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Review

Parasitology and Covid-19: epidemiological, immunological, pathological, and therapeutic aspects

Kamyar Nasiri[1], Zohreh Mortezania[2], Sanaz Oftadehbalani[3], Mohammad Khosousi Sani[4], Amin Daemi[5,*], Seyyedeh Touran Hosseini[6], Yusuf Döğüş[5] and Zafer Yönden[5]

[1] Department of Dentistry, Islamic Azad University, Tehran, Iran
[2] Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Infectious Diseases Specialist, Fatemeh Zahra Hospital, Iran University of Medical Sciences, Tehran, Iran
[4] Oral and Maxillofacial Surgery Resident, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Department of Medical Biochemistry, Faculty of Medicine, Cukurova University, Adana, Turkey
[6] Department of Biotechnology, Institute of Natural and Applied Sciences, Cukurova University, Adana, Turkey

* **Correspondence:** Email: phd_bio@yahoo.com.

Abstract: Studies suggest that there is a complex interaction between parasitic infections, human microbiota, and host immunity. Reports have shown that there is the prevalence of viral diseases have inverse correlations with their severities (as is the case for Covid-19), their resulting mortalities, and helminth infections in endemic areas. This review study was conducted to discover the possible association between parasitic infections and Covid-19 epidemics from immunological, pathological, and therapeutic aspects. Our studies were conducted by reviewing texts, reports, and articles on reputable websites such as PubMed, Science Direct, medRxvi, Google Scholar, and bioRxiv published by 2022 07 April for keywords such as a parasite, helminth, radioactive, COVID-19 or SARS-CoV-2. In particular, reports of co-infection with helminths with complications and severity of Covid-19 in endemic areas were considered. The findings indicate that parasitic helminths can regulate host immune responses associated with a viral infection. For example, intestinal parasitic infections may

be effective in reducing the symptoms of SARS-CoV-2 and the complications of Covid-19. Infected hosts can induce an innate and Th2-compatible immune response to $CD4^+$ T cells, eosinophils, and interleukins (IL-4, IL-5, and IL-10). Chronic helminth infections prevent strong immune responses by altering the host response to T helper 2 (Th2). Interestingly, some antimalarial drugs, such as Artemisinin-based combination therapies (ACTs), may inhibit SARS-CoV-2-induced severe acute respiratory syndrome (SARS). Parasitic infections may alter the host's immune response to SARS-CoV-2 with potentially beneficial or detrimental effects. However, more large-scale epidemiological studies are needed to uncover the links between parasitic infections and COVID-19 and to clarify existing ambiguities.

Keywords: Parasitology; Covid-19; Immunology; Pathology; treatment

1. Introduction

In regions with a high prevalence of helminthic infections, there are divergent views on the prevalence or severity of Covid-19. Because the pandemic has severely impacted some helminth endemic regions. There is a significant burden of soil-transmitted helminth infection (45–95%) among the Amerindian populations of the Brazilian Amazon. Covid-19 had a significant impact here, though, and the mortality rate was 250% higher than it was throughout the rest of Brazil [1]. Similarly, it is estimated that 65% of Venezuelan rural communities have soil-transmitted worms. However, the Covid-19 pandemic has had a significant impact on the area [2].

Because helminths cause the development of Regulatory T cells (Tregs) and the production of IL-10, the host's immune system will be compromised, making the host more vulnerable to microbial infections. The composition of the gut microbiome, on the other hand, may be altered by gastrointestinal parasites, which will lead to systemic immunomodulation [3].

According to a systematic review by Abdoli et al. [4], preexisting helminth infections may impair the body's ability to fight off SARS-CoV-2 in the early stages of the infection, which could increase Covid-19 morbidity and mortality [4].

According to ecological studies, parasites like malaria, schistosomiasis, or soil-transmitted helminths have an inverse relationship with the prevalence of Covid-19.

According to some reports, helminth co-infection may be able to control or even stop the progression of Covid-19 in endemic areas. A co-infection with any parasite, such as protozoa or helminth, reduces the likelihood of developing severe Covid-19. Additionally, it appears that patients without parasite co-infection are more likely to have poor hospital outcomes, such as the requirement for intensive care units, additional oxygen, or mechanical ventilation, in addition to death [5].

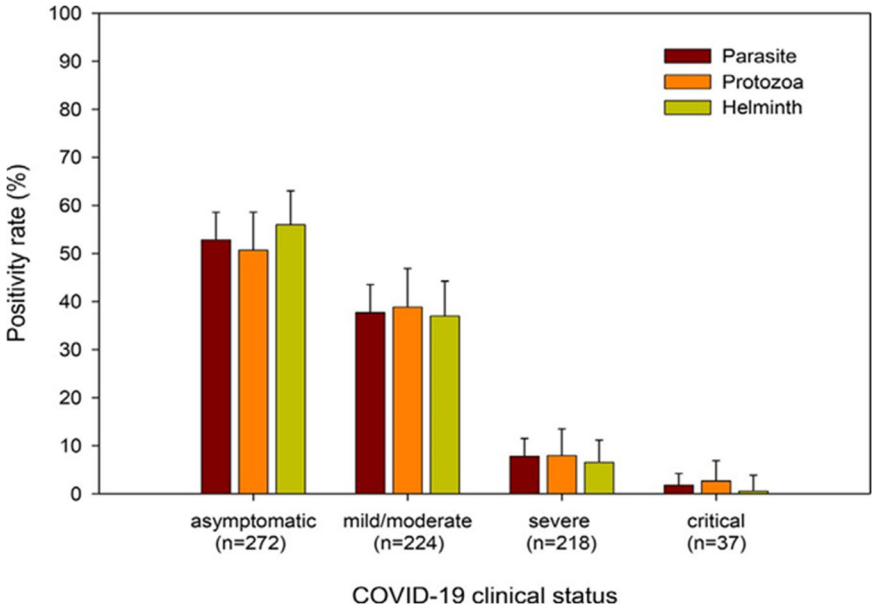

Figure 1. Relationship between concomitant parasite infection and Covid-19 severity categories based on Kruskal-Wallis ranking test.

The prevalence of SARS-CoV-2 suggests that low- and middle-income countries (LMICs) have a similar pattern to high-income countries, but they exhibit significantly lower mortality. Both malaria and parasitic neglected tropical diseases (NTDs) can cause cytokine storms and a pro-coagulant state akin to severe Covid-19, which can lead to immunological reactions to other infectious agents. Therefore, a co-infection with SARS-CoV-2 and malaria parasites can lead to much worse outcomes than a single infection with any of the pathogens and may cause the severe Covid-19 age pattern to shift to younger age groups [6].

Osborne et al. [7] found that co-infection with helminths and viruses reduced antiviral immunity, which is highly dependent on Ym1, a chitinase-like molecule that was linked to alternatively activated macrophages (AAM) without alterations in the microbiota. The neutralization of Ym1, however, helped to partially restore antiviral immunity [7].

Another study revealed for the first time that patients in Africa who have an intestinal parasite, protozoa, and helminth co-infections are less likely to experience severe Covid-19 [8]. Presumably, parasites reduce the severity of Covid-19 through their effects in modulating the systemic immune response. Chronic intestinal parasitic infections are often associated with the development of M2 macrophages, and type 2 innate lymphoid cells (ILC2s). These responses are associated with the induction of cytokines such as IL-4, IL-5, and IL-13 and an increase in eosinophils and Ige responses. Parasites-induced TH-2 responses are important in the control of parasitic infections and also play an important role in repairing tissue damage in such infections [9].

In parasitic infections, TH2 immune responses are also associated with the induction of potent T cell regulatory responses (Treg), which can affect responses to heterologous infections [10].

On the other hand, severe Covid-19 is associated with exacerbation of inflammation and increased production of proinflammatory cytokines [11]. Thus, TH2 and Treg responses due to parasitic

infections may balance overactive TH1 responses in severe Covid-19 conditions. It is possible for parasitic infections to directly affect the pathogenesis of Covid-19 by modulating the immune system and indirectly by balancing the parasite-based microbiome [12].

In African and Latin American countries, where helminth infections are still common, Covid-19-related deaths are significantly lower than those reported in high-income countries, so it has been hypothesized that helminth parasites and their derivatives may affect the entry of SARS-CoV-2 into host cells and have an anti-inflammatory effect in Covid-19 patients [13]. Living in areas with a high prevalence of helminth infection or being an active smoker [14] may paradoxically protect patients against Covid-19 through common factors, including an activated Th2 immune system [15] and high eosinophil counts.

Among helminth parasites, some molecules of *Fasciola hepatica* have shown strong immunomodulatory properties. Derivatives of these molecules, like a 68 mer peptide from the helminth defense molecule (HDM), inhibit inflammation and airway hypersensitivity in murine experimental asthma [16]. The fatty-acid-binding recombinant protein Fh15 also blocked lipopolysaccharide (LPS) induced cytokine storm in a murine model [17].

2. Immune responses to Covid-19

Helminth infections may restrain host immune responses through different mechanisms, including but not limited to suppression of Th1/Th2 response, manipulation of pattern recognition receptors (PRRs), stimulation of regulatory cells, and induction of apoptosis in immune cells [18].

Immunoregulation during helminth infections is induced by helminth-derived products, which can be either parasite secretions, excretions, proteins, or extracellular vesicles that constantly interact with the host immune system [19].

Detection of the virus by pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and retinoic acid-inducible gene (RIG-1) activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and interferon becomes regulatory factor 3 (IRF3). Finally, induction of proinflammatory cytokines, chemokines like interleukin (IL)-6, IL-1β, IL-8, CCL2, CCL8, and CXCL9, and type I interferons (IFNs) occurs [20]. Activation of complement pathways also leads to the overproduction of chemoattractants, C3a and C5a (anaphylatoxins), leading to a cytokine storm [21].

Cytokines and chemokines also invoke other immune cells to the site of inflammation, thereby increasing the intensification of the inflammatory response (Figure 2). Overproduction of proinflammatory cytokines (cytokine storm) leads to widespread tissue damage, including acute respiratory distress syndrome or multiorgan failure, which has been associated with mortality in Covid-19 patients [22].

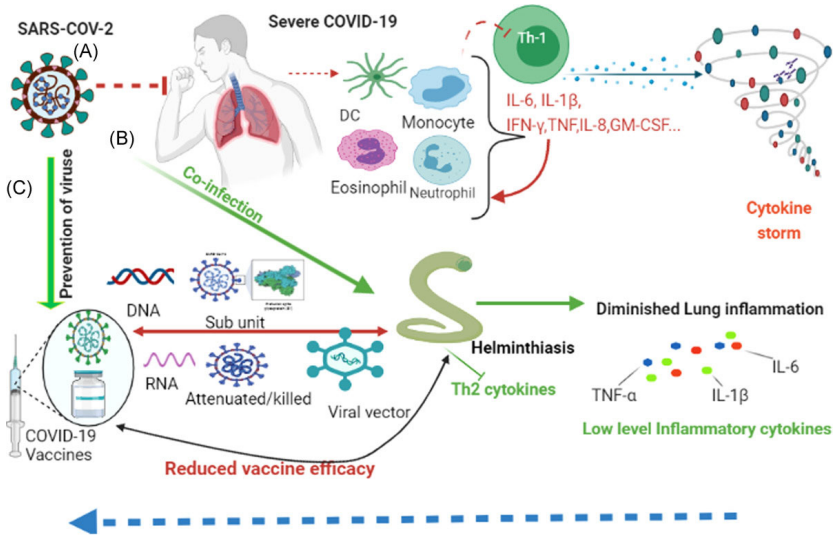

Figure 2. Severe immune response to Covid-19 [23].

3. The Eosinophil responses against RNA viruses

Th2 immune system is characterized by the presence of too many of two types of cells: (1) alternatively activated M2 macrophages, which are less inflammatory and more reparative than the classic M1 [24], and (2) eosinophils [25], which are potent antiviral cells [26] and can exhibit potent immune function against RNA viruses (including Covid-19 disease). The unique and specialized properties of eosinophils indicate their role as potential first-line defense cells in the fight against viruses such as the SARS-CoV-2 virus [27].

4. Procoagulant mode

SARS-CoV-2 induces pre-coagulation by inducing von Willebrand factor increasing, tissue factor expression, activation of Toll-like receptors, and endothelial dysfunction [28]. The presence of hypercoagulable markers, including increased D-dimer product levels and fibrin breakdown, and prolonged prothrombin time indicate a poor prognosis [29]. Clinically, extensive venous thromboembolism, pulmonary embolism, diffuse intravascular coagulation (DIC) [30], thrombocytopenia [28], and stroke due to arterial thrombosis also occur [31].

Similar to the mechanism proposed in Covid-19, in malaria, lysis of activated platelets, a tissue factor released from damaged vascular endothelial cells, enhances the pre-coagulation state. Thus, co-infection of *Plasmodium* spp. and SARS-CoV-2 may result in greater degrees of coagulation than any of these infections alone [32].

5. Potential interactions between NTDs and Covid-19

Helminths, including stool-transmitted helminths (STH), *Schistosoma* organisms, and filarial worms, typically push the immune system toward anti-inflammatory Th2 pathways through a variety

of regulatory mechanisms [33]. Protozoal parasites, such as trypanosomes or *Leishmania* spp., are more likely to induce a Th1, pro-inflammatory response. However, there are many deviations from this characterization. Some helminths induce Th1 responses in some stages of the life cycle (e.g., microfilariae of filarial parasites or schistosome eggs), resulting in symptomatic disease, but Th2 responses in other stages (e.g., adults of both filarial parasites and schistosomes).

The downregulation of the inflammatory response associated with helminths may reduce the development of immunity or response to vaccines, decrease inflammation associated with autoimmune diseases, reduce the ability to control *Mycobacterium tuberculosis* and *Mycobacterium leprae* coinfections, and reduce the severity of malarial coinfection. The pro-inflammatory effects of some protozoal infections may worsen the severity of some, but not all, viral infections [34].

In addition, polyparasitism is quite common, and the overall impact on inflammation depends on the sequence of infections and the burden of each. Thus, coinfection with parasitic NTDs could result in altered risks and severity of clinical manifestations of SARS-CoV-2 infection, with the potential for decreased development of immunity with increased viral loads.

Helminth parasites elicit a modulated T response (Th) in vertebrate hosts, including inhibition of proinflammatory cytokines and induction of a hyporesponsive state including interleukin-10 (IL-10)-producing T regulatory (Treg) cell populations [33]. Evidence suggests that the absence of helminth infections in the population of developed countries leads to a lack of immune stimuli associated with such infections in childhood and an increase in autoimmune diseases such as allergies, asthma, and rheumatoid arthritis [35].

6. Immune response against helminths

Metazoan parasites are able to survive for very long periods in the bloodstream, lymph, liver, or gastrointestinal tract of their host and cause pathological conditions such as anemia, cirrhosis, and lymphatic filariasis [36].

In the first encounter with helminths, human tissues, like any other foreign invader (whether virus, bacterium, mold, or protozoan), have an immediate immune response that begins with the activation of the innate immune system. With the identification of foreign molecules, the rapid uptake of inflammatory cells into the site of invasion begins [37].

Naturally, innate immunity is the first-line response to detecting pathogens based on germline-encoded receptors. Helminths and their excretory/secretory products are also detected by phagocyte receptors, T cells 2 (ILC2s), and mast cells [38]. The roles of the signaling modulation, helminth-derived immunomodulatory molecules such as cytokine & innate defense homologs, growth factors, enzymes, and inhibitors, lipids, and lipid-binding mediators have also been largely identified in modulating the innate immune response [39].

Most helminths inhibit the Th1 immune response through various molecular processes and instead stimulate the activation of the Th2 network [40]. The process activates the production of alternative cytokines (IL-4, IL-5, and IL-13) instead of the classic proinflammatory cytokines (TNFα, IL-1β, IFNγ) induced by the Th1 response. The new cytokines trigger a number of different cells (such as Th2 lymphocytes, IgE-producing B cells, mast cells, basophils, eosinophils, and M2 macrophages) [41].

In chronic parasitic infections, helminths modify their host's immune system, which increases their long-term survival and protects the host and parasite from the onset of inflammatory disorders [42]. The best example may be *Wuchereria bancrofti*, which causes lymphatic filariasis. *Wuchereria* secretes a phosphorylcholine fragment (called ES-62) that blocks the production of proinflammatory cytokines such as IFN-γ. It also suppresses antibody production by blocking the interaction between $CD4^+$ cells and B cells, activates the production of the anti-inflammatory cytokine IL-10 and suppresses the Th1 pathway [43]. The mentioned immune silencing is likely to occur among the approximately 2 billion people living in the helminth belt today, protecting them against Covid-19. A comparison of global maps shows a clear negative correlation between helminth prevalence and Covid-19 infection and, most importantly, mortality [41] (Figure 1).

7. Immunomodulatory role of helminths and Covid-19 co-infections

In developing and suburban areas of industrialized countries, the 2019 coronavirus disease (Covid-19) and helminth infections may be part of a synergistic epidemic. With CD4 T cells, eosinophils, interleukin-4, interleukin-5, and interleukin-10, the coinfected hosts will develop a parasite-specific Th2 innate and adaptive immune response. During the early stages of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, virus-specific Th1 cytotoxic CD8 T cell, interleukin-6, interferon, and interleukin-27 by the lung are crucial in regulating viral replication in the lung epithelial cells and limiting the pathology to other organs, like the intestine. During and after Covid-19, CD4, and CD8 T cells are linked to protective immunity. The severity of Covid-19, however, can be influenced by viral evasion mechanisms that interfere with interferon secretion, similar to how helminths modulate immunity. Depending on which helminth is coinfecting, immunomodulation can cause mild, moderate, or severe Covid-19 by regulating or avoiding host cytokine and pro-inflammatory response, lowering a viral load, and affecting vaccine-induced antibody response [44].

Suppression of the immune system caused by malaria has also been observed in many concomitant infections, significantly inhibiting immune responses to other infections such as *Salmonella* species [45]. Malaria-induced immunomodulation also protects against severe manifestations of some respiratory viruses. In the murine model, co-infection with *Plasmodium* spp. It can suppress the production of pulmonary cytokines, and reduce clinical signs and inflammation in pneumovirus infections and even SARS-CoV-2. Suppression of the immune system caused by malaria can lead to milder manifestations of Covid-19 [46].

High levels of eosinophils can be seen in people living in the helminth belt who are protected from viral infections [47]. Eosinophils, on the other hand, kill viruses through a variety of mechanisms, including RNases in specific granules, nitric oxide production [48], and increased expression of host antiviral proteins such as IRF-7, IFN, and MIP-1α [49].

In summary, helminth infections cause effects, all of which lead to low basal immune responsiveness and may be described as the Th2-IL-10 axis. During helminth infection, IL-10 inhibits the activity of cytotoxic T8 cells, $CD8^+$, and Th1, and it suppresses the interaction between natural

killer (NK) cells and myeloid dendritic cells (DCs). All of these activities are required for optimal clearance of pathogens as well as repair of tissue damage [50].

Also, helminth infection is often associated with the proliferation of regulatory T cells (Tregs), which reduce inflammation and prevent self-harm by an overactive immune system [51]. Interestingly, during chronic helminth infection, the immune system is equipped with Th2 $CD4^+$, Th9 $CD4^+$ T cells and their active agents, basophils, mast cells, and especially eosinophils [52].

In such a process, the survival of the host is as important as the survival of the helminths themselves. Hence, it seems that immunosuppressive agents have beneficial effects on the overall outcome of the disease [53], and, of course, the sooner immunosuppression begins (before the onset of the cytokine storm), the more effective it will be [41].

8. Conclusion

Although co-infection of helminths (and their molecules) with SARS-Cov-2 may be associated with fewer complications and mortality in endemic areas, further studies are needed to show its effect on Covid-19 severity. The findings support the hypothesis that co-infection with parasites may alleviate the hyper-inflammation associated with severe Covid-19.

Immunomodulatory effects of helminth infections have been demonstrated in a number of diseases. One of the possible explanations for why Covid-19 severity is still lower in countries with helminth endemicity is helminth co-infection in Covid-19 patients. According to recent studies, Covid-19 cases and deaths have been lower in helminth-endemic countries so far, and helminth co-infection may lessen Covid-19 severity.

The effectiveness of the Covid-19 vaccine has also been shown to be significantly reduced by helminth co-infection in other diseases, which may also be a factor. Helminths have an immunomodulatory effect that has both intended and unintended effects, both positive and negative, which may respectively lessen the severity of Covid-19 and the effectiveness of the Covid-19 vaccine.

Conflict of interest

The authors declare there is no conflict of interest.

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