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Review

Effectiveness and safety of pneumococcal vaccines used alone or combined with influenza vaccination in dialysis patients: A systematic review and meta-analysis

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ABSTRACT

Background: A lower conversion vaccination rate and a more rapid decline in antibody titers over time in dialysis patients raise concerns about the effectiveness of pneumococcal vaccination (PV) in this population, which has not been systematically reviewed.
Methods: We searched PubMed, Cochrane Library, Embase and three Chinese databases from inception until February 29th, 2020 for interventional, cohort and case–control studies evaluating PV alone or combined with influenza vaccination (IV) on outcomes (all-cause mortality, pneumonia, cardiovascular events, antibody response and safety). Independent reviewers completed citation screening, data extraction, risk assessment, meta-analysis, and GRADE rating of the quality of evidence.
Results: Five cohort studies and one quasirandomized control trial enrolling 394,299 dialysis patients with high to moderate quality were included. Compared with unvaccinated individuals, those receiving PV had lower risk of all-cause mortality [Adjusted relative risk (RR) 0.73, 95% CI 0.67–0.79, I^2 = 31.1%, GRADE low certainty] and cardiovascular events (adjusted RR 0.80, 95% CI 0.69–0.93, I^2 = 47.2%, GRADE low certainty) without serious adverse effect reported. Compared with no vaccination, lower all-cause mortality was observed in those receiving PV combined with IV (Adjusted RR 0.71, 95%CI 0.67–0.75, I^2 = 63.3%), PV alone (Adjusted RR 0.86, 95% CI 0.78–0.94,I^2 = 0%], and IV alone (Adjusted RR 0.76, 95% CI 0.73–0.79, I^2 = 0%]. There was no difference between pneumococcal vaccinated patients vs non-vaccinated patients with respect to pneumonia. Immune response to pneumococcal conjugate vaccine-13 was weaker in polysaccharide pneumococcal vaccine-23-pre-vaccinated compared with vaccine-naive patients.
Conclusions: The use of pneumococcal vaccine especially combined with influenza vaccination is associated with lower risks of all-cause mortality but may be affected by residual confounding/healthy vaccinee bias.

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Contents

1. Background

End-stage kidney disease (ESKD) is a globally prevalent chronic condition. According to a recent global survey, the median prevalence of kidney replacement therapy globally was around 759 per million population [1]. As a significant major complication of ESKD, infection is second to cardiovascular disease as the leading cause of death in people with ESKD, contributing to excess morbidity and health care costs [2]. Among those who die from infection, pneumonia is one of the most common reasons [3]. In dialysis patients, the risk of death from pneumonia was 14- to 16-fold higher than that in the general population [4] while streptococcus pneumoniae was the most common causative pathogen of pneumonia [5].

To reduce pneumococcal pneumonia burden on dialysis patients, global and national guidelines have been established to recommend that dialysis patients receive vaccination with pneumococcal vaccine(PV) per five years and influenza vaccine (IV) yearly [6,7]. However, some studies have indicated that patients receiving dialysis have a lower conversion vaccination rate and a more rapid decline in antibody titers over time [8,9]. These observations have raised some concerns and questions in relation to PV in dialysis patients: (1) whether PV works or not; (2) whether PV combined with IV is more effective than either agent alone; (3) the duration of protective effect; and, (4) whether pneumococcal conjugate vaccine 13 (PCV-13) or polysaccharide pneumococcal vaccine 23 (PPV-23) is more effective?

Here, we performed a systematic review and meta-analysis that summarized the available evidence on the effectiveness and safety of PV in the dialysis population.

2. Methods

2.1. PRISMA-guideline and study protocol

The systematic review and meta-analysis was conducted in compliance with the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" guidelines [10] and was prospectively registered with the international prospective register of systematic reviews (PROSPEOR Registration ID: CRD42019137874 and see Supplementary Item 1).

2.2. Eligibility criteria

We included randomized control trials or observational studies (cohort or case control studies) that assessed the effectiveness and/or safety of PV (alone or combined with IV) in ESKD patients receiving peritoneal dialysis (PD) or hemodialysis (HD), regardless of publication status and language. The intervention group included PV regardless of adjuvant IV, route of administration or dose. The control group was either unvaccinated or received placebo.

2.3. Outcome measurement

Primary outcomes were all-cause mortality, incident pneumonia and cardiovascular events. Secondary outcomes were antibody response and safety. All-cause mortality was identified from medical record. Incident pneumonia was hospitalizations from pneumonia regardless of pathogen. Cardiovascular events included death or hospitalizations from myocardial infarction, heart failure and unstable angina. Antibody titer could be measured by different

assays at different periods. As for safety, we considered all types of local and systemic adverse events reported in the included studies.

2.4. Literature search

We searched PubMed, Cochrane Library, Embase, three Chinese databases (China National Knowledge Infrastructure, China Biology Medicine and Wangfang databases) and reference list from inception until February 29th, 2020 for studies on PV (combined with or without IV) in dialysis patients.

Our search strategy included the relevant key terms: "dialysis" and "pneumococcal vaccine". We used the key words/MeSH terms in the key papers obtained from PubMed reminder to adapt the searching strategies (For the full strategies in Pubmed see Supplementary Item 2).

2.5. Data selection and extraction

All the search records from different databases were imported in ENDNOTE. After deduplication, eligible studies were listed and assessed independently by three authors (Y.M., J. Z, & C.X.). We independently screened titles, abstracts and full text articles, and the reasons for exclusion have been given. Disagreements between the review authors over article screening were resolved by discussion, with the involvement of a fourth review author (G.S.).

Two authors (Y.M. & J. Z.) used pre-defined forms to extract data from the studies. The following information was extracted: author, country, year, study design, study population, age of participants, years on dialysis, vaccine profile, study size, relative risks (RRs), and 95% confidence intervals (95% CIs), confounders, confounder-adjusted effect measure and side effects. If the RR was not available in the studies, the numbers or incidences of the outcomes were extracted to calculate the RRs.

2.6. Risk of bias assessment

Two authors (Y.M. & L.Z.) independently assessed the risk of bias. The Cochrane Collaboration's tool for assessing risk of bias was used for randomized controlled trials (RCTs): sequence generation; allocation concealment; blinding of participants, staff and outcome assessors; completeness of outcome data and evidence of selective outcome reporting and other potential threats to validity [11]. The Newcastle-Ottawa Scale (NOS) tool was used for cohort studies: selection of study participants (scores 0–4), comparability of subjects (scores 0–2), and exposure or outcome (scores 0-3), with the total score ranging from 0 to 9 (quality of study: low < 4; moderate: ≥4–<7; high ≥ 7– <8) [12]. Disagreements between the review authors over the risk of bias were resolved by discussion, with involvement of a third review author (G.S.).

2.7. Assessment of the quality of a body of evidence

For each outcome, the quality of the respective body of evidence was assessed using the GRADE methodology [13]. According to GRADE, evidence on the effects of an intervention was categorized into four levels of certainty: very low, low, moderate, and high. Bodies of evidence from RCTs start as high quality evidence, whereas those from studies with other designs (observational studies) start as low quality evidence. According to a set of predefined criteria, evidence quality could be increased or decreased. In order to assess the best available evidence, we used the results of the confounder-adjusted analyses to determine GRADE evidence quality.

2.8. Statistical analysis

RRs and corresponding 95%CIs (Confidence interval) were calculated or extracted directly from the publications. Hazard ratios and risk ratios were considered interchangeable in the analyses. Odds ratio(OR) were converted into risk ratio by the formula risk ratio = OR/[(1 − P_0) + (P_0 * OR)], in which P_0 was the event incidence in the control group [14].

Where data from more than one study for a given outcome were available, we performed a meta-analysis. Heterogeneity between trials was identified by the $\chi 2$ test. For each outcome measure of interest, random effects meta-analysis was conducted to pool RRs for the dichotomous composite outcome (all-cause mortality, cardiovascular events, incident pneumonia) in order to determine the effect of PV (yes/no) or PV combined with IV (yes/no) if heterogeneity (I^2 > 50%). Fixed-effect model was used when heterogeneity was acceptable ($I^2 \leq 50\%$). Descriptive analysis was performed in cases of unacceptable heterogeneity. Publication bias was assessed by using funnel plots. Calculations were done by STATA 15 (StataCorp, College Station, TX, USA).

3. Results

3.1. Selection of studies

Initially we identified a total of 7,869 records in electronic databases and no additional studies from the reference list. We finally included six studies after applying the inclusion and exclusion criteria. The reasons for excluding studies are reported in Fig. 1.

3.2. Study characteristics

Six studies were included, with five retrospective cohort studies [15–19] and one quasi-RCT [20] enrolling 394,299 patients in total. Two studies were conducted in the US [15,16], while other studies were in China [17], Czech Republic [18], Japan [19] and Belgium [20], respectively (Table 1). Most included participants were above 60 years old. The duration of dialysis was more than 90 days and the proportion of males ranged from 52.5 to 67.8% [15,16,19,20]. Four studies enrolled HD patients only [15,17,18,20] while one study also enrolled 7.3% PD patients [16] and one study had no description of dialysis modality [19]. Regarding pneumococcal vaccine types, three studies compared PPV23 with no vaccination [17–19], one study compared PPV23 with PCV13 [20], and the other two did not report what types of PV had been used [15,16]. Two studies investigated the combined effect of PV and IV [15,16].

As for reported outcomes, eleven different clinical outcomes were reported (Supplementary Table 1. All-cause mortality [15–17,19,20], cardiovascular disease [15,17,19], pneumonia outcomes [15,17,19,20] and antibody response [18,20] were addressed by at least two studies, whereas only one study reported infectious death [15], other-cause death [15], all-cause hospitalization [15], bacteremia/septicemia hospitalization [15], respiratory infection hospitalization [15], cerebrovascular events [17], and adverse effects [20]).

3.3. Risk of bias assessment

Risks of bias assessment of included studies were shown in Table 1 and Supplementary Table 2. The quality of the included observational studies was moderate to high according to the NOS criteria (three studies with high quality [15,16,19] and three studies with moderate quality [17,18,20]). The common issues identified included lack of representativeness of the exposed cohort [17–20], no description on variables considered in analysis

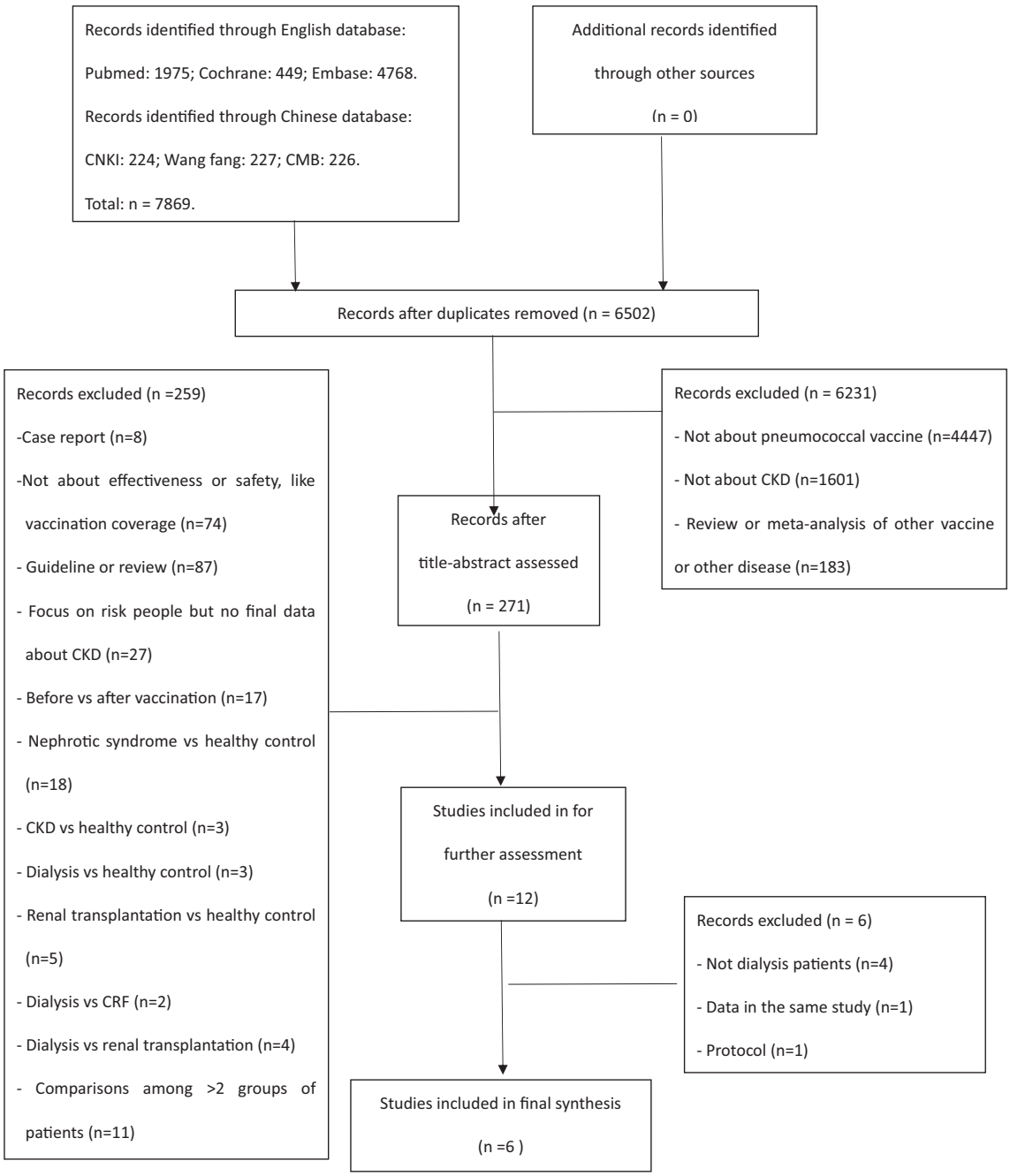

Fig. 1. Flow chart for the systematic literature search and study selection related to pneumococcal vaccine effectiveness outcomes in dialysis patients.

[17,18,20] and short duration of follow-up [15,18]. For Vandecasteele's study, the RCT part was moderate risk with unclear allocation concealment, blinding of participants and personnel and blinding of outcome assessment; and the observational study part was moderate risk because of no description of ascertainment of exposure and no description on variables considered in analysis [20].

3.4. All-cause mortality

Compared with controls, PV was associated with lower all-cause mortality in dialysis patients with low heterogeneity from four studies (pooled RR:0.73, 95% CI: 0.67–0.79, I^2 = 31.1%, P = 0.225, GRADE low certainty) [15–17,19] (Fig. 2, Supplementary Fig. 1 and Supplementary Table 3).

Compared with control dialysis patients, those who received either PV only or received both PV and IV were associated with a lower mortality. The pooled RRs of death from two studies [15,16] were 0.76 (95%CI: 0.73–0.79, I^2 = 0, P = 0.78), 0.86 (95% CI: 0.78–0.94, I^2 = 0, P = 0.34), and 0.71 (95%CI: 0.67–0.75, I^2 = 63.3%, P = 0.09) in those receiving IV only, PV only and both vaccines, respectively (Fig. 2 and Supplementary Fig. 1).

3.5. Cardiovascular events

Compared with non-pneumococcal vaccination, PV was associated with lower odds of cardiovascular events (pooled RR:0.80, 95% CI: 0.69–0.93, I^2 = 47.2, P = 0.42, GRADE low quality) [15,17,19] in dialysis patients (Fig. 3, Supplementary Fig. 2 and Supplementary Table 3).

Table 1
Characteristics of included studies on effectiveness and safety of pneumococcal vaccination in dialysis patients.

Author, year [Ref]	Country	Study design	Age in years	Male patients (%)	Years on dialysis	Patient source	[a]Study size (percentage of HD patients)	Duration of follow-up	Definition of vaccination	Outcomes	Confounder-adjusted model	Variables considered in the final adjusted analysis	Quality assessment
Gilbertson, 2011 [15]	USA	cohort	18-64y: 58.84%; 65-74y:24.24%; >75y: 16.92%.	53%	≤1y: 17.2%; 1-5y: 38.3%; ≥5y: 44.5%.	The Centers for Medicine & Medicaid Services, US	P+: n = 259091; P-: n = 93442. (100%)	6 months	[5] HCPCS codes 90,732 and G0009 were used to search for pneumococcal vaccination. HCPCS codes 90656, 90658, 90659, 90,660 and G0008 for influenza vaccination.	Mortality, cardiac death, infectious death, other cause of death, all-cause hospitalization, pneumonia hospitalization, bacteremia/ septicemia hospitalization, respiratory infection hospitalization	Cox proportional hazards models	patient characteristics, comorbidity, receiving influenza vaccinations	High
Bond, 2012 [16]	USA	cohort	P-/ I-:57.9 ± 15.9; P+/I-:59.3 ± 15.4; P-/I+:60.6 ± 15.2; P+/I+:64.2 ± 14.9.	52.5%	P-/ I-:4.8 ± 4.1; P+/I-:4.9 ± 4.1; P-/I+:4.5 ± 3.6; P+/I+:4.5 ± 3.5.	ESKD Networks Organization for the states of North Carolina, South Carolina and Georgia, US	[3]P-/ I-4:5994; P+/I-:1297; P-/I+:14226; P+/I+:12985. (92.7%)	12 months	Data from ESKD Networks organization (Unclear definition of pneumococcal vaccination)	Death and cause of death information was collected through the ESKD death notification form ([5]CMS 2746)	Multivariable logistics models	Age, race, sex, time on dialysis, modality, diabetes as primary cause of ESKD, comorbidities at dialysis initiation, and laboratory parameters.	High
Hsieh, 2016 [17]	Taiwan, China	cohort	>50y: 100%	NR	NR	The Chiayi Chang-Gung Memorial Hospital of Taiwan, China	P+:n = 168; P-: n = 377. (100%)	5 years	PPV23	Mortality, acute myocardial infarction, pneumonia, cerebrovascular events.	Multivariable logistics models	Not reported	Moderate
Trmal, 2005 [18]	Czech	cohort	Not reported	NR	NR	Not reported	P+/I+:35; P-/I+:19. (100%)	12 months	PPV23	Antibody response	/	/	Moderate
Ihara, 2019 [19]	Japan	cohort	P-: 64(31–91) P+:28(28–92)	67.8%	P-: 8.5 ± 8.2 P+:8.8 ± 8.0	a group of dialysis units (1 hospital and 7 clinics) in Japan	P-: n = 255; P+: n = 255. (NR)	5 years	PPV23 recorded in medical records	the time to first admission, or deaths from all-cause pneumonia or cardiac events	multivariate logistic regression analysis	age, sex, body mass index, duration of dialysis, serum level of albumin, influenza vaccination in 2010, history of arteriosclerotic heart disease, chronic heart failure, peripheral vascular disease, and diabetes mellitus.	High

Vandecasteele, 2018 [20]	Belgium	RCT	[b]Group 1: 72.4 ± 13.4; Group 2: 68.3 ± 13.9;	Group 1: 23 (57.5%); Group 2: 25 (62.5%);	Group 1: 2.04(0.82–4.85); Group 2: 2.45(1.41–3.87);	Two dialysis centers in Belgium (AZ Sint-Jan Brugge-Oostende AV in Bruges, Onze Lieve Vrouw Ziekenhuis in Aalst).	Group 1: 40; Group 2: 40; (100%)	1 years	pneumococcal vaccination (PPV23/ PCV13) status documented in the medical files	[5]ELISA and OPA antibody titers to the common PPV-23 and PCV-13 antigens (1, 3, 4, 5, 6B, 7F, 9 V, 14, 18C, 19A, 19F and 23F) and to the PCV13 (6A) specific serotype 6A were quantified were registered by patients and trained nurses. Vaccine adverse effects. Patient mortality and pneumonia (defined as acute respiratory illness with a new infiltrate on chest X-ray) incidence.	/	/	Moderate
		cohort	Group 3: 74.8 ± 8.7; Group 4: 74.6 ± 8.2.	Group 3: 17 (42.5%); Group 4: 23 (65.7%).	Group 3: 3.40(2.48–5.09); Group 4: 2.83(1.46–6.30).		Group 3: 40; Group 4: 35. (100%)						Moderate

Abbreviations: HD: hemodialysis; HCPCS: Current Procedural Terminology/Health Care Common Procedure Coding System; ESKD: end stage kidney disease; PPV: polysaccharide pneumococcal vaccine; PCV: pneumococcal conjugate vaccine; CMS: Centers for Medicare & Medicaid Services; ELISA: Enzyme-linked Immunosorbent Assay; OPA: Opsonophagocytic Assay; NR: not reported; P+: receive pneumococcal vaccination with/without influenza vaccination; P−: not receive pneumococcal vaccination with/without influenza vaccination; P-/I−: receive neither vaccination; P+/I−: only receive pneumococcal vaccination but no influenza vaccination; P−/I+: only receive influenza vaccination but no pneumococcal vaccination; P+/I+: receive both vaccinations.

[a] Total study population: 394,299 (P+: 279,986; P−: 114,313).

[b] Group 1: PPV-23-naive patients receiving PPV23; Group 2: PPV-23-naive patients receiving PCV13; Group 3: Patients who pre-vaccinated with PPV-23 > 4 years receiving PCV13; Group 4: Patients who pre-vaccinated with PPV-23 < 4 years receiving PCV13.

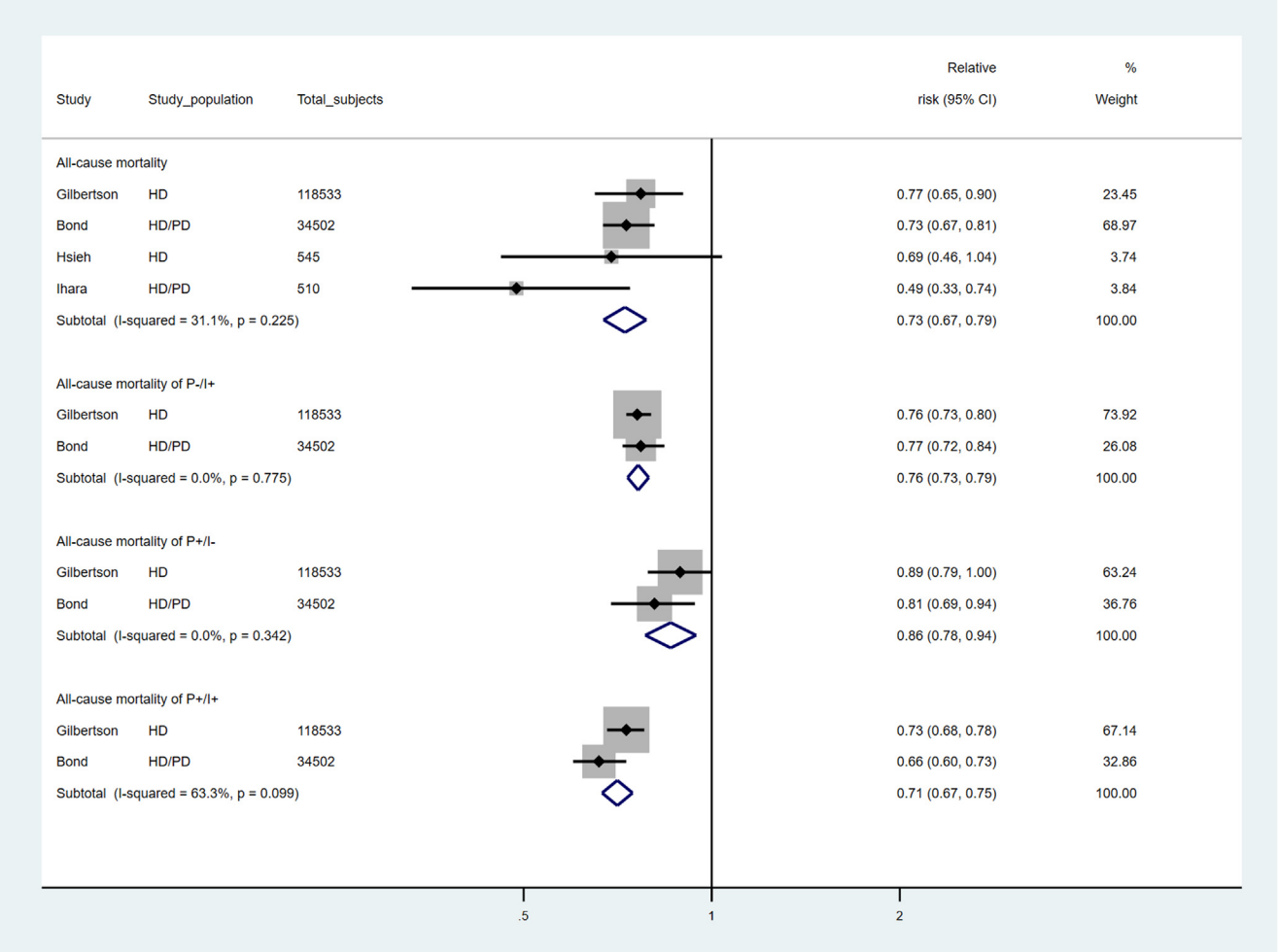

Fig. 2. Forest plots depicting the association between pneumococcal vaccine used alone or combined with influenza vaccine and all-cause mortality in dialysis patents (fixed-effect model).

3.6. Incident pneumonia

There was no difference between pneumococcal vaccinated patients vs non-vaccinated patients with respect to incident pneumonia (RR < 1, P > 0.05) [17], pneumonia hospitalization (pooled RR:1.32, 95%CI: 0.73–2.00, I^2 = 43.3%, P = 0.184, GRADE low certainty) [15,19] or pneumonia death(RR:1, 95%CI: 0.32–3.10) [19] (Fig. 4, Supplementary Fig. 3 and Supplementary Table 3).

3.7. Antibody response

Two studies reported antibody response [18,20]. The geometric mean concentrations of antibodies to PV increased 4.8 times after vaccination for dialysis patients but decreased to 1/3 one year later [18]. In those pneumococcal vaccination naive dialysis patients randomized to receive PCV13 or PPV23, ELISA antibody titers were significantly higher among PCV13 than PPV23 recipients for six serotypes (1.85-2.34 fold) after 28 days, and remained significantly higher for one serotype (1.57-fold) after 365 days [20]. Following PCV-13 vaccination, increases in ELISA antibody titers were significantly higher among PPV-23-naive versus PPV-23-pre-vaccinated patients for 12 serotypes after 28 days (1.68–7.74-fold) and remained significantly higher in ten serotypes (1.44–3.29-fold) after 365 days [20]. Immune response to PCV-13 was weaker in PPV-23-pre-vaccinated compared with vaccine-naive patients.

3.8. Safety

One study reported adverse effects of PV, including pain, fatigue, muscle aches, headache, itching and decreased mobility [20]. Local adverse effects, especially pain and decreased mobility, occurred in up to one-fifth of the patients, mainly during the first 3 days after vaccination. Local adverse effects, especially pain, tended to be more common in the PCV-13 groups than in the PPV-23 group.

3.9. Publication bias

Formal testing for publication bias was not performed because of the small number of identified studies.

4. Discussion

Our results indicated that PV was associated with reduced risks of all-cause mortality and cardiovascular events but made little difference to pneumonia with low certainty evidence. A lower risk of all-cause mortality was observed in those receiving PV combined with IV. For PV recipients, geometric mean concentrations of antibodies increased 4.8 times thereafter but decreased to 1/3 a year later. Compared with those vaccinated with PPV-23, those receiving PCV-13 had higher ELISA antibody titers of some serotypes

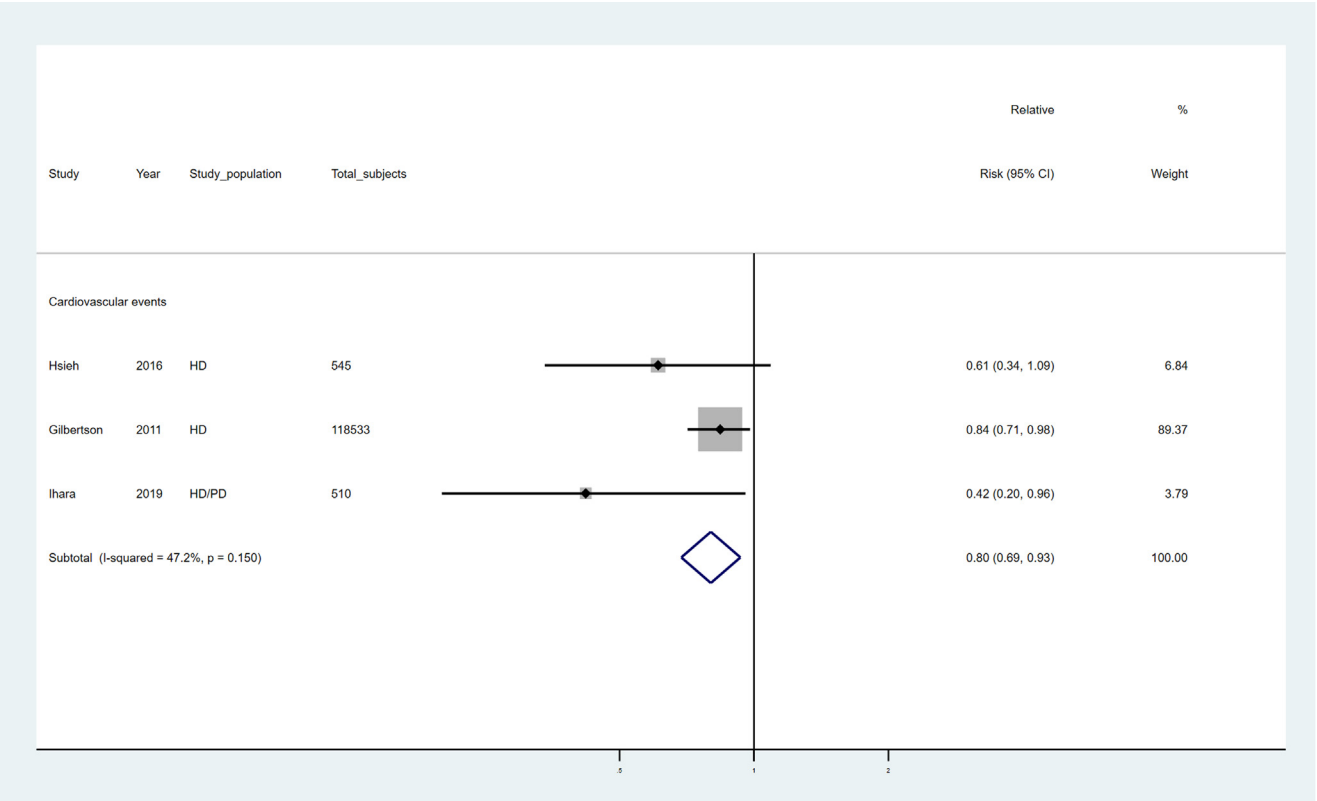

Fig. 3. Forest plots depicting the association between pneumococcal vaccine and cardiovascular disease in dialysis patents (fixed-effect model).

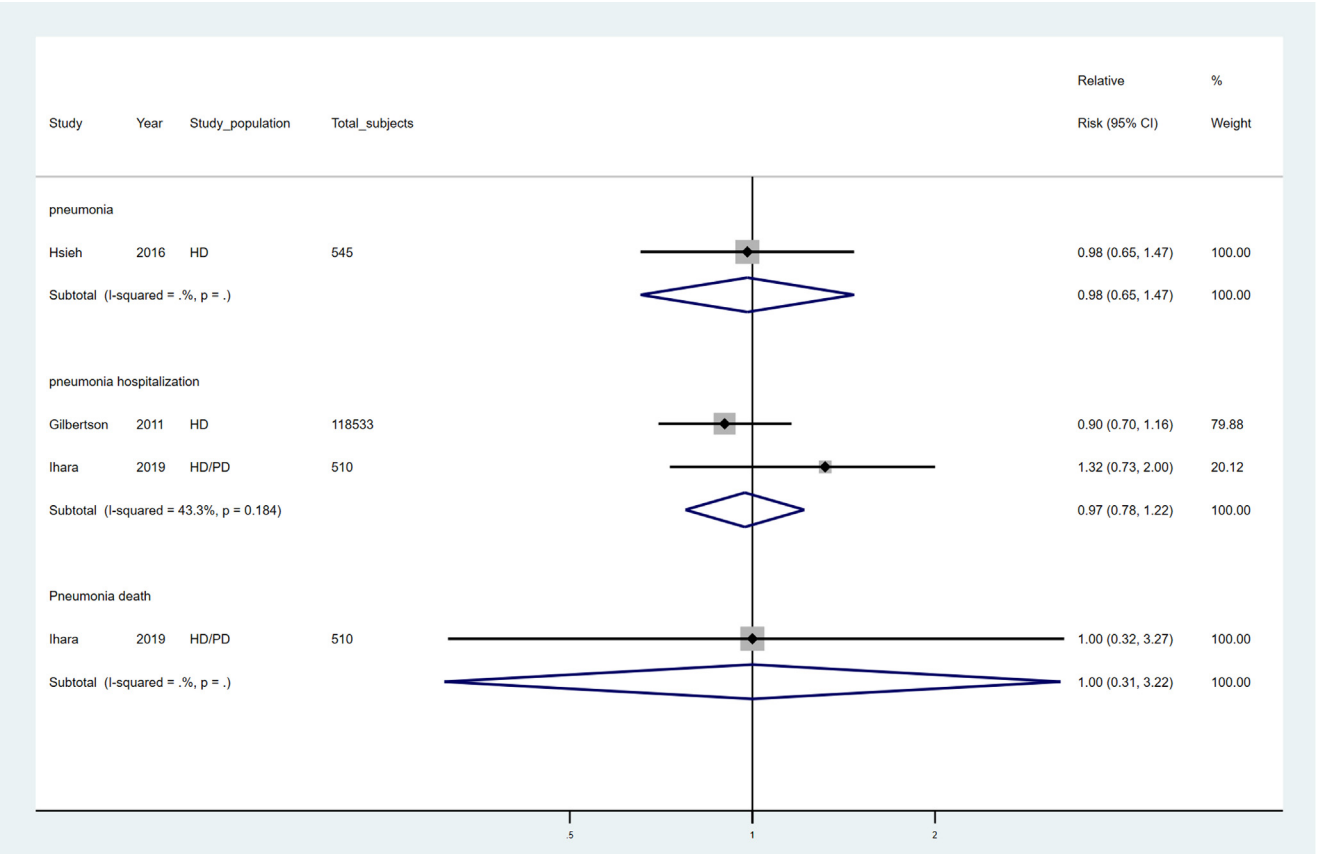

Fig. 4. Forest plots depicting the association between pneumococcal vaccine and pneumonia in dialysis patents (fixed-effect model).

after 28 and 365 days. No serious adverse effect of PV was reported.

Our analysis demonstrated that use of PV was associated with lower risks of all-cause mortality and cardiovascular events. First, previous studies have reported a higher risk of acute cardiac events following pneumonia in both the general and dialysis population [21,22]. PV may reduce the incidence of cardiovascular events by minimizing the severity of the pneumonia and its associated systematic inflammation [23,24]. Second, Reyes *et al* have found S. pneumoniae invaded the myocardium and induced cardiac injury with necroptosis and apoptosis in a non-human primate model. PV may prevent S. pneumoniae invading cardiac tissue [25]. Furthermore, vaccination with S. pneumoniae appears to induce the production of antibodies that cross-react with oxidized low density lipoprotein, a component of atherosclerotic plaques, resulting in reduced cardiovascular events [26]. Similar mechanisms have been identified with IV [27,28] and this may explain the observed reduced mortality in dialysis patients receiving a combination of IV and PV compared with either agent alone. However, our data did not support that this is the mechanism as there was no association with pneumonia-related outcomes. It may be instead that those patients who agreed to vaccination are more health literate and have associated better cardiovascular and all-cause mortality outcomes (healthy vaccinee bias). It is also possible that patients receiving a combination of IV and PV were more likely to be cared for by healthcare professionals who adhered to other best practice guideline recommendations (e.g. phosphate, anemia and blood pressure) that are associated with reduced mortality and cardiovascular disease in dialysis patients. Therefore, further RCTs are needed to evaluate its efficacy in this population objectively.

Our result of pneumonia outcomes that PV made no difference with respect to incident pneumonia was consistent with the finding in the elderly or patients with chronic diseases [29,30]. PV may not be effective in reducing the incident pneumonia in dialysis patients, but may reduce the mortality by minimizing the severity of the infection, similar to that in HIV patients and older adults [23,24]. In addition, PV can only induce certain serotype conversion and exert a protective effect [30,31]. The lack of serotype coverage from PV in specific area may also contribute to the null effects of PV. For example, a Japanese study showed that the serotypes addressed by PPV-23 (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23) only accounted for less than 51% of all pneumococcal pneumonia serotypes in adults [32]. Patients infected with serotype 6A pneumococcal pneumonia, which was not covered by PPV23, had a 25% higher risk of death than patients infected with other serotypes [32]. The included studies in our analysis only focused on all-cause pneumonia, but not certain serotypes of pneumococcal pneumonia. Another possible reason for why we did not observe lower pneumonia incidence and morbidity in vaccinated patients could be the effect of indication bias (i.e. patients with underlying comorbidities may have been more likely to have been vaccinated than healthier study participants). This could have biased the study findings in favour of the null hypothesis. Therefore, well-designed studies are needed to confirm the effectiveness of PV against serotype-specific pneumonia in dialysis patients.

Regarding type of PV, our systematic review showed PCV-13 seems to be more immunogenic than PPV-23 among vaccine-naive hemodialysis patients, which is similar to what has been previously demonstrated in immunocompetent adults [33]. As we know, PPV induces immunoreaction without the involvement of T cells, so PPV cannot sustain long-term immunity and cannot be enhanced through additional vaccination [34]. PCV elicits a T-cell dependent response resulting in memory B-cell formation and higher avidity of antibody production [35]. Therefore, it is possible that PCV may lead to a more durable antibody response compared to PPV. Secondly, immune response to PCV-13 is weaker in PPV23-pre-vaccinated compared with vaccine-naive patients. It has been reported that the responses to PCV-13 after PPV-23 vaccination were significantly lower than those initializing PCV-13 vaccination, which suggested that PPV-23 might diminish the response of subsequent PCV-13 vaccination [36]. Giving a PCV prior to a PPV has the potential to enhance the immune response to the PPV by stimulating memory B cells and priming the immune system, such that a vaccination combination of PCV-13 first and PPV-23 second is recommended for immunocompromised patients [37,38].

As for the timing of revaccination, our results showed the titers of antibody related to vaccination decreased quickly over time in dialysis patients, similar to previous studies [8,9]. The current guideline recommends revaccination in five years after first pneumococcal vaccination [6,37]. However, there are insufficient data to show whether this five-year interval is too long for dialysis patients and the levels of antibody required for protection have not been clearly delineated. Therefore, whether we should shorten the time for revaccination by monitoring titers of antibody has yet to be confirmed and needs further studies.

As for safety, similar to the findings of previous meta-analyses [33,39], we found that PV has a high safety profile, with local reactions at the injection site, and rare systemic side effects, such as fever.

4.1. Policy implication

PV was cost-effective among adults aged 50–64 years with CKD even when assuming the lowest vaccine efficacy [40]. However, PV coverage is low in many countries [41–43]. The results of our current study might raise awareness about the importance of pneumococcal vaccinations. Given its benefit of lower mortality and mild side effects, PV combined with IV seems to be beneficial for dialysis patients. Though PV is recommended to dialysis patients in global and national guidelines [6,7,37], the evidence to date is only low certainty according to the GRADE criteria. For policy makers, considering the indication bias and healthy vaccine bias of the observational studies, well-designed and adequately powered randomized control trials are needed to reduce uncertainty about its efficacy on risk of pneumonia and the time for revaccination in this population.

4.2. Strengths and limitation

Our study has several strengths. Our systematic review focused on PV in dialysis patients, a neglected population in previous systematic reviews. We performed comprehensive searches using not only English databases such as PubMed and Embase, but also Chinese databases to capture as many relevant studies as possible. Moreover, we performed an outcome-specific quality assessment of individual studies and considered the certainty of the body of evidence for each outcome by using GRADE. We have also covered a wide range of clinically important questions about vaccinations in dialysis patients, including effectiveness, the benefit if combined with influenza vaccination, which types (PPV or PCV) to use and the possible timing of revaccination.

We also acknowledged the following limitations should be considered when interpreting our findings: First, most included studies were retrospective cohort studies. Our data cannot prove causality and the possibility of residual or unmeasured confounding cannot be eliminated. We were unable to further investigate the effect of indication bias and healthy vaccinee bias, which might underestimate or overestimate the effectiveness of pneumococcal vaccine [44,45]. Second, we used the most adjusted RR as the estimator in our meta-analysis, which may have resulted in outcome reporting bias despite representing the most conservative risk esti-

mation. Third, we found overall moderate to high heterogeneity in some estimates. Heterogeneity may be attributed in part to different patient characteristics, follow-up periods, study quality and sample size and intervention type. However, we were unable to perform all these subgroup analyses owing to the limited data available and lack of access to the original, individual patient data. Fourth, patients included were from developed countries or regions. It should be cautious for the interpretation of our data in less-developed countries. Finally, although we have tried to summarize all of the available evidence, it should be noted that the number of included studies limited our ability to perform further meta-analysis. The interpretation of the results should take into consideration the fact that the results for all-cause mortality were largely driven by two studies [15,16], the results for cardiovascular disease and pneumonia hospitalization were restricted to one large study [15], the results for pneumonia incidence [17] and death [19] were limited to only one observational study each, safety was addressed by only one study [20], and antibody response was addressed by two studies [18,20]. Meanwhile the study sample was too small to formally test for publication bias, this form of bias cannot be ruled out.

5. Conclusion

The use of pneumococcal vaccine, especially combined with influenza vaccine, is associated with lower risks of all-cause mortality. High quality randomized controlled trials are needed to provide high certainty evidence regarding the effectiveness and safety of pneumococcal vaccines used alone or in combination with influenza vaccination in dialysis patients.

CRediT authorship contribution statement

Yenan Mo: Data curation, Formal analysis, Software, Validation, Writing - original draft. **Jiahao Zeng:** Data curation, Formal analysis, Software, Validation. **Cuixia Xiao:** Data curation, Formal analysis, Software, Validation. **La Zhang:** Data curation, Formal analysis, Software, Validation. **Lixin Wang:** Formal analysis, Validation, Writing - review & editing. **Fuhua Lu:** Formal analysis, Validation, Writing - review & editing. **Prof David W Johnson:** Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Prof Cecilia Stålsby Lundborg:** Formal analysis, Validation, Writing - review & editing. **Prof Dorothea Nitsch:** Conceptualization, Validation, Writing - review & editing. **Prof Xusheng Liu:** Formal analysis, Funding acquisition, Supervision, Validation, Writing - review & editing. **Guobin Su:** Conceptualization, Data curation, Funding acquisition, Software, Supervision, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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