Association between duration of dialysis and *Helicobacter pylori* infection in dialysis patients: a meta-analysis

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Abstract

Purpose The association between *Helicobacter pylori* (HP) infection and duration of dialysis in dialysis patients is conflicting, this meta-analysis was conducted to elucidate the association between duration of dialysis and HP infection status in dialysis patients, and subgroup study was conducted to explore its influencing factors. Furthermore, our study aims to provide advice on the treatment of dialysis patients.

Methods Articles published up to 30 September 2018 were searched from PubMed, Embase, Sinomed, Medline, China Knowledge Resource Integrated Database (CNKI) and Wang fang database. Two researchers independently identified whether studies met the eligibility criteria. The adjusted relative risk (RR) or the weighted mean difference (WMD) and their 95% CI were estimated. I^2 was performed to evaluate the statistical heterogeneity. Publication bias was evaluated using Egger's test and a funnel plot.

Results Fourteen studies were included involving 2087 dialysis patients, 815 of them were HP positive, 1272 of them were HP negative. Quantitative data and qualitative data were analyzed, respectively. For quantitative data, statistical differences were observed in the association between HP infection and duration of dialysis ($P = 0.008$), also in the hemodialysis subgroup ($P = 0.006$). After stratifying by detection methods, differences still existed in groups with different detection methods ($P = 0.001$, $P = 0.033$). For qualitative data, there was no statistical difference in the association between HP infection rate and duration of dialysis ($P = 0.295$). Furthermore, we found that the age was higher in HP positive patients than in HP negative patients ($P < 0.001$).

Conclusion Our meta-analysis found that HP infection rate was negatively correlated with accumulative dialysis time, and methods of HP detection did not influence the association between HP infection and accumulative dialysis time. We also found that age was the risk factor of HP infection in dialysis patients. Further studies need to be performed to elucidate the mechanism of the correlation between HP infection and duration of dialysis, to explore which timing period of dialysis is most susceptible to HP infection, then, improve the prognosis of patients with renal diseases.

Keywords Dialysis · *Helicobacter pylori* · Hemodialysis · Detection methods · Age · Meta-analysis

Introduction

Helicobacter pylori (HP), is the commonest infectious bacterium all over the world, and up to now, it was detected in almost 50% people around the world [1]. The HP infection is not only associated with gastroduodenal diseases, but also cardiovascular and cerebrovascular diseases [2, 3]. Recently, many studies have also shown that HP infection plays an important role in the pathogenesis of gastrointestinal complications in hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) patients [4, 5]. HP positive dialysis patients often have more gastrointestinal troubles than individuals with normal renal function, such as heartburn,

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peptic ulcer disease, gastric erosion [4–6]. Moreover, those patients with peptic ulcer disease are more prone to gastrointestinal bleeding [7]. Thus, *Helicobacter pylori* infection has become a major health problem and can contribute to the occurrence of gastrointestinal complications in dialysis patients.

The prevalence of HP infection in dialysis patients ranges from 20 to 64% [8, 9]. However, the association between HP status and dialysis patients or healthy controls remains inconsistent [10]. The reason for this discrepancy may be due to the different methods used for detection, methods of dialysis, sample size, duration of dialysis, and so on. Several studies are cross-sectional, or have short observation time for patients, or without observing natural remission in the same patients before and after dialysis. Therefore, duration of dialysis is an important factor affecting HP infection. In Iran, Khedmat et al. [6] found a significant increasing in HP infection rate among chronic dialysis patients. However, there were some conflicts about the association between HP infection and duration of dialysis. Some studies suggested that the duration of dialysis was independent of HP infection status in dialysis and non-dialysis patients. Nevertheless, Nakajima et al. [11] suggested that there was a negative correlation between dialysis duration and the relevant rate of HP infection. Therefore, we conducted a meta-analysis to sum up all available articles to clarify the association between HP infection and duration of dialysis, and to further explore the effects of detection methods and dialysis methods on this association.

Methods and materials

Search strategy

We searched PubMed, Embase, Sinomed, Medline, China Knowledge Resource Integrated Database (CNKI) and Wang fang database from inception to September, 2018 without language restrictions. The systematic review was independently conducted by 2 reviewers (A, B). Our overall search strategy (Fig. 1) included terms for dialysis, *Helicobacter pylori*, *H. pylori* and HP. Additionally; we also searched the references of included articles for additional relevant reports.

Selection criteria

We regarded studies as eligible for inclusion if they met the following criteria: (1) case–control or cohort studies had to report data on the relationship between HP infection status and duration of dialysis. (2) For qualitative data, they must provide relative risks (RR). For quantitative data, they must provide the effect size, mean and standard deviation.

The exclusion criteria were as follows: (1) inadequate information for data extraction. (2) Study design of review articles and case report. (3) Study that repeat published or conference literature. (4) Animal experiment.

Data extraction

According to the Selection criteria to access to the full text, two independent reviewers (A, B) extracted these data. Any disagreement was resolved by consensus in a panel meeting (A, B). For each study, the following information was extracted: the first author, year of publication, country of study population, study design, sample size, basic characteristics of patients, detection methods for HP, dialysis methods and duration of dialysis, the adjusted RR, the effect size, the mean and the standard deviation.

Statistical analysis

All statistical tests were performed using Stata12.0 (Stata-Corp, College Station, Texas). The combined relative risk (RR) value and the weighted mean difference (WMD) were chosen as the average effects of this meta-analysis on the qualitative data and the quantitative data, respectively. I^2 were performed in a heterogeneity assessment, and statistical significance for heterogeneity was considered if $P < 0.05$ or $I^2 > 50\%$, in which case the condition random-effects model was performed, otherwise a fixed-effects model was used. Publication bias was evaluated using the Egger's test and funnel plot.

Results

Study characteristics

The original literature search yielded 647 articles, finally 14 [4, 5, 9, 12–22] of these were included. The 14 articles involved 2087 dialysis patients, all patients received *Helicobacter pylori* detection, and 815 of them were HP positive, 1272 of them were HP negative, 1544 of them from quantitative data, 543 of them from qualitative data. All patients were Asian, and patients including the elderly, young people, and children. The basic inform and characteristics of included studies are shown in Table 1. Three [12, 20, 21] of these were qualitative data, 11 [4, 5, 9, 13–19, 22] of these were quantitative data. It's to be worthy that, there is another article [23] was excluded owing to the fact that the data extracted from it is lacking standard deviation.
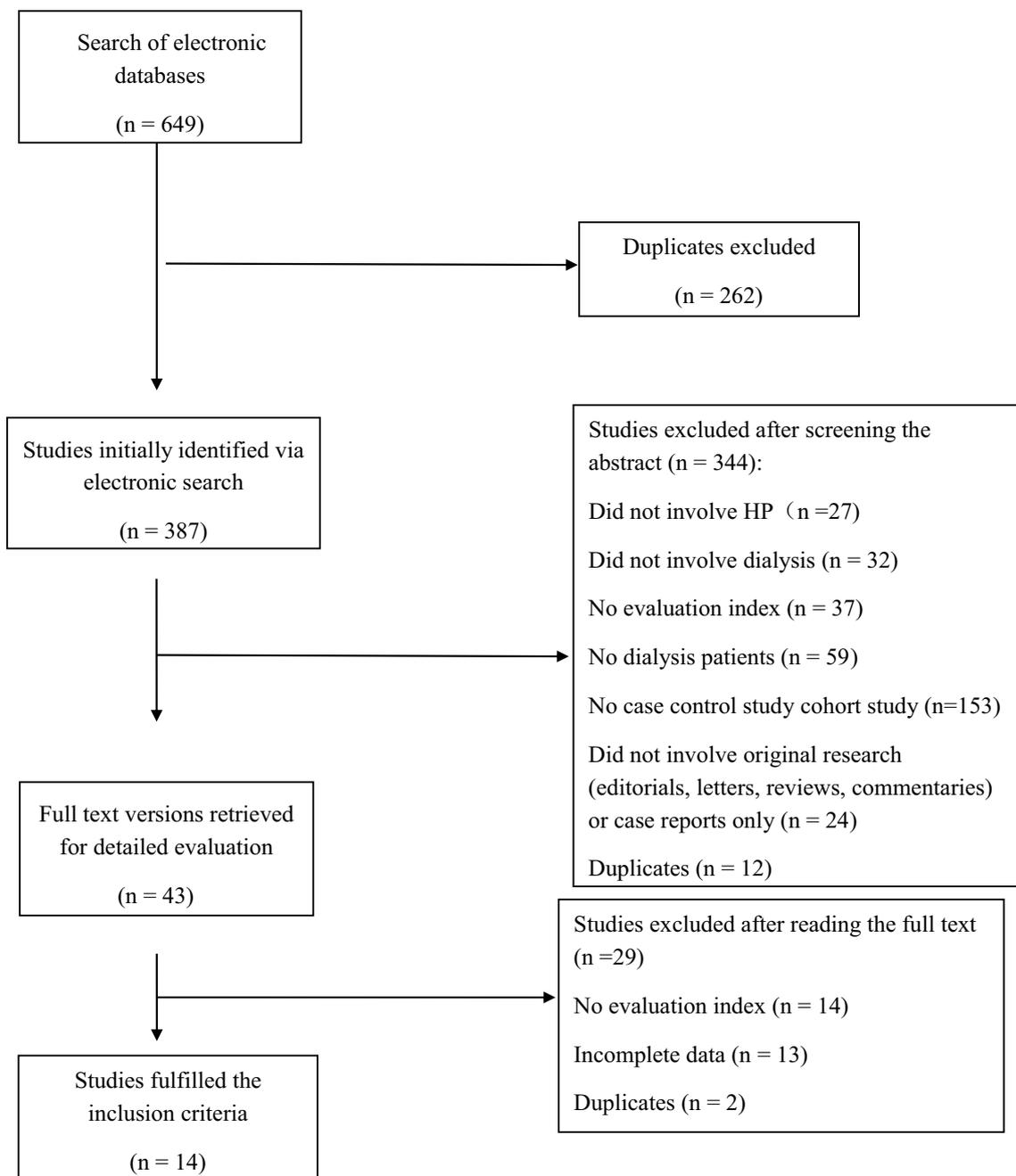
Fig. 1 Strategy search

Association between HP infection and dialysis duration

Some studies indicated that HP infection might relate to duration of dialysis, and some studies suggested that HP infection rate decreased with the accumulative time of dialysis extended. Sugimoto et al. [4] showed that HP infection rate decreased in the first 4 years of dialysis and plateaued after 5-year dialysis. In conclusion, there are conflicts about

the relationship between HP infection and duration of dialysis. Our study analyzed 14 articles, including 11 quantitative data, three qualitative data. Forest plots (Figs. 2 and 3) of the quantitative data and qualitative data were shown, respectively. Since I^2 was greater than 50%, a random model was performed both in quantitative data and qualitative data.

Figure 2 shows that duration of dialysis in HP (+) group was shorter than that in HP (−) group [WMD = − 15.26 (95% CI: − 26.54 to − 3.99)], $P = 0.008$, $I^2 = 93.2\%$. No statistical

Table 1 Characteristics of the 14 eligible studies in this meta-analysis

Quantitative data

Author	Year	District	Dialysis method	Detection method	HP (+)			HP (−)		
					N	Duration of dialysis (month)	Age	N	Duration of dialysis (month)	Age
Sing Leung Lui	2005	China	CAPD	Antibody method	35	50.61±36.6	64.9±9.5	101	54.9±44.1	60.7±13.2
Fumitaka Nakajima	2002	Japan	HD	Antibody method	14	8.1±7.5	63.8±7.6	37	56.2±60.9	63.7±9.9
Neslihan Seyrek	1996	Turkey	HD	Antibody method	13	26.0±28.0	44.3±12.4	78	22.3±20.0	40.9±13.8
S. Boyacioğlu	1997	Turkey	HD	Urease test	28	25.39±21.69		19	29.57±34.14	
Yildiz A	1999	Turkey	HD	Antibody method	31	26.6±23.5	38.4±12.3	16	44.19±32.1	33.2±11.2
FakhrossadatMortazavi	2008	Iran	HD	Urease test	20	7.6±4.9		11	21.2±13.9	
Mitsushige Sugimoto	2009	Japan	HD	antibody method	262	79.44±4.8		277	113.4±4.8	
Won-Chul Chang	2010	Korea	HD	Urease test	12	56.8±26.9	62.0±10.7	21	66.4±26.1	61.9±9.5
Gur	1999	Turkey	HD	Urease test	25	21.2±16.4	35.1±4.2	20	21.8±11.4	32.5±5.3
Mitsushige Sugimoto	2017	Japan	HD	Antibody method	75	55.2±45.6	68.5±10.9	425	87.6±15.6	64.8±13.0
Khazaei	2008	Iran	HD	Urease test	16	22.5±18.5		8	26.9±32.5	

Qualitative data

Author	Year	District	Dialysis method	Detection method	Duration time < 30 months		Duration time ≥ 30 months	
					HP (+)	HP (−)	HP (+)	HP (−)
YJ Ke	2015	China	HD	14C-UBT	92	56	67	81
Yousef Rasmi	2012	Iran	HD	Antibody method	49	40	49	13
Ibrahiem Saeed Abdul-Rahman	2012	Saudi Arabia	PD	Giemsa stain	23	25	4	44

Study	WMD (95% CI)	%
ID		Weight
Sing Leung Lui (2005)	-4.29 (-19.16, 10.58)	9.12
Fumitaka Nakajima (2002)	-48.10 (-68.11, -28.09)	8.08
NeslihanSeyrek (1996)	3.70 (-12.15, 19.55)	8.92
S. Boyaciog˘lu (1997)	-4.18 (-21.51, 13.15)	8.63
Yildiz A (1999)	-17.59 (-35.36, 0.18)	8.54
FakhrossadatMortazavi (2008)	-13.60 (-22.09, -5.11)	10.21
Mitsushige Sugimoto (2009)	-33.96 (-34.77, -33.15)	10.83
Won-Chul Chang (2010)	-9.60 (-28.47, 9.27)	8.31
Gur (1999)	-0.60 (-8.74, 7.54)	10.25
Mitsushige Sugimoto (2017)	-32.40 (-42.83, -21.97)	9.91
Khazaei (2008)	-4.40 (-28.68, 19.88)	7.21
Overall (I-squared = 93.2%, p = 0.000)	-15.26 (-26.54, -3.99)	100.00

NOTE: Weights are from random effects analysis

-68.1   0   68.1

Fig. 2 The association between HP infection and duration of dialysis (months)

Study	RR (95% CI)	%
ID		Weight
YJ Ke (2015)	1.37 (1.11, 1.71)	38.65
Yousef Rasmi (2012)	0.70 (0.55, 0.87)	38.52
Ibrahiem Saeed AbdulRahman (2012)	5.75 (2.15, 15.37)	22.83
Overall (I-squared = 93.3%, p = 0.000)	1.47 (0.72, 3.00)	100.00

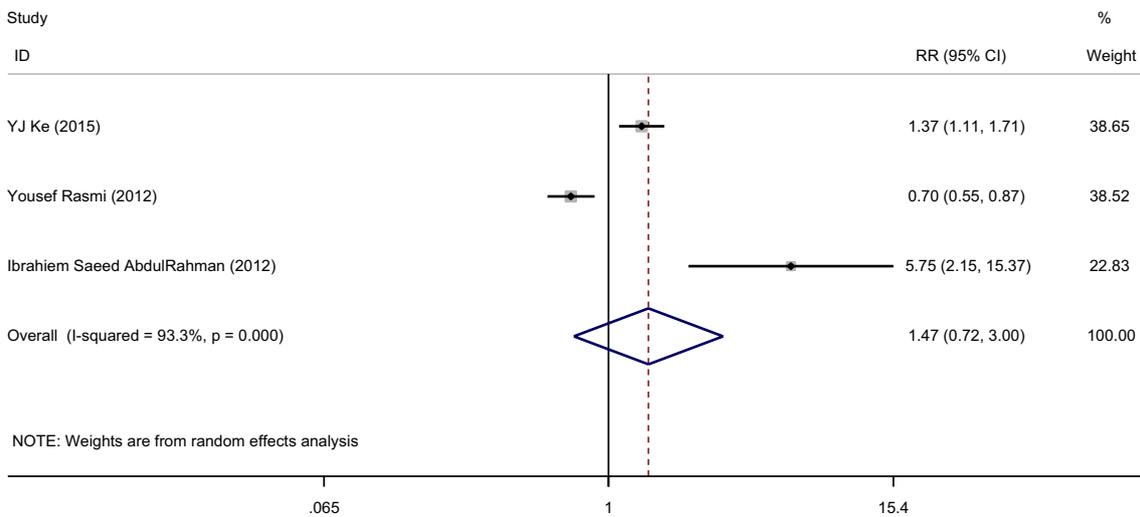NOTE: Weights are from random effects analysis

.065   1   15.4

Fig. 3 Qualitative data about the association between HP infection rate and dialysis time

difference was observed in qualitative data [RR = 1.466 (0.716, 3.001)], $P = 0.295$, $I^2 = 93.3\%$. Figure 3 suggests that the HP (+) in < 30 months group was higher than that in ≥ 30 months group, however, no statistical significance was observed in this meta-analysis.

Subgroup analysis of quantitative data

Our meta-analysis also conducted a subgroup analysis to identify the effect of dialysis methods and detection methods on the association between HP infection and duration of dialysis. Figures 4 and 5 show the forest plots of dialysis methods and detection methods, respectively.

Figure 2 shows that duration of dialysis in HP (+) group is shorter than that in HP (−) group. After stratifying by dialysis methods (Fig. 4), including continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD), the only one article involving CAPD demonstrated that no statistical significance was observed in CAPD (WMD = − 4.29 (95% CI: − 19.16 to 10.58) $P = 0.572$) and the forest plot showed there exited significance in HD (WMD = − 15.26 (95% CI: − 26.54 to − 3.99) $P = 0.006$, $I^2 = 93.3\%$). After stratifying by detection methods, including the antibody methods and the urease test (Fig. 5), significance were observed in the antibody methods group (WMD = − 22.40 (95% CI: − 35.29 to − 9.50) $P = 0.001$, $I^2 = 88.1\%$) and the urease test group

(WMD = − 6.72 (95% CI: − 12.91 to − 0.53) $P = 0.033$, $I^2 = 18.4\%$). Figures 4 and 5 suggest that dialysis methods might influence the association between HP infection and duration of dialysis and detection methods may be the main source of heterogeneity.

Association between age and HP infection

Some studies indicated that age might be an influencing factor of HP prevalence, so we conducted a meta-analysis to study the effect of age on the HP infection in patients with dialysis. Figure 6 shows the forest plot of the association between age and HP infection, since I^2 was 0.00%, a fixed model was performed. We found that the age was higher in HP (+) than in HP (−) dialysis patients [WMD = 3.00 (95% CI: 1.44–4.56)] $P < 0.001$, $I^2 = 0.00\%$.

Evaluation for publication bias

Publication bias was evaluated by Egger linear regression test and a funnel plot. There existed publication bias by the funnel plot and Egger's regression asymmetry test with $P = 0.007$ in analysis of association between HP infection and dialysis duration (Figs. 7 and 8).
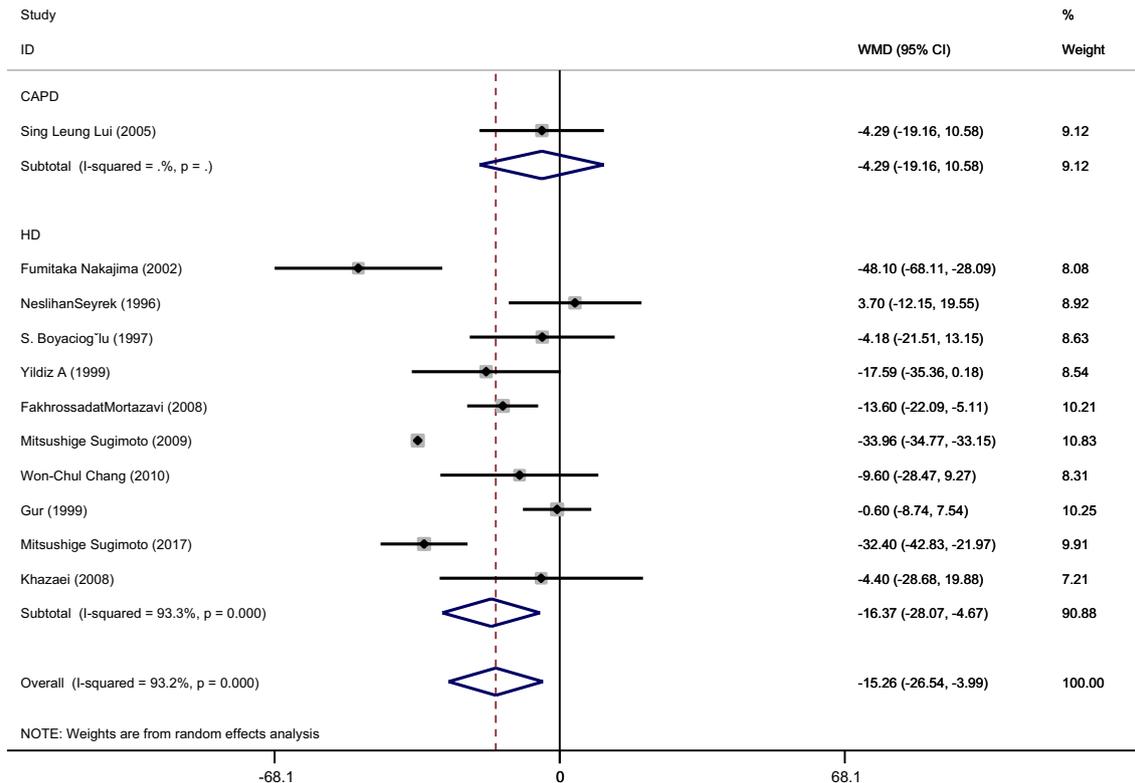

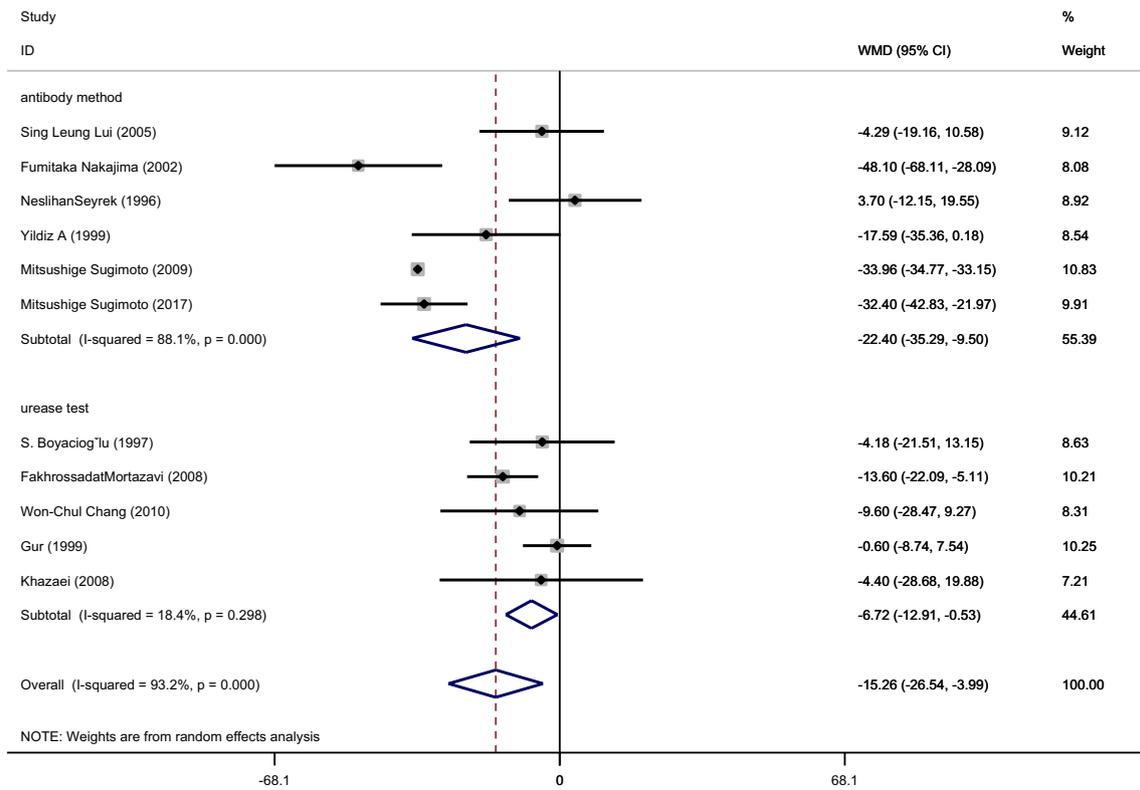**Fig. 4** Quantitative data was stratified by dialysis methods

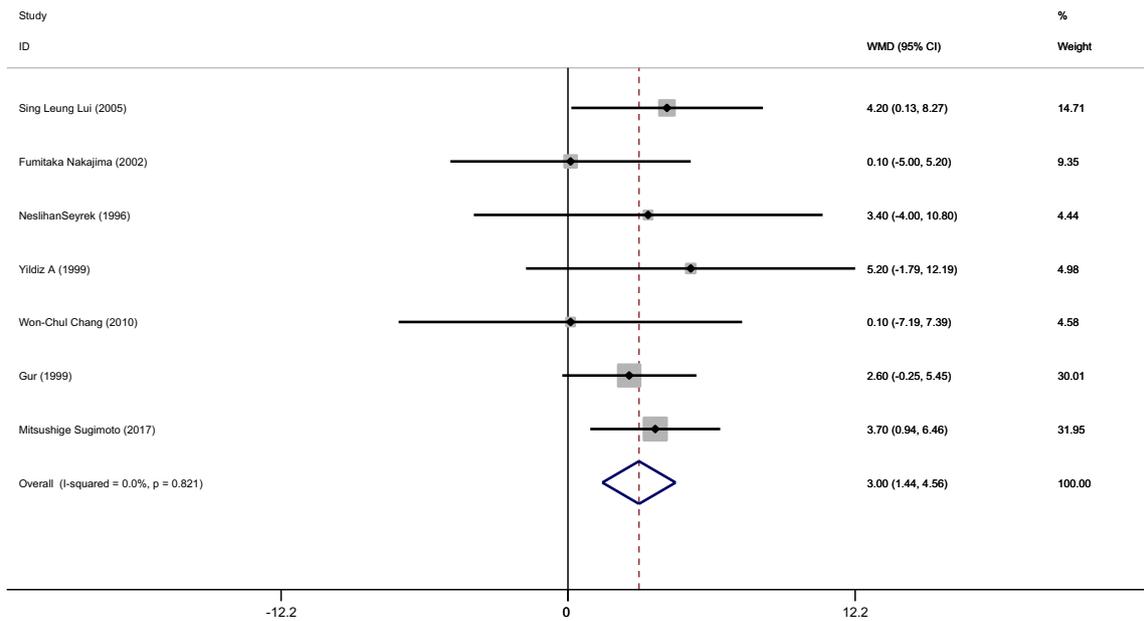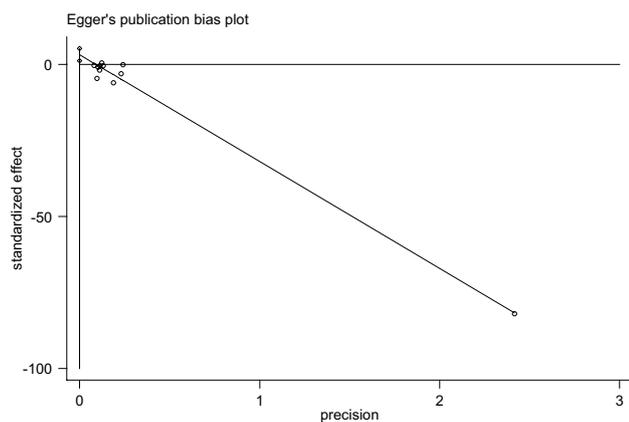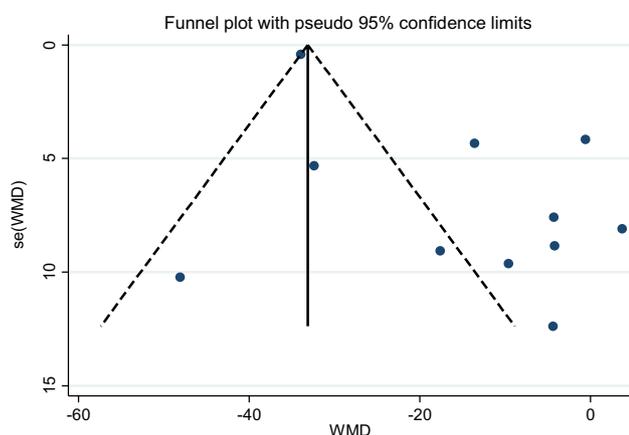**Fig. 5** Quantitative data was stratified by detection methods

Fig. 6 Association between age and HP infection

Fig. 7 Egger's publication bias plot for association between HP infection and duration of dialysis

Fig. 8 Funnel plot for association between HP infection and duration of dialysis

Discussion

In recent years, with the development of molecular detection technology, the detection rate of HP increased. People realized that HP infection not only related to some primary gastrointestinal diseases, but some renal function diseases. Many studies indicated that HP infection might affect the prognosis of kidney diseases, and HP was the main cause of secondary gastrointestinal diseases for patients with impaired renal function. Several studies suggested that the prevalence of HP might be lower in long-term dialysis patients than in short-term dialysis patients [11, 14, 24]. However, a few studies [9, 22] showed that no statistical differences were observed in the association between HP infection and duration of dialysis. Rasmi et al. [12] found that HP infection rate was higher in long time dialysis patients than in short-time dialysis patients.

There are some conflicts about the association between HP infection and duration of dialysis. In recent years, the number of hemodialysis patients is expanding at a rate of 7% per year [25]. One of the important factors affecting the long-term survival rate of hemodialysis patients is common complications which include gastroduodenal diseases, cardiovascular and cerebrovascular diseases, anemia and abnormal bone metabolism, and so on. Recent studies reported [26–28] that chronic HP infection might be a major cause of gastroduodenal and gastrointestinal bleeding in dialysis patients with renal failure. It can be inferred that HP infection may directly affect the survival rate of dialysis patients, and it is more important to know the influencing factors of HP infection in dialysis patients. Accumulation of time the patients are exposed to dialysis is the factor that increases susceptibility to infection with HP. HP infection rate might peak at certain accumulative dialysis time. Therefore, this study aims to identify the accumulative dialysis time with high susceptibility to the infection, so that we can give interventions at the most appropriate accumulative dialysis time to reduce the HP infection rate, then the incidence of secondary gastrointestinal diseases for renal diseases decreases.

Our study is the systematic review and we summarized all available studies that reported the association between HP infection and duration of dialysis. As above results showed that, duration of dialysis was shorter in HP positive group than in HP negative group, however, no statistical differences were observed in the prevalence of HP between < 30 months group and ≥ 30 months group, which was inconsistent with the 2013 meta-analysis [29]. The 2013 meta-analysis indicated that the HP infection rate was significantly lower in longer than 4 years dialysis individuals than in normal renal function group, and the duration of dialysis between HP positive and HP negative patients did not differ from each other. Due to the absence of data, we mainly analyzed the quantitative data, and only three articles could extract qualitative data, and another three articles [30–32] only provided the regression curve to show the relationship between HP infection and duration of time Our study suggested a shorter duration of dialysis in HP positive patients and HP infection rate is negatively correlated with duration of dialysis. Our study do not provide the exact time most susceptible to HP infection, thus the timing period of dialysis that most susceptible to HP infection should be verified by further multicenter randomized controlled trials.

Some studies suggested that the inconsistence of the association between HP infection and duration of dialysis is ascribed to the difference in detection methods, dialysis methods, or regions; hence we conducted a subgroup analysis to explore the effect of dialysis methods and detection methods on the association between HP infection and duration of dialysis. After stratifying by methods of dialysis, we

found that in HD group, statistical differences still existed, while the differences disappeared in CAPD group. However, there was one article involving CAPD, so our study can not reveal the relationship between HP infection and duration of dialysis in CAPD patients. The detection methods of HP include the urease test and the antibody detection. In past years, people inclined to use the urease test to detect HP, while IgG antibody detection was widely used in recent years. After stratifying by detection methods, statistical differences were observed in both urease test and antibody methods group, which suggested that methods of HP detection did not influence the association between HP infection and duration of dialysis. Owing to the fact that all the studies we included are from Asia, we can not analyze the effect of region on the association between HP infection and duration of dialysis. In our study, we still cannot rule out other feasible influencing factors, such as the size of the population, the clinical features of the study, the local prevalence of HP, and other unknown factors [33].

Although our meta-analysis found that HP infection rate was negatively correlated with duration of dialysis in dialysis patients, HP infection may spontaneously turn negative with the duration of dialysis increasing, we still believe that HP positive dialysis patients should undergo HP eradication therapy at the early stages of dialysis to prevent the occurrence of complications in dialysis patients. The Maastricht consensus conference on eradication of *Helicobacter pylori* indicated that spontaneous seroconversion of HP antibodies in hemodialysis patients does not represent the improvement for gastric mucosal lesions, and gastrointestinal complications such as gastrointestinal bleeding still occur under the influence of other factors. Gastrointestinal bleeding is one of the serious complications that threaten life of hemodialysis patients, and early eradication of HP can effectively reduce the risk of gastrointestinal bleeding and alleviate degree of anemia of renal failure patients [34].

Age was thought as the risk factor of many diseases, including hypertension, cancer, coronary heart disease, diabetes and so on. The metabolic mechanism and the body immunity of elderly people decrease, which enhances the opportunity of bacterium infection and lead to disease. Our study analyzed the association between age and HP infection, which suggested that age was positively correlated with the HP infection. Age is the risk factor of HP infection for dialysis patients. Medical workers should detect HP earlier and provide protective therapies for elderly dialysis patients.

Although our study was performed with rigorous and scientific attitude, and all included studies are of high quality, there are some limitations and the results should be interpreted with caution. Firstly, the heterogeneity of our quantitative data was high in this meta-analysis, which may due to the difference of samples, regions, times, ages, genders and demographic characteristics. Interestingly, we found that one study [4] from Japan led to the high heterogeneity, this research is retrospective cohort study and lasts for a long time, which may lead to recall bias. Secondly, all the studies we included are from Asia; therefore, our results only can reveal the Asian dialysis patients. Thirdly, because of the lack of qualitative data, the results of qualitative data and quantitative data are inconsistent, further studies are needed to analyze the qualitative data and identify the appropriate time of dialysis. Finally, the mechanism of the correlation between HP infection and duration of dialysis is still unclear. In some studies, we found that the mechanisms of the decreasing in HP infection rate along with the longer dialysis duration are as follows: Firstly, high levels of blood urea in hemodialysis patients can inhibit the growth of HP in the gastrointestinal [27, 34], the higher the blood urea level, the lower the HP infection rate with the prolongation of dialysis duration. Secondly, antibiotics inhibiting the growth of HP are frequently used in dialysis patients because bacterial infection is one of the common complications. Furthermore, hemodialysis patients who secrete a large number of inflammatory cytokines may occur severe gastric mucosal atrophy leading to decreased secretion of H^+, which may finally affect the colonization of HP in the gastric mucosa [35, 36]. So more studies are expected to elucidate it in the future.

Author contributions LC designed the study and revised the manuscript, K-JL collected and analyzed the data and wrote first draft of the manuscript. All authors had participated to approve the final manuscript.

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