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STATE OF THE ART REVIEWS

Hepatitis B virus infection and related factors in hemodialysis patients in China – systematic review and meta-analysis

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Abstract

Aims: To provide a comprehensive and reliable tabulation of available data on the epidemiological characteristics and risk factors for hepatitis B virus (HBV) infection in maintenance hemodialysis (HD) patients in China and help to inform prevention programs and guide future research. *Methods*: A systematic review was constructed based on the computerized literature database. Confidence intervals (95% CI) of infection rates were calculated using the approximate normal distribution model. Odds ratios (OR) and 95% CI were calculated by fixed or random effects models. Hepatitis B surface antigen positivity (HBsAg (+)) was set as the sign of HBV infection. *Results*: Fifty studies met our inclusion criteria. The pooled prevalence of HBV infection among HD patients in China was 11.9%. Blood transfusion was correlated with an increase in HBV infection ($p = 0.05$). HD patients with a long-term history were more likely to be infected than those with a short-term history. The levels of alanine aminotransferase were higher in the HBsAg (+) patients ($p < 0.001$). Large doses of HBV vaccine (80 μg/dose) increased the seroconversion rate. The response rate of intradermal injection of HBV vaccine was higher than that of intramuscular injection. *Conclusion*: Hepatitis B is still one of the main complications in HD patients in China, and the frequency of blood transfusion and duration of HD were the risk factors. Large doses and intradermal injection of HBV vaccine were recommended to prevent HBV infection in HD patients. The findings of this meta-analysis have implications for optimal prevention and treatment of Hepatitis B in HD patients.

Keywords: hepatitis B virus, hemodialysis, HBV vaccine, meta-analysis, Chinese

INTRODUCTION

Hemodialysis (HD) is an effective means for the treatment of end-stage renal disease (ESRD) and prolongs lives of patients with uremia, which has been widely used in clinic. However, because of long-term blood transfusion, the low immune ability of the body, as well as cross-iatrogenic infection, HD patients are highly vulnerable to viral hepatitis infection. In recent years, studies have found that hepatitis B is still one of the main complications in HD patients, which not only affects the quality of lives, but also increases the mortality rate and other complications including a decline in the long-term survival rate following renal transplantation. The prevalence of Hepatitis B virus (HBV) within dialysis units in developing countries appears higher (11–15%) than the developed countries. However, studies showed a different incidence of HBV infection among different countries. For example, study from India[1] reported that there were significant differences in death rates, hospitalizations, and hospitalized days between HBsAg (+) and HBsAg (–) patients on maintenance HD. However, different outcomes were noted in a retrospective study from the United States.[2] In China, some studies[3–6] showed that the levels of alanine aminotransferase (ALT) were significantly elevated in the HBsAg (+) HD patients.

The frequency of HBV infection in patients undergoing maintenance dialysis in the industrialized world is low, but not negligible.[7,8] Persistent HBsAg (+) is much higher in developing countries,[9] especially in China. Nowadays, HBV vaccination has been considered

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to be an effective method of prevention for hepatitis B. Reports also indicate that the inconsistent seroconversion rates of HBV vaccination were related with the total dose, inoculation times, and method of injection.

This article aims to collate and integrate the available data on the epidemiological characteristics and risk factors for HBV infection, and the response to different doses and administration methods for HBV vaccination in HD patients in China, and to provide a reliable basis to formulate prevention, treatment, control plans, and a clear direction for research.

MATERIALS AND METHODS

Search strategy

Electronic searches of EMBASE and PubMed were used to identify suitable studies from January 1987 to March 2010. Current contents and manual searches of selected specialty journals were performed to identify all pertinent literature. The search terms were "hepatitis B virus" or "HBV" or "hepatitis B virus vaccine" and "hemodialysis" and "China." A China National Knowledge Infrastructure search from January 1987 to March 2010 was also undertaken for Chinese articles related to HBV and HD. Reference lists from qualitative topical reviews and published clinical trials were also searched. Our search regarded human studies that were published in the English and Chinese literature.

Study selection

Data extractions were conducted independently by two investigators and consensus was achieved for all data. A study was included in the meta-analysis when it fulfilled the following criteria: (1) study designs: cohort, case–control study, cross-sectional study, (2) sample origin, (3) studies using EIA for testing seromarkers of HBV and HCV. The exclusion criteria were (1) trials that were only published as abstracts or as interim reports, (2) studies not specifying sample origins, (3) letters and review articles, (4) studies that could not be interpreted in terms of our objectives, (5) studies with overlapping time intervals of sample collection from the same origin, and (6) being a subset of a published article by the same authors.

Data extraction

Two reviewers independently evaluated each identified study and abstracted relevant characteristics including author, publication year, province of sample origin, sample size, number of subjects infected with HBV, or coinfected with HCV, duration of HD, levels of ALT, and response to HBV vaccine in HD patients.

Statistical analysis

Data analyzed for HBV among HD patients for each of the included studies were collected using the approximate normal distribution model. The OR with 95% CI was used to estimate the strength of association for each study. Before performing meta-analyses, homogeneity of effect sizes was assessed by the Q-statistic; and between-study heterogeneity was considered to be significant for $p < 0.05$. Data considered to be sufficiently homogeneous were pooled. Because publication bias is of concern for our meta-analysis, we tested for the potential presence of this bias using funnel plots and the Egger's test. If heterogeneity was observed, subgroup analyses and sensitivity analyses were used. Data calculation and statistical analyses were undertaken using STATA 7.0 (STATA Corporation, College Station, TX, USA, 2001) and Review Manager (RevMan) 4.2 (The Cochrane Collaboration, Oxford, UK, 2003).

RESULTS

We identified 207 full texts about the infection of HBV among HD patients from computerized literature databases and reference lists of systematic reviews. One hundred and fifty-seven (75.2%) studies were excluded because of one of the following reasons: the articles used the polymerase chain reaction method for detecting HBV or HCV, were not about HD patients, contained obvious errors, did not meet the selection criteria, were not of high quality, and the same authors published several reports on the same patients. Overall, 50 articles (46 Chinese and 4 English) were included in the meta-analysis. These 50 studies, published from January 1987 to March 2010 with the number of study subjects ranging from 20 to 786, included a total of 5941 patients.

Prevalence of HBV infection in different regions among HD patients in China

As seen in Table 1, data were obtained from 16 of the 34 administrative units. The pooled prevalence of HBV infection among HD patients in China was 11.9% (95% CI 11.1–12.7%). Dramatic geographical differences in the pooled HBsAg (+) rates among HD patients have been observed. The highest rates were found in the Henan Province (30.8%, 95% CI 20.5–41.0%), followed by the Zhejiang Province (29.6%, 95% CI 19–40.2%), then the Shandong Province (18.9%, 95% CI 15.4–22.4%) and the Hebei Province (18.9%, 95% CI 13.4–24.4%). Lower rates were found in the Qinghai Province (6.3%, 95% CI 2.1–14.6%) and the Liaoning Province (6.4%, 95% CI 5.2–7.5%).

Coinfection with HCV among HD patients in China

Our meta-analysis showed that the coinfection rate with HCV was 2.7% (95% CI 2.0–3.3%, Table 2). Dramatic geographical differences in pooled coinfection rate with HCV among HD patients have been observed, which was from 1.5% to 21.9%.

Table 1. The pooled prevalence of HBV infection among HD patients in China.

Province	References	HD	HBV prevalence and CI(%)	Pooled prevalence and CI(%)	Weight(%)
Shanxi	Wang et al. [6]	318	0.198(0.154–0.242)	0.167(0.136–0.199)	5.72
	Zhao[10]	54	0.037(–0.013–0.087)		
	Zhu et al.[11]	160	0.150(0.095–0.205)		
Shandong	Liu et al.[12]	142	0.134(0.078–0.190)	0.189(0.154–0.224)	4.65
	Ma et al.[13]	286	0.217(O.169–0.265)		
	Liu et al.[14]	48	0.188(0.077–0.298)		
Guangdong	Zheng et al.[15]	242	0.083(0.048–0.117)	0.121(0.100–0.141)	13.34
	Tan et al.[16]	68	0.132(0.052–0.213)		
	Xia et al.[17]	128	0.078(0.032–0.125)		
	Wang et al.[18]	120	0.125(0.066–0.184)		
	Jiang et al.[19]	62	0.113(0.034–0.192)		
	Jiang et al.[20]	134	0.119(0.065–0.174)		
	Yao et al.[21]	105	0.229(0.148–0.309)		
	Li et al.[22]	86	0.163(0.085–0.241)		
Liaoning	Wang[5]	69	0.174(0.084–0.263)	0.064(0.052–0.075)	41.12
	Yi et al.[23]	69	0.043(–0.005–0.092)		
	Qin and Li[24]	135	0.089(0.041–0.137)		
	Lu and Zhou[25]	576	0.073(0.052–0.094)		
	Zhao et al.[26]	786	0.045(0.030–0.059)		
Yunnan	Zhu et al.[27]	58	0.069(0.004–0.134)	0.128(0.060–0.195)	1.26
	Zhu et al.[28]	36	0.222(0.086–0.358)		
Shanghai	Wang et al.[29]	99	0.131(0.065–0.198)	0.089(0.065–0.113)	10.12
	Zhao et al.[30]	34	0.176(0.048–0.305)		
	Cui et al.[31]	24	0.208(0.046–0.371)		
	Wang et al.[32]	62	0.081(0.013–0.148)		
	Chen et al.[33]	301	0.066(0.038–0.095)		
	Wang et al.[34]	29	0		
Henan	Tang and Qiao[35]	20	0.250(0.060–0.440)	0.308(0.205–0.410)	0.55
	Yong[3]	58	0.328(0.207–0.448)		
Zhejiang	Li et al.[36]	32	0.469(0.296–0.642)	0.296(0.190–0.402)	0.51
	Lin and Xu[37]	39	0.154(0.041–0.267)		
Beijing	Chen et al.[4]	225	0.182(0.132–0.233)	0.165(0.127–0.203)	4.03
	Wei et al.[38]	22	0.182(0.132–0.233)		
	Liu et al.[39]	49	0.122(0.031–0.214)		
	Wang et al.[40]	38	0.132(0.024–0.239)		
	Li et al.[41]	36	0.139(0.026–0.252)		
Jiangsu	Zhang and Gao[42]	88	0.057(0.008–0.105)	0.116(0.059–0.173)	1.77
	Chen[43]	33	0.273(0.121–0.425)		
Anhui	Cao et al.[44]	448	0.078(0.053–0.103)	0.078(0.053–0.103)	9.32
Hunan	Tang et al.[45]	23	0.130(–0.007–0.268)	0.130(–0.007–0.268)	0.3
Qinghai	Ba[46]	32	0.063(–0.021–0.146)	0.063(–0.021–0.146)	0.82
Xinjiang	Liu[47]	120	0.125(0.066–0.184)	0.125(0.066–0.184)	1.64
Hubei	Qi et al.[48]	196	0.189(0.134–0.244)	0.189(0.134–0.244)	1.92
Fujian	Lin et al.[49]	251	0.151(0.107–0.196)	0.151(0.107–0.196)	2.93
Pooled		5941		0.119(0.111–0.127)	100

Risk factors for HBV infection among HD patients in China

Blood transfusion

The eligible studies included 436 HD patients with blood transfusion and 194 HD patients without blood transfusion. Meta-analysis showed that HD patients with blood transfusion were 1.68 times more likely to be infected with HBV than HD patients without blood transfusion (OR = 1.64, 95% CI 0.09–2.71, $p = 0.05$, Table 3). The Egger's test suggested that there was no significant publication bias.

Duration of hemodialysis

Eight studies included 1304 long-term (>1 year) HD patients and 844 short-term (<1 year) HD patients. There was no significant publication bias by the Egger's test. The analysis with the fixed-effect model demonstrated that there was a significant difference of HBV infection rates between the two groups (OR = 2.34, 95% CI 1.67–3.29, $p < 0.001$, Table 4). Studies showed that HD patients with longer-term (>3 years) HD had a higher incidence of HBV than HD patients with shorter-term (<3 years) HD (OR = 4.27, 95% CI 1.28–14.18, $p < 0.05$, Table 4). Therefore, the longer the dialysis, the higher the HBV infection rate among HD patients.

Comparison of the levels of ALT between HBsAg (+) and HBsAg (–) patients

The previous studies showed that the levels of ALT could be used for screening liver diseases and evaluating liver function both in general population[15] and in

Table 2. Coinfection with hepatitis C virus (HCV) among HD patients in China.

Reference	HD	HBsAg(+)HCV(+) prevalence	Prevalence and CI(%)	Weight(%)
Yong[3]	58	4	0.069(0.004–0.134)	1.08
Wang[5]	69	8	0.116(0.040–0.191)	0.8
Lin et al.[49]	69	8	0.116(0.040–0.191)	0.8
Li et al.[36]	32	7	0.219(0.076–0.362)	0.22
Lin et al.[49]	54	2	0.037(–0.013–0.231)	1.81
Zhao et al.[26]	786	12	0.015(0.007–0.024)	62.48
Cao et al.[44]	318	31	0.097(0.065–0.130)	4.32
Tang and Qiao[35]	20	2	0.100(–0.031–0.231)	0.27
Wei et al.[38]	22	0	0	0
Tan et al.[16]	68	2	0.029(–0.011–0.070)	2.85
Zheng et al.[15]	242	6	0.025(0.005–0.044)	11.96
Cui et al.[31]	225	7	0.031(0.008–0.054)	8.92
Li et al.[41]	36	1	0.028(–0.026–0.081)	1.59
Qin and Li[24]	135	8	0.059(0.019–0.099)	2.89
Pooled			0.027(0.020–0.033)	100

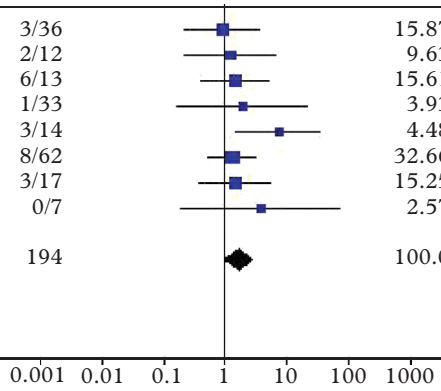
Table 3. Differences of HBV infection rate between HD patients with and without blood transfusion in China.

Review: Hepatitis B virus infection and related factors in hemodialysis patients in China – Systematic review and meta-analysis

Comparison: 04 Differences of HBV infection rate between HD patients with and without blood transfusion

Outcome: 01 with blood transfusion and without blood transfusion

Study or sub-category	With transfusion *n/N*	Without transfusion *n/N*	OR (fixed) 95% Cl	Weight %	OR (fixed) 95% Cl
Lingzhi Xia[17]	7/92	3/36		15.87	0.91 [0.22, 3.71]
Quilian Liu[14]	7/36	2/12		9.63	1.21 [0.21, 6.79]
Huilan Liu[39]	20/36	6/13		15.61	1.46 [0.41, 5.21]
Xiaohong Yi[23]	2/36	1/33		3.93	1.88 [0.16, 21.78]
Xingfei Li[36]	12/18	3/14		4.48	7.33 [1.47, 36.66]
Xinyu Zhu[11]	16/98	8/62		32.66	1.32 [0.53, 3.29]
Zhan Cheng Yao[21]	21/88	3/17		15.25	1.46 [0.38, 5.59]
Zhe Lin[37]	6/32	0/7		2.57	3.68 [0.19, 73.05]
Total (95% Cl)	436	194		100.0	1.64 [0.99, 2.71]
Total events: 91 (with transfusion), 26 (without transfusion)					
Test for heterogeneity: $\chi^2 = 4.70$, df = 7($p = 0.70$), $I^2 = 0\%$					
Test for overall effect: $Z = 1.93$ ($p = 0.05$)					



Note: OR: odds rate; CI: confidence interal; df: degrees of freedom.

HD patients.[3,12] In this study, the ALT level was set at ≥40 IU/L as the liver abnormal indicator. Because there was statistical heterogeneity ($\chi^2 = 22.06$, $p = 0.0002$) between the two groups, the random effect model was applied. The results of meta-analysis demonstrated that the levels of ALT were higher in the HBsAg (+) group (OR = 7.15, 95% CI 1.39–36.84, $p < 0.001$, Table 5). However, the levels of ALT among 63.3% HBsAg (+) HD patients were still in normal range.

Antibody response to HBV vaccine

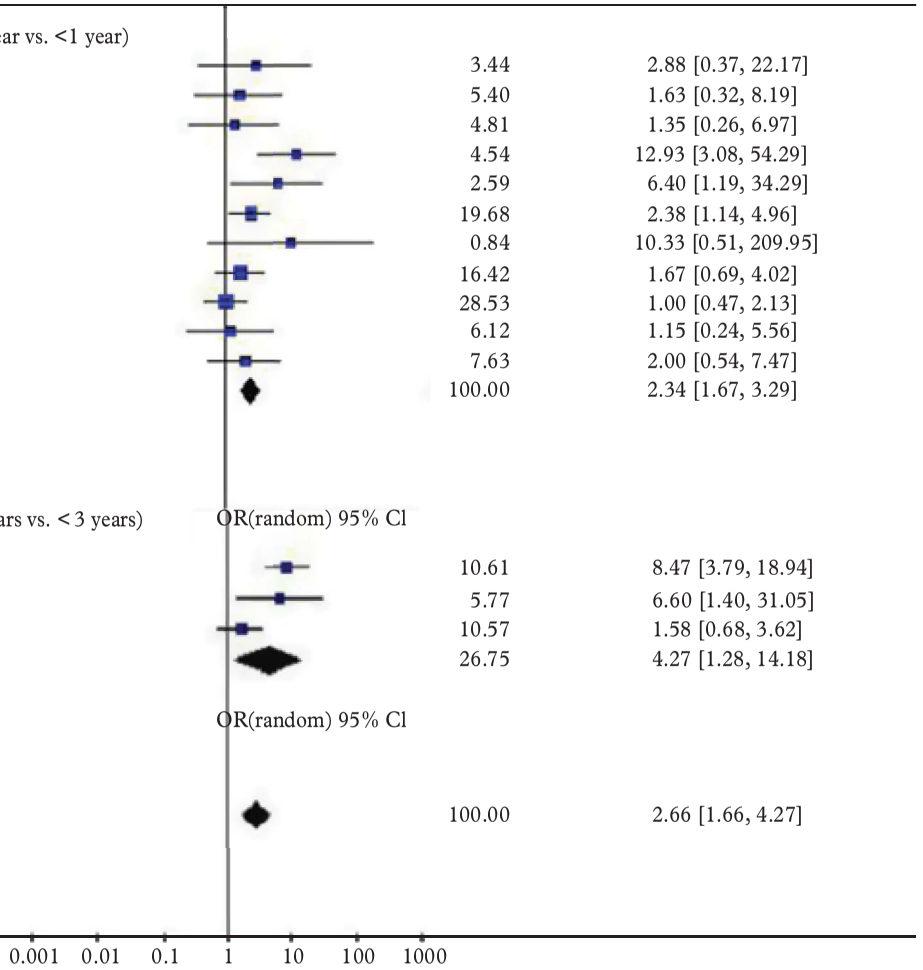
Dose of HBV vaccine was further evaluated by comparing the regimens of small doses (10 or 20 μg/dose) and large doses (40 or 80 μg/dose), respectively. Each of the HD patients with anti-hepatitis B surface antibody (anti-HBs) received recombinant HBV vaccine given intramuscularly in the deltoid muscle in a three-dose schedule at 0, 1, and 6 months or four-dose at 0, 1, 2, and 6 months. The anti-HBs ≥10 IU/L was defined as seroconversion. The results were that vaccine using large dose of 80 μg could increase seroconversion rate to 84.5% (95% CI 77.9–91.1%). Dose of 20 μg was associated with increased risk of nonresponse to HBV vaccine with the seroconversion rate 70.2% (95% CI 60.5–80.0%, Table 6).

The intradermal group was treated with 5 μg of recombinant HBV vaccine intradermally every week or every 2 weeks for a total of 7–10 times. Pooling of study results demonstrated a decreased risk of failure to respond to HBV vaccine among patients who were vaccinated by intradermal route, and the seroconversion rate achieved 85.7% (95% CI 75.1–96.3%, Table 6).

Table 4. Differences of HBV infection rates between different duration of hemodialysis.

Review: Hepatitis B virus infection and related factors in hemodialysis patients in China–Systematic review and meta-analysis
Comparison: 02 long-term versus short-term
Outcome: 02 differences of infection rates between different duration of hemodialysis

Study or sub-category	Long-term *n*/N	Short-term *n*/N	OR (fixed) 95% CI	Weight (%)	OR (fixed) 95% CI
01 difference of HBV infection rates between different duration of hemodialysis (>1 year vs. <1 year)					
Sheng Chen[33]	19/293	1/38		3.44	2.88 [0.37, 22.17]
Fengqi Qin[24]	7/93	2/42		5.40	1.63 [0.32, 8.19]
Quilian Liu[14]	2/13	10/84		4.81	1.35 [0.26, 6.97]
Hua Zhao[26]	33/454	2/332		4.54	12.93 [3.08, 54.29]
Huilan Liu[39]	24/39	2/10		2.59	6.40 [1.19, 34.29]
Junying Qi[48]	23/88	14/108		19.68	2.38 [1.14, 4.96]
Xingfei Li[36]	15/28	0/4		0.84	10.33 [0.51, 209.95]
Xinyu Zhu[11]	14/76	14/108		16.42	1.67 [0.69, 4.02]
Yueyong Lin[49]	19/149	13/102		28.53	1.00 [0.47, 2.13]
Yukun Song[28]	4/17	4/19		6.12	1.15 [0.24, 5.56]
Zhan Cheng Yao[21]	21/84	3/21		7.63	2.00 [0.54, 7.47]
Subtotal (95% CI)	1304	844		100.00	2.34 [1.67, 3.29]
Total events: 181 (long-term), 61 (short-term)					
Test for heterogeneity: $\chi^2 = 14.71$, df = 10 ($p = 0.14$), $I^2 = 32.0\%$					
Test for overall effect: $Z = 4.89$ ($p < 0.00001$					
02 difference of HBV infection rates between different duration of hemodialsis (> 3 years vs. < 3 years)			OR(random) 95% CI		
Hua Zhao[26]	27/241	8/545		10.61	8.47 [3.79, 18.94]
Xingfei Li[36]	11/16	4/16		5.77	6.60 [1.40, 31.05]
Yueyong Lin[49]	30/180	8/71		10.57	1.58 [0.68, 3.62]
Subtota (95% CI)	437	632		26.75	4.27 [1.28, 14.18]
Total events: 68 (long-term), 20 (short-term)					
Test for heterogeneity: $\chi^2 = 8.54$, df = 10(p =0.01), $I^2 = 76.6\%$			OR(random) 95% CI		
Test for overall effect: $Z = 2.37$ ($p = 0.02$)					
Total (95% CI)	1741	1476		100.00	2.66 [1.66, 4.27]
Total events: 249 (long-term), 81 (short-term)					
Test for heterogeneity: $\chi^2 = 27.40$, df = 13 ($p = 0.01$), $I^2 = 52.6\%$					
Test for overall effect: $Z = 4.08$ ($p < 0.0001$)					

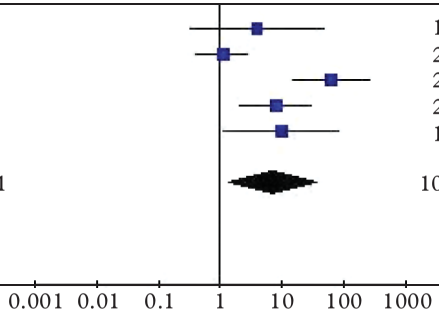


Note: OR: oods ratio; Cl:confidence interal; df: degrees of freedom.

Table 5. The influence of HBsAg(+) on the levels of ALT.

Review: Hepatitis B virus infection and related factors in hemodialysis patients in China – Systematic review and meta-analysis
Comparison: 02 HBsAg(+) VS HBsAg(–)
Outcome: 01 the influence of HBsAg (+) on ALT level

Study or subcategory	HBsAg (+) *n*/N	HBsAg (–) *n*/N	OR (random) 95% CI	Weight (%)	OR (random) 95% CI
Huan Wang[10]	2/12	1/21		15.96	4.00 [0.32, 49.60]
Limeng Chen[4]	9/41	14/58		23.47	1.08 [0.41, 2.86]
Qiang Wang[6]	29/63	2/149		21.17	62.69 [14.26, 275.58]
Yong Dang[3]	9/19	4/39		21.70	7.88 [2.00, 31.04]
Yukun Zhu[27]	2/4	5/54		17.69	9.80 [1.12, 85.42]
Total (95% CI)	139	321		100.00	7.15 [1.39, 36.84]
Total events: 51 (HBsAg (+)), 24 (HBsAg (–))					
Test for heterogeneity: $\chi^2 = 22.06$, df = 4 ($p = 0.0002$), $I^2 = 81.9\%$					
Test for overall effect: $Z = 2.35$ ($p = 0.02$)					



Note: OR: odds ratio; CI: confidence interal; df: degrees of freedom.

Table 6. Antibody response to HBV vaccine.

Vaccine	Reference	Doses	HD patients	Anti-HBs(+) rate and CI(%)	Prevalence and CI(%)
IM(small dose)	Cao et al.[50]	10 μg	29	0.517(0.335–0.699)	0.517(0.335–0.699)
IM(small dose)	Zhang and Yue[51]	20 μg	15	0.667(0.428–0.828)	0.702(0.605–0.80)
	Qian et al.[52]		31	0.806(0.667–0.946)	
	Kai et al.[53]		9	0.556(0.231–0.880)	
	Cao et al.[44]		29	0.655(0.482–0.828)	
IM(large dose)	Wang et al.[34]	40 μg	12	0.667(0.400–0.933)	0.667(0.400–0.933)
IM(large dose)	Kai et al.[53]	80 μg	23	0.870(0.732–1.007)	0.845(0.779–0.911)
	Kai et al.[53]		69	0.783(0.685–0.880)	
	Yao et al.[54]		24	0.958(0.878–1.038)	
ID(5 μg/w)	Zhang and Yue[51]	5 μg/2 w	15	0.933(0.807–1.060)	0.857(0.751–0.963)
	Ka et al.[55]	5 μg/w	27	0.815(0.668–0.961)	
Pooled					0.779 (0.732–0.827)

DISCUSSION

More than 2 billion people, about one-third of the world's living population, have been infected with HBV at some time in their lives; and of these about 350 million people remain infected. Every year 1 million people die of HBV-related cirrhosis or hepatocellular carcinoma, which means that HBV takes a life every 30 s. There is a significant difference in the HBsAg (+) rate geographically. HBV infection is highly prevalent in Asia, sub-Saharan Africa, and other parts of the developing world. The HBsAg (+) rate was 11.9% among Chinese HD patients. There is slight difference in the HBsAg (+) rate geographically. If we set the Yangtze River as the dividing line, the South has 12.0% whereas the North has 11.8%. According to the report of the World Health Organization (WHO), the HBV infection rate is 6–7.8% in the general population in the world and 9.75% in China. Because the HBV infection rate is higher in the general population in China, we would expect the prevalence rate of HBV in Chinese HD patients to also be higher.

The pooled prevalence of HCV infection in HD patients in China is 41.1%[56] and the coinfection rate of HBV and HCV is 2.7%. The HCV infection rate is 3.0% among the general population according to the WHO. Therefore, our study suggests that HD patients with HBV do not have an increased HCV infection rate.

Uremic patients are often accompanied by severe anemia and malnutrition and require blood transfusions to improve the situation of their fitness. In the HBsAg (+) group, there were more people with a history of blood transfusion than in the HBsAg (–) group. This phenomenon may be due to the fact that some of the donors who are infected with HBV are HBsAg false-negative. Previous data in developed countries[57] suggest that post-transfusion hepatitis B more often implicate HBsAg (–) donors. However, it has been demonstrated that transmission by blood components negative for HBsAg can still occur in the acute phase of infection during the seronegative window period, or during chronic stages of infection (i.e. "occult" HBV infection, OHB). OHB is defined as the presence of HBV-DNA in blood or liver tissues in patients but negative for HBsAg, with or without any HBV antibodies. To eliminate the residual risk of HBV transmission, nucleic acid amplification testing was implemented for HBV-DNA in Japan from 1999 to 2002. The initial 181 donations that were serologically negative but HBV-DNA positive were further tested by using a more sensitive chemiluminescence immunoassay (CLIA) for HBsAg. Of these 181 HBV-DNA positive donations, 96 (53%) and 76 (42%) were still negative by individual enzyme immunoassay (EIA) and CLIA testing, respectively. Similar findings were noted in a later survey.[58] Because of the low viral load in OHB, blood from donors should be tested for HBV-DNA because it is more sensitive and standardized.

The application of recombinant human erythropoietin (rHuEPO) to correct anemia in patients with renal anemia, which will reduce the blood transfusion volume, is considered to be an effective means to reduce the possibility of HBV infection in HD patients.[59] With the introduction of rHuEPO and more sensitive screening tests for blood donors, the risk of post transfusion hepatitis B could be reduced.

Prolonged dialysis could increase HBV infection, and the longer the dialysis treatment, the higher the HBsAg (+) rate. It suggests that HD patients with HBV infection are associated with dialysis-related iatrogenic transmission. There may be some reasons for transmission, such as reuse of the dialyzers and pipelines, repeated needle puncture during the treatment, sharing of dialysis machines and incomplete disinfection, and contamination in the operational process of the dialysis environment. Some studies found that HBV particles can penetrate through the dialysis membrane into ultrafiltrate samples and cause cross-infection through reverse osmosis. At present, normally adopted disinfection methods for reused dialyzers include formalin and peracetic acid, which can effectively kill HBV and HCV. However, there are higher incidences of HBV infection in the dialysis centers that reuse dialyzers than the nonreuse centers, inferring that there may be infection channels associated with the process of reuse.

To HD patients, the declining immune function – especially cellular immunity[50] together with a defect in neutrophil function and complement activity – weakens the host's ability to resist pathogenic micro-organisms and pathogenic viruses. HD patients with cellular immune status disturbances have difficulty in eliminating HBV,[60,61] therefore the HBsAg positive patients seldom turn out to be negative. The exact impact of HBV on liver function is still controversial. Some essays have reported that average levels of serum aminotransferases are decreased in HD patients.[62,63] However, our systemic review shows that the levels of ALT is elevated 7.15 times in HBsAg (+) HD patients compared with HBsAg (–) HD patients. This suggests that the serum aminotransferase should be monitored in HBsAg (+) HD patients to evaluate their liver injury.

Immunization with HBV vaccine remains the most effective way to prevent infection by HBV since the 1980s. In the United States, it is recommended that all HD patients should be administered HBV vaccine. However, it has been repeatedly observed that chronic uremic patients with or without dialysis treatment have an impaired immune response to the HBV vaccine.[63,64] The seroconversion rate is only 50–73%[65] in contrast to more than 90% in healthy subjects. Some scholars believe that dialysis patients with hypo-responsiveness to the HBV vaccine may be associated with cellular immune dysfunction. Recommendations include increasing the vaccine dose and/or the frequency of vaccination to maintain high levels of anti-HBs. Seaworth et al.[66] reported that recombinant HBV vaccine given

intramuscularly in the deltoid muscle in a three-dose schedule at 0, 1, and 6 months provided a seroconversion rate of 42%. After the dose was increased to 40 μg, the anti-HBs seroconversion rate increased to 69%. Another report shows that increasing the number of injections to four with 20 μg/dose at 0, 1, 2, and 6 months can increase the seroconversion rate to 81%.[55] In this meta-analysis the seroconversion rate was 84.5%, when a booster dose of vaccine (80 μg) was given and 70.2% when a small dose of vaccine (20 μg) was given. Our results suggest that a dose of 80 μg of vaccine could evidently increase the seroconversion rate. If the anti-HBs titers decrease to a non-protecting level, a booster dose of vaccine should be administered.[67]

Our review shows that in the dialysis population a low dose of vaccine injected intradermally achieves a higher seroprotection rate compared with when given intramuscularly. The results yielding an 85.7% seroconversion rate suggest that the better way to enhance the immune response is to administer the vaccine intradermally.

The mechanism of the better efficacy of HBV vaccine given by intradermal injection in active immunization among HD patients remains unclear. It has been suggested that the intradermal administration of antigen may activate specific epidermal cells and may be capable of inducing an effective lymphocyte response.[68] Many Langerhans cells, which are very capable antigen-presenting cells, are present in the epidermal area and are thought to participate in enhancing the immune response. A lower dosage also allows large-scale vaccination in the community at a lower cost. Therefore, booster doses of vaccine by intramuscular injection or low doses of vaccine by intradermal injection were required to maintain seroprotection for those who lost protecting anti-HBs.

The seroconversion rate induced by the HBV vaccine is reduced with older age, obesity, and diabetes mellitus.[53] It also diminishes with increasing severity of renal failure and ineffective dialysis.[69] Thus, one of the possible reasons for the lower response rate among overweight subjects could be related to their inadequate dialysis. Higher hemoglobin levels may have favorable effects on HBV vaccine immunogenicity.[70,71] Some relevant medicines have effects on the immune system. To correct renal anemia, rHuEPO and intravenous iron replacement therapy are commonly used in HD patients. One study[72] concluded that the levels of anti-HBs after HBV vaccination are positively correlated with the dose of the rHuEPO treatment during the vaccinated period among HD patients. Intravenous treatment with iron negatively impacts the responsiveness of anti-HBs titer after HBV vaccination in ESRD patients who have undergone rHuEPO therapy. Many factors affect the antibody response to HBV vaccine in dialysis patients. There is evidence that indicates that rHuEPO may influence the immune response by its effects on the cells of the humoral and cellular immune systems.[73] Intravenous iron can negatively affect the cell-mediated immune mechanisms that are directed against invading microorganisms and tumor cells.[74]

CONCLUSION

The incidence of HBV in maintenance HD patients is significantly higher than in the general population. The frequency of blood transfusion and duration of HD were the risk factors identified. Dialysis units should undertake more work to reduce the prevalence of HBV in HD patients including enhancement of disinfection and isolation measures, separation of dialysis machines between HBsAg (+) and HBsAg (–) patients, improvement in the quality of HD technology and the level of dialysis, reduction in blood loss and frequency and amount of blood transfused, use of EPO to correct anemia as far as possible, direct reasonable nutrition, and increase of the resistance of the body. The government needs to strengthen the management of blood donors and the detection of HBsAg and HBV-DNA. HBV vaccine is still the most effective way to prevent HBV infection, but procedures have not been standardized and wildly used in dialysis patients. We should emphasize the use of HBV vaccine and find a way for its application in this special group. Large doses of 80 μg HBV vaccine administrated by the intramuscular injection route are advocated in preventing HBV among HD patients in China. With the effective prevention of HBV in dialysis patients, it could prolong the life of patients and reduce the number of HD patients who proceed on to serious liver disease.

LIMITATIONS

These studies were observational and HD patients were not randomly chosen, so selection bias and confounding bias seems inevitable. Information about the cases and controls was not always complete and the interview was not necessarily reliably consistent, so the study quality could not be ensured. It is difficult for non-Chinese reviewers, editors, and readers to recheck the original materials because many of our data were extracted from articles written in Chinese.

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