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

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# 1 Title page

2	Title: ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis
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1	ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis
2	Abstract
3	Objective Hepatitis B virus (HBV) infection is a major public health problem worldwide. Several studies
4	have reported that ABO blood groups may be associated with HBV infection. However, its association is
5	still controversial. Thus, we performed a meta-analysis to investigate whether ABO blood groups were
6	associated with HBV infection.
7	Design Systematic review and meta-analysis.
8	Data sources Relevant studies available before December 1, 2017 were identified by searching PubMed,
9	EMBASE, Web of Science, ScienceDirect, and the Cochrane Library.
10	Eligibility criteria All cross-sectional or cohort studies that the data of the ABO blood group distribution
11	and HBV infection could be extracted.
12	Data extraction and synthesis Studies were identified and extracted by two reviewers independently.
13	Risk ratios (RRs) and 95% confidence intervals (CIs) were pooled by use of random-effects models to
14	quantify this association.
15	Results Thirty-five eligible articles including 241,056 HBV-infected subjects and 6,236,375 uninfected
16	subjects were included in this study. Overall, the risk of HBV infection had decreased by 8% in subjects
17	with the blood group B when compared with the blood group non-B (RR = $0.92$ , $95\%$ CI: $0.86-0.98$ ),
18	which was also observed in the subgroup analysis. In addition, subjects with blood group O had a 10%
19	increased risk of HBV infection (RR = 1.10, 95% CI: 1.02–1.19), which was observed both in higher
20	endemic areas (HBV prevalence $\geq$ 5%, RR = 1.16, 95% CI: 1.04–1.30) and in the Asian population (RR =
21	1.15, 95% CI: 1.04–1.27). In the sensitivity analysis, the pooled risk estimates were still stable.
22	Conclusions Our data suggested that the blood group B was associated with a lower risk of HBV infection,
23	while the blood group O was associated with a higher risk of HBV infection.

### 24 Strengths and limitations of this study

- $\succ$  The breadth of the comprehensive systematic literature search is a strength of this study.
- 26 > To our knowledge, this was the first meta-analysis of the association between ABO blood groups and
   27 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.

### 3 Introduction

Hepatitis B virus (HBV) infection is a major public health problem worldwide<sup>1</sup>, especially in Africa and
the Western Pacific Region<sup>2</sup>. 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<sup>2</sup> with about 0.88
million deaths caused by complications of chronic HBV infection every year<sup>2</sup>. HBV infection has caused
a high societal burden globally<sup>1,2</sup>.

The ABO blood group system, the most extensively investigated erythrocyte antigen system<sup>3</sup>, is widely used in clinical practice, and influences the host susceptibility<sup>4,5</sup>. 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<sup>6</sup>, coronary heart disease<sup>7</sup>, and tumorigenesis<sup>3,4,8</sup>. 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<sup>9</sup> due to A, B, and H antigens( H antigen is the biosynthetic precursor to A and B antigens<sup>5</sup>.) influence the half-life of the VWF by expressing on N-glycans of VWF<sup>9-11</sup>. 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<sup>5,12</sup>. 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<sup>5</sup>, and blood antigens are important as receptors for immune and inflammation response<sup>13,14</sup>, 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.<sup>15</sup> 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.<sup>16</sup> suggested that blood group O was associated with increased HBV infection. Mohammadali et al.<sup>17</sup> found that the percentage of hepatitis B surface antigen (HBsAg) was lower in donors who had blood group O. However, Szmuness et al.<sup>18,19</sup> and Behal et al.<sup>20</sup> 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

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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<sup>21</sup>.

### 5 Materials and methods

### 6 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.

### 12 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<sup>22</sup>. 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)<sup>23</sup> 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.

### 8 Statistical analysis

The main outcome was the prevalence of HBV infection (defining as HBsAg-positive) in our metaanalysis. 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<sup>2</sup> was used to evaluate heterogeneity among the studies. When I<sup>2</sup>  $\leq$  50%, the included studies were considered to have little heterogeneity; when I<sup>2</sup> > 50%, the included studies were considered to have substantial heterogeneity<sup>24</sup>.

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<sup>25</sup>. 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.

24 Patient and public involvement

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

Study selection and study characteristics

**Results** 

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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 metaanalysis. 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  $\geq$  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.

Author	Income group	Daas	Dopulation	Sample			HBV infection (	n/%)	
Author	Income group	Race	Population	size	Total	A, non-A <sup>a</sup>	B, non-B <sup>a</sup>	AB, non-AB <sup>a</sup>	O, non-Oª
Terrier, E.1970 <sup>26</sup>	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 <sup>27</sup>	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.197118	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 <sup>28</sup>	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 <sup>29</sup>	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 <sup>30</sup>	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 <sup>19</sup>	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, 102/15.8
Sebastian, V. J.1989 <sup>35</sup>	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 <sup>36</sup>	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 <sup>37</sup>	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-Zaman200939	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.201140	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, 72/48.6
Saeed Anwar, M.2011 <sup>41</sup>	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. 201242	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 <sup>17</sup>	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, 5132/0.4
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 <sup>15</sup>	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, 4497/9.4
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.201547	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.201649	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, 177/5.5
Bharadva, S.2016 <sup>51</sup>	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		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 <sup>16</sup>	Lower middle	Asian	General				58286/5.18, 157169/5.82		73651/6.34, 141804/5
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

blood group.

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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.

### 8 Main, subgroup, and sensitivity analyses

9 Overall, the risk of HBV infection had decreased by 8% in subjects with blood group B when compared 10 with blood group non-B (RR = 0.92, 95% CI: 0.86–0.98), while the risk of HBV infection had increased 11 by 10% in subjects with blood group O when compared with blood group non-O (RR = 1.10, 95% CI: 12 1.02–1.19) (Table 2). However, blood groups A and AB were not significantly associated with an HBV 13 infection risk (Table 2).

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### 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		
Subgroup	No. of studies	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  $\geq$  5%), Asian people, studies with larger sample sizes ( $\geq 2000$ ), 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  $\geq$ 5%), Asian people, studies with larger sample sizes ( $\geq 2000$ ) (Table 2).

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1	In higher endemic areas, subjects with blood group B had a significantly lower risk of HBV infection
2	(RR = 0.89, 95% CI: 0.82–0.98) than the non-B group (Figure 2A), while subjects with the blood group
3	O had a significantly higher risk of HBV infection ( $RR = 1.16, 95\%$ CI: 1.04–1.30) than the non-O group
4	(Figure 2B). According to the race of the subjects, blood group O was also found to be linked with an
5	increased risk of HBV infection (RR = 1.15, 95% CI: 1.04–1.27) in the Asian population, while blood
6	groups A and B were linked with decreased risk of HBV infection when compared to non-A and non-B,
7	respectively (OR = 0.91, 95%CI: 0.85–0.97; OR = 0.98, 95% CI: 0.97–0.99) (Table 2). However, no
8	association was found among the Caucasian or Black population.
9	
10	Insert Figure 2. Forest plots by prevalence: (A) B vs. non-B; (B) O vs. non-O.
11	
12	In the sensitivity analysis, when the study of Jue Liu and Fatemeh Mohammadali, which dominated the
13	results of the meta-analysis, were orderly removed, the pooled risk estimates were still stable (Table 2).
14	Publication bias
15	Funnel plots and Egger's tests were performed to assess publication bias. No obvious evidence of
15 16	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 ( $P = 0.219$ ; $P = 0.238$ ; $P =$
16	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.
16 17 18	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).
16 17 18 19	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.
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16 17 18 19 20 21	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
16 17 18 19 20 21 22	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
<ol> <li>16</li> <li>17</li> <li>18</li> <li>19</li> <li>20</li> <li>21</li> <li>22</li> <li>23</li> </ol>	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
<ol> <li>16</li> <li>17</li> <li>18</li> <li>19</li> <li>20</li> <li>21</li> <li>22</li> <li>23</li> <li>24</li> </ol>	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

28 exposure to the source of infection is directly related to the risk of infection. People living in higher

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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.<sup>15</sup>, Liu et al.<sup>16</sup> and Abate et al.<sup>50</sup> 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.<sup>16</sup> 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.<sup>17</sup>, 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.,<sup>16</sup> 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.<sup>16</sup> or Mohammadali et al.<sup>17</sup>, 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<sup>16</sup>, associations have been observed most likely related to the altered immune response<sup>15</sup> and

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systemic inflammatory response<sup>14</sup> 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<sup>55</sup>. 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.

9 Meanwhile, several limitations need to be considered. First, although we performed subgroup analyses, 10 analyses of previous studies have revealed that the heterogeneity cannot be ignored. Second, the analyzed 11 studies lacked the basic information of the ethnicity data and the prevalence of different HBV genotypes. 12 Third, few published studies on the association between HBV infection and blood group have controlled 13 HBV infection related risk factors such as family history of HBV infection, blood transfusion, and 14 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.

### 22 Supplementary

23 Additional file 1: Extracted Data from Included Studies. The number of HBV-infected and uninfected

24 subjects in each blood group is provided.

25 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,

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2	1	rhesus; RR, risk ratio; NOS, Newcastle-Ottawa Scales; AHRQ, Agency for Healthcare Research and
3 4	2	Quality.
5		
6	3	
7 8 9	4	Contributions All authors contributed to this work. ML and JL conceived and designed the study strategy;
10 11	5	SZ and WJ independently completed the processes of the article search, article assessment, data extraction,
12 13	6	quality assessment, and data analysis; and WJ wrote the manuscript. All authors read and approved the final
14	7	manuscript.
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26 27	13	Availability of data and material All data generated or analyzed during this study are included in this
28 29	14	published article and its supplementary information files.
30 31	15	Open access This is an open access article distributed in accordance with the Creative Commons Attribution
32	16	4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon
33 34 25	17	this work for any purpose, provided the original work is properly cited, a link to the licence is given, and
35 36	18	indication of whether changes were made. See: https://creativecommons. org/licenses/by/4.0/.
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27	20	54. Batool Z, Durrani SH, Tariq S. Association Of Abo And Rh Blood Group Types To Hepatitis B,
28 29	20	Hepatitis C, Hiv And Syphilis Infection, A Five Year' Experience In Healthy Blood Donors In A
30	21	Tertiary Care Hospital. J Ayub Med Coll Abbottabad 2017; <b>29</b> (1): 90-2.
31	22	55. Yuan X, Waterworth D, Perry JR, et al. Population-based genome-wide association studies reveal
32 33	23	six loci influencing plasma levels of liver enzymes. <i>Am J Hum Genet</i> 2008; <b>83</b> (4): 520-8.
34		six loci initidencing plasma levels of liver enzymes. Am J 11um Genet 2008, 85(4). 520-6.
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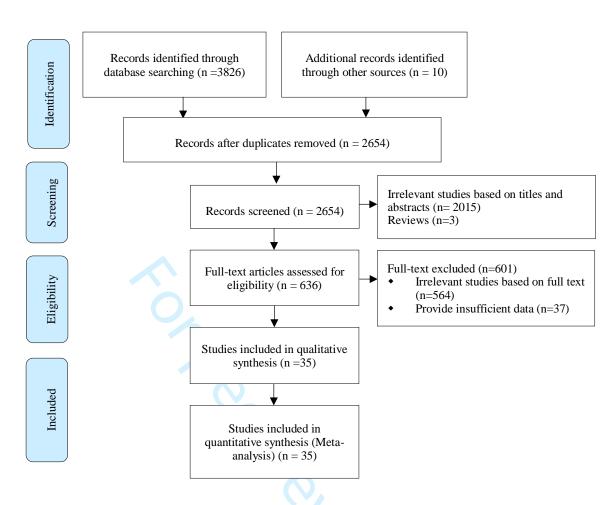


Figure 1. The process of study selection for the meta-analysis.

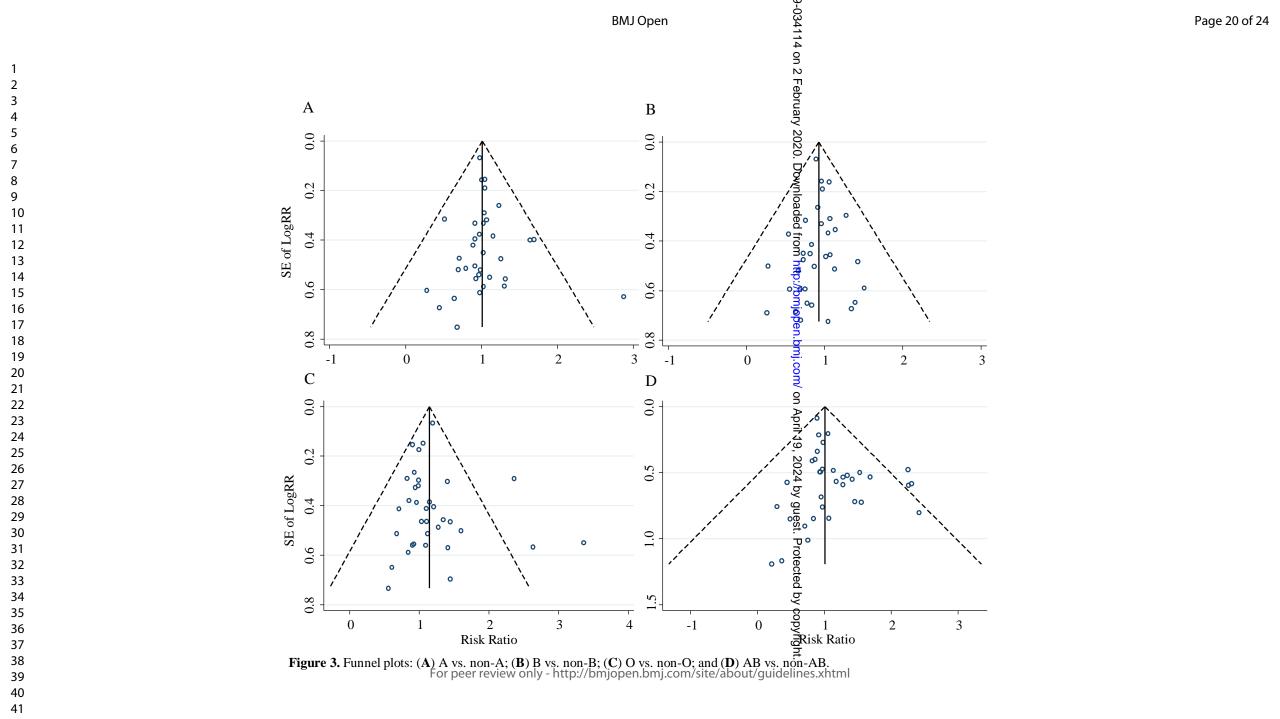
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8	Study		%	Study	
9 10	ID	RR (95% CI)	Weight		
11	<5%				i
12	Terrier, E. (1970)	0.69 (0.25, 1.90)	0.39	Tegrier, E. (1970)	
13 14	Szmuness, W. (1971)	1.01 (0.67, 1.54)	1.90	Szenuness, W. (1971)	÷ .
15	Zuberi, S. J. (1974)	0.26 (0.10, 0.67)	0.46	Zugheri, S. J. (1974)	
16	Vale, T. G. (1974) Moore, H. H. (1975)	0.83 (0.36, 1.95) 0.96 (0.77, 1.19)	0.54 4.61	Vage, T. G. (1974) Mozore, H. H. (1975)	_
17	Szmuness, W. (1975)	0.63 (0.25, 1.58)	0.47	Szäuness, W. (1975)	•
18	Lenka, M. R. (1981)	0.78 (0.34, 1.78)	0.57	Legka, M. R. (1981)	<del>.</del>
19 20	Nath, N. (1985)	0.75 (0.37, 1.49)	0.80	Nāgh, N. (1985)	• •
21	Sebastian, V. J. (1989)	0.81 (0.55, 1.21)	2.05	Segastian, V. J. (1989)	
22	Zhu, C. (2002) Joshi, S. K. (2003)	0.72 (0.49, 1.08) 1.04 (0.37, 2.92)	2.07 0.38	Zhg, C. (2002) Joooi, S. K. (2003)	
23	El-Gilany, A-H. (2006)	0.86 (0.53, 1.42)	0.38 1.44	El&Jilany, A-H. (2006)	L .
24 25	Behal, R. (2008)	1.07 (0.88, 1.29)	5.21	Behal, R. (2008)	
25 26	Saeed Anwar, M. (2011)	0.75 (0.62, 0.92)	5.01	Saged Anwar, M. (2011)	•
27	Tyagi, S. (2013)	0.73 (0.47, 1.13)	1.73	Tyagi, S. (2013)	
28	Sethi, B. (2014)	0.55 (0.28, 1.10)	0.80 8.77	Sethi, B. (2014)	1
29	Mohammadali, F. (2014) Nigam, J. S. (2014)	1.06 (1.01, 1.11) 0.68 (0.34, 1.36)	8.77 0.80	Menammadali, F. (2014) Nigam, J. S. (2014)	•
30 31	Navolan, D. (2015)	1.39 (0.61, 3.16)	0.58	Nayolan, D. (2015)	<u> </u>
32	Bharadva, S. (2016)	1.04 (0.80, 1.36)	3.63	Bharadva, S. (2016)	-
33	Naseri, Z. (2016)	1.28 (1.07, 1.51)	5.60	Nåseri, Z. (2016)	i de la companya de la
34	Memon, F. A. (2017)	1.13 (0.67, 1.89)	1.35	Momon, F. A. (2017)	l.
35	Batool, Z. (2017) Subtotal (I-squared = 50.0%, p = 0.004)	0.91 (0.79, 1.04) 0.93 (0.85, 1.02)	6.57 55.71	Bagool, Z. (2017) Support of the second sec	5
36 37	Subtotal (1-squared = $50.0\%$ , p = $0.004$ )	0.95 (0.85, 1.02)	55.71	$\Delta$	l l
38	>=5%			>\$\$	1
39	Leski, M. (1970)	1.34 (0.55, 3.26)	0.50	Leski, M. (1970)	
40	Kulkarni, A. G. (1986)	0.28 (0.17, 0.45)	1.45	Karni, A. G. (1986)	
41	Naidu, A. S. (1986) Rifat-uz-Zaman (2009)	0.83 (0.59, 1.16) 1.07 (0.71, 1.61)	2.66 1.99	Najdu, A. S. (1986) Rigat-uz-Zaman (2009)	•
42 43	Dirisu, J. O. (2011)	1.14 (0.89, 1.45)	3.97	Divisu, J. O. (2011)	+
44	Omar, A. A. (2012)	1.42 (0.90, 2.25)	1.64	Omar, A. A. (2012)	<b></b>
	Lao, T. T. (2014)	0.96 (0.91, 1.01)	8.82	Lao, T. T. (2014)	•
	Zhao, Y. (2014)	0.66 (0.39, 1.13)	1.28	Zhao, Y. (2014)	•
	Siransy, L. K. (2015)	0.97 (0.91, 1.04)	8.36	Signsy, L. K. (2015)	
	Bisetegen, F. S. (2016) Abate, M. (2016)	1.51 (0.76, 2.98) 0.54 (0.41, 0.70)	0.82 3.54	Bisetegen, F. S. (2016)	
	Liu, J. (2017)	0.89 (0.88, 0.90)	9.26	Li <sub>H</sub> J. (2017)	•
	Subtotal (I-squared = $82.7\%$ , p = 0.000)	0.89 (0.81, 0.98)	44.29	Subtotal (I-squared = $92.6\%$ , p = $0.000$ )	$\diamond$
52				024	
	Overall (I-squared = $76.3\%$ , p = $0.000$ )	0.92 (0.86, 0.98)	100.00	Overall (I-squared = $90.3\%$ , p = $0.000$ )	$\mathbf{\mathbf{\nabla}}$
54 55	NOTE: Weights are from random effects analysis			N TE: Weights are from random effects analysis	
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### RR (95% CI)

### % Weight

3.36 (1.86, 6.07)	1.34
0.96 (0.72, 1.29)	3.22
2.63 (1.40, 4.96)	1.21
0.84 (0.43, 1.66)	1.08
0.99 (0.83, 1.18)	4.60
1.12 (0.67, 1.87)	1.65
0.56 (0.19, 1.60)	0.50
1.27 (0.80, 2.02)	1.90
1.10 (0.79, 1.53)	2.86
1.20 (0.87, 1.66)	2.96
1.45 (0.56, 3.74)	0.60
1.34 (0.89, 2.02)	2.25
0.99 (0.81, 1.21)	4.26
1.40 (1.17, 1.68)	4.52
1.03 (0.68, 1.57)	2.16
1.09 (0.59, 2.02)	1.26
0.90 (0.86, 0.94)	5.83
1.41 (0.75, 2.67)	1.19
0.61 (0.27, 1.39)	0.77
0.85 (0.64, 1.13)	3.35
0.82 (0.70, 0.97)	4.70
0.68 (0.40, 1.13)	1.65
0.93 (0.81, 1.07)	5.02
1.06 (0.95, 1.17)	58.87
0.02 (0.50, 1.69)	1.20
0.92 (0.50, 1.68)	1.30
1.14 (0.86, 1.53)	3.24 2.84
0.71 (0.51, 0.99)	2.84 2.17
1.10 (0.73, 1.68)	2.17 4.17
0.94 (0.77, 1.16) 1.44 (0.94, 2.20)	4.17 2.15
1.44 (0.94, 2.20)	5.85
1.60 (0.98, 2.62)	1.75
1.00(0.98, 2.02)	5.76
0.99 (0.94, 1.05) 0.90 (0.49, 1.66)	3.70 1.27
2.36 (2.00, 2.79)	4.68
2.30 (2.00, 2.79)         1.19 (1.18, 1.20)	4.08 5.95
1.19 (1.18, 1.20)	5.95 41.13
1.10(1.04, 1.30)	41.15
1.10 (1.01, 1.19)	100.00

**6**.07



### Additional file 1:

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

	Α	Α	В	В	AB	AB	0	0
Author	HBsAg+	HBsAg-	HBsAg+	HBsAg-	HBsAg+	HBsAg-	HBsAg+	HBsAg-
Terrier, E.1970 <sup>26</sup>	9	2452	4	605	2	255	40	2601
Leski, M.1970 <sup>27</sup>	16	53	4	10	0	5	14	53
Szmuness, W.1971 <sup>18</sup>	61	2893	25	1104	13	351	78	3571
Zuberi, S. J.1974 <sup>28</sup>	9	259	5	402	2	53	22	359
Vale, T. G.1974 <sup>29</sup>	18	303	6	140	5	104	11	249
Moore, H. H.1975 <sup>30</sup>	127	3519	103	3109	17	532	248	7261
Szmuness, W.1975 <sup>19</sup>	22	19530	5	6633	4	2468	27	22330
Lenka, M. R.1981 <sup>31</sup>	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 <sup>34</sup>	49	195	42	297	11	51	43	341
Sebastian, V. J.1989 <sup>35</sup>	30	690	30	828	10	200	64	1424
Zhu, C.2002 <sup>36</sup>	44	2671	30	2158	18	678	61	3023
Joshi, S. K.2003 <sup>37</sup>	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-Zaman200939	5	161	35	493	23	306	30	411
Dirisu, J. O.2011 <sup>40</sup>	32	38	39	36	1	2	128	151
Saeed Anwar, M.2011 <sup>41</sup>	103	3856	139	5871	17	627	208	5874
Omar, A. A. 2012 <sup>42</sup>	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 <sup>17</sup>	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 <sup>15</sup>	2038	18543	1991	18753	468	4670	3289	28953
Zhao, Y.2014 46	17	135	16	147	15	75	18	77
Siransy, L. K.201547	947	12299	941	12943	187	2575	2044	27578
Navolan, D.2015 <sup>48</sup>	15	606	7	218	4	109	7	419
Bisetegen, F. S.2016 <sup>49</sup>	7	97	10	67	2	7	18	182
Abate, M.2016 50	114	1901	54	936	9	202	470	3141
Bharadva, S.2016 <sup>51</sup>	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 <sup>16</sup>	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	Tota
Terrier, E.1970 <sup>26</sup>	Y	Ν	Ν	U	U	Y	/	Ν	/	Y	Y	4
Leski, M.1970 <sup>27</sup>	Y	Ν	Y	Ν	U	Y	Ν	Ν	/	Y	Y	5
Szmuness, W.1971 <sup>18</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Zuberi, S. J.1974 <sup>28</sup>	Y	Ν	Y	Y	U	Y	/	Ν	/	Y	Y	6
Vale, T. G.1974 <sup>29</sup>	Y	Ν	Y	Y	U	Y	/	Ν	/	Y	Y	6
Moore, H. H.1975 <sup>30</sup>	Y	Ν	Y	Y	U	Y	/	Ν	/	Y	Y	6
Szmuness, W.1975 <sup>19</sup>	Y	Y	Y	Y	U	Y	Y	Ν	/	Y	Y	8
Lenka, M. R.1981 <sup>31</sup>	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Nath, N.1985 32	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Kulkarni, A. G.1986 33	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Naidu, A. S.1986 <sup>34</sup>	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Sebastian, V. J.1989 <sup>35</sup>	Y	Ν	Ν	Ν	U	Y	/	Ν	Ν	Y	Y	4
Zhu, C.2002 <sup>36</sup>	Y	Ν	Y	Y	U	Y	Ν	Ν	Ν	Ν	Y	5
Joshi, S. K.2003 <sup>37</sup>	Y	Y	Y	Ν	U	Y	/	Ν	/	Y	Y	6
El-Gilany, A-H.2006 38	Y	Y	Y	Ν	U	Y	/	Ν	Y	Ν	Y	6
Behal, R.2008 20	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Rifat-uz-Zaman2009 <sup>39</sup>	Y	Y	Y	1	U	Ν	/	Ν	Y	Y	Y	6
Dirisu, J. O.2011 <sup>40</sup>	Y	Y	Y	Y	U	Y	/	Ν	/	Y	Y	7
Saeed Anwar, M.2011 <sup>41</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Omar, A. A. 2012 <sup>42</sup>	Y	Ν	Y	Ν	U	Y	/	Ν	/	Y	Y	5
Tyagi, S.2013 <sup>43</sup>	Y	Y	Y	N	U	Y	/	Ν	Y	Y	Y	7
Sethi, B.2014 44	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Mohammadali, F.2014 <sup>17</sup>	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Nigam, J. S.2014 45	Y	Y	Y	Y	U	Y	1	Ν	Y	Y	Y	8
Zhao, Y.2014 46	Y	Ν	Y	Ν	U	Y		Ν	Y	Y	Y	6
Siransy, L. K.2015 <sup>47</sup>	Y	Y	Y	Y	U	Y	Y	N	1	Y	Y	8
Navolan, D.2015 <sup>48</sup>	Y	Y	Ν	Ν	U	Y	N	N	N	Y	Y	5
Bisetegen, F. S.201649	Y	Y	Y	Ν	U	Y	/	N	N	Y	Y	6
Abate, M.2016 <sup>50</sup>	Y	Ν	Y	Y	U	Y	/	Ν	Y	Y	Y	7
Bharadva, S.2016 <sup>51</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Naseri, Z.2016 52	Y	Ν	Y	Y	U	Y	/	Ν	Y	Y	Y	7
Memon, F. A.2017 53	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Liu, J.2017 <sup>16</sup>	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.

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Author         Year         Selection         Comparability         Outcome           T. T. Lao 2014 <sup>45</sup> 2014         3         1         3	Year	Selection	Comparability	Outcome
	2014	3	1	3

BMJ Open



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# PRISMA Checklist

136/bmjopen-20

Section/topic	#	Checklist item 41	Reported on page #
TITLE		4 4 0	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT	<u> </u>		
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	1		
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, in prventions, 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 needs as of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	5



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# **PRISMA Checklist**

Pa	ge 25 of 24		BMJ Open	
1 2	PRISMA C	hec	klist njopen-2019	
3 4 5	Section/topic	#	Checklist item	Reported on page #
6 7 8	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
9 10	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
11	RESULTS	-	202	
13 14	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
15 16 17	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
18	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
19 20 21	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summar data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
22	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of	8
23	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
25	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
26 27	DISCUSSION			
28 29	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
30 31 32	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., ine omplete retrieval of identified research, reporting bias).	12
33	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
34 35	FUNDING			
36 37	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
38 39 40 41 42 43		<u>.</u>	Page 2 of 2	<u>.                                    </u>
44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

BMJ Open

# **BMJ Open**

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

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Manuscript ID	bmjopen-2019-034114.R1
Article Type:	Original research
Date Submitted by the Author:	17-Dec-2019
Complete List of Authors:	Jing, wenzhan; Peking University, School of Public Health, Department of Epidemiology & Biostatistics Zhao, Siyu; Peking University, School of Public Health, Department of Epidemiology & Biostatistics Liu, Jue; Peking University, School of Public Health, Department of Epidemiology & Biostatistics Liu, Min; Peking University, School of Public Health, Department of Epidemiology & Biostatistics
<b>Primary Subject Heading</b> :	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology, Global health, Public health, Infectious diseases
Keywords:	Hepatitis B virus, ABO blood group, meta-analysis





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1	Title page
2	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  $\geq$  5%), Asian people, larger sample size studies ( $\geq$  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.

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- 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.

### 5 Introduction

Hepatitis B virus (HBV) infection is a major public health problem worldwide,<sup>1</sup> especially in Africa and
the Western Pacific Region.<sup>2</sup> 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.<sup>2</sup> HBV infection has caused
a high societal burden globally.<sup>1,2</sup>

The ABO blood group system, the most extensively investigated erythrocyte antigen system,<sup>3</sup> is widely used in clinical practice, and influences the host susceptibility.<sup>4,5</sup> 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,<sup>6</sup> coronary heart disease,<sup>7</sup> and tumorigenesis.<sup>3,4,8</sup> 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<sup>5</sup>) impact the half-life of VWF, so VWF survival in O subjects is significantly shorter versus (vs.) in non-O subjects.<sup>9-11</sup> Therefore, because of the lower VWF levels, O subjects have lower risk of venous thromboembolism.<sup>10</sup> Recently, a meta-analysis also found that hepatocellular carcinoma (HCC) patients might have a lower proportion of O subjects than healthy subjects.<sup>12</sup> 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.<sup>5,13</sup> 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,<sup>5</sup> and blood antigens are important as receptors for immune and inflammation response,<sup>14,15</sup> 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.<sup>16</sup> found that HBV prevalence was lower in blood group B

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(9.6%) and AB (9.1%), but higher in blood group O (10.2%). Liu et al.<sup>17</sup> suggested that blood group O was associated with increased HBV infection. Mohammadali et al.<sup>18</sup> found that the percentage of hepatitis B surface antigen (HBsAg) was lower in donors who had blood group O. However, Szmuness et al.<sup>19,20</sup> and Behal et al.<sup>21</sup> 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.<sup>22</sup>

## 10 Materials and methods

### 11 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.

### 18 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.

26 According to the inclusion and exclusion criteria, studies were identified by two reviewers (SZ and WJ)

- 27 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.

9 The quality of selected cohort studies were assessed using the Newcastle-Ottawa Scales (NOS) with a 10 score ranging from 0 to 9.<sup>23</sup> A score of 4–6 indicated moderate quality, and a score of 7–9 indicated high 11 quality. The quality of the selected cross-sectional studies were assessed using an 11-item checklist 12 recommended by the Agency for Healthcare Research and Quality (AHRQ)<sup>24</sup> with a score ranging from 0 13 to 11. A score of 4–7 indicated moderate quality, and a score of 8–11 indicated high quality.

### 14 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<sup>2</sup> was used to evaluate heterogeneity among the studies. When I<sup>2</sup>  $\leq$  50%, the included studies were considered to have little heterogeneity; when  $I^2 > 50\%$ , the included studies were considered to have substantial heterogeneity.<sup>25</sup> 

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.<sup>26</sup> Sensitivity analyses were performed by excluding large sample size studies orderly or at the same time, which dominated the results

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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.

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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  $\geq$ 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.

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Author	Sample         HBV infection (n/%)           Author         Income group         Race         Population								
Author	Income group	Race	Fopulation	size	Total	A, non-A <sup>a</sup>	B, non-B <sup>a</sup>	AB, non-AB <sup>a</sup>	O, non-Oª
Terrier, E.1970 <sup>27</sup>	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 <sup>28</sup>	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.197119	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 <sup>29</sup>	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.197430	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 <sup>31</sup>	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 <sup>20</sup>	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, 102/15.8
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 <sup>38</sup>	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, 318/2.20
Rifat-uz-Zaman200940	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.201141	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, 72/48.6
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. 201243	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 <sup>45</sup>	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 <sup>18</sup>	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, 5132/0.4
Nigam, J. S.2014 <sup>46</sup>	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 <sup>16 b</sup>	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.
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, 48/11.8
Siransy, L. K.2015 <sup>48</sup>	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, 2075/6.9
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 <sup>50</sup>	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 <sup>51</sup>	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, 177/5.5
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 <sup>17</sup>	Lower middle	Asian	General				58286/5.18, 157169/5.82		73651/6.34, 141804/5
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, 692/2.4
Ngassaki-Y, C-D.2018 <sup>56</sup>	Upper middle	African	Blood donors	4744	81/1.71	-	-	-	34/1.22, 47/2.41
Fu, X.2018 <sup>57</sup>	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, 253/20.5
Nkansah, C.201958	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, 112/1

<sup>a</sup> 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 58

59 blood group. <sup>b</sup> A cohort study.

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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  $\geq$  5%), Asian people, studies with larger sample sizes ( $\geq$ 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.

S	No. of	Sample	B vs. Non-	В	O vs. Non-	-0	A vs. Non-	A	AB vs. Nor	1-AB
Subgroup	studies	size	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 study17	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 <sup>18</sup>	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 <sup>17,18</sup>	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

3 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

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2	1	the Caucasian or African population. In general population, blood group A, B and AB had a decreased risk
3 4	2	of HBV infection compared to non-A, non-B and non-AB, respectively (OR = 0.98, 95%CI: 0.96–1.00;
5 6 7	3	OR = 0.93, 95% CI: 0.87–0.99 and OR = 0.89, 95% CI: 0.88–0.90, respectively) (Table 2).
7 8	4	
9 10	5	<b>Insert Figure 2.</b> Forest plots by prevalence: (A) B vs. non-B; (B) O vs. non-O.
11 12	6	
13 14	7	In the sensitivity analysis, when the study of Liu et al. <sup>17</sup> and Mohammadali et al. <sup>18</sup> , which dominated
15 16	8	the results of the meta-analysis, were orderly removed or both removed at the same time, the pooled risk
17 18	9	estimates were still stable, showing that blood B was associated with a lower risk of HBV infection (Table
19 20 21	10	2).
22 23	11	Publication bias
24 25	12	Funnel plots and Egger's tests were performed to assess publication bias. No obvious evidence of
26 27 28	13	publication bias was present for A vs. non-A, B vs. non-B, and O vs. non-O ( $P = 0.148$ ; $P = 0.223$ ; $P = 0$
28 29 30 31	14	0.364, respectively), while a publication bias of AB vs. non-AB was observed ( $P = 0.002$ ) (Figure 3).
32	15	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.
33 34	16	
35 36 37	17	Discussion
38 39	18	To our knowledge, this was the first meta-analysis of the association between ABO blood groups and HBV
40 41	19	infection. Our meta-analysis results suggested that blood group B was associated with a lower risk of HBV
42 43	20	infection, which was observed in subgroups and still stable in sensitive analyses, giving supportive
44 45	21	evidence that not only statistical association but also biologic association between ABO blood groups and
46 47 48	22	HBV infection probably exists.
48 49 50	23	As an infectious disease, aside from genetic susceptibility factors, there is the question of whether
50 51 52	24	exposure to the source of infection is directly related to the risk of infection. People living in higher
52 53 54	25	endemic areas are at higher risk of exposure to HBV than those living in lower endemic areas, which might
54 55 56	26	be the reason why the association between ABO blood group and HBV infection was only found in higher
57	27	endemic areas but not in lower endemic areas. Additionally, this association might be partly attributed to the
58	21	

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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.<sup>16</sup>, Liu et al.<sup>17</sup> and Abate et al.<sup>51</sup> 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.<sup>17</sup> 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.<sup>18</sup>, 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.,<sup>17</sup> 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.<sup>12</sup> 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.<sup>17</sup> or Mohammadali et al.<sup>18</sup>, 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

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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,<sup>17</sup> associations have been observed most likely related to the altered immune response<sup>16</sup> and systemic inflammatory response<sup>15</sup> 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<sup>59</sup>. 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.

### 23 Supplementary

- 24 Additional file 1: The electronic search strategy for PubMed.
- 25 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,

2	1	rhesus; RR, risk ratio; NOS, Newcastle-Ottawa Scales; AHRQ, Agency for Healthcare Research and
3 4	2	Quality.
5		
6 7	3	
8 9	4	Contributions All authors contributed to this work. ML and JL conceived and designed the study strategy;
10 11	5	SZ and WJ independently completed the processes of the article search, article assessment, data extraction,
12 13	6	quality assessment, and data analysis; and WJ wrote the manuscript. All authors read and approved the final
14 15	7	manuscript.
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20 21	10	Competing interests The authors declare that they have no competing interests.
22 23	11	Patient consent for publication Not required.
23 24 25	12	Provenance and peer review Not commissioned; externally peer reviewed.
25 26 27	13	Availability of data and material All data generated or analyzed during this study are included in this
27 28 29	14	published article and its supplementary information files.
30	15	Open access This is an open access article distributed in accordance with the Creative Commons Attribution
31 32	16	4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon
33 34	17	this work for any purpose, provided the original work is properly cited, a link to the licence is given, and
35 36	18	indication of whether changes were made. See: https://creativecommons. org/licenses/by/4.0/.
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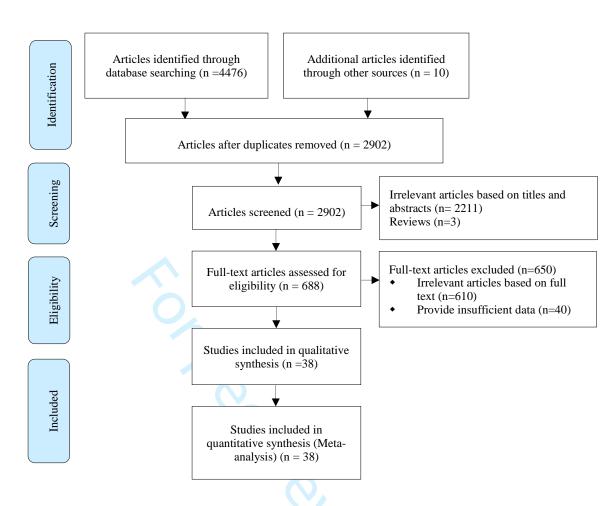
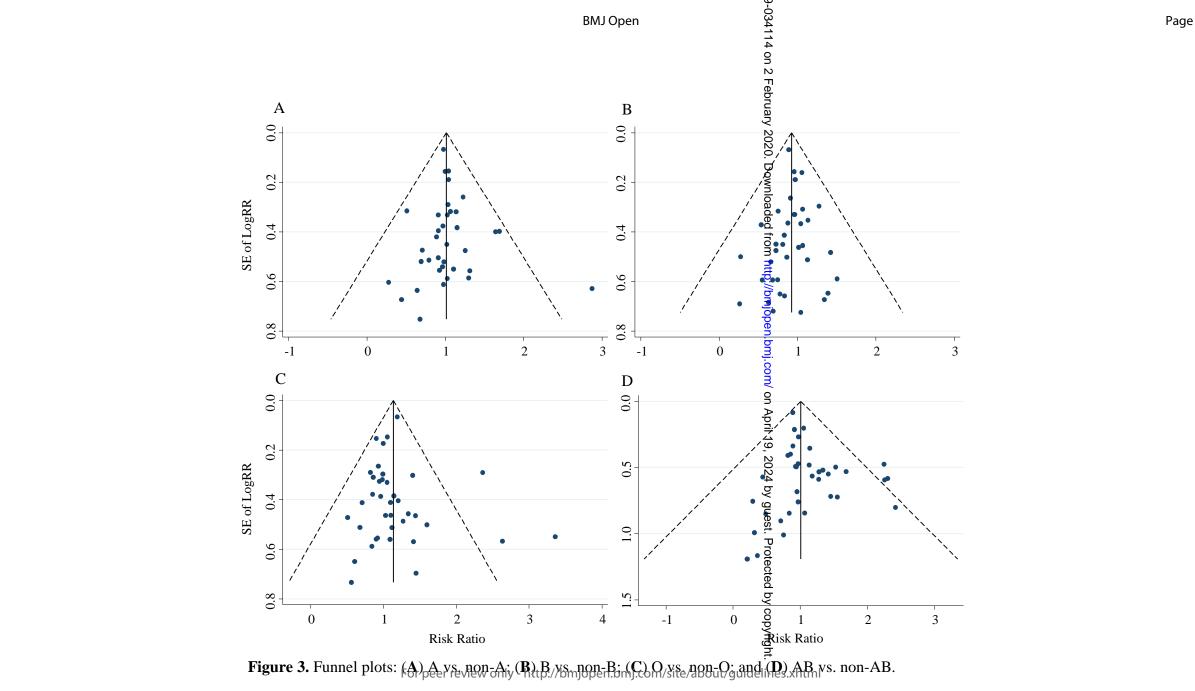


Figure 1. The process of study selection for the meta-analysis.

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1	Study ID	RR (95% CI)	% Weight	Study 14 ID 9		RR (95% CI)	% Weight
2	<5%		0.05	<5% Terrier, E. (1970) Szmuness, W. (1971) Zuberi, S. J. (1974)	· · · · · · · · · · · · · · · · · · ·	3.36 (1.86, 6.07)	1.23
3	Terrier, E. (1970)	0.69 (0.25, 1.90)	0.35 1.73	Szmuness, W. (1970)	<b>_</b>	).96 (0.72, 1.29)	2.92
4	Szmuness, W. (1971) Zuberi, S. J. (1974)	1.01 (0.67, 1.54) 0.26 (0.10, 0.67)	0.41	Zuberi, S. J. (1974)		2.63 (1.40, 4.96)	1.11
5	Vale, T. G. (1974)	0.20 (0.10, 0.07)	0.41	Vale, T. G. (1974)		0.84 (0.43, 1.66)	0.99
	Moore, H. H. (1975)	0.85 (0.50, 1.95)	4.24	Vale, T. G. (1974) Moore, H. H. (1975) Szmuness, W. (1975)		0.99 (0.83, 1.18)	4.14
6	Szmuness, W. (1975)	0.63 (0.25, 1.58)	0.43	Szmuness, W. (1975)		1.12 (0.67, 1.87)	1.51
7	Lenka, M. R. (1981)	0.78 (0.34, 1.78)	0.51	Lenka, M. R. (1981)		0.56 (0.19, 1.60)	0.46
8	Nath, N. (1985)	0.75 (0.37, 1.49)	0.73	Lenka, M. R. (1981) Nath, N. (1985) Sebastian, V. J. (1989) Zhu, C. (2002)		1.27 (0.80, 2.02)	1.74
9	Sebastian, V. J. (1989)	0.81 (0.55, 1.21)	1.86	Sebastian, V. J. (1989)		1.10 (0.79, 1.53)	2.60
10	Zhu, C. (2002)	0.72 (0.49, 1.08)	1.88	Zhu, C. (2002)		1.20 (0.87, 1.66)	2.69
11	Joshi, S. K. (2003)	1.04 (0.37, 2.92)	0.34	Joshi, S. K. (2003)		1.45 (0.56, 3.74)	0.55
	El-Gilany, A-H. (2006)	0.86 (0.53, 1.42)	1.31	El-Gilany, A-H. (2006)		1.34 (0.89, 2.02)	2.05 3.85
12	Behal, R. (2008)	1.07 (0.88, 1.29)	4.80	Behal, R. (2008) <u>Saeed Anwar, M. (2011)</u>		).99 (0.81, 1.21) 1.40 (1.17, 1.68)	3.83 4.07
13	Saeed Anwar, M. (2011)	0.75 (0.62, 0.92)	4.62	Tyagi, S. (2013)		1.03 (0.68, 1.57)	1.98
14	Tyagi, S. (2013)	0.73 (0.47, 1.13)	1.57	Sethi, B. (2014)		1.09 (0.59, 2.02)	1.16
15	Sethi, B. (2014)	0.55 (0.28, 1.10)	0.72	Mohammadali, F. (2014)		0.90 (0.86, 0.94)	5.21
16	Mohammadali, F. (2014)	1.06 (1.01, 1.11)	8.22	Tyagi, S. (2013)         Sethi, B. (2014)         Mohammadali, F. (2014)         Nigam, J. S. (2014)         Navolan, D. (2015)         Bharadva, S. (2016)         Naseri, Z. (2016)         Memon, F. A. (2017)         Batool, Z. (2017)		1.41 (0.75, 2.67)	1.10
17	Nigam, J. S. (2014) Navolan, D. (2015)	0.68 (0.34, 1.36) 1.39 (0.61, 3.16)	0.72	Navolan, D. (2015)		0.61 (0.27, 1.39)	0.71
	Bharadva, S. (2016)	1.04 (0.80, 1.36)	0.52 3.32	Bharadva, S. (2016)		0.85 (0.64, 1.13)	3.04
18	Naseri, Z. (2016)	1.28 (1.07, 1.51)	5.17	Naseri, Z. (2016)		0.82 (0.70, 0.97)	4.23
19	Memon, F. A. (2017)	1.13 (0.67, 1.89)	1.22	Memon, F. A. (2017)		0.68 (0.40, 1.13)	1.51
20	Batool, Z. (2017)	0.91 (0.79, 1.04)	6.10			0.93 (0.81, 1.07)	4.50
21	Subtotal (I-squared = $50.0\%$ , p = $0.004$ )	0.93 (0.85, 1.02)	51.28	Ngassaki-Y, C-D. (2018)		0.51 (0.33, 0.78)	1.89
22				Subtotal (I-squared = $69.7\%$ , <b>g</b> = $0.000$ )	T T	1.03 (0.93, 1.15)	55.23
23	>=5%			· >=5% pr	i.		
	Leski, M. (1970)	1.34 (0.55, 3.26)	0.45	Leski, M. (1970) $=$	• · · · · · · · · · · · · · · · · · · ·	).92 (0.50, 1.68)	1.19
24	Kulkarni, A. G. (1986)	0.28 (0.17, 0.45)	1.32	Kulkarni, A. G. (1986)		1.14 (0.86, 1.53)	2.94
25	Naidu, A. S. (1986)	0.83 (0.59, 1.16)	2.43			0.71 (0.51, 0.99)	2.59
26	Rifat-uz-Zaman (2009)	1.07 (0.71, 1.61)	1.81	Naidu, A. S. (1986) 20 Rifat-uz-Zaman (2009) 24		1.10 (0.73, 1.68)	1.99
27	Dirisu, J. O. (2011)	1.14 (0.89, 1.45)	3.64			0.94 (0.77, 1.16)	3.76
28	Omar, A. A. (2012)	1.42 (0.90, 2.25)	1.49	Omar, A. A. (2012)		1.44 (0.94, 2.20)	1.96
29	Lao, T. T. (2014)	0.96 (0.91, 1.01)	8.27	Dirisu, J. O. (2011)     B       Omar, A. A. (2012)     G       Lao, T. T. (2014)     G       Zhao, Y. (2014)     Stronger, L. K. (2015)		1.05 (1.01, 1.10)	5.22
	Zhao, Y. (2014)	0.66 (0.39, 1.13)	1.16	Zhao, Y. (2014)		1.60 (0.98, 2.62)	1.61
30	Siransy, L. K. (2015) Bisetegen, F. S. (2016)	0.97 (0.91, 1.04) 1.51 (0.76, 2.98)	7.82 0.74			0.99 (0.94, 1.05)	5.14
31	Abate, M. (2016)	0.54 (0.41, 0.70)	3.24	Bisetegen, F. S. (2016)     The set of t		0.90(0.49, 1.66)	1.16
32	Liu, J. (2017)	0.89 (0.88, 0.90)	8.70	Abate, M. (2016)		2.36 (2.00, 2.79) 1.19 (1.18, 1.20)	4.21 5.31
33	Fu, X. (2018) $$	0.97 (0.78, 1.19)	4.25	Fu, X. (2018)		0.86 (0.71, 1.04)	3.98
34	Nkansah, C. (2019)	0.88 (0.68, 1.14)	3.40	Nkansah, C. (2019)		1.05 (0.85, 1.30)	3.70
35	Subtotal (I-squared = $79.7\%$ , p = 0.000)	0.90 (0.83, 0.98)	48.72	Subtotal (I-squared = $91.9\%$ , <b>g</b> = 0.000)	$\mathbf{r}$	1.12 (1.01, 1.24)	44.77
36				. Ď			
	Overall (I-squared = 75.0%, $p = 0.000$ )	0.92 (0.86, 0.98)	100.00	Overall (I-squared = $90.1\%$ , $\vec{p} = 0.000$ )	$\mathbf{\Theta}$	1.07 (0.99, 1.15)	100.00
37	NOTE: Weights are from random effects analysis			NOTE: Weights are from random effects analysi			
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39	0.103 1	For peer review only - htt	h://pwlobe	n.bmj.com/site/about/guidelines.xhtml	1 6.07	,	
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<sup>40</sup><sub>41</sub> Figure 2. Forest plots by prevalence: (A) B vs. non-B; (B) O vs. non-O.



### 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[Text Word]] OR hepatitis B[Tex

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### 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	Tota
Terrier, E.1970 <sup>27</sup>	Y	Ν	Ν	U	U	Y	/	N	/	Y	Y	4
Leski, M.1970 <sup>28</sup>	Y	Ν	Y	Ν	U	Y	Ν	N	/	Y	Y	5
Szmuness, W.1971 <sup>19</sup>	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Zuberi, S. J.1974 <sup>29</sup>	Y	Ν	Y	Y	U	Y	/	N	/	Y	Y	6
Vale, T. G.1974 <sup>30</sup>	Y	Ν	Y	Y	U	Y	/	N	/	Y	Y	6
Moore, H. H.1975 <sup>31</sup>	Y	Ν	Y	Y	U	Y	/	N	/	Y	Y	6
Szmuness, W.1975 <sup>20</sup>	Y	Y	Y	Y	U	Y	Y	Ν	/	Y	Y	8
Lenka, M. R.1981 32	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Nath, N.1985 33	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Kulkarni, A. G.1986 34	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Naidu, A. S.1986 35	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Sebastian, V. J.1989 36	Y	Ν	Ν	Ν	U	Y	/	Ν	Ν	Y	Y	4
Zhu, C.2002 37	Y	Ν	Y	Y	U	Y	Ν	Ν	Ν	Ν	Y	5
Joshi, S. K.2003 <sup>38</sup>	Y	Y	Y	Ν	U	Y	/	Ν	/	Y	Y	6
El-Gilany, A-H.2006 39	Y	Y	Y	Ν	U	Y	/	Ν	Y	Ν	Y	6
Behal, R.2008 21	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Rifat-uz-Zaman200940	Y	Y	Y	/	U	Ν	/	Ν	Y	Y	Y	6
Dirisu, J. O.2011 <sup>41</sup>	Y	Y	Y	Y	U	Y	/	Ν	/	Y	Y	7
Saeed Anwar, M.2011 <sup>42</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Omar, A. A. 2012 <sup>43</sup>	Y	Ν	Y	N	U	Y	/	Ν	/	Y	Y	5
Tyagi, S.2013 44	Y	Y	Y	N	U	Y	/	Ν	Y	Y	Y	7
Sethi, B.2014 45	Y	Y	Y	Y	U	Y	/	N	Y	Y	Y	8
Mohammadali, F.2014 <sup>18</sup>	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Nigam, J. S.2014 46	Y	Y	Y	Y	U	Y	1	Ν	Y	Y	Y	8
Zhao, Y.2014 47	Y	Ν	Y	Ν	U	Y		Ν	Y	Y	Y	6
Siransy, L. K.2015 <sup>48</sup>	Y	Y	Y	Y	U	Y	Y	N	1	Y	Y	8
Navolan, D.2015 <sup>49</sup>	Y	Y	Ν	Ν	U	Y	N	N	N	Y	Y	5
Bisetegen, F. S.2016 <sup>50</sup>	Y	Y	Y	N	U	Y	/	N	Ν	Y	Y	6
Abate, M.2016 51	Y	Ν	Y	Y	U	Y	/	Ν	Y	Y	Y	7
Bharadva, S.2016 52	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Naseri, Z.2016 53	Y	Ν	Y	Y	U	Y	/	Ν	Y	Y	Y	7
Memon, F. A.2017 54	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Liu, J.2017 <sup>17</sup>	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	9
Batool, Z.2017 55	Y	Y	Y	Y	U	Y	U	Ν	U	Ν	Y	6
Ngassaki-Y, C-D.2018 <sup>56</sup>	Y	Y	Y	Y	U	Y	/	N	/	Y	Y	7
Fu, X.2018 <sup>57</sup>	Y	Y	Y	Y	U	Y	Y	N	Ν	Y	Y	8
Nkansah, C.2019 <sup>58</sup>	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).

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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 <sup>16</sup>	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.

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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.

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

# ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and

### Meta-Analysis

Cri	teria	Brief description of how the criteria were handled in the meta-analysis				
Rep	porting 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.				
$\checkmark$	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				
Rep	porting 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				

Do	porting of methods should include	for the data, but nobody responded to us
ne	Description of relevance or	
	appropriateness of studies assembled for	Detailed inclusion and exclusion criteria
•	assessing the hypothesis to be tested	described in the paper.
	Rationale for the selection and coding of data	(1) the basic information of the studies including first author, publication year, survey time, study design; (2) the characteristics of the study population including country, income group, race, population type (e.g., blood donors, pat general population), sample size, the nu of HBV-infected and uninfected subject range, mean age, sex ratio; (3) the outcome measure: the number of HBV-infected a uninfected subjects in each ABO blood and (4) the author's general conclusions
$\checkmark$	Documentation of how data were classified and coded	The prevalence of HBV infection was calculated in each study based on the n of HBV-infected and uninfected subject Studies were divided into Caucasian, A and Negroid subgroups depending on the major national race and divided into his upper middle, lower middle and low in groups according to the World Bank liss economies.
$\checkmark$	Assessment of confounding	Subgroup analyses were performed by prevalence, race, sample size, population income group, study type, and publicat 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 w assessed using the Newcastle-Ottawa S (NOS). The quality of the selected cross sectional studies were assessed using an item checklist recommended by the Ag Healthcare Research and Quality (AHR
	Assessment of heterogeneity	$I^2$ was used to evaluate heterogeneity at the studies. When $I^2 \leq 50\%$ , the includ studies were considered to have little heterogeneity; when $I^2 > 50\%$ , the inclu studies were considered to have substar heterogeneity.
$\checkmark$	Description of statistical methods in sufficient detail to be replicated	RRs and 95% CIs (A vs. non-A, B vs. r O vs. non-O, AB vs. non-AB) were poor using of random-effect models with the estimate of heterogeneity being taken fr Mantel-Haenszel model, and P < 0.05 v

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		deemed significantly.
$\checkmark$	Provision of appropriate tables and graphics	Figure 2,3 and Table 2
Rej	porting of results should include	
$\checkmark$	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
$\checkmark$	Indication of statistical uncertainty of findings	RR, 95% CI, $I^2$ and P
Rej	porting of discussion should include	
	Quantitative assessment of bias	Results of subgroup analyses and sensitive analyses were discussed.
V	Justification for exclusion	<ul> <li>(1) the article was not relevant to the subject of the study (animal experiments, pathological researches, molecular researches); (2) reviews;</li> <li>(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.</li> </ul>
	Assessment of quality of included studies	Table S1-1 and Table S1-2
Rej	porting of conclusions should include	
$\checkmark$	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.
$\checkmark$	Generalization of the conclusions	In conclusion, blood group B was associated with a lower risk of HBV infection.
$\checkmark$	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.
$\checkmark$	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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# **BMJ Open**

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

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<b>Primary Subject Heading</b> :	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology, Global health, Public health, Infectious diseases
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1	Title page
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### **BMJ** Open

### 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  $\geq$  5%), Asian people, larger sample size studies ( $\geq$  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.

### 27 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.

### 5 Introduction

Hepatitis B virus (HBV) infection is a major public health problem worldwide,<sup>1</sup> especially in Africa and
the Western Pacific Region.<sup>2</sup> 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.<sup>2</sup> HBV infection has caused
a high societal burden globally.<sup>1,2</sup>

The ABO blood group system, the most extensively investigated erythrocyte antigen system,<sup>3</sup> is widely used in clinical practice, and influences the host susceptibility.<sup>4,5</sup> 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,<sup>6</sup> coronary heart disease,<sup>7</sup> and tumorigenesis.<sup>3,4,8</sup> 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<sup>5</sup>) impact the half-life of VWF, so VWF survival in O subjects is significantly shorter versus (vs.) in non-O subjects.<sup>9-11</sup> Therefore, because of the lower VWF levels, O subjects have lower risk of venous thromboembolism.<sup>10</sup> Recently, a meta-analysis also found that hepatocellular carcinoma (HCC) patients might have a lower proportion of O subjects than healthy subjects.<sup>12</sup> 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.<sup>5,13</sup> 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,<sup>5</sup> and blood antigens are important as receptors for immune and inflammation response,<sup>14,15</sup> 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.<sup>16</sup> found that HBV prevalence was lower in blood group B

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(9.6%) and AB (9.1%), but higher in blood group O (10.2%). Liu et al.<sup>17</sup> suggested that blood group O was associated with increased HBV infection. Mohammadali et al.<sup>18</sup> found that the percentage of hepatitis B surface antigen (HBsAg) was lower in donors who had blood group O. However, Szmuness et al.<sup>19,20</sup> and Behal et al.<sup>21</sup> 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.<sup>22</sup>

# 10 Materials and methods

### 11 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.

### 18 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.

26 According to the inclusion and exclusion criteria, studies were identified by two reviewers (SZ and WJ)

- 27 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.

9 The quality of selected cohort studies were assessed using the Newcastle-Ottawa Scales (NOS) with a 10 score ranging from 0 to 9.<sup>23</sup> A score of 4–6 indicated moderate quality, and a score of 7–9 indicated high 11 quality. The quality of the selected cross-sectional studies were assessed using an 11-item checklist 12 recommended by the Agency for Healthcare Research and Quality (AHRQ)<sup>24</sup> with a score ranging from 0 13 to 11. A score of 4–7 indicated moderate quality, and a score of 8–11 indicated high quality.

### 14 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. Betweenstudy heterogeneity was evaluated with the I<sup>2</sup> 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.<sup>25</sup> 

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.<sup>26</sup> Sensitivity analyses were performed by excluding large sample size studies orderly or at the same time, which dominated the results

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< 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  $\geq$ 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.

1

A 4h	T	Dava	Denvlation	Sample	HBV infection (n/%)							
Author	Income group	Race	Population	size	Total	A, non-A <sup>a</sup>	B, non-B <sup>a</sup>	AB, non-AB <sup>a</sup>	O, non-Oª			
Terrier, E.1970 <sup>27</sup>	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 <sup>28</sup>	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.197119	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 <sup>29</sup>	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.197430	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 <sup>31</sup>	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, 247/3.3			
Szmuness, W.1975 <sup>20</sup>	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.			
Sebastian, V. J.1989 <sup>36</sup>	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 <sup>37</sup>	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 <sup>38</sup>	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 <sup>39</sup>	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 <sup>21</sup>	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, 318/2.2			
						5/3.01, 88/6.90						
Rifat-uz-Zaman2009 <sup>40</sup>	Lower middle	Caucasian	General	1464	93/6.35		35/6.63, 58/6.20	23/6.99, 70/6.17	30/6.80, 63/6.10			
Dirisu, J. O.2011 <sup>41</sup>	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.			
Saeed Anwar, M.2011 <sup>42</sup>	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, 259/2.4			
Omar, A. A. 2012 <sup>43</sup>	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, 39/14.2			
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 <sup>18</sup>	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			
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 <sup>16 b</sup>	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			
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, 48/11.8			
Siransy, L. K.201548	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.			
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 <sup>50</sup>	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.			
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, 169/0.5			
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, 430/0.3			
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			
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, 692/2.4			
Ngassaki-Y, C-D.201856	Upper middle	African	Blood donors	4744	81/1.71	-	-	-	34/1.22, 47/2.41			
Fu, X.2018 <sup>57</sup>	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, 253/20.5			
Nkansah, C.201958	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				

<sup>a</sup> 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 58

59 blood group. <sup>b</sup> A cohort study.

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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  $\geq$  5%), Asian people, studies with larger sample sizes ( $\geq$ 2000), general population and blood donors, lower middle income group, and articles published before in the second 2010 years (Table 2).

### **Table 2.** The main, subgroup and sensitivity analyses.

Subgroup	No. of	Sample _	B vs. Non-	В	O vs. Non	-0	A vs. Non-	AB vs. Non-AB		
Subgroup	studies	size	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
All studies	38	6487481	0.92 (0.86,0.98)	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 study17	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 <sup>18</sup>	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 <sup>17,18</sup>	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

3 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

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1 2	1	the Caucasian or African population. In general population, blood group A, B and AB had a decreased risk
3 4	2	of HBV infection compared to non-A, non-B and non-AB, respectively (RR = 0.98, 95%CI: 0.96–1.00;
5 6 7	3	RR = 0.93, 95% CI: 0.87–0.99 and RR = 0.89, 95% CI: 0.88–0.90, respectively) (Table 2).
, 8 9	4	
10 11	5	<b>Insert Figure 2.</b> Forest plots by prevalence: ( <b>A</b> ) B vs. non-B; ( <b>B</b> ) O vs. non-O.
12	6	
13 14 15	7	In the sensitivity analysis, when the study of Liu et al. <sup>17</sup> and Mohammadali et al. <sup>18</sup> , which dominated
15 16	8	the results of the meta-analysis, were orderly removed or both removed at the same time, the pooled risk
17 18	9	estimates were still stable, showing that blood B was associated with a lower risk of HBV infection (Table
19 20 21	10	2).
22 23 24	11	Publication bias
25 26	12	Funnel plots and Egger's tests were performed to assess publication bias. No obvious evidence of
27 28	13	publication bias was present for A vs. non-A (Figure 3A), B vs. non-B (Figure 3B), and O vs. non-O
29 30	14	(Figure 3C) ( $p = 0.148$ ; $p = 0.223$ ; $p = 0.364$ , respectively), while a publication bias of AB vs. non-AB
31 32 33	15	was observed (Figure 3D) ( $p = 0.002$ ).
34 35	16	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.
36	17	
37 38	18	Discussion
39	18	
40 41	19	To our knowledge, this was the first meta-analysis of the association between ABO blood groups and HBV
42 43	20	infection. Our meta-analysis results suggested that blood group B was associated with a lower risk of HBV
44 45	21	infection, which was observed in subgroups and still stable in sensitive analyses, giving supportive
46 47	22	evidence that not only statistical association but also biologic association between ABO blood groups and
48 49	23	HBV infection probably exists.
50 51	24	As an infectious disease, aside from genetic susceptibility factors, there is the question of whether
52 53	25	exposure to the source of infection is directly related to the risk of infection. People living in higher
54 55	26	endemic areas are at higher risk of exposure to HBV than those living in lower endemic areas, which might
56 57 58 59 60	27	be the reason why the association between ABO blood group and HBV infection was only found in higher

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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.<sup>16</sup>, Liu et al.<sup>17</sup> and Abate et al.<sup>51</sup> 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.<sup>17</sup> 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.<sup>18</sup>, 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.,<sup>17</sup> 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.<sup>12</sup> 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

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the results, we orderly removed the study of Liu et al.<sup>17</sup> or Mohammadali et al.<sup>18</sup>, 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.<sup>17</sup> associations have been observed that are most likely related to the altered immune response<sup>16</sup> and systemic inflammatory response,<sup>15</sup> 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<sup>59</sup>. 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.

### 26 Supplementary

27 Additional file 1: The electronic search strategy for PubMed.

28 Additional file 2: Quality assessment tables.

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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. Funding This study was supported by the National Natural Science Foundation of China (Grant No. 71934002, No. 71874003 and No. 81703240). **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. Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. REFERENCES Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014; 384(9959): 2053-63. 1. WHO. Global hepatitis report, 2017. 2017. http://www.who.int/hepatitis/publications/global-hepatitis-2. report2017/en/#. Li B, Tan B, Chen C, Zhao L, Qin L. Association between the ABO blood group and risk of common cancers. J Evid Based Med 2014; 7(2): 79-83. 4. Wang W, Liu L, Wang Z, et al. ABO blood group and esophageal carcinoma risk: from a case-control study in Chinese population to meta-analysis. Cancer Causes Control 2014; 25(10): 1369-77. 5. Cooling L. Blood Groups in Infection and Host Susceptibility. Clin Microbiol Rev 2015; 28(3): 801-70. 6. Alpoim PN, de Barros Pinheiro M, Junqueira DR, et al. Preeclampsia and ABO blood groups: a systematic review and meta-analysis. Mol Biol Rep 2013; 40(3): 2253-61. 7. He M, Wolpin B, Rexrode K, et al. ABO blood group and risk of coronary heart disease in two prospective cohort studies. Arterioscler Thromb Vasc Biol 2012; 32(9): 2314-20. Miao SY, Zhou W, Chen L, Wang S, Liu XA. Influence of ABO blood group and Rhesus factor on breast 8.

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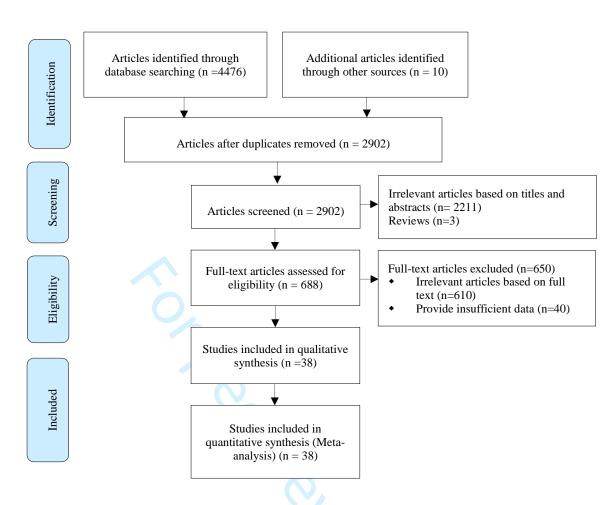
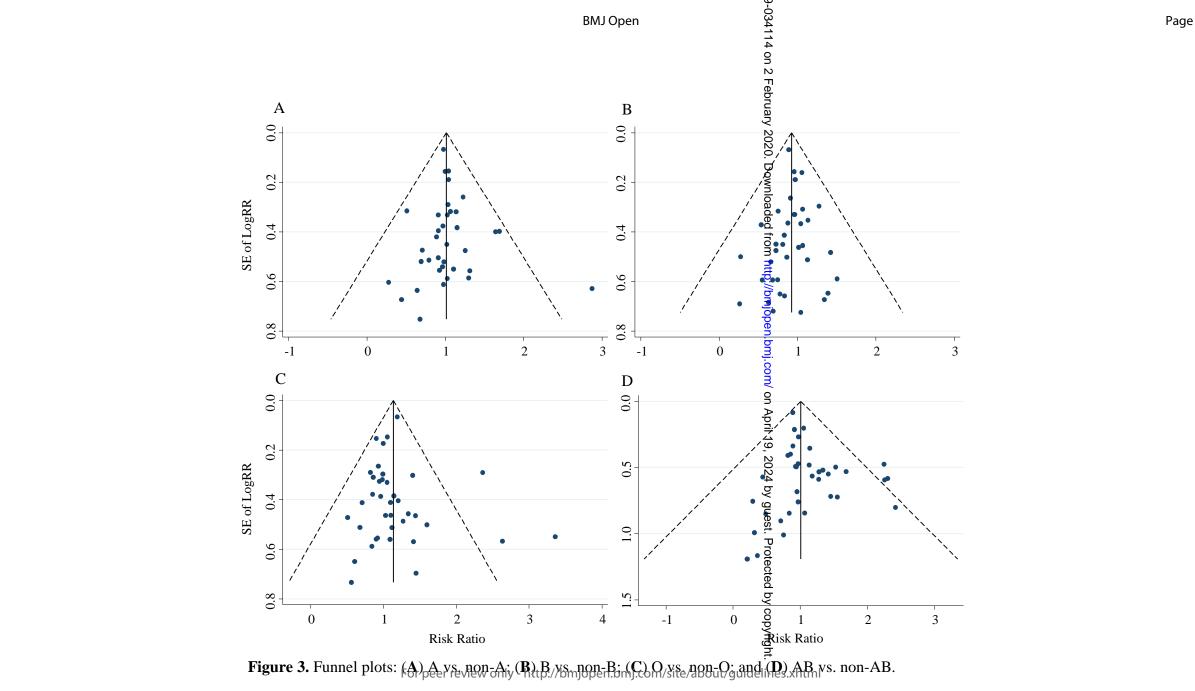


Figure 1. The process of study selection for the meta-analysis.

Page	e 19 <b>4</b> of 26		BM.	J Op <b>B</b> n 411 Study 14			
1	Study ID	RR (95% CI)	% Weight	Study <sup>1</sup> ID 9	RR	(95% CI)	% Weight
2	<5%		0.05	<5% P Terrier, E. (1970) B Szmuness, W. (1971) Zuberi, S. J. (1974) P		6 (1.86, 6.07)	1.23
3	Terrier, E. (1970)	0.69 (0.25, 1.90)	0.35 1.73	Szmuness, W. (1971)		6(0.72, 1.29)	2.92
4	Szmuness, W. (1971) Zuberi, S. J. (1974)	1.01 (0.67, 1.54) 0.26 (0.10, 0.67)	0.41	Zuberi, S. J. (1974)		3 (1.40, 4.96)	1.11
5	Vale, T. G. (1974)	0.83 (0.36, 1.95)	0.41	Vale, T. G. (1974)		4 (0.43, 1.66)	0.99
	Moore, H. H. (1975)	0.96 (0.77, 1.19)	4.24	Vale, T. G. (1974) Moore, H. H. (1975) Szmuness, W. (1975)		9 (0.83, 1.18)	4.14
6	Szmuness, W. (1975)	0.63 (0.25, 1.58)	0.43	Szmuness, W. (1975)		2 (0.67, 1.87)	1.51
7	Lenka, M. R. (1981)	0.78 (0.34, 1.78)	0.51		0.5	6 (0.19, 1.60)	0.46
8	Nath, N. (1985)	0.75 (0.37, 1.49)	0.73	Lenka, M. R. (1981) Nath, N. (1985) Sebastian, V. J. (1989) Zhu, C. (2002)	1.2	7 (0.80, 2.02)	1.74
9	Sebastian, V. J. (1989)	0.81 (0.55, 1.21)	1.86	Sebastian, V. J. (1989)		0 (0.79, 1.53)	2.60
10	Zhu, C. (2002)	0.72 (0.49, 1.08)	1.88	Zhu, C. (2002)		0 (0.87, 1.66)	2.69
	Joshi, S. K. (2003)	1.04 (0.37, 2.92)	0.34	Joshi, S. K. (2003)	1.4	5 (0.56, 3.74)	0.55
11	El-Gilany, A-H. (2006)	0.86 (0.53, 1.42)	1.31	El-Gilany, A-H. (2006)		4 (0.89, 2.02)	2.05
12	Behal, R. (2008)	1.07 (0.88, 1.29)	4.80	Behal, R. (2008)		9 (0.81, 1.21)	3.85
13	Saeed Anwar, M. (2011)	0.75 (0.62, 0.92)	4.62	Saeed Anwar, M. (2011) $\overrightarrow{F}$		0(1.17, 1.68)	4.07
14	Tyagi, S. (2013)	0.73 (0.47, 1.13)	1.57	Tyagi, S. (2013) Sethi, B. (2014)		3 (0.68, 1.57) 9 (0.59, 2.02)	1.98 1.16
15	Sethi, B. (2014)	0.55 (0.28, 1.10)	0.72	Mohammadali, F. (2014)		0(0.39, 2.02) 0(0.86, 0.94)	5.21
	Mohammadali, F. (2014)	1.06 (1.01, 1.11)	8.22	Tyagi, S. (2013)         Sethi, B. (2014)         Mohammadali, F. (2014)         Nigam, J. S. (2014)         Navolan, D. (2015)         Bharadva, S. (2016)         Naseri, Z. (2016)         Memon, F. A. (2017)         Batool, Z. (2017)		1(0.75, 2.67)	1.10
16	Nigam, J. S. (2014)	0.68 (0.34, 1.36)	0.72	Navolan, D. (2015)	•	(0.27, 1.39)	0.71
17	Navolan, D. (2015)	1.39 (0.61, 3.16)	0.52	Bharadva, S. (2016)		5 (0.64, 1.13)	3.04
18	Bharadva, S. (2016)	1.04 (0.80, 1.36)	3.32	Naseri, Z. (2016)		2 (0.70, 0.97)	4.23
19	Naseri, Z. (2016)	1.28 (1.07, 1.51)	5.17	Memon, F. A. (2017)		8 (0.40, 1.13)	1.51
20	Memon, F. A. (2017)	1.13 (0.67, 1.89)	1.22	Batool, Z. (2017) 8		3 (0.81, 1.07)	4.50
	Batool, Z. (2017)	0.91 (0.79, 1.04)	6.10	Ngassaki-Y. C-D. (2018)		1 (0.33, 0.78)	1.89
21	Subtotal (I-squared = $50.0\%$ , p = $0.004$ )	0.93 (0.85, 1.02)	51.28	Subtotal (I-squared = $69.7\%$ , <b><math>g = 0.000</math>)</b>		3 (0.93, 1.15)	55.23
22				-			
23	>=5% Leski, M. (1970)	- 1.34 (0.55, 3.26)	0.45	· >=5% Locki M (1070)			
24	Kulkarni, A. G. (1986)	0.28 (0.17, 0.45)	1.32	Leski, M. $(1970)$		2 (0.50, 1.68)	1.19
25	Naidu, A. S. (1986)	0.83 (0.59, 1.16)	2.43			4 (0.86, 1.53)	2.94
26	Rifat-uz-Zaman (2009)	1.07 (0.71, 1.61)	1.81	Naidu, A. S. (1986) Rifat-uz-Zaman (2009)		1(0.51, 0.99)	2.59
27	Dirisu, J. O. (2011)	1.14 (0.89, 1.45)	3.64			0 (0.73, 1.68) 4 (0.77, 1.16)	1.99 3.76
	Omar, A. A. (2012)	1.42 (0.90, 2.25)	1.49	Omar, A. A. (2012)		4 (0.94, 2.20)	3.70 1.96
28	Lao, T. T. (2014)	0.96 (0.91, 1.01)	8.27	Diffsul, J. O. (2011)     by       Omar, A. A. (2012)     g       Lao, T. T. (2014)     g       Zhao, Y. (2014)     g       Simmery L. K. (2015)     g	• 10	5(1.01, 1.10)	5.22
29	Zhao, Y. (2014)	0.66 (0.39, 1.13)	1.16	Zhao, Y. (2014)		0 (0.98, 2.62)	1.61
30	Siransy, L. K. (2015)	0.97 (0.91, 1.04)	7.82		• 0.9	9 (0.94, 1.05)	5.14
31	Bisetegen, F. S. (2016)	1.51 (0.76, 2.98)	0.74	Bisetegen, F. S. (2016)     The set of t		0 (0.49, 1.66)	1.16
32	Abate, M. (2016)	0.54 (0.41, 0.70)	3.24	Abate, M. (2016)		6 (2.00, 2.79)	4.21
	Liu, J. (2017)	0.89 (0.88, 0.90)	8.70	Liu, J. (2017)	1.1	9 (1.18, 1.20)	5.31
33	Fu, X. (2018)	0.97 (0.78, 1.19)	4.25	1 4, 11. (2010)		6 (0.71, 1.04)	3.98
34	Nkansah, C. (2019)	0.88 (0.68, 1.14)	3.40	Nkansah, C. (2019) 😽	1.0	5 (0.85, 1.30)	3.70
35	Subtotal (I-squared = 79.7%, $p = 0.000$ )	0.90 (0.83, 0.98)	48.72	Subtotal (I-squared = $91.9\%$ , <b>g</b> = $0.000$ )	1.1	2 (1.01, 1.24)	44.77
36 37	Overall (I-squared = $75.0\%$ , p = $0.000$ )	0.92 (0.86, 0.98)	100.00	Overall (I-squared = 90.1%, $\vec{E} = 0.000$ )		7 (0.99, 1.15)	100.00
38	NOTE: Weights are from random effects analysis			NOTE: Weights are from random effects analys	518		
		For peer review only - htt	p://bmione	n.bmj.com/site/about/guidelines.xhtml			
39 40	0.103 1	9.7		0.165	1 6.07		

<sup>40</sup><sub>41</sub> Figure 2. Forest plots by prevalence: (A) B vs. non-B; (B) O vs. non-O.



### 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[Text Word]] OR hepatitis B[Text

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### 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	Tota
Terrier, E.1970 <sup>27</sup>	Y	Ν	N	U	U	Y	/	Ν	/	Y	Y	4
Leski, M.1970 <sup>28</sup>	Y	Ν	Y	N	U	Y	Ν	Ν	/	Y	Y	5
Szmuness, W.1971 <sup>19</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Zuberi, S. J.1974 <sup>29</sup>	Y	Ν	Y	Y	U	Y	/	Ν	/	Y	Y	6
Vale, T. G.1974 <sup>30</sup>	Y	Ν	Y	Y	U	Y	/	Ν	/	Y	Y	6
Moore, H. H.1975 <sup>31</sup>	Y	Ν	Y	Y	U	Y	/	Ν	/	Y	Y	6
Szmuness, W.1975 <sup>20</sup>	Y	Y	Y	Y	U	Y	Y	Ν	/	Y	Y	8
Lenka, M. R.1981 32	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Nath, N.1985 33	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Kulkarni, A. G.1986 <sup>34</sup>	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Naidu, A. S.1986 35	Y	Ν	Ν	Ν	U	Y	/	Ν	Y	Y	Y	5
Sebastian, V. J.1989 <sup>36</sup>	Y	Ν	Ν	Ν	U	Y	/	Ν	Ν	Y	Y	4
Zhu, C.2002 <sup>37</sup>	Y	Ν	Y	Y	U	Y	Ν	Ν	Ν	Ν	Y	5
Joshi, S. K.2003 <sup>38</sup>	Y	Y	Y	Ν	U	Y	/	Ν	/	Y	Y	6
El-Gilany, A-H.2006 <sup>39</sup>	Y	Y	Y	Ν	U	Y	/	Ν	Y	Ν	Y	6
Behal, R.2008 <sup>21</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Rifat-uz-Zaman200940	Y	Y	Y	/	U	Ν	/	Ν	Y	Y	Y	6
Dirisu, J. O.2011 <sup>41</sup>	Y	Y	Y	Y	U	Y	/	Ν	/	Y	Y	7
Saeed Anwar, M.2011 <sup>42</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Omar, A. A. 2012 <sup>43</sup>	Y	Ν	Y	N	U	Y	/	Ν	/	Y	Y	5
Tyagi, S.2013 44	Y	Y	Y	N	U	Y	/	Ν	Y	Y	Y	7
Sethi, B.2014 45	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Mohammadali, F.2014 <sup>18</sup>	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Nigam, J. S.2014 46	Y	Y	Y	Y	U	Y	1	Ν	Y	Y	Y	8
Zhao, Y.2014 47	Y	Ν	Y	Ν	U	Y		Ν	Y	Y	Y	6
Siransy, L. K.2015 <sup>48</sup>	Y	Y	Y	Y	U	Y	Y	Ν	1	Y	Y	8
Navolan, D.2015 <sup>49</sup>	Y	Y	Ν	Ν	U	Y	N	N	N	Y	Y	5
Bisetegen, F. S.2016 <sup>50</sup>	Y	Y	Y	Ν	U	Y	/	Ν	N	Y	Y	6
Abate, M.2016 51	Y	Ν	Y	Y	U	Y	/	Ν	Y	Y	Y	7
Bharadva, S.2016 <sup>52</sup>	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Naseri, Z.2016 53	Y	Ν	Y	Y	U	Y	/	Ν	Y	Y	Y	7
Memon, F. A.2017 54	Y	Y	Y	Y	U	Y	/	Ν	Y	Y	Y	8
Liu, J.2017 <sup>17</sup>	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	9
Batool, Z.2017 55	Y	Y	Y	Y	U	Y	U	Ν	U	Ν	Y	6
Ngassaki-Y, C-D.2018 <sup>56</sup>	Y	Y	Y	Y	U	Y	/	Ν	/	Y	Y	7
Fu, X.2018 <sup>57</sup>	Y	Y	Y	Y	U	Y	Y	Ν	Ν	Y	Y	8
Nkansah, C.2019 <sup>58</sup>	Y	Y	Y	Y	U	Y	Y	Ν	/	Y	Y	8

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

Note:

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

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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 <sup>16</sup>	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.

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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.

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

# ABO Blood Groups and Hepatitis B Virus Infection: A Systematic Review and

**Meta-Analysis** 

Criteria Reporting of background should include		Brief description of how the criteria were handled in the meta-analysis	Page No.	
		•		
	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	
	porting of search strategy should lude			
$\checkmark$	Qualifications of searchers	Two reviewers (SZ and WJ) searched for articles independently.	P4/Line12	
$\checkmark$	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	
$\checkmark$	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.	
$\checkmark$	Method of addressing articles published in languages other than English	There was no limitation of language.	P4/Line16-1
	Method of handling abstracts and unpublished studies	We did not include unpublished studies. If abstract could provide full information, it was included.	None
$\checkmark$	Description of any contact with authors	When needed, we contacted the original author for the data, but nobody responded to us.	None
Re	porting 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/Line19-2
V	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/Line24-2

$\checkmark$	Assessment of confounding	divided into high, upper middle, lower middle and low income groups according to the World Bank list of economies. Subgroup analyses were performed by HBV prevalence, race, sample size, population, income group, study type, and publication year.	P5/Line23-2
$\checkmark$	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 <sup>2</sup> statistic. When I <sup>2</sup> $\leq$ 50%, the included studies were considered to have little heterogeneity; when I <sup>2</sup> > 50%, the included studies were considered to have substantial heterogeneity.	P5/Line19-2
	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/Line17-1
	Provision of appropriate tables and graphics	Figure 2,3 and Table 2	P9 and Figur 2,3
Re	porting 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
$\checkmark$	Indication of statistical uncertainty of findings	RR, 95% CI, $I^2$ and P	Р9
	porting of discussion should		
inc	lude		
$\checkmark$	Quantitative assessment of bias	Results of subgroup analyses and sensitive analyses were discussed.	P8-10
	Justification for exclusion	<ul> <li>(1) the article was not relevant to the subject of the study (animal experiments, pathological researches, molecular researches);</li> <li>(2) reviews;</li> <li>(3) overlapped studies, where if studies overlapped, we</li> </ul>	P4/Line22-2

		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.	
√ D	Assessment of quality of included studies	Table S1-1 and Table S1-2	Additional file 2
	porting of conclusions should lude		
V	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
$\checkmark$	Generalization of the conclusions	In conclusion, blood group B was associated with a lower risk of HBV infection.	P12/Line22
V	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. This study was supported by the National	P12/Line22- 24
$\checkmark$	Disclosure of funding source	Natural Science Foundation of China (Grant No. 71934002, No. 71874003 and No. 81703240).	P13/Line9-10