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META-ANALYSIS

Sex bias in response to hepatitis B vaccination in end-stage renal disease patients: Meta-analysis

Hossein Khedmat, Aghdas Aghaei, Mohammad Ebrahim Ghamar-Chehreh, Shahram Agah

Hossein Khedmat, Aghdas Aghaei, Mohammad Ebrahim Ghamar-Chehreh, Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran 14155-3651, Iran

Shahram Agah, Colorectal Research Center, Iran University of Medical Sciences, Tehran 19979-97653, Iran

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Correspondence to: Mohammad Ebrahim Ghamar-Chehreh, MD, Assistant Professor, Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, MullaSadra Street, Tehran 14155-3651, Iran. ghamarchehreh@gmail.com
Telephone: +98-21-88934125
Fax: +98-21-88934125

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Abstract

AIM: To systematically review the literature for studies investigating the potential effect of gender of dialysis patients on the immunogenicity of hepatitis B virus vaccines.

METHODS: Literature searches were conducted by the MEDLINE and Google Scholar. The key words used included "hepatitis B (HB)", "vaccine", "dialysis", "hemodialysis", "sex", "male" and "female". Data of seroresponse to HB vaccine in clinical trials regarding sex of the recipients have been achieved and analyzed. Finally data from 19 clinical trials have been pooled and analyzed.

RESULTS: Analysis of response to HB vaccination in our dialysis population showed males significantly respond less to hepatitis B vaccination (P = 0.002, Z = 3.08) with no significant heterogeneity detected [P = 0.766; heterogeneity χ^2 = 14.30 (df = 19); I^2 = 0%]. A reanalysis of the pooled data was conducted regarding the dialysis mode to evaluate potential differential impact of sex on HB vaccine response. Hemodialysis was the only subgroup that showed a significant difference regarding dialysis mode in response to HB vaccination regarding sex (P = 0.042, Z = 2.03).

CONCLUSION: This Meta-analysis showed significant effect for the sex of chronic kidney disease and dialysis patients on the immunogenicity of HB vaccine. This sex discrimination was most prominent among hemodialysis patients.

Key words: Hepatitis B virus vaccination; Hepatitis B virus; Immunogenicity; Dialysis patients; Gender; Sex

Core tip: This study showed that gender of the dialysis patients is a significant factor affecting serresponse to hepatitis B vaccination (HBV) in the immunocompromised population of hemodialysis population. This gender bias was most significantly prominent when patients were under hemodialysis (*vs* other renal replacement therapies including peritoneal dialysis). The relevance of such a finding is to enable the practitioners to be alerted on the effects of HBV vaccinations in dialysis patients and give them clues to individualize vaccination protocols for patients with specific epidemiological characters.

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INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most widespread chronic viral infections in the world with two billion people infected worldwide, and a matter of substantial amounts of financial and health burden throughout the world[1]. The significance of HBV infection in dialysis setting is even higher, because of the high rate of infection due to contaminations, transfusions and injections, and also the high rate of associated survival disadvantage[2]. To tackle this problem in this population, hygienic precautions have been developed whose effectiveness has been very well established[3]. Nevertheless, despite all the precautions, there are still a relatively large proportion of dialysis patients who develop the infection[4]. For the same reason, hepatitis B vaccination is an inevitable part of any preventive protocol that has been developed and proposed by health societies for the dialysis setting[5].

As mentioned, vaccination against HBV infection, though very effective, has not thoroughly eradicated the infection in the dialysis patients[6]. It has been shown that seroconversion due to HBV vaccination in dialysis patients is not perfect; and systematic reviews have shown that there are a number of factors adversely affecting response rate to HBV vaccination in dialysis patients. Erythropoietin use, diabetes mellitus, dialysis mode, vaccine administration mode, adjuvant use, vaccine type (recombinant *vs* plasma-derived), and the effect of age and nutritional status of dialysis patients on the immunogenicity of HBV vaccine are among them. Considering these factors, in a previous paper we proposed individualization of HBV vaccination in dialysis patients based on the epidemiology of the associated factors in their patient population. In the current paper, we systematically review the existing literature for studies investigating the potential effect of sex of dialysis patients on the immunogenicity of HBV vaccines in their patient population.

MATERIALS AND METHODS

Search strategy and data acquisition

The literature has been searches through the National Library of Medicine's (MEDLINE) database, and Google Scholar; the latter database has been particularly used to find relevant citations of the trials of interest; as well, specific journals have been searched to identify all the associated evidence. The key words used included "hepatitis B", "vaccine", "dialysis", "hemodialysis", "haemodialysis", "peritoneal dialysis", "gender", "sex", "male" and "female". The search has also been repeated using the reference lists of the associated systematic reviews and meta-analyses. There was no restriction in regard to the time of publication for our searches; and all the studies fulfilling the inclusion criteria were included into the analysis, irrespective of their publication year.

Inclusion and exclusion criteria

We used a number of inclusion criteria for the found studies in this systematic review: (1) they had to be available as full text (wherever the full text was not available, we contacted the corresponding author with a kind requests for the full text papers); and (2) their data is presented in a form that could be used construct a database for meta analysis were considered eligible for inclusion. There was no restriction regarding the type of vaccines employed in the trials and they were included into the meta-analysis if their vaccine was either plasma-derived or recombinant DNA preparations. The administered dosages or follow up times or vaccination routs were also not subjects to any preferable inclusion or exclusion. Studies were excluded if: (1) they reported not data on response to HBV vaccination separately for either gender in term of epidemiology of seroconversion for either gender groups; and (2) trials were published as abstracts with no enough methodology description.

End point

The association of the gender of dialysis patients has been associated with seroresponse to HB vaccine in the included trials. In cases both seroprotection and seroconversion had been reported by the included trials, seroconversion has been used as the end-point.

Source of support

This meta-analysis was not supported by any pharmaceutical company. The source of support in this study is a grant from Baqiyatallah University of Medical Sciences, Tehran, Iran.

Literature review

After excluding studies not fulfilling inclusion criteria, 19 clinical trials[7-25] have been remained whose demo-

Table 1 Basic demographic data of the included clinical trials

Study ID	First author	Ref.	Year of publish	Country of origin	Participant number	Dialysis mode
1	Abdul N Khan	[7]	1996	United States	97	HD and CAPD
2	Kai Ming Chow	[8]	2010	China	87	CAPD
3	Ismail Hamdi Kara	[9]	2004	Turkey	34	HD
4	Baris Afsar	[10]	2009	Turkey	188	HD
5 (ID) 6 (IM)	Andre F Charest	[11]	2000	Canada	97	HD
7	Yao-Lung Liu	[12]	2005	Taiwan	69	HD and CAPD
8	Nancy M Waite	[13]	1995	Canada	77	HD
9	Salwa Ibrahim	[14]	2006	Egypt	29	HD
10	Shih-Yi Lin	[15]	2012	Taiwan	156	HD and CAPD
11	Dede sit	[16]	2007	Turkey	64	HD
12	Gerald DaRoza	[17]	2003	Canada	165	CKD
13	Jamshid Roozbeh	[18]	2005	Iran	62	HD
14	Khalid Al Saran	[19]	2014	Saudi Arabia	144	HD
15	Kevin S Eardley	[20]	2002	United Kingdom	105	HD
16	Sabahattin Ocak	[21]	2008	Turkey	49	HD
17	EO Morais	[22]	2007	Brazil	70	CKD
18	Sh Taheri	[23]	2005	Iran	125	CKD (32), HD (93)
19	Carol Dacko	[24]	1996	United States	32	CAPD
20	Gerald M Fraser	[25]	1994	United States	59	HD and CAPD

CAPD: Continuous ambulatory peritoneal dialysis; HD: Hemodialysis; ID: Intra-dermal; IM: Intramuscular.

Table 2 Demography of the participants in the studies included in the meta-analysis

Author	Ref.	Age (mean ± SD)	Gender male (%)	Duration of dialysis (mo)
Abdul N Khan	[7]	47 ± 14 (CAPD) 51 ± 18 (HD)	26(55%; CAPD) 26 (52%; HD)	18 ± 23 (CAPD) 56 ± 73 (HD)
Kai Ming Chow	[8]	60 ± 11	51/87 (59)	5.8 (median)
Ismail Hamdi Kara	[9]	44 ± 15	19 (56)	27 ± 15
Baris Afsar	[10]	NA (for total)	66 (35)	NA (for total)
Andre F Charest	[11]	52 ± 2 (ID) 46 ± 2 (IM)	73 (75)	3.4 ± 1.0 (ID) 4.8 ± 2.0 (IM)
Yao-Lung Liu	[12]	52 ± 16 (CAPD) 61 ± 11 (HD)	28 (41)	43 ± 33 (CAPD) 60 ± 49 (HD)
Nancy M Waite	[13]	NA (for total)	49 (64)	NA (for total)
Salwa Ibrahim	[14]	46 ± 11	19 (66)	80 ± 59
Shih-Yi Lin	[15]	NA(for total)	64/156(41)	NA
Dede sit	[16]	NA (for total)	31 (48)	NA (for total)
Gerald DaRoza	[17]	60 ± 15	106 (46)	NA
Jamshid Roozbeh	[18]	NA(for total)	37/62 (60)	NA
Khalid Al Saran	[19]	51 ± 15	78/66 (54)	40
Kevin S Eardley	[20]	61 ± 13	58/47 (55)	18
Sabahattin Ocak	[21]	54 ± 13	56/30 (65)	30 ± 18
EO Morais	[22]	54.5 (median)	40 (57)	26
Sh Taheri	[23]	50 ± 17	77 (62)	NA
Carol Dacko	[24]	NA (for total)	19 (59)	NA (for total)
Gerald M Fraser	[25]	NA (for total)	117 (58)	NA

SD: Standard deviation; CAPD: Continuous ambulatory peritoneal dialysis; HD: Hemodialysis; NA: Not available; ID: Intra-dermal; IM: Intramuscular.

graphic data is summarized in Table 1. Demographic data of the 1709 dialysis patients reported in the 19 published papers included in this meta-analysis is presented in Table 2. Details of the vaccination approaches employed in the studies is summarized in Table 3.

Statistical analysis

The Meta analysis has been performed using a random-effects approach. Test of heterogeneity between the studies has been assessed using the I^2 statistics, which describes the proportion of total variation across studies that is the result of heterogeneity rather than chance. Statistical heterogeneity was present, defined as $P \leqslant 0.05$ or $I^2 > 50\%$. All statistical analyses was conducted using "metan" user-written commands. The meta-analysis has been performed using software Stata v.9.0 (Stata corp, TX, United States).

RESULTS

Patient characteristics

Demographic and clinical characteristics of the included

Table 3 Vaccination information details in the included clinical trials

Author	Ref.	Vaccination mode	Vaccine type	Vaccine dose	Schedule (mo)
Abdul N Khan	[7]	IM	Recombinant (Engerix-B)	40 mcg	0, 1, (2), 6
Kai Ming Chow	[8]	IM	Recombinant (Engerix-B)	40 mcg and 80 mcg	0, 1, 6
Ismail Hamdi Kara	[9]	IM	Recombinant (Engerix-B)	40 mcg	0, 1, 2, 6
Baris Afsar	[10]	IM	Recombinant	-	0, 1, 2, 6
Andre F Charest	[11]	ID and IM	Recombinant (Engerix-B)	40 mcg (IM); 5 mcg (ID)	0, 1, 2, 6
Yao-Lung Liu	[12]	IM	Recombinant (Engerix-B)	40 mcg	0, 1, 2, 6
Nancy M Waite	[13]	IM	Recombinant (Engerix-B)	40 mcg	0,1,2,6
Salwa Ibrahim	[14]	IM	Recombinant (Engerix-B)	40 mcg	0, 1, 2, 6
Shih-Yi Lin	[15]	IM	Recombinant (Engerix-B)	40 mcg	0, 1, 2, 6
Dede sit	[16]	IM	Recombinant (Hepavax)	40 mcg	0, 1, 2, 6
Gerald DaRoza	[17]	IM	Recombinant and plasma derived	20, 40 and 80 mcg	0, 1, 6
Jamshid Roozbeh	[18]	IM and ID	Recombinant (Herberbiovac-HB)	40 mcg (IM); 20 mcg (ID)	0, 1, 4
Khalid Al Saran	[19]	IM	Recombinant (Engerix-B)	40 mcg	0, 1, 2, 6
Kevin S Eardley	[20]	IM	Recombinant (Aventis MSD)	40 mcg	0, 1, 2, 12
Sabahattin Ocak	[21]	IM	Recombinant (Euvax-B)	40 mcg	0, 1, 2, 6
EO Morais	[22]	ID	Recombinant (Greencross)	2 × 5 mcg	16 injection within 8 wk
Sh Taheri	[23]	IM	Recombinant (Havana)	40 mcg	0, 1, 6
Carol Dacko	[24]	IM	Recombinant (Engerix)	40 mcg	0, 1, 2, 6
Gerald M Fraser	[25]	NA	Recombinant (Engerix-B)	20 mcg	0, 1, 2, 6

ID: Intra-dermal; IM: Intramuscular.

trials have been summarized in Table 1. All of the included clinical trials were published in English and the date of publication ranged from 1994 to 2014. Eight out of the nineteen studies (42%) were from the Middle East [Turkey (4), Iran (2), Saudi Arabia and Egypt each one study] and the remaining were from Canada (3 studies), United States (3 studies), China and Taiwan (3 studies), and United Kingdom and Brazil (1 study, each). In 10 (52.6%) studies, all patients were under hemodialysis while in two (10.5%) only patients under continuous ambulatory peritoneal dialysis (CAPD) was investigated, in 2 (10.5%) patients were chronic kidney disease (CKD) not on renal replacement therapy, in one study patients were either on maintenance hemodialysis or CKD not on dialysis, and in the remaining 4 (21%) studies, both of the dialysis modes were used.

Mean age of the participants in the included cohorts ranged from 44 to 61 years, mean duration of dialysis also ranged from 3.4 to over 80 mo and gender distribution ranged from 35% to 75% in favor of males (Table 2). In two of the studies intradermal mode of vaccination has been used besides the intramuscular mode, and in one study only intradermal mode of vaccine administration had been used. In only one study, some of the patients received plasma-derived vaccines, while in all others, the vaccine was recombinant productions. In 13 trials with intramuscular administration of the vaccine, 40 mcg had been prescribed in all patients, in one study either 40 or 80 mcg was used, and in one another 20, 40 or 80 mcg were used for vaccination. Intradermal administration of vaccine was used in doses ranging from 5 mcg to 20 mcg in different trials. One study had not declared mode of vaccine administration. Schedule of vaccination in four of the studies was 3 times (with different time intervals) and in the others but one, were a 4-times schedule (0, 1, 2, 6). In the remaining one trial, patients either received a 3 or 4 times vaccine administration schedule.

Summary of outcome

Analysis of response to HB vaccination in our dialysis population showed a significant relation to their gender with females significantly responding a better response to vaccination (P = 0.002, Z = 3.08; Figure 1). As well no significant heterogeneity has been detected in the analysis of the included studies [P = 0.766; heterogeneity χ^2 = 14.30 (df = 19); I^2 = 0%].

Reanalysis regarding dialysis mode

Then, a reanalysis of the pooled data was conducted regarding the dialysis mode to evaluate potential differential impact of gender on HB vaccine response. Hemodialysis was the only subgroup that showed a significant difference regarding dialysis mode in response to HB vaccination regarding gender and in other subgroups, gender was not discriminatory factor in vaccine response (Figure 2; HD group: P = 0.042, Z = 2.03; CAPD group: P = 0.136, Z = 1.49; HD/CAPD group: P = 0.618, Z = 0.5; CKD group: P = 0.302, Z = 1.03; CKD/HD group: P = 0.448, Z = 0.76).

Reanalysis regarding vaccination schedule

Again, the data had been reanalyzed regarding potential effect of vaccination schedule between the patient groups on the differential vaccine response regarding gender of the patients. Despite a relatively lower p value achieved for schedule "4 times vaccination", none of the subgroups showed any significant difference (Figure 3; "4 times vaccination" group: P = 0.055, Z = 1.92; "3 times vaccination" group: P = 0.088, Z = 1.71; "others" group: P = 0.393, Z = 0.86).

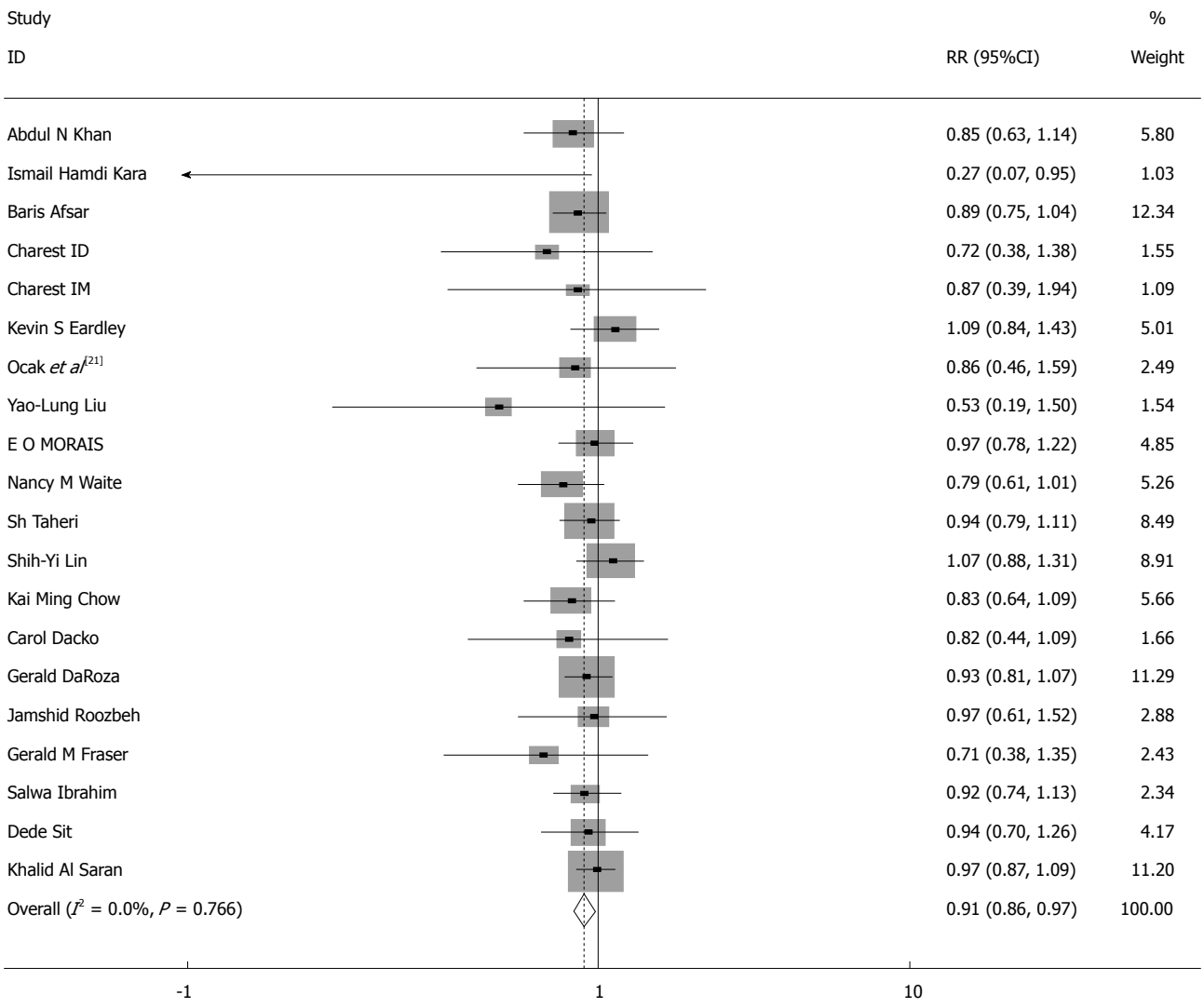

Figure 1 Forest plot: Meta-analysis of the association between gender of the end-stage renal disease patients and seroresponse to hepatitis B vaccination.

Reanalysis regarding vaccine type

The data then had been reanalyzed after removing the only trial in which a plasma-derived vaccine had been used, in order to censor potential effects of vaccine type on the study results. Nonetheless, the findings didn't change significantly ("Recombinant vaccine" group: P = 0.014, Z = 2.47; "Recombinant or plasma-derived vaccines" group: P = 0.288, Z = 1.06).

DISCUSSION

In the dialysis setting, HBV vaccination has been confirmed as an essential part of immunization, and guidelines proposed by several experts as well as health organizations almost universally recommended this procedure for this patient population[5,26,27]. These recommendations are despite the fact that patients with advanced kidney diseases have compromised immune system function, and cannot well respond to any immunization attempt made through vaccination.

The impaired immunogenicity in renal disease patients has been explained by different mechanisms, most notably impaired cellular immunity system in this population[28-30]. However, clinical trials have also proposed several other factors having predictive values in this era; but due to the controversial evidence provided by different reports, systematic reviews and meta-analyses have been conducted to pool data of all the published trials to provide a thorough conclusion from the cumulative data. Most of the published systematic reviews on this subject have been performed by Fabrizi *et al*[31] investigating potential effects of a large number of factors on HBV vaccination in dialysis patients. For example they found no significant effects for using erythropoetin (Epo)[31] and some other adjuvants[32] on the immunogeneity of HB vaccination in kidney disease patients; while several other factors significantly associated with seroconversion have also been reported by the same authors that included use of levamisole[33], granulocyte macrophage-colony stimulating factor[32] and thymopentin use[34]. Seroresponse of patients on maintenance hemodialysis *vs* peritoneal dialysis

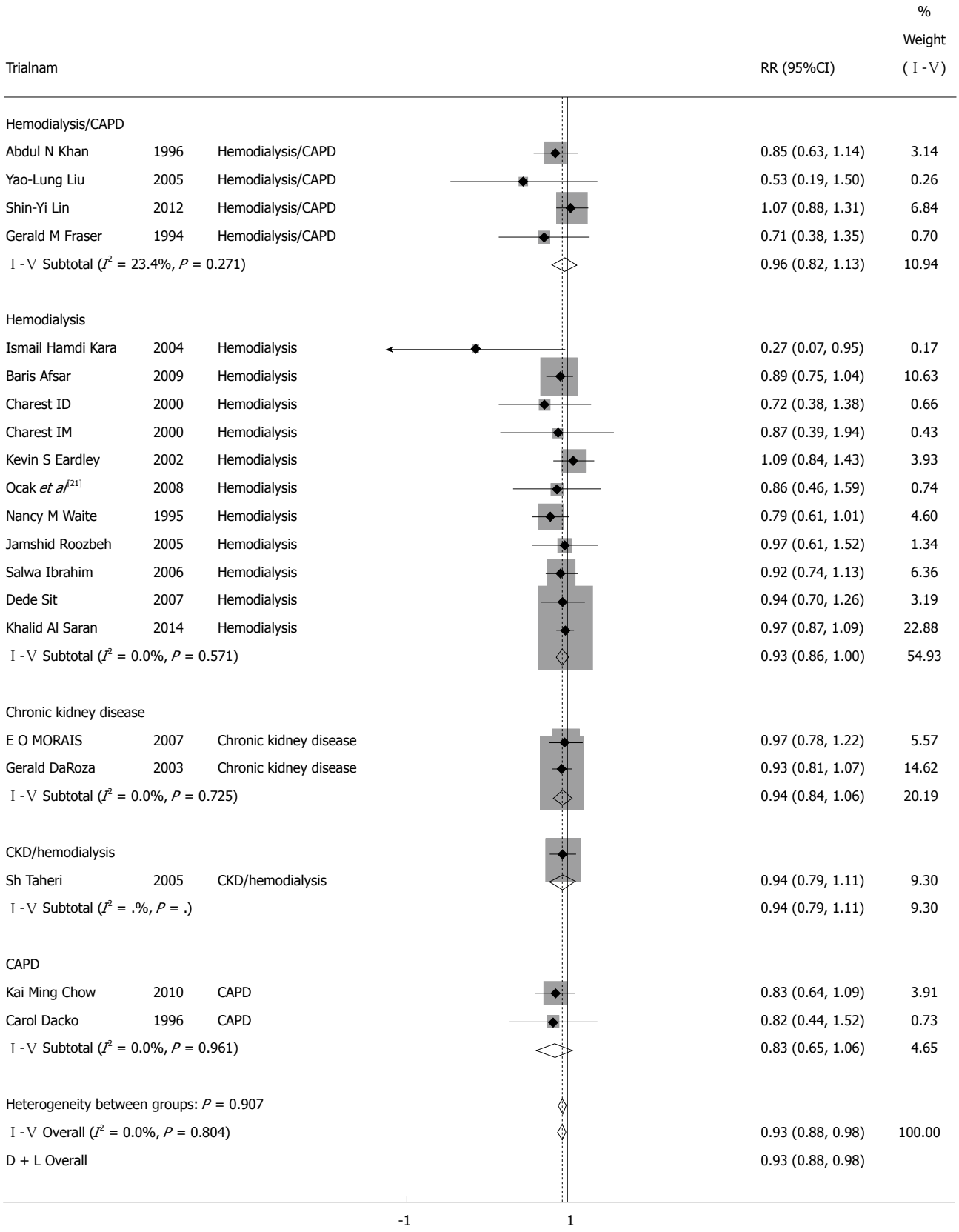

Figure 2 Forest plot: Meta-analysis of the association between gender of the end-stage renal disease patients and seroresponse to hepatitis B vaccination in patients with different therapy modality.

showed no significant difference[35]; whereas intradermal (*vs* intramuscular) administration of HB vaccine had been associated with a significantly higher vaccine response[36]. Diabetes mellitus[37] and older age[38] were

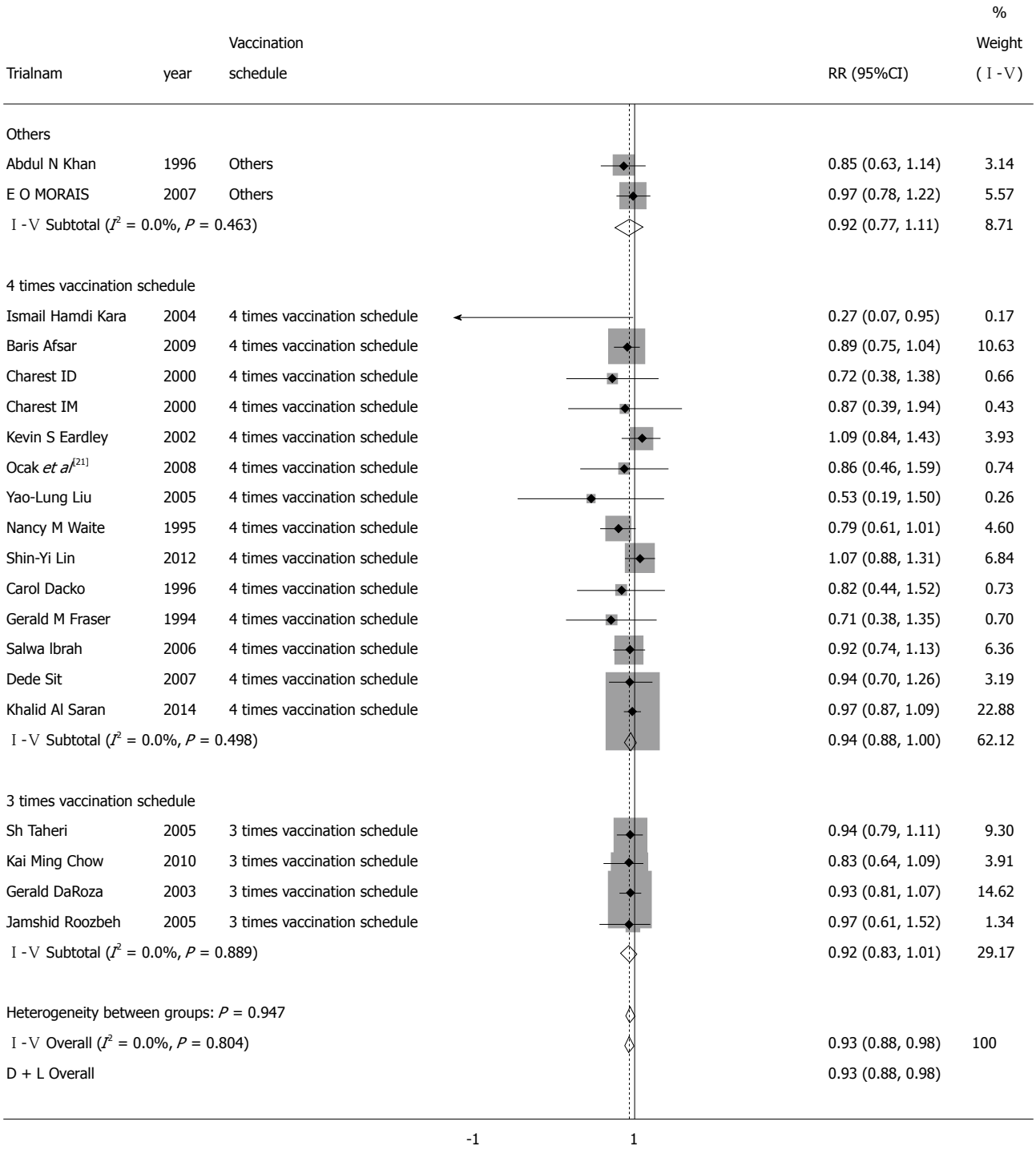

Figure 3 Forest plot: Meta-analysis of the association between gender of the end-stage renal disease patients and seroresponse to hepatitis B vaccination in patients with different vaccination schedules.

also significantly associated with poorer response to HB vaccination.

Very limited data coming from the previous clinical trials proposes that gender is a major interfering factor in the context of HB vaccine immunogenicity[9]. On the other hand, most of the existing clinical trials represent no significant role for gender on response to HB vaccination, either in kidney disease patients[7,10] or other end-stage organ disease patients[39]. However, the patient population in each of the clinical trials was limited, and in case there is a delicate difference in seroresponse to HB vaccine between the two genders, it can be easily lost. In fact, looking to most of the included clinical trials, males had relatively but not statistically significantly less percentages of response rate to HB vaccination[10,13]. This urged us to conduct this meta-analysis to pool the existing data to represent a universal outlook to the issue.

This meta-analysis showed that in the kidney disease setting, males significantly represent lower

seroconversion due to HB vaccination than females. This finding is of clinical relevance. In a previous study, it had been proposed that immunization against HB in dialysis patients should be individualized based on factors that significantly affect seroresponse in these patients[6]. So, according to the data derived from the current meta-analysis, male patients should be more rigorously surveyed after HB vaccination in dialysis setting. Moreover, future studies are recommended to find more potent immunization programs especially in this vulnerable population.

For having a more precise view on the subject, the data has been reanalyzed after stratifying the included trials based on their patients' dialysis mode, and found that the observed sex bias in the seroconversion due to HB vaccine was only significant in hemodialysis patients, and no significant difference has been observed for patients on peritoneal dialysis or CKD patients not on dialysis. Although on one hand this finding may urge us to pay more attention in men under maintenance hemodialysis therapy, we should have in mind that lack of detecting any sex discrimination in other study groups may be simply due to the comparatively limited sample size in the latter groups.

Once again, the data has been stratified based on their vaccination schedule, mainly in patients receiving 3 or 4 doses of vaccination. Although in none of the two schedules any significant difference in the seroresponse to HB vaccination has been detected regarding patients' sex, those on 4 times vaccination schedule represented a *P* value of 0.055 for sex; which might be of some value for some investigators.

Although this study is of some limitations, we believe that the findings of this study add significantly to the literature, and helps specialists to monitor their kidney disease patients more effectively and protect them against HBV infection attainment. This systematic review represents the strongest evidence on the significance of sex on the seroresponse to HB vaccination in kidney disease patients with males having more impaired immune response to the vaccination. Moreover, this sex bias was significantly more prominent among hemodialysis (*vs* other therapeutic procedures) patients, and in those on 4 times vaccination schedule (*vs* 3 times), although the latter failed to reach the significance level. It should also be mentioned that the age range of the included patients in the current meta-analysis (44-61 years) is much younger than the general age of the dialysis population, which might put some limitations in the globalization of our study results. In conclusion, this Meta analysis showed significant effect for the sex of CKD and dialysis patients on the immunogenicity of HB vaccine, with a better response for females. This sex discrimination was most prominent among hemodialysis patients. This finding suggests us to specify a sex-dependent vaccine dosage administration for patients with kidney disease. Future studies directing to find strategies with more efficacy, as well as surveys directing to find other interfering factors in this regard are recommended.

COMMENTS

Background

Dialysis patients are substantially at higher risk of developing hepatitis B virus (HBV) infection, so preventive measures are of extreme importance in this population. Anti-HBV vaccination has been the most popular preventive strategy in this population for a long time; nonetheless, its feasibility in this population has been under serious doubt. Several factors have been documented as players of significant roles in the seroresponse to HBV vaccination.

Research frontiers

During the past decades, several surveys have been performed to unveil the potential associations between dialysis patients demographic data and their seroresponse to HBV vaccination. Moreover, several systematic reviews as well as meta analyses were published to investigate these associations using pooled data of the randomized trials. To the authors' knowledge, this is the first meta-analysis that have ever investigated an citation between dialysis patents gender and their seroconversion rate after HBV vaccination.

Innovations and breakthroughs

Based on the current meta-analysis, gender is a significant factor determining response to HBV vaccination in kidney disease patients, with females significantly better responding to the vaccination. This may led future scientists to develop some individualized vaccination protocols that improve the response rate of the males to the vaccination.

Applications

Sex is a significant factor predicting seroresponse to HBV vaccination. Cumulation of data of different factors playing roles in this context can help authors to develop specific vaccination protocols for specific groups that maximizes immunization rate in this population.

Terminology

Hemodialysis is a type of renal replacement therapy which purifies the blood from unwanted materials in a way similar to kidney function. Peritoneal dialysis is a type of renal replacement therapy that uses peritoneal space for purification of the blood contents using dialysates getting injected into it. Chronic kidney disease patients are those who have significant renal function disturbance without a need to renal replacement therapy.

Peer-review

The paper is well-written and the results have potential clinical applications.

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