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Positive Toxoplasma IgG Serology Is Associated with Increased Overall Mortality – A Propensity Score–Matched Analysis

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Abstract. *Toxoplasma gondii* is a prevalent parasitic disease with significant morbidity and mortality in immunocompromised populations. We lack long-term outcomes for latent infections. We aimed to elucidate the relationship between latent *T. gondii* infection and mortality risk. We queried TriNetX, a international multicenter network, to validate mortality risk differences among patients with positive or negative toxoplasma IgG through propensity score matching (PSM). We excluded patients with toxoplasmosis disease by International Classification of Diseases codes or polymerase chain reaction testing. We found 28,138 patients with available toxoplasma IgG serology. Seropositive patients were older and had a male preponderance. More seropositive patients identified as Hispanic, Latino, or Black persons. Patients who were positive for *T. gondii* IgG serology were slightly more likely to have underlying heart failure, a transplanted organ or tissue, malignant neoplasms of lymphoid or hematopoietic tissues, and diseases of the nervous system than seronegative controls. After PSM of patients with positive ($N = 6{,}475$) and negative ($N = 6{,}475$) toxoplasma IgG serologies, toxoplasmosis-positive patients were more likely to have long-term drug use but less likely to suffer from behavioral disorders. The overall PSM 1- and 5-year mortality was higher among patients with a positive toxoplasma IgG serology. The risk of schizophrenia was increased at 5 years. We found a prevalence of toxoplasma IgG positivity of 0.03% during the last 3 years. Latent *T. gondii* associates with a higher overall mortality risk. The study of social determinants of health and follow-up studies are necessary to corroborate the findings and find possible causal mechanisms.

INTRODUCTION

Toxoplasmosis is a parasitic infection caused by the protozoan *Toxoplasma gondii* infection. It is a prevalent disease affecting humans and animals worldwide, with an estimated exposure rate of over 33% of the global population.[1] Although that number is lower in the United States, estimates are that 7–13% of the U.S. population has been exposed to the parasite.[2,3] Infection can occur through ingesting undercooked meat containing cysts, consuming contaminated food or water, or contacting infected animal feces, most commonly that of cats. Infections can be asymptomatic or may present with severe illness, most commonly in immunocompromised individuals.

A recent study conducted in the United States examined the seroprevalence of toxoplasmosis and associated factors among adults, finding a 13.3% seroprevalence rate, with males and Latino patients more likely to be IgG seropositive, whereas higher education or socioeconomic status was associated with lower rates of positive toxoplasmosis serology.[3]

Although the disease burden from toxoplasmosis is extensive, resulting in encephalitis, myocarditis, pneumonia, and blindness, severe toxoplasmosis disease most commonly occurs in patients with suboptimal immune systems (e.g., a fetus), with organ transplantation, or with advanced HIV. Severe manifestations of acute toxoplasmosis have also been reported in immunocompetent individuals.[4,5] However, growing medical literature supports a risk of adverse patient outcomes even without clinical toxoplasmosis.[1] Research thus far indicates a possible relationship between positive serology for toxoplasmosis or latent toxoplasmosis and the development of psychiatric disorders such as obsessive-compulsive disorder (OCD) and schizophrenia.[6–9] Patients with treatment-resistant OCD were found to have higher rates of IgG-positive toxoplasma serology, although this relationship was not supported in children.[7,10] Latent toxoplasmosis has also been shown to increase the risk of depression and suicidal behavior.[7] Higher rates of toxoplasmosis serology have been shown to correlate with an increased need for psychiatric hospitalization.[11,12] Many observational studies have also revealed a modest to significant association between toxoplasmosis and schizophrenia.[9] Although a spectrum of clinical illness and severity is associated with toxoplasmosis, less information is known about seropositive patients with toxoplasma IgG antibodies who do not yet manifest clinical disease. This body of patients represents an extensive volume as a result of the prevalence of toxoplasma IgG worldwide. Latent toxoplasma (IgG seropositive) is thought not to confer clinical problems. However, we lack data on long-term outcomes from large observational studies. We aimed to characterize the clinical features of latent toxoplasmosis and the factors related to 5-year mortality using an international global health network database.

MATERIALS AND METHODS

This was a multicentric retrospective case-control study using a global federated research network of aggregated patient data and outcomes for those with available toxoplasma IgG serology results.

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Global federated research network. The TriNetX global research network database (https://trinetx.com/) was queried to identify adult patients with available toxoplasma IgG serology until December 2022. TriNetX has global data for approximately 100 million patients from more than 80 medical centers in the United States, Canada, Europe, Australia, Indonesia, and other countries. Our group has published several reports with the same methodology.[13–17] TriNetX, LLC complies with the Health Insurance Portability and Accountability Act (HIPAA), the U.S. federal law protecting healthcare data privacy and security, and any additional data privacy regulations applicable to the contributing healthcare organizations (HCOs). Each HCO delivers electronic medical record systems data collected to provide patient care. Received data are either structured or unstructured data processed by Natural Language Processing Technology. Most participating HCOs are large academic medical institutions with inpatient and outpatient facilities. The data they provide represent the entire patient population at the HCO. Most give an average of 7 years of historical data. TriNetX receives data directly from an HCO research repository into the TriNetX environment, or the HCO sends TriNetX data extracts in the form of comma-separated values files coded in the TriNetX Data Dictionary. Healthcare organizations and other data providers update their data at various times, with more than 80% refreshing in 1-, 2-, or 4-week frequency intervals. The average lag time for an HCO's source data to refresh is 1 month. TriNetX maps the data to a standard, controlled set of clinical terminologies and transforms it into a proprietary data model. This transformation process includes extensive data quality assessment that includes data cleaning, which rejects records that do not meet TriNetX quality standards.

Study design and population. Data for this study were acquired from electronic medical records in 68 HCOs. All patients included were 18 years of age or older and had undergone serology testing for *T. gondii*. Toxoplasma IgG antibodies (units/volume) were reported in serum (laboratory result: positive or $\geq$ 12 IU/mL). Data were captured in December 2022. The study included two groups of patients who were categorized based on their toxoplasma serology results: those who tested positive for *T. gondii* IgG antibodies in serum (cases) and those who tested negative (controls). However, patients who had active toxoplasmosis disease by *International Classification of Diseases, Tenth Revision* codes (including pulmonary toxoplasmosis, toxoplasma oculopathy, meningoencephalitis, hepatitis, or any other organ involvement) or those who had positive *T. gondii* DNA in a clinical specimen through nucleic acid amplification during or before the index event (presence of toxoplasma serology) were excluded from the study. Additional information about these exclusions can be found in the Supplemental Material.

The study captured various data points related to the patients, including demographic characteristics, diagnoses, procedures, medications, and measurements such as laboratory test results (Supplemental Tables 1–3). These data points were collected 6 months before the index event (toxoplasma serology). For those who underwent testing more than once, data points collected were based on the first time they underwent serology testing.

Propensity score matching was subsequently performed. Patients were matched utilizing the following baseline characteristics: age, sex, ethnicity, race, HIV status, heart failure, transplanted organ or tissues, type 2 diabetes mellitus, cirrhosis of the liver, chronic kidney disease, current pregnancy, aplastic anemia, bone marrow failure, chronic disease of the respiratory system, lymphoid malignancy, and neoplasm. We chose the selected variables because of their association with increased mortality.

Outcome measures. Primary (mortality) and secondary (new occurrence of disease toxoplasmosis, all-cause hospitalization, bipolar disorder, suicide, schizophrenia, substance use disorder, type 2 diabetes mellitus, cardiomyopathy, chronic kidney disease, and heart disease) outcomes were analyzed at 1- and 5-years after toxoplasmosis serology (Supplemental Table 4).

Prevalence analysis. To analyze the prevalence of positive toxoplasma IgG serology, we used the TriNetX platform and included all visits within the system for individuals aged 18 years and older. We designed a query that focused on adult patients who were immunocompromised or at higher risk owing to conditions such as aplastic anemia, neoplasm, lymphoid malignancies, transplant status, HIV, pregnancy, or inflammatory bowel disease. We also queried prevalence among pregnant women. The query was conducted from January 1, 2020 through December 31, 2022.

Statistical analyses. Using the TriNetX research network to conduct statistical analysis, we reported descriptive statistics in counts, frequencies by percentage of the cohort, mean, and SD. The *t*-test statistic compared the two cohorts after propensity matching to report differences between cohorts. A P value < 0.05 was used to indicate statistical significance. A Kaplan-Meier analysis was used to estimate the probability of survival with time using a log-rank test, hazard ratio (HR), and proportionality test. Using a built-in proportional hazard model, we calculated the HR to describe the survival risk by comparing time with event rates. Propensity score matching was performed using a 1:1 greedy nearest-neighbor algorithm utilizing a caliper width of 0.1 pooled SDs (SD0). Balance on covariates was assessed using standardized mean difference, and absolute values > 0.1 were considered positive for residual imbalance. We conducted a sensitivity analysis of mortality, excluding deaths within 6 months from the index event or initial diagnosis. Additional graphs were designed using GraphPad Prism (version 8.0.0 for Windows, GraphPad Software, San Diego, CA; www.graphpad.com).

Data access. The corresponding author had full access to data in the study and had final responsibility for the decision to submit the manuscript for publication. The datasets generated and analyzed in the current study are available from those subscribed to TriNetX or from the corresponding author upon reasonable request.

RESULTS

Clinical features of seropositive patients for *T. gondii* IgG without toxoplasmosis. Patients who were identified as seropositive for *T. gondii* IgG yet negative for clinical toxoplasmosis disease (n = 6,768) were compared with seronegative controls (n = 21,370). Seropositive patients were older and had a male preponderance, and fewer were pregnant. More seropositive patients identified as Hispanic

or Latino, Black, or African American, and fewer identified as White (Supplemental Table 5).

Patients who were positive for *T. gondii* IgG serology yet lacked clinical toxoplasmosis disease were slightly more likely to have underlying heart failure; a transplanted organ or tissue; malignant neoplasms of lymphoid, hematopoietic, and related tissue; diseases of the respiratory system; and diseases of the nervous system than seronegative controls. Compared with controls, they had lower rates of HIV, liver cirrhosis, and chronic kidney disease.

Regarding psychiatric diagnoses, patients with positive toxoplasma serology had higher rates of schizoaffective disorder bipolar and depressive subtypes and fewer mood disorders than controls. There was no difference in the rates of schizophrenia. Patients with positive serology for toxoplasma were more likely to have a history of extreme poverty. Regarding laboratory values, seropositive patients had higher leukocyte counts, lower platelet counts, and serum creatinine levels. The two cohorts had no difference in C-reactive protein values.

After the cohorts were balanced for the selected covariates, TriNetX matched 6,475 patients in each group (by toxoplasma IgG seropositivity). Table 1 shows clinical characteristics for patients with and without a positive toxoplasmosis serology after propensity score matching. Toxoplasmosis-positive patients were generally more likely to have long-term drug

TABLE 1
Clinical characteristics after propensity score matching among patients with or without Toxoplasma IgG positivity

Clinical features	Toxoplasma IgG seropositive (N = 6,475)	Toxoplasma IgG seronegative (N = 6,475)	P value
Age at index (years), mean (SD)	49 (16.4)	48.5 (16)	0.055
Male	3,678 (56.8%)	3,733 (57.7%)	0.329
Ethnicity			
Hispanic or Latino	859 (13.3%)	822 (12.7%)	0.333
Not Hispanic or Latino	4,852 (74.9%)	4,624 (71.4%)	< 0.001
Race			
White	3,989 (61.6%)	4,002 (61.8%)	0.814
Black or African American	1,303 (20.1%)	1,277 (19.7%)	0.567
Asian	153 (2.4%)	143 (2.2%)	0.557
American Indian or Alaska Native	27 (0.4%)	24 (0.4%)	0.674
Native Hawaiian or other Pacific Islander	15 (0.2%)	21 (0.1%)	0.031
Medical comorbidities			
Diseases of the respiratory system	1,865 (28.8%)	1,857 (28.7%)	0.877
Neoplasms	1,779 (27.5%)	1,942 (30%)	0.002
Long-term (current) drug therapy	1,682 (26%)	1,487 (23%)	< 0.001
Diseases of the nervous system	1,620 (25%)	1,599 (24.7%)	0.669
Aplastic anemias	1,464 (22.6%)	1,431 (22.1%)	0.486
Chronic kidney disease	1,509 (23.3%)	1,437 (22.2%)	0.106
Lymphoid malignancy	1,068 (16.5%)	1,023 (15.8%)	0.268
Type 2 diabetes mellitus	941 (14.5%)	877 (13.5%)	0.105
HIV	902 (13.9%)	836 (12.9%)	0.089
Heart failure	738 (11.4%)	686 (10.6%)	0.118
Transplanted organ and tissue status	504 (7.8%)	488 (7.5%)	0.597
Pregnancy	475 (7.3%)	440 (6.8%)	0.23
Fibrosis and cirrhosis of liver	299 (4.6%)	284 (4.4%)	0.525
Pregnant state	177 (2.7%)	172 (2.7%)	0.786
Systemic connective tissue disorders	158 (2.4%)	135 (2.1%)	0.174
Bone marrow transplant status	87 (1.3%)	109 (1.7%)	0.113
Sarcoidosis	42 (0.6%)	54 (0.8%)	0.219
Systemic lupus erythematosus	41 (0.6%)	44 (0.7%)	0.744
Rheumatoid arthritis with rheumatoid factor	17 (0.3%)	11 (0.2%)	0.256
Psychiatric comorbidities			
Suicide attempt	21 (0.3%)	29 (0.4%)	0.257
Schizophrenia and other non-mood psychotic disorders	106 (1.6%)	73 (1.1%)	0.013
Inhalant abuse	52 (0.8%)	67 (1%)	0.167
Other psychoactive substance related disorders	192 (3%)	176 (2.7%)	0.397
Mental, behavioral disorders	1,582 (24.4%)	1,752 (27.1%)	0.001
Mood disorders	738 (11.4%)	712 (11%)	0.469
Laboratory values			
Platelets ($10^3/\mu L$)	207.2 (104.6)	210.5 (106.3)	0.093
Leukocytes ($10^3/\mu L$)	24.8 (269.3)	9.2 (88.5)	< 0.001
Creatinine (mg/dL)	1.8 (2.6)	1.8 (2.5)	0.875
Sodium (mmol/L)	138.2 (3.8)	138.6 (3.7)	< 0.001
Lymphocytes ($10^3/\mu L$)	2.5 (1.6)	2.5 (1.5)	0.175
Activated partial thromboplastin time	31.5 (10.8)	32.6 (10)	< 0.001
Hemoglobin A1c (%)	6.2 (1.5)	6.2 (1.5)	0.161
γ-glutamyl transferase (U/L)	76.6 (130.7)	90.5 (160.6)	0.023
C-reactive protein (mg/L)	25 (50.3)	24.9 (52.9)	0.963
Medications			
Folate	12.7 (5.3)	11.9 (4.8)	0.019
Anticonvulsant	865 (13.4%)	819 (12.6%)	0.229
Cannabidiol	10 (0.2%)	10 (0.2%)	1

Data are presented as N (%) or mean (SD).

use but less likely to suffer from behavioral disorders. They were also more likely to experience schizophrenia.

Outcome after propensity score match analysis 1 year after serology testing. After propensity score matching, 6,475 *T. gondii* IgG patients and 6,475 seronegative controls were included. The mortality risk in 1 year was greater in seropositive patients (odds ratio [OR]: 1.2, 95% CI: 1.08–1.36, $P = 0.001$) (risk ratio: 1.2 and risk difference: 0.018). Kaplan-Meier survival analysis also demonstrated that the survival probability for *Toxoplasma*-positive patients was lower (HR: 1.2, 95% CI: 1.07–1.33, $P = 0.014$) (Figure 1). Seven hundred eighteen seropositive patients, compared with 605 seronegative patients, died within 1 year. At 1 year, more seropositive patients had been hospitalized than seronegative patients, although this was not statistically significant (Figure 2). The risk of toxoplasmosis at 1 year was higher in seropositive patients than in seronegative controls. The risk of bipolar disorder and cardiomyopathy was decreased among seropositive patients (Figure 2), although the bipolar disorder was not significant (Figure 1). There were no statistically significant differences in schizophrenia (Figures 1 and 2), substance use disorder, suicide, type 2 diabetes mellitus, chronic kidney disease, and heart disease between cases and controls.

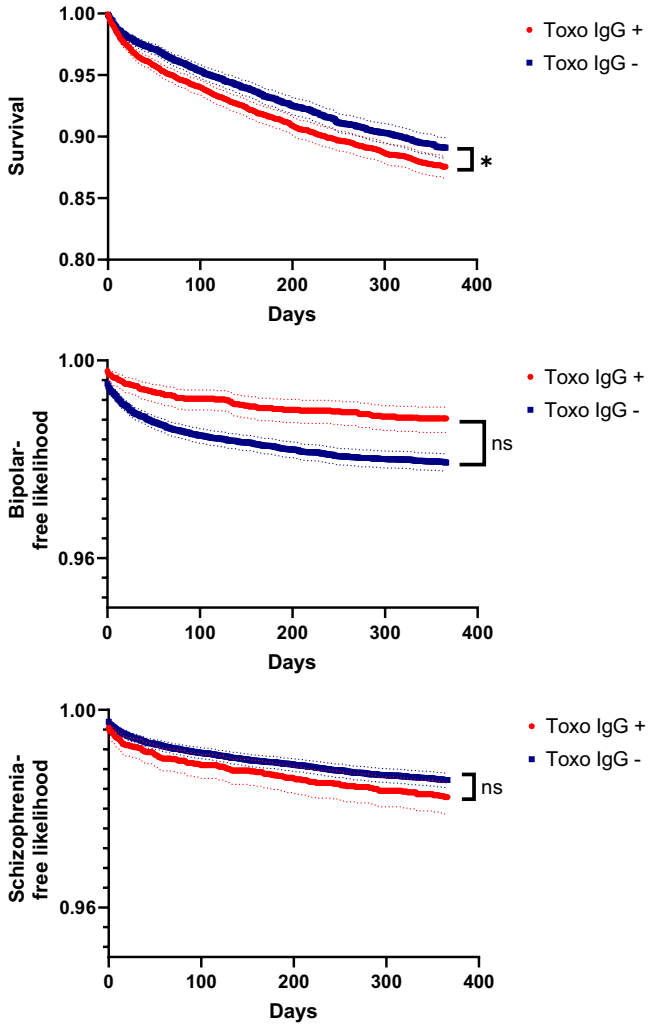

FIGURE 1. After propensity score matching, Kaplan-Meier survival and disease-free likelihood at 1 year were stratified by Toxoplasma IgG serology. Toxo = toxoplasmosis. *P value < 0.05; ns = nonsignificant.

Outcome after propensity score match analysis 5 years after serology testing. Seropositive patients had a higher mortality rate at 5 years than seronegative patients. Kaplan-Meier analysis revealed that seropositive patients were less likely to survive 5 years after diagnosis (HR: 1.1, 95% CI: 1.01–1.18, $P = 0.015$). Hospitalization and development of toxoplasmosis at 5 years were higher in seropositive patients, although only the development of toxoplasmosis was statistically significant (Figure 2). The risk of bipolar disorder was decreased among seropositive patients, and the risk of schizophrenia was increased among seropositive patients. There were no statistically significant differences in substance use disorder, suicide, type 2 diabetes mellitus, cardiomyopathy, chronic kidney disease, and heart disease between cases and controls. When the analysis was rerun after excluding deaths within the initial 6 months from diagnosis, patients with a positive toxoplasma serology remained at a higher risk of death at 5 years (OR: 1.1, 95% CI: 1.02–1.24, $P = 0.023$), although the time-to-event analysis was not significant (HR: 1.1, 95% CI: 0.97–1.17, $P = 0.146$).

Prevalence. Within approximately 90 million adult visits in the TriNetX platform, we found an annual positive toxoplasma IgG proportion of 0.004–0.006% and a prevalence of 0.02–0.03% during the last 3 years (2020–2022). Prevalence was greater among 35- to 39-year-olds (0.04%), males (0.03% versus 0.02% in women), Black patients (0.03%–0.04%), and Hispanic patients (0.03%). Among patients with a form of immunocompromise, the prevalence of positive toxoplasma IgG increased to 0.06%. Prevalence in pregnancy was 0.1%.

DISCUSSION

The results of this study suggest that patients with positive serology for *T. gondii* (IgG+) have an adjusted higher overall mortality risk than patients with negative serology (IgG−). In 1 year, there was an excess of 113 deaths among patients with positive serology for toxoplasma. Toxoplasma-exposed patients were 20% more likely to die within 1 year of diagnosis. For every 100 individuals exposed to toxoplasmosis, there were 1.8 more deaths in 1 year compared with unexposed individuals. Approximately 15.7% of the incidence of death among the exposed toxoplasmosis group can be directly attributed to the exposure in question.

Previous studies have suggested that latent *T. gondii* infection is associated with poor health outcomes. A recent cross-sectional epidemiologic study found that latent infections with *T. gondii* were associated with increased chronic inflammation and vascular injury biomarkers.[18] A meta-analysis found a significantly higher incidence of mental and physical health problems and increased severity of various diseases, including Alzheimer's disease, certain cancers such as brain cancer and lymphoma, and cardiovascular disease in seropositive toxoplasma patients.[19] Although research is available on mortality rates from toxoplasmosis, studies on the association between latent *T. gondii* and mortality are limited.[20] Latent *T. gondii* infection is a potential risk factor for suicide attempts and traffic accidents.[21] Another study found that *T. gondii* infections were directly or indirectly associated with higher mortality in patients with

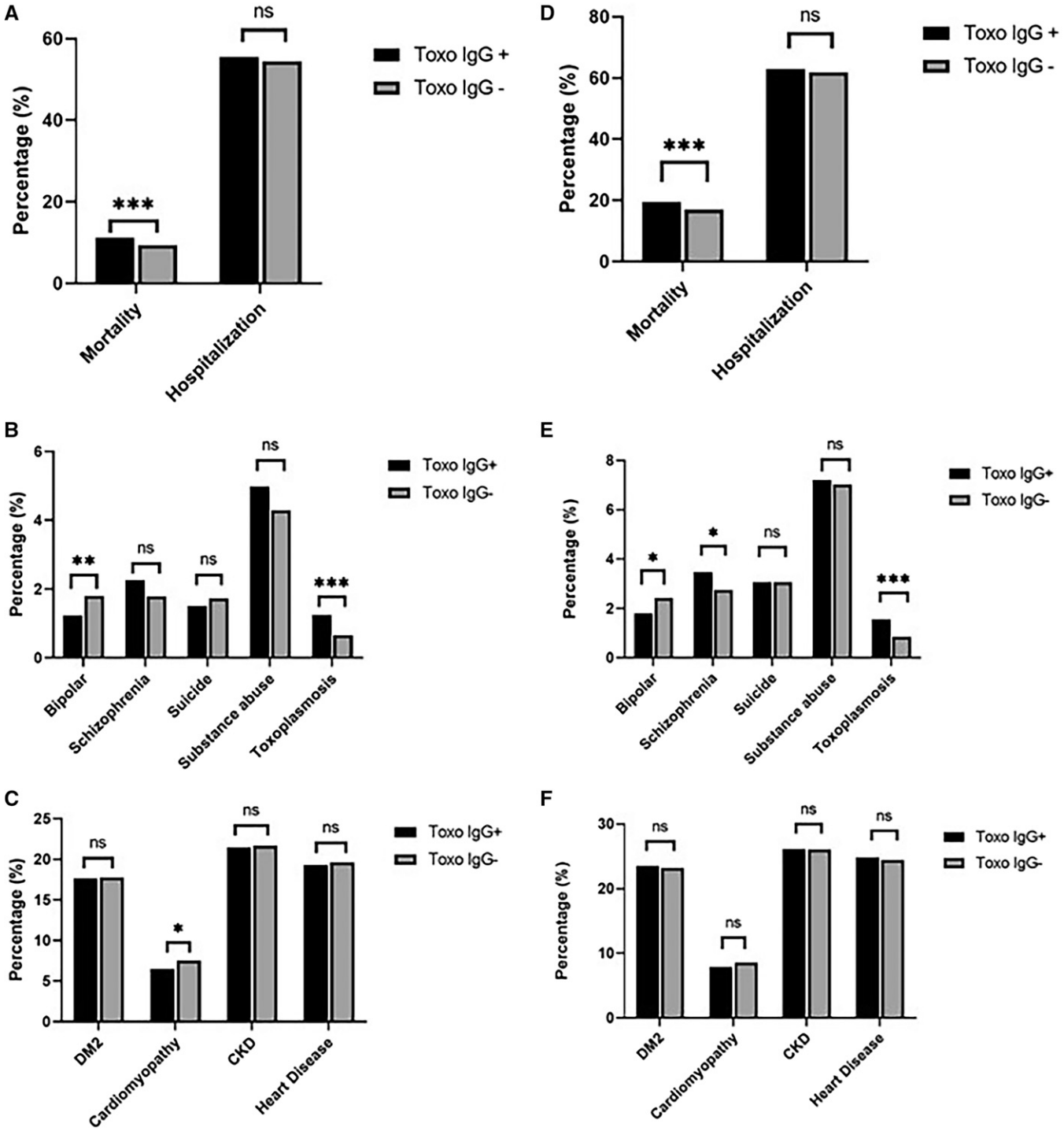

FIGURE 2. After propensity score matching, outcomes were compared between patients seropositive for *Toxoplasma gondii* IgG (black) and seronegative controls (gray). (**A–C**) Outcomes at 1 year. (**D–F**) Outcomes at 5 years. CKD = chronic kidney disease; DM2 = type 2 diabetes mellitus; Toxo = toxoplasmosis. *P value < 0.05; **P value < 0.001; ***P value < 0.0001; ns = nonsignificant.

COVID-19 and a history of schizophrenia.[22] Another study examined epidemiologic data from 88 countries and found an association between the seroprevalence of *T. gondii* and disease burden, particularly all-cause mortality and morbidity. However, data were limited to a countrywide level.[23]

One possible explanation for the increased mortality risk is alterations to the immune system by latent *T. gondii* infection. Basic science models have described the role of latent *T. gondii* in modulating the immune system by T cell exhaustion.[24] Perhaps this strain on the immune system is underestimated in immunocompetent individuals and leads to increased susceptibility to infection, contributing to the differences in mortality risk observed. Another explanation for the association of *T. gondii* seropositivity and mortality

risk is the role of chronic disease and chronic inflammation. Latent *T. gondii* has been repeatedly observed as a risk factor for chronic illnesses such as cancer and cardiovascular disease, leading causes of death worldwide. Toxoplasma IgG seropositivity may represent a surrogate marker of lifestyles, including eating habits or behaviors or lack of access to a healthy diet. For example, people with more liberal diets, including consumption of undercooked meats, shellfish, oysters, etc., may also have other factors that contribute to the increased risk of death, including excess alcohol intake or diets that increase cardiovascular risk. Zip code, educational level, and overall socioeconomic status are potent social health determinants,[25] which may correlate with toxoplasma seropositivity.

Another potential explanation for this association is the role of central nervous system modulation. Active toxoplasmosis has been long known to infect the central nervous system, causing toxoplasma encephalitis in immunocompromised populations. It can also reflect potential unaccounted, unbalanced conditions associated with increased mortality. In the last few decades, a well-described base of studies has emerged demonstrating that latent *T. gondii* is a risk factor for neurocognitive diseases such as schizophrenia, Alzheimer's disease, and brain cancers, which may also mediate the observed increase in mortality risk.[5,8,15,18,19,22,26] Because mortality was more pronounced during the initial time since diagnosis and the time-to-death analysis was not significant at 5 years, differences may have been driven possibly by decreased transplantation options for those with positive serology.

In addition to mortality risk, our study found no difference in schizophrenia 1 year after serology. However, there was an increased risk of schizophrenia among seropositive patients at 5 years after serology. The relationship between latent *T. gondii* infection and schizophrenia and other neuropsychiatric disorders such as bipolar disorder, epilepsy, and OCD has been the subject of many studies.[24,26–28] There is no current scientific consensus on this relationship. However, several studies have demonstrated that latent *T. gondii* is associated with an increased risk of schizophrenia. These results are mixed with a minority of studies that have not seen this association.[15,18,23] In a recent systematic review and meta-analysis, many observational studies revealed a modest to large association between toxoplasmosis and schizophrenia.[9] The authors concluded that further association studies are unlikely to change this association and are unjustified. They also concluded that it is time to test this association in randomized, double-blind, placebo-controlled clinical trials of Trimethoprim/sulfamethoxazole in toxoplasma-seropositive patients with schizophrenia. Proposed mechanisms mediating this response include immune or neurotransmitter dysregulation.[29,30] The discrepancy between the association was not observed in the present study at the 1-year follow-up but was shown to be significant at the 5-year follow-up, which may suggest that a mediating mechanism, such as immune or neurotransmitter dysregulation, requires a latency period before its effects can be clinically observed. An increased risk of schizophrenia may also be an alternative explanation for the found increased mortality rate, as schizophrenia is associated with a 2- to 3-fold increase in mortality compared with that of the general population.[31]

This study also found that the risk of cardiomyopathy was decreased among *T. gondii*–seropositive patients at 1 year after serology, with no significant difference at 5 years. Because this finding did not persist for 5 years, it likely does not represent a clinically significant finding. Interestingly, cardiovascular manifestations have been described in toxoplasmosis (active infection) but are rare overall. Epidemiologic data have suggested that latent toxoplasma accounted for significant variability in mortality attributed to cardiovascular diseases in European countries; thus, this finding may represent a true association.[23] In addition, Dragomir et al.[32] recently reported that *T. gondii* seroprevalence was significantly higher in Romanian patients with hypertension and unstable angina. Our found prevalence among pregnant women of 0.1% is 10-fold to 80-fold lower than that in Colombia, South America, of 1.3–8.0%,[33] reflecting exposure discrepancies due to different poverty levels and access to safe food and healthcare.

Limitations of this study include potential selection bias. Data were collected from TriNetX, a research network of data collected from electronic medical records. Thus, people who do not have access to healthcare were not included in the study, which may result in mortality rates being underestimated, as *T. gondii* is more prevalent in lower-income populations. In addition, because cases and controls were required to have undergone toxoplasma serology testing, the results may not be generalizable to people with no testing indications. We could not examine several economic and social health determinants, time since diagnosis (for covariates), or the treatment of comorbidities as potential confounding factors. There are limitations to using the propensity score matching methodology, including the inability to analyze the covariates to understand their impact on the outcomes. In addition, the potential low reliability of some covariate collection or measurements in the dataset could lead to unstable or invalid inferences.

Public health efforts surrounding *T. gondii* currently focus on congenital infection and infections in immunosuppressed individuals, such as people living with HIV or undergoing organ transplantation. Latent *T. gondii* infection in immunocompetent individuals has been traditionally considered asymptomatic and benign.[34,35] However, in conjunction with the current body of research, our study's findings suggest a possible shift in how public health and medicine should regard latent *T. gondii*, as its burden may be underestimated. *Toxoplasma gondii* is designated a neglected tropical disease by the CDC, meaning that it afflicts the world's poorest populations and has not received as much research or public health attention as other diseases. Thus, there are significant gaps in *T. gondii* research.[9] It is estimated that an astounding third of the human population worldwide is currently infected with latent *T. gondii*, including 10% of the U.S. population.[18] Further studies—including prospective cohorts—are needed to replicate the association with increased mortality in other patient populations. Additional research is needed to understand the mechanism and mediating factors between the association of latent *T. gondii* and mortality. Educational efforts should focus on ways to help patients reduce or prevent toxoplasmosis infection, as latent toxoplasmosis does not seem to be a benign condition. Although the frequency of positive serology is high, education about the disease is lacking in most patient communities.

CONCLUSION

The results of this study suggest that patients with positive serology for *T. gondii* (IgG+) have a higher overall mortality risk than seronegative controls. Social determinants of health and access to organ transplantation may have impacted the results. Additional unaccounted for confounders or chance might still explain the differences. Follow-up research is needed to understand the clinical significance of this association and possible mitigating factors with a third of the world's population infected.

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Note: Supplemental material appears at www.ajtmh.org.

Disclosure: Any data displayed on the TriNetX platform in aggregate form or any patient-level data provided in a dataset generated by the TriNetX platform contain only de-identified data per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. Geographic reporting at the regional level prevents potential re-identification through the localization of patients or HCOs. Research utilizing TriNetX does not require ethical approval because patient-identifiable information is not accessible to users. The current project is in HIPAA compliance, according to the Colorado Multiple Institutional Review Board (COMIRB#21-3754) at the University of Colorado Denver.

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