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Overall prevalence of human parvovirus B19 among blood donors in mainland China

A PRISMA-compliant meta-analysis

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Abstract

Background: Human parvovirus B19 (B19V) infection exhibits a broad range of clinical outcomes. Blood transfusion is a common route of B19V transmission. However, information about the overall prevalence of B19V infection and B19V genotypes among blood donors in mainland China is lacking.

Methods: This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search for studies reporting the B19V prevalence among blood donors in mainland China from 2000 to 2018 was performed. The prevalence of B19V was estimated through a meta-analysis of the relevant literature. A comprehensive meta-analysis program was used for data processing and statistical analysis.

Results: Twenty-one eligible articles were included, involving 48,923 participants assessed for B19V-DNA, 12,948 participants assessed for anti-B19V immunoglobulin M (IgM), and 8244 participants assessed for anti-B19V immunoglobulin G (IgG). The analysis revealed the pooled estimates of the prevalence rates of B19V-DNA, anti-B19V IgM, and anti-B19V IgG among blood donors to be 0.7% (95% confidence interval [CI] 0.2–2.4%), 2.7% (95% CI 1.7–4.3%), and 33.6% (95% CI 28.2–39.4%), respectively. Moreover, phylogenetic analyses indicated that 142 of 169 (84.0%) B19V isolates belonged to Genotype 1.

Conclusions: The overall prevalence of B19V among blood donors is not high in mainland China, and most isolates belong to Genotype 1.

Abbreviations: B19V = human parvovirus B19, CI = confidence interval, CNKI = China National Knowledge Infrastructure, ELISA = enzyme-linked immunosorbent assay, FDA = Food and Drug Administration, IgG = immunoglobulin G, IgM = immunoglobulin M, NAT = nucleic acid test, PRCA = pure red cell aplasia, RA = rheumatoid arthritis, SLE = systemiclupus erythematosus, TAC = transient aplastic crisis, TTI = transfusion-transmitted infection.

Keywords: blood donors, genotypes, human parvovirus B19, mainland China, meta-analysis, prevalence

1. Introduction

In 1975, Australia virologist Cossart observed human parvovirus B19 (B19V) particles under an electron microscope when screening serum samples from patients with hepatitis B.[1] Because the parvovirus virus-like particle was found in a sample marked as No. 19, Cossart named it the human parvovirus B19.[1] As the smallest and structurally most simple human virus, it is a small, non-enveloped DNA virus with a single-stranded linear DNA genome and measures only 20 to 25 nm in diameter.[2–6] B19V belongs to the genus Erythroparvovirus in

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the family Parvoviridae, and infection with B19V may have a broad range of clinical outcomes, including transient aplastic crisis (TAC), rash-fever illnesses, rheumatoid arthritis (RA), systemiclupus erythematosus (SLE), pure red cell aplasia (PRCA), hydrops fetalis, and fetal death, especially for patients with abnormal hematology or immunestatus.[7–16] B19V is transmitted mainly through the respiratory route, blood transfusions, organ/bone marrow transplantations, and mother-to-child transmission.[3,7,15,17–19] Recently, commonly used detection methods of B19V infection have included enzyme-linked immunosorbent assays (ELISA) for anti-B19V immunoglobulin G (IgG) and anti-B19V immunoglobulin M (IgM) antibodies and nucleic acid tests (NAT) for B19V-DNA.[20,21] In some countries, regulations or guidelines for screening and monitoring B19V have been proposed to ensure the safety of blood products as much as possible. Thus, information about the overall prevalence of B19V infection and B19V genotypes among blood donors in mainland China is lacking. To provide a reference for evaluating and developing appropriate strategies, we conducted a meta-analysis based on available data from mainland China between 2000 and 2018.

2. Methods

This work was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1, http://links.lww.com/MD/E74).[22] In addition, these analyses were based on previously published studies; therefore, no ethical approval was necessary for this study.

2.1. Literature search

Search strings were established by combining the following terms using Boolean operators: "parvovirus B19, human," "blood donors," and "China." We searched for relevant studies published from 2000 to 2018 in the China National Knowledge Infrastructure (CNKI), PubMed, and Wanfang databases. To include as many relevant studies as possible, a search of the reference lists of published articles was also manually conducted.

2.2. Data selection and extraction

Two investigators independently and carefully screened the studies and extracted the relevant data in accordance with the inclusion and exclusion criteria. Any disagreement was resolved by discussion. The inclusion criteria were as follows: the literature selected must be related to the epidemiological investigation or genotype research of B19V and the subjects of the selected studies were blood donors in mainland China. The exclusion criteria were articles published in non-academic journals; dissertations, review papers, conference abstracts, or presentations; irrelevant research; and studies from regions of China outside the mainland (i.e., Hong Kong, Macao, and Taiwan).

2.3. Study quality evaluation

Researchers used a cross-sectional/prevalence study quality assessment tool recommended by the Agency for Healthcare Research and Quality (AHRQ) to determine the quality of the included studies.[23] This tool has been widely used to evaluate the quality of cross-sectional/prevalence studies.[24,25] The checklist consisted of 11 items. If the answer was "Yes," the score of an item was recorded as"1"; otherwise, the score was recorded as "0." The total score range was 0 to 11 for each study. The included studies were categorized as low, medium, or high quality according to a total score of 0 to 3, 4 to 7, or 8 to 11, respectively.

2.4. Statistical analysis

Comprehensive Meta-Analysis version 2.0 (CMA 2.0; Biostat Inc., Englewood, NJ) was used for data manipulation and statistical analyses. Conversion of the prevalence to the logit prevalence was performed as follows: logit $p = \ln(p/[1-p])$, where p is the prevalence and ln is the natural logarithm; the data distribution was normalized. The sampling variance of each logit prevalence, $V_{(\text{logit } p)}$, was equal to $1/(np) + 1/(n[1-p])$, with n representing the sample size. To facilitate the final interpretation, the logit p was back-transformed into the prevalence rate after the statistical analyses were conducted.[26] The prevalence estimates and their 95% confidence intervals (CIs) were determined based on fixed or random effects models, taking into consideration the heterogeneity among studies, which was calculated with the Q test ($P < .10$ represents statistically significant heterogeneity) and I^2 test (values of 75%, 50%, and 25% were considered high, medium, and low levels of heterogeneity, respectively). Potential publication bias was examined using a funnel plot (logit prevalence vs standard error), Begg's test and Egger's test ($P < .05$ was considered indicative of statistically significant publication bias). The trim and fill method was also used to adjust the data for publication bias. Stratified analyses were performed by study locations, sex, and sample size of the included studies. Furthermore, the B19V genotypes of infected blood donors on the Chinese mainland were evaluated.

3. Results

3.1. Process of study selection

In total, 544 articles were initially retrieved from the PubMed (9), CNKI (469), and Wanfang (66) databases using the literature search strategy mentioned above. Based on the inclusion and exclusion criteria, 455 articles were excluded after abstract review, and another 5 articles were excluded after the full text was read. Twenty-one articles on B19V infection, including 11 articles examining B19V-DNA, 10 articles examining anti-B19V IgM, 12 articles examining anti-B19V IgG,[27–47] and 4 articles examining B19V genotypes, were eventually included in the present study.[45,48–50] The study selection process is shown in Fig. 1.

3.2. Characteristics of the included studies

All 21 included studies of blood donors with B19V infection were cross-sectional; data from 11 provinces, 2 autonomous regions, and 1 municipality were included in these studies. The present analysis included 48,923 participants with NAT results, 12,948 with anti-B19V IgM results, and 8244 with anti-B19V IgG results. Most blood samples were from blood centers. The sample sizes for the NATs ranged from 110 to 10,452 (median 3957, interquartile range 450–8288), and the sample sizes of the selected studies using ELISAs ranged from 96 to 4500 (median 872, interquartile range 370–1098). In addition, 14 studies were categorized as moderate quality, and 7 were categorized as high quality, according to the

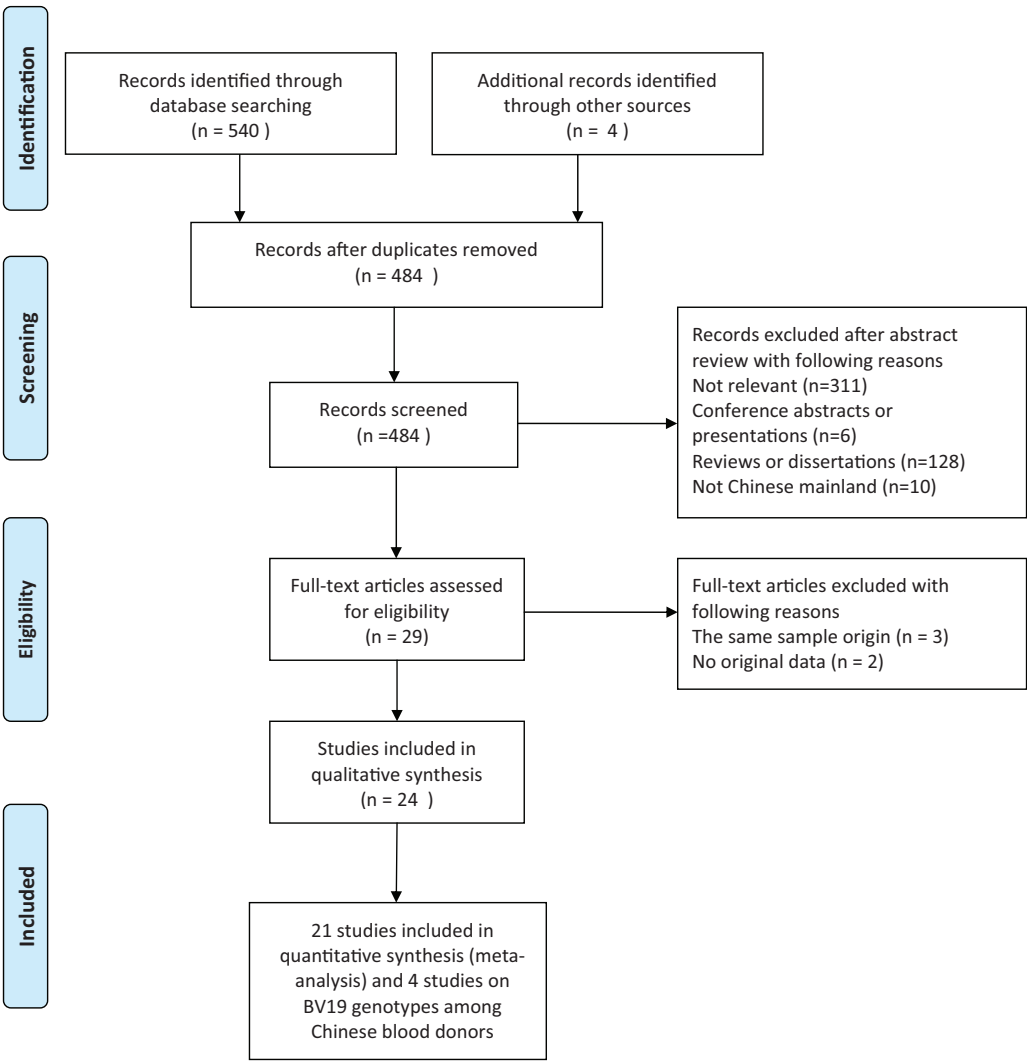

Figure 1. PRISMA flow diagram of the literature search process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

checklist of Cross-sectional/Prevalence Study Quality (Supplementary Table 2, http://links.lww.com/MD/E75). The overall quality of the included studies was moderate to high. Please see Table 1 for the relevant details of each study.

3.3. Prevalence of B19V infection among blood donors in mainland China

The overall prevalence of B19V-DNA was evaluated from the analysis of 11 studies.[28,29,31,32,34,36,38,40,43–45] Substantial heterogeneity was found among these studies ($I^2 = 98.2\%$, $P < .001$). Therefore, the pooled prevalence of B19V-DNA was estimated with a random effects model. The estimated prevalence of B19V-DNA was 0.7% (95% CI 0.2–2.4%), and the forest plot for the pooled estimate is illustrated in Fig. 2. Some degree of asymmetry was observed in the funnel plot (Supplementary Figure 1, http://links.lww.com/MD/E71), and publication bias among the included studies was detected using Begg's test and Egger's test ($P_{\text{Begg's test}} = .10$, and $P_{\text{Egger's test}} = .03$). Thus, the trim and fill method was applied to adjust data for publication bias. The adjusted pooled prevalence of B19V-DNA was also 0.7% (95% CI 0.2–2.4%).

Similarly, the estimated prevalence rates of anti-B19V IgM and IgG were also calculated among the included studies.[27,30,33–35,37–39,41,42,44–47] As shown in Figs. 3 and 4 and Table 2, the estimates were 2.7% (95% CI 1.7–4.3%) and 33.6% (95% CI 28.2–39.4%), respectively. The funnel plots are also shown in Supplementary Figure 2, http://links.lww.com/MD/E72 and 3, http://links.lww.com/MD/E73.

3.4. Stratified analysis of B19V-DNA screening data

Generally, mainland China can be divided into a south and north region according to geography. The study included 9 epidemiological studies of B19V-DNA in south China and 4 in north China.[28,29,31,32,34,38,40,43–45] In south China, the pooled prevalence of B19V-DNA was 0.4% (95% CI 0.1–1.6%), and the estimated prevalence of B19V-DNA was 2.5% (95% CI 0.4–15.7%) in north China. No significant statistical difference was found between the south and north regions of China ($x^2 = 2.26$, $P = .13$).

Four studies investigated the association between sex and the prevalence of B19V-DNA among blood donors.[31,34,38,40] The prevalence of B19V-DNA among male donors was 1.0% (95%

Table 1

Summary of data from the included articles on B19V prevalence among blood donors in mainland China.

First author and year of publication	Language	Study location	Sample collection year(s)	Target population	Sample size for NAT	NAT (+)	Sample size for ELISA	ELISA for B19V IgM antibody(+)/ IgG antibody(+)	Quality assessment score
Ou SH, 2016	Chinese	Fujian	2013	Blood donors	10,452	6	1078	50/181	8
Yan JX, 2016	Chinese	Guangdong	NA	Blood donors	NA	NA	368	2/92	8
Zhang LH, 2016	English	Zhejiang	2014–2015	Blood donors	NA	NA	96	2/21	9
Wang ZX, 2015	Chinese	Shandong	2013–2014	Blood donors	NA	NA	960	57/347	7
Zheng RB, 2015	Chinese	Guangdong	2013–2014	Blood donors	6000	16	NA	NA/NA	7
Zeng FX, 2015	Chinese	Sichuan	2011–2013	Blood donors	10,150	3	810	NA/367	8
Qin WW, 2015	Chinese	Chongqing	2012–2013	Blood donors	NA	NA	1104	56/405	7
Bao HE, 2015	Chinese	Hubei	2013	Blood donors	NA	NA	934	23/405	7
Han T, 2015	English	Sichuan	2012	Blood donors	10,070	3	NA	NA/NA	9
Liu YB, 2014	Chinese	Guangdong	NA	Blood donors	147	10	376	NA/110	6
Ling HS, 2014	Chinese	Guangdong	NA	Blood donors	NA	NA	1700	27/NA	6
Hou JF, 2012	Chinese	NA	NA	Blood donors	6505	6	NA	NA/NA	8
Liang LL, 2012	Chinese	Liaoning	NA	Blood donors	NA	NA	4500	47/NA	6
Ling K, 2011	English	Henan, Guangxi, Xinjiang, Yunnan	2008–2009	Blood donors	3957	23	448	31/110	9
Li BD, 2009	Chinese	Shandong	2009	Blood donors	632	42	NA	NA/NA	6
Zheng YR, 2009	Chinese	Guangdong	2004–2005	Blood donors	NA	NA	1760	33/679	7
Zhang NH, 2009	Chinese	Shandong	2006–2007	Blood donors	300	19	NA	NA/NA	6
Wei Q, 2006	Chinese	Jilin	2015	Blood donors	NA	NA	184	NA/102	6
Yang ZX, 2003	Chinese	Hubei	2000	Blood donors	110	23	NA	NA/NA	5
Wang R, 2002	Chinese	Jiangsu	2001	Blood donors	600	16	NA	NA/NA	5
Li SQ, 2000	Chinese	Fujian	2000	Blood donors	NA	NA	126	NA/48	4

B19V = human parvovirus B19, ELISA = enzyme-linked immunosorbent assay, NA = not available, NAT = nucleic acid test.

CI 0.1–6.6%), while that among female donors was 1.1% (95% CI 0.2–7.1%). No significant difference was observed in the prevalence of B19V-DNA between male and female donors ($x^2 = 0.005$, $P = .94$).

Six studies had large sample sizes (>1000), and the estimate of B19V-DNA prevalence was 0.1% (95% CI 0–0.2%).[34,36,40,43–45] The other 5 studies had sample sizes of <1000, and the pooled estimate of B19V-DNA prevalence was 7.1% (95% CI 3.2–14.9%).[28,29,31,32,38] A statistically significant difference was observed between the 2 groups ($x^2 = 52.3$, $P < .001$).

3.5. B19V-DNA genotypes among blood donors

Four included studies conducted phylogenetic analyses of NS1/VP1-unique regions to analyze the genotype of 169 B19V-DNA sequences from positive samples.[45,48–50] These phylogenetic

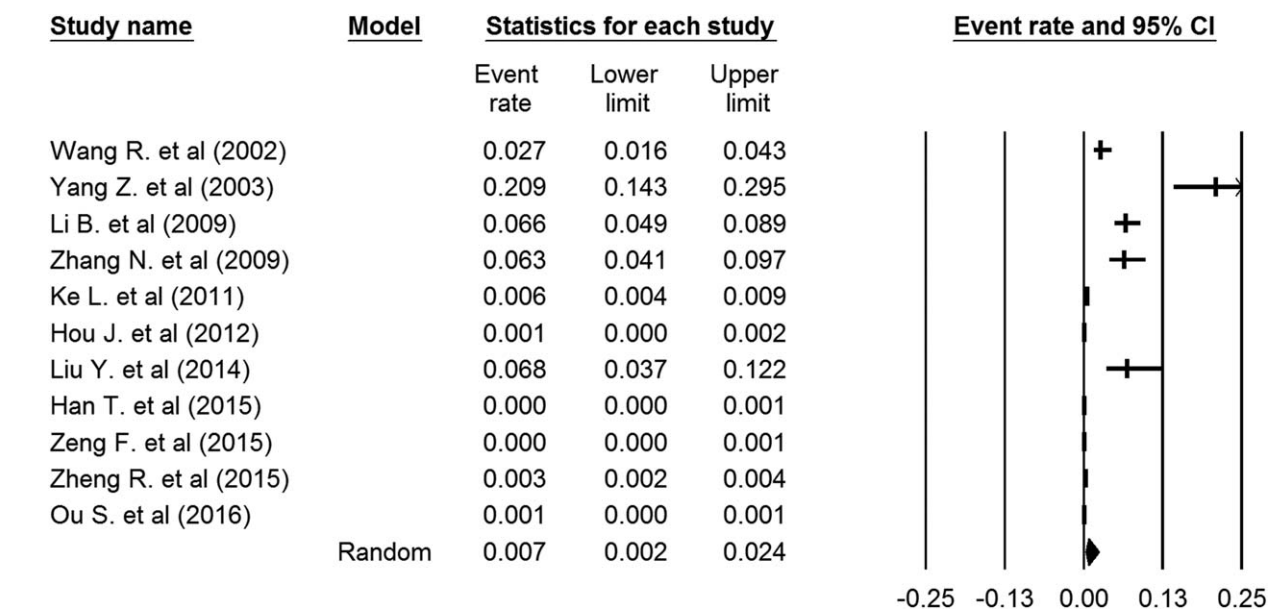

Figure 2. Forest plot of the meta-analysis of B19V-DNA prevalence among blood donors. B19V = Human parvovirus B19.

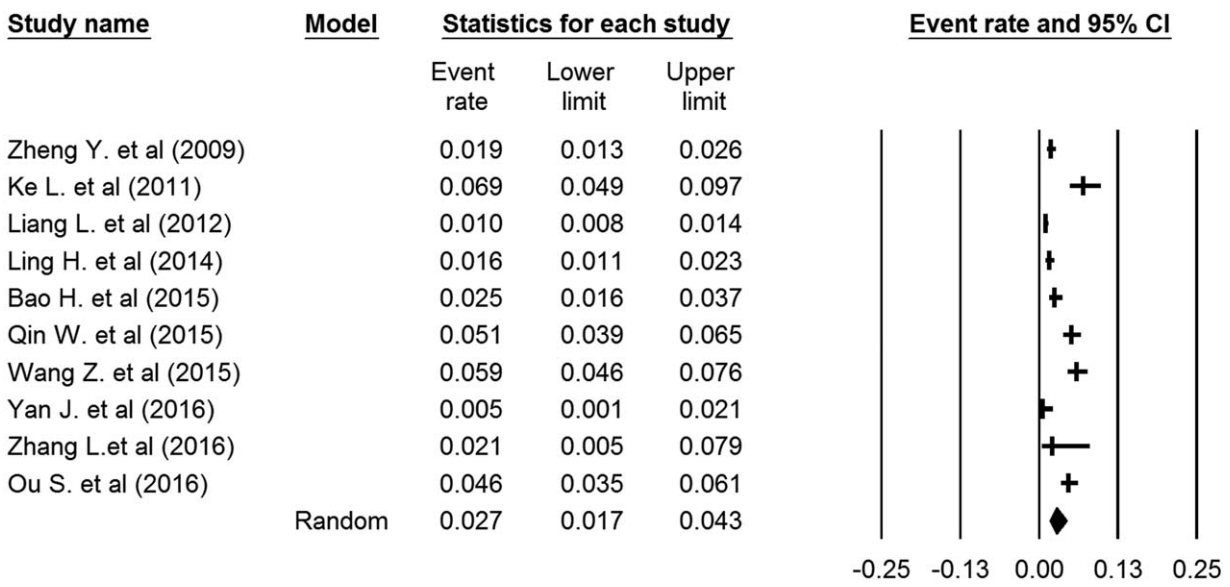

Figure 3. Forest plot of the meta-analysis of the prevalence of anti-B19V IgM antibodies among blood donors. B19V = Human parvovirus B19.

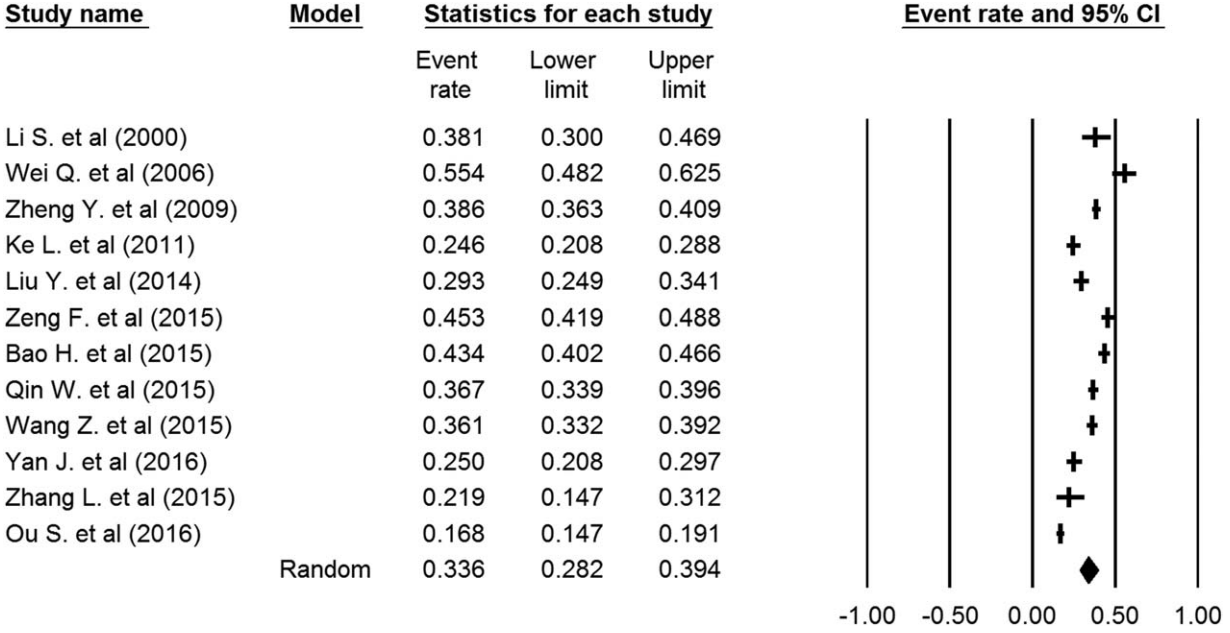

Figure 4. Forest plot of the meta-analysis of the prevalence of anti-B19V IgG antibodies among blood donors. B19V = Human parvovirus B19.

Table 2

Prevalence of B19V infection among blood donors in mainland China.

Markers	Studies	Prevalence % (95% CI) Point estimate	Heterogeneity I^2 (%)	Heterogeneity *P*-value	Model	Publication bias $P_{Begg's\ Test}$-value	Publication bias $P_{Egger's\ Test}$-value
BV19-DNA	11	0.7 (0.2–2.4)	98.2	<.001[c]	REM[a]	.10	.03[b]
Anti-BV19 IgM	10	2.7 (1.7–4.3)	94.1	<.001[c]	REM[a]	.33	.44
Anti-BV19 IgG	12	33.6 (28.2–39.4)	96.4	<.001[c]	REM[a]	.41	.39

B19V = human parvovirus B19.

[a] REM = random effect model.

[b] *P*-values represent significant differences ($P < .05$).

[c] *P*-values represent significant statistical heterogeneities ($P < .10$).

analyses indicated that 2 B19V genotypes (Genotype 1 and Genotype 3) were present in mainland China, and none of the samples clustered with Genotype 2 sequences; 142 of 169 (84.0%) B19V isolates belonged to Genotype 1, and the remaining isolates belonged to Genotype 3.

4. Discussion

Although B19V infection generally does not result in serious health problems, it can cause serious complications in some high-risk groups, such as pregnant women, potential hematological malignancy patients, and patients with immunodeficiency. Since the beginning of this century, Germany, the Netherlands, and Poland have performed B19V NATs to screen blood donors.[21,51–53] In Germany, NATs for B19V DNA were introduced into blood donor screening programs in 2000. Blood products containing $\geq 10^5$ IU/mL of B19V DNA are discarded, while minipools of blood products with $<10^5$ IU/mL of B19V DNA are released.[52] In the Netherlands, it has been proposed that "B19V-safe" cellular blood products be administered to the high-risk groups mentioned above. "B19-safe" cellular blood products are defined as those from a donor in which anti-B19V IgG antibodies have been detected in 2 separate blood samples taken at least 6 months apart.[53] B19V screening of blood products was subsequently expanded in some regions and countries. To reduce the risk of transmission via transfusion, relevant regulations in the European Pharmacopoeia were initiated to control the potential B19V burden in pooled virus-inactivated plasma and anti-D immunoglobulins in 2004.[21,54,55] The US Food and Drug Administration (FDA) also issued similar guidelines and standards that limit the level of B19V DNA in plasma derivatives to 10^4 IU/mL; however, no blood donor screening test for B19V has been licensed.[21,55–57] In 2008, Japan started to introduce B19V screening of all blood donations.[21,55,58] Published studies show that the prevalence rates of B19V infection among blood donors worldwide range from 0.7% to 7.5% for IgM and from 6.0% to 79.1% for IgG.[21,59–62] Generally, the B19V-DNA prevalence among blood donors is low, ranging from 0% to 1.3%.[21,34,63–65]

In mainland China, there are currently no specific strategies for monitoring and screening B19V in blood donations or products. Prevention and control strategies for transfusion-transmitted infections (TTIs) should be established based on epidemiological evidence. Considering the high cost of detecting and removing B19V, the overall prevalence in donors in mainland China needs to be elucidated to develop appropriate prevention strategies. Therefore, the B19V prevalence among blood donors was evaluated based on previous research in this area. Twenty-one articles on the prevalence of B19V infection in blood donors were identified. The pooled estimates of the prevalence rates were 0.7% for B19V-DNA, 2.7% for anti-B19V IgM, and 33.6% for anti-B19V IgG. Therefore, the present study found a low, non-endemic prevalence of B19V among blood donors in mainland China. Whether it is necessary to screen and monitor B19V in blood donation or products in mainland China needs further study; future studies should include strategy evaluations, cost-effectiveness, etc.

Moreover, stratified analysis suggested that no significant geographic difference in the prevalence of B19V-DNA existed, although the estimated prevalence of B19V-DNA in south China was lower than that in north China. There are several possible reasons for this, including large-scale population migration, economic development, and improved living and sanitary conditions. The prevalence of B19V-DNA was not significantly different between male and female donors, indicating that both male and female donors have the same susceptibility to B19V. Our work also determined that in studies with large sample sizes (>1000), the prevalence of B19V-DNA in blood donors was lower than that in studies with small sample sizes. The small-study effect is obvious in these small-sample studies. The possible impact of this effect on the results is an increased estimate of BV19 prevalence. Therefore, the use of large sample sizes is recommended for future B19V epidemiological studies of blood donors.

Phylogenetic analysis identified three main genotypes of B19V, including Genotype 1, which is prevalent worldwide, acting as the prototypical and most common B19V,[66,67] Genotype 2, which is sporadically found circulating in Europe and North America and is a rare genotype,[49,68–70] and Genotype 3, which appears to be principally endemic to Ghana and has also been found in Brazil, France, North India, and the United States.[49,71] This study showed that the majority of B19V isolates in mainland China belonged to Genotype 1, followed by Genotype 3, and Genotype 2 was not detected. It would be beneficial to understand the source, spread, and control of B19V in the Chinese mainland.

There are several limitations of this work. The included studies only involved 14 of the 31 provinces in mainland China (i.e., 11 provinces, 2 autonomous regions, and 1 municipality). Other areas of mainland China lacked epidemiological studies on B19V in blood donors. Further analyses such as stratified analysis and meta regression are needed to provide additional data support. Additionally, because some important information provided in the included studies was not detailed, the ability to evaluate the quality of the research was limited. Moreover, some studies were from different regions in the same province, such as Guangdong Province. Although these studies were independently performed by different research teams, B19V-positive donors might have been resampled due to population migration, design overlap, etc. Considering the population of about 1.3 billion and blood donation rate of 9‰ in mainland China, the population of blood donors in each province is large.[72] The chance of being resampled is probably low; therefore, such risks have little effect on the estimated prevalence of B19V. Finally, blood donors were not chosen randomly in the included studies. Thus, selection bias and confounding seem to be inevitable, especially in the small-sample size studies of B19V prevalence in which there may exist a small-sample effect. A small sample size means studies are susceptible to selection bias and confounding. However, given the poor representation of small-sample studies, we are still inclined to conclude that the pooled prevalence of B19V in blood donors is not high in mainland China. In addition, readers whose native language is not Chinese would find it difficult to use the original materials included because most of the studies were written in Chinese. However, we are confident in the results because the included studies were obtained from multiple sources, combining data from 48,923 samples subjected to NATs, 12,948 samples tested for anti-B19V IgM, and 8244 samples tested for anti-B19V IgG by ELISAs, which are large sample sizes.

In summary, this research provides comprehensive and objective data on the prevalence of BV19 in blood donors. The results indicate that the prevalence of B19V among blood

donors in mainland China is not high, and most B19V isolates belong to Genotype 1.

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