BMC Nephrology

RESEARCH Open Access

Dose-response relationship between lipids and all-cause mortality in the dialysis population: a meta-analysis

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Abstract

Background The use of lipid-lowering drugs in the dialysis population has been controversial and there is no target for the dialysis population.

Objectives To elucidate the dose-response relationship between lipids and all-cause mortality in the dialysis population.

Methods Computer searches of PubMed, Embase, Web of Science, CNKI, and Wanfang. Data were conducted to collect published cohort studies on lipids and all-cause mortality in the dialysis population from home and abroad up to February 2023. Meta-analysis was applied to calculate the combined effect size (Hazard ratio) and its 95% confidence interval and dose-response relationship by applying Stata17.0.

Results A total of 11 publications with a cumulative total of 106,808 individuals were included. All-cause mortality was statistically different between the highest dose total cholesterol (TC) group and the low TC group (HR = 0.82, 95% CI = 0.75–0.90, $P < 0.05$). The TC range for lower all-cause mortality is > 140.5 mg/dL, and on this basis, TC in the range of 180–220 mg/dL may have a better prognosis for dialysis population. There was a nonlinear relationship between Non-high-density lipoprotein cholesterol (NHDL-C) cholesterol and all-cause mortality, with no statistical difference between the high and low dose group. In contrast, Low-density lipoprotein cholesterol (LDL-C) masked its association with all-cause mortality due to changes in death spectrum, differences in relative time risks, and other factors. In the 50–450 mg/dL range, all-cause mortality in the dialysis population was positively associated with triglycerides (TG), with a 2.5% increase in all-cause mortality per 50 mg/dL increase in TG (HR = 1.025, 95% CI = 1.003–1.048, $P = 0.01$).

Conclusion TC is a target for monitoring the dialysis population, which has the lowest all-cause mortality in the range of 180–220 mg/dL. However, NHDL-C and LDL-C monitoring is not clinically meaningful. Increased TG can contribute to the risk of higher all-cause mortality in dialysis patients.

Keywords Dose-response relationship, Dialysis, Lipids

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Introduction

In the general population, hypercholesterolemia is associated with a higher risk of cardiovascular events. However, in clinical practice, hypercholesterolemia appears to be associated with better survival in chronic kidney disease (CKD) dialysis patients, and the use of statin lipid-lowering drugs does not necessarily benefit dialysis patients. The latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for lipid management in dialysis patients recommend not initiating statins, and for patients already receiving statins at the start of dialysis, it is recommended continued. The American College of Cardiology (ACC) and the European Society of Cardiology (ESC) agree, which seemed to reach a consensus. Regular monitoring of LDL-C is not recommended, and there are certainly no recommendations for LDL-C or other lipid class targets [1–3]. However, for clinicians, following the guidelines, lipids in dialysis patients seem like a gray area that need not be concerned with, as if everything remains consistent with the pre-dialysis protocol and the target for lipids remains a blank slate.

Guidelines for lipid management in dialysis patients are based on randomized controlled trial (RCT) studies and numerous meta-analyses. Several large RCTs in the past, such as the 4D, SHARP, and AURORA studies, had demonstrated that statins did not significantly improve effect on all-cause mortality in dialysis patients [4–6]. Many meta-analyses examining the effect of statin use on all-cause mortality in dialysis patients have also had a large number of conflicting recommendations [7–13].

In this context, dialysis patients using statins lipid-lowering drugs is still controversial. If the focus on statin use could be bypassed and the range of lipid with the lowest all-cause mortality could be explored directly, it would provide better evidence for clinical guidance of lipid management in dialysis patients.

In this meta-analysis, we retrieved cohort studies that grouped dialysis patients according to their lipid levels to obtain the effect of lipid levels on all-cause mortality, intending to obtain targets for lipid control in dialysis patients and thus clearly guide the lipid-lowering treatment of dialysis patients.

Method

Search strategy

The following databases were searched: PubMed, Embase, Web of Science, CNKI, and Wanfang data (as of February 2023). The keywords used were related to the study objectives. The search strategy was conducted using MeSH and non-MeSH keywords, with no language restrictions. The terms used in the electronic search included: ((((“Lipids“[Mesh]) OR “Cholesterol“[Mesh]) OR “Triglycerides“[Mesh]) OR “Dyslipidemias“[Mesh]) AND (“Renal Dialysis“[Mesh] OR “Dialysis“[Mesh]). The electronic database search was performed together with reference lists and manual searches.

Selection of articles

Search results were imported into EndNote and duplicate documents were removed. A manual search was performed by reading the titles, abstracts, and full texts of relevant articles. The study included the following inclusion criteria: (1) cohort study; (2) population with hemodialysis or abdominal dialysis for more than 1 months; (3) a clear lipid grouping; and (4) complete and available data for follow-up analysis. The exclusion criteria were as follows: (1) the outcome did not include all-cause mortality; (2) no survival analysis or risk ratio was performed;

Lipid doses in this systematic review are taken as the median or mean of the original exposure dose interval. For open intervals containing the lowest and highest dose, 0.5 times or 1.5 times the width of the adjacent interval is taken.

Data extraction

The following data were extracted from the full text of the included studies: the first author’s surname, year of publication, study type, target population, age and sex of subjects, total sample size, follow-up time, adjusted confounders, detailed groupings of lipids, effect sizes for outcome events and effect sizes for standard errors. For unit conversions where mentioned, the conversions used in the original text were used; otherwise, the following conversions were taken TC, NHDL-C, LDL-C: 1.0 mmol/L = 38.6 mg/dL; TG: 1.0 mmol/L = 88.5 mg/dL.

Research quality assessment

The quality of the included literature was evaluated according to the Newcastle-Ottawa scale (NOS). A score of ≥ 7 was defined as high-quality literature.

Statistical analysis

All analyses were performed using STATA 17.0 and its generalized least squares method (glst) command [14]. Both I^2 and *P* value of the Q statistic were used to test f the magnitude of heterogeneity of the included studies. If the *P* value of the Q statistic was < 0.05 or I^2 > 50%, heterogeneity among the included studies was considered to exist and a random-effects model was used. Otherwise, a fixed effects model was used. Subgroup analysis and meta-regression were performed to exclude sources of heterogeneity when necessary. The Egger method was used to test for potential publication bias. To determine the robustness of the results sensitivity analyses were performed. Each study was excluded in turn to calculate the effect value and its 95% confidence interval (CI) of the remaining literature. For studies where the number of cases occurring in each stratum is missing, the number of

cases occurring in each stratum can be extrapolated from the overall number of cases occurring, the total number of cases/total person-years in each stratum, and the HR, if the total number/total person-years is known. A few of the original studies used the nonlowest dose groups as the reference. Based on the theory proposed by Greenland and Longnecke, Hamling et al. made it into an Excel Macro file to realize that all studies were converted to the low-dose group as the reference [15–17]. The data were fitted using the restricted cubic spline (RCS) method combined with the glst command to construct linear and nonlinear relationship models, and the nonlinear dose-response relationship was considered to exist if $P<0.05$ by the Wald test.

Result

Literature search and inclusion of study overview

The detailed steps of the literature search and article screening are shown in Fig. 1 which shows the PRISMA flowchart for inclusion in the trial. Two researchers screened each record independently. As shown in Fig. 1, a total of 11 articles fit the search strategy. A total of

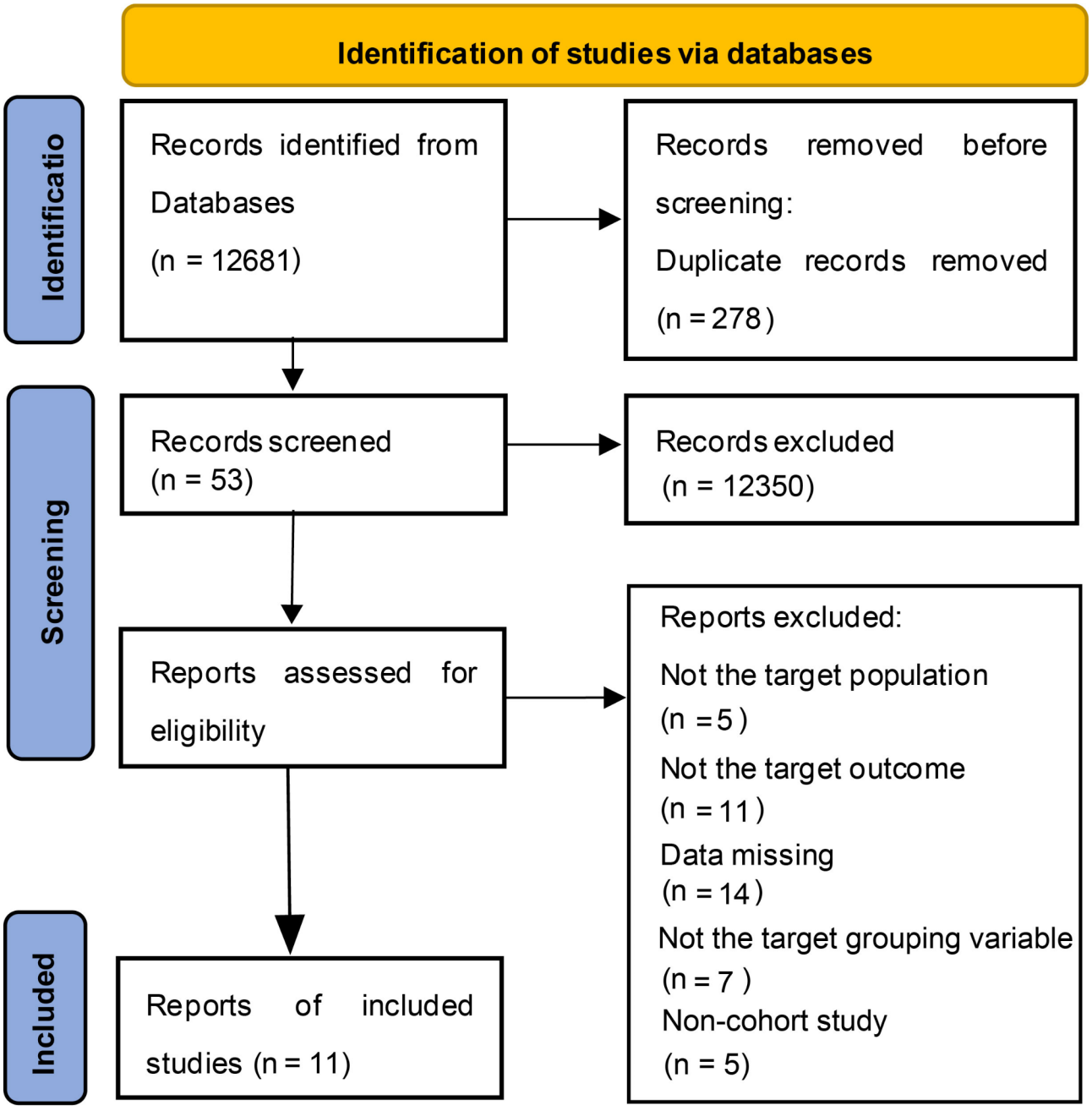


Fig. 1 Flowchart of literature search

12,681 articles were found from five electronic databases using the predefined search strategy, of which 278 were removed due to duplicate titles. The 12,350 irrelevant articles were removed by reading the titles and abstracts, and the full texts of the remaining 53 articles were searched. Of these studies, those with not target population ($n=5$), inconsistent outcomes ($n=11$), incomplete data ($n=14$), no clear lipid grouping ($n=7$) and non-cohort ($n=5$) were excluded. Finally, 11 articles with more complete data were eligible for inclusion in the final analysis [18–28].

Table 1 summarizes the main characteristics of the included studies. The studies were published between 2004 and 2021. Five of the studies were conducted in Asian countries (China, Japan, Korea), four in American countries (USA), and two in Europe (Netherlands, Portugal). The sample size ranged from 189 to 51,185, with a total of 106,808 individuals. The follow-up period for inclusion in the studies ranged from 1 to 10 years.

Quality evaluation of the literature

Two researchers evaluated the quality of the literature based on the NOS. The results of the quality evaluation showed that there was two study with a score of 9, six with a score of 8, and three with a score of 7. The overall quality of the literature was relatively high, as shown in Table 2.

Meta-analysis results

TC and all-cause mortality

Among the 11 retrieval results, there were 6 studies with TC as the independent variable. Heterogeneity results showed $I^2=46\%$, $P=0.10>0.05$. Using a fixed effects model combined, there was a significant difference in all-cause mortality in dialysis patients between the high dose TC group and the low dose (HR = 0.82, 95% CI = 0.75–0.90, $P<0.05$), as shown in Fig. 2A. Egger's test showed no statistically significant publication bias ($P=0.64$) for the inclusion of the 6 studies (Fig. 2B). Sensitivity analysis showed significant changes in the amount of effect of excluding any of the outcome indicators from any of the papers. Because each included study had different high and low-dose groupings, the highest dose group of a cohort may be close to the lowest dose group of another included study. This can lead to clinical heterogeneity with less stable results (Fig. 2C).

Further dose-response meta-analysis was performed for the above 6 follow-up cohorts. The glst command was used to develop the dose-response model. The χ^2 value of nonlinear regression parameter test was 32.16 ($p<0.05$), and the nonlinear model was accepted. The testparm command displays χ^2=6.02, $P=0.049$ ($P<0.05$). It is verified as a nonlinear relationship again. The χ^2 value of fixed or random effect simulation was 21.33 ($P=0.13$), and both were acceptable. Dose-effect analysis using a fixed-effects nonlinear model fitted for the relationship between TC and all-cause mortality showed a U-shaped relationship between TC and all-cause mortality (Fig. 2D). For a statistically significant reduction in all-cause mortality, the TC range is >140.5 mg/dL and the relatively safer TC range is 180–220 mg/dL.

LDL-C and all-cause mortality

Among the 11 retrieval results, there were 3 studies with LDL-C as the independent variable. Heterogeneity results showed $I^2=79\%$, $P=0.01<0.05$. Using the random effects model, there was no significant difference in all-cause mortality between high dose LDL-C and low dose LDL-C in dialysis patients (HR = 0.73, 95% CI = 0.40–1.35, $p=0.31>0.05$) (Fig. 3A). Egger's test showed no statistically significant publication bias ($P=0.58$) for the inclusion of the 3 papers (Fig. 3B). Besides, the effect size of the remaining articles did not change significantly after excluding any study at each time (Fig. 3C). A dose-response meta-analysis was performed for the 3 follow-up cohorts described above. The goodness-of-fit test for the nonlinear dose-response relationship model ($P=0.18$) showed that the relationship did not conform to the nonlinear dose-response relationship model, and the linear model was adopted. Dose-response analysis using a fixed-effect linear model fitted for the relationship between LDL-C and all-cause mortality showed a linear relationship between LDL-C and all-cause mortality. Each 20 mg/dL increase in LDL-C was associated with a 1.9% decrease in all-cause mortality in the range of 25–145 mg/dL (HR = 0.98, 95% CI = 0.97–0.99, $P=0.04$) (Fig. 3D). It was not possible to predict all-cause mortality at LDL-C < 25 mg/ dL or > 145 mg/ dL.

NHDL-C and all-cause mortality

Among the 11 retrieval results, there were 4 studies with NHDL-C as the independent variable. The heterogeneity results showed $I^2=97.3\%$, $P=0.00<0.05$. Using the random effects model, there was no significant difference in all-cause mortality between high dose NHDL-C and low dose NHDL-C in dialysis patients (HR = 0.80, 95% CI = 0.41–1.54, $P=0.50>0.05$) (Fig. 4A). Egger's test showed no statistically significant publication bias ($P=0.83$) for the inclusion of the 4 papers (Fig. 4B). Besides, the effect size of the remaining articles did not change significantly after excluding any study at each time (Fig. 4C). The χ^2 value of nonlinear regression parameter test was 346.14 ($p<0.05$), and the testparm command test also suggested that there was a nonlinear relationship in the study, and the results showed that $\chi^2=27.88$ ($P=0.00$). Therefore, the nonlinear model is selected for fitting. The χ^2 value for the fixed-effects simulation fit was 199.25 ($P=0.00$), so a fixed-effects

Table 1 Characteristics of included studies

Author	Study type	Population	Followup (years)	Age(years) Mean(± SD)	Gender (male%)	di-alysis mode	Number	Lipid measurement information	Lipid (mg/dL) grouping	Confounding factor adjustment
Liu Y. 2004	Prospective	Americans	2.4 median[a]	58.2 ± 14	52.4%	HD: 154 PD: 35	189	blood specimens were drawn at a median of 5.0 months from the initiation of dialysis	TC: ≤160, 160–199, 200–239, ≥ 240	age, race, sex, clinic, Alb, CRP, IL–6 levels
Habib AN. 2006	Retrospective	Americans	1.9 mean[b]	57.2 ± 15.3	52.0%	PD	1053	NK[c]	TC: ≤125, 126–175, 176–225, 226–275, ≥ 275 TG: ≤100, 101–200, 201–300, 301–400, ≥ 400	age, gender, race, weight, height, the primary cause of ESRD, Hb, Alb, serum Ca-P product, serum bicarbonate, residual kidney creatinine clearance, PD parameters [dialysate effluent volume, dialysis creatinine clearance, dialysate-to-plasma (D/P) creatinine ratio after a 4-h dwell], use of lipid-modifying medications, comorbidity characteristics [DM, CAD, CHF, LVH, CVD, PVD]
Kilpatrick RDI. 2007	Prospective	Americans	3 research-set[d]	61 ± 16	55.0%	HD	1418	Mean values for the first 3 months after enrollment	LDL: <40, 40 to < 70, 70 to < 100, 100 to < 130, ≥130	age, gender, race, ethnicity, DM, vintage categories, primary insurance, marriage status, comorbid conditions, tobacco smoking, residual renal function, Kt/V, 9 indicators of nutritional state and inflammation[e]
Chmielewski M. 2011	Prospective	Dutch	2.3 median	NK	61.4%	HD: 765 PD: 426	1191	3 months after dialysis initiation	TC: <200, 200–240, > 240	age, gender, DM, dialysis modality, inflammation(hsCRP > 10 mg/L), PEW, Hb, Kt/V, smoking, use of erythropoiesis-stimulating agents
Shoji T. 2011	Prospective	Japanese	1 research-set	62 median	59.1%	HD	45,390	NK	TC: <134, 134 to < 157, 157 to < 182, ≥182 NHDL: <88, 88 to < 109, 109 to < 133, ≥133 LDL: <69, 69 to < 88, 88 to < 109, ≥109 TG: <67, 67 to < 96, 96 to < 137, ≥137	age, gender, dialysis vintage, DM, BMI, Alb, CRP
Sameiro-Faria MD.2013	Prospective	Portugal	2 research-set	66.4 Mean	55.0%	HD	189	Before the HD procedure, in the midweek dialysis day	TG: <90.5, 90.5–117.0, 117.0–176.5, ≥ 176.5	age, BMI, Alb, urea reduction ratio, KT/Ve, ultrafiltration volume, Scr, Ion of electrolyte, Hb, Multiple blood cells, transferrin, ferritin, IL–6, CRP, adiponectin, TC, LDL-C, HDL-C, Lp(a), D-dimers, previous time

Table 1 (continued)

Author	Study type	Population	Followup (years)	Age(years) Mean(± SD)	Gender (male%)	di-alysis mode	Number	Lipid measurement information	Lipid (mg/dL) grouping	Confounding factor adjustment
Yang WL. 2016	Prospective	Chinese	4 research-set	59.75 ± 13.4	48.5%	HD: 132 PD: 179	311	NK	NHDL: <100, 100 to < 130, 130–190, > 190	dialysis mode, age at enrollment, ALB, sCr, serum Phosphate, corrected calcium phosphate product, DBP, SBP, serum potassium, FCRS risk categories, CCI, LDL/TC lipids categories
Park CH. 2017	Prospective	Korean	3 median	59.6 ± 14.1	55.5%	PD	749	Time-varying(calculated and updated every 6 months over the entire follow-up period)	TC: <150, 150 to < 180, 180 to < 210, ≥210 LDL: <70, 70 to < 100, 100 to < 130, ≥130 TG: <100, 100 to < 150, 150 to < 200, ≥200	age, sex, comorbid conditions(DM, hypertension, CAD, CHF, peripheral artery disease), total weekly Kt/V, use of icodextrin solution, rGFR, lipid-modifying drugs, malnutrition, BMI, Alb, CRP
Chang TI. 2018	Prospective	Americans	1.6 median	62.8 ± 14.9	56.4%	HD	51,185	Time-dependent(calculated and updated at each quarter over the entire follow-up)	NHDL: <60, 60 to < 85, 85 to < 100, 100 to < 115, 115 to < 130, 130 to < 145, 145 to < 160, ≥160	age, sex, race, primary insurance, initial vascular access type, DM, hypertension, ASHD, CHF, other atherosclerotic diseases, cerebrovascular disease, dyslipidemia, COPD, malignancy, Kt/V, Hb, WBC, Alb, Ca, P, iPTH, bicarbonate, total iron-binding capacity, ferritin, LDL-C, BMI, statin therapy
Nakano T. 2020	Prospective	Japanese	10 research-set	NK	60.0%	HD	3517	A single measurement of TC at baseline	TC: <131, 131–151, 152–177, ≥ 178	age, sex, history of CVD, pre-dialysis SBP, dialysis duration, dialysis time, dry weight, DM, Hb, Alb, creatinine, Ca, P, log-CRP, Kt/V
Yu J. 2021	Prospective	Chinese	4 median	47.5 ± 15.2	59.8%	HD	1616	three months after PD therapy initiation, fasted state	NHDL:<188.15, 188.15–142.08, 142.08–173.75, > 173.75	age, sex, DM, a history of cardiovascular events, BMI, SBP, Hb, Alb, hs-CRP, eGFR, Kt/V, stain use

[a] Mean value, [b] Median value, [c] Not know, [d] The follow-up time set by the research had no special meaning, [e] 9 indicators: albumin, nitrogen appearance, serum total iron binding capacity, serum ferritin, serum creatinine, peripheral white blood cell count, percentage of lymphocytes in the white blood cells count, blood hemoglobin, serum bicarbonate

CRP: C-reactive protein, hs-CRP: high-sensitivity C-reactive protein, IL–6: interleukin–6, ESRD: end-stage renal disease, Alb: albumin, PD: peritoneal dialysis, DM: diabetes mellitus CAD: coronary artery disease, CHF: congestive heart failure, LVH: left ventricular hypertrophy, CVD: cerebrovascular disease, PVD: peripheral vascular disease, PEW: Protein-energy wasting, Hb: hemoglobin, BMI: body mass index, sCr: serum creatinine, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, FCRS: Framingham cardiovascular risk scoring algorithm. CCI: The Charlson comorbidity index, rGFR: residual glomerular filtration rates, ASHD: atherosclerotic heart disease, COPD: chronic obstructive pulmonary disease, WBC: white blood cells, Ca: calcium, P: phosphate, iPTH: immunoreactive parathyroid hormone, eGFR: estimated glomerular filtration rate

Table 2 The NOS score of the study

Study	Representativeness of the intervention cohort	Selection of the nonintervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	score
Liu Y. 2004	1	1	0	1	1	1	1	1	7
Habib AN. 2006	1	1	0	1	2	1	1	1	8
Kilpatrick RDI. 2007	1	1	1	1	1	1	1	1	8
Chmielewski M. 2011	1	1	0	1	2	1	1	1	8
Shoji T. 2011	1	1	0	1	2	1	0	1	7
Sameiro-Faria MD.2013	1	1	0	1	2	1	0	1	7
Yang WL. 2016	1	1	0	1	2	1	1	1	8
Park CH. 2017	1	1	1	1	2	1	1	1	9
Chang TI. 2018	1	1	1	1	2	1	1	1	9
Nakano T. 2020	1	1	0	1	2	1	1	1	8
Yu J. 2021	1	1	0	1	2	1	1	1	8

model could be used. There was a U-shaped relationship between NHDL-C and all-cause mortality fitted by the nonlinear fixed model (Fig. 4D). However, no significant interval with HR lower than 1 was observed, indicating that the statistical difference between NHDL-C and all-cause mortality was not significant.

TG and all-cause mortality

Among the 11 retrieval results, there were 4 studies with TG as the independent variable. The heterogeneity results showed $I^2 = 75.9\%$, $P = 0.01 < 0.05$. Using the random effects model, there was no significant difference in all-cause mortality between high dose TG and low dose TG in dialysis patients (HR = 1.06, 95% CI = 0.94–1.19, $P = 0.36 > 0.05$) (Fig. 5A). Egger's test showed no statistically significant publication bias ($P = 0.45$) for the inclusion of the 4 papers (Fig. 5B). Besides, the effect size of the remaining articles did not change significantly after excluding any study at each time (Fig. 5C). A dose-response meta-analysis was performed for the 4 follow-up cohorts described above. The glst command was used to develop the dose-response model, and the χ^2 value of the nonlinear regression parameter test was 8.75 ($P < 0.05$). But the result of testparm command showed that the nonlinear model was not valid with $\chi^2 = 3.64$ and $P = 0.16$ ($P > 0.05$). The fixed effect linear model showed that, in the range of 50–450 mg/dL, each 50 mg/dL increase in TG was associated with a 2.5% increase in all-cause mortality (HR = 1.025, 95% CI = 1.003–1.048, $P = 0.02$) (Fig. 5D).

Discussion

Lipid management in patients with CKD has been recommended with statins, and ironically the most severe dialysis patients with CKD do not seem to benefit. Non-dialysis patients with CKD is a high-risk population of CVD, and LDL-C has attracted the strict standard of 70/50 mg/dL [3, 29]. For dialysis patients, the ESC, ACC, and KDIGO opinions are unanimous in not initiating statins, and patients already receiving statins at the start of dialysis are advised to keep using these drugs.

The present study suggests that TC may have a nonlinear dose-response relationship with all-cause mortality in dialysis patients. The lower lipid levels did not provide the protective effect we expected. The dose-response results suggest a U-shaped relationship between all-cause mortality and TC in dialysis patients. One reason is that even in the general population, lipids are not positively correlated with all-cause mortality. As observed by S. Yi et al. in a 10.5-year observational study of 120 000 general population in Korea, there was a U-shaped relationship between TC and mortality, with lowest mortality in the TC range of 210–240 mg/dL [30]. A reasonable interpretation is that lower levels of cholesterol may be associated

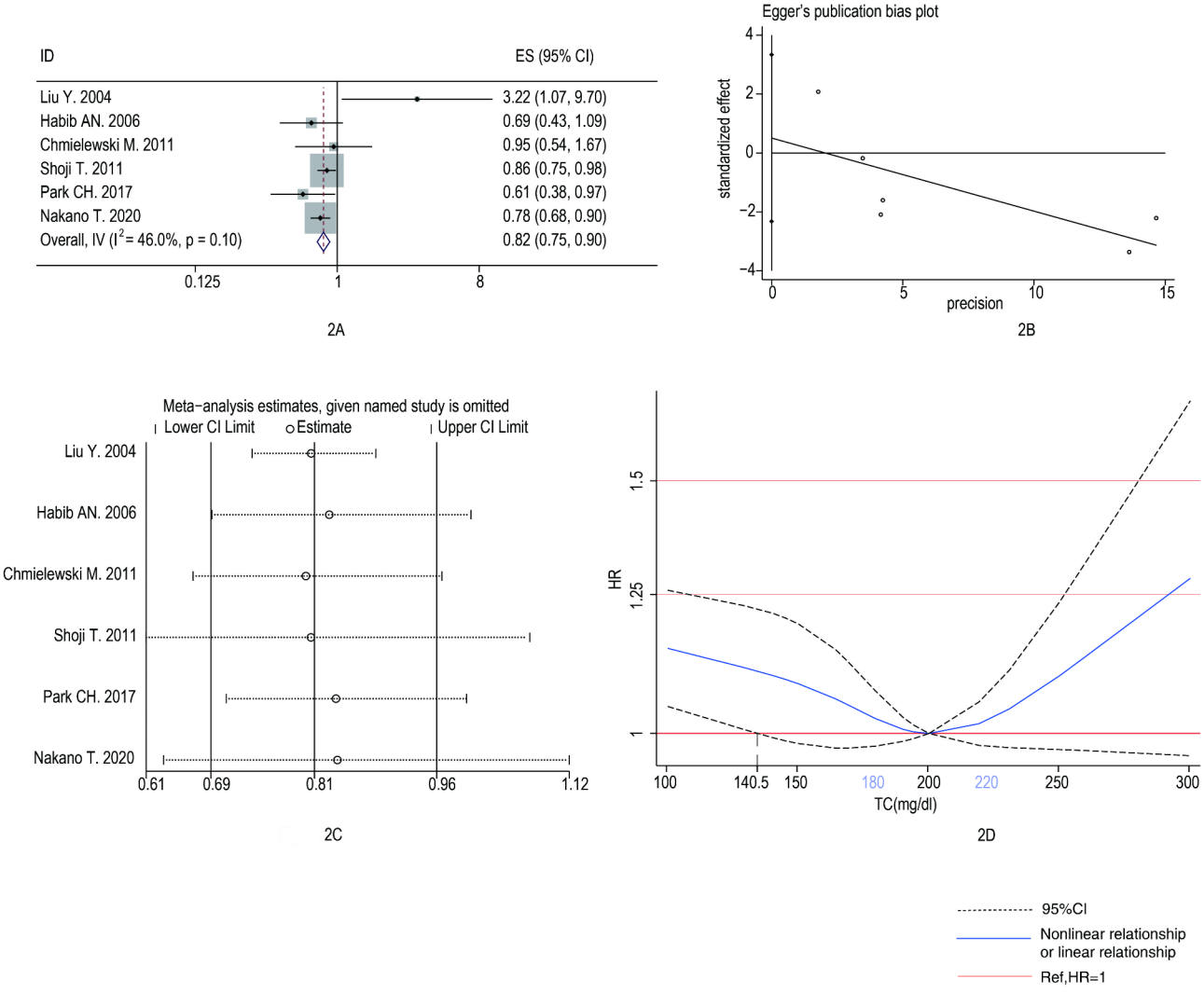


Fig. 2 Forest plot, publication bias, sensitivity analysis, and dose-response curve of TC and all-cause mortality in dialysis patients

with an increased risk of a range of adverse health outcomes, such as hemorrhagic stroke, chronic obstructive pulmonary disease, liver disease, and cancer.

Analogously, in dialysis patients, cholesterol has a more limited capacity to influence adverse outcomes, and the mortality spectrum is more skewed toward noncoronary deaths that cannot be reversed by statins. As Baigent et al. mentioned congestive heart failure, which accounted for 40% of deaths, there was mainly cardiac fibrosis and malignant arrhythmias in patients with CKD. Nonvascular deaths accounting for 40% of deaths such as cancer among them were negatively associated with TC [31, 32]. Furthermore, even for statin-sensitive outcomes such as myocardial infarction, dialysis patients do not obtain the same therapeutic benefit as the general population. In addition to the complex lipid dysmorphisms in CKD, the major causes of cardiovascular disease (CVD) in dialysis patients are oxidative stress, inflammation, calcium metabolism disorders, and uremic toxins, which cannot be corrected by inhibiting cholesterol synthesis [33, 34]. Even the Vriese et al. review mentioned that statin-induced calcium ions may exacerbate an already severely elevated cardiovascular risk [35].

Except for normal population showing a U-shaped curve and the altered death spectrum of dialysis patients deviating from CVD deaths, the second is because even if CVD events occur in dialysis patients, low dose of TC do not necessarily mean high survival rates. A 2006 review by Shoji et al. noted that the risk of death is a product of two components, the incidence of a hazardous event and the mortality after the event. In dialysis patients, lipids level affect both the former and the latter at the same time. Mortality after the event may be more important than the incidence of hazardous events. Hyperlipidemia is definitely not a protective factor against CVD, but low cholesterol level due to malnutrition predict a high risk of

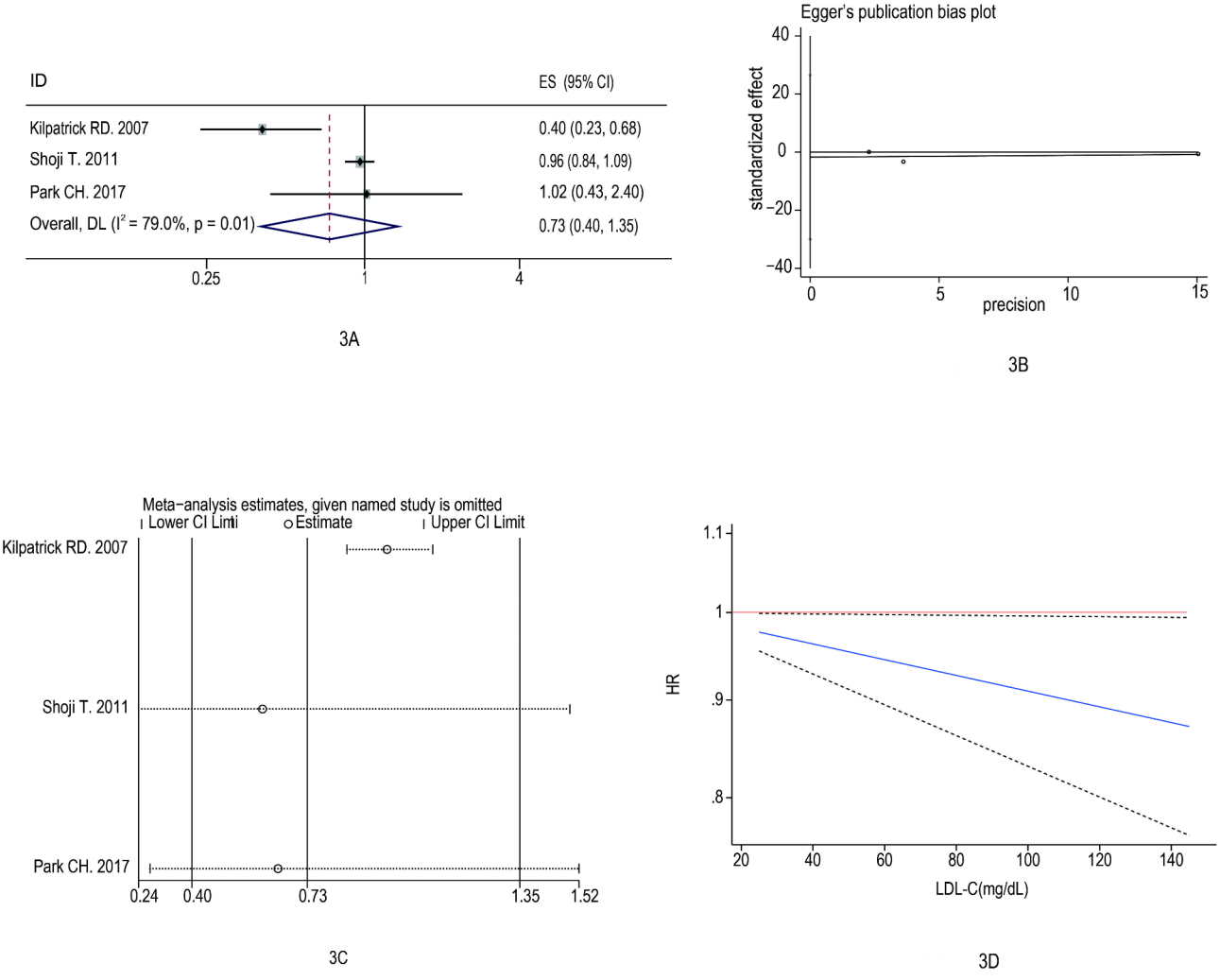


Fig. 3 Forest plot, publication bias, sensitivity analysis, and dose-response curve of LDL-C and all-cause mortality in dialysis patients

death after CVD [36]. If it is possible to lower cholesterol without worsening nutritional status, then theoretically lowering cholesterol is promising to reduce the risk of CVD and thus the risk of death from CVD. For instance, in a prospective study by Liu et al. in 2004, for a subgroup without inflammatory malnutrition, each 40 mg/dL increase in baseline TC level was positively associated with all-cause mortality (HR, 1.51; 95% CI, 1.12–2.04) [22]. A prospective study conducted by Shoji et al. in 2011 also showed that for hemodialysis patients every 1 mg/dL increase in CRP levels was positively associated with all-cause mortality (OR, 1.13; 95% CI 1.12–1.16) [25]. Nevertheless, it is not rare for all-cause mortality to be negatively associated with TC in models adjusted for inflammation and malnutrition [24, 25, 37].

Finally, in dialysis patients, the benefits associated with statins are long-term and far exceed the median survival of dialysis patients [34]. This can be explained by the relative temporal risk difference, where it can take up to decades for atherosclerosis to progress to death in hemodialysis patients and where inflammation and impaired nutritional metabolism can lead to death in the near term.

Why TC range for achieving the least all-cause mortality is not less than 140.5 mg/dL, and the optimal TC range is 180–220 mg/dL In comparison to the general population, the range of TC correlated with the lowest mortality in the 10.5-year-long observational study of the general population by S. Yi et al. mentioned above was 210–240 mg/dL [30], a region considered the critical high range in the National Cholesterol Education Program (NCEP) consensus and the 2023 Chinese guidelines for lipid management [38]. The optimum TC scope achieved in the general population that does not correspond to the guideline recommendations, exhibiting in the category of borderline high values. Because TC < 201 mg/dL is not necessarily a sign of fitness when taking other diseases into account, from which diseases associated with

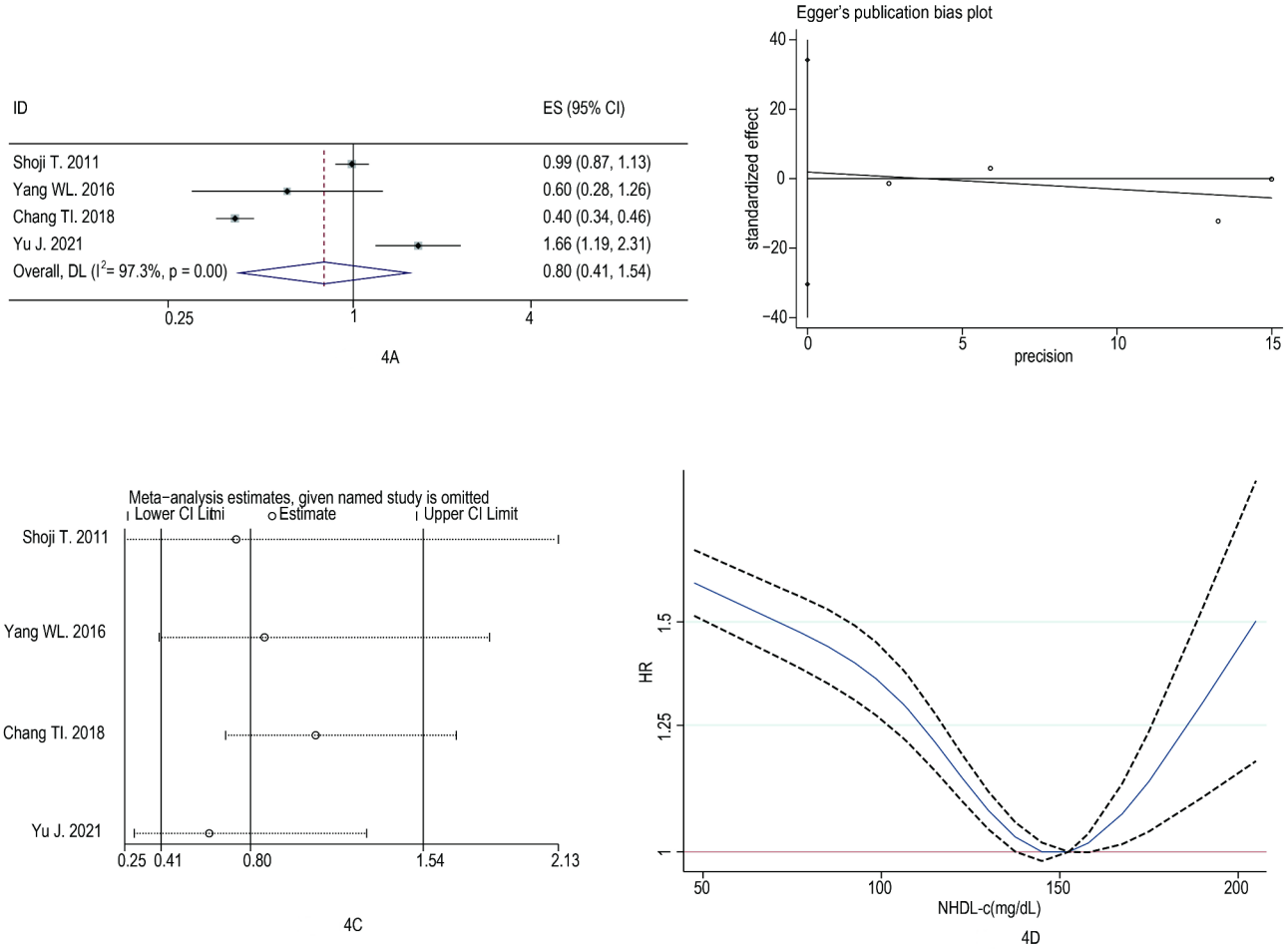


Fig. 4 Forest plot, publication bias, sensitivity analysis, and dose-response curve of NHDL-C and all-cause mortality in dialysis patients

lower TC levels should be identified, contributing to an improvement of health outcomes in the general population. The optimal TC range derived from this study for dialysis patients, then, will have slightly more stringent in comparison to the general population. If contrasted with patients with pre-dialysis CKD stage 3–5, the 2023 Chinese guidelines for lipid management refer to a population at very high risk or higher for non-dialysis CKD stage 3–5 patients with previous ASCVD events, with a TC target control of 120 mg/dL, while for primary prevention without previous ASCVD events, non-dialysis CKD stage 3–5 patients are a high-risk population with a TC target of 158 mg/dL [39]. Compared with our conclusion, it can be seen that when patients with chronic kidney disease progress to the dialysis phase the management of TC is more liberal than in the pre-dialysis phase (Fig. 6). This seems to coincide with the guidelines for recommending dialysis patients to follow a pre-dialysis approach to lipid management. After all, our conclusions do not appear to yield more stringent lipid goals during the dialysis phase. It is important to note that TC management in dialysis patients should not be less than 140.5 mg/dL.

The all-cause mortality in the highest dose group of NHDL-C tended to be lower than that in the lowest dose group, but it was not statistically significant (Fig. 4A). In the dose-response model, there was a U-shaped correlation between NHDL-C and all-cause mortality in dialysis patients, but no significant range of HR lower than 1 was found (Fig. 4D). Therefore, NHDL-C has insufficient sensitivity in predicting all-cause mortality in dialysis patients.

LDL-C plays a crucial role in the development and progression of atherosclerosis. Our conclusion seems to be that an increase in LDL-C is associated with a reduction in the risk of all-cause mortality in dialysis patients. Within the range of 25 < LDL-C < 145 mg/dL, for every 20 mg/dL increase in LDL-C, the all-cause mortality rate of dialysis patients decreases by 1.9%.

The KDIGO guidelines proposed that LDL-C is a significant risk factor for CVD in the general population but is not a suitable marker for assessing cardiovascular risk in dialysis patients. Because even patients with low

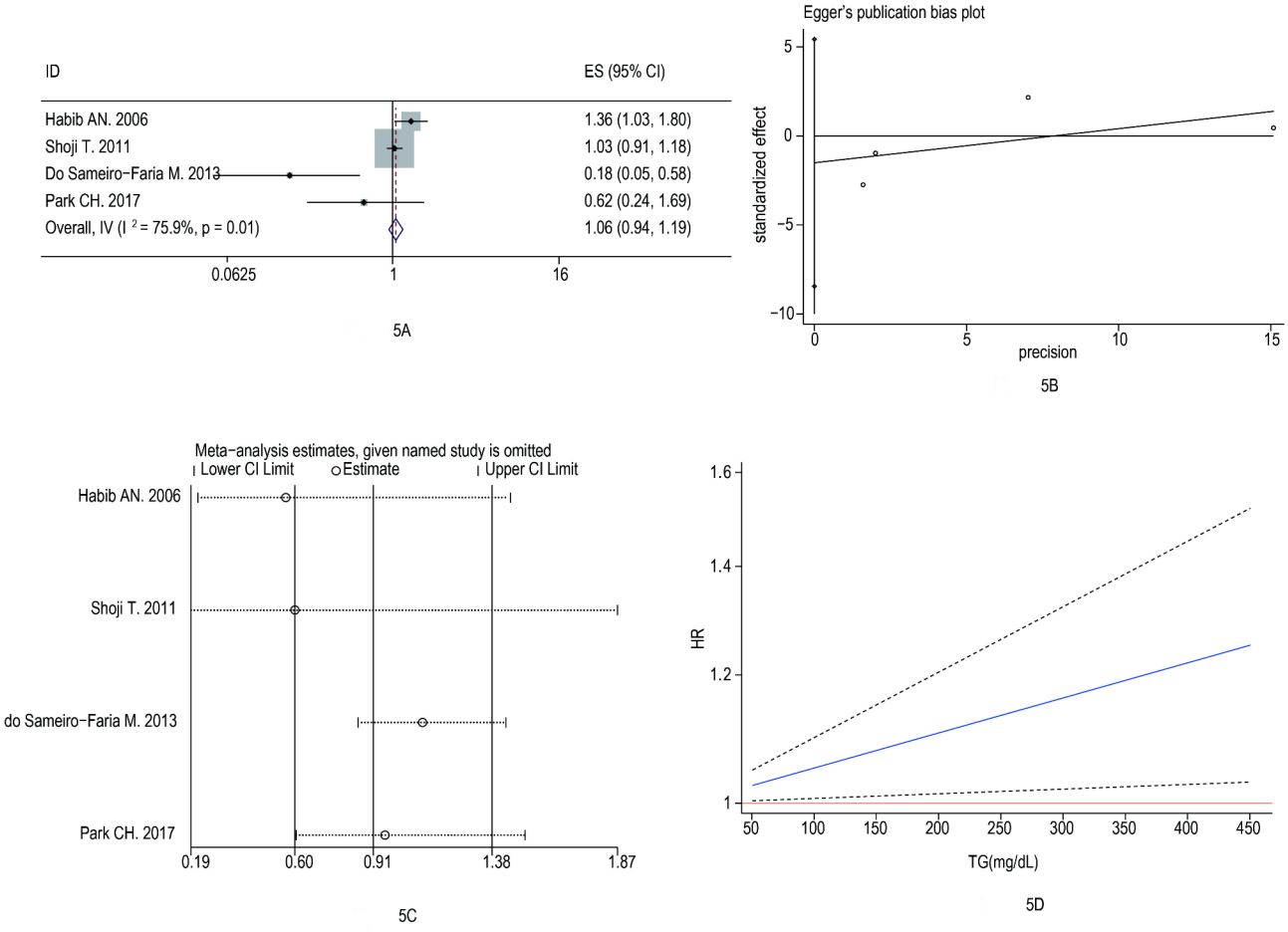


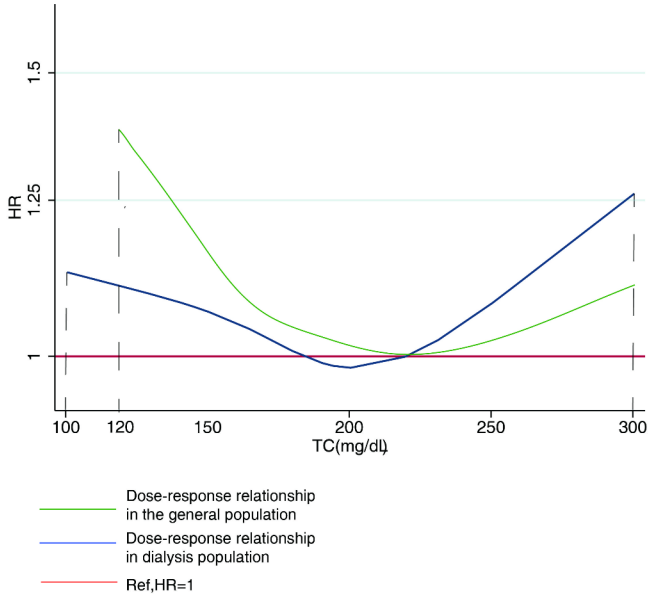
Fig. 5 Forest plot, publication bias, sensitivity analysis, and dose-response curve of TG and all-cause mortality in dialysis patients

LDL-C levels are still at very elevated risk of cardiovascular death. The prevalence of malnutrition and inflammation is higher than the prevalence of elevated cholesterol levels. And malnutrition and inflammation are important risk factors for cardiovascular disease in dialysis patients, surpassing LDL-C, so the prognostic value of LDL-C for dialysis patients is uncertain [40]. Our preliminary findings also reverse validate the masking effect of LDL-C on all-cause mortality.

The risk of all-cause mortality in dialysis patients is increased by an elevated TG at $50 < TG < 450$ mg/dL. TG is highly variable within and between individuals, and TG levels in the same individual are influenced by factors such as diet and varying time of day, so TG measurements may vary considerably in the same individual over multiple measurements. In the present study, four studies with TG as the independent variable were included, only one of which indicated that the TG measurement was the mean value during the follow-up period, while the other three should have been single measurements at the time of enrollment [20, 24, 25]. This study can only speculate on the tendency of increased TG to increase the risk of all-cause mortality in dialysis patients, and more evidence is required from high-quality RCT studies.

This study is the first to propose and attempt a meta-analysis of lipid subgroups in dialysis patients, trying TC, LDL-C, NHDL-C, and TG. Most of the included studies adjusted for inflammation, malnutrition, cardiovascular disease, and diabetes as confounding factors, thus mitigating the intervention of confounding factors on all-cause mortality and providing a clear reference target for primary or secondary prevention of cardiovascular events in dialysis patients.

Limitations of the present study should also be addressed. The independent variable was determined differently in the included studies, with some studies selecting time-varying lipids over the entire period and others using the mean of the first 3 months after enrollment as the baseline independent variable. Furthermore, the lipid grouping criteria were not uniform among the included studies. There are divisions based on the quartile of the population and divisions based on exactly taking the whole number. Differences in the criteria for the delineation of the independent variable may lead to



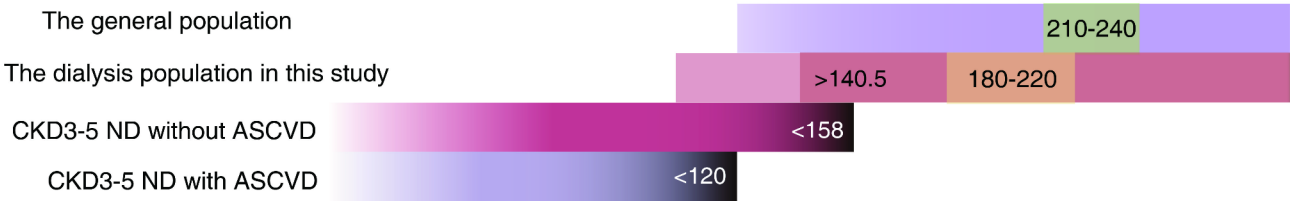


Fig. 6 Comparison of targets for TC in different populations

methodological bias throughout the study. For subsequent cohort studies that are conducted, it is preferable to group by population quartile lipid levels, and when conducting a dose-response analysis, the median or mean of the intervals grouped by population quartiles is more representative of the dose in that group. Ultimately, the number of cohort studies analyzing all-cause mortality in dialysis patients for lipid subgroups is currently limited, and more high-quality original studies should be expected to validate them.

Conclusion

Lipid modulation in dialysis patients has a role in all-cause mortality, and there is a non-linear dose-response relationship between TC and all-cause mortality in dialysis patients, which is not less than 140.5 mg/dL and controlled in the range of 180–220 mg/dL may have the minimum all-cause mortality for dialysis patients. NHDL-C is not a sensitive clinical test for the prediction of all-cause mortality in dialysis patients. LDL-C is not a reliable marker for assessing cardiovascular risk in dialysis patients and masks the association with all-cause mortality. At 50 < TG < 450 mg/dL, elevated TG can increase the risk of all-cause mortality associated with dialysis patients. In addition, large, high-quality, standardized observational studies are needed to explore the relationship between lipid levels and the risk of all-cause mortality in the dialysis population based on a stratified analysis of confounders of interest.

Abbreviations

HR	Hazard Ratio
CKD	Chronic Kidney Disease
KDIGO	Kidney Disease: Improving Global Outcomes:
ACC	American College of Cardiology
ESC	European Society of Cardiology
LDL-C	Low-Density Lipoprotein Cholesterol
RCT	Randomized Controlled Trial
TC	Total Cholesterol
NHDL-C	Non-High-Density Lipoprotein Cholesterol
TG	Triglyceride
NOS	The Newcastle-Ottawa Scale
glst	Generalized Least Squares Method
CI	Confidence Intervals
RCS	Restricted Cubic Spline
ASCVD	Arteriosclerotic Cardiovascular Disease

CVD Cardiovascular Disease
NCEP National Cholesterol Education Program

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-03981-z .

Supplementary Material 1

Author contributions

Conceptualization: Jing Xiong; Formal analysis: Jing Xiong; Investigation: Jing Xiong; Methodology: Ye Yao, Mi-Yuan Wang; Project administration: Jing Xiong; Software: Ye Yao, Mi-Yuan Wang; Supervision: Jing Xiong; Validation: Jing Xiong; Visualization: Ye Yao; Writing-original draft: Ye Yao; Writing-review and editing: Ye Yao, Jing Xiong and Mi-Yuan Wang.

Funding

The work was supported by the National Natural Science Foundation of China [grant numbers. 81770736] and Scientific research project of Traditional Chinese Medicine Department of Hubei Province Administration of Traditional Chinese Medicine[grant numbers.ZY2023F026].

Data availability

Data is provided within the supplementary information files.

Declarations

Ethics approval and consent to participate

Study participation was entirely anonymous and no informed consent was required.

Consent for publication

All authors reviewed and approved the manuscript for publication.

Competing interests

The authors declare no competing interests.

Disclosures

All authors have no conflicts of interest. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Received: 23 August 2024 / Accepted: 24 January 2025
Published online: 04 February 2025

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