations will enable a better understanding of pathogenesis mechanisms [67,109,112,123]. 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 [20,102]. Spike (S) and nucleocapsid (N) epitopes induce an immune response [110]. Targeting S protein both cellular and humoral immunity can be developed by inducing neutralising antibodies and by developing protective cellular immunity [102], 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 [24,109]. 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 [109].

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 [123]. SARS-CoV-2 is a single strand RNA virus. Spike protein (S) helps SARS-CoV-2 in binding and entry into cells [60,68,109]. S1 subunit of S glycoprotein enables strong binding to the ACE2 receptor while as S2 subunit ensures fusion with the host cell [30,47,113]. Within the host respiratory tract and gastrointestinal tract, epithelial cells can be affected [11,96]. In general, respiratory epithelial cells (pneumocytes) and enteric cells (enterocytes) are infected by CoVs, causing cytopathic changes [44]. Type 2 pneumocytes and unciliated bronchial epithelial cells are prime targets [44,112]. Cytopathic effects on respiratory epithelial cells and cessation of the cilium beating of the cells have been noted [11,133]. Though cytokine storm is believed to be responsible for this pathogenesis, however, the actual pathogenic mechanisms are yet to be elucidated.

2.4. Immunopathology

In COVID-19, high leukocytes counts and neutrophil-lymphocyte-ratio were 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 [90]. A decrease in helper T cells along with

suppressor T cells has been published in patients with less severe COVID-19, however, in critical 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 [90].

COVID-19 patients show higher plasma levels of proinflammatory 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 [9,90]. 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 [24,90].

Upregulation of proinflammatory cytokines in serum was found to be associated with severe pulmonary damage and inflammation in SARS-CoV [121] and MERS-CoV infections [70], and also in COVID-19 [9]. Surprisingly, in SARS-CoV-2 disease, elevated levels of both Th1 and Th2 cytokines were reported in comparison to SARS and MERS where only Th1 cytokines were upregulated [9,121].

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 proinflammatory 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 [28]. 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 [91].

2.5. 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 [66,135]. Based upon bioinformatics profiling of the class I and class II MHC molecules researchers have analysed the binding potentials of the SARS-CoV-2 proteins and epitopes to MHC molecules within the host body cells and can also predict the probable mutational hotspots [49]. With the help of netMHCpan suite of software, it was elaborated that when proteins-peptides of SARS-CoV-2 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 [52].

Immune vulnerability maps of SARS, MERS and SARS-CoV-2 were compared for B and T cell epitope profile, and findings emphasised that there is variation in T-cell biology and response to SARS-CoV-2. At the same time, no significant difference was observed in B cell epitope profiling [98]. Albeit that, vaccine development is still underway. At ClinicalTrials.gov, there are 37 vaccine trials registered (June 1, 2020) from China, United Kingdom, Egypt, Canada, USA, Netherlands, Pakistan, Australia, Denmark, Colombia, Austria, Brazil, France, Pakistan, Spain, and Tunisia; 17 of them now recruiting.

An overview of COVID-19 clinical pathology, pathogenesis and immunopathology is presented in Fig. 2.

2.6. COVID-19 mitigation measures

Under the present pandemic situation, mitigation measures include strict vigilance, social distancing, enhanced screening, surveillance, monitoring, isolation, and quarantine of suspected patients, strengthening medical facilities, adopting best health care and biosafety measures by healthcare workers in contact with COVID-19 patient, following good hygiene, sanitation and disinfectant practices, limiting tours and travels, cancellation of visas, issuing of advisories and updates for the general population as large scale awareness programmes for the public with tips to avoid infection from this virus. Personal and community measures are also essential and include personnel hygiene, especially hand hygiene and reducing touching of nose and face, “lockdown” measures such as the closing of schools, colleges, malls, and offices, advising the public to stay at home in affected areas. All the measures above are being used to some extent in countries affected by the pandemic, and there are many challenges ahead [19,39,44,45,57,72,92,117].

Considering COVID-19 as a public health emergency of international concern (PHEIC) and subsequently as a pandemic, efforts are being directed at prevention and control at case, cluster, and community level with measures implemented at both national and international levels [46,117]. 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 [97,103,118]. Several affected countries have shifted response from the containment to mitigation strategies, with a vast number of them with weeks of lockdown such as most countries in Europe, many in Latin America, and some in Africa and Asia [19,38,119]. Community sanitation, restriction of free movement and gatherings, cancellation of social and 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 [38]. It is important to note that lower-income and middle-income countries must be supported technically and financially to develop the capacity for PCR testing and management of COVID-19 successfully [16].

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 minimise the risk of further entry and spread and to prevent future transmission, severity and loss of lives [38]. 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 [69]. 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 **c**ases; first **c**ases; first **c**lusters, and **c**ommunity transmission and spread) [16,119]. Given the proven zoonotic linkages, One Health approach may play a crucial role in countering this virus [17,27,36,73,81].

Quarantine, isolation, and physical distancing, in this context, are of utmost relevance [116]. Work and study activities should be carried out virtually. Still, many commercial activities should be partially restricted [37]. Cases with mild respiratory symptoms should stay at home in respiratory isolation and be treated with hydration and paracetamol if needed. Visits to health centres should only be made when justified by the presence of risk factors (underlying severe disease) or warning signs (such as breathing difficulties or cognitive impairment) [37]. Older patients are especially susceptible to complications, and then, this population should be restricted at home. However, to reduce transmission, people of all ages must be committed to the prevention, education, and health promotion. Thus, in the absence of vaccines (that will take at least a year) or other preventive strategies, reducing the contact rate will be the only strategy to slow the progression of this pandemic [26,37].

These measures and the proper support and advice from scientific societies, such as the Brazilian Society of Infectious Diseases, in addition to the international organisations, such as the World Health Organization (WHO), adequately applied, will help to slow the number of new cases expected, will help to decrease them [37]. It is difficult to predict how long these preventive measures must be maintained, but

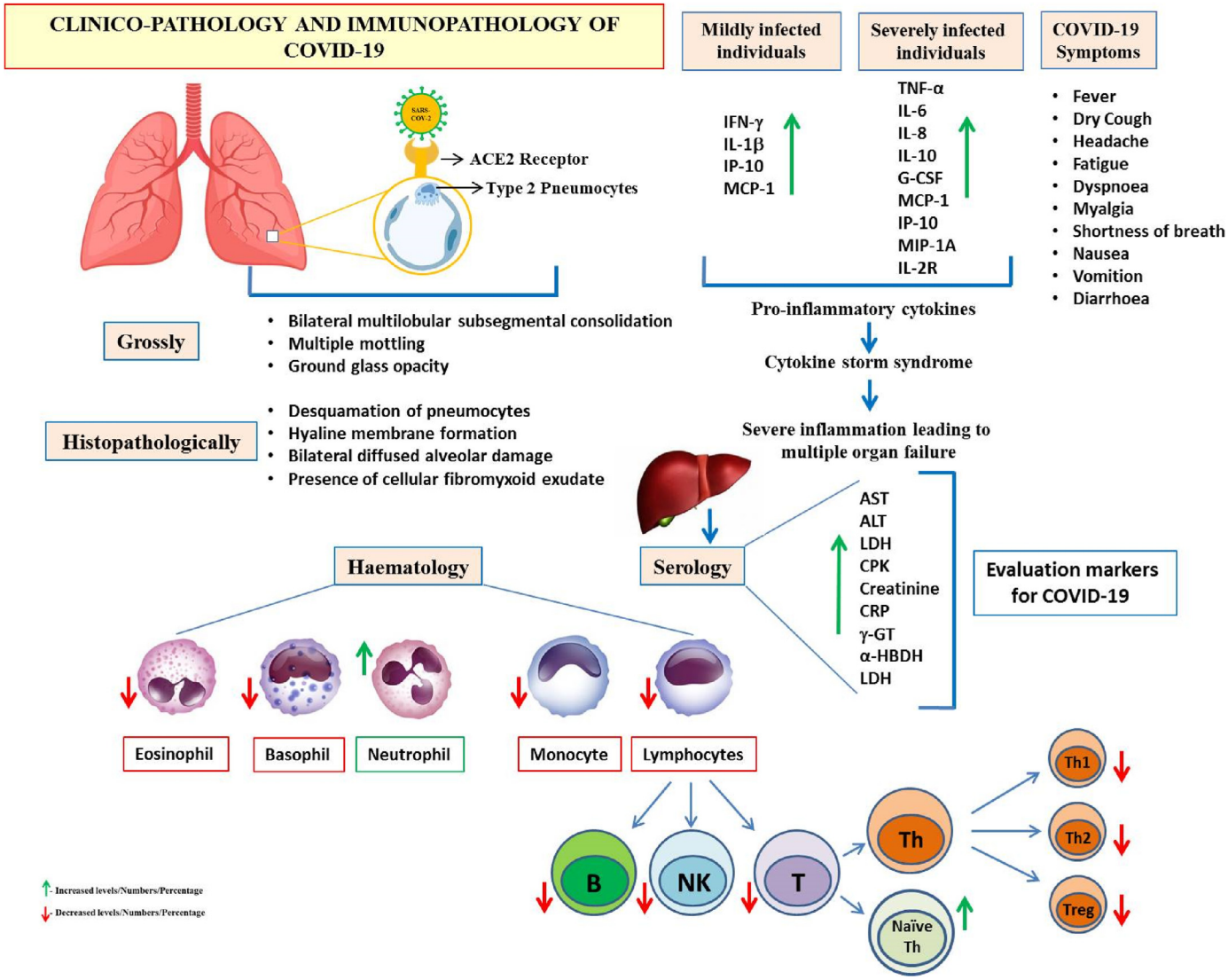

Fig. 2. An overview of COVID-19 clinical pathology, pathogenesis and immunopathology.

the epidemiological situation should be carefully and closely assessed to redefine strategic intervention approaches. As has been indicated before, the earlier and more rigorously they are incorporated, the faster the epidemiological conditions will be reversed, and our regular routines resumed [26,37].

3. Conclusion and prospects

The SARS-CoV-2 continues to expand in the form of pandemic and will be responsible for significant morbidity and mortality and will leave the world in a situation of substantial economic loss. 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 such as fever, coughing, sneezing, headache, respiratory distress, chest pain and fatigue are suggestive of the massive involvement of lungs as a principal organ leading to severe pneumonia and subsequently death. Bilateral multilobular subsegmental consolidation, multiple mottling, and ground-glass opacity with a variable degree of alterations in the lungs on CT imaging may suggest the degree of involvement.

Cytokine storm associated with the rampant inflammation resulted into the release of proinflammatory 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. 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 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.

Author contributions

All the authors substantially contributed to the conception, design, analysis, and interpretation of data, checking and approving the final version of the manuscript, and agree to be accountable for its contents.

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Declaration of competing interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

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