Review

The interplay of co-infections in shaping COVID-19 severity: Expanding the scope beyond SARS-CoV-2

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ABSTRACT

High mortality has been reported in severe cases of COVID-19. Emerging reports suggested that the severity is not only due to SARS-CoV-2 infection, but also due to coinfections by other pathogens exhibiting symptoms like COVID-19. During the COVID-19 pandemic, simultaneous respiratory coinfections with various viral (*Retroviridae, Flaviviridae, Orthomyxoviridae,* and *Picoviridae*) and bacterial (*Mycobacteriaceae, Mycoplasmataceae, Enterobacteriaceae* and *Helicobacteraceae*) families have been observed. These pathogens intensify disease severity by potentially augmenting SARSCoV-2 replication, inflammation, and modulation of signaling pathways. Coinfection emerges as a critical determinant of COVID-19 severity, principally instigated by heightened pro-inflammatory cytokine levels, as cytokine storm. Thereby, in co-infection scenario, the severity is also driven by the modulation of inflammatory signaling pathways by both pathogens possibly associated with interleukin, interferon, and cell death exacerbating the severity. In the current review, we attempt to understand the role of co- infections by other pathogens and their involvement in the severity of COVID-19.

Contents

Introduction

Many viruses and bacteria are involved in pathogenesis of diseases. During lifespan, the hosts are continuously exposed to potential pathogens. They chronically or latently get infected and carry these pathogens in colonizing microbial flora. Each infection is most likely a co-infection [1]. During SARS-CoV-2 pandemic prevalence of co-infection has been reported by several studies [2,3]. It is also quite likely that immunosuppression caused by one infecting agent paves the way for more infections, thus worsening the condition of the host. Depending on its interactions with the host, co-infection has a synergistic or antagonistic effect depending on its interactions with the host. In a positive interaction, both pathogens support one another in a constructive engagement, which eventually escalating the sickness. Conversely pathogens may interact negatively by impeding each other through resource competition or by interfering through, for example, non-interferon-mediated cellular response and enhanced resistance to either pathogen [4]. Such opposing interactions are frequently present among viral infections.

The case in point is when one pathogen promotes the replication of another pathogen and increases the severity of the infection, but at the same time, it may result in the early clearance of infection through a phenomenon known as viral interference [5,6]. The latest statistics suggest that SARS-CoV-2 infected more than 238 million individuals across the globe, and at least 4.8 million people died. The clinical presentations of COVID-19 related illness range from asymptomatic infection to life-threatening consequences. The virus has been evolving since it first appeared and new strains are emerging, most with improved infectivity [7]. Continuous efforts are being made to make a standard accepted treatment strategy for COVID-19. In most cases, comorbid disorders are linked to severity. However, co-infections also contribute to illness severity, and despite this, less attention has been paid to other pathogens that are concurrently present and how they may exacerbate the COVID-19 sickness [8]. The situation therefore becomes challenging to differentiate SARS-CoV-2 infection clinically from other respiratory pathogen co-infections.

Host responses other than direct interactions among pathogens are associated with disease consequences. One pathogen may modulate the host environment to favor the other pathogen's survival and pathogenesis. Among the noted host responses, oxygen stress is common and mainly responsible for endothelial barrier dysfunctions and lung tissue damage [9]. When two infections co-exist, the chance of developing oxidative burst is more, which increases the severity of the condition. Reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), superoxide ($O^{2\bullet-}$), nitric oxide (NO), and hydroxyl radical ($\cdot$OH) linked to typical physiological processes, are often formed from mitochondria and peroxisomes organelles. Some antioxidant enzymes can remove ROS from the body. Superoxide dismutase (SOD), catalase (CAT) is part of anti-oxidative enzymatic defense, whereas glutathione (GSH) is a part of the non-enzymatic machinery. Therefore, the production of ROS and its neutralization are maintained in equilibrium. However, when dysregulation occurs, the system's redox equilibrium is compromised, resulting in oxidative stress. These consequences may alter cellular energy homeostasis. Oxygen stress has also been linked to HIV, EBV, and HCV infection, in addition to disease conditions [10–12]. In HIV/HCV co-infection, increased oxidative stress is associated with severe liver damage [13]. The current review discusses the possible pathological consequences of co-infection of different pathogens with SARS-CoV-2 (Fig. 1).

SARS-CoV-2 pathogenesis

Coronaviruses carry an encapsulated positive-stranded RNA virus genome. SARS-CoV-2 is composed of four major structural proteins: Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) [14]. SARS-CoV, MERS-CoV, and SARS-CoV-2 are sub-grouped as mild coronaviruses. In contrast, severe coronaviruses include HKU1, NL63, and OC43 (Betacoronaviruses) and 229E (Alphacoronavirus). The risk of developing severe COVID-19 is higher in patients with co-morbidities and/or co-infections like hypertension, obesity, AIDS/HIV, tuberculosis (TB), metabolic syndrome, diabetes, cardiovascular disease, renal disease, and respiratory illness. SARS-CoV-2 utilizes several host factors to enter the recipient cell. The primary entry point is binding to angiotensin-converting enzyme 2 (ACE2) receptor as virus's spike protein (S), primed by the host factor TMPRSS2 makes the attachment. This leads to the fusion of viral and cellular membranes, further allowing the entry of the viruses into the cells. Mutations in RBD region of spike protein are critical for the enhanced infectivity of SARS-CoV-2 [15]. The 805 amino-acid long ACE2 is primarily expressed in alveolar epithelial cells of the lungs, nasal epithelial, venous endothelium and arterial cells, arterial smooth muscle, and enterocytes. A 70 kDa serine protease TMPRSS2
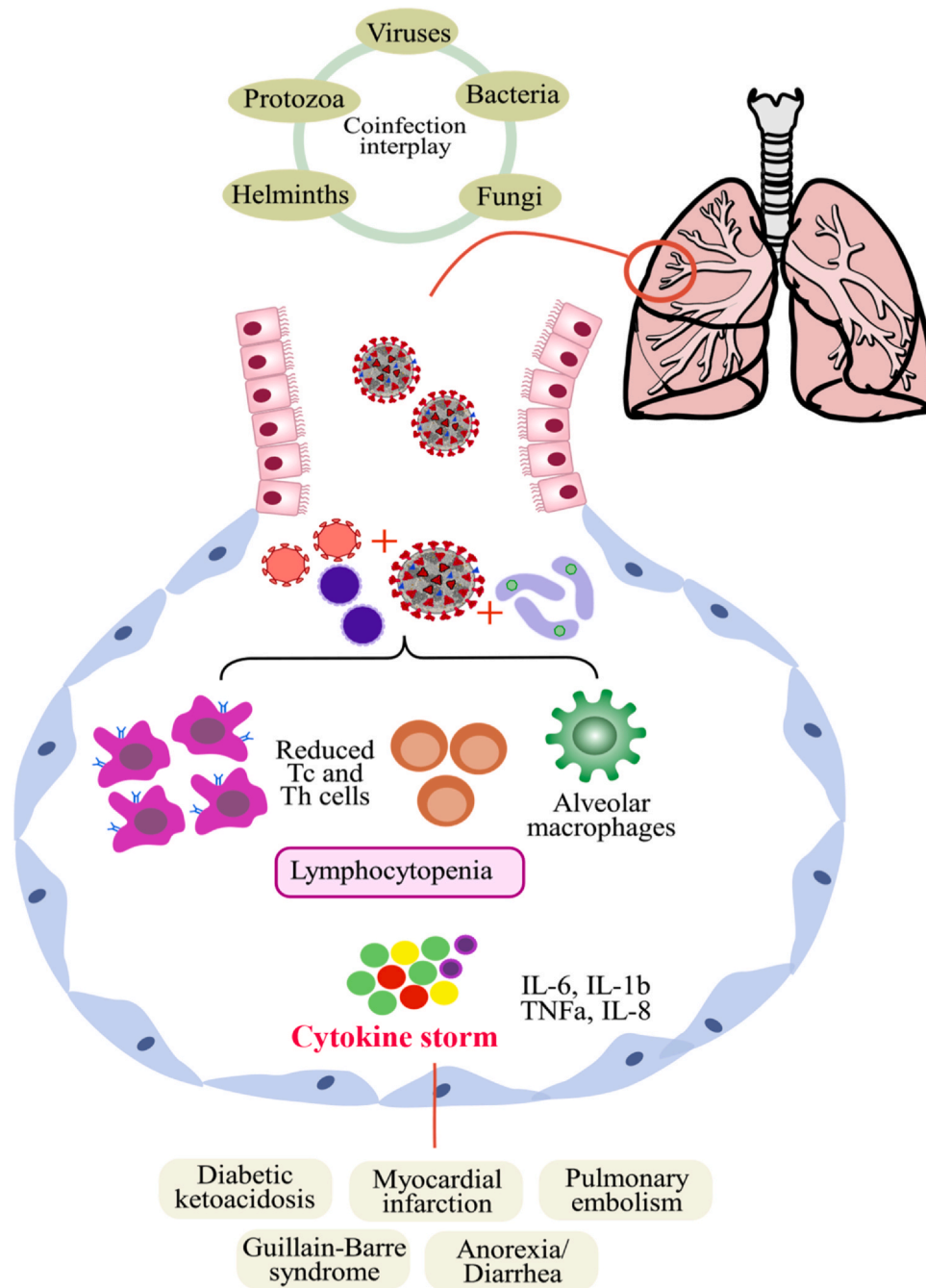
Fig. 1. SARS-CoV-2 infection infects different cell types, including helper T-cells and cytotoxic T-cells, causing lymphocytopenia in the alveolar region. As alveoli are in direct contact with the bloodstream, numerous inflammatory mediators can travel through this route to induce organ damage in distant parts of the body. Such damage can be compounded by confection with other viruses, bacteria, fungi and helminths.

is involved in several physiological and pathological processes, including blood clotting, digestion, tumor cell invasion, tissue remodeling, apoptosis, and inflammatory responses [16]. Studies have revealed that TMPRSS2 and ACE2 often present in bronchial transient secretory cells, cause SARS-CoV-2 entry and pathogenesis, leading to excess ROS and affecting cardiovascular and respiratory abnormalities [17]. Compared to adults, children have a lower infection risk for SARS-CoV-2, milder symptoms, and better clinical outcomes, possibly due to lower ACE2 expression in nasal epithelia [18]. The majority of COVID-19 symptoms is primarily respiratory and includes difficulty breathing, lung infection, pneumonia, and fever [19]. Infected individuals may exhibit digestive symptom such as diarrhea and vomiting as part of their disease presentation [20].

An increase in serum inflammatory markers is strongly associated with the severity of COVID-19. It exacerbates cytokine release and chemokines, indicating a cytokine storm in the infected patients [21]. Table 1 lists the signature molecules commonly observed in co-infection of SARS-CoV-2 and associated pathogens.

Viral co-infections associated with SARS-CoV-2

The COVID-19 pandemic impacted mass circulation and seasonality of various pathogens. Reportedly, the morbidity burden was higher in several respiratory viruses, such as influenza virus co-infections, which were exclusively observed during the first pandemic wave [40]. Therefore, SARS-CoV-2, as an opportunistic pathogen,

Table 1

Pathogens are critically involved in co-infection with SARS-CoV-2. The infective agents and associated molecules are listed. The signature molecules are indicators of pathogen-specific co-infections with SARS-CoV-2.

S.no.	Pathogens associated with SARS-CoV-2 coinfection	Family	Signatory molecules specific to coinfection	Reference
1	Human Immunodeficiency virus (HIV)	Retroviridae (ssRNA)	TNFα, Capase 8, Caspase 3, RIPK1-RIPK3	[22,23]
2	Influenza virus	Orthomyxoviridae (ssRNA)	TLR, IL-6, IL-1β, JAK-STAT	[24,25]
3	Dengue virus (DENV)	Flaviviridae (ssRNA)	Interferons α, β, and γ, IL-8	[26,27]
4	Rhinovirus	Picornaviridae (ssRNA)	IFN type1, IL-4,−5,−9,−33, Caspase 8, RIPK1	[28,29]
5	*Mycobacterium tuberculosis*	Mycobacteriaceae (Gram +ve)	IL2, IL1β, IL4, IL6, IFNγ, TNFα, JAK-STAT	[30,31]
6	*Mycoplasma pneumoniae*	Mycoplasmataceae (Gram -ve)	Nrf2, TLR2, NF-kB, MyD88	[32,33]
7	*Klebsiella pneumoniae*	Enterobacteriaceae (Gram -ve)	NF-kB	[34]
8	*Helicobacter pylori*	Helicobacteraceae (Gram -ve)	NF-kB, STAT-3, IL-6	[35,36]
9	Helminth	Helminths	IL-33, −35, MAPK, ERK1/2	[37]
10	*Rhizopus oryzae*	Rhizopodaceae (fungus)	NF-kB, JAK-STAT, GRP78	[38]
11	*Plasmodium*	Plasmodiidae	RIG-1, NF-kB, IL-6, IL-12	[39]

must be studied in conjunction with other viral pathogens, as detailed in the upcoming sections.

Human Immunodeficiency virus (HIV)

HIV, a member of the retrovirus family, is known to cause acquired immune deficiency syndrome (AIDS), wherein the patient develops flu-like symptoms as the viral burden increases while immune function declines. HIV typically infects CD4 + T lymphocytes in addition to monocytes and thymocytes and enters the cell by targeting surface molecules such as CD4, CXCR4, and CCR5. As this virus attacks CD4-expressing helper T cells (Th), their numbers decrease, leading to increased susceptibility of infected person to contract other disorders. According to WHO, HIV infection enhances the propensity of SARS-CoV-2 infection and doubles the risk of death [41]. HIV infection alters numerous signaling pathways, including NF-kB-mediated cytokine production and T-cell proliferation. Additionally, the virus stimulates CTL, macrophages, and NK cells to activate the TNF-mediated signaling pathway as viral protein gp120 interacts with CD4, activating caspase 8 and 3, ultimately leading to cell death [42]. In contrast, in SARS-CoV2-infection, the cell death is due to pyroptosis, necroptosis, and apoptosis [30]. The activation of TNFα pathway leads to RIPK1-RIPK3 complex formation during the infection causing oligomerization of MLKL ultimately leading to necroptosis [23]. The caspase 8 activation in both the HIV-induced apoptosis and SARS-CoV-2-mediated necroptosis could be the possible reason of severity observed in the co-infected patients. Although precise mechanisms of co-infection and subsequent disease occurrence are not known, it has been found that CD4 + T-cells are considerably lower in such patients. As the number of CD4 + T-cells reduces, cytokine storm followed to the tissue damages. Even though patients who are HIV-157 SARS-CoV-2 co-infected and those who are exclusively SARS-CoV-2 infected have different immune cell distributions. SARS-CoV-2 infection has been more common in AIDS patients, particularly in those with concomitant conditions and high blood HIV RNA titers [43].

Influenza virus

The Orthomyxoviridae family of viruses includes influenza viruses, which are negative-sense, single-stranded, segmented enveloped viruses. Broadly, the influenza viruses are grouped into four genera: IAV, IBV, ICV, and IDV, of which IAV and IBV pose a more significant threat to humans [44]. The error-prone RNA polymerase modifies hemagglutinin (HA) and neuraminidase (NA) of influenza, which further promotes antigenic drift in IAVs and IBVs. This leads to altered antigenic surface properties, aiding in subsequent epidemics worldwide. Like coronavirus, influenza virus can also spread among non-human reservoirs, among which the clinical symptoms differ slightly. Influenza-infected patients experience fever, myalgia, and

malaise, wherein the upper respiratory tract is affected [24]. Influenza virus enters the host cell through PRRs such as TLR1, 2, and 6. Cellular infection with IAV induces expression and activates IL-1β, IL-18, and caspase-1 [25]. In addition, NF-kB and IRFs get translocated into the nucleus to initiate expression of pro-inflammatory cytokines such as TNFα, IL-6, IL-1β. Infection-mediated expression of IFN-γ genes activates JAK-STAT pathway further phosphorylating STAT1 and 2 [45]. The coronavirus-encoded protein Nsp1 interferes with the JAK-STAT pathway and reduces the expression of interferon-stimulated genes (ISGs), thus facilitating immune evasion. This strategy adopted by SARS-CoV-2 might alter the infection susceptibility of the host towards influenza virus infection. Numerous cases of SARS-CoV-2 co-infection with Influenza virus were reported in the earlier half of 2020. High prevalence of SARS-CoV-2 infection with influenza A variations were seen in China as well. The diagnostic concern for this dual infection was thus raised. The specific coinfections that contribute to poor illness outcomes have also been observed. Among the symptoms reported, acute respiratory distress syndrome (ARDS), pneumonia, and death were seen in severely infected individuals. As H5N1 infection has been linked to multiple organ dysfunction, influenza has a severe impact on individuals within the age range between the 10–19 years age group, with the lowest risk group over 50 years. During an infection, the host machinery plays a dual role by removing the pathogen and maintaining homeostatic functionality. Although an overactive immune system removes the pathogen, it may also lead to tissue damage. SARS-CoV-2 and influenza virus infections exhibit similar phenomena in the host cells. Hosts employ various defense methods, such as disease tolerance and resistance, based on the type of pathogen and its cellular tropism. Complex interactions between the immune and structural cells occur in the respiratory environment, determining whether the tissue milieu is characterized by resistance or tolerance properties. Epithelial and endothelial structural cells define the resistance or tolerance state. Initially, the host attempts to control viral replication, however, when this resistance is broken, it tries to tolerate the infection and maintains important functions like alveolar gas exchange [46]. An in vivo study in mice elucidated that influenza A virus and SARS-CoV-2 co-infection leads to increased IAV burden. Interestingly, a prior influenza infection reduced the comorbidities [47]. Taken together, these studies underscore the urgency of understanding the co-infection mechanisms of these two viruses.

Dengue virus (DENV)

Dengue is one of the most dangerous vector-borne diseases that prevail in tropical and subtropical regions [48]. The DENV 1–4 serotypes are members of the *Flaviviridae* family. It is a single stranded, positive-sense RNA virus commonly acquired through a mosquito bite by an infected *Aedes aegypti* mosquito. In some instances, life-threatening conditions such as multi-organ failure, plasma leakage

coagulopathy, and dengue hemorrhagic fever may occur [49]. SARS-CoV-2 infection has been prominently documented in dengue-endemic areas such as Latin America and Southeast Asia. In several studies from Indonesia, dengue antibodies have been found in COVID-positive individuals [50]. Interestingly, DENV NS1 disrupts endothelial cell permeability, which was inhibited in the presence of anti-S1-RBD IgG in vitro [51]. Similarities exist in HR2 domain of SARS-CoV-2 spike protein and the DENV envelope protein, as shown by in silico studies indicating possible antigenic cross-reactivity [26]. DENV activates numerous hosts signaling pathways, leading to severe inflammation. The virus undergoes endocytosis by cell surface receptors such as C-type lectins. The innate antiviral response is triggered with expression of α, β, and γ-interferons further activating the JAK-STAT pathway [27]. As the dimerized STATs enter nucleus, expression of proinflammatory cytokines such as IL-8 leads to an intense cytokine storm [52]. Interestingly, the initial signs of both dengue and COVID-19 infections are similar and include fever, headache, and myalgia, but as the illness progresses, clinical manifestations may diverge with the development of illnesses such as constricted intravascular volume hypovolemic shock and plasma leakage [53]. In one study, five COVID-19-positive patients were found to be infected also with DENV2. Three of the five patients died, while the remaining two were hospitalized for the entire duration of the study. There were 31 SARS-CoV-2 and dengue co-infected patients across the dengue endemic countries, and among them, five succumbed (16.13 %), indicating a significantly higher mortality rate compared to single infection for both diseases individually. Thus, akin to other viruses and their co-infection with SARS-CoV-2, DENV posed a significant hazard throughout the COVID-19 pandemic. Both infections cause harm to different body parts, which eventually may exacerbate respiratory, CNS, cardiovascular, liver, and renal disorders. Despite variances in pathophysiology, the overlapping symptoms and shared biomarkers make the co-infection challenging to detect. Further studies to better understand the interaction between these two viruses will help mitigate the cumulative damage by them.

Rhinovirus

Besides co-infection with respiratory and influenza viruses, the COVID-19 pandemic also witnessed an increased rhinovirus involvement. Usually prevalent among children, RSV also shares its infection burden with rhinovirus, adenovirus, and SARS-CoV-2. Rhinovirus is a non-enveloped RNA virus associated with its connectivity with COVID-19 among children [54]. The virus enhances the prolonged persistence of SARS-CoV-2 thereby increasing the potential for transmission.

Interestingly, an in vitro study on discernment of SARS-CoV-2 and rhinovirus co-infection elucidated that the presence of rhinovirus infection in human bronchial epithelial cells (HBEC) blocked SARS-CoV-2 replication by triggering an interferon response [28]. The triggered innate immune response of rhinovirus leads to the activation of dendritic cells, hence enhancing the antiviral response through IFN type 1 signaling [29]. Moreover, the virus enhances IL-4, − 5, − 9, and − 33 [55]. The activation of TNFα signaling leads to the activation of caspase 8, followed by apoptosis. SARS-CoV-2 co-infection might be responsible for RIPK1-mediated necroptosis, thus enhancing its severity [14]. Therefore, the co-infection of these pathogens suggests dual responses, either by blocking the SARS-CoV-2 replication or enhancing the severity of infection through inflammatory damage. The co-infection of viruses is often affected by the host's innate immune response towards these viruses. Co-infection enhances the opportunity for viruses to evade the innate immune system and survive sustainably in the infected host, compounding the damage caused by either virus alone.

Bacterial infections

Numerous studies have reported differing rates of bacterial co-infection and super-infection during the COVD-19 pandemic. It relies on several aspects, including the clinical nature of the SARS-CoV-2 infection, the use of steroids, lymphopenia, and the use of acute antibiotics before being hospitalized. Patients who are chronically sick, hospitalized in the ICU settings, and exhibit lymphopenia have higher rates of bacterial superinfection. Although the microbial superinfection caused by SARS-CoV-2 is not fully understood, it is believed to function akin to influenza. Disruption of the cells that line the respiratory tract makes it simpler for the nasopharynx-residing bacteria to enter the airway and the injured mucosa.

Mycobacterium tuberculosis (Mtb)

Tuberculosis (TB) remains a major medical and social problem in many countries. With its high mortality rates, it is among the top 10 deadliest diseases globally. Mycobacteria are gram-positive, acid-fast bacilli, due to their lipid-rich cell wall composition. Lipoarabinomannan and mycolic acid, which form the glycolipid layers in the mycobacterial wall, are associated with several peculiar immunological properties [56]. According to the Global TB Network, several nations have reported COVID-19-TB co-infection. Patients with pulmonary and extrapulmonary TB were reported to be co-infected with COVID-19. Eight investigations revealed 80 human COVID-19-TB co-infections from nine different countries, with the highest percentage of active pulmonary TB cases (51 %) found in Italy [56]. Co-infection of TB and COVID-19 were frequently observed during the COVID-19 period, making the diagnosis difficult due to overlapping symptoms such as fever and cough. The clinical implications of concurrent COVID-19 and TB infections are still not fully comprehended, as reports indicate diverse outcomes ranging from severe to favorable consequences. The diagnosis of TB and COVID-19 may be challenging due to their resemblances. However, TB is characterized by a more gradual onset of symptoms that last for an extended period, ranging from weeks to months. Further tests and evaluations revealed the simultaneous presence of *Mtb* and SARS-CoV-2 organisms in several COVID-19 patients who were admitted to the hospital with typical TB symptoms [57]. The pulmonary damage resulting from TB enhances susceptibility to additional airborne infections, suggesting that TB could serve as a potential risk factor for worsening the severity of COVID-19 in patients [58]. Moreover, impaired immune response and excessive production of cytokines are crucial in the worsening of TB. Consequently, COVID-19 might act as a predisposing element for the activation of latent TB, leading to the deterioration of both COVID-19 severity and the progression of TB [59]. The case of COVID-19 and pulmonary TB co-infection was reported by Aissaoui *et al.* [60]. The process of TB identification was pneumonia caused by COVID-19. In that scenario, a bronchoesophageal fistula deteriorated TB, which emerged as a parenchymal and endobronchial pseudotumoral lesion. The lung consolidation in the right middle lobe and interstitial alveolar involvement with nodules in the left lower lobe and lingula were observed on the chest computed tomography scan (CT scan). Additionally, Lawati *et al.* reported another case with COVID-19 and pulmonary TB co-infection where the patient's chest X-ray exhibited a diffuse nodular pattern along with airspace opacities affecting the entire right lung zone [30]. Additionally, there was a small nodule in the left mid-lung zone and an airspace opacity in the left upper lung zone, which are signs of coexisting infection and pulmonary TB [30]. SARS-CoV-2 and *Mtb* may act synergistically in the infected host cells [61]. *Mtb* interacts with the pulmonary microenvironment during latent TB infection and triggers immunological responses. It has been reported that SARS-CoV-2 can trigger hostile and proinflammatory responses characterized by high IL-2, IL-1β, IL-4, IL-6, IFN-γ, and TNF-α

expression [19]. Additionally, a cytokine storm is likely caused by several stimuli that combine in COVID-19-TB co-infection. Pyroptosis and necrosis observed in the lungs may spread damage-related molecular patterns. The significantly more intense pyroptosis of SARS-CoV-2 promotes immunopathology and tissue destruction [62]. Several PRRs, including the Fcγ receptor, the Scavengers, and Mannose receptors, recognize *Mtb* throughout the bacterial infection. The interaction of *Mtb* with these receptors activates the protein kinase C (PKC) pathway. This pathway has a role in *Mtb* survival, macrophage attack, and cytoskeletal configurations [31]. *Mtb* stimulates a variety of signaling pathways that stimulate the expression of cytokines and chemokines. TNF-α, IL-1β, and IL-6 are among those that are released quickly following macrophage infection and are produced before the synthesis of anti-inflammatory cytokines like TGF-β and IL-10 [31]. The immune response, driven by cytokines, in many COVID-19 patients is also hostile and causes harm, leading to macrophage and monocyte infiltration of the alveoli. One of the key participants in inflammatory, immune response, and cytokine storms IL-6. The correlation between the increased IL-6 levels and COVID-19 severity suggests that this cytokine plays a crucial role in the development and pathophysiology of the COVID-19 disease [63]. The IL-6 signaling pathway is widely connected to tissue fibrosis, including lung damage. The IL-6/JAK/STAT3 pathway is crucial for the emergence of several disorders, including cancer and diseases linked to inflammation. Following the virus detection by host cells, signaling pathways such as JAK/STAT3 and nuclear factor-B (NF-kB) signaling pathways are activated [64]. Patients with COVID-19 have significantly high levels of IL-6, one of the primary activators of the JAK/STAT signaling pathway [65]. Ang II, produced by the inflamed vessels in a JAK/STAT dependent condition, has thus been shown to activate the generation and secretion of IL-6. It has been observed that the JAK/STAT pathway gets activated, which leads to downstream production of IL-6 when Ang II binds to AT1R. The S protein of the SARS-CoV-2, on the other hand, has been reported to downregulate ACE2 expression, leading to an abundance of Ang II. It is thus believed that an increase in IL-6 by SARS-CoV-2 is AT1R/JAK/STAT-dependent and may be responsible for the clinical features of COVID-19 infection due to increased inflammation and lung injury.

Mycoplasma pneumoniae

Mycoplasma pneumonia is a common respiratory pathogen that mainly causes various illnesses, from mild upper respiratory infections to severe atypical pneumonia [66]. It can infect the upper and lower respiratory tracts, resulting in various conditions such as bronchitis, bronchiolitis, community-acquired pneumonia, tracheobronchitis, and upper respiratory tract infection. In 2019, numerous reports of atypical pneumonia were associated with SARS-CoV-2, accompanied by symptoms such as fever, cough, headaches, fatigue, and diarrhea. However, distinguishing COVID-19 from community-acquired pneumonia caused by other atypical pathogens can be challenging due to similar symptoms and other characteristics [67]. Our understanding of co-infections involving *M. pneumoniae* and other respiratory pathogens is limited. Among these co-infections, bacterial co-infections are the most reported in recent literature. Co-infection with *M. pneumoniae* has been observed in adult and pediatric populations. Chest radiography findings in patients co-infected with *M. pneumoniae* and SARS-CoV-2 demonstrate mild lung infiltration increases. The progression of bilateral ground glass patches was observed on chest radiographs in co-infected patients. High-resolution computed tomography (HRCT) scans revealed the presence of multiple ground-glass opacity patches, a pattern referred to as crazy-paving, as well as peribronchial consolidation in the right upper lobe, middle lobe, and bilateral lower lobes [67]. Mycoplasma adhesion to the membranes of the host cell epithelium is associated with the first stage of infection. Considering the surface lipoproteins (LAMPs) of *M. pneumoniae*, it has also been shown

that activating Nrf2 can alter inflammatory responses [68]. The findings reported by Hu *et al.* show that mycoplasma factors also activate the Nrf2, which determines the anti-inflammatory activities. At the same time, *M. pneumoniae* LAMPs stimulate NF-κB signaling pathways, which determine proinflammatory activities [32]. It is likely that Nrf2/ARE and NF-κB signaling pathways 'crosstalk' in regards to LAMPs. The binding of Mycoplasma proteins to PRRs, including TLRs and NOD-like (nucleotide-binding and oligomerization domain) receptors, is the key strategy by which *M. pneumoniae* infection stimulates the immune system to respond. Changes in several cellular processes trigger inflammation and DNA repair. A change in cellular DNA methylation also affects the cellular epigenetic landscape. Furthermore, the most probable mechanism by which SARS-CoV-2 molecular patterns are recognized and used to trigger immunological responses is through cell surface TLRs [69]. The interaction of SARS-CoV-2 with host cell receptors depends on the virally encoded S protein, a critical structural protein. The S protein is an effective viral PAMP detected by TLR2 in macrophages, monocytes, and lung epithelial cells because of its direct binding to angiotensin-converting enzyme II (ACE2) [33]. By creating heterodimers with TLR1 and 6, TLR2 facilitates the development of a MyD88 and IRAK kinase family complex. This leads to increased NF-kB and MAPK signaling resulting in the release of inflammatory cytokines and chemokines. Besides the S protein, immunogenic characteristics of other structural proteins were also examined. Recent studies have observed that TLR2 binds to both the E and N proteins of SARS-CoV-2, however only the SARS-CoV-2 N protein activates TLR2, which has not been noted with other N proteins generated from coronaviruses.

Klebsiella pneumoniae

Klebsiella pneumoniae, characterized as a gram-negative bacterium enveloped by a protective capsule, is ubiquitously distributed in both environmental and human settings. Notably, this pathogen is associated with a spectrum of infectious diseases, encompassing pneumonia, bloodstream infections, surgical site infections, and meningitis. Significantly, in the pediatric population, the mortality rate for *K. pneumoniae* infections, particularly meningitis, is estimated to be approximately 20 % [70]. *K. pneumoniae* poses a concern for sick patients undergoing treatment for other conditions, such as SARS-CoV-2 infection. This bacterium can cause opportunistic infections in individuals with weak immune systems, resulting in additional complications and treatment challenges.

According to a study by Bazaid *et al.*, *K. pneumoniae* was the most frequently identified species in ICU and non-ICU patients infected with SARS-CoV-2. They also identified numerous virulent factors that are the cause of high mortality. Montrucchio *et al.* observed that seven patients with COVID-19 who were treated in ICU were co-infected with carbapenemase-producing *K. pneumoniae* (CP-Kp) [71]. The first death due to COVID-19 in Taiwan was attributed to severe community-acquired pneumonia caused by initially localized *K. pneumoniae* infection, as reported by Cheng *et al.* [72]. Although numerous molecular mechanisms of *Klebsiella* pathogenesis have been elucidated, IL-18 activation is a recent uncovering [34]. SARS-CoV-2 infection utilizes this opportunistic *Klebsiella* infection by further enhancing IL-18 levels. The primary inflammation driver, NLRP3, leads to the activation of caspase 1, further secreting proinflammatory cytokines such as IL-18 and IL-1β [73]. Beyond inflammation in the lung, IL-18 contributes to cardiovascular dysfunction, further underlining the possible severity of the co-infection of these pathogens.

Helicobacter pylori

Helicobacter pylori, a microaerophilic, gram-negative bacterium with a spiral shape, is one of the most widespread bacterial pathogens affecting humans. It is known for its role in causing peptic

ulcers and is particularly prevalent in industrialized countries, impacting up to 50 % of the world's population. Co-infection between *H. pylori* and COVID-19 is prevalent due to the high incidence of *H. pylori* infection in global populations. Individuals with *H. pylori* infections exhibit high susceptibility to SARS-CoV-2 compared to those without such infections [74]. Furthermore, *H. pylori* can increase the expression of ACE2 in the GI tract, which may be related to the progression of infection and immunological dysregulation caused by its virulent components. *H. pylori*-positive COVID-19 patients showed increased lymphocytes, neutrophils, and WBC counts compared to COVID-19 patients without *H. pylori* [74]. Balamtekin *et al.* have observed a significant association between the presence of *H. pylori* and symptoms such as abdominal pain and diarrhea in individuals diagnosed with COVID-19 [74]. *H. pylori* infection accelerates respiratory inflammation in COVID-19 by triggering cytokine production, inflammatory cell recruitment, and endothelial dysfunction. This can lead to virus-induced acute lung injury. In an experimental animal model, the presence of *H. pylori* was found to exert a notable impact on lung morphology. This effect was characterized by the recruitment of inflammatory cells to the pulmonary tissue, which produced significant quantities of proinflammatory cytokines. Additionally, the infection induced the upregulation of endothelial dysfunction markers, specifically Intercellular Adhesion Molecule (ICAM) and Vascular Cell Adhesion Molecule (VCAM). Consequently, in the context of *H. pylori*-positive COVID-19 patients, an exaggerated immune response may ensue, potentially contributing to the development of lung injury and related complications [35]. Upon encountering *H. pylori* infection, the bacteria release virulent factors that modulate downstream protein targets. This could trigger signaling pathways, including NF-κB, ERK/MAPK, and JAK/STAT, while also activating cytokine receptors. These molecular events contribute to an amplified inflammatory response, fostering conditions conducive to the progression of gastric cancer (GC). The STAT3 signaling pathway is activated by releasing cytokines, particularly IL-6, which also promotes the production of p-STAT3. TIP-Tumor necrosis factor-inducible protein (TIP), a newly discovered membrane protein secreted by *H. pylori*, is a potent inducer of epithelial-mesenchymal transition (EMT) and human inter-trypsin inhibitor heavy chain 4 (ITIH4) is an acute phase response protein that is positively regulated by IL-6 [36]. Tip- and ITIH4 may trigger the IL-6/STAT3 pathway to accelerate GC. Similarly, a cytokine storm driven by SARS-CoV-2 infection promotes JAK-STAT signaling in the targeted cells, including inflammatory and endothelial cells. In order to encourage widespread macro and microvascular thrombosis, active JAK-STAT upregulates tissue factors and other thrombotic factors, such as von Willebrand factor (vWF), to start an extrinsic coagulation cascade [61]. The above clinical investigations suggest that SARS-CoV-2 and *H. pylori* may have a complicated relationship. *H. pylori*-positive individuals might exhibit a higher susceptibility to SARS-CoV-2 infection relative to *H. pylori*-negative COVID-19 patients due to increased ACE2 receptor expression induced by *H. pylori* within the GI tract and immune response modulation.

Other pathogens

Helminths

Helminths are extracellular, multicellular parasites that can pass through epithelial barriers and parasitize a host. Helminths can disrupt the epithelial layer and result in infections, which set off a series of inflammatory processes [75]. Intestinal helminths can be passed orally, wherein larvae or eggs are ingested or punctured through the skin. Whether zoonotic or not, this form of parasitic penetration into the human body aids in the establishment by creating an inflammatory microenvironment and a series of excretory-secretory (ES) helminth products. Enzymes, including

proteases and glycolytic enzymes, are helminths' most common ES products. These products are responsible for activating Th2 immune response receptivity. The first line of defense against helminths is the innate immune response, among which mast cells, basophils, neutrophils, CD4 + T cells, innate lymphoid cells of the type Th2 response (ILC2s), and neutrophils are critical role players [76]. An ES product, alarmin, also activates dendritic cells (DCs). Hematopoietic stem/progenitor cells are recruited by IL-33, IL-25, alarmins, and thymic stromal lymphopoietin to produce a type 2 immune response. When the parasite breaks through the skin, the reaction starts. Furthermore, type 2 cytokines are released, triggering both the immunological and adaptive anti-helminth responses. Three different types of immune cells, such as the production of type 2 macrophages, immunoglobulin E (IgE)-positive macrophages, and lymphocyte type 2 cell response, T-helper (Th2), are crucial in this process [77]. Eosinophils and type 2 macrophage activity may lead to parasite evacuation and epithelial tissue healing. Adult schistosome tolerogenic responses can be elevated by type 2 immune response [78]. For instance, hepatic granuloma around eggs will allow Schistosoma to live in the host and maintain chronic sickness conditions for many years [37]. Helminth-derived products activate multiple cell surface receptors such as TLRs and dectins [79]. This leads to activation of downstream molecules such as MyD88 and MAPK signaling. ERK1/2 are hence activated, leading to Treg cell induction and other transcription factors leading to inflammation [79]. There is an ongoing debate regarding the relationship between viral and helminth infections. However, evidence linking lymphatic filariasis and Schistosoma haematobium to HIV infection has been observed [80]. The molecular mechanisms of SARS-CoV-2 and helminthic co-infection have been examined and can possibly be predicted from animal model research. Mice infected with *Heligmosomoides polygyrus* were more susceptible to flavivirus infection. It was discovered that the brain, spinal cord, colon, and small intestine all had higher viral loads, exhibiting a synergistic effect [81]. Moreover, the mortality rates for COVID-19 vary significantly among continents, regions, and nations. Various factors, including age, limited access to diagnostic testing, and other variables, have been suggested to explain unexpected mortality rates. Besides population genetic backgrounds, SARS-CoV-2 mutational changes depend on geographical context and factors such as ambient temperature, humidity, and BCG vaccination [82]. Additionally, the human body develops a response to cease helminth infection. The host system activates Th-2 cells with type 2 immune responses, which causes the production of various cytokines, particularly IL-4, IL-5, and IL-13 [83]. Helminths modulate immune systems to adapt to their hosts, hence inducing immunomodulatory, fibrogenic, and anti-inflammatory pathways. The helminth-stimulated immune system adapts to anti-inflammatory and immunosuppressive characteristics. It has been noted that COVID-19 lethality is low in Sub-Saharan Africa. African patients with parasitic co infection exhibit COVID-19 symptoms that are less severe, indicating that the parasitic infections may reduce COVID-19-related hyperinflammation [84].

Fungal infections

Rare, fatal fungal infection Mucormycosis, formerly known as Zygomycosis, typically affects patients with impaired immune systems. The fatality increases if the infection remains unidentified and untreated. Commonly, *Rhizopus oryzae* is the causative organism provoking mucormycosis. Fungal spores obstruct breathing or inhalation, primarily affecting the sinuses and lungs [38]. Following inhalation, an immunological response begins as the circulating macrophages detect these fungal spores in immunocompromised patients. Neutrophils infected with *R. oryzae* showed an upregulated Toll-like receptor 2 (TLR) expression and a rapid induction of proinflammatory NF-kB signaling [85]. Additionally, an exacerbated
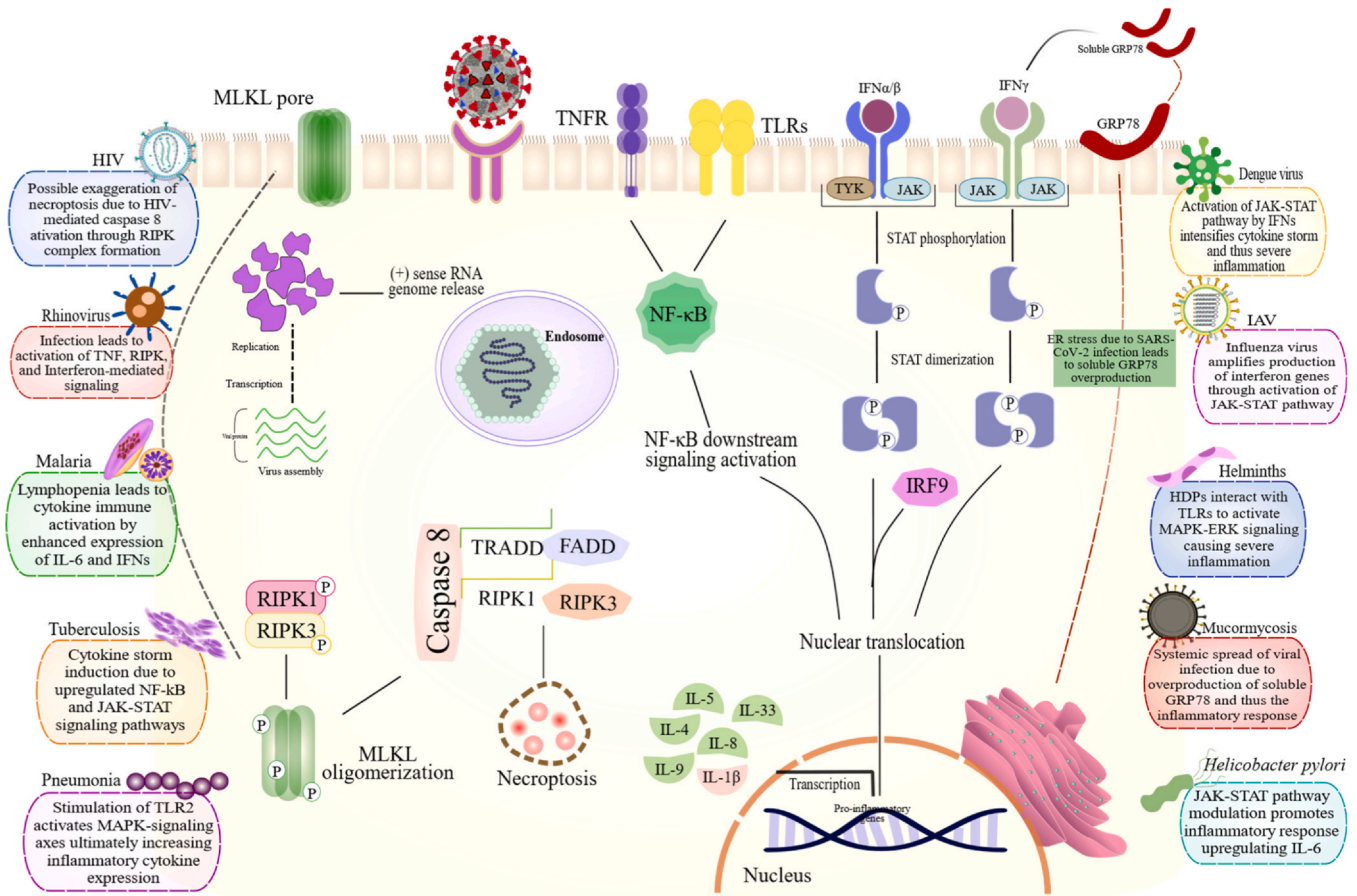
Fig. 2. Molecular pathways altered by possible co-infection of SARS-CoV-2 and other pathogens like HIV, rhinovirus, Plasmodium, Mycobacterium, Pneumoniae, dengue virus, influenza virus, helminths, Rhizopus, and *H. pylori*. The damage observed in these co-infections is likely due to modulations in primarily JAK-STAT and NF-kB signaling pathways. The alteration of these pathways causes enhanced cytokine production in SARS-CoV-2-infected individuals.

response is seen in individuals with diabetic ketoacidosis (DKA) due to low pH and hyperglycemic conditions, eventually leading to mucormycosis [86]. Mucormycosis is associated with several illnesses, including HIV infection, diabetes, and systemic lupus erythematosus (SLE). *Diabetes mellitus* patients with SARS-CoV-2 and mucormycosis infections were also shown to be at high risk in this outbreak. Numerous investigations have suggested a connection between the fungus and SARS-CoV-2 infection. A similar relationship has been observed during the earlier SARS-CoV outbreaks. Recently, in COVID-19 patients, a significant number of cases of mucormycosis were recorded in Saudi Arabia [87]. The cause of COVID-associated mucormycosis has not been fully clarified. The fungal hyphae with spore coat protein homologs (CoTH) interact with the host GRP78 receptor. SARS-CoV-2 replication induces ER stress, which can further cause overproduction of GRP78, which is further utilized by the fungal hyphae for its entry into the host cell [88]. Soluble GRP78 increases the systemic spread of viral infection. The inflammatory response is potentiated by enhanced NF-kB and JAK/STAT pathway expression. The virus-infected patients were administered corticosteroids to reduce inflammation, possibly encouraging mucormycosis infection due to immunosuppressive conditions [89]. It was discovered that hospitalized COVID patients with steroid medication administration had more severe conditions. It is interesting to note that many mucormycosis patients also had bacterial co-infections [90]. The usage of zinc supplements by COVID-19 patients could be another factor, as these supplements reduce inflammatory cytokines, which in turn might prove beneficial for the fungus to thrive [91]. Therefore, as a countermeasure, hosts sequester zinc to retard

fungus growth. Candida albicans, on the other hand, established a unique system for its growth known as a "zincophore" [92]. Giving zinc supplements therefore to COVID-19 patients could promote fungus growth by creating a zinc microenvironment that ultimately leads to co-infection.

Malaria

Malaria is caused by a unicellular protozoan called Plasmodium. *Plasmodium falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi* are five common species, among which the first four are known to infect humans [93]. Malaria continues to be a global threat despite numerous treatment efforts. Depending on the insect vector, which is typically a mosquito, Plasmodium species transmit across vertebrate hosts. The life cycle of this pathogen initiates in the human liver and then gets multiplied in erythrocytes. Some parallels exist between COVID-19 and malaria, particularly regarding their initial signs and symptoms like fever, fatigue, and headache. During the COVID-19 pandemic, malaria was often misdiagnosed as COVID-19 and vice versa, significantly when the symptoms range from low to mild infectivity [94]. SARS-CoV-2 and *P. falciparum* typically have an estimated incubation span of 2–17 days and 7–14 days respectively. The data gathered from several investigations show that this co-infection has diverse outcomes. While some studies claim that this co-infection is more severe, others contend that in malaria endemic areas, malaria may protect SARS-CoV-2. The possible reactivation of this malarial parasite could be due to the immunocompromised condition of the host upon SARS-CoV-2 infection. Chronic

parasitemia is controlled in humans because of effective CD4 + T-cells that aid B-cells in immune robustness. However, COVID-19 patients show a remarkable expression of T-cell exhaustion markers, such as programmed cell death 1 and mucin 3, indicating T-cell dysfunction [39]. Also, CD4 + lymphopenia in SARS-CoV-2 infected patients possibly accounts for reactivation of Plasmodium species. During a pathogenic encounter, RIG-1-like receptors, NLRs, TLRs, etc, sense the innate immune response. These receptors trigger downstream signaling pathways, ultimately resulting in a cytokine storm immune cascade producing cytokines such as IL-6, IL-12, and IFN-γ. The resultant immunopathology can damage malarial and SARSCoV-2 infections. Although developed non-endemic nations like those in Europe have also been reported to exhibit COVID-19 and malaria comorbidity, a lackluster surveillance system during the Ebola virus outbreak also led to the misdiagnosis of malaria patients. Dengue, malaria, TB, and Ebola were the most common infectious diseases that prevailed on Africa before the eruption of COVID-19. Previous research has demonstrated simultaneous transmission and co-infection of various viral pathogens associated with malaria [94]. Interestingly, the COVID-19 fatality rate is relatively low in low- and middle-income countries (LMICs), particularly on the African continent. Therefore, it is hypothesized that malaria protects those patients from SARS-CoV-2 infection [95]. Even in malaria non-endemic countries, COVID-19 cases have been observed less in specific regions where the malaria rate is high. According to the study, there are fewer COVID positive cases in specific Italian regions where malaria incidence was the highest [96]. Similar observations have been made regarding Middle East Respiratory Syndrome (MERS-CoV). Cases of MERS-CoV and SARS-CoV were low in malaria-affected areas. Interestingly, antimalarial medications, including chloroquine and hydroxychloroquine, have been recommended for COVID-19 patients as they could prevent the multiplication of SARS-CoV-2, as demonstrated through in vitro study [97]. Intriguingly, an Indian study revealed that among healthcare workers who were simultaneously infected with SARS-CoV-2 and malaria, their recovery from COVID-19 was accelerated (on average eight days) than COVID-positive healthcare workers uninfected with malaria. Therefore, misdiagnosing or mistreating one of these conditions could decrease the likelihood of accurately identifying the other. From a therapeutic approach, clinical trials are underway to determine the effectiveness of antimalarial drugs in treating COVID-19.

Conclusion

Co-infections may influence clinical symptoms, progression, severity, mortality, and overall disease outcome in COVID-19 patients. During the COVID-19 pandemic, numerous instances of co-infection were observed with viruses, bacteria, helminths, fungi, etc. (Fig. 2). These pathogens exacerbate the pathogenic potential and might lead to increased SARS-CoV-2 replication and significant inflammation. As the local microenvironment of the host is impeded, numerous responses are observed particularly the cytokine storm. Eventually, there is a possibility that the co-infection leads to the spread of pathogens to different organs. Additionally, as the coinfecting pathogens have an overlapping effect on molecular pathways on the cell death and inflammatory pathways, the co-infection of these pathogens with SARS-CoV-2 could also integrate with these pathways, leading to an aggravated response. Efficient management of COVID-19 needs accurate and differential diagnosis of co-infections based on the overlapping symptoms and appropriate treatment to overcome the severity caused by co-infection. It is also vital to consider co-infections to draw the prognosis of the COVID-19 patients.

CRediT authorship contribution statement

HCJ: Conceptualization, BB, VS, MK and PK: Prepared the primary draft, VS: Prepared the figures, BB, AKD, HSP, AKM and PT: Edited the manuscript, HCJ: Administration.

Declaration of Competing Interest

None.

Acknowledgments

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