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ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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Title page

Title: ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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. Thus, 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 December 1, 2017 were identified by searching PubMed, EMBASE, Web of Science, ScienceDirect, and the Cochrane Library.

Eligibility criteria All cross-sectional or cohort studies that the data of the 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% confidence intervals (CIs) were pooled by use of random-effects models to quantify this association.

Results Thirty-five eligible articles including 241,056 HBV-infected subjects and 6,236,375 uninfected subjects were included in this study. Overall, the risk of HBV infection had decreased by 8% in subjects with the blood group B when compared with the blood group non-B (RR = 0.92, 95% CI: 0.86–0.98), which was also observed in the subgroup analysis. In addition, subjects with blood group O had a 10% increased risk of HBV infection (RR = 1.10, 95% CI: 1.02–1.19), which was observed both in higher endemic areas (HBV prevalence ≥5%, RR = 1.16, 95% CI: 1.04–1.30) and in the Asian population (RR = 1.15, 95% CI: 1.04–1.27). In the sensitivity analysis, the pooled risk estimates were still stable.

Conclusions Our data suggested that the blood group B was associated with a lower risk of HBV infection, while the blood group O was associated with a higher risk of HBV infection.

Strengths and limitations of this study

- The breadth of the comprehensive systematic literature search is a strength of this study.
- To our knowledge, this was 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.

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 with HBV infection worldwide[2] 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 not only statistically but also biologically associated with many chronic diseases such as vascular disease[6], coronary heart disease[7], and tumorigenesis[3,4,8]. For example, O subjects have lower risk of venous thromboembolism (VTE) versus (vs.) non-O subjects because of a shorter von Willebrand factor (VWF) survival[9] due to A, B, and H antigens(H antigen is the biosynthetic precursor to A and B antigens[5].) influence the half-life of the VWF by expressing on N-glycans of VWF[9-11]. Meanwhile, the association between ABO blood groups and host susceptibility to infectious diseases (such as helicobacter pylori, plasmodium falciparum, and human immunodeficiency virus, etc.) has been shown in several studies[5,12]. Previous studies have found the reasons for this association were that 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 response[13,14], which means the biologic association between ABO blood groups and HBV infection probably exist.

Epidemiologic studies have explored the relationship between blood group and HBV infection, however, the results have been contradictory. Lao et al.[15] 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.[16] suggested that blood group O was associated with increased HBV infection. Mohammadali et al.[17] found that the percentage of hepatitis B surface antigen (HBsAg) was lower in donors who had blood group O. However, Szmuness et al.[18,19] and Behal et al.[20] 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[21].

Materials and methods

Data sources and search strategy

Two reviewers (SZ and WJ) searched for articles, which were available online before December 1, 2017, 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. There was no limitation of language or region.

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 number 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; and (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 (e.g., 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; and (4) the author's general conclusions.

The quality of selected cohort studies were assessed using the Newcastle-Ottawa Scales (NOS) with a score ranging from 0 to 9[22]. 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 were assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ)[23] 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 (defining 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% confidence intervals (CIs). RRs and 95% CIs (A vs. non-A, B vs. non-B, O vs. non-O, AB vs. non-AB) were pooled by use of random-effects models. Meanwhile, I^2 was used to evaluate heterogeneity among the studies. 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[24].

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 Black subgroups depending on the major national race and divided into high, upper middle, lower middle and low income groups according to the Word Bank list of economies[25]. Sensitivity analyses were performed by excluding the study which dominated the results of the meta-analysis. Publication bias was evaluated by funnel plots and Egger's tests. All statistical analyses were performed with STATA version 12.0.

Patient and public involvement

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

Results

Study selection and study characteristics

A total of 3836 articles (3826 from database and 10 from other sources) were searched, of which 1182 were duplicate results. After reading the abstracts, 2015 were deemed irrelevant and three reviews were excluded. After reading the full text, 601 articles were excluded, of which 564 were irrelevant articles, and 37 studies provided insufficient information. Eventually, 35 eligible articles were included in the meta-analysis. A flow-chart of study selection was generated according to the PRISMA requirements (Figure 1).

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

The basic characteristics of the selected studies are shown in Table 1 (More details are shown in Additional file 1). All selected articles were observational studies and published between 1970 and 2017. A total of 6,477,431 subjects were included with 241,056 HBV-infected subjects and 6,236,375 uninfected subjects. Among the Caucasian, Asian, and Black population, there were 23, six, and six studies, respectively. In addition, there were seven, seven, 17 and four study in high income, upper middle income, lower middle income and low income group, respectively. Furthermore, there were 12 studies in higher (HBV prevalence ≥ 5%) endemic and 23 studies in lower (HBV prevalence <5%) endemic areas, respectively. Meanwhile, there were 34 cross-sectional studies and one cohort study in the meta-analysis.

Table 1. Characteristics of the included studies.

Author	Income group	Race	Population	Sample size	HBV infection (n/%)				
					Total	A, non-A[a]	B, non-B[a]	AB, non-AB[a]	O, non-O[a]
Terrier, E.1970[26]	High	Caucasian	Blood donors	5968	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, M.1970[27]	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, W.1971[18]	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, S. J.1974[28]	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, T. G.1974[29]	Lower middle	Black	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, H. H.1975[30]	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, W.1975[19]	High	Caucasian	Blood donors	51019	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, M. R.1981 [31]	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, N.1985 [32]	Lower middle	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, A. G.1986 [33]	Lower middle	Black	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, A. S.1986 [34]	High	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, V. J.1989 [35]	Upper middle	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, C.2002 [36]	Low	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, S. K.2003[37]	Lower middle	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, A-H.2006 [38]	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, R.2008 [20]	Lower middle	Caucasian	Blood donors	20000	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-Zaman2009[39]	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, J. O.2011[40]	Lower middle	Black	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, M.2011 [41]	Upper middle	Caucasian	Blood donors	16695	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, A. A. 2012[42]	Lower 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, S.2013 [43]	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, B.2014 [44]	Upper 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, F.2014 [17]	Lower 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, J. S.2014 [45]	High	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, T. T.2014 [15]	Upper middle	Asian	General	78705	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, Y.2014 [46]	Lower 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
Siransy, L. K.2015[47]	Lower middle	Black	Blood donors	59514	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, D.2015 [48]	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, F. S.2016[49]	Lower middle	Black	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, M.2016 [50]	Upper middle	Black	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
Bharadva, S.2016 [51]	Lower middle	Caucasian	Blood donors	41909	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, Z.2016 [52]	High	Caucasian	Blood donors	228409	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, F. A.2017 [53]	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, J.2017 [16]	Lower middle	Asian	General	3827125	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, Z.2017 [54]	Low	Caucasian	Blood donors	41084	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

[a] 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.

The HBV infection prevalence in the 35 eligible articles ranged from 0.11% to 46.84%, and the HBV infection prevalence of blood group 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 Additional file 2, with 13 high quality studies and 22 moderate quality studies. The score of the 34 articles assessed by AHRQ ranged from 3 to 9, while 12 of them were of high-quality with a score from 8 to 9, and 22 of them were of moderate-quality with a score from 4 to 7. The article assessed by NOS scored 7 and was of high-quality.

Main, subgroup, and sensitivity analyses

Overall, the risk of HBV infection had decreased by 8% in subjects with blood group B when compared with blood group non-B (RR = 0.92, 95% CI: 0.86–0.98), while the risk of HBV infection had increased by 10% in subjects with blood group O when compared with blood group non-O (RR = 1.10, 95% CI: 1.02–1.19) (Table 2). However, blood groups A and AB were not significantly associated with an HBV infection risk (Table 2).

Table 2. The main, subgroup and sensitivity analyses.

Subgroup	No. of studies	B vs. Non-B		O vs. Non-O		A vs. Non-A		AB vs. Non-AB	
		RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
All studies	35	0.92 (0.86,0.98)	0.009	1.10 (1.02,1.19)	0.020	1.00 (0.94, 1.06)	0.987	1.03 (0.94,1.13)	0.493
HBV prevalence									
Higher endemic (≥5%)	12	0.89 (0.82,0.98)	0.018	1.16 (1.04,1.30)	0.007	0.96 (0.88,1.06)	0.459	0.99 (0.87,1.13)	0.864
Lower endemic (<5%)	23	0.93 (0.85,1.02)	0.126	1.06 (0.95,1.17)	0.306	1.03 (0.95,1.11)	0.471	1.06 (0.95,1.18)	0.292
Race									
Caucasian	23	0.96 (0.87, 1.05)	0.386	1.04 (0.94, 1.16)	0.465	1.03 (0.94, 1.13)	0.472	1.05 (0.93, 1.18)	0.461
Asian	6	0.91(0.85, 0.97)	0.003	1.15 (1.04, 1.27)	0.008	0.98 (0.97, 0.99)	0.000	0.93 (0.85, 1.01)	0.077
Black	6	0.76 (0.53, 1.10)	0.144	1.15 (0.79, 1.67)	0.456	0.96 (0.67, 1.36)	0.806	1.08 (0.65, 1.80)	0.760
Sample size									
≥2000	21	0.93 (0.87, 0.99)	0.025	1.10 (1.01, 1.21)	0.030	0.98 (0.93, 1.04)	0.516	0.99 (0.91, 1.08)	0.759
<2000	14	0.85 (0.64, 1.13)	0.275	1.08 (0.90, 1.29)	0398	1.07 (0.85, 1.33)	0.577	1.20 (0.89, 1.61)	0.238
Population									
General	6	0.93 (0.87, 0.99)	0.016	1.11 (0.99, 1.24)	0.078	0.98 (0.96, 1.00)	0.035	0.89 (0.88, 0.90)	0.000
Blood donors	27	0.89 (0.81, 0.98)	0.013	1.11 (0.99, 1.23)	0.070	1.00 (0.91, 1.10)	0.990	1.08 (0.95, 1.23)	0.218
Patients	2	0.86 (0.44, 1.70)	0.666	1.25 (0.73, 2.14)	0.422	0.92 (0.62, 1.36)	0.663	1.28 (0.76, 2.14)	0.357
Income group									
High	7	0.96 (0.91,1.00)	0.065	1.17 (0.95,1.44)	0.135	0.91 (0.74,1.11)	0.343	0.97 (0.84,1.13)	0.712
Upper middle	7	1.01 (0.88,1.17)	0.857	1.06 (0.89, 1.28)	0.512	1.00 (0.95,1.05)	0.981	0.99 (0.85,1.16)	0.943
Lower middle	17	0.86 (0.75,0.97)	0.014	1.03 (0.93,1.14)	0.630	1.12 (1.00,1.26)	0.044	1.14 (0.96,1.35)	0.142
Low	4	0.88 (0.56,1.38)	0.572	1.34 0.72, 2.48)	0.353	0.71 (0.42,1.21)	0.209	0.84 (0.43,1.64)	0.613
Study design									
Cross-sectional	34	0.91 (0.84, 0.98)	0.009	1.10 (1.01, 1.20)	0.031	1.00 (0.93,1.07)	0.958	1.06 (0.96, 1.17)	0.279
Cohort	1	0.96 (0.92, 1.01)	0.098	1.05 (1.01, 1.10)	0.016	1.00 (0.95, 1.05)	0.957	0.92 (0.84, 1.00)	0.053
Publication year									
Before 2010	17	0.80 (0.67, 0.96)	0.015	1.12 (0.97, 1.29)	0.112	1.02 (0.85, 1.22)	0.830	1.22 (1.01, 1.46)	0.040
After 2010	18	0.95 (0.88, 1.02)	0.146	1.09 (0.99, 1.20)	0.095	0.98 (0.93, 1.05)	0.601	0.97 (0.88, 1.06)	0.478
Sensitive analyses									
Removed Liu's study	34	0.91 (0.84, 0.98)	0.015	1.09 (1.00, 1.19)	0.041	1.00 (0.92, 1.08)	0.941	1.06 (0.96, 1.18)	0.242
Removed Mohammedali's study	34	0.91 (0.85, 0.97)	0.003	1.11 (1.03, 1.20)	0.008	0.99 (0.93, 1.06)	0.875	1.03 (0.94, 1.13)	0.526

RR: Risk ratio.

The results of the subgroup analyses are shown in Table 2. In 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 the higher endemic areas (HBV prevalence ≥ 5%), Asian people, studies with larger sample sizes (≥ 2000), general population and blood donors, lower middle income group, and articles published before 2010 years (Table 2). In addition, the relationship between blood group O and HBV infection also remained stable in the higher endemic areas (HBV prevalence ≥ 5%), Asian people, studies with larger sample sizes (≥ 2000) (Table 2).

In higher endemic areas, subjects with blood group B had a significantly lower risk of HBV infection (RR = 0.89, 95% CI: 0.82–0.98) than the non-B group (Figure 2A), while subjects with the blood group O had a significantly higher risk of HBV infection (RR = 1.16, 95% CI: 1.04–1.30) than the non-O group (Figure 2B). According to the race of the subjects, blood group O was also found to be linked with an increased risk of HBV infection (RR = 1.15, 95% CI: 1.04–1.27) in the Asian population, while blood groups A and B were linked with decreased risk of HBV infection when compared to non-A and non-B, respectively (OR = 0.91, 95%CI: 0.85–0.97; OR = 0.98, 95% CI: 0.97–0.99) (Table 2). However, no association was found among the Caucasian or Black population.

Insert Figure 2. Forest plots by prevalence: (**A**) B vs. non-B; (**B**) O vs. non-O.

In the sensitivity analysis, when the study of Jue Liu and Fatemeh Mohammadali, which dominated the results of the meta-analysis, were orderly removed, the pooled risk estimates were still stable (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 vs. non-A, B vs. non-B, and O vs. non-O (P = 0.219; P = 0.238; P = 0.537, respectively), while a publication bias of AB vs. non-AB was observed (P = 0.002) (Figure 3).

Insert Figure 3. Funnel plots: (**A**) A vs. non-A; (**B**) B vs. non-B; (**C**) O vs. non-O; and (**D**) AB vs. non-AB.

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, while blood group O was associated with a higher risk of HBV infection. The relationship between ABO blood group and HBV infection was observed in several subgroups, especially in higher endemic areas and in the Asian population, which gave supportive evidence that not only statistical association but also biologic 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 than those living in lower endemic areas, which might be the reason why the association between ABO blood group and HBV infection was only found in higher endemic areas but not in lower endemic areas.

The implementation of universal hepatitis B vaccination program for newborns was started in 1992 proposed by WHO. All the selected articles were published between 1970 and 2017, which meant that even in the same country, the prevalence of HBV infection has changed significantly due to increasing coverage of hepatitis B vaccination. However, no enough information could be extracted from the previous studies to compare the pooled association of ABO blood group and HBV infection between vaccinated group and unvaccinated group. To partially examine the impact of hepatitis B vaccination on the results, we did subgroup analyses according to publication year before and after 2010. Subjects in the selected articles were mainly people 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 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 type and HBV infection.

Our results were consistent with some previous studies of Lao et al.[15], Liu et al.[16] and Abate et al.[50] in high endemic areas, which showed that participants with blood group O were at higher risk of HBV infection. That means more measures should be taken to ensure the "universal" group-O blood safety in high endemic areas because of the large unvaccinated population among the main blood donors in current era and the window period for detection among the HBV-infected blood donors.[16] Interestingly, our result that blood group B was associated with a lower risk of HBV infection compared with blood group non-B was few reported explicitly by other studies, possibly because of the different analysis methods.

However, the study of Mohammadali et al.[17], with the second largest sample size, reported that HBV infection was lower in group-O donors, opposing to the study with the largest sample by Liu et al.,[16] probably due to the different geography and ethnicity. To examine the reliable and stable of the results, we orderly removed the study of Liu et al.[16] or Mohammadali et al.[17], and the results were still stable. Therefore, we still thought that these findings were worthy of consideration due to the subgroup analyses, the sensitive 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[16], associations have been observed most likely related to the altered immune response[15] and

systemic inflammatory response[14] associated with different blood group phenotypes. A previous study has reported that the appearance of intestinal alkaline phosphatase in the plasma was associated with the ABO blood group and secretor status, which may be due to genetically determined variations in the proportion of isoenzymes among the different blood types[55]. Our study may indicate that specific histo-bloodgroup antigen may be a natural resistance factor for HBV infection, and that probably provides clues for correlative fundamental researches of etiologies and novel therapeutic targets for HBV. Further studies are warranted to elucidate the association between blood group 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 analyzed studies lacked the basic information of 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, blood transfusion, and acupuncture, thus we were not able to conduct the corresponding subgroup analyses.

In conclusion, blood group B was associated with a lower risk of HBV infection, while blood group O was associated with a higher risk of HBV infection, especially in higher endemic areas and in the Asian population. Therefore, individuals with blood group O should be given more attention to reduce the incidence rate of HBV infection, particularly in clinical practice to ensure the safety of blood for recipients. Furthermore, more researches are needed to clarify the precise role of the ABO blood group in HBV infection to address the global question of HBV infection.

Supplementary

Additional file 1: Extracted Data from Included Studies. The number of HBV-infected and uninfected subjects in each blood group is provided.

Additional file 2: Quality assessment tables.

Abbreviations HBV, Hepatitis B virus; OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism; vs., versus; VWF, von Willebrand factor; HBsAg, hepatitis B surface antigen; Rh,

rhesus; RR, risk ratio; NOS, Newcastle-Ottawa Scales; AHRQ, Agency for Healthcare Research and Quality.

Contributions 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; and WJ wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Availability of data and material All data generated or analyzed during this study are included in this published article and its supplementary information files.

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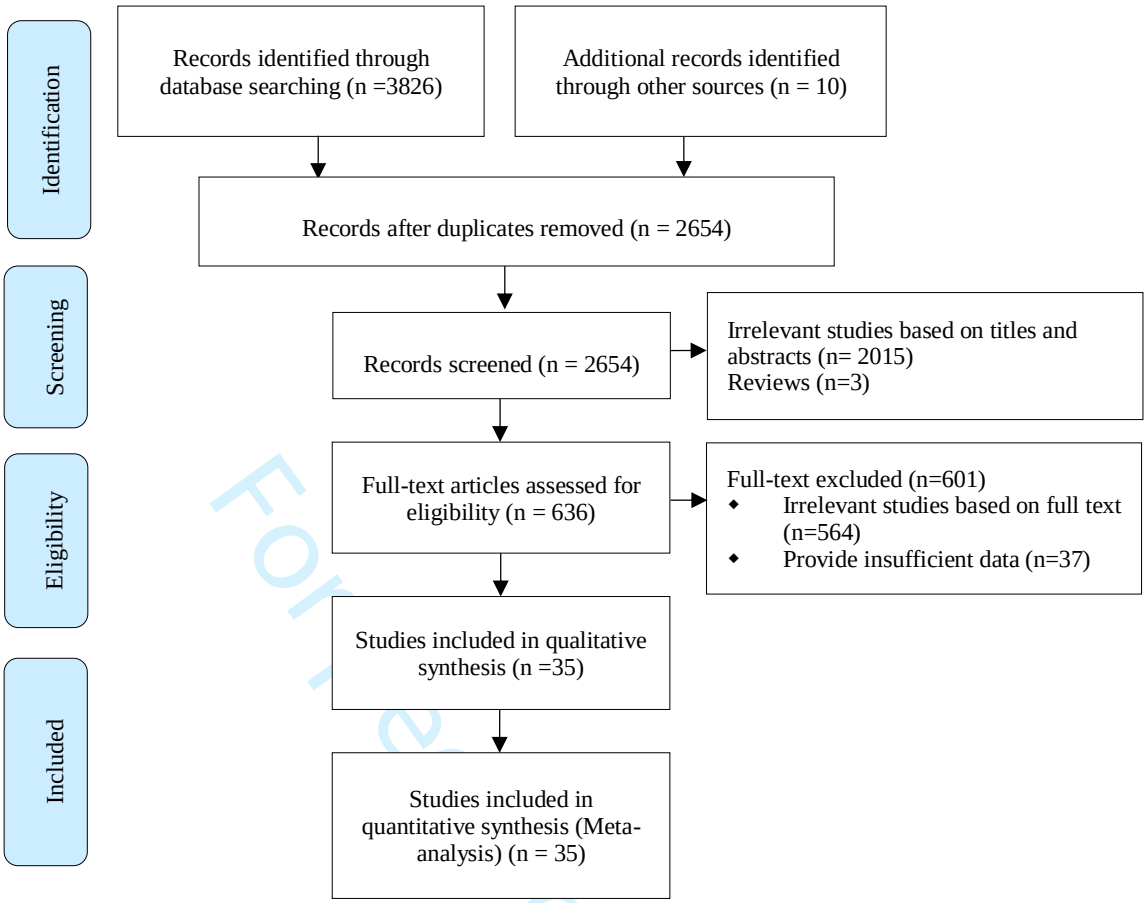

Figure 1. The process of study selection for the meta-analysis.

A

Study ID	RR (95% CI)	% Weight
<5%		
Terrier, E. (1970)	0.69 (0.25, 1.90)	0.39
Szmuness, W. (1971)	1.01 (0.67, 1.54)	1.90
Zuberi, S. J. (1974)	0.26 (0.10, 0.67)	0.46
Vale, T. G. (1974)	0.83 (0.36, 1.95)	0.54
Moore, H. H. (1975)	0.96 (0.77, 1.19)	4.61
Szmuness, W. (1975)	0.63 (0.25, 1.58)	0.47
Lenka, M. R. (1981)	0.78 (0.34, 1.78)	0.57
Nath, N. (1985)	0.75 (0.37, 1.49)	0.80
Sebastian, V. J. (1989)	0.81 (0.55, 1.21)	2.05
Zhu, C. (2002)	0.72 (0.49, 1.08)	2.07
Joshi, S. K. (2003)	1.04 (0.37, 2.92)	0.38
El-Gilany, A-H. (2006)	0.86 (0.53, 1.42)	1.44
Behal, R. (2008)	1.07 (0.88, 1.29)	5.21
Saeed Anwar, M. (2011)	0.75 (0.62, 0.92)	5.01
Tyagi, S. (2013)	0.73 (0.47, 1.13)	1.73
Sethi, B. (2014)	0.55 (0.28, 1.10)	0.80
Mohammadali, F. (2014)	1.06 (1.01, 1.11)	8.77
Nigam, J. S. (2014)	0.68 (0.34, 1.36)	0.80
Navolan, D. (2015)	1.39 (0.61, 3.16)	0.58
Bharadva, S. (2016)	1.04 (0.80, 1.36)	3.63
Naseri, Z. (2016)	1.28 (1.07, 1.51)	5.60
Memon, F. A. (2017)	1.13 (0.67, 1.89)	1.35
Batool, Z. (2017)	0.91 (0.79, 1.04)	6.57
Subtotal (I-squared = 50.0%, p = 0.004)	0.93 (0.85, 1.02)	55.71
>=5%		
Leski, M. (1970)	1.34 (0.55, 3.26)	0.50
Kulkarni, A. G. (1986)	0.28 (0.17, 0.45)	1.45
Naidu, A. S. (1986)	0.83 (0.59, 1.16)	2.66
Rifat-uz-Zaman (2009)	1.07 (0.71, 1.61)	1.99
Dirisu, J. O. (2011)	1.14 (0.89, 1.45)	3.97
Omar, A. A. (2012)	1.42 (0.90, 2.25)	1.64
Lao, T. T. (2014)	0.96 (0.91, 1.01)	8.82
Zhao, Y. (2014)	0.66 (0.39, 1.13)	1.28
Siransy, L. K. (2015)	0.97 (0.91, 1.04)	8.36
Bisetegen, F. S. (2016)	1.51 (0.76, 2.98)	0.82
Abate, M. (2016)	0.54 (0.41, 0.70)	3.54
Liu, J. (2017)	0.89 (0.88, 0.90)	9.26
Subtotal (I-squared = 82.7%, p = 0.000)	0.89 (0.81, 0.98)	44.29
Overall (I-squared = 76.3%, p = 0.000)	0.92 (0.86, 0.98)	100.00

NOTE: Weights are from random effects analysis

.103 1 9.7

B

Study ID	RR (95% CI)	% Weight
<5%		
Terrier, E. (1970)	3.36 (1.86, 6.07)	1.34
Szmuness, W. (1971)	0.96 (0.72, 1.29)	3.22
Zuberi, S. J. (1974)	2.63 (1.40, 4.96)	1.21
Vale, T. G. (1974)	0.84 (0.43, 1.66)	1.08
Moore, H. H. (1975)	0.99 (0.83, 1.18)	4.60
Szmuness, W. (1975)	1.12 (0.67, 1.87)	1.65
Lenka, M. R. (1981)	0.56 (0.19, 1.60)	0.50
Nath, N. (1985)	1.27 (0.80, 2.02)	1.90
Sebastian, V. J. (1989)	1.10 (0.79, 1.53)	2.86
Zhu, C. (2002)	1.20 (0.87, 1.66)	2.96
Joshi, S. K. (2003)	1.45 (0.56, 3.74)	0.60
El-Gilany, A-H. (2006)	1.34 (0.89, 2.02)	2.25
Behal, R. (2008)	0.99 (0.81, 1.21)	4.26
Saeed Anwar, M. (2011)	1.40 (1.17, 1.68)	4.52
Tyagi, S. (2013)	1.03 (0.68, 1.57)	2.16
Sethi, B. (2014)	1.09 (0.59, 2.02)	1.26
Mohammadali, F. (2014)	0.90 (0.86, 0.94)	5.83
Nigam, J. S. (2014)	1.41 (0.75, 2.67)	1.19
Navolan, D. (2015)	0.61 (0.27, 1.39)	0.77
Bharadva, S. (2016)	0.85 (0.64, 1.13)	3.35
Naseri, Z. (2016)	0.82 (0.70, 0.97)	4.70
Memon, F. A. (2017)	0.68 (0.40, 1.13)	1.65
Batool, Z. (2017)	0.93 (0.81, 1.07)	5.02
Subtotal (I-squared = 67.7%, p = 0.000)	1.06 (0.95, 1.17)	58.87
>=5%		
Leski, M. (1970)	0.92 (0.50, 1.68)	1.30
Kulkarni, A. G. (1986)	1.14 (0.86, 1.53)	3.24
Naidu, A. S. (1986)	0.71 (0.51, 0.99)	2.84
Rifat-uz-Zaman (2009)	1.10 (0.73, 1.68)	2.17
Dirisu, J. O. (2011)	0.94 (0.77, 1.16)	4.17
Omar, A. A. (2012)	1.44 (0.94, 2.20)	2.15
Lao, T. T. (2014)	1.05 (1.01, 1.10)	5.85
Zhao, Y. (2014)	1.60 (0.98, 2.62)	1.75
Siransy, L. K. (2015)	0.99 (0.94, 1.05)	5.76
Bisetegen, F. S. (2016)	0.90 (0.49, 1.66)	1.27
Abate, M. (2016)	2.36 (2.00, 2.79)	4.68
Liu, J. (2017)	1.19 (1.18, 1.20)	5.95
Subtotal (I-squared = 92.6%, p = 0.000)	1.16 (1.04, 1.30)	41.13
Overall (I-squared = 90.3%, p = 0.000)	1.10 (1.01, 1.19)	100.00

NOTE: Weights are from random effects analysis

.165 1 6.07

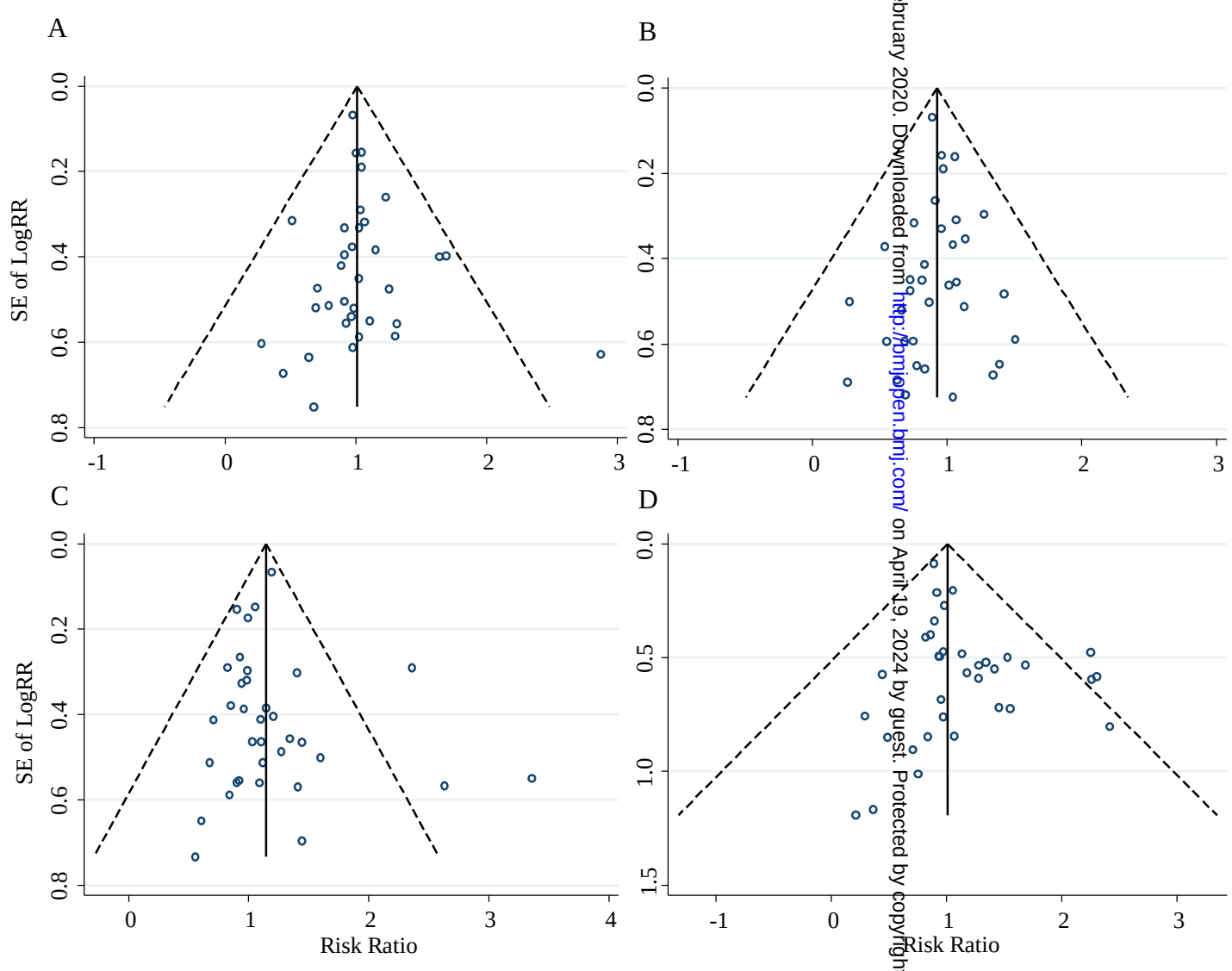

Figure 3. Funnel plots: (**A**) A vs. non-A; (**B**) B vs. non-B; (**C**) O vs. non-O; and (**D**) AB vs. non-AB.

Additional file 1:

Table S1: The number of HBV-infected and uninfected subjects in each blood group.

Author	A HBsAg+	A HBsAg-	B HBsAg+	B HBsAg-	AB HBsAg+	AB HBsAg-	O HBsAg+	O HBsAg-
Terrier, E.1970[26]	9	2452	4	605	2	255	40	2601
Leski, M.1970[27]	16	53	4	10	0	5	14	53
Szmuness, W.1971[18]	61	2893	25	1104	13	351	78	3571
Zuberi, S. J.1974[28]	9	259	5	402	2	53	22	359
Vale, T. G.1974[29]	18	303	6	140	5	104	11	249
Moore, H. H.1975[30]	127	3519	103	3109	17	532	248	7261
Szmuness, W.1975[19]	22	19530	5	6633	4	2468	27	22330
Lenka, M. R.1981 [31]	12	117	8	188	0	43	4	128
Nath, N.1985 [32]	22	524	9	260	3	69	34	664
Kulkarni, A. G.1986 [33]	51	338	17	530	18	78	79	749
Naidu, A. S.1986 [34]	49	195	42	297	11	51	43	341
Sebastian, V. J.1989 [35]	30	690	30	828	10	200	64	1424
Zhu, C.2002 [36]	44	2671	30	2158	18	678	61	3023
Joshi, S. K.2003[37]	4	187	5	170	1	46	7	193
El-Gilany, A-H.2006 [38]	27	763	19	475	12	192	35	634
Behal, R.2008 [20]	106	4512	174	7252	38	1994	132	5792
Rifat-uz-Zaman2009[39]	5	161	35	493	23	306	30	411
Dirisu, J. O.2011[40]	32	38	39	36	1	2	128	151
Saeed Anwar, M.2011 [41]	103	3856	139	5871	17	627	208	5874
Omar, A. A. 2012[42]	15	105	21	77	3	53	32	124
Tyagi, S.2013 [43]	27	1415	27	2096	9	445	32	1949
Sethi, B.2014 [44]	15	2480	10	2446	11	850	14	2058
Mohammadali, F.2014 [17]	2553	638825	1952	481845	627	153900	2707	745659
Nigam, J. S.2014 [45]	12	1011	11	1462	2	399	15	1216
Lao, T. T.2014 [15]	2038	18543	1991	18753	468	4670	3289	28953
Zhao, Y.2014 [46]	17	135	16	147	15	75	18	77
Siransy, L. K.2015[47]	947	12299	941	12943	187	2575	2044	27578
Navolan, D.2015 [48]	15	606	7	218	4	109	7	419
Bisetegen, F. S.2016[49]	7	97	10	67	2	7	18	182
Abate, M.2016 [50]	114	1901	54	936	9	202	470	3141
Bharadva, S.2016 [51]	62	9784	85	14548	22	3974	68	13366
Naseri, Z.2016 [52]	208	72275	180	53450	42	17213	210	84831
Memon, F. A.2017 [53]	15	1077	21	1350	9	297	21	1893
Liu, J.2017 [16]	64811	1103922	58286	1067812	18707	351184	73651	1088752
Batool, Z.2017 [54]	321	11468	289	12787	82	3771	277	12089

Additional file 2:

Table S2-1: Agency for Healthcare Research and Quality table.

Author	1	2	3	4	5	6	7	8	9	10	11	Total
Terrier, E.1970[26]	Y	N	N	U	U	Y	/	N	/	Y	Y	4
Leski, M.1970[27]	Y	N	Y	N	U	Y	N	N	/	Y	Y	5
Szmuness, W.1971[18]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zuberi, S. J.1974[28]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Vale, T. G.1974[29]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Moore, H. H.1975[30]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Szmuness, W.1975[19]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8
Lenka, M. R.1981 [31]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Nath, N.1985 [32]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Kulkarni, A. G.1986 [33]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Naidu, A. S.1986 [34]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Sebastian, V. J.1989 [35]	Y	N	N	N	U	Y	/	N	N	Y	Y	4
Zhu, C.2002 [36]	Y	N	Y	Y	U	Y	N	N	N	N	Y	5
Joshi, S. K.2003[37]	Y	Y	Y	N	U	Y	/	N	/	Y	Y	6
El-Gilany, A-H.2006 [38]	Y	Y	Y	N	U	Y	/	N	Y	N	Y	6
Behal, R.2008 [20]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Rifat-uz-Zaman2009[39]	Y	Y	Y	/	U	N	/	N	Y	Y	Y	6
Dirisu, J. O.2011[40]	Y	Y	Y	Y	U	Y	/	N	/	Y	Y	7
Saeed Anwar, M.2011 [41]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Omar, A. A. 2012[42]	Y	N	Y	N	U	Y	/	N	/	Y	Y	5
Tyagi, S.2013 [43]	Y	Y	Y	N	U	Y	/	N	Y	Y	Y	7
Sethi, B.2014 [44]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Mohammadali, F.2014 [17]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Nigam, J. S.2014 [45]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zhao, Y.2014 [46]	Y	N	Y	N	U	Y	/	N	Y	Y	Y	6
Siransy, L. K.2015[47]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8
Navolan, D.2015 [48]	Y	Y	N	N	U	Y	N	N	N	Y	Y	5
Bisetegen, F. S.2016[49]	Y	Y	Y	N	U	Y	/	N	N	Y	Y	6
Abate, M.2016 [50]	Y	N	Y	Y	U	Y	/	N	Y	Y	Y	7
Bharadva, S.2016 [51]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Naseri, Z.2016 [52]	Y	N	Y	Y	U	Y	/	N	Y	Y	Y	7
Memon, F. A.2017 [53]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Liu, J.2017 [16]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	9
Batool, Z.2017 [54]	Y	Y	Y	Y	U	Y	U	N	U	N	Y	6

Y, Yes; N, No; U, Unclear; /, not applicable.

Table S2-2: Newcastle-Ottawa Scales table.

Author	Year	Selection	Comparability	Outcome	Total
T. T. Lao 2014[15]	2014	3	1	3	7

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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Title page

Title: ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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 December 1, 2019 were identified by searching PubMed, EMBASE, Web of Science, ScienceDirect, and the Cochrane Library.

Eligibility criteria All cross-sectional or cohort studies that 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% confidence intervals (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 blood group non-B (RR = 0.92, 95% CI: 0.86–0.98). In the subgroup analyses, the inverse relationship between blood group B and HBV infection remained stable in higher endemic areas (HBV prevalence ≥ 5%), Asian people, larger sample size studies (≥ 2000), general population and blood donors, lower middle income group and studies published before 2010 years. Additionally, subjects with blood group O had a 12% increased risk of HBV infection (RR = 1.12, 95% CI:1.01-1.24) 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 researches are needed to clarify the precise role of ABO blood group in HBV infection to address the global question of HBV infection.

Strengths and limitations of this study

- The breadth of the comprehensive systematic literature search is a strength of this study.

- To our knowledge, this was 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.

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 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 not only statistically but also biologically associated with many chronic diseases such as vascular disease,[6] coronary heart disease,[7] 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 (vs.) 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 hepatocellular carcinoma (HCC) patients 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, and human immunodeficiency virus, etc.) has been shown in several studies.[5,13] Previous studies have found the reasons for this association were that 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 response,[14,15] which means the biologic association between ABO blood groups and HBV infection probably exist.

Epidemiologic 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 hepatitis B surface antigen (HBsAg) was lower in donors who had 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 December 1, 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 are shown in 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 number 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; and (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 (e.g., 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; and (4) the author's general conclusions.

The quality of selected cohort studies were 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 were 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 (defining 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% confidence intervals (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 of random-effect models with the estimate of heterogeneity being taken from the Mantel-Haenszel model, and $P < 0.05$ was deemed significantly. Meanwhile, I^2 was used to evaluate heterogeneity among the studies. 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 size 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 $P < 0.05$ was deemed significantly. All statistical analyses were performed with STATA version 12.0.

Patient and public involvement

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

Results

Study selection and study characteristics

A total of 4486 articles (4476 from database and 10 from other sources) were searched, of which 1584 were duplicate results. After reading the abstracts, 2211 were deemed irrelevant and three 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 was shown as Figure 1.

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

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 6,487,481 subjects were included with 241,868 HBV-infected subjects and 6,245,613 uninfected subjects. Among the Caucasian, Asian, and African population, there were 23, 7, and 8 studies, respectively. In addition, there were 7, 9, 18 and 4 study in high income, upper middle income, lower middle income and low income group, respectively. Furthermore, there were 14 studies in higher (HBV prevalence ≥5%) endemic and 24 studies in lower (HBV prevalence <5%) endemic areas, respectively. Meanwhile, there were 37 cross-sectional studies and 1 cohort study in the meta-analysis.

Table 1. Characteristics of the included studies.

Author	Income group	Race	Population	Sample size	HBV infection (n/%)				
					Total	A, non-A[a]	B, non-B[a]	AB, non-AB[a]	O, non-O[a]
Terrier, E.1970[27]	High	Caucasian	Blood donors	5968	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, M.1970[28]	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, W.1971[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, S. J.1974[29]	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, T. G.1974[30]	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, H. H.1975[31]	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, W.1975[20]	High	Caucasian	Blood donors	51019	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, M. R.1981 [32]	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, N.1985 [33]	Lower middle	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, A. G.1986 [34]	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, A. S.1986 [35]	High	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, V. J.1989 [36]	Upper middle	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, C.2002 [37]	Low	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, S. K.2003[38]	Lower middle	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, A-H.2006 [39]	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, R.2008 [21]	Lower middle	Caucasian	Blood donors	20000	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-Zaman2009[40]	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, J. O.2011[41]	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, M.2011 [42]	Upper middle	Caucasian	Blood donors	16695	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, A. A. 2012[43]	Lower 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, S.2013 [44]	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, B.2014 [45]	Upper 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, F.2014 [18]	Lower 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, J. S.2014 [46]	High	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, T. T.2014 [16 b]	Upper middle	Asian	General	78705	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, Y.2014 [47]	Lower 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
Siransy, L. K.2015[48]	Lower middle	African	Blood donors	59514	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, D.2015 [49]	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, F. S.2016[50]	Lower middle	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, M.2016 [51]	Upper middle	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
Bharadva, S.2016 [52]	Lower middle	Caucasian	Blood donors	41909	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, Z.2016 [53]	High	Caucasian	Blood donors	228409	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, F. A.2017 [54]	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, J.2017 [17]	Lower middle	Asian	General	3827125	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, Z.2017 [55]	Low	Caucasian	Blood donors	41084	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, C-D.2018[56]	Upper middle	African	Blood donors	4744	81/1.71	-	-	-	34/1.22, 47/2.41
Fu, X.2018[57]	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, C.2019[58]	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

[a] 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. [b] A cohort study.

The HBV infection prevalence in the 38 eligible articles ranged from 0.11% to 46.84%, and the HBV infection prevalence of blood group 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 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. The article assessed by NOS scored 7 and was of high-quality.

Main, subgroup, and sensitivity analyses

Overall, the risk of HBV infection had decreased by 8% in subjects with blood group B when compared with blood group non-B (RR = 0.92, 95% CI: 0.86–0.98). However, blood groups A, O and AB were not significantly associated with an HBV infection risk (Table 2). The results of the subgroup analyses are shown in Table 2. In 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 the higher endemic areas (HBV prevalence ≥ 5%), Asian people, studies with larger sample sizes (≥ 2000), general population and blood donors, lower middle income group, and articles published before 2010 years (Table 2).

Table 2. The main, subgroup and sensitivity analyses.

Subgroup	No. of studies	Sample size	B vs. Non-B		O vs. Non-O		A vs. Non-A		AB vs. Non-AB	
			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 (0.86,0.98)	0.007	1.07 (0.99,1.15)	0.082	1.01 (0.96, 1.07)	0.728	1.04 (0.95,1.13)	0.419
HBV prevalence										
Higher endemic (≥5%)	14	3983732	0.90 (0.83,0.98)	0.013	1.12 (1.01,1.24)	0.025	0.99 (0.91,1.08)	0.820	1. 00 (0.89,1.14)	0.962
Lower endemic (<5%)	24	2503749	0.93 (0.85,1.02)	0.126	1.03 (0.93,1.15)	0.566	1.03 (0.95,1.11)	0.471	1.06 (0.95,1.18)	0.292
Race										
Caucasian	23	2488675	0.96 (0.87, 1.05)	0.386	1.04 (0.94, 1.16)	0.465	1.03 (0.94, 1.13)	0.472	1.05 (0.93, 1.18)	0.461
Asian	7	3920902	0.91(0.86, 0.97)	0.003	1.10 (0.99, 1.22)	0.075	0.98 (0.97, 0.99)	<0. 001	0.96 (0.87, 1.06)	0.451
African	8	77904	0.78 (0.58, 1.05)	0.099	1.04 (0.77, 1.40)	0.803	0.99 (0.73, 1.33)	0.919	1.02 (0.62, 1.67)	0.953
Sample size										
≥2000	24	6475196	0.93 (0.87, 0.99)	0.018	1.07 (0.98, 1.16)	0.135	0.99 (0.94, 1.05)	0.795	1.00 (0.92, 1.08)	0.914
<2000	14	12285	0.85 (0.64, 1.13)	0.275	1.08 (0.90, 1.29)	0.398	1.07 (0.85, 1.33)	0.577	1.20 (0.89, 1.61)	0.238
Population										
General	6	3910128	0.93 (0.87, 0.99)	0.016	1.07 (0.99, 1.15)	0.078	0.98 (0.96, 1.00)	0.035	0.89 (0.88, 0.90)	<0.001
Blood donors	29	2574698	0.89 (0.81, 0.97)	0.011	1.08 (0.97, 1.20)	0.154	1.01 (0.92, 1.10)	0.885	1.08 (0.95, 1.23)	0.248
Patients	3	2655	0.92 (0.71, 1.19)	0.517	1.04 (0.71, 1.54)	0.828	1.09 (0.91, 1.30)	0.345	1.17 (0.94, 1.46)	0.169
Income group										
High	7	148804	0.96 (0.91,1.00)	0.065	1.17 (0.95,1.44)	0.135	0.91 (0.74,1.11)	0.343	0.97 (0.84,1.13)	0.712
Upper middle	9	6101344	1.01 (0.88,1.15)	0.927	0.97 (0.82, 1.15)	0.756	1.00 (0.96,1.06)	0.791	1.02 (0.88,1.17)	0.814
Lower middle	18	214587	0.86 (0.76,0.97)	0.011	1.03 (0.93,1.13)	0.582	1.13(1.01,1.25)	0.030	1.13 (0.95,1.34)	0.173
Low	4	22746	0.88 (0.56,1.38)	0.572	1.34 0.72, 2.48)	0.353	0.71 (0.42,1.21)	0.209	0.84 (0.43,1.64)	0.613
Study design										
Cross-sectional	37	6408776	0.91 (0.85, 0.97)	0.007	1.07 (0.98, 1.17)	0.111	1.01 (0.95,1.08)	0.780	1.06 (0.96, 1.17)	0.244
Cohort	1	78705	0.96 (0.92, 1.01)	0.098	1.05 (1.01, 1.10)	0.016	1.00 (0.95, 1.05)	0.957	0.92 (0.84, 1.00)	0.053
Publication year										
Before 2010	17	123268	0.80 (0.67, 0.96)	0.015	1.12 (0.97, 1.29)	0.112	1.02 (0.85, 1.22)	0.830	1.22 (1.01, 1.46)	0.040
After 2010	21	6364213	0.95 (0.88, 1.01)	0.106	1.05 (0.95, 1.15)	0.335	1.00 (0.94, 1.06)	0.910	0.98 (0.89, 1.07)	0.627
Sensitive analyses										
Removed Liu's study[17]	37	2660356	0.91 (0.85, 0.98)	0.012	1.06 (0.98, 1.15)	0.138	1.01 (0.94, 1.08)	0.816	1.06 (0.97, 1.17)	0.213
Removed Mohammedali's study[18]	37	4459413	0.91 (0.85, 0.97)	0.002	1.08 (1.00, 1.16)	0.044	1.01 (0.94, 1.07)	0.857	1.04 (0.95, 1.14)	0.445
Removed both Liu's and Mohammedali's study[17,18]	36	632288	0.90 (0.83, 0.97)	0.007	1.07 (0.98, 1.17)	0.115	1.00 (0.92, 1.09)	0.946	1.08 (0.96, 1.20)	0.211

RR: Risk ratio.

In higher endemic areas, subjects with blood group B had a significantly lower risk of HBV infection (RR = 0.90, 95% CI: 0.83–0.98) than the non-B group (Figure 2A), while subjects with the blood group O had a significantly higher risk of HBV infection (RR = 1.12, 95% CI: 1.01–1.24) than the non-O group (Figure 2B). According to the race of the subjects, blood group A and B were linked with decreased risk of HBV infection in the Asian population when compared to non-A and non-B, respectively (OR = 0.98, 95%CI: 0.97–0.99; OR = 0.91, 95% CI: 0.86–0.97) (Table 2). However, no association was found among

the Caucasian or African population. In general population, blood group A, B and AB had a decreased risk of HBV infection compared to non-A, non-B and non-AB, respectively (OR = 0.98, 95%CI: 0.96–1.00; OR = 0.93, 95% CI: 0.87–0.99 and OR = 0.89, 95% CI: 0.88–0.90, respectively) (Table 2).

Insert Figure 2. Forest plots by prevalence: (**A**) B vs. non-B; (**B**) O vs. non-O.

In the sensitivity analysis, when the study of 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 vs. non-A, B vs. non-B, and O vs. non-O (P = 0.148; P = 0.223; P = 0.364, respectively), while a publication bias of AB vs. non-AB was observed (P = 0.002) (Figure 3).

Insert Figure 3. Funnel plots: (**A**) A vs. non-A; (**B**) B vs. non-B; (**C**) O vs. non-O; and (**D**) AB vs. non-AB.

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 subgroups and still stable in sensitive analyses, giving supportive evidence that not only statistical association but also biologic 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 than those living in lower endemic areas, which might be the reason why the association between ABO blood group and 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 region.

The implementation of universal hepatitis B vaccination program for newborns was started in 1992 proposed by WHO. All the selected articles were published between 1970 and 2019, which meant that even in the same country, the prevalence of HBV infection has changed significantly due to increasing coverage of hepatitis B vaccination. However, no enough information could be extracted from the previous studies to compare the pooled association of ABO blood group and HBV infection between vaccinated group and unvaccinated group. To partially examine the impact of hepatitis B vaccination on the results, we did subgroup analyses according to publication year before and after 2010. Subjects in the selected articles were mainly people 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 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 type and HBV infection.

Our results found that subjects with blood group O were at higher risk of HBV infection in higher endemic areas, which was consistent with some previous studies of Lao et al.[16], Liu et al.[17] and Abate et al.[51] That means more measures should be taken to ensure the "universal" group-O blood safety in high endemic areas because of the large unvaccinated population among the main blood donors in current era and the window period for detection among the HBV-infected blood donors.[17] However, this relationship was unobserved in other subgroup analysis, so whether this relationship was true remains to be further explored. Interestingly, our result that blood group B was associated with a lower risk of HBV infection compared with blood group non-B was few reported explicitly by other studies, possibly because of the different analysis methods, such as the different reference of blood group in analysis.

However, the study of Mohammadali et al.[18], with the second largest sample size, reported that HBV infection was lower in group-O donors, opposing 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 the recently meta-analysis, which found that HCC patients might have a lower proportion of O subjects than healthy subjects.[12] The possible explanation for the inconsistence is the long-term and complicated process from HBV infection to the occurrence of HCC. To examine the reliable and stable of the results, we orderly removed the study of Liu et al.[17] or Mohammadali et al.[18], as well as removed both of them at the same time. In the sensitive analysis, the relationship between blood group O and HBV infection may be unstable. However, the inverse relationship between blood group B and HBV infection

was extremely stable. Therefore, we still thought that these findings were worthy of consideration due to the subgroup analyses, the sensitive 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 most likely related to the altered immune response[16] and systemic inflammatory response[15] associated with different blood group phenotypes. A previous study has reported that the appearance of intestinal alkaline phosphatase in the plasma was associated with the ABO blood group and secretor status, which may be due to genetically determined variations in the proportion of isoenzymes among the different blood types[59]. Our study may indicate that specific histo-bloodgroup antigen may be a natural resistance factor for HBV infection, and that probably provides clues for correlative fundamental researches of etiologies and novel therapeutic targets for HBV. Further studies are warranted to elucidate the association between blood group 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 analyzed studies lacked the basic information of 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 was associated with a lower risk of HBV infection. In the future, more researches are needed to clarify the precise role of the ABO blood group in HBV infection to address the global question of HBV infection.

Supplementary

Additional file 1: The electronic search strategy for PubMed.

Additional file 2: Quality assessment tables.

Abbreviations HBV, Hepatitis B virus; OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism; vs., versus; VWF, von Willebrand factor; HBsAg, hepatitis B surface antigen; Rh,

rhesus; RR, risk ratio; NOS, Newcastle-Ottawa Scales; AHRQ, Agency for Healthcare Research and Quality.

Contributions 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; and WJ wrote the manuscript. All authors read and approved the final manuscript.

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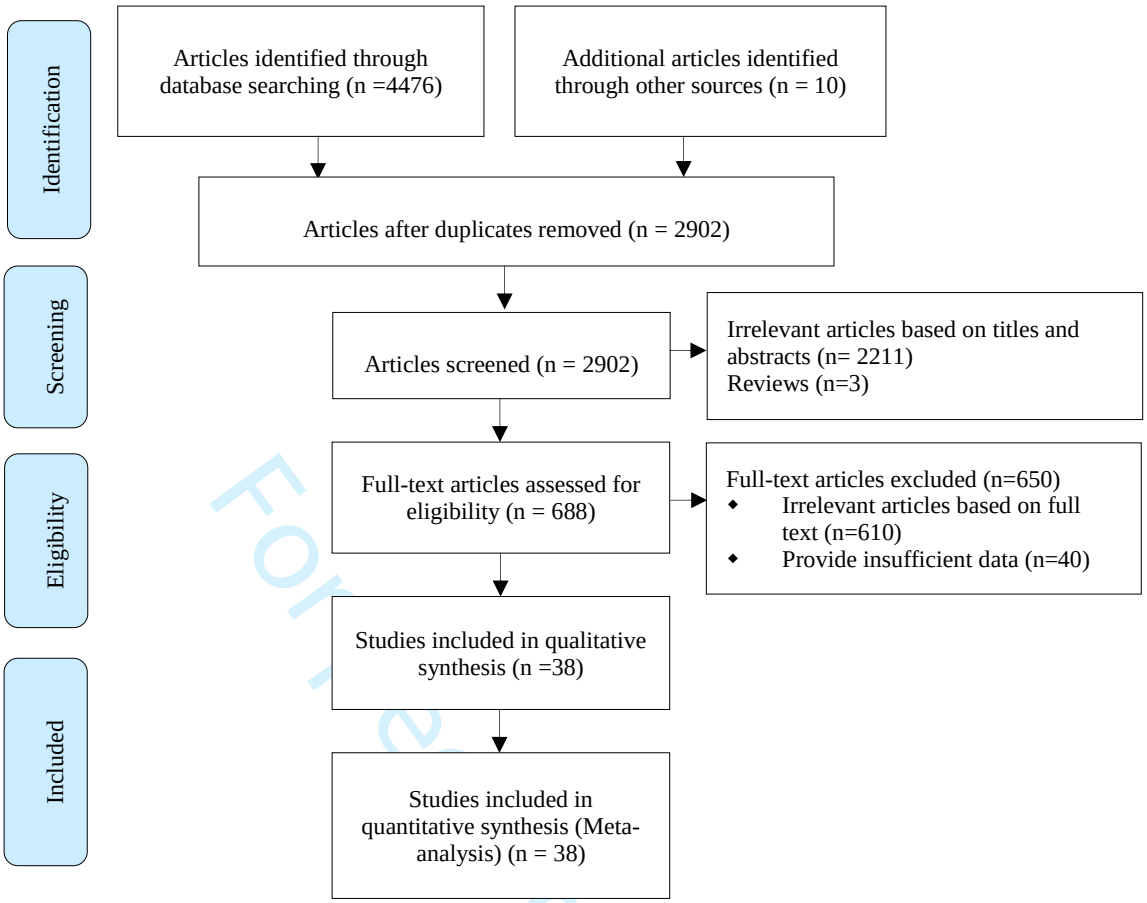

Figure 1. The process of study selection for the meta-analysis.

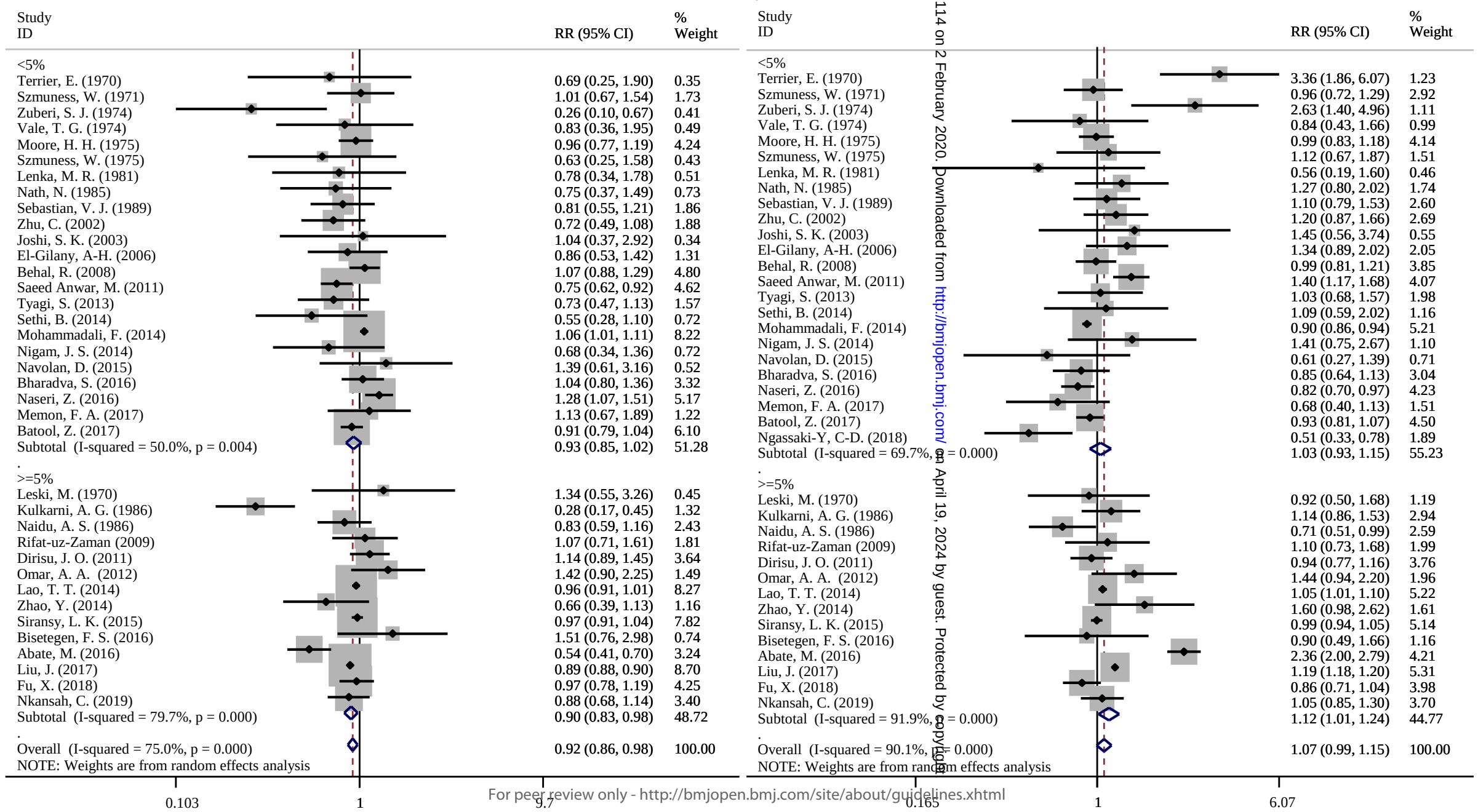

Figure 2. Forest plots by prevalence: (**A**) B vs. non-B; (**B**) O vs. non-O.

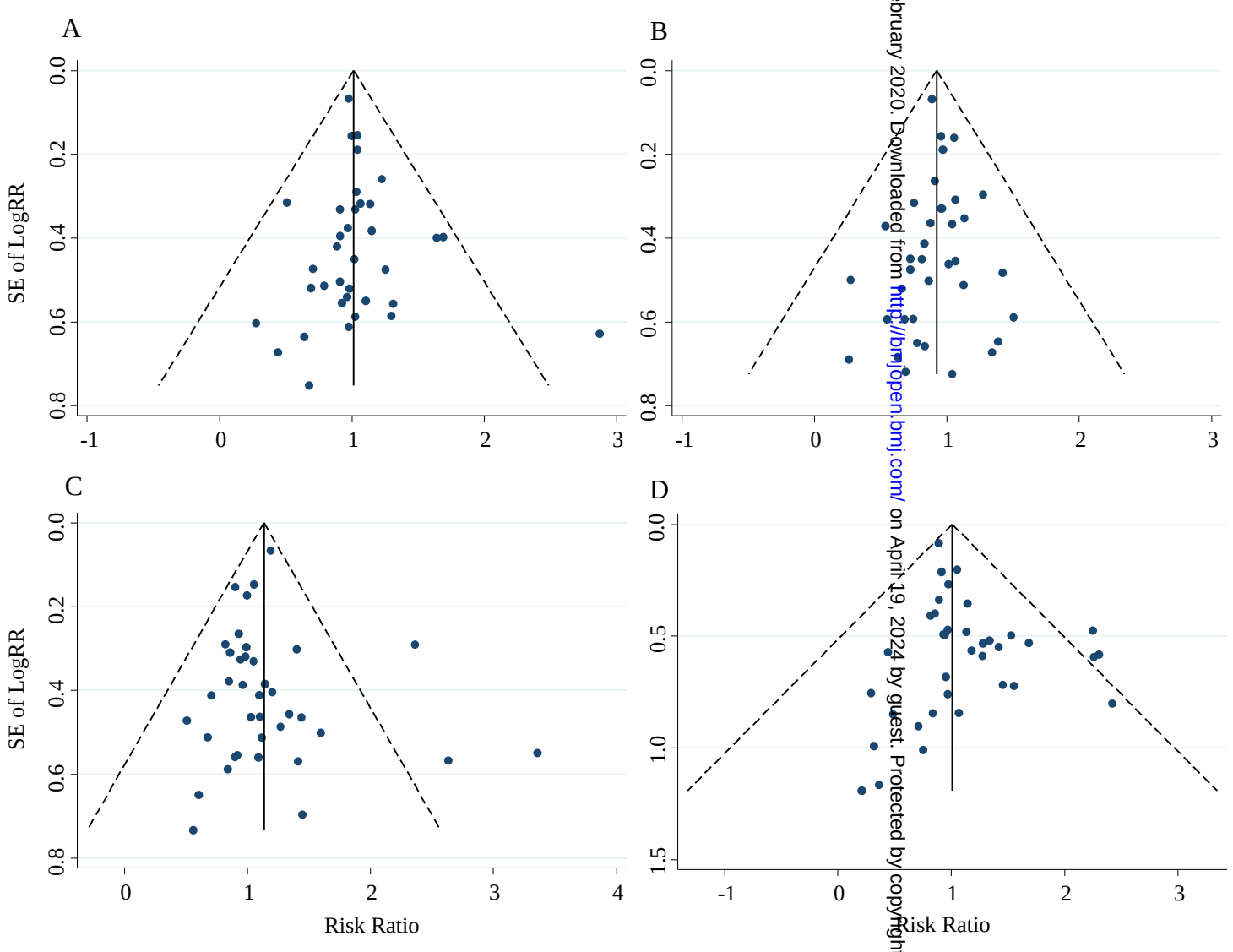

Figure 3. Funnel plots: (**A**) A vs. non-A; (**B**) B vs. non-B; (**C**) O vs. non-O; and (**D**) AB vs. non-AB.

Additional file 1:

The electronic search strategy for PubMed：

(((((((hepatitis B[MeSH Terms]) OR hepatitis B virus[MeSH Terms]) OR Hepatitis B Surface Antigens[MeSH Terms]) OR hepatitis B[Text Word]) OR hepatitis B virus[Text Word]) OR HBV[Text Word]) OR HBsAg[Text Word]) AND ("0001/01/01"[PDat] : "2019/11/30"[PDat]) AND (((((((ABO Blood-Group System[MeSH Terms]) OR Rh-Hr Blood-Group System[MeSH Terms]) OR blood type[Text Word]) OR blood group[Text Word]) OR ABO[Text Word]) OR Rh[Text Word]) OR rhesus[Text Word]) AND ("0001/01/01"[PDat] : "2019/11/30"[PDat])

Additional file 2:

Table S1-1: Quality assessment for cross-sectional studies by Agency for Healthcare Research and Quality table.

Author	1	2	3	4	5	6	7	8	9	10	11	Total
Terrier, E.1970[27]	Y	N	N	U	U	Y	/	N	/	Y	Y	4
Leski, M.1970[28]	Y	N	Y	N	U	Y	N	N	/	Y	Y	5
Szmuness, W.1971[19]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zuberi, S. J.1974[29]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Vale, T. G.1974[30]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Moore, H. H.1975[31]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Szmuness, W.1975[20]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8
Lenka, M. R.1981 [32]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Nath, N.1985 [33]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Kulkarni, A. G.1986 [34]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Naidu, A. S.1986 [35]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Sebastian, V. J.1989 [36]	Y	N	N	N	U	Y	/	N	N	Y	Y	4
Zhu, C.2002 [37]	Y	N	Y	Y	U	Y	N	N	N	N	Y	5
Joshi, S. K.2003[38]	Y	Y	Y	N	U	Y	/	N	/	Y	Y	6
El-Gilany, A-H.2006 [39]	Y	Y	Y	N	U	Y	/	N	Y	N	Y	6
Behal, R.2008 [21]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Rifat-uz-Zaman2009[40]	Y	Y	Y	/	U	N	/	N	Y	Y	Y	6
Dirisu, J. O.2011[41]	Y	Y	Y	Y	U	Y	/	N	/	Y	Y	7
Saeed Anwar, M.2011 [42]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Omar, A. A. 2012[43]	Y	N	Y	N	U	Y	/	N	/	Y	Y	5
Tyagi, S.2013 [44]	Y	Y	Y	N	U	Y	/	N	Y	Y	Y	7
Sethi, B.2014 [45]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Mohammadali, F.2014 [18]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Nigam, J. S.2014 [46]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zhao, Y.2014 [47]	Y	N	Y	N	U	Y	/	N	Y	Y	Y	6
Siransy, L. K.2015[48]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8
Navolan, D.2015 [49]	Y	Y	N	N	U	Y	N	N	N	Y	Y	5
Bisetegen, F. S.2016[50]	Y	Y	Y	N	U	Y	/	N	N	Y	Y	6
Abate, M.2016 [51]	Y	N	Y	Y	U	Y	/	N	Y	Y	Y	7
Bharadva, S.2016 [52]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Naseri, Z.2016 [53]	Y	N	Y	Y	U	Y	/	N	Y	Y	Y	7
Memon, F. A.2017 [54]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Liu, J.2017 [17]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	9
Batool, Z.2017 [55]	Y	Y	Y	Y	U	Y	U	N	U	N	Y	6
Ngassaki-Y, C-D.2018[56]	Y	Y	Y	Y	U	Y	/	N	/	Y	Y	7
Fu, X.2018[57]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Nkansah, C.2019[58]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8

Y, Yes; N, No; U, Unclear; /, not applicable.

Note:

Item 1: Define the source of information (survey, record review).

Item 2: List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications.
Item 3: Indicate time period used for identifying patients.
Item 4: Indicate whether or not subjects were consecutive if not population-based.
Item 5: Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants.
Item 6: Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements).
Item 7: Explain any patient exclusions from analysis.
Item 8: Describe how confounding was assessed and/or controlled.
Item 9: If applicable, explain how missing data were handled in the analysis.
Item 10: Summarize patient response rates and completeness of data collection.
Item 11: Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.

Table S1-2: Quality assessment for cohort studies by Newcastle-Ottawa Scales table.

Author	Selection	Comparability	Outcome	Total
T. T. Lao 2014[16]	3	1	3	7

Note:
Selection: 1) Representativeness of the exposed cohort; 2) Selection of the non-exposed cohort; 3) Ascertainment of exposure; 4) Demonstration that outcome of interest was not present at start of study.
Comparability: 1) Comparability of cohorts on the basis of the design or analysis.
Outcome: 1) Assessment of outcome; 2) Was follow-up long enough for outcomes to occur; 3) Adequacy of follow up of cohorts.

Meta-analysis of Observational Studies in Epidemiology (MOOSE) Checklist

ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Controversy remains with regard to whether blood group is related to HBV infection and which antigen is a protective or a risk factor.
√	Hypothesis statement	We performed a systematic review and meta-analysis to elucidate the association between ABO blood groups and HBV infection risk.
√	Description of study outcomes	HBV infection
√	Type of exposure or intervention used	ABO blood group
√	Type of study designs used	Cross-sectional or cohort studies
√	Study population	Unrestricted
Reporting of search strategy should include		
√	Qualifications of searchers	Two reviewers (SZ and WJ) searched for articles independently.
√	Search strategy, including time period included in the synthesis and keywords	Available online before December 1, 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”.
√	Effort to include all available studies	Highly relevant reference articles were also searched by reviewing the list of references.
√	Databases and registries searched	PubMed, EMBASE, Web of Science, ScienceDirect, and Cochrane Central
√	Search software used, name and version, including special features	We did not employ a search software. Endnote was used to merge retrieved citations.
√	Use of hand searching	Highly relevant reference articles were also searched by reviewing the list of references.
√	List of citations located and those excluded, including justifications	Figure 1
√	Method of addressing articles published in languages other than English	There was no limitation of language.
√	Method of handling abstracts and unpublished studies	We did not include unpublished studies. If abstract could provide full information, it was included.
√	Description of any contact with authors	When needed, we contacted the original author

		for the data, but nobody responded to us.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the paper.
√	Rationale for the selection and coding of data	(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 (e.g., 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; and (4) the author's general conclusions.
√	Documentation of how data were classified and coded	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 Negroid 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.
√	Assessment of confounding	Subgroup analyses were performed by HBV prevalence, race, sample size, population, income group, study type, and publication year.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The quality of selected cohort studies were assessed using the Newcastle-Ottawa Scales (NOS). The quality of the selected cross-sectional studies were assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ).
√	Assessment of heterogeneity	I^2 was used to evaluate heterogeneity among the studies. When $I^2 \leqslant 50\%$, the included studies were considered to have little heterogeneity; when $I^2 > 50\%$, the included studies were considered to have substantial heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	RRs and 95% CIs (A vs. non-A, B vs. non-B, O vs. non-O, AB vs. non-AB) were pooled by using of random-effect models with the estimate of heterogeneity being taken from the Mantel-Haenszel model, and $P < 0.05$ was

		deemed significantly.
√	Provision of appropriate tables and graphics	Figure 2,3 and Table 2
Reporting of results should include		
√	Graphic summarizing individual study estimates and overall estimate	Table 1 and Table 2
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Table 2
√	Indication of statistical uncertainty of findings	RR, 95% CI, I^2 and P
Reporting of discussion should include		
√	Quantitative assessment of bias	Results of subgroup analyses and sensitive analyses were discussed.
√	Justification for exclusion	(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; and (4) duplicated studies, where if the same study was found in different databases, we only included the article once.
√	Assessment of quality of included studies	Table S1-1 and Table S1-2
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	First, although we performed subgroup analyses, analyses of previous studies have revealed that the heterogeneity cannot be ignored. Second, the analyzed studies lacked the basic information of 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.
√	Generalization of the conclusions	In conclusion, blood group B was associated with a lower risk of HBV infection.
√	Guidelines for future research	In the future, more researches are needed to clarify the precise role of the ABO blood group in HBV infection to address the global question of HBV infection.
√	Disclosure of funding source	This study was supported by the National Natural Science Foundation of China (Grant No. 71874003 and No. 81703240).

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Title page

Title: ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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 December 1, 2019 were identified by searching PubMed, EMBASE, Web of Science, ScienceDirect, and the Cochrane Library.

Eligibility criteria All cross-sectional or cohort studies that 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% confidence intervals (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 blood group non-B (RR = 0.92, 95% CI: 0.86–0.98). In the subgroup analyses, the inverse relationship between blood group B and HBV infection remained stable in higher endemic areas (HBV prevalence ≥ 5%), Asian people, larger sample size studies (≥ 2000), general population and blood donors, lower middle income group and studies published before 2010 years. Additionally, subjects with blood group O had a 12% increased risk of HBV infection (RR = 1.12, 95% CI:1.01-1.24) 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 researches are needed to clarify the precise role of ABO blood group in HBV infection to address the global question of HBV infection.

Strengths and limitations of this study

- The breadth of the comprehensive systematic literature search is a strength of this study.

- To our knowledge, this was 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.

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 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 not only statistically but also biologically associated with many chronic diseases such as vascular disease,[6] coronary heart disease,[7] 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 (vs.) 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 hepatocellular carcinoma (HCC) patients 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, and human immunodeficiency virus, etc.) has been shown in several studies.[5,13] Previous studies have found the reasons for this association were that 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 response,[14,15] which means the biologic association between ABO blood groups and HBV infection probably exist.

Epidemiologic 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 hepatitis B surface antigen (HBsAg) was lower in donors who had 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 December 1, 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 are shown in 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 number 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; and (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 (e.g., 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; and (4) the author's general conclusions.

The quality of selected cohort studies were 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 were 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 (defining 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% confidence intervals (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 of random-effect models with the estimate of heterogeneity being taken from the Mantel-Haenszel model, and a $p < 0.05$ 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 size 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 $p < 0.05$ was deemed significant. All statistical analyses were performed with STATA version 12.0.

Patient and public involvement

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

Results

Study selection and study characteristics

A total of 4486 articles (4476 from database and 10 from other sources) were searched, of which 1584 were duplicate results. After reading the abstracts, 2211 were deemed irrelevant and three 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 was shown as Figure 1.

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

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 6,487,481 subjects were included with 241,868 HBV-infected subjects and 6,245,613 uninfected subjects. Among the Caucasian, Asian, and African population, there were 23, 7, and 8 studies, respectively. In addition, there were 7, 9, 18 and 4 study in high income, upper middle income, lower middle income and low income group, respectively. Furthermore, there were 14 studies in higher (HBV prevalence ≥5%) endemic and 24 studies in lower (HBV prevalence <5%) endemic areas, respectively. Meanwhile, there were 37 cross-sectional studies and 1 cohort study in the meta-analysis.

Table 1. Characteristics of the included studies.

Author	Income group	Race	Population	Sample size	HBV infection (n/%)				
					Total	A, non-A[a]	B, non-B[a]	AB, non-AB[a]	O, non-O[a]
Terrier, E.1970[27]	High	Caucasian	Blood donors	5968	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, M.1970[28]	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, W.1971[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, S. J.1974[29]	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, T. G.1974[30]	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, H. H.1975[31]	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, W.1975[20]	High	Caucasian	Blood donors	51019	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, M. R.1981 [32]	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, N.1985 [33]	Lower middle	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, A. G.1986 [34]	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, A. S.1986 [35]	High	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, V. J.1989 [36]	Upper middle	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, C.2002 [37]	Low	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, S. K.2003[38]	Lower middle	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, A-H.2006 [39]	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, R.2008 [21]	Lower middle	Caucasian	Blood donors	20000	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-Zaman2009[40]	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, J. O.2011[41]	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, M.2011 [42]	Upper middle	Caucasian	Blood donors	16695	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, A. A. 2012[43]	Lower 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, S.2013 [44]	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, B.2014 [45]	Upper 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, F.2014 [18]	Lower 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, J. S.2014 [46]	High	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, T. T.2014 [16 b]	Upper middle	Asian	General	78705	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, Y.2014 [47]	Lower 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
Siransy, L. K.2015[48]	Lower middle	African	Blood donors	59514	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, D.2015 [49]	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, F. S.2016[50]	Lower middle	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, M.2016 [51]	Upper middle	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
Bharadva, S.2016 [52]	Lower middle	Caucasian	Blood donors	41909	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, Z.2016 [53]	High	Caucasian	Blood donors	228409	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, F. A.2017 [54]	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, J.2017 [17]	Lower middle	Asian	General	3827125	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, Z.2017 [55]	Low	Caucasian	Blood donors	41084	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, C-D.2018[56]	Upper middle	African	Blood donors	4744	81/1.71	-	-	-	34/1.22, 47/2.41
Fu, X.2018[57]	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, C.2019[58]	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

[a] 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. [b] A cohort study.

The HBV infection prevalence in the 38 eligible articles ranged from 0.11% to 46.84%, and the HBV infection prevalence of blood group 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 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 (Table S1-1). The article assessed by NOS scored 7 and was of high-quality (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 blood group non-B (RR = 0.92, 95% CI: 0.86–0.98). 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 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 the higher endemic areas (HBV prevalence ≥ 5%), Asian people, studies with larger sample sizes (≥ 2000), general population and blood donors, lower middle income group, and articles published before 2010 years (Table 2).

Table 2. The main, subgroup and sensitivity analyses.

Subgroup	No. of studies	Sample size	B vs. Non-B		O vs. Non-O		A vs. Non-A		AB vs. Non-AB	
			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 (0.86,0.98)	0.007	1.07 (0.99,1.15)	0.082	1.01 (0.96, 1.07)	0.728	1.04 (0.95,1.13)	0.419
HBV prevalence										
Higher endemic (≥5%)	14	3983732	0.90 (0.83,0.98)	0.013	1.12 (1.01,1.24)	0.025	0.99 (0.91,1.08)	0.820	1. 00 (0.89,1.14)	0.962
Lower endemic (<5%)	24	2503749	0.93 (0.85,1.02)	0.126	1.03 (0.93,1.15)	0.566	1.03 (0.95,1.11)	0.471	1.06 (0.95,1.18)	0.292
Race										
Caucasian	23	2488675	0.96 (0.87, 1.05)	0.386	1.04 (0.94, 1.16)	0.465	1.03 (0.94, 1.13)	0.472	1.05 (0.93, 1.18)	0.461
Asian	7	3920902	0.91(0.86, 0.97)	0.003	1.10 (0.99, 1.22)	0.075	0.98 (0.97, 0.99)	<0. 001	0.96 (0.87, 1.06)	0.451
African	8	77904	0.78 (0.58, 1.05)	0.099	1.04 (0.77, 1.40)	0.803	0.99 (0.73, 1.33)	0.919	1.02 (0.62, 1.67)	0.953
Sample size										
≥2000	24	6475196	0.93 (0.87, 0.99)	0.018	1.07 (0.98, 1.16)	0.135	0.99 (0.94, 1.05)	0.795	1.00 (0.92, 1.08)	0.914
<2000	14	12285	0.85 (0.64, 1.13)	0.275	1.08 (0.90, 1.29)	0.398	1.07 (0.85, 1.33)	0.577	1.20 (0.89, 1.61)	0.238
Population										
General	6	3910128	0.93 (0.87, 0.99)	0.016	1.07 (0.99, 1.15)	0.078	0.98 (0.96, 1.00)	0.035	0.89 (0.88, 0.90)	<0.001
Blood donors	29	2574698	0.89 (0.81, 0.97)	0.011	1.08 (0.97, 1.20)	0.154	1.01 (0.92, 1.10)	0.885	1.08 (0.95, 1.23)	0.248
Patients	3	2655	0.92 (0.71, 1.19)	0.517	1.04 (0.71, 1.54)	0.828	1.09 (0.91, 1.30)	0.345	1.17 (0.94, 1.46)	0.169
Income group										
High	7	148804	0.96 (0.91,1.00)	0.065	1.17 (0.95,1.44)	0.135	0.91 (0.74,1.11)	0.343	0.97 (0.84,1.13)	0.712
Upper middle	9	6101344	1.01 (0.88,1.15)	0.927	0.97 (0.82, 1.15)	0.756	1.00 (0.96,1.06)	0.791	1.02 (0.88,1.17)	0.814
Lower middle	18	214587	0.86 (0.76,0.97)	0.011	1.03 (0.93,1.13)	0.582	1.13(1.01,1.25)	0.030	1.13 (0.95,1.34)	0.173
Low	4	22746	0.88 (0.56,1.38)	0.572	1.34 0.72, 2.48)	0.353	0.71 (0.42,1.21)	0.209	0.84 (0.43,1.64)	0.613
Study design										
Cross-sectional	37	6408776	0.91 (0.85, 0.97)	0.007	1.07 (0.98, 1.17)	0.111	1.01 (0.95,1.08)	0.780	1.06 (0.96, 1.17)	0.244
Cohort	1	78705	0.96 (0.92, 1.01)	0.098	1.05 (1.01, 1.10)	0.016	1.00 (0.95, 1.05)	0.957	0.92 (0.84, 1.00)	0.053
Publication year										
Before 2010	17	123268	0.80 (0.67, 0.96)	0.015	1.12 (0.97, 1.29)	0.112	1.02 (0.85, 1.22)	0.830	1.22 (1.01, 1.46)	0.040
After 2010	21	6364213	0.95 (0.88, 1.01)	0.106	1.05 (0.95, 1.15)	0.335	1.00 (0.94, 1.06)	0.910	0.98 (0.89, 1.07)	0.627
Sensitive analyses										
Removed Liu's study[17]	37	2660356	0.91 (0.85, 0.98)	0.012	1.06 (0.98, 1.15)	0.138	1.01 (0.94, 1.08)	0.816	1.06 (0.97, 1.17)	0.213
Removed Mohammedali's study[18]	37	4459413	0.91 (0.85, 0.97)	0.002	1.08 (1.00, 1.16)	0.044	1.01 (0.94, 1.07)	0.857	1.04 (0.95, 1.14)	0.445
Removed both Liu's and Mohammedali's study[17,18]	36	632288	0.90 (0.83, 0.97)	0.007	1.07 (0.98, 1.17)	0.115	1.00 (0.92, 1.09)	0.946	1.08 (0.96, 1.20)	0.211

RR: Risk ratio.

In higher endemic areas, subjects with blood group B had a significantly lower risk of HBV infection (RR = 0.90, 95% CI: 0.83–0.98) than the non-B group (Figure 2A), while subjects with the blood group O had a significantly higher risk of HBV infection (RR = 1.12, 95% CI: 1.01–1.24) than the non-O group (Figure 2B). According to the race of the subjects, blood group A and B were linked with decreased risk of HBV infection in the Asian population when compared to non-A and non-B, respectively (RR = 0.98, 95%CI: 0.97–0.99; RR = 0.91, 95% CI: 0.86–0.97) (Table 2). However, no association was found among

the Caucasian or African population. In general population, blood group A, B and AB had a decreased risk of HBV infection compared to non-A, non-B and non-AB, respectively (RR = 0.98, 95%CI: 0.96–1.00; RR = 0.93, 95% CI: 0.87–0.99 and RR = 0.89, 95% CI: 0.88–0.90, respectively) (Table 2).

Insert Figure 2. Forest plots by prevalence: (**A**) B vs. non-B; (**B**) O vs. non-O.

In the sensitivity analysis, when the study of 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 vs. non-A (Figure 3A), B vs. non-B (Figure 3B), and O vs. non-O (Figure 3C) (p = 0.148; p = 0.223; p = 0.364, respectively), while a publication bias of AB vs. non-AB was observed (Figure 3D) (p = 0.002).

Insert Figure 3. Funnel plots: (**A**) A vs. non-A; (**B**) B vs. non-B; (**C**) O vs. non-O; and (**D**) AB vs. non-AB.

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 subgroups and still stable in sensitive analyses, giving supportive evidence that not only statistical association but also biologic 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 than those living in lower endemic areas, which might be the reason why the association between ABO blood group and 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 region.

The implementation of universal hepatitis B vaccination program for newborns was started in 1992 proposed by WHO. 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, no enough information could be extracted from the previous studies to compare the pooled association of ABO blood groups and HBV infection between vaccinated group and unvaccinated group. 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 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 that of non-O subjects in higher endemic areas, which was consistent with some previous studies of Lao et al.[16], Liu et al.[17] and Abate et al.[51] That means more measures should be taken to ensure the "universal" group-O blood safety in high endemic areas because of the large unvaccinated population among the main blood donors in current era and the window period for detection among the HBV-infected blood donors.[17] However, this relationship was unobserved in other subgroup analysis, so whether this relationship was true remains to be further explored. Interestingly, our result that blood group B was associated with a lower risk of HBV infection compared with blood group non-B was few reported explicitly by other studies, possibly because of the different analysis methods, such as the different reference of blood group in analysis.

However, the study of Mohammadali et al.[18], with the second largest sample size, reported that HBV infection was lower in group-O donors, opposing 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 the recently meta-analysis, which found that HCC patients might have a lower proportion of O subjects than healthy subjects.[12] The possible explanation for the inconsistence is the long-term and complicated process from HBV infection to the occurrence of HCC. To examine the reliable and stable of

the results, we orderly removed the study of Liu et al.[17] or Mohammadali et al.[18], as well as removed both of them at the same time. In the sensitive 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 thought that these findings were worthy of consideration due to the subgroup analyses, the sensitive 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 response[16] 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 the ABO blood group and secretor status, which might be due to genetically determined variations in the proportion of isoenzymes among the different blood types[59]. Our study may indicate that specific histo-bloodgroup antigen may be a natural resistance factor for HBV infection, and that probably provides clues for correlative fundamental researches of etiologies 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 analyzed studies lacked the basic information of 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 was associated with a lower risk of HBV infection. In the future, more researches are needed to clarify the precise role of the ABO blood group in HBV infection to address the global question of HBV infection.

Supplementary

Additional file 1: The electronic search strategy for PubMed.

Additional file 2: Quality assessment tables.

Abbreviations HBV, Hepatitis B virus; RR, risk ratio; CI, confidence interval; VTE, venous thromboembolism; vs., versus; VWF, von Willebrand factor; HBsAg, hepatitis B surface antigen; Rh, rhesus; NOS, Newcastle-Ottawa Scales; AHRQ, Agency for Healthcare Research and Quality.

Contributions 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; and WJ wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Availability of data and material All data generated or analyzed during this study are included in this published article and its supplementary information files.

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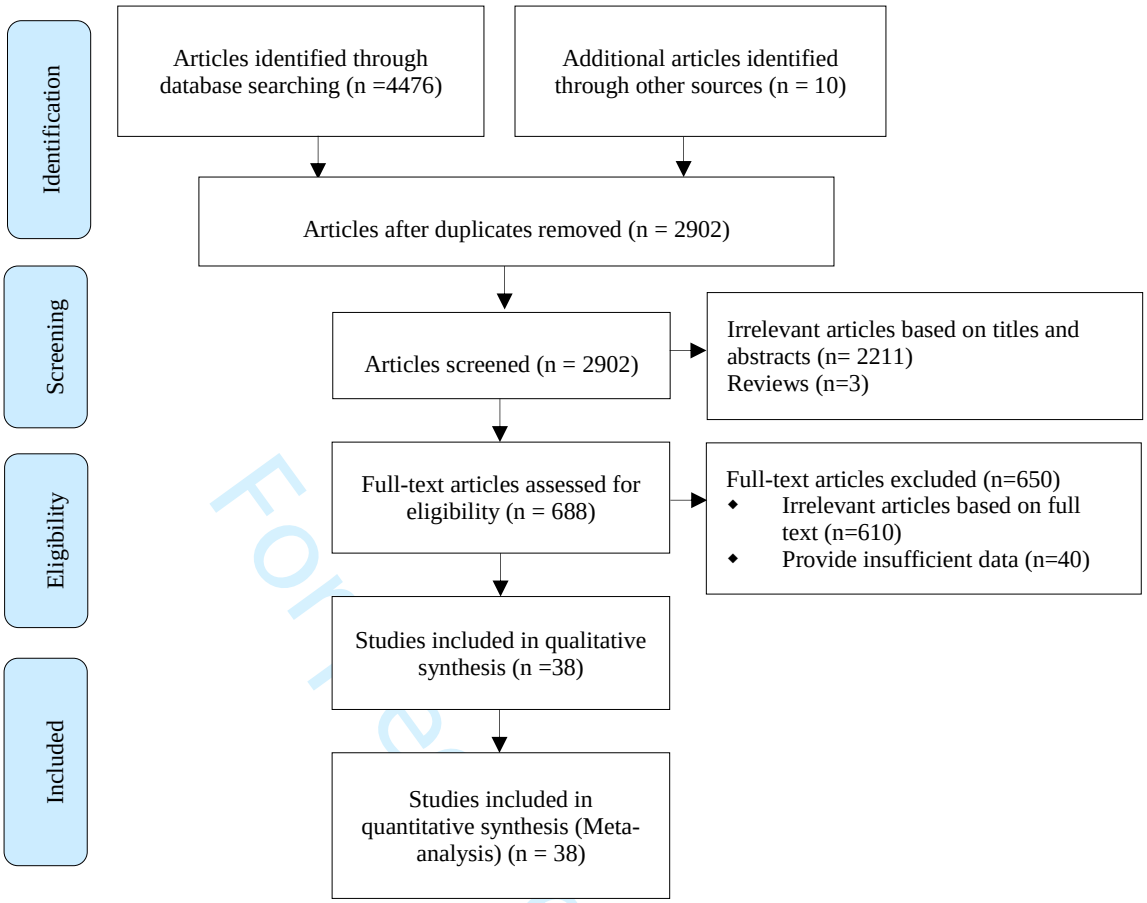

Figure 1. The process of study selection for the meta-analysis.

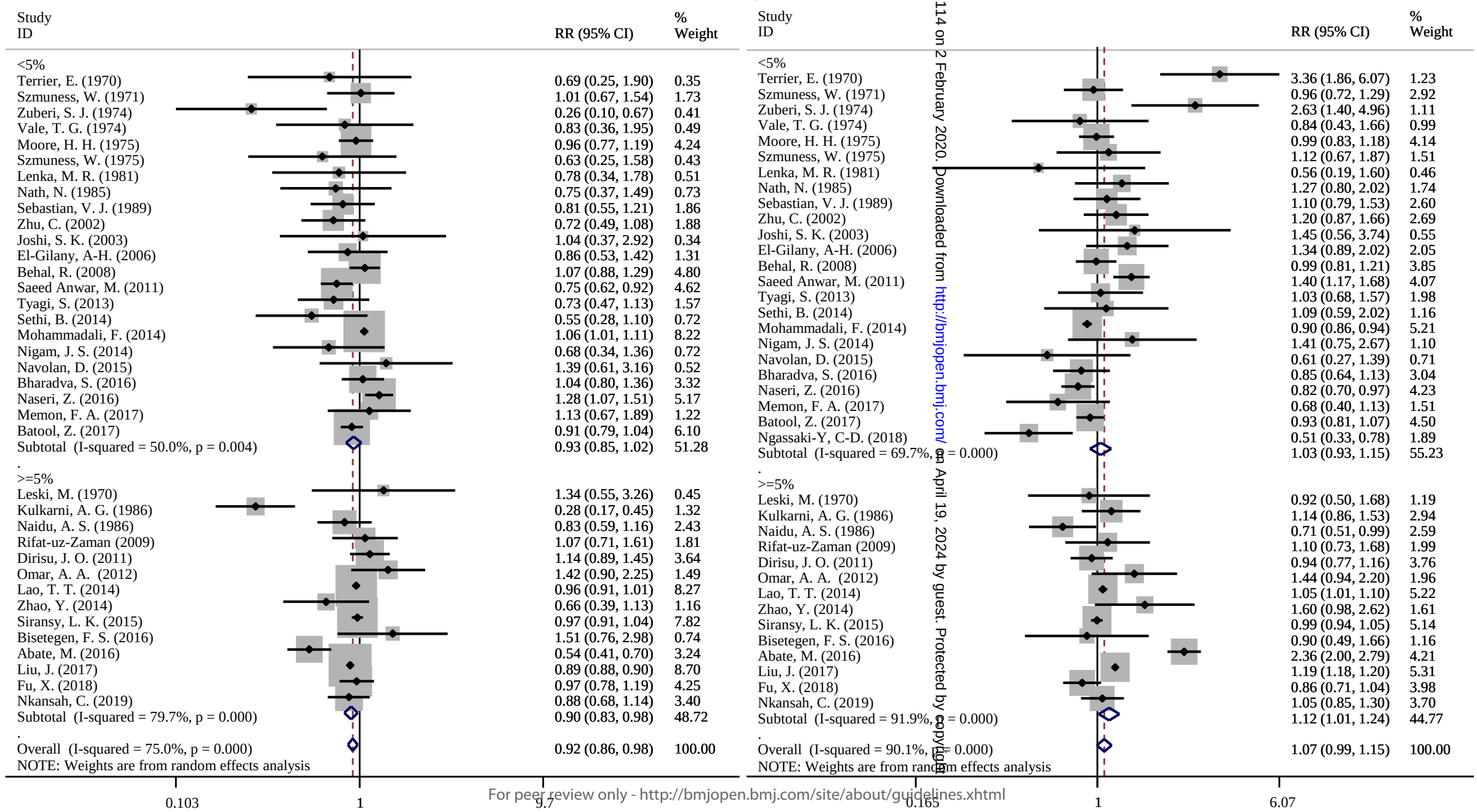

Figure 2. Forest plots by prevalence: (**A**) B vs. non-B; (**B**) O vs. non-O.

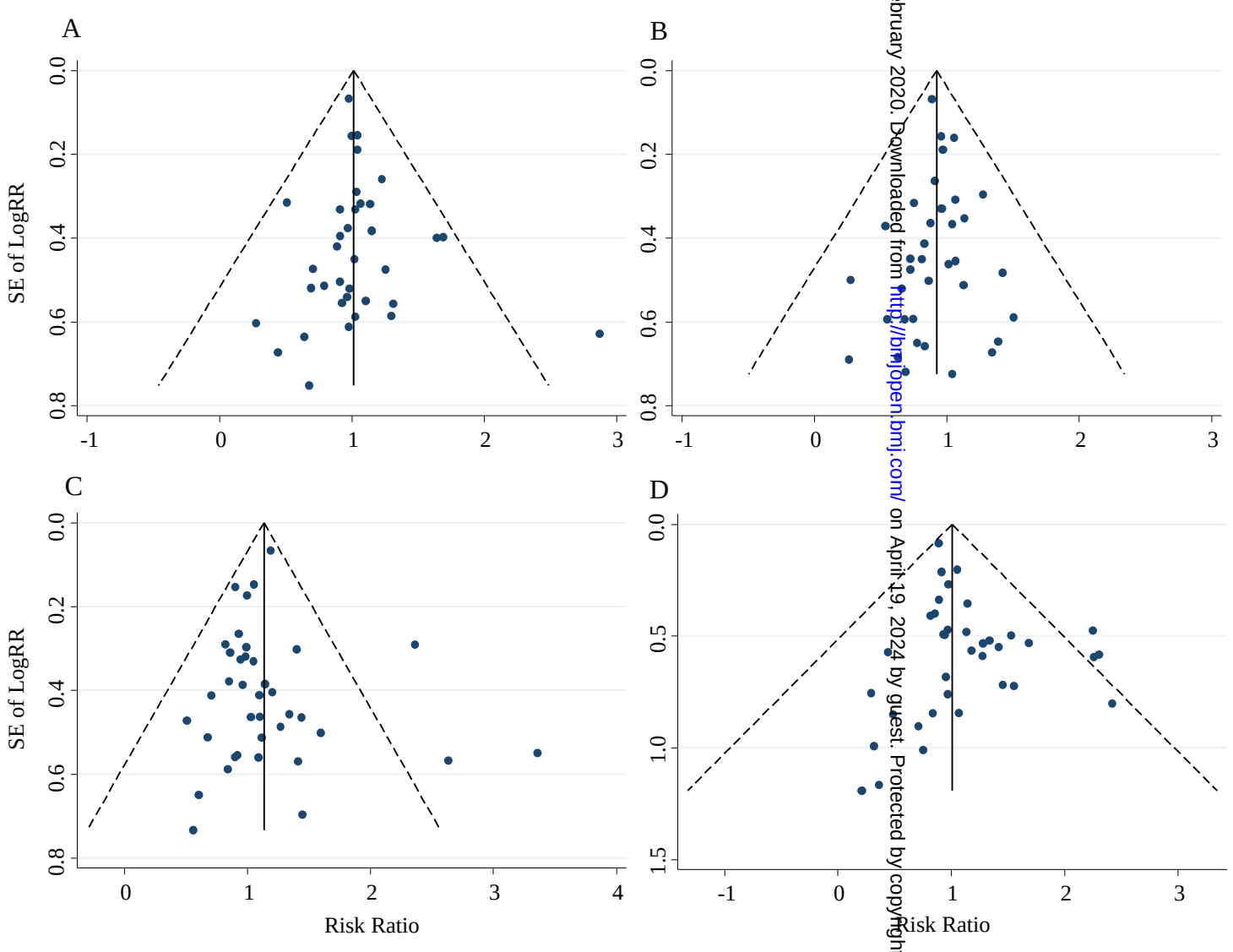

Figure 3. Funnel plots: (**A**) A vs. non-A; (**B**) B vs. non-B; (**C**) O vs. non-O; and (**D**) AB vs. non-AB.

Additional file 1:

The electronic search strategy for PubMed：

(((((((hepatitis B[MeSH Terms]) OR hepatitis B virus[MeSH Terms]) OR Hepatitis B Surface Antigens[MeSH Terms]) OR hepatitis B[Text Word]) OR hepatitis B virus[Text Word]) OR HBV[Text Word]) OR HBsAg[Text Word]) AND ("0001/01/01"[PDat] : "2019/11/30"[PDat]) AND (((((((ABO Blood-Group System[MeSH Terms]) OR Rh-Hr Blood-Group System[MeSH Terms]) OR blood type[Text Word]) OR blood group[Text Word]) OR ABO[Text Word]) OR Rh[Text Word]) OR rhesus[Text Word]) AND ("0001/01/01"[PDat] : "2019/11/30"[PDat])

Additional file 2:

Table S1-1: Quality assessment for cross-sectional studies by Agency for Healthcare Research and Quality table.

Author	1	2	3	4	5	6	7	8	9	10	11	Total
Terrier, E.1970[27]	Y	N	N	U	U	Y	/	N	/	Y	Y	4
Leski, M.1970[28]	Y	N	Y	N	U	Y	N	N	/	Y	Y	5
Szmuness, W.1971[19]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zuberi, S. J.1974[29]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Vale, T. G.1974[30]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Moore, H. H.1975[31]	Y	N	Y	Y	U	Y	/	N	/	Y	Y	6
Szmuness, W.1975[20]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8
Lenka, M. R.1981 [32]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Nath, N.1985 [33]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Kulkarni, A. G.1986 [34]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Naidu, A. S.1986 [35]	Y	N	N	N	U	Y	/	N	Y	Y	Y	5
Sebastian, V. J.1989 [36]	Y	N	N	N	U	Y	/	N	N	Y	Y	4
Zhu, C.2002 [37]	Y	N	Y	Y	U	Y	N	N	N	N	Y	5
Joshi, S. K.2003[38]	Y	Y	Y	N	U	Y	/	N	/	Y	Y	6
El-Gilany, A-H.2006 [39]	Y	Y	Y	N	U	Y	/	N	Y	N	Y	6
Behal, R.2008 [21]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Rifat-uz-Zaman2009[40]	Y	Y	Y	/	U	N	/	N	Y	Y	Y	6
Dirisu, J. O.2011[41]	Y	Y	Y	Y	U	Y	/	N	/	Y	Y	7
Saeed Anwar, M.2011 [42]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Omar, A. A. 2012[43]	Y	N	Y	N	U	Y	/	N	/	Y	Y	5
Tyagi, S.2013 [44]	Y	Y	Y	N	U	Y	/	N	Y	Y	Y	7
Sethi, B.2014 [45]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Mohammadali, F.2014 [18]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Nigam, J. S.2014 [46]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zhao, Y.2014 [47]	Y	N	Y	N	U	Y	/	N	Y	Y	Y	6
Siransy, L. K.2015[48]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8
Navolan, D.2015 [49]	Y	Y	N	N	U	Y	N	N	N	Y	Y	5
Bisetegen, F. S.2016[50]	Y	Y	Y	N	U	Y	/	N	N	Y	Y	6
Abate, M.2016 [51]	Y	N	Y	Y	U	Y	/	N	Y	Y	Y	7
Bharadva, S.2016 [52]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Naseri, Z.2016 [53]	Y	N	Y	Y	U	Y	/	N	Y	Y	Y	7
Memon, F. A.2017 [54]	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Liu, J.2017 [17]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	9
Batool, Z.2017 [55]	Y	Y	Y	Y	U	Y	U	N	U	N	Y	6
Ngassaki-Y, C-D.2018[56]	Y	Y	Y	Y	U	Y	/	N	/	Y	Y	7
Fu, X.2018[57]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	8
Nkansah, C.2019[58]	Y	Y	Y	Y	U	Y	Y	N	/	Y	Y	8

Y, Yes; N, No; U, Unclear; /, not applicable.

Note:

Item 1: Define the source of information (survey, record review).

Item 2: List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications.
Item 3: Indicate time period used for identifying patients.
Item 4: Indicate whether or not subjects were consecutive if not population-based.
Item 5: Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants.
Item 6: Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements).
Item 7: Explain any patient exclusions from analysis.
Item 8: Describe how confounding was assessed and/or controlled.
Item 9: If applicable, explain how missing data were handled in the analysis.
Item 10: Summarize patient response rates and completeness of data collection.
Item 11: Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.

Table S1-2: Quality assessment for cohort studies by Newcastle-Ottawa Scales table.

Author	Selection	Comparability	Outcome	Total
T. T. Lao 2014[16]	3	1	3	7

Note:
Selection: 1) Representativeness of the exposed cohort; 2) Selection of the non-exposed cohort; 3) Ascertainment of exposure; 4) Demonstration that outcome of interest was not present at start of study.
Comparability: 1) Comparability of cohorts on the basis of the design or analysis.
Outcome: 1) Assessment of outcome; 2) Was follow-up long enough for outcomes to occur; 3) Adequacy of follow up of cohorts.

Meta-analysis of Observational Studies in Epidemiology (MOOSE) Checklist

ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

Criteria		Brief description of how the criteria were handled in the meta-analysis	Page No.
Reporting of background should include			
√	Problem definition	Controversy remains with regard to whether blood group is related to HBV infection and which antigen is a protective or a risk factor.	P4/Line5-6
√	Hypothesis statement	We performed a systematic review and meta-analysis to elucidate the association between ABO blood groups and HBV infection risk.	P4/Line6-7
√	Description of study outcomes	HBV infection	P3/Line6-10
√	Type of exposure or intervention used	ABO blood group	P3/Line11-26
√	Type of study designs used	Systematic Review and Meta-Analysis	P4/Line6
√	Study population	Unrestricted	None
Reporting of search strategy should include			
√	Qualifications of searchers	Two reviewers (SZ and WJ) searched for articles independently.	P4/Line12
√	Search strategy, including time period included in the synthesis and keywords	Available online before December 1, 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”.	P4/Line12-15
√	Effort to include all available studies	Highly relevant reference articles were also searched by reviewing the list of references.	P4/Line15-16
√	Databases and registries searched	PubMed, EMBASE, Web of Science, ScienceDirect, and Cochrane Central	P4/Line13-14
√	Search software used, name and version, including special features	We did not employ a search software. Endnote was used to merge retrieved citations.	None
√	Use of hand searching	Highly relevant reference articles were also searched by reviewing the list of references.	P4/Line15-16
√	List of citations located and those excluded, including justifications	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	P4/Line19-25

		be extracted to calculate the risk ratio (RR), which meant that the number 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; and (4) duplicated studies, where if the same study was found in different databases, we only included the article once.	
√	Method of addressing articles published in languages other than English	There was no limitation of language.	P4/Line16-17
√	Method of handling abstracts and unpublished studies	We did not include unpublished studies. If abstract could provide full information, it was included.	None
√	Description of any contact with authors	When needed, we contacted the original author for the data, but nobody responded to us.	None
Reporting of methods should include			
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the paper.	P4/Line19-25
√	Rationale for the selection and coding of data	(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 (e.g., 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; and (4) the author's general conclusions.	P5/Line3-8
√	Documentation of how data were classified and coded	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 Negroid subgroups depending on the major national race and	P5/Line24-27

		divided into high, upper middle, lower middle and low income groups according to the World Bank list of economies.	
√	Assessment of confounding	Subgroup analyses were performed by HBV prevalence, race, sample size, population, income group, study type, and publication year.	P5/Line23-24
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The quality of selected cohort studies were assessed using the Newcastle-Ottawa Scales (NOS). The quality of the selected cross-sectional studies were assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ).	P5/Line9-13
√	Assessment of heterogeneity	Between-study heterogeneity was evaluated with the I^2 statistic. When $I^2 \leqslant 50\%$, the included studies were considered to have little heterogeneity; when $I^2 > 50\%$, the included studies were considered to have substantial heterogeneity.	P5/Line19-22
√	Description of statistical methods in sufficient detail to be replicated	RRs and 95% CIs (A vs. non-A, B vs. non-B, O vs. non-O, AB vs. non-AB) were pooled by using of random-effect models with the estimate of heterogeneity being taken from the Mantel-Haenszel model, and a $p < 0.05$ was deemed significant.	P5/Line17-19
√	Provision of appropriate tables and graphics	Figure 2,3 and Table 2	P9 and Figure 2,3
Reporting of results should include			
√	Graphic summarizing individual study estimates and overall estimate	Table 1 and Table 2	P7 and P9
√	Table giving descriptive information for each study included	Table 1	P7
√	Results of sensitivity testing	Table 2	P9
√	Indication of statistical uncertainty of findings	RR, 95% CI, I^2 and P	P9
Reporting of discussion should include			
√	Quantitative assessment of bias	Results of subgroup analyses and sensitive analyses were discussed.	P8-10
√	Justification for exclusion	(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	P4/Line22-25

		only included the last published; and (4) duplicated studies, where if the same study was found in different databases, we only included the article once.	
√	Assessment of quality of included studies	Table S1-1 and Table S1-2	Additional file 2
Reporting of conclusions should include			
√	Consideration of alternative explanations for observed results	First, although we performed subgroup analyses, analyses of previous studies have revealed that the heterogeneity cannot be ignored. Second, the analyzed studies lacked the basic information of 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.	P12/Line16-21
√	Generalization of the conclusions	In conclusion, blood group B was associated with a lower risk of HBV infection.	P12/Line22
√	Guidelines for future research	In the future, more researches are needed to clarify the precise role of the ABO blood group in HBV infection to address the global question of HBV infection.	P12/Line22-24
√	Disclosure of funding source	This study was supported by the National Natural Science Foundation of China (Grant No. 71934002, No. 71874003 and No. 81703240).	P13/Line9-10