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Higher Toxoplasma Gondii Seropositivity in COVID-19 and Tuberculosis Patients: A Case-Control Study

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ABSTRACT

Using a case-control study, we compared the antibody-positive profiles for Toxoplasma gondii in patients infected with SARS-CoV-2, tuberculosis (TB), HBV, and HIV-1 in Wuxi of China. As an important pathogen, Toxoplasma gondii has higher co-infection and reactivation rates in patients with SARS-CoV-2 and TB infection.

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Patients and Methods

This study enrolled patients infected with SARS-CoV-2, tuberculosis (TB), HBV, and HIV-1 who were on active treatment in our hospital in 2020 and 2022. We also enrolled the health examination population as health control (HC) during the same period. The medical records and demographic information were collected through a clinical data system. The inclusion criteria were as follows: ① Patients whose diagnosis met the medical criteria; ② Patients aged ≥ 18 years. ③ Patients in 2022 who have immunized with the third dose of inactivated COVID-19 vaccine. This study was conducted following the Declaration of Helsinki (as revised in 2013) and approved by our hospital ethics committee (No. 2021-004-1). Toxoplasma gondii (T. gondii) IgM (or IgG) seropositivity was tested using indirect ELISA (Zhuhai Haitai Biotech, Zhuhai, China) following the product manuals. SARS-CoV-2 IgG was tested using INNOVITA® 2019-nCoV IgM/IgG kit following the manufacturer's instructions.

Results

Based on the COVID-19 patients' symptoms over the past three years, patients over 46 years with comorbidities were prone to developing severe illness, so we divided them into two age groups [1]. We have reported that TB patients had the weakest immunogenicity after vaccinating with the third dose of inactivated COVID-19 vaccine [2]. In this case-control study, compared to the SARS-CoV-2 IgG positivity (59.9%) of healthy control (HC), the IgG positivity (after vaccinating with the third dose of inactivated COVID-19 vaccine) of TB patients (25.9%), HBV patients (43.0%), or HIV-1 patients (33.9%) was significantly lower ($P < 0.05$). In addition, SARS-CoV-2 IgG positivity of the HBV female patients was significantly lower than that of the HC female group ($P < 0.05$). The SARS-CoV-2 IgG positivity of COVID-19 patients was the initial antibody result (induced by vaccination) after admission, similar to that of the HC (Table 1).

T. gondii, as an opportunistic pathogen, infects nearly a third of people in the world; its prevalence closely relates to economic development and lifestyle [3, 4]. It still lacks research on COVID-19 and TB patients with T. gondii status in the Yangtze River Delta region of China, especially universal vaccination with the third dose of inactivated COVID-19 vaccine. In this case-control study, SARS-CoV-2 [T. gondii IgM: 60.8% ($P = .0000$)] and TB [T. gondii IgG: 33.0% ($P = .0073$), IgM: 53.6% ($P = .0000$)] infected patients had significantly higher T. gondii seropositivities compared with the HC (T. gondii IgG: 18.2%, IgM: 19.0%). On the contrary, HBV [T. gondii IgG: 5.1% ($P = .0062$), IgM: 3.8% ($P = .0016$)] and HIV-1 [T. gondii IgM: 6.5% ($P = .0222$)] infected patients had significantly lower T. gondii seropositivities than HC. T. gondii IgG positivity rankings (co-infection in 2022): TB (33.0%) > COVID-19 (24.9%) > HC (18.2%) > HIV-1 (9.7%) > HBV (5.1%). Our study demonstrated that SARS-CoV-2- and TB-infected patients also had significantly higher reactivation or new infection rates of T. gondii (IgM positive) compared with HC. In addition, IgM positivity of T. gondii showed significant gender and age differences in patients with COVID-19, TB, and HBV ($P < 0.05$). Notably, COVID-19 patients had ~2.4-fold higher T. gondii IgM positivity than IgG, and this fold was higher than in other groups. TB patients had ~1.6-fold higher T. gondii IgM positivity than IgG. The higher T. gondii infection status (IgM positive) suggests that T. gondii-infected patients may be susceptible to SARS-CoV-2 or TB co-infection (Table 1).

Table 1: Comparison of Toxoplasma Gondii Seropositivity in Patients Infected with SARS-CoV-2, TB, HBV, and HIV-1

Groups	Positive SARS-CoV-2 IgG, n/N (%)	*P*[a]	Toxoplasma Gondii				Positive Gondii IgG			
			Positive IgM, n/N (%)	*P*[a]	Positive IgG, n/N (%)	*P*[a]	Positive SARS-CoV-2 IgG, n/N (%)	*P*[a]	Negative SARS-CoV-2 IgG, n/N (%)	*P*[a]
HC	82/137 (59.9)	NA	26/137 (19.0)	NA	25/137 (18.2)	NA	9/82 (11.0)	NA	16/55 (29.1)	NA
Male	28/54 (51.9)	NA	11/54 (20.4)	NA	13/54 (24.1)	NA	2/28 (7.1)	NA	11/26 (42.3) §	NA
Female	54/83 (65.1)	NA	15/83 (18.1)	NA	12/83 (14.5)	NA	7/54 (13.0)	NA	5/29 (17.2)	NA
18-45	48/81 (59.3)	NA	12/81 (14.8)	NA	10/81 (12.3) §	NA	5/48 (10.4)	NA	5/33 (15.2) #	NA
≥46	34/56 (60.7)	NA	14/56 (25.0)	NA	15/56 (26.8)	NA	4/34 (11.8)	NA	11/22 (50.0)	NA
COVID-19	174/309 (56.3)	.4851	188/309 (60.8)	.0000	77/309 (24.9)	.1218	41/174 (23.6)	.0178	36/135 (26.7)	.7339
Male	100/184 (54.3)	.7463	110/184 (59.8)	.0000	28/184 (15.2)&	.1297	13/100 (13.0)*	.3944	15/84 (17.9) #	.0103
Female	74/125 (59.2)	.3949	78/125 (62.4)	.0000	49/125 (39.2)	.0001	28/74 (37.8)	.0018	21/51 (41.2)	.0024
18-45	93/158 (58.9)	.9527	113/158 (71.5) ¶	.0000	56/158 (35.4) ¶	.0002	35/93 (37.6) &	.0007	21/65 (32.3)	.0691
≥46	81/151 (53.6)	.3630	75/151 (49.7)	.0014	21/151 (13.9)	.0299	6/81 (7.4)	.4492	15/70 (21.4)	.0094
TB	29/112 (25.9)	.0000	60/112 (53.6)	.0000	37/112 (33.0)	.0073	9/29 (31.0)	.0118	28/83 (33.7)	.5665
Male	17/78 (21.8)	.0000	44/78 (56.4)	.0000	24/78 (30.8)	.3998	5/17 (29.4)	.0457	19/61 (31.1)	.3161
Female	12/34 (35.3)	.0032	16/34 (47.1)	.0013	13/34 (38.2)	.0044	4/12 (33.3)	.0867	9/22 (40.9)	.0064
18-45	15/51 (29.4)	.0008	25/51 (49.0)	.0000	14/51 (27.5)	.0285	2/15 (13.3) §	.7537	12/36 (33.3)	.0800
≥46	14/61 (23.0)	.0000	35/61 (57.4)	.0004	23/61 (37.7)	.2077	7/14 (50.0)	.0042	16/47 (34.0)	.2056
HBV	34/79 (43.0)	.0170	3/79 (3.8)	.0016	4/79 (5.1)	.0062	2/34 (5.9)	.3941	2/45 (4.4)	.0014
Male	24/51 (47.1)	.4411	3/51 (5.9)	.0291	3/51 (5.9)	.0095	2/24 (8.3)	.8724	1/27 (3.7)	.0008
Female	10/28 (35.7)	.0066	0/28 (0)	.0156	1/28 (3.6)	.1214	0/10 (0)	.2276	1/18 (5.6)	.7822
18-45	19/42 (45.2)	.1387	2/42 (4.8)	.0821	3/42 (7.1)	.3735	2/19 (10.5)	.9894	1/23 (4.3)	.1985
≥46	15/37 (40.5)	.0565	1/37 (2.7)	.0012	1/37 (2.7)	.0026	0/15 (0)	.1657	1/22 (4.5)	.0007
HIV-1	25/62 (40.3)	.0105	4/62 (6.5)	.0222	6/62 (9.7)	.1226	3/25 (12.0)	.8870	3/37 (8.1)	.0148
Male	19/56 (33.9)§	.0575	4/56 (7.1)	.0433	6/56 (10.7)	.0639	3/19 (15.8)	.0000	3/37 (8.1)	.0013
Female	6/6 (100.0)	.0778	0/6 (0)	.2535	0/6 (0)	.3167	0/6 (0)	.3481	0	NA
18-45	25/42 (59.5)	.9774	4/42 (9.5)	.0821	5/42 (11.9)	.6272	3/17 (17.6)	.4355	2/25 (8.0)	.7437
≥46	8/20 (40.0)	.1098	1/20 (5.0)	.0537	1/20 (5.0)	.0402	0/8 (0)	.3078	1/12 (8.3)	.0151

Notes: All selected people completed the vaccination of a third dose of inactivated COVID-19 vaccine, including COVID-19 patients in 2022. The quantification of the SARS-CoV-2 IgG against the virus spike protein was carried out using INNOVITA® 2019-nCoV

IgM (or IgG) kit (Beijing Yinnuo Biotech, China). Toxoplasma gondii seropositivities were tested using the Diagnostic Kit for IgM (or IgG) Antibody to Toxoplasma (Zhuhai Haitai Biotech, China) by following the manufacturer's instructions. COVID-19, coronavirus disease 2019; HC, healthy control; TB, Tuberculosis; HBV, hepatitis B virus; HIV-1, human immunodeficiency virus type 1; NA, not available; a, means a statistical comparison of the corresponding data between the people with underlying disease and HC in each age group; §, $P < 0.05$; #, $P < 0.01$; *, $P < 0.001$; ¶, $P < 0.0001$; &, $P < 0.00001$; These special symbol beside bracket indicates the comparison within the subgroups. Statistical analyses were performed using Chi-square test (P-value); A p-value < 0.05 is considered statistically significant.

We further analyzed whether co-infection with T. gondii has a negative effect on the immunogenicity of inactivated COVID-19 vaccine, such as in TB patients. Compared with the T. gondii IgG positive plus SARS-CoV-2 IgG-positive population, the T. gondii IgG positive plus SARS-CoV-2 IgG-negative population in HC (29.1% vs. 11.0%), COVID-19 (26.7% vs. 23.6%), TB patients (33.7% vs. 31.0%) were higher. Our results also showed that aged TB patients (≥ 46 years) had significantly higher SARS-CoV-2 and T. gondii double-IgG seropositivity (50.0%, P< 0.05) than the 18-45-years-old subgroup and HC (≥ 46 years) (Table 1). However, two-way logistic regression analysis showed no significant relevance between T. gondii IgG and SARS-CoV-2 IgG positivity in these patients. The gender and age differences in all groups did not show significant relevance in patients with T. gondii IgG positive plus SARS-CoV-2 IgG negative (Figure 1).

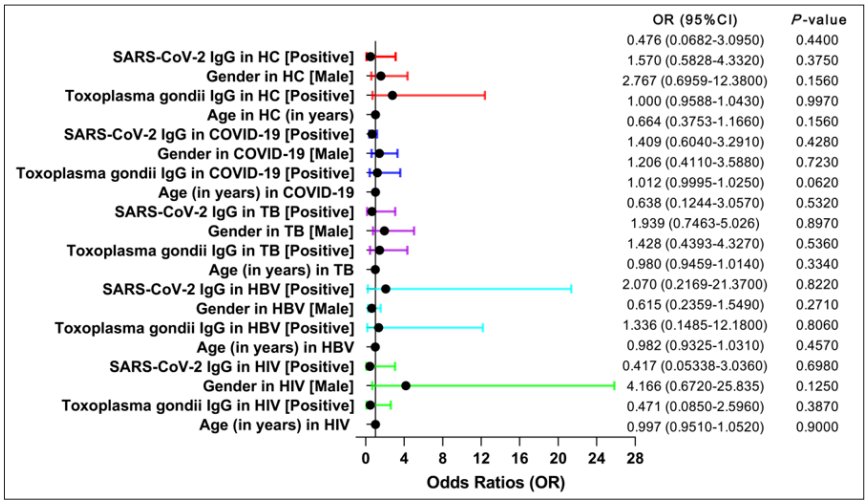

Figure 1: Risk Factors Analysis of Toxoplasma Gondii IgG Seropositivity in Healthy Control (HC), COVID-19, Tuberculosis (TB), HBV, and HIV-1 Individuals during the Omicron SARS-CoV-2 Epidemic

Two-way regression analysis was used to calculate the Odds Ratios (OR) and 95%CI between Toxoplasma gondii serum IgG positivity and other risk factors, including SARS-CoV-2 IgG positive, gender, Toxoplasma gondii, and age. CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

After that, we focused on comparing the T. gondii seropositivity in patients infected with SARS-CoV-2 and TB in 2020 and 2022. Our results showed that T. gondii IgM seropositivities in COVID-19 [> 2.4-fold (IgM/IgG) in 2020 or 2022] and TB (> 1.6-fold in 2022) patients were significantly higher than IgG (P < 0.05). In addition, patients infected with SARS-CoV-2 and TB showed no significant differences in T. gondii IgM and IgG seropositivity between 2020 and 2022 (Figure 2). It suggests that the rates of co-infection or reactivation of T. gondii is not associated with COVID-19 vaccination.

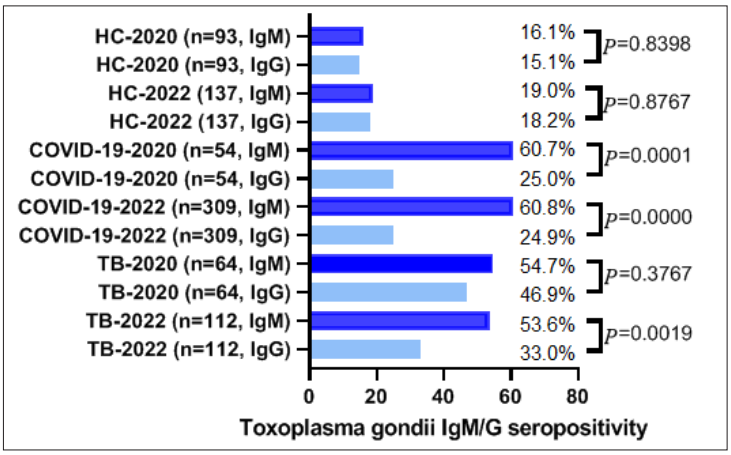

Figure 2: Comparison of Toxoplasma Gondii IgM or IgG Seropositivity in Healthy, COVID-19 or Tuberculosis Individuals between 2020 and 2022

Peripheral blood samples from healthy control (HC), COVID-19 or tuberculosis individuals were collected and aliquoted during the 2020 Wuhan strain and 2022 Omicron variants prevalence. From January to June 2022, all individuals were immunized with the third dose of inactivated COVID-19 vaccines during the Omicron variants pandemic. Toxoplasma gondii IgM (or IgG) seropositivity was tested following the product manual. Statistical analysis is presented as positive serum rate. A p-value <0.05 is considered statistically significant.

Discussion

Given that Toxoplasma gondii and TB are intracellular parasites, these pathogens can cause $CD4^+$ T-cell exhaustion and establish latent infections, which differ from HIV-1 and HBV in immunosuppression [3-5]. Furthermore, both T. gondii and TB easily transform from latent into an active state in immunosuppressed individuals by reducing the production of Th1-polarized cytokines and overproduction of Th2-polarized cytokines. However, regarding the clinical importance of co-infection, there is a lack of understanding of the effects of T. gondii co-infection in SARS-CoV-2 and TB patients. Therefore, this case-control study aims to investigate the underlying links between this co-infection using serological techniques.

Based on the clinical manifestations (from asymptomatic to severe) of TB co-infection cases, evidence indicates that it may be an immunosuppressive pathogen and induce opportunistic infections [3,5]. However, whether SARS-CoV-2 has similar effects to opportunistic infection remains to be addressed. A study has shown that latent pathogens can have different genetic strains and effects on a second pathogen [5]. T. gondii has higher seropositivities in ill pulmonary patients compared to healthy individuals and can complicate symptoms in immunosuppressed and immunodeficient patients [3,6]. Some studies suggest that latent protozoan parasite infections reduce the severity of viral infections [5]. Therefore, we sought to investigate the T. gondii seropositivities of original COVID-19 and recent infectious disease patients. It will help to understand the real world of the population infected with SARS-CoV-2 strains and vaccinated with the third-dose inactivated COVID-19 vaccine in Wuxi from September 2021.

SARS-CoV-2 virus and inactivated COVID-19 vaccine comprise all viral structural proteins that may induce a broader immune response profile, including Th2-polarized cytokines and neutralizing antibodies against receptor-binding domain (RBD). According to a previous study, SARS-CoV-2 can cause lower levels of CD4+ or CD8+ T cells and higher levels of IL-6 and IL-10 in severely ill patients, similar to the reactivate responses of T. gondii or TB [3,6,7]. Furthermore, previous cohort studies have not disclosed the effects of gender and age on the COVID-19 mRNA vaccine immunogenicity, possibly due to the high immunogenicity of mRNA vaccines, and being difficult to find such differences [8-11]. Our study has elucidated that the gender and age differences can affect the SARS-CoV-2 or T. gondii antibody response.

In summary, seroprevalence rates of T. gondii seropositivity show large geographical differences between countries, including HBV or HIV-1 co-infection. Our findings of T. gondii with HBV or HIV-1 co-infection rates (IgG) suggest that, unlike previous reports in other countries, levels of such co-infection were relatively low in the developed business hub of southeastern China [12-14]. Patients with SARS-CoV-2 and TB had higher rates of T. gondii IgM seropositivity. They also developed higher T. gondii IgG seropositivities in SARS-CoV-2 IgG-negative individuals, which may be related to T. gondii reactivation or infection weakening the host's response to the SARS-COV-2 genome of the COVDI-19 vaccine. This phenomenon also requires further mechanistic studies to reveal the specific relevance, which may help to know the reason why TB patients vaccinated with the inactivated COVID-19 vaccine have the lowest immunogenicity.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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