

BMJ Open ABO blood groups and hepatitis B virus infection: a systematic review and meta-analysis

Wenzhan Jing, Siyu Zhao, Jue Liu, Min Liu 

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Department of Epidemiology & Biostatistics, Peking University, School of Public Health, Beijing, China

Correspondence to
Professor Min Liu;
liumin@bjmu.edu.cn

ABSTRACT

Objective Hepatitis B virus (HBV) infection is a major public health problem worldwide. Several studies have reported that ABO blood groups may be associated with HBV infection. However, its association is still controversial. We performed a meta-analysis to investigate whether ABO blood groups were associated with HBV infection.

Design Systematic review and meta-analysis.

Data sources Relevant studies available before 1 December 2019 were identified by searching PubMed, EMBASE, Web of Science, ScienceDirect and the Cochrane Library.

Eligibility criteria All cross-sectional or cohort studies from which the data of ABO blood group distribution and HBV infection could be extracted.

Data extraction and synthesis Studies were identified and extracted by two reviewers independently. Risk ratios (RRs) and 95% CIs were pooled by random-effect models to quantify this association.

Results Thirty-eight eligible articles including 241 868 HBV-infected subjects and 6 487 481 uninfected subjects were included. Overall, the risk of HBV infection had decreased by 8% in subjects with blood group B when compared with non-B blood group (RR=0.92, 95% CI 0.86 to 0.98). In the subgroup analyses, the inverse relationship between blood group B and HBV infection remained stable in higher endemic areas (HBV prevalence $\geq 5\%$), Asian people, larger sample size studies (≥ 2000), general population and blood donors, lower middle income group and studies published before the year 2010. Additionally, subjects with blood group O had a 12% increased risk of HBV infection (RR=1.12, 95% CI 1.01 to 1.24) in higher endemic areas. In the sensitivity analysis, the pooled risk estimates of blood group B and HBV infection were still stable.

Conclusions Our data suggested that the blood group B was associated with a lower risk of HBV infection. More research is needed to clarify the precise role of the ABO blood group in HBV infection to address the global question of HBV infection.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major public health problem worldwide,¹ especially in Africa and the Western Pacific region.² According to the global hepatitis report in 2017, it is estimated that 257 million people, 3.5% of the general population, are living

Strengths and limitations of this study

- The breadth of the comprehensive systematic literature search is a strength of this study.
- To our knowledge, this is the first meta-analysis of the association between ABO blood groups and HBV infection.
- Although we performed subgroup analyses, the heterogeneity cannot be ignored because few published studies described the related risk factors of HBV infection in detail.

with HBV infection worldwide with about 0.88 million deaths caused by complications of chronic HBV infection every year.² HBV infection has caused a high societal burden globally.^{1 2}

The ABO blood group system, the most extensively investigated erythrocyte antigen system,³ is widely used in clinical practice, and influences the host susceptibility.^{4 5} As an easily accessible factor in an individual's genetic makeup, ABO blood groups have been statistically and biologically associated with many chronic diseases such as vascular disease,⁶ coronary heart disease⁷ and tumorigenesis.^{3 4 8} For instance, by expressing on N-glycans of von Willebrand factor (VWF), ABH antigens (H antigen is the biosynthetic precursor to A and B antigens)⁵ impact the half-life of VWF, so VWF survival in O subjects is significantly shorter versus in non-O subjects.^{9–11} Therefore, because of the lower VWF levels, O subjects have lower risk of venous thromboembolism.¹⁰ Recently, a meta-analysis also found that patients with hepatocellular carcinoma (HCC) might have a lower proportion of O subjects than healthy subjects.¹² Meanwhile, the association between ABO blood groups and host susceptibility to infectious diseases (such as *Helicobacter pylori*, *Plasmodium falciparum*, HIV, etc) has been shown in several studies.^{5 13} Previous studies have found that this association is because ABO antibodies are part of the

innate immune system against some bacteria, parasites and enveloped viruses,⁵ and blood antigens are important as receptors for immune and inflammation responses,^{14,15} which means that a biological association between ABO blood groups and HBV infection probably exists.

Epidemiological studies have explored the relationship between blood group and HBV infection, however, the results have been contradictory. Lao *et al*¹⁶ found that HBV prevalence was lower in blood group B (9.6%) and AB (9.1%), but higher in blood group O (10.2%). Liu *et al*¹⁷ suggested that blood group O was associated with increased HBV infection. Mohammadali *et al*¹⁸ found that the percentage of the hepatitis B surface antigen (HBsAg) was lower in donors with blood group O. However, Szmuness *et al*^{19,20} and Behal *et al*²¹ failed to find a link between blood group and HBV infection. Thus, controversy remains with regard to whether blood group is related to HBV infection and which antigen is a protective or a risk factor. We performed a systematic review and meta-analysis to elucidate the association between ABO blood groups and HBV infection risk to provide evidence on improving blood safety and preventing HBV infection, which can help to achieve the target of eliminating HBV as an international public health challenge.²²

MATERIALS AND METHODS

Data sources and search strategy

Two reviewers (SZ and WJ) searched independently for articles, which were available online before 1 December 2019, from five databases including PubMed, EMBASE, Web of Science, ScienceDirect and Cochrane Central using the following keywords: 'hepatitis B' OR 'hepatitis B virus' OR 'HBV' OR 'HBsAg' and 'blood type' OR 'blood group' OR 'ABO' OR 'Rh' OR 'rhesus'. Meanwhile, highly relevant reference articles were also searched by reviewing the list of references. There was no limitation of language or region. The full electronic search strategy for PubMed is shown in online additional file 1.

Inclusion and exclusion criteria

Articles were included in the meta-analysis if: (1) The article was a cross-sectional or cohort study. (2) The data of the ABO blood group distribution and HBV infection could be extracted to calculate the risk ratio (RR), which meant that the numbers of HBV-infected and uninfected subjects were reported in each blood group. The exclusion criteria were as follows: (1) The article was not relevant to the subject of the study (animal experiments, pathological researches, molecular researches). (2) Reviews. (3) Overlapped studies, where if studies overlapped, we only included the last published. (4) Duplicated studies, where if the same study was found in different databases, we only included the article once.

According to the inclusion and exclusion criteria, studies were identified by two reviewers (SZ and WJ) independently. Discrepancies were solved by consensus or decided by a third reviewer (JL).

Data extraction and quality assessment

According to the piloted forms, four main parts of the information were extracted independently by two reviewers (SZ and WJ) from the selected studies: (1) The basic information of the studies including first author, publication year, journal, survey time, study design. (2) The characteristics of the study population including country, income group, race, population type (eg, blood donors, patients, general population), sample size, the number of HBV-infected and uninfected subjects, age range, mean age, sex ratio. (3) The outcome measure: the number of HBV-infected and uninfected subjects in each ABO blood group. (4) The author's general conclusions.

The quality of selected cohort studies was assessed using the Newcastle-Ottawa Scales (NOS) with a score ranging from 0 to 9.²³ A score of 4–6 indicated moderate quality, and a score of 7–9 indicated high quality. The quality of the selected cross-sectional studies was assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ)²⁴ with a score ranging from 0 to 11. A score of 4–7 indicated moderate quality, and a score of 8–11 indicated high quality.

Statistical analysis

The main outcome was the prevalence of HBV infection (defined as HBsAg-positive) in our meta-analysis. The relationship between the ABO blood groups and HBV infection was quantified using RR values and the corresponding 95% CIs. RRs and 95% CIs (A vs non-A, B vs non-B, O vs non-O, AB vs non-AB) were pooled by using random-effect models with the estimate of heterogeneity being taken from the Mantel-Haenszel model, and a value of $p < 0.05$ was deemed significant. Between-study heterogeneity was evaluated with the I^2 statistic. When $I^2 \leq 50\%$, the included studies were considered to have little heterogeneity; when $I^2 > 50\%$, the included studies were considered to have substantial heterogeneity.²⁵

Subgroup analyses were performed by HBV prevalence, race, sample size, population, income group, study type and publication year. The prevalence of HBV infection was calculated in each study based on the number of HBV-infected and uninfected subjects. Studies were divided into Caucasian, Asian and African subgroups depending on the major national race and divided into high, upper-middle, lower-middle and low income groups according to the World Bank list of economies.²⁶ Sensitivity analyses were performed by excluding large sample sized studies orderly or at the same time, which dominated the results of the meta-analysis. Publication bias was evaluated by funnel plots and two-sided Egger's tests, and a value of $p < 0.05$ was deemed statistically significant. All statistical analyses were performed using STATA V.12.0.

Patient and public involvement

There was no direct patient or public involvement in this review.

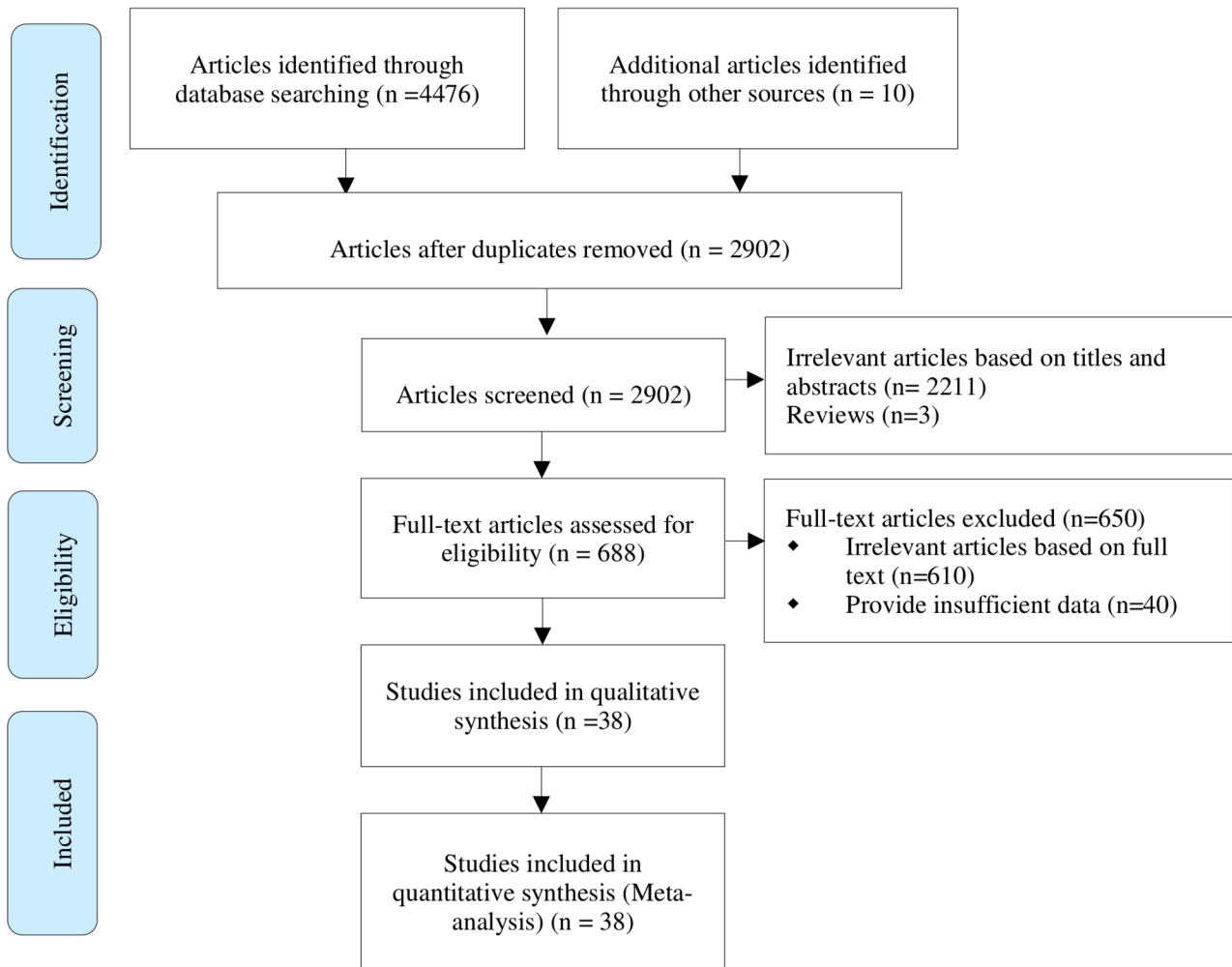


Figure 1 The process of study selection for the meta-analysis.

RESULTS

Study selection and study characteristics

A total of 4486 articles (4476 from the database and 10 from other sources) was searched, of which 1584 were duplicate results. After reading the abstracts, 2211 were deemed irrelevant and 3 reviews were excluded. After reading the full text, 650 articles were excluded, of which 610 were irrelevant articles, and 40 studies provided insufficient information. Eventually, 38 eligible articles were included in the meta-analysis. A flow chart of study selection is shown in [figure 1](#).

The basic characteristics of the selected studies are shown in [table 1](#). All selected articles were observational studies and published between 1970 and 2019. A total of 6487 481 subjects was included with 241 868 HBV-infected subjects and 6245 613 uninfected subjects. Among the Caucasian, Asian and African populations, there were 23, 7 and 8 studies, respectively. In addition, there were 7, 9, 18 and 4 studies in high income, upper middle income, lower middle income and low income groups, respectively. Furthermore, there were 14 studies in higher (HBV prevalence $\geq 5\%$) endemic and 24 studies in lower (HBV prevalence $< 5\%$) endemic areas. Meanwhile, there

were 37 cross-sectional studies and 1 cohort study in the meta-analysis.

The HBV infection prevalence in the 38 eligible articles ranged from 0.11% to 46.84%, and the HBV infection prevalence of blood groups A, B, AB, O ranged from 0.11% to 45.71%, 0.08% to 52.00%, 0.00% to 33.33% and 0.12% to 45.88%, respectively. The results of the quality assessment are shown in online additional file 2, with 15 high quality studies and 23 moderate quality studies. The score of the 37 articles assessed by AHRQ ranged from 3 to 9, while 14 of them were of high quality with a score from 8 to 9, and 23 of them were of moderate quality with a score from 4 to 7 (online supplementary table S1–1). The article assessed by the NOS scored 7 and was of high quality (online supplementary table S1–2).

Main, subgroup and sensitivity analyses

Overall, the risk of HBV infection had decreased by 8% in subjects with blood group B when compared with the non-B blood group (RR=0.92, 95% CI 0.86 to 0.98). However, blood groups A, O and AB were not significantly associated with an HBV infection risk ([table 2](#)). The results of the subgroup analyses were shown in [table 2](#). In

Table 1 Characteristics of the included studies

Author	Income group	Race	Population	Sample size	HBV infection (n/%)				O, non-O*
					Total	A, non-A*	B, non-B*	AB, non-AB*	
Terrier <i>et al</i> ²⁹	High	Caucasian	Blood donors	5988	55/0.92	9/0.37, 46/1.31	4/0.66, 51/0.95	2/0.78, 53/0.93	40/1.51, 15/0.45
Leski <i>et al</i> ³⁰	High	Caucasian	Patients	155	34/21.94	16/23.19, 18/20.93	4/28.57, 30/21.28	0/0, 34/22.67	14/20.9, 20/22.73
Szmuness <i>et al</i> ¹⁹	High	Caucasian	Blood donors	8096	177/2.19	61/2.06, 116/2.26	25/2.21, 152/2.18	13/3.57, 164/2.12	78/2.14, 99/2.23
Zuberi and Lodi ³¹	Lower middle	Caucasian	Blood donors	1111	38/3.42	9/3.36, 29/3.44	5/1.23, 33/4.69	2/3.64, 36/3.41	22/5.77, 16/2.19
Vale <i>et al</i> ³²	Lower middle	African	General	836	40/4.78	18/5.61, 22/4.27	6/4.11, 34/4.93	5/4.59, 35/4.81	11/4.23, 29/5.03
Moore <i>et al</i> ³³	Low	Caucasian	Blood donors	14916	495/3.32	127/3.48, 368/3.27	103/3.21, 392/3.35	17/3.1, 478/3.33	248/3.3, 247/3.33
Szmuness <i>et al</i> ²⁰	High	Caucasian	Blood donors	51 019	58/0.11	22/0.11, 36/0.11	5/0.08, 53/0.12	4/0.16, 54/0.11	27/0.12, 31/0.11
Lenka <i>et al</i> ³⁴	Lower middle	Caucasian	Blood donors	500	24/4.8	12/9.3, 12/3.23	8/4.08, 16/5.26	0/0, 24/5.25	4/3.03, 20/5.43
Nath <i>et al</i> ³⁵	High	Caucasian	Blood donors	1585	68/4.29	22/4.03, 46/4.44	9/3.35, 59/4.48	3/4.17, 65/4.30	34/4.87, 34/3.83
Kulkarni <i>et al</i> ³⁶	Lower middle	African	Blood donors	1860	165/8.87	51/13.11, 114/7.85	17/3.11, 148/11.27	18/18.75, 147/8.33	79/9.54, 86/8.33
Naidu and Rajyalakshmi ³⁷	Lower middle	Caucasian	Blood donors	1029	145/14.09	49/20.08, 96/12.40	42/12.39, 103/14.93	11/17.74, 134/13.86	43/11.20, 102/15.81
Sebastian <i>et al</i> ³⁸	High	Asian	Blood donors	3276	134/4.09	30/4.17, 104/4.08	30/3.50, 104/4.30	10/4.76, 124/4.04	64/4.30, 70/3.91
Zhu <i>et al</i> ³⁹	Upper middle	Asian	Blood donors	8683	153/1.76	44/1.62, 109/1.83	30/1.37, 123/1.89	18/2.59, 135/1.69	61/1.98, 92/1.64
Joshi and Ghimire ⁴⁰	Low	Asian	General	613	17/2.77	4/2.09, 13/3.08	5/2.86, 12/2.74	1/2.13, 16/2.83	7/3.5, 10/2.42
El-Gilany and El-Fedawy ⁴¹	Lower middle	Caucasian	Blood donors	2157	93/4.31	27/3.42, 66/4.87	19/3.85, 74/4.45	12/5.88, 81/4.15	35/5.23, 58/3.90
Behal <i>et al</i> ²¹	Lower middle	Caucasian	Blood donors	20 000	450/2.25	106/2.30, 344/2.24	174/2.34, 276/2.20	38/1.87, 412/2.29	132/2.23, 318/2.26
Rifat-uz-Zaman ⁴²	Lower middle	Caucasian	General	1464	93/6.35	5/3.01, 88/6.90	35/6.63, 58/6.20	23/6.99, 70/6.17	30/6.80, 63/6.16
Dirisu <i>et al</i> ⁴³	Lower middle	African	Blood donors	427	200/46.84	32/45.71, 168/47.06	39/52, 161/45.74	1/33.33, 199/46.93	128/45.88, 72/48.65
Saeed Anwar <i>et al</i> ⁴⁴	Lower middle	Caucasian	Blood donors	16 695	467/2.80	103/2.60, 364/2.86	139/2.31, 328/3.07	17/2.64, 450/2.80	208/3.42, 259/2.44
Omar <i>et al</i> ⁴⁵	Upper middle	Caucasian	Blood donors	430	71/16.51	15/12.5, 56/18.06	21/21.43, 50/15.06	3/5.36, 68/18.18	32/20.51, 39/14.23
Tyagi and Tyagi ⁴⁶	Lower middle	Caucasian	Blood donors	6000	95/1.58	27/1.87, 68/1.49	27/1.27, 68/1.75	9/1.98, 86/1.55	32/1.62, 63/1.57
Sethi <i>et al</i> ⁴⁷	Lower middle	Caucasian	Blood donors	7884	50/0.63	15/0.60, 35/0.65	10/0.41, 40/0.74	11/1.28, 39/0.56	14/0.68, 36/0.62
Mohammadali and Pourfathollah ¹⁸	Upper middle	Caucasian	Blood donors	2028068	7839/0.39	2553/0.40, 5286/0.38	1952/0.40, 5887/0.38	627/0.41, 7212/0.38	2707/0.36, 5132/0.40
Nigam <i>et al</i> ⁴⁸	Lower middle	Caucasian	Blood donors	4128	40/0.97	12/1.17, 28/0.90	11/0.75, 29/1.09	2/0.50, 38/1.02	15/1.22, 25/0.86
Lao <i>et al</i> ¹⁶	High	Asian	General	78 705	7786/9.89	2038/9.90, 5748/9.97	1991/9.60, 5795/10.00	468/9.11, 7318/9.95	3289/10.20, 4497/9.68
Zhao <i>et al</i> ⁴⁹	Upper middle	Asian	Patients	500	66/13.20	17/11.18, 49/14.71	16/9.82, 50/14.84	15/16.67, 51/12.44	18/18.95, 48/11.85
Sitransy <i>et al</i> ⁵⁰	Upper middle	African	Blood donors	59 514	4119/6.92	947/7.15, 3172/6.86	941/6.78, 3178/6.96	187/6.77, 3932/6.93	2044/6.9, 2075/6.94
Navolan <i>et al</i> ⁵¹	Upper middle	Caucasian	General	1385	33/2.38	15/2.42, 18/2.37	7/3.11, 26/2.24	4/3.54, 29/2.28	7/1.64, 26/2.71
Bisetegen <i>et al</i> ⁵²	Low	African	Blood donors	390	37/9.49	7/6.73, 30/10.49	10/12.99, 27/8.63	2/22.22, 35/9.19	18/9, 19/10
Abate and Wolde ²⁷	Low	African	Blood donors	6827	647/9.48	114/5.66, 533/11.10	54/5.45, 593/10.16	9/4.27, 638/9.64	470/13.02, 177/5.50

Continued

Table 1 Continued

Author	Income group	Race	Population	Sample size	HBV infection (n/%)				
					Total	A, non-A*	B, non-B*	AB, non-AB*	O, non-O*
Bharadvaj et al ⁵³	Lower middle	Caucasian	Blood donors	41 909	237/0.57	62/0.63, 175/0.55	85/0.58, 152/0.56	22/0.55, 215/0.57	68/0.51, 169/0.59
Naseri et al ⁵⁴	Upper middle	Caucasian	Blood donors	228 409	640/0.28	208/0.29, 432/0.28	180/0.34, 460/0.26	42/0.24, 598/0.28	210/0.25, 430/0.30
Memon et al ⁵⁵	Lower middle	Caucasian	Blood donors	4683	66/1.41	15/1.37, 51/1.42	21/1.53, 45/1.36	9/2.94, 57/1.30	21/1.10, 45/1.63
Liu et al ¹⁷	Upper middle	Asian	General	3827 125	215455/5.63	64811/5.55, 150644/5.71	58286/5.18, 157169/5.82	18707/5.06, 196748/5.69	73651/6.34, 141804/5.32
Batool et al ⁵⁶	Lower middle	Caucasian	Blood donors	41 084	969/2.36	321/2.72, 648/2.22	289/2.21, 680/2.43	82/2.13, 887/2.38	277/2.24, 692/2.41
Ngassaki-Y et al ⁶⁷	Upper middle	African	Blood donors	4744	81/1.71	-	-	-	34/1.22, 47/2.41
Fu et al ⁵⁸	Upper middle	Asian	Patients	2000	389/19.45	105/21.43, 284/18.81	89/18.94, 300/19.61	59/21.85, 330/19.08	136/17.66, 253/20.57
Nkansah et al ⁵⁹	Lower middle	African	Blood donors	3306	342/10.34	48/11.76, 294/10.21	63/9.35, 279/10.67	1/3.33, 341/10.47	230/10.48, 112/10.07

*The number of HBV infected people in the X blood group/HBV prevalence (%) in the X blood group; the number of HBV-infected people in the non-X blood group/HBV prevalence (%) in the non-X blood group.
HBV, Hepatitis B virus.

the subgroup analyses, the relationship between blood group B and HBV infection remained stable. The inverse relationship between blood group B and HBV infection was still observed in higher endemic areas (HBV prevalence $\geq 5\%$), Asian people, studies with larger sample sizes (≥ 2000), the general population and blood donors, the lower middle income group and articles published before the year 2010 (table 2).

In higher endemic areas, subjects with blood group B had a significantly lower risk of HBV infection (RR=0.90, 95% CI 0.83 to 0.98) than the non-B blood group (figure 2A), while subjects with the blood group O had a significantly higher risk of HBV infection (RR=1.12, 95% CI 1.01 to 1.24) than the non-O blood group (figure 2B). According to the race of the subjects, blood groups A and B were linked with decreased risk of HBV infection in the Asian population when compared with non-A and non-B groups, respectively (RR=0.98, 95% CI 0.97 to 0.99; RR=0.91, 95% CI 0.86 to 0.97) (table 2). However, no association was found among the Caucasian or African populations. In the general population, blood group A, B and AB had a decreased risk of HBV infection compared with the non-A, non-B and non-AB groups, respectively (RR=0.98, 95% CI 0.96 to 1.00; RR=0.93, 95% CI 0.87 to 0.99 and RR=0.89, 95% CI 0.88 to 0.90, respectively) (table 2).

In the sensitivity analysis, when the studies by Liu *et al*¹⁷ and Mohammadali *et al*,¹⁸ which dominated the results of the meta-analysis, were orderly removed or both removed at the same time, the pooled risk estimates were still stable, showing that blood B was associated with a lower risk of HBV infection (table 2).

Publication bias

Funnel plots and Egger's tests were performed to assess publication bias. No obvious evidence of publication bias was present for A versus non-A (figure 3A), B versus non-B (figure 3B) and O versus non-O (figure 3C) (p=0.148; p=0.223; p=0.364, respectively), while a publication bias of AB versus non-AB was observed (figure 3D) (p=0.002).

DISCUSSION

To our knowledge, this was the first meta-analysis of the association between ABO blood groups and HBV infection. Our meta-analysis results suggested that blood group B was associated with a lower risk of HBV infection, which was observed in the subgroups and was still stable in sensitive analyses, giving supportive evidence that statistical association and biological association between ABO blood groups and HBV infection probably exists.

As an infectious disease, aside from genetic susceptibility factors, there is the question of whether exposure to the source of infection is directly related to the risk of infection. People living in higher endemic areas are at higher risk of exposure to HBV infection than those living in lower endemic areas, which might be the reason why the association between the ABO blood group and

Table 2 The main, subgroup and sensitivity analyses

Subgroup	No. of studies	B versus non-B		O versus non-O		A versus non-A		AB versus non-AB		
		Sample size	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
All studies	38	6487481	0.92 (0.86 to 0.98)	0.007	1.07 (0.99 to 1.15)	0.082	1.01 (0.96 to 1.07)	0.728	1.04 (0.95 to 1.13)	0.419
HBV prevalence										
Higher endemic areas (>5%)	14	3983732	0.90 (0.83 to 0.98)	0.013	1.12 (1.01 to 1.24)	0.025	0.99 (0.91 to 1.08)	0.82	1.00 (0.89 to 1.14)	0.962
Lower endemic areas (<5%)	24	2503749	0.93 (0.85 to 1.02)	0.126	1.03 (0.93 to 1.15)	0.566	1.03 (0.95 to 1.11)	0.471	1.06 (0.95 to 1.18)	0.292
Race										
Caucasian	23	2488675	0.96 (0.87 to 1.05)	0.386	1.04 (0.94 to 1.16)	0.465	1.03 (0.94 to 1.13)	0.472	1.05 (0.93 to 1.18)	0.461
Asian	7	3920902	0.91 (0.86 to 0.97)	0.003	1.10 (0.99 to 1.22)	0.075	0.98 (0.97 to 0.99)	<0.001	0.96 (0.87 to 1.06)	0.451
African	8	77904	0.78 (0.58 to 1.05)	0.099	1.04 (0.77 to 1.40)	0.803	0.99 (0.73 to 1.33)	0.919	1.02 (0.62 to 1.67)	0.953
Sample size										
≥2000	24	6475196	0.93 (0.87 to 0.99)	0.018	1.07 (0.98 to 1.16)	0.135	0.99 (0.94 to 1.05)	0.795	1.00 (0.92 to 1.08)	0.914
<2000	14	12285	0.85 (0.64 to 1.13)	0.275	1.08 (0.90 to 1.29)	0.398	1.07 (0.85 to 1.33)	0.577	1.20 (0.89 to 1.61)	0.238
Population										
General	6	3910128	0.93 (0.87 to 0.99)	0.016	1.07 (0.99 to 1.15)	0.078	0.98 (0.96 to 1.00)	0.035	0.89 (0.88 to 0.90)	<0.001
Blood donors	29	2574698	0.89 (0.81 to 0.97)	0.011	1.08 (0.97 to 1.20)	0.154	1.01 (0.92 to 1.10)	0.885	1.08 (0.95 to 1.23)	0.248
Patients	3	2655	0.92 (0.71 to 1.19)	0.517	1.04 (0.71 to 1.54)	0.828	1.09 (0.91 to 1.30)	0.345	1.17 (0.94 to 1.46)	0.169
Income group										
High	7	148804	0.96 (0.91 to 1.00)	0.065	1.17 (0.95 to 1.44)	0.135	0.91 (0.74 to 1.11)	0.343	0.97 (0.84 to 1.13)	0.712
Upper middle	9	6101344	1.01 (0.88 to 1.15)	0.927	0.97 (0.82 to 1.15)	0.756	1.00 (0.96 to 1.06)	0.791	1.02 (0.88 to 1.17)	0.814
Lower middle	18	214587	0.86 (0.76 to 0.97)	0.011	1.03 (0.93 to 1.13)	0.582	1.13 (1.01 to 1.25)	0.03	1.13 (0.95 to 1.34)	0.173
Low	4	22746	0.88 (0.56 to 1.38)	0.572	1.34 (0.72 to 2.48)	0.353	0.71 (0.42 to 1.21)	0.209	0.84 (0.43 to 1.64)	0.613
Study design										
Cross-sectional	37	6408776	0.91 (0.85 to 0.97)	0.007	1.07 (0.98 to 1.17)	0.111	1.01 (0.95 to 1.08)	0.78	1.06 (0.96 to 1.17)	0.244
Cohort	1	78705	0.96 (0.92 to 1.01)	0.098	1.05 (1.01 to 1.10)	0.016	1.00 (0.95 to 1.05)	0.957	0.92 (0.84 to 1.00)	0.053
Publication year										
Before 2010	17	123268	0.80 (0.67 to 0.96)	0.015	1.12 (0.97 to 1.29)	0.112	1.02 (0.85 to 1.22)	0.83	1.22 (1.01 to 1.46)	0.04
After 2010	21	6364213	0.95 (0.88 to 1.01)	0.106	1.05 (0.95 to 1.15)	0.335	1.00 (0.94 to 1.06)	0.91	0.98 (0.89 to 1.07)	0.627
Sensitive analyses										
Removed Liu's study ¹⁷	37	2660356	0.91 (0.85 to 0.98)	0.012	1.06 (0.98 to 1.15)	0.138	1.01 (0.94 to 1.08)	0.816	1.06 (0.97 to 1.17)	0.213
Removed Mohammedali's study ⁸	37	4459413	0.91 (0.85 to 0.97)	0.002	1.08 (1.00 to 1.16)	0.044	1.01 (0.94 to 1.07)	0.857	1.04 (0.95 to 1.14)	0.445
Removed both Liu's and Mohammedali's study ^{17,18}	36	632288	0.90 (0.83 to 0.97)	0.007	1.07 (0.98 to 1.17)	0.115	1.00 (0.92 to 1.09)	0.946	1.08 (0.96 to 1.20)	0.211

HBV, Hepatitis B virus; RR, risk ratio.

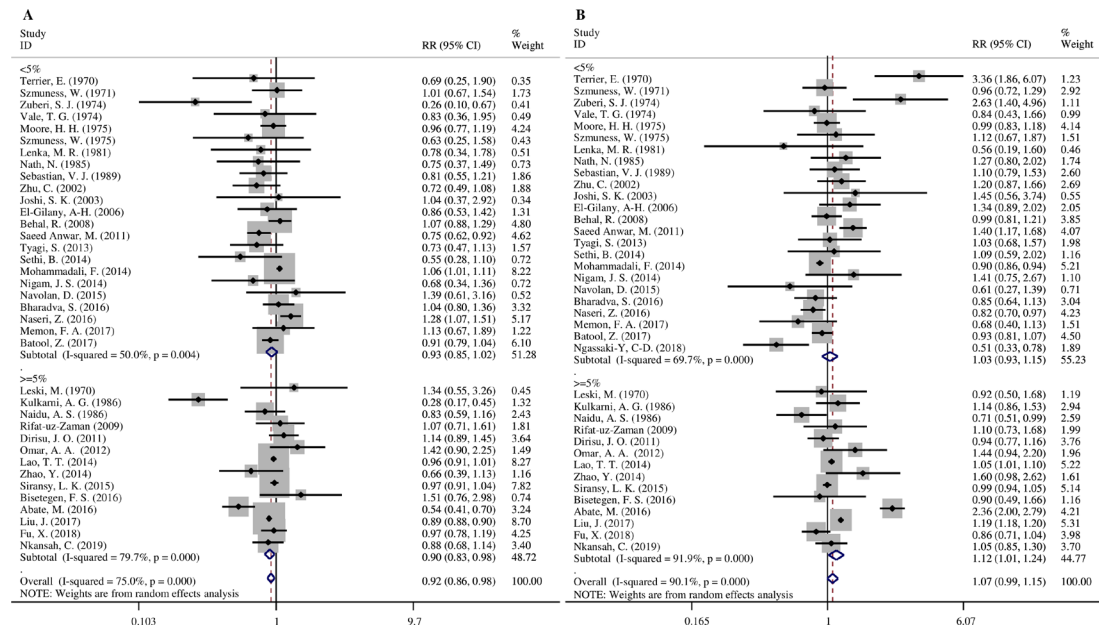


Figure 2 Forest plots by prevalence: (A) B versus non-B. (B) O versus non-O.

HBV infection was only found in higher endemic areas but not in lower endemic areas. Additionally, this association might be partly attributed to the regional factors, due to the high relevance between HBV endemic and regional health and economic development.

The universal hepatitis B vaccination programme, proposed by WHO, was implemented for newborns from 1992. All the selected articles were published between 1970 and 2019, which meant that even in the same country, the prevalence of HBV infection had changed significantly due to the increasing coverage of hepatitis

B vaccination. However, not enough information could be extracted from previous studies for comparing the pooled association of ABO blood groups and HBV infection between the vaccinated and unvaccinated groups. To partially examine the impact of hepatitis B vaccination on the results, we did subgroup analyses according to the publication year before and after 2010. Subjects in the selected articles were mainly over 18 years old. Thus, subjects in articles published after 2010 were more likely to be vaccinated at the time of birth, while subjects were mostly not vaccinated at birth in the articles published

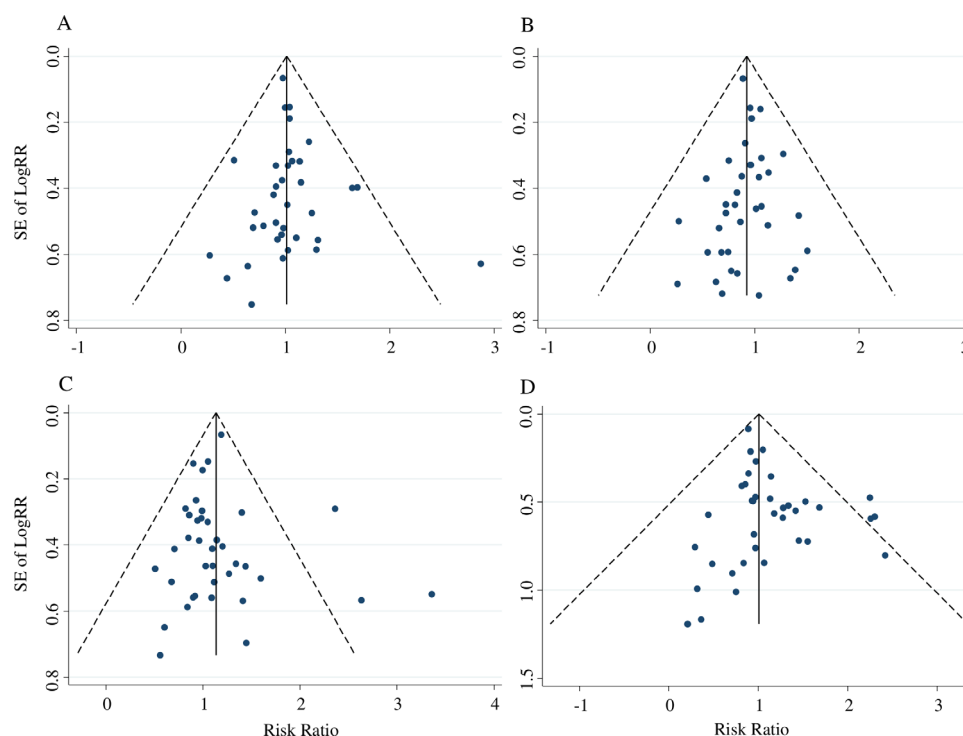


Figure 3 Funnel plots: (A) A versus non-A. (B) B versus non-B. (C) O versus non-O. (D) AB versus non-AB.



before 2010. We observed the association of blood group B and HBV infection in the articles published before 2010 rather than after 2010. The gradual establishment of an HBV immune barrier in the population may affect the occurrence of the relationship between ABO blood groups and HBV infection.

Our results found that subjects with blood group O were at higher risk of HBV infection than non-O blood group subjects in higher endemic areas, which was consistent with some previous studies by Lao *et al.*,¹⁶ Liu *et al.*¹⁷ and Abate *et al.*²⁷ That means more measures should be taken to ensure blood safety of the 'universal' blood group O population in high endemic areas because of the large unvaccinated population among the main blood donors in the current era and the window period for detection among the HBV-infected blood donors.¹⁷ However, this relationship was unobserved in other subgroup analyses, so whether this relationship is true remains to be further explored. Interestingly, our result that blood group B was associated with a lower risk of HBV infection compared with the non-B blood group was reported explicitly by few other studies, possibly because of the different analysis methods, such as the different reference of blood group in analysis.

However, the study by Mohammadali *et al.*,¹⁸ with the second largest sample size, reported that HBV infection was lower in blood group O donors, in contrast to the study with the largest sample by Liu *et al.*,¹⁷ probably due to the different HBV prevalence, geography and ethnicity. Our meta-analysis was inconsistent with a recent meta-analysis which found that patients with HCC might have a lower proportion of blood group O subjects than healthy subjects.¹² The possible explanation for the inconsistency is the long-term and complicated process from HBV infection to the occurrence of HCC. To examine the reliability and stability of the results, we orderly removed the study by Liu *et al.*¹⁷ or Mohammadali *et al.*,¹⁸ as well as removed both of them at the same time. In the sensitivity analysis, the relationship between blood group O and HBV infection might be unstable. However, the inverse relationship between blood group B and HBV infection was extremely stable. Therefore, we still think these findings are worthy of consideration due to the subgroup analyses, the sensitivity analyses and the relatively conservative random effects model.

Although the precise role that ABO blood groups play in host susceptibility and HBV infection has yet to be clarified,¹⁷ associations have been observed that are most likely related to the altered immune response¹⁶ and systemic inflammatory response,¹⁵ which are associated with different blood group phenotypes. A previous study has reported that the appearance of intestinal alkaline phosphatase in the plasma was associated with ABO blood group and secretor status, which might be due to genetically determined variations in the proportion of isoenzymes among the different blood types.²⁸ Our study may indicate that a specific histo-blood group antigen may be a natural resistance factor for HBV infection, and

that probably provides clues for correlative fundamental research of aetiologies and novel therapeutic targets for HBV. Further studies are warranted to elucidate the association between blood groups and HBV infection, and the way the blood type influences the process of HBV infection.

Meanwhile, several limitations need to be considered. First, although we performed subgroup analyses, analyses of previous studies have revealed that the heterogeneity cannot be ignored. Second, the analysed studies lacked basic information on the ethnicity data and the prevalence of different HBV genotypes. Third, few published studies on the association between HBV infection and blood group have controlled HBV infection related risk factors such as family history of HBV infection, age group, blood transfusion and acupuncture, thus we were not able to conduct the corresponding subgroup analyses.

In conclusion, blood group B is associated with a lower risk of HBV infection. In future, more research is needed to clarify the precise role of blood group ABO in HBV infection to address the global issue of HBV infection.

Contributors All authors contributed to this work. ML and JL conceived and designed the study strategy; SZ and WJ independently completed the processes of the article search, article assessment, data extraction, quality assessment and data analysis; WJ wrote the manuscript. All authors read and approved the final manuscript.

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ORCID ID

Min Liu <http://orcid.org/0000-0002-5059-3743>

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