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REVIEW

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A role for T-cell exhaustion in Long COVID-19 and severe outcomes for several categories of COVID-19 patients

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Abstract

Unusual mortality rate differences and symptoms have been experienced by COVID-19 patients, and the postinfection symptoms called Long COVID-19 have also been widely experienced. A substantial percentage of COVID-19-infected individuals in specific health categories have been virtually asymptomatic, several other individuals in the same health categories have exhibited several unusual symptoms, and yet other individuals in the same health categories have fatal outcomes. It is now hypothesized that these differences in mortality rates and symptoms could be caused by a SARS-CoV-2 virus infection acting together with one or more latent pathogen infections in certain patients, through mutually beneficial induced immune cell dysfunctions, including T-cell exhaustion. A latent pathogen infection likely to be involved is the protozoan parasite *Toxoplasma gondii*, which infects approximately one third of the global human population. Furthermore, certain infections and cancers that cause T-cell exhaustion can also explain the more severe outcomes of other COVID-19 patients having several disease and cancer comorbidities.

KEYWORDS

brain infections, latent infections, protozoa, protozoan infections, SARS-CoV-2 mortality

1 | INTRODUCTION

1.1 | Background

Unusual mortality rate differences and symptoms have been observed in COVID-19 infections and in individuals showing the postinfection symptoms known as Long COVID-19 (Carvalho-Schneider et al., 2021; Kozloff et al., 2020; Mendelson et al., 2020; Nemani et al., 2021; Yelin et al., 2020; H. Y. Zheng et al., 2020; M. Zheng et al., 2020). A substantial percentage of COVID-19-infected individuals in various health categories have been virtually asymptomatic, while other individuals in the same health categories have exhibited several unusual symptoms, and still other patients in the same health categories have fatal outcomes (Carvalho-Schneider et al., 2021; Kozloff et al., 2020; Mendelson et al., 2020; Nemani et al., 2021; Yelin et al., 2020; H. Y. Zheng et al., 2020; M. Zheng et al., 2020). It is hypothesized that these mortality rate differences and symptoms result from a SARS-CoV-2 virus infection acting together with one or more latent pathogen infections in certain patients, through mutually beneficial induced immune cell dysfunctions, such as T-cell exhaustion (Król-Turmińska & Olender, 2017; Varikuti et al., 2018; Xiao et al., 2018; H. Y. Zheng et al., 2020; M. Zheng et al., 2020). The definition and causes of T-cell exhaustion and the factors determining the prevalence and severity of T-cell exhaustion will be discussed in detail later. One latent pathogen infection that after the passage of time could create T-cell exhaustion is the pervasive protozoan parasite *Toxoplasma gondii* (Król-Turmińska & Olender, 2017; Varikuti et al., 2018; Xiao et al., 2018).

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1.2 | Protozoan parasite infections

T. gondii and other protozoan parasites have achieved intracellular infections in over a billion people (Król-Turmińska & Olender, 2017; Varikuti et al., 2018; Xiao et al., 2018). *T. gondii* protozoan parasites typically infect people after food or water ingestion (Król-Turmińska & Olender, 2017). *T. gondii* experiences three life stages: tachyzoites during active infections, bradyzoite tissue cysts during latent infections, and sporozoites to infect new hosts from contaminated food or water (Xiao et al., 2018). Besides *T. gondii* infections by congenital transmission from mother to fetus, or sporadic-infected organ or tissue transplants, a new host is acquired by ingestion of sporozoites that release activated protozoa to breach the gastrointestinal epithelium, particularly in the small intestine, and enter the host's circulatory system (Xiao et al., 2018).

T. gondii and other protozoan parasites can create latent infections of the brain and central nervous system (CNS), through tissue cysts in hosts and cause immune system dysfunctions (Xiao et al., 2018). *T. gondii* has documented links to several neuropathologies, especially recent onset psychiatric illnesses in some individuals, including schizophrenia, bipolar disorders, obsessive-compulsive disorders, autism, and general anxiety disorders (Xiao et al., 2018).

Significance

Unusual mortality rate differences and symptoms are seen in many COVID-19 patients, and the postinfection symptoms called Long COVID-19 are also widespread. These mortality rate differences and symptoms could be caused by a SARS-CoV-2 virus infection acting together with one or more latent pathogen infections in certain patients, through mutually beneficial induced immune cell dysfunctions, including T-cell exhaustion. A latent pathogen infection likely to be involved is the protozoan parasite *Toxoplasma gondii*, which infects approximately one third of the global human population. T-cell exhaustion from infections and cancers can also cause more severe outcomes in other COVID-19 patients.

2 | DISCUSSION

T. gondii bradyzoites have been observed in muscles, brain neurons, and the CNS including eye retinas (Xiao et al., 2018). Individuals having *T. gondii* infections exhibit brain neuroinflammation, activated microglia and astrocytes in the brain, and complement factor C1q, which can ultimately initiate the classical complement pathway (Xiao et al., 2018). In addition, *T. gondii* cysts in the brain can induce major disruptions in the levels of the metabolite kynurenine and neurotransmitters including glutamate, gamma-aminobutyric acid, and dopamine (Xiao et al., 2018). These neurotransmitter disruptions could also explain some cases of schizophrenia (Xiao et al., 2018). Long duration latent *T. gondii* infections can also result in CD8 T-cell exhaustion, which is capable of ultimately inducing *T. gondii* reactivations and localized tissue inflammations (Xiao et al., 2018). It is interesting that T-cell exhaustion, such as CD8 T-cell exhaustion, and a weaker antiviral response have also been documented in COVID-19 patients who have more severe infections and outcomes (H. Y. Zheng et al., 2020; M. Zheng et al., 2020).

2.1 | Evidence of microglial activation and microglial nodules in brain autopsies of COVID-19 fatalities

It has been recently reported that 41 patients, with ages ranging from 38 to 97 years, who died from COVID-19, had brain autopsies in 2020 at the Columbia University Irving Medical Center (Thakur et al., 2021). The patients tested before death showed elevated inflammatory cytokines, including elevated interleukin-6 (IL-6) in 26 (96%) of the 27 patients tested (Thakur et al., 2021). The neuropathological examination of 20 and up to 30 areas from each brain found microglial activation in 34 of the 41 brains (81%) (Thakur et al., 2021). Microglial clusters (microglial nodules) were found in 26 of the brains (63%), being most prevalent in the brainstem, and neurons were found in some of the microglial nodules, which were interpreted as neuronophagia (Thakur et al., 2021). However, viral RNA and viral proteins were not significantly detected in the brain cells or the microglial nodules, while acute and subacute hypoxic damage was reported for every brain; thus the formation of the microglial nodules was attributed to hypoxia, instead of the RNA virus SARS-CoV-2 (Thakur et al., 2021).

It is well documented that brain hypoxia disrupts the blood–brain barrier (BBB), causing leakage of pro-inflammatory plasma proteins, including immunoglobulins, fibrinogen, and complement (Lana et al., 2020). It is also well documented that microglial activation and perivascular microglial clusters can be caused by fibrin deposition from perivascular leakage of plasma protein fibrinogen into areas of BBB disruption (Devalos et al., 2012). In addition, the formation of apoptotic neuron–astrocyte–microglia triads and extensive damage to the myelin sheath (demyelination) from oxidative stress and inflammatory stress has been well documented for brain hypoxia/ischemia (Lana et al., 2020). But while neurons were found in some microglial nodules, no apoptotic neuron–astrocyte–microglia triads were reported, and there was no evidence of any demyelination seen in any of the brains autopsied (Thakur et al., 2021). If there was brain hypoxia, it was apparently of such short duration that not even demyelination from the death of the hypoxia sensitive oligodendrocytes could occur (Lana et al., 2020; Marinelli et al., 2018). Therefore, brain hypoxia may not be the main explanation for the microglial nodules. However, there is another well-documented explanation for the microglial nodules that were observed during these brain autopsies.

2.2 | Extensive evidence of microglial brain nodules in *T. gondii* infections

T. gondii infections have shown an ability to use microglia as "Trojan Horses" for intracellular tachyzoite replication and the spread of these active protozoan parasites throughout the brains of infected hosts (Dellacasa-Lindberg et al., 2011). Infected microglia once activated have demonstrated an ability to transmigrate through astrocytes, which are part of the brain parenchyma and BBB (Dellacasa-Lindberg et al., 2011). Rapid transfers of these pathogens from infected glial cells to effector T-cells have also been demonstrated (Dellacasa-Lindberg et al., 2011). Microglial nodules in the brain and CNS have also been widely observed in AIDS patients, where the microglial nodules were caused by *T. gondii* infections, cytomegalovirus infections, or HIV itself (Dellacasa-Lindberg et al., 2011; Nebuloni et al., 2000; Zhang et al., 2014). Activated microglia from reactivated *T. gondii* have also been observed to cause neuronal apoptosis, which could precede neuronophagia (Gottlieb et al., 2020). *T. gondii*-activated microglia also lead to elevated levels of the inflammatory cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (Zhang et al., 2014).

In view of the preceding *T. gondii* symptoms, it is interesting that microglial activation was also found in 81% of the brains of COVID-19 fatalities, and microglial nodules were found in 63% of the brains of COVID-19 fatalities (Thakur et al., 2021). But while neurons were found in some microglial nodules, no apoptotic neuron–astrocyte–microglia triads were reported, and there was no demyelination found in any of the brains autopsied (Thakur et al., 2021). But one of the main consequences of brain hypoxia, BBB breakdown, and oxidative and inflammatory stress is axonal demyelination of the neurons (Lana et al., 2020). If there was brain hypoxia, it apparently had such short duration that not even demyelination occurred. Therefore, *T. gondii* infections may be an explanation for the microglial activation and microglial nodules observed in the brain autopsies.

2.3 | Increased COVID-19 mortality rates for patients with schizophrenia

Furthermore, in another study a strong link between schizophrenia and a higher mortality rate from SARS-CoV-2 has been observed, with a mortality odds ratio (OR) of 2.67 above normal patients, after adjustment of the OR for age, sex, race, and extra risk factors (Nemani et al., 2021). The extra schizophrenia risk factors are smoking, cardiovascular disease, diabetes, chronic respiratory disease, antipsychotic medication effects, etc. (Kozloff et al., 2020).

2.4 | Increased COVID-19 mortality of other categories of patients

COVID-19 has unusual hospitalization and mortality risks (Gottlieb et al., 2020; Hamer et al., 2020; Harrison et al., 2020; Roe, 2021). Two studies, of 31,461 patients in the United States, and of 334,329 patients in the United Kingdom, indicated progressively older COVID-19 patients experienced progressively higher hospitalization rates (an adjusted OR of 0.92 in individuals under 19 years, 1.0 in individuals aged 19–44, 1.67 in individuals aged 45–54, 1.99 in individuals aged 55–64, 4.55 in individuals aged 65–74, and 7.32 in older individuals), and an increasing mortality rate in older individuals (with the OR increasing by at least 1.06 per year; Gottlieb et al., 2020; Hamer et al., 2020; Harrison et al., 2020). There is an explanation provided later in the section that discusses the factors that will increase the severity of T-cell exhaustion that can explain why the mortality rate continues to increase with age without reaching a plateau. In addition, an increased mortality rate for males compared to females (adjusted OR for males of at least 1.6 relative to females), and an increased mortality rate for patients having body mass indexes of 30 to 35 (adjusted OR of 1.2 to 1.37) have also been reported (Gottlieb et al., 2020; Hamer et al., 2020; Harrison et al., 2020; Roe, 2021).

2.5 | *T. gondii* infection rates

Interesting matches are noticeable between the OR of mortality of these individual categories and each category's corresponding OR of *T. gondii* infections (Gottlieb et al., 2020; Hamer et al., 2020; Harrison et al., 2020; Roe, 2021; Wilking et al., 2016). In 6,663 German adults, the detection of serum IgG antibodies to *T. gondii* progressively increased from 20% for ages 18–29 to 77% for ages 70–79(Wilking et al., 2016). Males had increased *T. gondii* rates of infection compared to females (OR of 1.8), and there were increased *T. gondii* infection rates for individuals having body mass indexes over 30 (OR of 1.3) (Wilking et al., 2016). If *T. gondii* infection rates are similar in Germany, the United States and the United Kingdom, the OR matches in specific categories of individuals between higher COVID-19 mortality rates and higher *T. gondii* infection rates suggest immune system dysfunctions, including CD8 T-cell exhaustion, worsening both COVID-19 and *T. gondii* infections. Furthermore, T-cell exhaustion could also explain Long COVID-19.

2.6 | T-cell exhaustion explanation for Long COVID-19

Latent infections, such as *T. gondii* infections, may in some cases explain the increased mortality rates for some COVID-19 patient categories. Furthermore, latent infections in some cases may be the reason why some patients suffer severe COVID-19 symptoms, and may also be the reason why a large number of individuals experience "Long COVID-19" (Carvalho-Schneider et al., 2021; Mendelson et al., 2020; Yelin et al., 2020). A considerable percentage of post-COVID-19 individuals exhibit numerous and long duration neurological and psychological symptoms, such as: dyspnea (labored breathing), anosmia (impaired sense of smell), dysgeusia (impaired

sense of taste), fatigue, chest pain, joint pain, hair loss, memory and attention deficits, anxiety, depression, sleep disorders, tinnitus (ringing in the ear), vertigo (dizziness), otalgia (earache), speech and swallowing deficits (Almufarrij & Munro, 2021; Amenta et al., 2020; Carvalho-Schneider et al., 2021; Mendelson et al., 2020; Yelin et al., 2020).

2.7 | Toxoplasmosis

It is interesting that the unusual symptoms of Long COVID-19 match the symptoms caused by a partially or fully reactivated *T. gondii* toxoplasmosis (Bordoni et al., 2021; Costa, 2018; Halonen & Weiss, 2013; Sonne & Lopez-Ojeda, 2021; Vidal, 2019). Toxoplasmosis patients also exhibit several matching symptoms, such as dyspnea, fevers, seizures, headaches, changes in vision, altered mental status, focal neurological deficits, mental confusion, cognitive dysfunction, ataxia, behavioral or psychomotor changes, involuntary movements, pneumonia, chorioretinitis, and a variety of cranial nerve palsies (Amenta et al., 2020; Bordoni et al., 2021; Costa, 2018; de Souza et al., 2021; Halonen & Weiss, 2013; Sonne & Lopez-Ojeda, 2021; Vidal, 2019).

The most unusual and distinctive Long COVID-19 symptoms can be explained by toxoplasmosis-induced cranial nerve palsies capable of affecting the functions of the 12 cranial nerves (C.N.) that create symptoms such as anosmia from a palsy of the olfactory nerve (C.N. I), vertigo (dizziness), tinnitus and otalgia (earache) from a palsy of the vestibulocochlear nerve (C.N. VIII), and dysgeusia from palsies of the facial nerve (C.N. VII), glossopharyngeal nerve (C.N. IX), and vagus nerve (C.N. X) (Amenta et al., 2020; Bordoni et al., 2021; Halonen & Weiss, 2013; Sonne & Lopez-Ojeda, 2021; Vidal, 2019). Speech and swallowing deficits can be caused by nerve palsies of one or more of the following cranial nerves: the trigeminal nerve (C.N. V), facial nerve (C.N. VII), glossopharyngeal nerve (C.N. IX), vagus nerve (C.N. X), accessory nerve (C.N. XI), and hypoglossal nerve (C.N. XII) (Costa, 2018).

Table 1 compares the symptoms of COVID-19 and/or Long COVID-19 and the matching symptoms possible from toxoplasmosis. One symptom discrepancy is chorioretinitis. Chorioretinitis has been sporadically reported in COVID-19 patients, but apparently has not yet been reported in Long COVID-19 patients (de Souza et al., 2021).

2.8 | Two pathways for SARS-CoV-2 virus to infect the brain and CNS

Questions may be raised concerning the ability of the SARS-CoV-2 virus to infect the brain and CNS to work together with latent infections in the brain and CNS. It is now recognized that coronaviruses, including the SARS-CoV-2 virus, can infect the brain and CNS by either a blood circulation pathway through the BBB, and/or by a neuronal pathway through sensory nerves (e.g., the olfactory nerve) or through motor nerve endings (Wu et al., 2020). An increased BBB permeability has been shown, due to elevated levels of interleukin-1β and TNF-α in COVID-19 patients having severe symptoms, and these elevated inflammatory cytokines can be released from injured lung epithelial tissues and/or blood vessel endothelial tissues (McFarland et al., 2021). Increased BBB permeability will also assist brain entry by the SARS-CoV-2 virus (Kumari et al., 2021; McFarland et al., 2021; Wherry & Kurachi, 2015).

To summarize at this point, a latent protozoan parasite infection in the brain and CNS, such as *T. gondii*, can over time create T-cell exhaustion that interacts with SARS-CoV-2 virus in the brain and CNS to create long-term neurological and psychological symptoms, and this interaction may explain many of the unusual and diverse symptoms of COVID-19 or Long COVID-19 (Carvalho-Schneider et al., 2021; Mendelson et al., 2020; Yelin et al., 2020).

2.9 | Other comorbidities and pathogen synergies with SARS-CoV-2 by T-cell exhaustion

It should be noted that the mutually beneficial T-cell exhaustion induced by a SARS-CoV-2 virus infection and a latent pathogen infection is not exclusive to *T. gondii*. T-cell exhaustion can, in certain circumstances, be induced by other latent infections of bacterial, viral or fungal pathogens, including *Cryptococcus neoformans*, the hepatitis B virus, hepatitis C virus, and certain members of the alpha, beta, and gamma herpes virus families, such as cytomegalovirus (Dittfeld et al., 2016; Handous et al., 2020; McHugh et al., 2019; Pallett et al., 2019; Schildermans & De Vlieger, 2020; Virgin et al., 2009; Wherry & Kurachi, 2015). For example, a synergy between the SARS-CoV-2 virus and the hepatitis B and C viruses could explain the adjusted OR of 2.62 in COVID-19 mortality that was observed in moderate to severe liver disease patients within a study of 31,461 COVID-19 patients, if some of these patients have hepatitis B or C infections (Harrison et al., 2020). In conclusion, several other latent pathogen infections that over time induce T-cell exhaustion can also affect the outcome for COVID-19 patients, and explain the symptoms of patients with Long COVID-19 (Cader et al., 2018; Carvalho-Schneider et al., 2021; Dittfeld et al., 2016; Dyck & Mills, 2017; Handous et al., 2020; Kong et al., 2016; Kurachi, 2019; McHugh et al., 2019; Meier et al., 2018; Mendelson et al., 2020; Pallett et al., 2019; Schildermans & De Vlieger, 2020; Virgin et al., 2009; Wherry & Kurachi, 2015; Yelin et al., 2020).

There is a fundamental question concerning the prevalence and severity of T-cell exhaustion. Why is T-cell exhaustion so widely induced by both virulent and latent pathogen infections, and also induced by several cancers, such as leukemias and lymphomas (Cader et al., 2018; Carvalho-Schneider et al., 2021; Das et al., 2017; Dyck & Mills, 2017; Kong et al., 2016; Kurachi, 2019; Makary, 2020; Mendelson et al., 2020; Yelin et al., 2020)? T-cell exhaustion is caused by long duration antigen exposures and persistent inflammation, and these conditions can result from several long duration virulent pathogen infections (e.g., coronaviruses such as SARS-CoV-2), long duration latent pathogen infections (e.g., viral, fungal, or protozoan

TABLE 1 Symptoms of COVID-19 and/or Long COVID-19 compared to the symptoms of *T. gondii* infection

Symptom	COVID-19	*T. gondii* infection	Explanation
Dyspnea/Labored breathing	Reported	Reported	Match
Neurological deficits	Reported	Reported	Match
Fatigue	Reported	Reported	Match
Fever	Reported	Reported	Match
Cognitive dysfunction[a]	Reported	Reported	Match
Altered mental status[a]	Reported	Reported	Match
Mental confusion[a]	Reported	Reported	Match
Behavioral changes[a]	Reported	Reported	Match
Involuntary movements[b]	Reported	Reported	Match
Ataxia/incoordination[b]	Reported	Reported	Match
Vertigo/Dizziness	Reported	Possible in nerves	By C. N. nerve palsy
Tinnitus/Ear ringing	Reported	Possible in nerves	By C. N. nerve palsy
Otalgia/Earache	Reported	Possible in nerves	By C. N. nerve palsy
Speech and Swallow deficits	Reported	Possible in nerves	By C. N. nerve palsies
Anosmia/Impaired smell	Reported	Possible in nerves	By C. N. nerve palsy
Dysgeusia/Impaired taste	Reported	Possible in nerves	By C. N. nerve palsy
Chest pain	Reported	Possible	Possible nerve palsy
Arthralgia/Joint pain	Reported	Possible	Possible nerve palsy
Hair loss	Reported	Possible	Possibly stress-caused
Depression	Reported	Possible	Possibly stress-caused
Anxiety	Reported	Possible	Possibly stress-caused
Seizures	Possible	Reported	Match to COVID-19
Vision changes	Possible	Reported	Match to COVID-19
Headaches	Possible	Reported	Match to COVID-19
Pneumonia	Reported	Reported	Match to COVID-19
Chorioretinitis	Possible	Reported	Rare for COVID-19

Note: C. N. palsy means cranial nerve palsy. Almufarrij and Munro (2021), Amenta et al. (2020), Bordoni et al. (2021), Carvalho-Schneider et al. (2021), Costa (2018), de Souza et al. (2021), Halonen and Weiss (2013), Mendelson et al. (2020), Sonne and Lopez-Ojeda (2021), Vidal (2019), Yelin et al. (2020).

[a]These are not precise symptoms and may be reported interchangeably.

[b]These are not precise symptoms and may be reported interchangeably.

parasites such as *T. gondii*), and cancers (Cader et al., 2018; Dyck & Mills, 2017; Kong et al., 2016; Kurachi, 2019). And the severity of T-cell exhaustion is determined by both the abundance (titer) of the antigens, such as from increased pathogen numbers (e.g., increased pathogen and antigen levels from primary or secondary viremia), and by the time duration of the antigen stimulation (Cader et al., 2018; Dyck & Mills, 2017; Kong et al., 2016; Kurachi, 2019). This is significant, because this also implies that long duration cancers and latent pathogen infections in combination with sufficient inflammation and antigen abundance can cause more severe T-cell exhaustion. Therefore, older individuals will generally also be more likely to have more severe T-cell exhaustion with all its consequences for higher mortality. This would be yet another logical explanation for the increasing mortality rate of older individuals infected by SARS-CoV-2, in addition to the increasing number of comorbidities and general weakening of the immune system with increasing age.

2.10 | Synergies between cancers and SARS-CoV-2 by T-cell exhaustion

T-cell exhaustion is associated with the loss of T-cell effector functions, reduced proliferative and cytotoxic capacities and impaired production of interleukin-2 and pro-inflammatory cytokines, and increased expression of inhibitory receptors, including the programmed cell death protein 1 (PD-1) receptor, cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, the lymphocyte-activation gene 3 (LAG3) receptor, and the T-cell immunoglobulin domain and mucin domain 3 (Tim-3) receptor, etc. (Cader et al., 2018; Das et al., 2017; Dyck & Mills, 2017; Kong et al., 2016; Kurachi, 2019; Makary, 2020; Saleh et al., 2020; Virgin et al., 2009). This is noteworthy because several cancers produce ligands, such as PD-L1 and PD-L2, that induce T-cell exhaustion by binding to the inhibitory PD-1 T-cell receptor (Cader et al., 2018; Dyck & Mills, 2017; Kong et al., 2016;

Kurachi, 2019). Furthermore, several COVID-19 patients have certain cancer comorbidities that can cause T-cell exhaustion and also have significantly increased OR for critical illness and mortality, including lung cancers (OR of mortality 2.89), leukemias or lymphomas (OR of critical illness 3.53; OR of mortality 2.2), colorectal cancer (OR of mortality 1.73), etc. (Cader et al., 2018; Das et al., 2017; Dyck & Mills, 2017; Gottlieb et al., 2020; Harrison et al., 2020; Kong et al., 2016; Makary, 2020; Saleh et al., 2020). The worse outcomes for these COVID-19 cancer patients can be explained by a bidirectional synergy between the SARS-CoV-2 virus and certain cancers through T-cell exhaustion and other immune cell dysfunctions.

2.11 | Can antigen-specific T-cell exhaustion cause other T-cells' exhaustion?

One fundamental question that should be addressed is whether T-cell exhaustion in antigen-specific T-cells can affect other T-cells that are not specific for the same antigen as the exhausted antigen-specific T-cells. There are actually several reasons to believe that T-cell exhaustion, or at least T-cell inhibition, can occur (Goh et al., 2013; Kurachi, 2019; Norris et al., 2013; Sevilla et al., 2004; Wilson et al., 2012). T-cell exhaustion can be caused by inhibitory receptors and desensitization of co-stimulatory receptors for antigen-specific T-cells (Kurachi, 2019). Furthermore, just like many of the chronic cancers listed earlier, chronic infections with *T. gondii* have also shown a progressive increase in T-cell expression of the inhibitory PD-1 receptor and a progressive increase in PD-L1 expression by *T. gondii*-infected cells (Bhadra et al., 2011). This also progressively increases the probability of eventual cross-activation of the inhibitory T-cell receptor PD-1 on T-cells by cells infected by both *T. gondii* and a virus like SARS-CoV-2, thus potentially inducing CD8 T-cell exhaustion for antigens of both types of pathogens.

Furthermore, there are also several mobile mediators that inhibit T-cell functions, including immunosuppressive cytokines interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and indoleamine 2,3 dioxygenase (IDO); inflammatory cytokines including interferons α/β that can in some cases also promote immune suppression of T-cells; dendritic cells, macrophages, and B cells that can be transformed into immunoregulatory antigen-presenting cells that secrete elevated levels of IL-10, IDO, and TGF-β; upregulated immunoregulatory T_{REG} cells; and myeloid-derived suppressor cells that can inhibit T-cell functions and/or promote T-cell exhaustion (Goh et al., 2013; Kurachi, 2019; Norris et al., 2013; Sevilla et al., 2004; Wilson et al., 2012). Therefore, there are multiple nonspecific pathways for antigen-specific T-cell exhaustion induced by one pathogen or cancer to inhibit T-cells and/or cause T-cell exhaustion in naive T-cells or other T-cells specific for other antigens.

Table 2 lists several different categories of COVID-19 patients and the various intracellular pathogens that can induce mutually beneficial T-cell exhaustion leading to more severe consequences for COVID-19 patients in a particular category. Some mortality OR were also determined from the U.S. FAIR Health National Private Insurance Claims repository, which included data from 467,773 COVID-19 patients (Makary, 2020).

TABLE 2 Pathogens that could provide mutually beneficial T-cell exhaustion to SARS-CoV-2

Patient category	1st Agent	2nd Agent	Consequence
Long COVID-19[a]	SARS-CoV-2	*T. gondii*	Long COVID-19
Schizophrenia[b]	*T. gondii*	SARS-CoV-2	Fatal (OR 2.67)
Older adults[c]	*T. gondii*	SARS-CoV-2	Fatal (OR 7.32)
Male adults[c]	*T. gondii*	SARS-CoV-2	Fatal (OR 1.75)
Higher BMI[c]	*T. gondii*	SARS-CoV-2	Fatal (OR 1.37)
Liver disease[d]	Hepatitis B/C	SARS-CoV-2	Fatal (OR 2.62)
Lung cancers[e]	Lung cancer	SARS-CoV-2	Fatal (OR 2.89)
Leukemias[f]	Leukemia	SARS-CoV-2	Fatal (OR 2.2)
Lymphomas[g]	Lymphoma	SARS-CoV-2	Fatal (OR 2.2)
Colorectal cancers[h]	Colo. cancer	SARS-CoV-2	Fatal (OR 1.73)

Note: Several intracellular pathogens, latent or active, can induce T-cell exhaustion, especially CD8 T-cell exhaustion, that will benefit themselves or a second intracellular pathogen, such as SARS-CoV-2. *T. gondii* can also benefit from SARS-CoV-2 to create the symptoms of Long COVID-19.

Abbreviations: BMI, body mass index; OR, odds ratio.

[a]Almufarrij and Munro (2021), Amenta et al. (2020), Bordoni et al. (2021), Costa (2018), de Souza et al. (2021), Halonen and Weiss (2013), Sonne and Lopez-Ojeda (2021), Vidal (2019), Wu et al. (2020).

[b]Nemani et al. (2021).

[c]Gottlieb et al. (2020), Hamer et al. (2020), Harrison et al. (2020).

[d]Dittfeld et al. (2016), Dyck and Mills (2017), Handous et al. (2020), Harrison et al. (2020), Kurachi (2019), McHugh et al. (2019), Meier et al. (2018), Pallett et al. (2019), Schildermans and De Vlieger (2020), Virgin et al. (2009), Wherry and Kurachi (2015).

[e]Makary (2020).

[f]Cader et al. (2018), Das et al. (2017), Dyck and Mills (2017), Gottlieb et al. (2020), Harrison et al. (2020), Kong et al. (2016), Makary (2020), Saleh et al. (2020).

[g]Cader et al. (2018), Das et al. (2017), Dyck and Mills (2017), Gottlieb et al. (2020), Harrison et al. (2020), Makary (2020), Saleh et al. (2020).

[h]Goh et al. (2013), Saleh et al. (2020), Sevilla et al. (2004).

2.12 | There are several types of *T. gondii* with very substantial differences

It is important to note that there are actually at least 11 different genetic types (haplogroups) of *T. gondii*, with major differences in their growth, migration, and transmission characteristics, and very substantial differences exceeding five orders of magnitude in terms of their effects on the immune system and their virulence (Halonen & Weiss, 2013). It should also be noted that there is a very significant geographical influence on the distribution of the specific *T. gondii* haplogroups (Halonen & Weiss, 2013). For example, the *T.*

gondii haplogroups (predominantly Type II) of North America are the same as in Europe, but they are much less virulent compared to the very virulent *T. gondii* haplogroups (e.g., Type I) of South America (Halonen & Weiss, 2013). Therefore, the specific haplogroup of *T. gondii* being studied in a specific country or continent should be identified and specified because of their very substantial immunological differences. Such differences could also explain some differences in COVID-19 severity in various populations.

2.13 | Early drug treatments for toxoplasmosis can block T-cell dysfunctions and T-cell exhaustion, and could maintain effective T-cell functions to block latent pathogen reactivations and moderate later viral infections

There are several drug treatments for *T. gondii* infections, such as sulfamethoxazole and trimethoprim, and it has been demonstrated that early initiation of such drug treatments for *T. gondii* infections can greatly reduce later induced T-cell dysfunctions, including CD8 T-cell exhaustion, in the late stage of chronic infection (Bhadra et al., 2011). CD8 T-cells normally produce interferon-γ and cytotoxic granzyme B to control toxoplasmosis and block reactivation of *T. gondii* cysts, but these are also generally used to suppress viral infections (Bhadra et al., 2011). Therefore, if T-cell exhaustion and other dysfunctions can be blocked by early drug treatments for protozoan parasite infections, then effective CD8 T-cell responses to later viral infections, including SARS-CoV-2, could essentially be maintained (Bhadra et al., 2011). These drug treatments, if timely, could essentially mitigate the increased risk of mortality of COVID-19 patients having protozoan parasite infections.

2.14 | In the absence of T-cell exhaustion, latent pathogen infections can sometimes improve immune responses to other pathogens

In summary, T-cell exhaustion is caused by the combination of long duration pathogen infections or cancers that produce inflammation and long duration antigen stimulation with significant titers of antigens. However, if one or more of these criteria are not satisfied, it is possible for a relatively recent latent pathogen infection, or a latent pathogen infection producing little inflammation or a low titer of antigens, to induce very little or no T-cell exhaustion. Furthermore, if some circumstance or treatment can block T-cell exhaustion that reduces T-cell functions, some latent pathogen infections, including some types of protozoan parasite infections, can induce CD4 T-cells and CD8 T-cells to release higher levels of antiviral interferon-γ that can promote an improved response to a later infection by a virus (Abdel-Hamed et al., 2021; Bhadra et al., 2011).

A recent paper summarized a clinical study of 375 COVID-19 patients in Egypt and the relationship between their SARS-CoV-2 viral infection outcomes and the presence in almost 69% of the patients of various protozoan parasite infections, including *T. gondii* (Abdel-Hamed et al., 2021). However, there was no indication of whether any of these patients had received early drug treatments for their protozoan parasite infections that would have blocked later T-cell exhaustion (Abdel-Hamed et al., 2021). This clinical study concluded that the protozoan parasite stimulation of T-cells significantly increased the levels of interferon-γ, and that existing protozoan parasite infections with increased levels of interferon-γ resulted in a large majority of cases with more moderate COVID-19 symptoms (Abdel-Hamed et al., 2021). It should be noted that this study did not address the following: (a) whether the protozoan parasite-infected patients had previously received any early anti-protozoan parasite drug treatments that would have blocked T-cell exhaustion and dysfunctions, thereby improving later T-cell responses to COVID-19, (b) the vastly different immune effects of the various haplogroups of *T. gondii*, (c) the possibility or consequences of T-cell exhaustion from protozoan parasite infections that satisfied the necessary criteria to induce T-cell exhaustion, (d) an opposite role for SARS-CoV-2 in reactivating latent infections of *T. gondii*, and (e) the possibility that such latent pathogen reactivations could produce the symptoms now called Long COVID-19 (Bhadra et al., 2011).

3 | METHODS

3.1 | Suggestions for further research

One way to directly prove the connection between Long COVID-19 and toxoplasmosis is to measure the IgG antibodies to *T. gondii* in the blood of people suffering from Long COVID-19, and compare their IgG antibody measurements to people who did not suffer any Long COVID-19 after their COVID-19 infection. Other options include taking computed tomography scans of the brains or extracting brain tissue samples from both groups of people during postmortem autopsies to compare the prevalence of lesions from *T. gondii* infections in patients to cases of Long COVID-19 or fatal COVID-19. It would also be worthwhile to determine the specific haplogroup of *T. gondii* being studied, since these haplogroups have enormous differences in their characteristics and consequences.

4 | CONCLUSION

Active brain infections by protozoan parasite *T. gondii* can cause neuroinflammations, activation of microglia, astrocytes and complement, major neurotransmitter disruptions. Furthermore, some long duration active or latent infections by *T. gondii* can cause immune dysfunctions, including CD8 T-cell exhaustion. *T. gondii* infections have an extensively documented involvement in some schizophrenia cases. A statistically increased mortality rate for COVID-19 schizophrenia patients could be logically explained by a subset of schizophrenia patients having long duration *T. gondii* brain infections that cause immune dysfunctions, such as CD8 T-cell exhaustion. This

could cause more severe outcomes for these COVID-19 patients. More importantly, the matches in corresponding patient categories between the OR of COVID-19 mortality and *T. gondii* infection suggest *T. gondii* in certain cases, especially in cases without early protozoan parasite drug treatments, can induce immune dysfunctions which cause more severe outcomes for these COVID-19 patient categories. In addition, some cancers and pathogens which also induce T-cell exhaustion can explain the more severe outcomes of COVID-19 patients experiencing certain cancer or disease comorbidities. Furthermore, latent pathogen infections that are partially or fully reactivated for any reason could explain why certain post-COVID-19 individuals experience the long duration symptoms of Long COVID-19.

CONFLICT OF INTEREST

The author has no potential conflict of interest.

AUTHOR CONTRIBUTIONS

The author was the sole contributor in all aspects.

ETHICS STATEMENT

The author confirms that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is an article with no original research data.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

Transparent Peer Review Report

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