

## RESEARCH ARTICLE

# The impact of ABO and RhD blood types on *Babesia microti* infection

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## Abstract

### OPEN ACCESS

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## Background

Babesiosis is an emerging infectious disease caused by intraerythrocytic *Babesia* parasites that can cause severe disease and death. While blood type is known to affect the mortality of *Plasmodium falciparum* malaria patients, associations between red blood cell (RBC) antigens and *Babesia microti* infection and disease severity are lacking.

## Methods

We evaluated RhD and ABO blood types of *Babesia*-infected (18S rRNA reactive) blood donors in 10 endemic states in the Northeastern and northern Midwestern United States. We also assessed possible associations between RhD and ABO blood types and disease severity among hospitalized babesiosis patients in Connecticut.

## Results

A total of 768 *Babesia*-infected blood donors were analyzed, of which 750 (97.7%) had detectable *B. microti*-specific antibodies. *B. microti*-infected blood donors were more likely to be RhD- (OR of 1.22, p-value 0.024) than RhD+ donors. Hospitalized RhD- babesiosis patients were more likely than RhD+ patients to have high peak parasitemia (p-value 0.017), which is a marker for disease severity. No differences in RhD+ blood type were noted between residents of the Northeast (OR of 0.82, p-value 0.033) and the Midwest (OR of 0.74, p-value 0.23). Overall, ABO blood type was not associated with blood donor *B. microti* infection, however, *B. microti*-infected donors in Maine and New Jersey were more likely to be blood type B compared to non-type B (OR 2.49 [p = 0.008] and 2.07 [p = 0.009], respectively), while infected donors from Pennsylvania were less likely to be type B compared to non-type B (OR 0.32 [p = 0.02]).

and analysis, decision to publish, or preparation of the manuscript.

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## Conclusions

People expressing RhD antigen may have a decreased risk of *B. microti* infection and babesiosis severity. The association of B antigen with *B. microti* infection is less clear because the antigen appeared to be less prevalent in infected Pennsylvania blood donors but more prevalent in Maine and New Jersey infected donors. Future studies should quantify associations between *B. microti* genotypes, RBC antigens, and the frequency and severity of *B. microti* infection to increase our understanding of human *Babesia* pathogenesis and improve antibody, vaccine, and RBC exchange transfusion strategies.

## Author summary

We found an association between *Babesia microti* infection and both red blood cell RhD and B antigens. Numerous studies have quantified the impact of ABO blood type on *Plasmodium falciparum* (*Pf*) infection, an intraerythrocytic pathogen in the same Apicomplexa phylum as *Babesia*. For example, type O blood has been noted to protect against severe malaria, which may explain why type O is prevalent in *Pf*-endemic regions. Studies of ABO and RhD blood types and *B. microti* infection are lacking. The American Red Cross has a large blood donor dataset from *B. microti*-endemic states that can be used to study how ABO and RhD blood types are linked to *B. microti* infection, as measured by the presence of *B. microti* 18S rRNA. Data from 10 *B. microti*-endemic states showed that *B. microti*-infected blood donors were significantly less likely to be RhD+ (OR 0.82, p-value 0.024) than RhD- donors. A review of babesiosis patients admitted to Yale New Haven Hospital between 2011 and 2021 revealed that RhD+ patients were significantly less likely than RhD- patients to have a high (>5%) peak parasitemia (p = 0.017), which correlates with disease severity. Thus, the RhD antigen on the RBC membrane may decrease the risk of *B. microti* infection and disease severity. The blood type B antigen may affect the frequency of *B. microti* infection. The odds ratios (ORs) of *B. microti* infection in blood donors for blood type B compared to non-type B were 2.49 (p = 0.008) in Maine and 2.07 (p = 0.009) in New Jersey, but 0.32 (p = 0.02) in Pennsylvania. Future studies should quantify the impact of RhD, ABO, and other RBC antigens on *Babesia* infection, and the mechanisms by which they impact RBC invasion and babesiosis severity.

## Introduction

The United States (US) has the highest number of human babesiosis cases worldwide, and the marked increase in cases over the past two decades has led to its classification as an “emerging infectious disease” [1,2]. Babesiosis is caused by Apicomplexan parasites known as *Babesia*, which are unicellular intraerythrocytic organisms. Almost all cases in the US are caused by *Babesia microti* and primarily transmitted to humans by *Ixodes scapularis* ticks. However, *Babesia* can also be acquired via blood transfusion, perinatal transmission, and organ transplantation [3]. *B. microti* usually causes a mild to moderate infection but can also present as an asymptomatic infection or severe, life-threatening disease requiring hospital admission. Severe disease often occurs in people aged 50 or older and those who are immunocompromised, including patients with asplenia, malignancy, HIV/AIDS, or on immunosuppressive medication. The mortality rate in immunocompromised patients can exceed 20% [4].

Red blood cells (RBCs or erythrocytes) are essential for the growth and replication of *Babesia* and *Plasmodium* protozoan parasites [5]. These parasites bind to RBC surface antigens, invade, and express adherence antigens on the RBC surface [6]. This can cause severely impaired microvascular blood flow, leading to disease and sometimes death. RBC surface antigens may impact the risk of infection and disease severity. Duffy antigen negative reticulocytes resist *Plasmodium vivax* invasion [7]. Certain *P. falciparum* (*Pf*) strains require sialic acid for invasion [8,9], while basigin (CD147) may be essential for invasion of all *Pf* strains [10]. Both *Pf* and *B. divergens* use glycophorins A and B to invade RBCs [11], and *Pf* can also use glycophorin C (Gerbich blood group system) [12]. Blood group O patients have substantial protection against severe *Pf* malaria infection and death due to decreased RBC rosetting (binding of uninfected RBCs to a central parasitized RBC) and vascular endothelial cell adherence (cytadherence) [13]. This likely explains the high prevalence of blood group O in *Pf* malaria “hot zones.” [14] Little is known about how RBC antigens impact *B. microti* invasion and babesiosis complications.

In this study, we sought to determine if RhD and ABO RBC antigens are associated with *B. microti* infection, as determined by *B. microti* 18S rRNA, or babesiosis disease severity. We calculated the odds ratios (ORs) linking blood type and *B. microti* 18S rRNA test reactivity for blood donors in 10 Midwestern and Northeastern *B. microti*-endemic states where blood donations are routinely screened for the parasite. We also determined whether RhD and ABO blood types are associated with peak parasitemia and clinical outcomes among babesiosis patients hospitalized for severe disease.

## Methods

### *Babesia*-infected blood donors

American Red Cross (ARC) blood donations were collected between May 2020 and December 2021 in 10 states (Maine, New Hampshire, Vermont, Massachusetts, Connecticut, New York, New Jersey, Pennsylvania, Wisconsin, and Minnesota). ABO and RhD blood type was determined by routine testing performed by the ARC using the PK7400 Automated Microplate System from Beckman Coulter. Testing donated blood for the presence of *Babesia* parasite and *Babesia* antibodies has been previously described [15]. In brief, testing was performed at Creative Testing Solutions (CTS) as a routine operational blood screening. *Babesia* nucleic acid testing (NAT) was performed using the Procleix *Babesia* assay (Grifols Diagnostic Solutions, San Diego, CA) from whole blood lysates. This FDA-licensed assay detects 18S rRNA from *B. microti*, *B. divergens*, *B. duncani*, and *B. venatorum* using transcription-mediated amplification (TMA). Samples were tested in pools of 16. If the pool result was reactive, each of the lysates were tested individually to identify the reactive donation. The assay was repeated on a newly prepared lysate to confirm the initial result. Donations that tested reactive in both individual tests were considered repeat reactive (RR); donations that were not repeatedly reactive on the secondary lysate were considered initial reactive (IR). Both IR and RR were considered reactive, and the donors were deferred for two years. *B. microti*-specific immunofluorescence using a research assay was performed on all reactive donations.

### Hospitalized babesiosis patients

We analyzed a database of babesiosis patients 18 years and older who were admitted to Yale New Haven Hospital in New Haven, CT, between 2011 and 2021, as previously described [16]. The diagnosis of babesiosis was confirmed by microscopic detection of *Babesia* on blood smears and/or amplification of *B. microti* DNA by polymerase chain reaction (PCR) testing.

## Statistical analyses

For blood-donor analyses, contingency tables with chi-square testing were made using GraphPad Prism software, version 9.3.1. For hospitalized patients, contingency tables were made and analyzed in SAS Studio 3.8 using Chi-squared; Fisher's exact testing was used when the sample count in a given category was  $<5$ . P-values less than 0.05 were considered statistically significant.

## Results

### Babesia-reactive blood donors

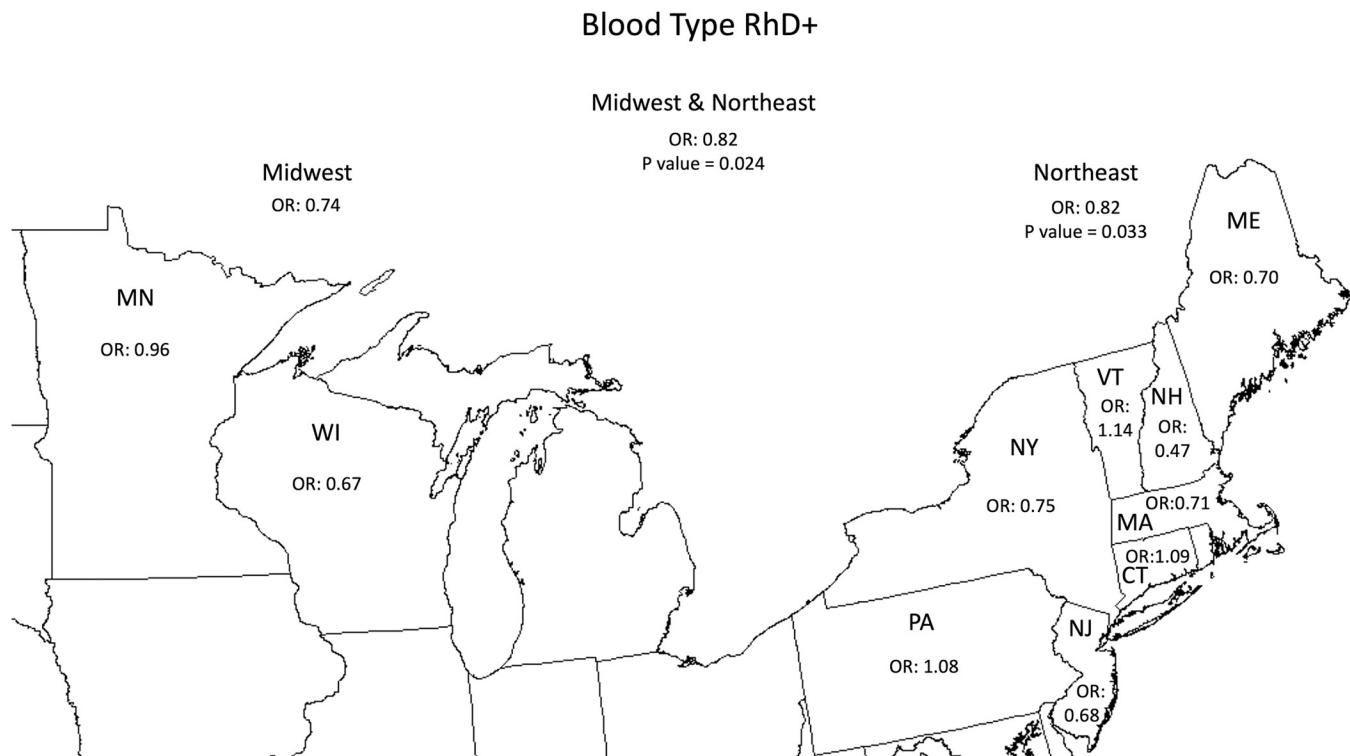
A total of 861,712 *Babesia*-tested blood donations from unique donors were included in this study (Table 1). Of these, 768 individuals (0.089%) were *Babesia* NAT reactive, with 750 (97.7%) positive by a *B. microti*-specific antibody assay. ARC data from 10 states were analyzed: Maine (ME), New Hampshire (NH), Vermont (VT), Massachusetts (MA), Connecticut (CT), New York (NY), New Jersey (NJ), and Pennsylvania (PA) in the Northeast region, and Wisconsin (WI) and Minnesota (MN) in the Midwest region. *B. microti* is the only *Babesia* species that has been identified in these states, although different genotypic strains exist [5,17,18].

Data from all 10 states showed that *Babesia* NAT reactive blood donors were less likely to be RhD+ (OR 0.82, p-value 0.024) than RhD- donors. The Northeast region had an OR of 0.82 (p-value 0.033), while the Midwest had an OR of 0.74 (p-value 0.23). In both regions, the OR for *Babesia* NAT reactivity was decreased in RhD+ donors. No statistically significant association for RhD+ blood type was found for any individual state (Fig 1).

**Table 1. Comparing the ABO and RhD blood types of *Babesia*-NAT reactive and non-reactive blood donors.** CI = confidence interval.

Blood type	A	B	AB	O	RhD+
<b>Northeast</b>					
Non-reactive	212,884	68,111	24,670	307,823	496,269
Reactive	235	92	23	336	533
Chi-square	0.06	3.70	0.79	0.39	4.53
p-value	0.81	0.054	0.37	0.531	<b>0.033</b>
OR	0.98	1.24	0.83	0.95	0.82
95% CI	0.84–1.15	1.00–1.55	0.55–1.26	0.82–1.11	0.69–0.99
<b>Midwest</b>					
Non-reactive	93,128	26,570	10,866	116,892	197,393
Reactive	30	9	3	40	61
Chi-square	0.04	0.005	0.10	0.08	1.47
p-value	0.84	0.94	0.75	0.78	0.23
OR	0.96	1.03	0.83	1.06	0.74
95% CI	0.61–1.50	0.51–2.05	0.26–2.62	0.69–1.64	0.45–1.21
<b>All 10 States</b>					
Non-reactive	306,012	94,681	35,536	424,715	693,662
Reactive	265	101	26	376	594
Chi-square	0.36	3.64	1.07	0.04	5.10
p-value	0.55	0.057	0.30	0.84	<b>0.024</b>
OR	0.96	1.23	0.81	0.99	0.82
95% CI	0.82–1.11	0.99–1.51	0.55–1.20	0.86–1.14	0.70–0.97

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**Fig 1. The association of *Babesia*-reactive blood donors with blood type RhD+ compared to RhD-.** The associations were statistically significant ( $p<0.05$ ) in the Northeast and the combined Northeast and Midwest using a chi-square test. This map was cropped from a public domain version created by Brian Szymanski found at Wikimedia Commons website <https://commons.wikimedia.org/wiki/File:Usa-state-boundaries-lower48%2B2.png>.

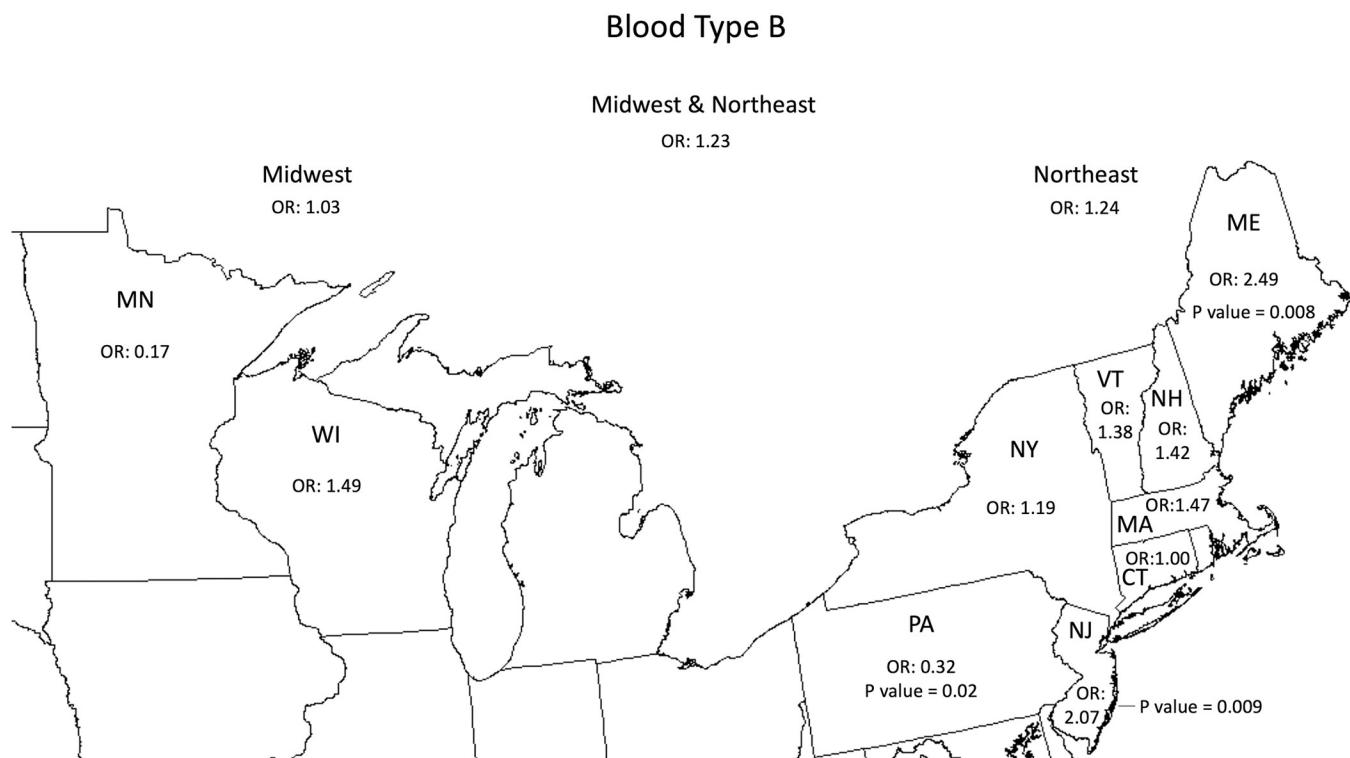
<https://doi.org/10.1371/journal.pntd.0011060.g001>

The analysis of state-specific data revealed limited associations between ABO antigens and *Babesia* infection. The OR for *Babesia* infection was significantly lower for B blood type donors than for non-B blood donors in Pennsylvania (0.32 [p = 0.02]), whereas the ORs for *Babesia* infection were higher for B blood type donors in Maine and New Jersey (2.49 [p = 0.008] and 2.07 [p = 0.009]), respectively (Fig 2). No other statistically significant results were found at the individual state level (S1–S3 Figs).

## Hospitalized inpatients with babesiosis

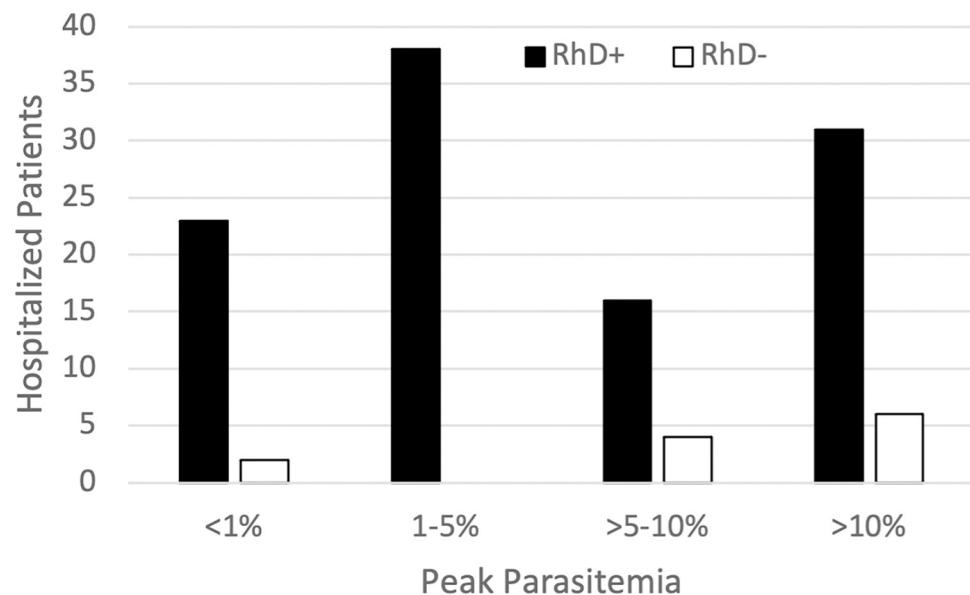
Blood types and *Babesiosis* disease severity were assessed in babesiosis patients admitted to Yale New Haven Hospital between 2011 and 2021. Possible associations between RhD or ABO blood types and peak parasitemia, the length of hospital stay, and intensive care unit (ICU) admission were evaluated. Peak parasitemia was defined as the highest percentage of RBCs containing *Babesia* parasites identified on peripheral blood smears during hospitalization. A total of 120 patients were evaluated with the following frequency of blood types: A (n = 47), B (n = 11), AB (n = 6) and O (n = 56). The majority of patients were RhD+ (n = 108, 90.0%) and the rest were RhD- (12, 10.0%).

RhD+ patients were less likely (p-value 0.017) to have high parasitemia levels of >5% (Fig 3). There were no significant associations between RhD or ABO blood types and length of hospital stay or intensive care unit admission. A review of 139 hospitalized babesiosis patients in the state of New York found six clinical and laboratory factors that were significantly associated with disease severity. The one with the strongest association was parasitemia levels of 4% or more with a relative risk of 2.48 (p<0.001) [19].



**Fig 2. The association of *Babesia*-reactive blood donors with blood type B compared to non-type B.** The associations were statistically significant ( $p < 0.05$ ) for PA, NJ, and ME using a chi-square test. This map was cropped from a public domain version created by Brian Szymanski found at Wikimedia Commons website <https://commons.wikimedia.org/wiki/File:Usa-state-boundaries-lower48%2B2.png>.

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**Fig 3. Peak parasitemia percentages in babesiosis patients at Yale New Haven Hospital by RhD blood type.** The p-value for Fisher's exact test was 0.017, indicating a significant association between peak parasitemia and RhD- blood type.

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## Discussion

We found that blood donors who have the RhD RBC antigen (RhD+) are less likely to be *Babesia*-infected than donors without the antigen (RhD-). The odds ratio for RhD+ blood donors in the Midwest and Northeast were both less than 1.0, despite differences in *B. microti* genotypes in these two regions [20]. Among hospitalized babesiosis patients from Connecticut, those with the RhD+ RBC antigen had lower peak parasitemia ( $p = 0.017$ ), compared to those who were RhD-. Peak parasitemia has been shown to be strongly associated with disease severity [16]. Thus, data from both our blood donor and hospitalized babesiosis patient populations suggest that the RhD antigen may play a role in inhibiting *B. microti* entrance and/or proliferation within RBCs. We found that ABO blood type generally does not correlate with *Babesia* infection or disease, although type B blood donors from Maine and New Jersey were more likely to be *Babesia*-infected while those from Pennsylvania were less likely to be *Babesia*-infected.

The mechanism(s) of RBC antigen enhancement or inhibition of *Babesia* infection and/or disease is unknown. Studies comparing RhD+ and RhD- individuals with *Plasmodium* infection in Africa have yielded inconsistent findings with some studies showing RhD+ individuals more likely to be *Plasmodium* infected and other studies showing RhD+ individuals less likely to be *Plasmodium* infected [21–25]. Differences in results may be due to differences in *Plasmodium* species or genotypes—which were not always accounted for. In one study, *Pf*-parasites and RBCs of four different blood groups were co-cultured. Parasite invasion was less for type B RBCs than for type A and type O RBCs. This appeared to be due, at least in part, to the amount of surface H antigen in each blood group [26]. Different *Babesia* strains have different surface antigens that may bind more or less strongly to B antigens on RBCs. It has been shown that inland and coastal *Babesia* genotypes in Massachusetts differ [20]. Differences in *Babesia* surface antigens may explain why type B blood donors in Maine and New Jersey (coastal states) were more likely to be *Babesia*-infected and those from Pennsylvania (an inland state) were less likely to be infected. Thus, the RBC B antigen may promote invasion for some *B. microti* genotypes while resisting invasion for other genotypes.

Establishing a connection between blood type and an infectious disease can be problematic, as illustrated by the often-discrepant findings of research on ABO blood group and SARS-CoV-2 infection and COVID-19 severity. Differing findings may be due, at least in part, to viral genetic variants, which were not always identified in these studies [27–31]. There are several suggested mechanisms of protection in those studies that identified patients with blood type O as having fewer SARS-CoV-2 infections and milder COVID-19 severity. Anti-A and/or anti-B antibodies that are found in patients with type O blood, are thought to neutralize A and/or B antigens on the SARS-CoV-2 viral envelope or S protein [27,32]. Other possible mechanisms of protection involve RBC blood group only indirectly. ABO(H) glycans on the viral S protein or lung epithelial cells may impact viral infection [32], while ABO(H) antigens on von Willebrand factor (vWF) and coagulation factor VIII (FVIII) are known to impact thromboembolic risk, which may impact COVID-19 disease severity [32,33].

Our study has several limitations. The ARC and Yale New Haven Hospital data do not include information about the *Babesia* species or genotypes. The *Babesia* assay used to test blood donors does not distinguish between *B. microti*, *B. divergens*, *B. duncani*, and *B. venatorum*, however, *B. microti* is the only *Babesia* species found at our study sites. In addition, 97.7% of *Babesia*-reactive blood donors had *B. microti*-specific antibodies. The only *Babesia* species that is endemic in Connecticut is *B. microti*. The blood-donor analysis did not include percent parasitemia, and blood donors are not exactly representative of the general population. For example, blood donors in the US tend to be healthier than the general population [34],

and minorities are underrepresented in the blood-donor pool [35]. Statistically significant associations with the B antigen and *B. microti* infection were only found in three states and Pennsylvania had an opposite OR compared to New Jersey and Maine. It is possible that the B antigen does not impact RBC invasion and that *B. microti* genotypes do not differ in inland Pennsylvania and coastal New Jersey and Maine. Only 12 of the hospitalized babesiosis patients were RhD- blood type. Finally, more comprehensive RBC genotype and phenotype data could have great value because antigens other than ABO(H) and RhD may be important for parasite invasion and disease severity.

Identifying the mechanisms of RBC blood type risk factors for the development of *Babesia* infection and severe babesiosis may help improve the treatment and prevention of babesiosis. Current antibiotic therapy is effective in most cases but inducible antibiotic resistance can develop in *B. microti* during prolonged duration with standard antibiotic regimens in immunocompromised hosts [36–39]. A better understanding of the mechanism of *Babesia* entrance into RBCs might help in the development of antibiotics that impair parasite invasion. RBC exchange transfusion is an adjunct therapy used in severe cases of babesiosis [36,40]. Use of *Babesia*-resistant RBCs might improve the efficacy of exchange transfusion. For example, M- and/or S-antigen negative RBCs show resistance to *B. divergens* invasion *in vitro* and have been recently proposed for use in RBC exchange transfusion for the treatment of this type of babesiosis [41]. *B. divergens* mortality can exceed 40% in immunocompromised patients and rebound parasitemia can occur after RBC exchange transfusion. Similarly, because type O RBCs offer protection against severe *Pf* malaria, due to decreased rosetting and cytoadherence, they have been proposed for use in RBC exchange transfusion [42].

Additional studies that clarify possible associations between blood types and *Babesia* acquisition and babesiosis mortality are needed. For example, narrowly focused genotyping of the *Babesia* strains isolated from the *Babesia*-reactive type-B blood donors in Pennsylvania, New Jersey, and Maine might be an efficient way to identify different *Babesia* antigens and genotypes, revealing pathogen diversity that might promote development of effective monoclonal antibody combinations and/or a human *Babesia* vaccine.

## Supporting information

**S1 Fig. The association of *Babesia*-reactive blood donors with blood type A compared to non-type A.** The association was not statistically significant using a chi-square test. This map was cropped from a public domain version created by Brian Szymanski found at Wikimedia Commons website <https://commons.wikimedia.org/wiki/File:Usa-state-boundaries-lower48%2B2.png>.  
(TIFF)

**S2 Fig. The association of *Babesia*-reactive blood donors with blood type AB compared to non-type AB.** The association was not statistically significant using a chi-square test. This map was cropped from a public domain version created by Brian Szymanski found at Wikimedia Commons website <https://commons.wikimedia.org/wiki/File:Usa-state-boundaries-lower48%2B2.png>.  
(TIFF)

**S3 Fig. The association of *Babesia*-reactive blood donors with blood type O compared to non-type O.** The association was not statistically significant using a chi-square test. This map was cropped from a public domain version created by Brian Szymanski found at Wikimedia Commons website <https://commons.wikimedia.org/wiki/File:Usa-state-boundaries-lower48%2B2.png>.  
(TIFF)

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**Writing – review & editing:** Ryan Philip Jajosky, Jane O'Bryan, Anne Spichler-Moffarah, Philip G. Jajosky, Peter J. Krause, Laura Tonnelli.

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