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Association of serum uric acid with all-cause and cardiovascular mortality in peritoneal dialysis patients: a systematic review and meta-analysis of observational studies

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Complete List of Authors:	Xue, Xue; Beijing University of Chinese Medicine, Centre for Evidence-Based Chinese Medicine Lu, Chun-li; Beijing University of Chinese Medicine Jin, Xin-yan; Beijing University of Chinese Medicine Liu, Xue-han; Beijing University of Chinese Medicine Yang, Min; Hubei Provincial Hospital of Traditional Chinese Medicine Wang, Xiao-qin ; Hubei Provincial Hospital of Traditional Chinese Medicine Cheng, Hong; Hubei Provincial Hospital of Traditional Chinese Medicine Yuan, Jun; Hubei Provincial Hospital of Traditional Chinese Medicine Liu, Qiang ; Hubei Provincial Hospital of Traditional Chinese Medicine Zheng, Ruo-xiang; Beijing University of Chinese Medicine Liu, Jian-Ping; Beijing University of Chinese Medicine, Centre for Evidence-Based Chinese Medicine
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Title Page

Title: Association of serum uric acid with all-cause and cardiovascular mortality in peritoneal dialysis patients: a systematic review and meta-analysis of observational studies

Authors： Xue Xue1,2, Chun-li Lu2, Xin-yan Jin2, Xue-han Liu2, MinYang3, Xiao-qin Wang4, Hong Cheng4, Jun Yuan4, Qiang Liu4, Ruo-xiang Zheng2, and Jian-ping Liu2*

1 The first clinical college and affiliated hospital, Hubei University of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

2 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

3 Basic Medical School and affiliated hospital, Hubei University of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

4 Department of nephrology, Hubei provincial hospital of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

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Email addresses: Xue Xue (xue025004138@163.com); Chun-li Lu (annyzhenni@163.com); Xin-yan Jin (20170941260@bucm.edu.cn); Xue-han Liu (xuehan_liu@foxmail.com); MinYang (1750096103@qq.com); Xiao-qin Wang (wangxiao773@hotmail.com); Hong Cheng (chenghong@hbhtcm.com); Jun Yuan (yjun_92@hbtcm.edu.cn); Qiang Liu (leonjordan23@sina.com); Ruo-xiang Zheng (zhengruox@

foxmail.com); Jian-ping Liu (Liujp@bucm.edu.cn).

***Corresponding**

Jian-ping Liu*

Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China. E-mail: Liujp@bucm.edu.cn

Telephone number: 13718004410.

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Abstract

Objectives To analyze association of serum uric acid (SUA) with all-cause and cardiovascular (CV) mortality in peritoneal dialysis (PD) patients to inform clinical practice and further research.

Design A systematic review of observational studies.

Data sources We searched PubMed, Embase, Web of Science, the Cochrane Library, CNKI, SinoMed, VIP and Wan Fang electronic databases from their inception to January 2021. We included cohort studies and case-control studies reporting SUA and mortality in PD patients.

Methods Effect estimates were presented as hazard ratio (HR) with 95% confidence interval (CI) in meta-analysis using STATA 16.0, and synthesized studies qualitatively when data not suitable for pooling analysis.

Results Fourteen cohort studies with 24031 patients involved were finally included. No case-control study was identified. In prospective cohort study, pooled result of highest

SUA category was significantly higher than lowest for all-cause (1 study; 1287 participants; HR 1.79; 95%CI 1.17-2.75) and CV mortality (1 study; 1287 participants; HR 2.63; 95%CI 1.62-4.27). And an increase of 1mg/dl in SUA level was associated with an 16% increased risk of all-cause mortality (1 study; 1287 participants; HR 1.16; 95%CI 1.03-1.32) and 34% increased CV mortality risk (1 study; 1287 participants; HR 1.34; 95%CI 1.16-1.55). While, in retrospective cohort studies, highest SUA category was not found to elevate all-cause (5 studies; 4570 participants; HR 1.09; 95%CI 0.70-1.70) and CV mortality (3 studies; 3748 participants; HR 1.00; 95%CI 0.44-2.31) compared with lowest. And there was also no increase in all-cause (8 studies; 11541 participants; HR 0.94; 95%CI 0.88-1.02) and CV mortality (3 studies; 7427 participants; HR 0.90; 95%CI 0.76-1.06) with every 1mg/dl increase in SUA level.

Conclusions Results of prospective cohort study and retrospective cohort studies were inconsistent. Consequently, prospective, multicenter, long term follow-up studies are required in future to confirm association of SUA and mortality in PD patients.

Trial registration number International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY.COM) registration number:202140020.

Strengths and limitations of this study

This is the first systematic review of observational studies exploring the correlation between SUA level and mortality in PD patients.

We used critical systematic review and subgroup analysis to describe the results, and proposed future research direction.

In spite of many important confounding factors had been adjusted in the studies,

residual and unknown confounding still can not be excluded entirely.

Part of necessary data in the studies was not obtained, exploration of dose-response relationship failed, it needs to be further determined in future.

Introduction

End-stage renal disease (ESRD) is one of the major diseases affecting human health, which causes enormous pressure and burden on medical care and society. Peritoneal dialysis (PD), as one of the effective alternative treatments for ESRD, has many features, such as stable hemodynamics, protection of residual renal function (RRF), good removal of middle molecular toxins, low risk of infectious disease infection, health economics advantage and home treatment [1]. Currently, PD has been widely used all over the world. Epidemiological survey results showed that as of 2013, the total number of people receiving peritoneal dialysis worldwide reached approximately 220,000 [2]. Of concern, patients with ESRD treated with dialysis still have a high mortality rate [3]. Therefore, the identification of potential risk factors that can be intervened is still an important topic in the field of PD, which is of great significance for improving the prognosis of patients and increasing the quality of life.

Uric acid (UA) is the final product of purine nucleotide metabolism in humans. Previous studies have demonstrated that elevated serum uric acid (SUA) was closely related to the increased risk of hypertension, peripheral arterial disease, cardiovascular (CV) event and chronic kidney disease (CKD) in general population [4-7]. And higher SUA level also appeared to be an independent risk factor for all-cause and CV mortality in CKD subjects [8,9]. However， there were conflicting results about the relationship

between SUA level and risk of death among dialysis patients. For hemodialysis population, many studies have confirmed that hypouricemia significantly increased the mortality of maintenance hemodialysis patients [10-12]. Nevertheless, SUA's role for all-cause and CV mortality in PD patients has been controversial. One study in PD patients indicated that elevated SUA level was an independent risk factor for all-cause and CV mortality in men treated with PD [13]. The result of another study showed that the prognostic value of SUA in all-cause and CV mortality was weak in PD patients [14]. Whereas hyperuricemia was found to predict lower risk of all-cause mortality in PD patients with lower relative appendicular skeletal muscle in another study [15]. In short, results regarding the effect of SUA on the prognosis of PD patients appeared to be inconsistent.

At present, there is a lack of systematic reviews on the relationship between SUA, all-cause and CV mortality in PD population. We hypothesized that there may be exist independent correlation between elevated SUA level and mortality in participants with PD. Thus, we systematically analyze available studies to determine whether the hypothesis was right.

Methods

Protocol and registration

Methods of this review were specified in advance and documented in International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY.COM). (**Registration number**:**202140020**). The content of this review was reported according to the guidelines of "Meta-analysis of Observational Studies in

Epidemiology guidelines" (MOOSE) [16].

Eligibility criteria

Types of studies

Cohort studies and case-control studies were identified.

Participants

All participants who had received PD for more than 3 months. There was no restriction on the type of PD, including continuous ambulatory PD, intermittent PD, automated PD, continuous cyclic PD and tidal PD.

Exposure factor

Hyperuricemia in PD population was the exposure factor of this study. Either categorization according to baseline SUA level or time-average SUA concentration was acceptable. Definition of hyperuricemia and the categorization for the SUA level was based on the definition in each included article respectively.

Outcome

Primary outcome: all-cause mortality. The death was determined by the hospital medical record and death certificate.

Secondary outcome: CV mortality. The definition of "CV events": coronary events (myocardial infarction, unstable angina), cardio myopathy, cardiac arrest, cardiac dysrhythmia, congestive heart failure, ischemic brain injury, cerebrovascular accident and peripheral vascular disease. The cause of death was determined through medical history, hospital medical records and death certificates.

Exclusion criteria

(1) Hazard ratio (HR) and its corresponding 95% confidence interval (CI) (or other data to calculate them) of all-cause or CV mortality for 1mg/dl change in SUA level, or for the highest versus lowest SUA category or the lowest versus highest category could not be obtained from the original article; (2) Cohort studies with a total sample size of less than 100 participants; (3) If studies originated from the same series of cohort samples, or part of the cohort samples were published repeatedly, only the literature with the largest sample size and the longest follow-up could be included, and the rest of the literature need to be excluded.

Search strategy

Two authors (X.X. and H.C.) searched the following Chinese and English databases from their inception to 15th January 2021. Chinese databases included China National Knowledge Infrastructure (CNKI), SinoMed, Chinese Science and Technology Journal Database (VIP), and Wan Fang Database. English databases included PubMed, EMBASE, the Cochrane Library, and Web of Science. Trial registers including Clinical Trials. gov and the World Health Organization International Clinical Trials Registry Platform were also searched. Additionally, related reviews, conference papers, references lists and gray literatures also were searched manually to minimize the missed detection rate. No language or publication type was imposed, published abstracts were also considered. If there was a lack of information in the retrieved literature, it was necessary to contact the author via email to obtain the missing data to ensure that literatures could be included in a comprehensive way. Taking "PubMed" as an example, the retrieval strategy was as follows: ("Uric Acid" [Mesh] OR "Uric Acid"

OR “serum uric acid”) AND (“Mortality” [Mesh] OR “Mortality”) AND (“Peritoneal Dialysis” [Mesh] OR “Peritoneal Dialysis” OR “PD” OR “continuous ambulatory PD” OR “CAPD” OR “intermittent PD” OR “IPD” OR “automated PD” OR “APD” OR “continuous cyclic PD” OR “CCPD” OR “tidal PD” OR “TPD”).

Studies selection and data extraction

The titles and the abstracts were screened first, then the full-text versions were checked according to inclusion and exclusion criteria. Two authors (X.X. and Q.L.) examined the full text to identify the eligible trials independently. We made a data extraction sheet in advance. Two authors (X.X. and H.C.) extracted data independently. Disagreements of studies selection and data extraction were resolved by consulting corresponding author JP Liu. Information was extracted from each included trial on: first author, publication year, age, gender, study design, dialysis duration, sample size, study location, center, length of follow up, categories according to serum uric acid, comparison, adjustments, adjusted HR (95%CI).

Methodological quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of observational studies [17]. NOS allocated a maximum of 9 points for quality of selection, comparability, and outcome of study population. Two authors (X.X. and J.Y.) assessed and validated the quality of included studies independently. Any disagreements were resolved by discussion with corresponding author JP Liu. Overall study quality scores were defined as poor (0–3), fair (4–6), or good (7–9).

Statistical analysis

SUA was analyzed not only as a categorical variable, but also as a continuous variable in the included studies. The statistical analysis for the overall association between SUA levels and death risk (all-cause and CV mortality) were based on random effects model and on comparisons of highest versus lowest category of SUA level, or by increase of 1mg/dl. HR and 95% CI were used as effect indicators. HR and corresponding 95% CI of each study were transformed to their natural logarithm (lnHR, lnlCI and lnUCI), and overall HR and its 95% CI was calculated by exponentiation of the pooled lnHR, lnlCI and lnUCI.

If data of cases, person-years, and HR and 95% CI for each category were available in included studies, then a dose-response analysis would be performed to further explore the relationship between SUA and mortality. The potential non-linearity association was examined by modeling SUA levels using restricted cubic splines with three knots at 25, 50, and 75% of the distribution. We assigned the median or middle point of the upper and lower boundaries in each category as the corresponding dose to the related HR for each study. In case of P value >0.05, the linear regression model should be considered.

square (I^2) was applied to test the statistical heterogeneity among studies (Higgins and Thompson, 2003) [19]. When $I^2>85\%$, we believed that the results could not be poolled. Data not suitable for statistical pooling were synthesized qualitatively. To explore the source of heterogeneity among studies, subgroup analyses were conducted according to study design, study location, publication years, adjustment for sex, adjustment for DM and adjustment for albumin. Additionally, the meta-regression

analysis was also performed to detect potential heterogeneity based on the above variables when about 10 studies were included. Sensitivity analysis was performed with removing one study at a time to explore the robustness of results if data were available. The possibility of publication bias was detected by funnel plots and Egger's test if there were about 10 studies. STATA16.0 software (StataCorp, College Station, Texas, 77845 USA) was used for data analysis.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our study.

Results

Search results

Two hundred and forty-two relevant citations were retrieved. After scanning the full texts, five literatures were excluded. We excluded cohort samples of the same series [13,15,20], only the studies with the largest sample size and the longest follow-up time were included [21,22]. Besides, we excluded a published abstract [23], due to its total sample size of entire cohort was only 60 participants. And another study was excluded due to whose pooled effect estimation were reported as odds ratio (OR) with 95% CI [24]. Finally, fourteen literatures were eligible for this review. Details of search and selection process were illustrated in Fig.1.

Characteristic of included trials

A total of fourteen literatures involving 24031 participants were included [14,21,22,25-35]. The included studies were all cohort studies, including prospective and

retrospective studies. The main characteristics of included studies were demonstrated in Table 1.

Methodological quality of included studies

The overall quality of included studies was good with a mean NOS score of 7.57, with a range of 7–9. All studies receiving a NOS greater than or equal to 7 (eTable1 in the Supplement). Among them, in terms of "comparability", the most important confounding factors that need to be adjusted should include indicators of estimated glomerular filtration rate (eGFR) or serum creatinine (Scr) or urinary volume (UV) or residual renal function (RRF), which can reflect the patient's current residual renal function status. In addition, according to literature and clinical observations, other confounding factors that need to be adjusted should include gender, age, diabetes history, cardiovascular disease (CVD) history, Kt/v (urea clearance index, representing dialysis adequacy), use of UA-lowering drugs, and serum albumin (representing nutritional status).

Primary outcome

Association of serum uric acid in categories with all-cause mortality

In order to reduce the heterogeneity of methodology, we discussed the results respectively according to different study designs. In prospective cohort studies, summary HR and 95% CI of all-cause mortality for the highest SUA category compared with the lowest category came from one included study including 1287 patients [21]. As presented in Fig.2, pooled result of the highest SUA category was significantly higher than the lowest for all-cause mortality (HR 1.79; 95% CI 1.17-2.75).

In retrospective cohort studies, five studies with 4570 patients reported HR and 95% CI of all-cause mortality for the highest versus the lowest SUA category [14,28,29,33,34]. The highest SUA category was not found to elevate all-cause mortality (HR 1.09; 95% CI 0.70-1.70; Fig.2) compared with the lowest category of PD patients.

HR and corresponding 95% CI were reported in three retrospective cohort studies for the lowest versus the highest SUA category [26,27,31]. Among them, the data of one of the articles [27] was supplemented by the corresponding author Changxiu via e-mail. The pooled HR was 1.52 (95%CI 0.79-2.89), with heterogeneity of I^2=32.8%.

Association of Serum uric acid per 1mg/dl increase with all-cause mortality

Only one prospective study with 1287 PD patients reported HR and 95% CI of all-cause mortality for 1mg/dl increase in SUA level [21]. And pooled result showed that for every 1mg/dl increase in SUA level, risk of all-cause death increased by 16% (HR 1.16; 95%CI 1.03-1.32; Fig.3).

In retrospective cohort studies, eight studies with 11541 PD patients reported HR and 95% CI of all-cause mortality for 1mg/dl increase in SUA level [14,22,27-30,33,35]. When the unit of SUA concentration in the literature was different, 60 μmol/l was approximately equal to 1mg/dl. In short, each 1mg/dl increase in SUA level didn't appear to significantly increase the risk of all-cause mortality in PD population (HR 0.94; 95% CI 0.88-1.02; Fig.3).

Dose-response relationship between serum uric acid with all-cause mortality

Most of the included literature [14,21,22,26,28,30,31,33-35] only reported the number

of outcomes of the entire cohort population, we were unable to obtain the number of all-cause and CV deaths and person-years in each category. Despite we tried our best to contact authors by email or phone in order to acquire necessary data for non-linearity test, only one auther responded and provided relevant data [27]. At last, dose-response analysis failed.

Secondary outcome

Association of serum uric acid in categories with cardiovascular mortality

One prospective cohort study with 1287 patients reported HR and 95% CI of CV mortality for the highest SUA category compared with the lowest [21]. Pooled result of HR in the highest versus the lowest category was 2.63 (95% CI 1.62-4.27). (eFigure1 in the Supplement)

Three retrospective cohort studies with 3748 patients reported HR and 95% CI of CV mortality for the highest versus the lowest SUA category [14,28,29]. And the highest SUA category was not found to increase CV mortality (HR 1.00; 95% CI 0.44-2.31) compared with the lowest category of PD patients (eFigure1 in the Supplement).

Association of serum uric acid per 1mg/dl increase with cardiovascular mortality

One prospective cohort study with 1287 patients reported HR and 95% CI of CV mortality for 1mg/dl increase in SUA level [21]. And an increase of 1mg/dl in SUA level was associated with an 34% increased risk of CV mortality (HR 1.34; 95%CI 1.16-1.55; eFigure2 in the Supplement).

Three retrospective cohort studies with 7427 patients reported HR and 95% CI of CV mortality for 1mg/dl increase in SUA level [14,29,35]. By meta-analysis, each 1

mg/dl increase in SUA level didn't appear to significantly increase the risk of CV death in PD population (HR 0.90; 95% CI 0.76-1.06; eFigure2 in the Supplement).

Additional analysis

Subgroup analysis and meta-regression

We explored the source of heterogeneity for subgroup analysis and meta-regression. Subgroup analysis only included literatures which were on comparisons of the highest versus the lowest category of SUA level, or by change of 1mg/dl increase. The pooled HR (95% CI) and I^2 of subgroup analysis for association of SUA with all-cause and CV mortality were presented in Table 2a and Table 2b, respectively.

As mentioned before, whether SUA was a categorical variable or a continuous variable, results of prospective cohort studies differed from those of retrospective studies. Besides, combined with the results of subgroup analysis, when SUA was estimated as a categorical variable, association of higher SUA level with increased all-cause and CV mortality was significant in studies of mainland in China, but not in the rest of the locations. SUA as a continuous variable, relationship of higher CV mortality for 1 mg/dl increase in SUA level was significant in studies of mainland China, but not in the rest of the locations. Furthermore, we analyzed the relevant studies published in the past ten years, and results of studies completed during 2011-2016 were different from the results during 2017-2021 period.

In addition, in studies of association between SUA (as a continuous variable) and all-cause mortality, study design, study location, publication years, adjusted for sex and DM were the heterogeneous sources by meta-regression (Table 2a).

Test of Publication bias

The funnel plots and Egger's test (t=1.07, p=0.309) indicated that there was no obvious publication bias of studies for association of all-cause mortality and SUA level per 1mg/dl increase. The funnel plot was presented in eFigure3 in the Supplement.

Sensitivity analysis

In retrospective cohort studies, primary outcome showed that there was no significant effect on the pooled HR values of other studies with one study removed at a time. The above indicated that the results were robust.

Discussion

Principal findings and comparison with prior reviews

For PD population, previous original studies indicated inconsistent relationship between SUA and mortality. After searching systematically, we found that there were some meta-analyses of investigating the correlation between SUA and mortality in different population [36-39], however, we have not yet found one only for PD patients. A systematic review published in 2016 showed that elevated SUA level was significantly associated with the risk of death in patients with CKD, including dialysis and non-dialysis subjects [40]. Subgroup analysis of this review demonstrated that hyperuricemia was an independent predictor for mortality in PD population, while, this predictive value was not found in the hemodialysis (HD) population. Only 1 prospective cohort study and 2 retrospective cohort studies were included in PD subgroup. In our study, we included a total of 14 cohort studies, of which 2 were prospective studies and 12 were retrospective studies. Quality of all studies was good

by NOS assessment. Only one prospective cohort study suggested that regardless of whether SUA was estimated as a continuous or a categorical variable, elevated SUA level was significantly associated with increased risk of all-cause and CV mortality in PD patients. Whereas, no significant associations between them in retrospective study. Considering that only one prospective study [21] was included in analysis, so the result should be interpreted with caution.

Although the detrimental effect of SUA is obvious, which is an endothelial toxin and plays a role in endothelial dysfunction [41], as a powerful free radical scavenger in human at the same time, SUA may be expected to offer a number of benefits within the CV system in PD patients [42,43]. Besides, the problem of protein loss and malnutrition is prominent in PD population [44]. "Malnutrition-inflammation complex syndrome (MICS)" is believed to be the main cause of high rate of CV atherosclerotic disease and increased mortality and hospitalization in HD patients [45,46]. The underlying mechanism of MICS may also be present in PD patients. As a nutritional marker，SUA might be involved in the MICS axis. The pooled result of the retrospective studies did not find that elevated SUA was associated with increased risk of mortality, perhaps related to complex interaction mechanisms. Further investigations are warranted to clarify the precise mechanisms.

In addition, heterogeneous among included studies was generally high. The different study location was one of the main sources of heterogeneity among studies by meta-regression test. Subgroup analysis results further suggested that hyperuricemia was associated with a high risk of CV death in the PD population in mainland China.

As a result, the correlation between the SUA level and the risk of death in different regions needs to be explored and verified by prospective studies in future.

Implications further research

Since the results of prospective and retrospective cohort studies were inconsistent, and different regions of the study seemed to produce different result. Therefore, prospective, multicenter, long term follow-up studies are required in future to explore the correlation between SUA level and the risk of death in different regions, as well as to determine the range of SUA concentrations which can reduce mortality and improve prognosis in PD patients.

Additionally, since PD patients often suffered from underlying diseases and complex conditions. Therefore, confounding factors must be adjusted comprehensively in observational study to explore the relationship between etiology and prognosis in future. For PD population, the following confounding factors should be considered to make the conclusion more convincing. Such as: traditional independent risk factors of CV events (age, gender, total lipoprotein cholesterol, low or high density lipoprotein cholesterol, hypertension, diabetes, smoking [47]), history of CV, emotion status, residual renal function, the related parameters of PD, the parameters of nutritional status, use of diuretic and lower UA agents and so forth.

Besides, necessary information should be reported in detail in study report. Not only can readers become more familiar with the details of the study, but also can conveniently carry out secondary research and avoid waste of research resources.

Conclusions

The results of the prospective and retrospective cohort studies were inconsistent. Only one prospective cohort study showed that elevated SUA level was significantly associated with increased risk of all-cause and CV mortality in PD patients. Nevertheless, pooled result of retrospective cohort studies did not appear to indicate a prominent association. So it is necessary to use SUA-lowering agents with caution for PD patients in clinics. And prospective, multicenter, long term follow-up studies are needed in future to investigate the correlation between SUA level and the risk of death in different regions, as well as to explore the range of SUA concentration associated with the lowest mortality in PD patients.

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Author Contributions Research idea and study design: XX and JPL. Protocol and Registration: XX, CLL, XYJ and XHL. Acquisition, analysis, or interpretation of data: XX, HC, QL, JY, and JPL. Drafting of the manuscript: XX, XHL, CLL, XYJ and RXZ. Statistical analysis: MY, XX and XQW. Critical revision of the manuscript: XQW and JPL. Supervision: JPL.

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Competing interests None.

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Data sharing statement The datasets used for meta-analyses are available from the corresponding author on reasonable request.

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Table 1 Characteristics of included studies

Study ID	Study location (Region)	Study design/ Center	Age (years)	Male/ Total Sample(n)	Dialysis duration (months)	Follow-up (months)	Deaths AC/CV (n)	Definition of hyperuricemia or categories according to serum uric acid	Comparison	Adjustments	Adjusted HR (95%CI)
Sheng F 2013 [25]	China: Mainland	RCS/ Single	54.1±17.4	98/156	31.3±17.5	31.3±17.5	41/23	Group 1:≤7.0mg/dl; Group 2: 7.0-10.0 mg/dl; Group 3: ≥10.0 mg/dl.	Group 1 vs. Group 2 Group 3 vs. Group 2	Age, Alb, DM, HN, RRF , phosphate , Log CRP	ACM: 1.15(0.20-2.57) ACM: 2.96(1.29-6.80)
Jie D 2014 [14]	China: Mainland	RCS/ 7 centers	58.1±15.5	1078/2193	At least > 3	Median 26.5	586/231	Men: Tertile 1: 2.09-5.79mg/dl; Tertile 2: 5.80-7.38 mg/dl; Tertile 3: 7.39-16.7 mg/dl. FM: Tertile 1: 1.74-5.37mg/dl; Tertile 2: 5.38-6.65 mg/dl; Tertile 3: 6.66-8.08 mg/dl.	Tertile 3 vs. Tertile 1 (Gender-specific) Tertile 2 vs. Tertile 1 (Gender-specific) Per 1 mg/dl increase	Age, RRF, Hb, Alb, phosphate, LDLC, CRP, histroy of CVD and DM, BMI, MAP, center size, gender adjusted only SUA as continuous variable.	ACM: 1.21(0.85-1.73) CVM: 1.35(0.74-2.46) ACM: 1.23(0.90-1.70) CVM: 1.29(0.75-2.23) ACM: 1.05(0.96-1.14) CVM: 1.04(0.89-1.20)
XX 2016 [21]	China: Mainland	PCS/ Single	47.6±15.0	757/1287	At least > 3	Median 30.7	231/126	Men: Tertile 1: < 6.46mg/dl; (DM)Tertile 2: 6.46-7.38 mg/dl; Tertile 3: ≥7.38 mg/dl. Men: Tertile 1: < 7.00mg/dl; (NDM)Tertile2: 7.70-7.89mg/dl; Tertile 3: ≥7.89 mg/dl. FM: Tertile 1: < 5.89mg/dl; (DM)Tertile 2: 5.89-7.09 mg/dl ; Tertile 3: ≥7.09 mg/dl. FM: Tertile 1: < 6.46mg/dl; (NDM)Tertile2: 6.46-7.48mg/dl; Tertile 3: ≥7.48 mg/dl.	Tertile 3 vs. Tertile 1 (DM: Gender specific) Tertile 3 vs. Tertile 1 (NDM: Gender specific) Per 1 mg/dl increase	Age, gender, BMI, history of CVD and hypertension, Hb, Alb, Scr, P, HDL-C; RRF, log-transformed Hs-CRP, glycated Hb, use of allopurinol and ACEI or ARB.	ACM: 1.46(0.92-2.32) CVM: 2.26(1.14-4.48) ACM: 2.26(1.36-3.75) CVM: 3.07(1.54-6.08) ACM (DM, MEN):1.09(0.91-1.32); ACM (DM, FM):1.06(0.83-1.35); ACM(NDM, MEN):1.36(1.14-1.64); ACM (NDM, FM):1.09(0.80-1.47); CVM (DM, MEN):1.42(1.13-1.79); CVM (DM, FM):1.12(0.78-1.61); CVM(NDM, MEN):1.41(1.09-1.82); CVM (NDM, FM):1.24(0.85-1.82).
Eunjin B2016	South	PCS/mult	NR	NR/651	At least > 3	Median	AC 106	Group 1: TA-UA<5.5 mg/dl;	Group 1 vs. Group 2	Age, sex, BMI, SBP, Ca, P,	ACM: 1.478(0.602-3.627)

[26]	Korea	-icenter				43.9		Group 2: TA-UA≥5.5 mg/dl.		Alb, TC, DM, SGA.	
ChangWX2018 [27]	China: Mainland	RCS/ Single	55.2±14.9	171/300	At least > 3	22.6±15.9	AC 44	Group1: TA-UA < 6mg/dL; Group2: TA-UA 6–8mg/dL; Group3: TA-UA ≥8mg/dL.	Group 3 vs. Group 2 Group 1 vs. Group 2 Group 1 vs. Group 3 Per 1 mg/dl increase (Baseline-UA)	Sex, age, DM, CVD history, RRF, BMI, SBP, Hb, Alb, BUN, SCr, Na, K, CO2, Ca, P, LDL-C, CRP, RASi, diuretic.	ACM: 4.69(1.24-17.72) ACM: 3.24(1.25-8.39) ACM: 0.603 (0.158-2.309) ACM: 0.86(0.67-1.12)
ZhangQL2018 [28]	China: Mainland	RCS/ Single	Median 51	557/1063	At least > 6	Median 33	167/64	Group 1: < 420μmol/l; Group 2: ≥420μmol/l; Hyperuricemia≥420μmol/l	Group 2 vs. Group 1 Per 1 μmol/l increase	Age, Scr, P, Alb, BG, iPTH, history of DM, DBP, Charlson score.	ACM: 1.572(1.155-2.141) CVM: 1.734(1.033-2.912) ACM: 1.002(1.001-1.004)
Lai KJ 2018 [29]	China: Taiwan	RCS/ Single	53.5±15.3	237/492	At least > 3	Median 36.4	127/74	Men: Tertile 1: ≤6.8mg/dl; Tertile 2: 6.9-8mg/dl; Tertile 3: ≥8.1mg/dl. FM: Tertile 1: ≤6.5mg/dl; Tertile 2: 6.6-7.6mg/dl; Tertile 3: ≥7.7mg/dl. Men: Hyperuricemia≥7mg/dl FM: Hyperuricemia≥6mg/dl	Tertile 3 vs. Tertile 1 (Gender-specific) Tertile 2 vs. Tertile 1 (Gender-specific) Men: Per 1mg/dl increase FM: Per 1 mg/dl increase	Age, sex, BMI, pre-dialysis status, smoking, present medications, comorbidities of CVD, hyper-tension, DM, Charlson score, PD related parameters, Kt/v, BUN, Scr, GPT, WBC, ALP, Alb, Hb, ferritin, TC, TG, Ca, P, iPTH, transferrin saturation.	ACM: 0.4(0.24-0.68) CVM: 0.4(0.2-0.81) ACM: 1.06(0.7-1.58) CVM: 1.04(0.62-1.77) ACM: 0.84(0.69-0.9) CVM: 0.79(0.61-1.01) ACM: 0.57(0.44-0.73) CVM: 0.6(0.41-0.87)
Yang FY 2018 [30]	China: Mainland	RCS/ Single	51.8±14.4	232/487	Median 29.5	Median 29.5	197/109	Men: Hyperuricemia≥7mg/dl; FM: Hyperuricemia≥6mg/dl.	Per 1 mg/dl increase	Sex,, BMI, hypertension , dialysis duration, eGFR, Kt/v, LDL-C, iPTH.	ACM: 0.773(0.62-0.97)
ChangWX2019 [31]	China: Mainland	RCS/ Single	18—80	150/309	At least > 3	NR	AC 50	Group 1: SUA decliner; Group 2: SUA non-decliner. ("SUA decliner" and "SUA non-decliner" according to run-in and longitudinal changes in the follow-up)	Group 1 vs. Group 2	Gender, age, BMI, SBP, Hb, Na, K, Cl, BUN, Scr, CO2, Ca, P, Alb, TG, FBG, CRP, RRF, PET type, Kt/V, DM, use of CCB, RASi , diuretic , β-	ACM: 2.23(1.13-4.40)

										blocker.	
Xiang SL 2019 [32]	China: Mainland	RCS/ 98centers	52.5±14.6	5163/9405	At least > 3	Median 29.4	1226/515	Quintile1: < 6.06mg/dl; Quintile2: 6.06-6.67mg/dl; Quintile3: 6.68–7.27mg/dl Quintile4: 7.28-8.03mg/dl; Quintile5: ≥8.04 mg/dl. Hyperuricemia≥7.28mg/dl.	Quintile5 vs. Quintile3 Quintile4 vs. Quintile3 Quintile2 vs. Quintile3 Quintile1 vs. Quintile3	Age, sex, BMI, DM, CVD, RRF, Hb, Alb, K, Na, P, Ca, iPTH, Scr, FPG.	ACM: 1.482(1.187-1.849) CVM: 1.144(0.786-1.665) ACM: 1.335(1.073-1.662) CVM: 1.146(0.796-1.648) ACM: 1.160(0.938-1.434) CVM: 1.311(0.932-1.843) ACM: 1.162(0.945-1.427) CVM: 1.166(0.820-1.657)
Qiu SF 2020 [33]	China: Mainland	RCS/ Single	44—65	63/140	Median 31.9	Median 31.9	AC 48	Tertile 1: < 387μmol/l; Tertile 2: 387-519μmol/l; Tertile 3: ≥519μmol/l.	Tertile 3 vs. Tertile 1 Tertile 2 vs. Tertile 1 Per 20μmo/l increase	Gender, age, DM , hypertension, CVD, BMI, K, ESA, RRF , use of diuretic and LUA.	ACM: 2.308(1.062-5.017) ACM: 0.959(0.423-2.174) ACM: 1.003(1.00-1.005)
Goelho I 2020 [34]	Portugal	RCS/ Single	60.2±14.6	407/682	At least > 3	31.4±25.6	NR	Group 1: below median; Group 2: above median.	Group 2 vs. Group 1	Age, comorbidities, DM and baseline RRF.	ACM: 0.997(0.74-1.35)
Naoki S 2020 [35]	Japan	RCS/mult -icenter	63±14	2916/4742	Median 28	Deadline : the end of 2012	AC 379	Group 1: < 5.0mg dl; Group 2: 5.0- < 5.5mg dl; Group 3: 5.5- < 6.0mg dl; Group 4: 6.0- < 6.5mg dl; Group 5: 6.5- < 7.0mg dl; Group 6: 7.0- < 7.5mg dl; Group 7: 7.5- < 8.0mg dl; Group 8: 8.0- < 8.5mg dl; Group 9: ≥8.5mg dl;	Group 1 vs. Group 5 Group 2 vs. Group 5 Group 3 vs. Group 5 Group 4 vs. Group 5 Group 5 vs. Group 5 Group 7 vs. Group 5 Group 8 vs. Group 5 Group 9 vs. Group 5 Per 10μmo/l increase	Age, gender, BMI , UV , dialysis duration, under-lying disease, comorbid disease, medication and laboratory data.	ACM: 1.80(1.13-2.86) ACM: 1.43(0.88-2.32) ACM: 1.22(0.75-1.98) ACM: 1.37(0.86-2.20) ACM: 1.54(0.75-2.49) ACM: 1.58(0.94-2.63) ACM: 1.88(1.06-3.35) ACM: 1.93(1.15-3.24) ACM: 1.00(0.99-1.02) CVM: 1.00(0.98-1.03)
Xiao X 2020	China:	RCS/	47.0±15.2	1269/2124	At least > 3	Median	554/275	Tertile 1: < 384μmol/l;	Tertile 3 vs. Tertile 1	Age, sex, DM , CVD , BMI ,	ACM: 0.924(0.547-1.727)

[32]	Mainland	Single	42	Tertile 2: 384-460μmol/l;	Tertile 1 vs. Tertile 3:	eGFR, DBP, use of diuretic	ACM: 0.993(0.598-1.651)
	d			Tertile 3: > 460μmol/l.	Per 1μmol/l increase:	and LUA, Hb, Alb, TC.	ACM: 0.999(0.997-1.001)

Abbreviations: AC: All-cause; ACM: All-cause mortality; CV: Cardiovascular; CVM: Cardiovascular mortality; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; RCS: Retrospective cohort study; PCS: Prospective cohort study; vs.: versus; Alb: Serum albumin; DM: Diabetes mellitus; NDM: Non diabetes mellitus; HN: Hypertensive nephropathy; RRF: Residual renal function; CRP: C-reactive protein; BMI: Body mass index; Hb:Hemoglobin; SUA: Serum uric acid; Scr: Serum creatinine; MAP: Mean arterial pressure; BUN: Blood urea nitrogen; P: Serum phosphorus; Na: Serum sodium; Ca: Serum calcium; K: Serum potassium; Cl: Serum chlorine; CO2: Venous carbon dioxide; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; FM: Female; NR:Not reported; TA-UA: Time average-uric acid; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SGA: Subjective global assessment; RASi: Renin-angiotensinsystem inhibitor; LUA: lower uric acid agent; iPTH: intact parathyroid hormone; PD: Peritoneal dialysis; Kt/v: Urea clearance index; GPT: Glutamic-pyruvic transaminase; WBC: White blood cell counts; ALP: Alkaline phosphate; eGFR: estimated glomerular filtration rate; FBG: Fasting blood glucose; FPG: Fasting plasma glucose; PET: Peritoneal equilibration test; CCB: Calcium blocker; NLR: Neutrophil to lymphocyte ratio; ECW/TBW: Extracellular water/Total body water; ASMI: Appendicular skeletal muscle mass index; ESA: Erythropoiesis stimulating agentts; UV: Urinary volume.

518 **Table 2a** Subgroup analyses of cohort studies for the association of serum uric acid with all-cause mortality

	Serum uric acid (categorical variable)				Serum uric acid (continuous variable)				
	No. of study	Sample size	HR (95%CI)	Heterogeneity(I^2)	No. of study	Sample size	HR (95%CI)	Heterogeneity (I^2)	Meta-regression (*P* value)
Study design									*P*=0.007
Prospective cohort study	1	1287	1.79(1.17-2.75)	35.8%	1	1287	1.16(1.03-1.32)	25.5%	
Retrospective cohort study	5	4570	1.09(0.70-1.70)	83.1%	8	11541	0.94(0.88-1.02)	83.7%	
Study location									
China—mainland	4	4683	1.57(1.26-1.96)	21.1%	7	7594	1.04(0.97-1.11)	73.0%	*P*=0.000
China—Taiwan	1	492	0.40(0.24-0.68)	-	1	492	0.70(0.48-1.03)	85.9%	
Other	1 (Portugal)	682	1.00(0.74-1.35)	-	1 (Japan)	4742	1.00(0.89-1.13)	-	*P*=0.002
Publication years									
2011—2016	2	3480	1.53(1.08-2.18)	48.9%	2	3480	1.12(1.01-1.24)	37.9%	*P*=0.017
2017—2021	4	2377	1.07(0.59-1.93)	87.3%	7	9348	0.92(0.84-1.01)	85.5%	
No. of center									*P*=0.539
Single center	5	3664	1.27(0.82-1.98)	83.7%	7	5893	0.97(0.89-1.06)	83.3%	
Multicenter	1	2193	1.21(0.85-1.73)	-	2	6935	1.03(0.96-1.11)	0%	
Adjusted for sex									*P*=0.000
Yes	4	4112	1.27(0.72-2.26)	84.9%	8	11765	0.97(0.90-1.04)	76.7%	
No	2	1745	1.25(0.80-1.95)	76.7%	1	1063	1.13(1.06-1.20)	_	
Adjusted for diabetes mellitus									*P*=0.019
Yes	6	5857	1.26(0.88-1.81)	80.5%	8	12341	1.00(0.94-1.07)	80.0%	
No	0	0	-	-	1	487	0.77(0.62-0.97)	-	
Adjusted for serum albumin									*P*=0.108
Yes	4	5035	1.22(0.76-1.96)	84.7%	7	12201	0.99(0.90-1.09)	81.0%	

No	2	822	1.40(0.62-3.14)	74.4%	2	627	0.90(0.70-1.17)	81.6%

Abbreviations: HR: Hazard ratio; CI: Confidence interval; I^2: I-square; No.: Number.

Table 2b Subgroup analyses of cohort studies for the association of serum uric acid with cardiovascular mortality

	Serum uric acid (categorical variable)				Serum uric acid (continuous variable)			
	No. of study	Sample size	HR (95%CI)	Heterogeneity(I^2)	No. of study	Sample size	HR (95%CI)	Heterogeneity (I^2)
Study design								
Prospective cohort study	1	1287	2.63(1.62-4.27)	0.0%	1	1287	1.34(1.16-1.55)	0.0%
Retrospective cohort study	3	3748	1.00(0.44-2.31)	82.5%	3	7474	0.90(0.76-1.06)	70.2%
Study location								
China—mainland	3	4543	1.93(1.39-2.68)	13.9%	2	3480	1.22(1.05-1.43)	44.6%
China—Taiwan	1	492	0.40(0.20-0.80)	-	1	492	0.71(0.55-0.93)	29.5%
Other					1 (Japan)	4794	1.00(0.91-1.10)	-
Publication years								
2011—2016	2	3480	2.06(1.27-3.34)	38.7%	2	3480	1.22(1.05-1.43)	44.6%
2017—2021	2	1555	0.85(0.20-3.57)	90.8%	2	5234	0.82(0.62-1.08)	77.7%
No. of center								
Single center	3	2842	1.49(0.66-3.38)	84.7%	2	1779	1.06(0.80-1.39)	80.3%
Multicenter	1	2193	1.35(0.74-2.46)	-	2	6935	1.01(0.93-1.09)	0.0%
Adjusted for sex								
Yes	3	3972	1.39(0.60-3.24)	84.4%	4	8714	1.05(0.90-1.23)	74.0%
No	1	1063	1.73(1.03-2.91)	-	0	0	_	_
Adjusted for diabetes mellitus								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8714	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	_	-
Adjusted for serum albumin								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8714	1.05(0.90-1.23)	74.0%

No	0	0	-	-	0	0	_	-			

Abbreviations: HR: Hazard ratio; CI: Confidence interval; I^2: I-square; No.: Number.

Figure legends

Fig.1 Flow diagram of study search and selection.

Fig.2 Forest plot and pooled HR for association of SUA in categories (the highest SUA category versus the lowest) with all-cause mortality in PD patients

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis**.**

Fig.3 Forest plot and pooled HR for association of SUA per 1mg/dl increase with all-cause mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis**.**

Supplement legends

eFigure 1. Forest plot and pooled HR for association of SUA in categories (the highest SUA category versus the lowest) with cardiovascular mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis**.**

eFigure 2. Forest plot and pooled HR for association of SUA per 1mg/dl increase with cardiovascular mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis**.**

eFigure 3. Funnel plot for association of serum uric acid level per 1mg/dl increase with all-cause mortality in peritoneal dialysis patients.

eTable 1. Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

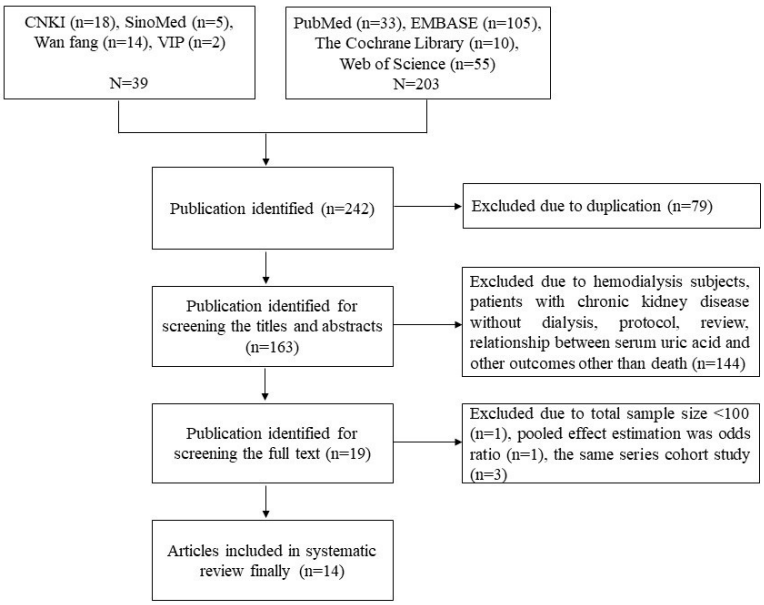

Fig.1 Flow diagram of study search and selection.

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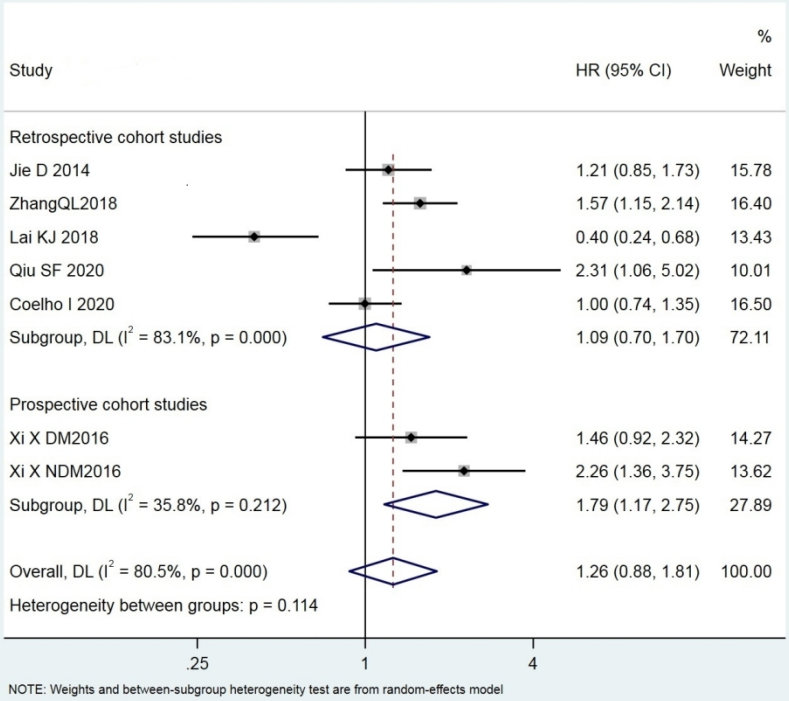

Fig.2 Forest plot and pooled HR for association of SUA in categories (the highest SUA category versus the lowest) with all-cause mortality in PD patients
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

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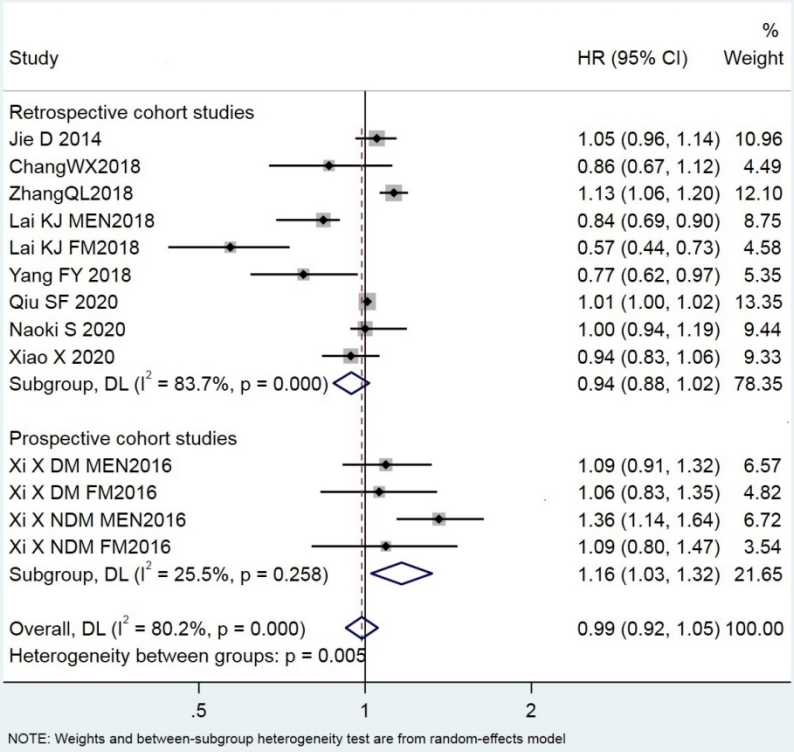

Fig.3 Forest plot and pooled HR for association of SUA per 1mg/dl increase with all-cause mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Famale; PD: Peritoneal dialysis.

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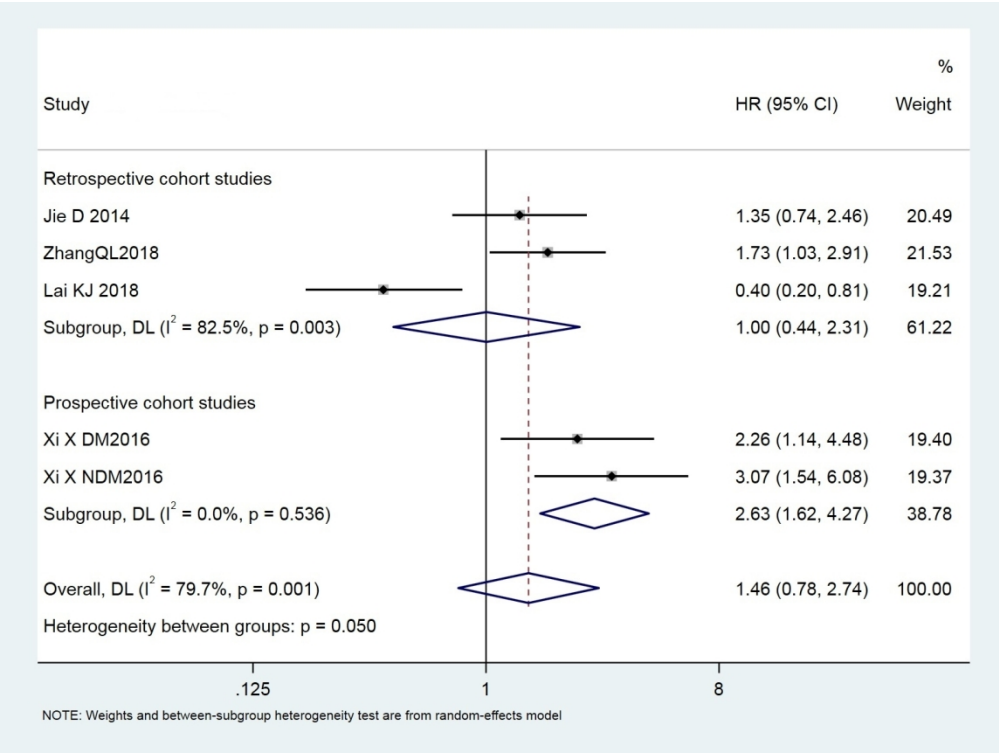

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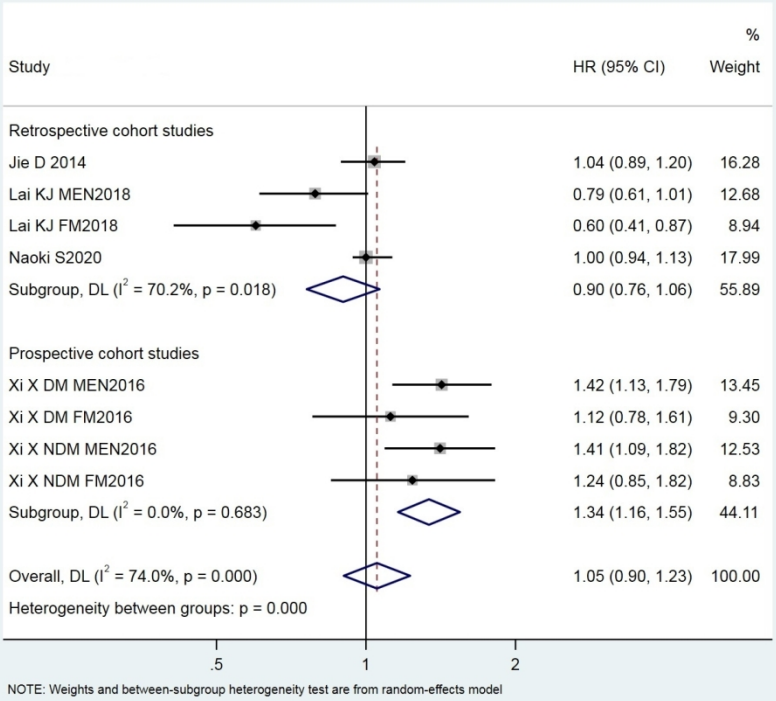

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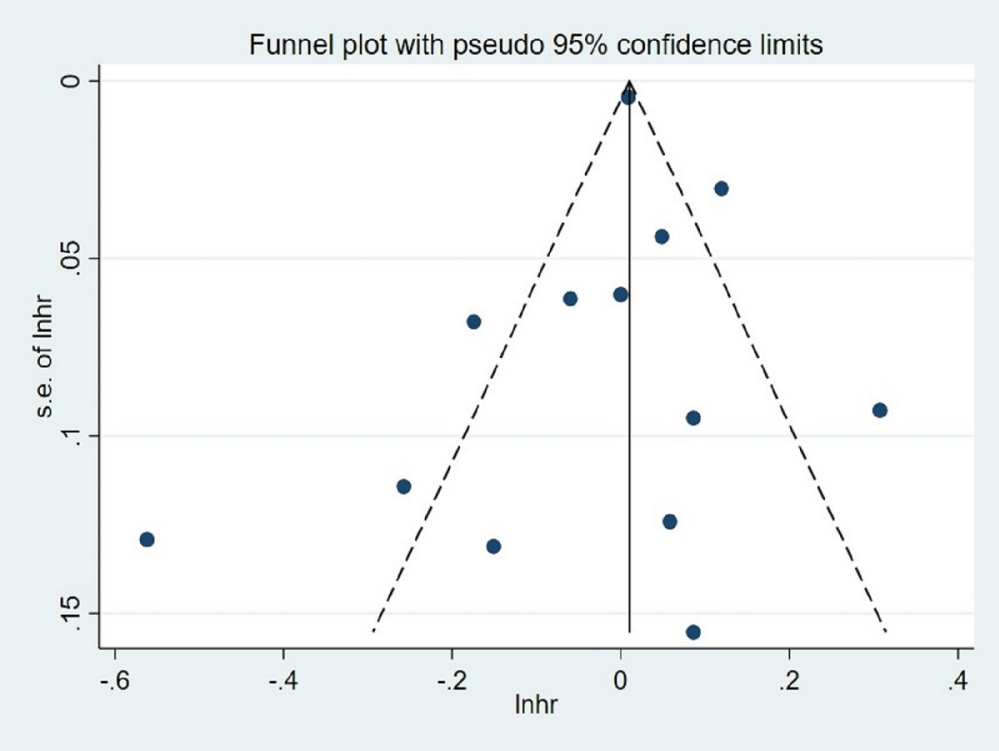

101x76mm (300 x 300 DPI)

eTable 1 Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

Study ID	Selection				Comparability	Outcome			Total score
	Representativeness of exposed group	Representativeness of non-exposed group	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of groups on the basis of design or analysis	Assessment of outcome	Follow up long enough	Adequacy of follow-up of groups	
Sheng F 2013[25]	☆	☆	☆	☆	☆	☆	☆	-	7
Jie D 2014[14]	☆	☆	☆	☆	☆	☆	☆	☆	8
Xi X 2016[21]	☆	☆	☆	☆	☆	☆	☆	☆	8
Eunjin B2016[26]	☆	☆	☆	☆	-	☆	☆	☆	7
ChangWX2018[27]	☆	☆	☆	☆	☆	☆	☆	☆	8
ZhangQL2018[28]	☆	☆	☆	☆	☆	☆	☆	-	7
Lai KJ 2018[29]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yang FY 2018 [30]	☆	☆	☆	☆	☆	☆	☆	-	7
ChangWX2019[31]	☆	☆	☆	☆	☆	☆	☆	-	7
Xiang SL 2019[32]	☆	☆	☆	☆	☆	☆	☆	☆	8

Qiu SF 2020[33]	☆	☆	☆	☆	☆	☆	☆	-	7
Coelho I 2020[34]	☆	☆	☆	☆	☆	☆	☆	-	7
Naoki S 2020[35]	☆	☆	☆	☆	☆	☆	☆	☆	8
Xiao X 2020[22]	☆	☆	☆	☆	☆	☆	☆	☆	8

MOOSE Checklist——A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Checklist Item	Answer
Reporting of background should include	
Problem definition	Introduction section
Hypothesis statement	Introduction section
Description of study outcome(s)	Introduction section
Type of exposure or intervention used	Introduction section
Type of study designs used	Introduction section
Study population	Introduction section
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	Methods section—Search strategy
Search strategy, including time period included in the synthesis and keywords	Methods section—Search strategy
Effort to include all available studies, including contact with authors	Methods section—Search strategy
Databases and registries searched	Methods section—Search strategy
Search software used, name and version, including special features used (eg, explosion)	Methods section—Search strategy
Use of hand searching (eg, reference lists of obtained articles)	Methods section—Search strategy
List of citations located and those excluded, including justification	Methods section—Search strategy
Method of addressing articles published in languages other than English	Methods section—Search strategy
Method of handling abstracts and unpublished studies	Methods section—Search strategy
Description of any contact with authors	Methods section—Search strategy
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Methods section—Eligibility criteria
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Methods section—Studies selection and data extraction
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Methods section—Statistical analysis

MOOSE Checklist——A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Methods section—Methodological quality assessment
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Methods section—Methodological quality assessment
Assessment of heterogeneity	Methods section—Statistical analysis
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Methods section—Statistical analysis
Provision of appropriate tables and graphics	Results section
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Results section—Fig.1 and Fig.2
Table giving descriptive information for each study included	Results section—Table 1
Results of sensitivity testing (eg, subgroup analysis)	Results section—Additional analysis
Indication of statistical uncertainty of findings	Results section—Additional analysis
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Results section—Additional analysis
Justification for exclusion (eg, exclusion of non–English-language citations)	Results section—Search results
Assessment of quality of included studies	Results section—Methodological quality of included studies
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Conclusions section
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review	Conclusions section
Guidelines for future research	Conclusions section
Disclosure of funding source	Article Information

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.

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Relationship between serum uric acid, all-cause mortality and cardiovascular mortality in peritoneal dialysis patients: systematic review and meta-analysis of cohort studies

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Renal medicine, Evidence based practice
Keywords:	Nephrology < INTERNAL MEDICINE, End stage renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY

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Title Page

Title: Relationship between serum uric acid, all-cause mortality and cardiovascular mortality in peritoneal dialysis patients: systematic review and meta-analysis of cohort studies

Authors： Xue Xue1,2, Chun-li Lu2, Xin-yan Jin2, Xue-han Liu2, MinYang3, Xiao-qin Wang4, Hong Cheng4, Jun Yuan4, Qiang Liu4, Ruo-xiang Zheng2, Nicola Robinson2,5, and Jian-ping Liu2*

1 The First Clinical College and Affiliated Hospital, Hubei University of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

2 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

3 Basic Medical School and Affiliated Hospital, Hubei University of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

4 Department of Nephrology, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

5 Institute of Health and Social Care, London South Bank University, 103 Borough Road, London SE1 0AA, UK

Key words： serum uric acid, all-cause mortality, cardiovascular mortality, peritoneal dialysis, systematic review.

Email addresses: Xue Xue (xue025004138@163.com); Chun-li Lu (annyzhenni@163.com); Xin-yan Jin (20170941260@bucm.edu.cn); Xue-han Liu (xuehan_liu@foxmail.com); MinYang (1750096103@qq.com); Xiao-qin Wang (wangxiao773@

hotmail.com); Hong Cheng (chenghong@hbhtcm.com); Jun Yuan (yjun_92@hbtcm.edu.cn); Qiang Liu (leonjordan23@sina.com); Ruo-xiang Zheng (zhengruox@foxmail.com); Nicola Robinson (nicky.robinson@lsbu.ac.uk); Jian-ping Liu (Liujp@bucm.edu.cn).

***Corresponding**

Jian-ping Liu*

Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China. E-mail: Liujp@bucm.edu.cn

Telephone number: 13718004410.

Word count of full text： 4105.

Abstract

Objectives To analyze the relationship between serum uric acid (SUA), all-cause mortality and cardiovascular (CV) mortality in peritoneal dialysis (PD) patients to inform clinical practice and future research.

Design A systematic review of observational studies.

Data sources PubMed, Embase, Web of Science, the Cochrane Library, CNKI, SinoMed, VIP and Wan Fang electronic databases were searched from their inception to January 2021 for cohort and case-control studies reporting SUA and mortality in PD patients.

Methods Effect estimates were presented as hazard ratios (HR) with 95% confidence intervals (CI) in a meta-analysis using STATA 16.0. Data not suitable for pooling were

synthesized qualitatively.

Results Fourteen cohort studies with 24031 patients were included. No case-control studies were identified. For prospective cohort studies, pooled results for the highest SUA category was significantly greater than the lowest for all-cause (1 study; 1287 participants; HR 1.79; 95%CI 1.17-2.75) and CV mortality (1 study; 1287 participants; HR 2.63; 95%CI 1.62-4.27). An increase of 1mg/dl in SUA level was associated with a 16% increased risk of all-cause mortality (1 study; 1287 participants; HR 1.16; 95%CI 1.03-1.32) and 34% increased CV mortality risk (1 study; 1287 participants; HR 1.34; 95%CI 1.16-1.55). For retrospective cohort studies, the highest SUA category did not demonstrate an elevated all-cause mortality (5 studies; 4570 participants; HR 1.09; 95%CI 0.70-1.70) or CV mortality (3 studies; 3748 participants; HR 1.00; 95%CI 0.44-2.31) compared with the lowest SUA category. Additionally, there was no increase in all-cause mortality (8 studies; 11541 participants; HR 0.94; 95%CI 0.88-1.02) or CV mortality (3 studies; 7427 participants; HR 0.90; 95%CI 0.76-1.06) for every 1mg/dl increase in SUA level.

Conclusions Results of prospective and retrospective cohort studies were inconsistent. Consequently, prospective, multi-center, long term follow-up studies are required to confirm the relationship between SUA and mortality in PD patients.

Strengths and limitations of this study

- This is the first systematic review of observational studies which has explored the relationship between SUA level and mortality in PD patients.
- We used critical appraisal of included studies and subgroup analysis to present the

results, and proposed future research directions based on the results.

- Of the included studies, eleven were conducted in China, two in other Asian countries and one in Europe, this limits the generalizability of our results.
- Dose-response relationship could not be determined from these data.

Introduction

End-stage renal disease (ESRD) is one of the major diseases affecting human health, and causes enormous pressure and burden on medical care and society. One of the effective treatments for ESRD is peritoneal dialysis (PD) which is characterized by enabling stable hemodynamics, protecting residual renal function (RRF), and demonstrates good removal of middle molecular toxins, and is associated with a low risk of infection, and can be delivered at home [1]. Currently, PD is widely used globally. The total number of people receiving PD worldwide in 2013 reached approximately 220,000 [2]. Of concern is that patients with ESRD treated with dialysis still have high mortality [3]. The identification of potential risk factors has great significance if patients' prognosis and quality of life is to be improved.

Uric acid (UA) is the final product of purine nucleotide metabolism in humans. Previous studies have demonstrated that elevated serum uric acid (SUA) is closely related to the increased risk of hypertension, peripheral arterial disease, cardiovascular (CV) event and chronic kidney disease (CKD) in the general population [4-7]. Higher SUA levels also appear to be an independent risk factor for all-cause and CV mortality in CKD subjects [8,9]. However， there have been conflicting results about the relationship between SUA level and risk of death among dialysis patients. In the

hemodialysis population, hypouricemia significantly increased mortality [10-12]. Nevertheless, the role of SUA in all-cause and CV mortality in PD patients has been controversial. An elevated SUA level has been shown to be an independent risk factor for all-cause and CV mortality in men treated with PD [13]. Another study showed that the prognostic value of SUA in all-cause and CV mortality was weak in PD patients [14]. Hyperuricemia has also been found to predict lower risk of all-cause mortality in PD patients with lower relative appendicular skeletal muscle [15]. In short, the effect of SUA on the prognosis of PD patients appears to be inconsistent.

Currently, systematic reviews on the relationship between SUA, all-cause and CV mortality in the PD population are lacking. We hypothesized that there may be an independent correlation between elevated SUA level and mortality in participants with PD. Thus, we systematically analyzed available studies to determine whether this hypothesis could be confirmed.

Methods

The methods in this review were specified in advance. The review was reported according to the "Meta-analysis of Observational Studies in Epidemiology guidelines" (MOOSE) [16].

Eligibility criteria

Types of studies

Cohort and case-control studies were identified.

Participants

Participants had to receive PD for more than 3 months. There was no restriction on the

type of PD, including continuous ambulatory PD, intermittent PD, automated PD, continuous cyclic PD and tidal PD.

Exposure factor

Hyperuricemia in PD population was the exposure factor in this study. Either categorization according to baseline SUA level or time-average SUA concentration was acceptable. Definition of hyperuricemia and the categorization for the SUA level was based on the definition reported in each included article.

Outcome

The primary outcome was all-cause mortality and death was determined by the hospital medical record or death certificate.

The secondary outcome was CV mortality, defined as a "CV events": coronary events (myocardial infarction, unstable angina), cardio myopathy, cardiac arrest, cardiac dysrhythmia, congestive heart failure, ischemic brain injury, cerebrovascular accident and peripheral vascular disease. The cause of death was determined through medical history, hospital medical records or death certificates.

Exclusion criteria

(1) Unable to obtain the following information from the original article. Hazard ratio (HR) and its corresponding 95% confidence interval (CI) (or other data required in order perform the calculation) for all-cause or CV mortality for 1mg/dl change in SUA level, or for the highest versus lowest SUA category or the lowest versus highest category; (2) Cohort studies with a total sample size of less than 100 participants; (3) Studies originating from the same cohort sample, or part of a cohort sample that had

been previously published. Only the literature which reported the largest sample size and the longest follow-up could be included.

Search strategy

Two authors (X.X. and H.C.) searched the following Chinese and English databases from their inception to 15th January 2021. Chinese databases included China National Knowledge Infrastructure (CNKI), SinoMed, Chinese Science and Technology Journal Database (VIP), and Wan Fang Database. English databases included PubMed, EMBASE, the Cochrane Library, and Web of Science. Trial registers including Clinical Trials. gov and the World Health Organization International Clinical Trials Registry Platform were also searched. Additionally, related reviews, conference papers, references lists and gray literatures were also searched manually. No language or publication type was imposed, published abstracts were also considered. If the retrieved literature had missing information, it was necessary to contact the author via email to obtain the data to ensure that literature could be included. Taking "PubMed" as an example, the searching strategy was as follows: ("Uric Acid"[Mesh] OR "Uric Acid" [Title/Abstract] OR "serum uric acid"[Title/Abstract]) AND ("Mortality"[Mesh] OR "Mortality"[Title/Abstract]) AND (" Peritoneal Dialysis"[Mesh] OR "Peritoneal Dialysis"[Title/Abstract] OR "PD"[Title/Abstract] OR "continuous ambulatory PD" [Title/Abstract] OR "CAPD"[Title/Abstract] OR "intermittent PD"[Title/Abstract] OR "IPD"[Title/Abstract] OR "automated PD"[Title/Abstract] OR "APD"[Title/Abstract] OR "continuous cyclic PD"[Title/Abstract] OR "CCPD"[Title/Abstract] OR "tidal PD"[Title/Abstract] OR "TPD"[Title/Abstract]). The searching strategies for other

databases are presented in eTable1 in the Supplement.

Studies selection and data extraction

The titles and the abstracts were initially screened, then the full-text versions were checked according to the inclusion and exclusion criteria. Two authors (X.X. and Q.L.) examined the full text to identify the eligible studies independently. Two authors (X.X. and H.C.) extracted data independently and entered information into a data extraction sheet. Disagreements on study selection and data extraction were resolved by consulting corresponding author JP Liu. The following information was extracted from each included study: first author, publication year, age, gender, study design, dialysis duration, sample size, study location, center, length of follow up, categories according to SUA, comparison, adjustments, and adjusted HR (95%CI).

Methodological quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to appraise the quality of observational studies [17]. NOS allocates a maximum of 9 points for quality of selection, comparability, and outcome of study population. Two authors (X.X. and X.Y.J.) appraised the quality of included studies independently. Any disagreements were resolved by discussion with corresponding author JP Liu. Overall study quality scores were defined as poor (0–3), fair (4–6), or good (7–9).

Statistical analysis

SUA was analyzed not only as a categorical variable, but also as a continuous variable in the included studies. The statistical analysis for the overall relationship between SUA level and death risk (all-cause and CV mortality) were based on the random effects

model and on comparisons of the highest versus the lowest category of SUA level, or by increase of 1mg/dl. HR and 95% CI were used as effect indicators. HR and corresponding 95% CI of each study were transformed to their natural logarithm (lnHR, lnlCI and lnUCI), and overall HR and its 95% CI was calculated by exponentiation of the pooled lnHR, lnlCI and lnUCI.

If data on cases, person-years, and HR and 95% CI for each category were available in the included studies, then a dose-response analysis would be performed to further explore the relationship between SUA and mortality. The potential non-linearity association was examined by modeling SUA levels using restricted cubic splines with three knots at 25, 50, and 75% of the distribution. We assigned the median or middle point of the upper and lower boundaries in each category as the corresponding dose to the related HR for each study. In general, if there is a dose-response relationship between SUA and mortality, and *P* value for non-linear < 0.05, non-linear regression model should be considered. When the *P* value was close to the critical value of 0.05, both linear and non-linear models needed to be fitted.

The square (I^2) was applied to test the statistical heterogeneity among studies (Higgins and Thompson, 2003) [18]. When $I^2 > 85\%$, we believed that the results could not be pooled. Data not suitable for statistical pooling were synthesized qualitatively. To explore the source of heterogeneity among studies, subgroup analyses were conducted according to study design, study location, publication years, adjustment for sex, adjustment for DM and adjustment for albumin. Additionally, the meta-regression analysis was also performed to detect potential heterogeneity based on the above

variables when about 10 studies were included. Sensitivity analysis was performed removing one study at a time to explore the robustness of results if data were available. The possibility of publication bias was detected by funnel plots and Egger's test if there were about 10 studies. STATA16.0 software (StataCorp, College Station, Texas, 77845 USA) was used for data analysis.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our study.

Results

Search results

Two hundred and forty-two relevant citations were retrieved. After scanning the full texts, five articles were excluded. Cohort samples from the same study were excluded [13,15,19], and only the studies with the largest sample size and the longest follow-up time were included [20,21]. In addition, a published abstract was excluded, because the total sample size of the entire cohort was only 60 participants [22]. Another study was excluded due to its pooled effect estimation which was reported as an odds ratio (OR) with 95% CI [23]. Finally, fourteen studies were eligible for this review. Details of the search and selection process are illustrated in Fig.1.

Characteristic of included trials

A total of fourteen studies consisting of 24031 participants were included [14,20,21,24-34]. All were cohort studies, including prospective and retrospective studies. The main characteristics of included studies are given in Table 1 and Table2.

Methodological quality of included studies

The overall quality of included studies was good with a mean NOS score of 7.57 (range 7–9). All studies scored greater than or equal to 7 (eTable2 in the Supplement). In terms of "comparability", the most important confounding factors that required adjustment were: estimated glomerular filtration rate (eGFR) or serum creatinine (Scr) or urinary volume (UV) or residual renal function (RRF). The above indicators can reflect the patient's current residual renal function status. In addition, according to the literature and clinical observations, other confounding factors needing adjustment should include gender, age, diabetes history, cardiovascular disease (CVD) history, Kt/v (urea clearance index, representing dialysis adequacy), use of UA-lowering drugs, and serum albumin (representing nutritional status).

Primary outcome

Relationship between serum uric acid by categories and all-cause mortality

In order to reduce the heterogeneity of methodology, we discussed the results according to different study designs. For prospective cohort studies, the summary HR and 95% CI of all-cause mortality for the highest SUA category compared with the lowest category came from one study which included 1287 patients [20]. As presented in Fig.2, the pooled result of the highest SUA category was significantly higher than the lowest for all-cause mortality (HR 1.79; 95% CI 1.17-2.75).

In retrospective cohort studies, five studies with 4570 patients reported HR and 95% CI of all-cause mortality for the highest versus the lowest SUA category [14,27,28,32,33]. All cause mortality (HR 1.09; 95% CI 0.70-1.70; Fig.2) was not

significantly elevated compared with the lowest category of PD patients.

HR and corresponding 95% CI were reported in three retrospective cohort studies for the lowest versus the highest SUA category [25,26,30]. Among them, the data from one article [26] was supplemented by the corresponding author via e-mail. The pooled HR was 1.52 (95%CI 0.79-2.89), with heterogeneity of I^2=32.8%.

Relationship between serum uric acid per 1mg/dl increase and all-cause mortality

Only one prospective study with 1287 PD patients reported HR and 95% CI of all-cause mortality for every 1mg/dl increase in SUA level [20]. The pooled result showed that for every 1mg/dl increase in SUA level, risk of all-cause death increased by 16% (HR 1.16; 95%CI 1.03-1.32; Fig.3).

For the retrospective cohort studies, eight studies with 11541 PD patients reported HR and 95% CI of all-cause mortality for every 1mg/dl increase in SUA level [14,21,26-29,32,34]. When the units of SUA concentration in the literature were different, 60 μ mol/l was approximately equal to 1mg/dl. In short, each 1mg/dl increase in SUA level did not appear to significantly increase the risk of all-cause mortality in the PD population (HR 0.94; 95% CI 0.88-1.02; Fig.3).

Dose-response relationship between serum uric acid and all-cause mortality

Most of the included studies [14,20,21,25,27,29,30,32-34] only reported the number of outcomes for the entire cohort population. It was not possible to obtain the number of all-cause and CV deaths and person-years for each category. We tried our best to contact authors by email or phone in order to acquire the necessary data for the non-linearity test, only one author responded and provided relevant data [26]. A dose-

response analysis was not possible.

Secondary outcome

Relationship between serum uric acid by categories and cardiovascular mortality

One prospective cohort study with 1287 patients reported HR and 95% CI of CV mortality for the highest SUA category compared with the lowest [20]. The pooled result of HR comparing the highest versus the lowest category was 2.63 (95% CI 1.62-4.27). (Fig.4).

Three retrospective cohort studies with 3748 patients reported HR and 95% CI of CV mortality for the highest versus the lowest SUA category [14,27,28]. The highest SUA category was no more in terms of elevated CV mortality (HR 1.00; 95% CI 0.44-2.31) compared with the lowest category of PD patients. (Fig.4).

Relationship between serum uric acid per 1mg/dl increase and cardiovascular mortality

One prospective cohort study with 1287 patients reported HR and 95% CI of CV mortality for per 1mg/dl increase in SUA level [20]. An increase of each 1mg/dl in SUA level was associated with a 34% increased risk of CV mortality (HR 1.34; 95%CI 1.16-1.55). (Fig.5).

Three retrospective cohort studies with 7427 patients reported HR and 95% CI of CV mortality per1mg/dl increase in SUA level [14,28,34]. Meta-analysis showed that each 1 mg/dl increase in SUA level did not appear to significantly increase the risk of CV death in PD population (HR 0.90; 95% CI 0.76-1.06). (Fig.5).

Additional analysis

Subgroup analysis and meta-regression

We explored the source of heterogeneity through subgroup analysis and meta-regression. Subgroup analysis only included literature which compared the highest versus the lowest category of SUA level, or explored a change of 1mg/dl increase. The pooled HR (95% CI) and I^2 of subgroup analysis of the relationship between SUA and all-cause and CV mortality are presented in Table 3 and Table 4, respectively.

As mentioned before, whether SUA was a categorical variable or a continuous variable, the results of the prospective cohort study differed from those of retrospective studies. Besides, combined with the results of subgroup analysis, when SUA was estimated as a categorical variable, the association of higher SUA level with increased all-cause and CV mortality was significant in studies from mainland China, but not in other countries. SUA as a continuous variable showed that the relationship of higher CV mortality for 1 mg/dl increase in SUA level was significant in studies from mainland China, but not elsewhere. Furthermore, we analyzed the relevant studies published in the past ten years, and results of studies completed during 2011-2016 were different from the results during 2017-2021 period.

In addition, in studies of the relationship between SUA (as a continuous variable) and all-cause mortality, study design, study location, publication years, adjusted for sex and DM were heterogeneous by meta-regression (Table 3).

Test of Publication bias

Funnel plots and Egger's test (t=1.07, p=0.309) indicated there was no obvious publication bias of studies for the relationship between all-cause mortality and SUA level per 1mg/dl increase. The funnel plot is presented in eFigure1 in the Supplement.

Sensitivity analysis

In retrospective cohort studies, results of primary outcome showed there was no significant effect on the pooled HR values of other studies with one study removed at a time. The above indicated the results were robust.

Discussion

Principal findings and comparison with prior reviews

For PD population, previous original studies indicated inconsistent relationship between SUA and mortality. After searching systematically, we found that there were some meta-analyses investigating the correlation between SUA and mortality in different populations [35-38], however, we have not yet found a review only of PD patients. A systematic review published in 2016 showed that elevated SUA level was significantly associated with the risk of death in patients with CKD, including dialysis and non-dialysis subjects [39]. Subgroup analysis in this review demonstrated that hyperuricemia was an independent predictor for mortality in PD population, while, this predictive value was not found in the hemodialysis (HD) population. As only 1 prospective cohort study and 2 retrospective cohort studies were included in the subgroup analysis, results should be interpreted with caution.

In our study, we included a total of 14 cohort studies, of which 2 were prospective studies and 12 were retrospective studies. There was no obvious publication bias of studies according to funnel plots and Egger's test. Researchers can not control the process of data accumulation in retrospective cohort studies, but researchers can directly acquire relevant data on exposure and outcome according to the study design

in prospective studies, so the risk of bias is small. Thus, instead of pooling results of the two studies, we reported them individually. Only one prospective cohort study suggested that regardless of whether SUA was estimated as a continuous or a categorical variable, elevated SUA level was significantly associated with increased risk of all-cause and CV mortality in PD patients. Whereas, there was no significant associations between them in the retrospective studies. Below we have attempted to discuss the inconsistency of the results from the aspects of participants, exposure, comparability and outcomes.

First of all, the prospective cohort study clearly indicated that participants on PD were consecutively enrolled. It is well known that consecutive recruitment is very important to reduce selection bias. While, in some retrospective studies, the process of enrollment was not detailed. The follow-up of the participants was also a prominent issue, including the duration and adequacy of follow-up and the rate of loss to follow-up. In a prospective study, effective measures can be taken to reduce the loss to follow-up rate to avoid bias. The rate of loss to follow-up in a prospective study by Xia X et al. (2016) was only 3.5% [20], but in some retrospective cohorts, the adequacy and lost follow-up rates were not reported.

Second, hyperuricemia in the PD population was the exposure factor of this study. Both prospective and retrospective cohort studies, the definition of hyperuricemia and the categorization for the SUA level was based on the definition provided in each included article. It should be noted that in retrospective multi-center studies, the measurement methods of SUA may not be uniform across centers. This may lead to

measurement bias and have a slight impact on results.

Third, control of the most important and other confounding factors is very important for the comparability between the groups. The most important confounding factors included indicators that can reflect the patient's current residual renal function status. Other confounding factors need to be adjusted and should include gender, age, diabetes history, CVD history, Kt/v, use of UA-lowering drugs, and serum albumin. Most of the studies did not adjust for all potential risk factors. For example, the prospective study of Xia X et al. (2016) lacked adjustment for the confounding factor Kt/v [20]. Therefore, we can not exclude the potential impact of these uncontrolled confounding factors.

Regarding the outcomes, the definition of all-cause and cardiovascular death was clear. However, the handling of patients transferring to hemodialysis therapy, loss to follow-up, and renal transplantation was different for prospective and retrospective studies. The above information from patients was used as censoring data for survival analysis in the prospective study [20]. Whereas, in some retrospective studies, they were directly excluded from the study [32]. This may affect the results and lead to inconsistencies between the prospective and retrospective studies. Although the risk of bias in the design type of prospective study was relatively small, the interpretation of the results should still be cautious due to the limited quality and quantity of prospective study.

SUA, known for its detrimental effect, is an endothelial toxin and plays a role in endothelial dysfunction [40]. However, as a powerful free radical scavenger in human

at the same time, SUA may be expected to offer a number of benefits within the CV system in PD patients [41,42]. Besides, the problem of protein loss and malnutrition is prominent in PD population [43]. "Malnutrition-inflammation complex syndrome (MICS)" is believed to be the main cause of the high rate of CV atherosclerotic disease and increased mortality and hospitalization in HD patients [44,45]. The underlying mechanism of MICS may also be present in PD patients. As a nutritional marker，SUA might be involved in the MICS axis. Therefore, the relationship between SUA and mortality in PD patients is a complex proposition. Taking into account the feature of SUA itself, we hypothesize that both extremely low and high SUA level may increase the risk of death. In our study, we also would like to explore the dose-response relationship between SUA level and mortality in PD population, but in the end the analysis to explore a dose-response relationship was impossible due to insufficient data. Further investigations are warranted to clarify this relationship and explore the range of SUA concentration associated with the lowest mortality in the PD patients.

Moreover, in addition to different study designs, different study location was also one of the main sources of heterogeneity among studies according to the meta-regression test. Subgroup analysis results further suggested hyperuricemia was associated with a high risk of CV death in PD population only in mainland China. As a result, the relationship between SUA level and the risk of death in different regions needs to be explored and verified by prospective studies in future.

Implications further research

Since the results of prospective and retrospective cohort studies were inconsistent, and

the different regions seemed to lead to different results, prospective, multicenter, long term follow-up studies are required in future. It is important to explore the relationship between SUA level and the risk of death in different regions, as well as to determine the range of SUA concentrations which can reduce mortality and improve prognosis in the PD patients.

Additionally, since PD patients often suffer from underlying diseases and complex conditions, adjustment is required for confounding factors to explore the relationship between these factors and prognosis. For the PD population, the following confounding factors should be considered to make the evidence more compelling. Such as: traditional independent risk factors of CV events (age, gender, total lipoprotein cholesterol, low or high density lipoprotein cholesterol, hypertension, diabetes, smoking [46]), history of CV, emotion status, residual renal function, the related parameters of PD, the parameters of nutritional status, use of diuretic and lower UA agents etc.

Comprehensive information should be reported in detail in the study report so that readers can become more familiar with the details of the study, and can conduct secondary research to avoid wasting research resources.

Study limitations

There were several limitations in this review. Systematic reviews of observational studies can provide a higher level of evidence, but they also have methodological limitations. For example, the included original studies may differ in their design, data collection methods, and definitions of exposure, confounding factors and outcomes.

These differences may have a slight influence on the true effect size. Second, in this review, the included studies were mainly from Asian populations (only one from Europe), and the generalizability of the results was limited. Third, in spite of many important confounding factors that to be adjusted in the studies, residual and unknown confounding factors can not be entirely excluded. Fourth, the duration of follow up in all studies was less than 5 years. It is difficult to determine long-term impact of elevated SUA level on mortality. Finally, some necessary data was not obtained, and the exploration of dose-response relationship could not be conducted, but will need to be determined in future studies.

Conclusions

The results from the prospective and retrospective cohort studies were inconsistent. Only one prospective cohort study showed that elevated SUA level was significantly associated with increased risk of all-cause and CV mortality in PD patients. Nevertheless, the pooled result of retrospective cohort studies did not appear to indicate a prominent association. So it is necessary to use SUA-lowering agents with caution for PD patients in clinics. International prospective, multicenter, long term follow-up studies are needed in the future to investigate the relationship between SUA level and the risk of death, and to explore the range of SUA concentrations associated with the lowest mortality in the PD patients.

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Author Contributions Research idea and study design: XX and JPL. Protocol and

Registration: XX, CLL, XYJ and XHL. Acquisition, analysis, or interpretation of data: XX, HC, QL, JY, and JPL. Drafting of the manuscript: XX, XHL, CLL, XYJ and RXZ. Statistical analysis: MY, XX and XQW. Critical revision of the manuscript: XQW, NR and JPL. Supervision: JPL.

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Competing interests None.

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Ethics approval statement

Dear editors,

Our study was to systematically evaluate the relationship between serum uric acid, all-cause and cardiovascular mortality in peritoneal dialysis patients based on the observational studies that have been published. As the nature of the study, ethics approval is not applicable for this study.

With best regards,

Yours sincerely,

(Corresponding author)

Jian-ping Liu,

Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

E-mail: LiuJP@bucm.edu.cn

Table 1 Characteristics of included studies (2013-2018 years)

Study ID	Study location (Region)	Study design/ Center	Age (years)	Male/ Total Sample(n)	Dialysis duration (months)	Follow-up (months)	Deaths AC/CV (n)	Definition of hyperuricemia or categories according to serum uric acid	Comparison	Adjustments	Adjusted HR (95%CI)
Sheng F 2013 [24]	China: Mainland	RCS/ Single	54.1±17.4	98/156	31.3±17.5	31.3±17.5	41/23	Group 1:≤7.0mg/dl; Group 2: 7.0-10.0 mg/dl; Group 3: ≥10.0 mg/dl.	Group 1 vs. Group 2 Group 3 vs. Group 2	Age, Alb, DM, HN, RRF , phosphate , Log CRP	ACM: 1.15(0.20-2.57) ACM: 2.96(1.29-6.80)
Jie D 2014 [14]	China: Mainland	RCS/ 7 centers	58.1±15.5	1078/2193	At least > 3	Median 26.5	586/231	Men: Tertile 1: 2.09-5.79mg/dl; Tertile 2: 5.80-7.38 mg/dl; Tertile 3: 7.39-16.7 mg/dl. FM: Tertile 1: 1.74-5.37mg/dl; Tertile 2: 5.38-6.65 mg/dl; Tertile 3: 6.66-8.08 mg/dl.	Tertile 3 vs. Tertile 1 (Gender-specific) Tertile 2 vs. Tertile 1 (Gender-specific) Per 1 mg/dl increase	Age, RRF, Hb, Alb, phosphate, LDLC, CRP, histroy of CVD and DM, BMI, MAP, center size, gender adjusted only SUA as continuous variable.	ACM: 1.21(0.85-1.73) CVM: 1.35(0.74-2.46) ACM: 1.23(0.90-1.70) CVM: 1.29(0.75-2.23) ACM: 1.05(0.96-1.14) CVM: 1.04(0.89-1.20)
Xin X 2016 [20]	China: Mainland	PCS/ Single	47.6±15.0	757/1287	At least > 3	Median 30.7	231/126	Men: Tertile 1: < 6.46mg/dl; (DM)Tertile 2: 6.46-7.38 mg/dl; Tertile 3: ≥7.38 mg/dl. Men: Tertile 1: < 7.00mg/dl; (NDM)Tertile2: 7.70-7.89mg/dl; Tertile 3: ≥7.89 mg/dl. FM: Tertile 1: < 5.89mg/dl; (DM)Tertile 2: 5.89-7.09 mg/dl ; Tertile 3: ≥7.09 mg/dl. FM: Tertile 1: < 6.46mg/dl; (NDM)Tertile2: 6.46-7.48mg/dl; Tertile 3: ≥7.48 mg/dl.	Tertile 3 vs. Tertile 1 (DM: Gender specific) Tertile 3 vs. Tertile 1 (NDM: Gender specific) Per 1 mg/dl increase	Age, gender, BMI, history of CVD and hypertension, Hb, Alb, Scr, P, HDL-C; RRF, log-transformed Hs-CRP, glycated Hb, use of allopurinol and ACEI or ARB.	ACM: 1.46(0.92-2.32) CVM: 2.26(1.14-4.48) ACM: 2.26(1.36-3.75) CVM: 3.07(1.54-6.08) ACM (DM, MEN):1.09(0.91-1.32); ACM (DM, FM):1.06(0.83-1.35); ACM(NDM, MEN):1.36(1.14-1.64); ACM (NDM, FM):1.09(0.80-1.47); CVM (DM, MEN):1.42(1.13-1.79); CVM (DM, FM):1.12(0.78-1.61); CVM(NDM, MEN):1.41(1.09-1.82); CVM (NDM, FM):1.24(0.85-1.82).
Eunjin B2016 [25]	South Korea	PCS/mult -icenter	NR	NR/651	At least > 3	Median 43.9	AC 106	Group 1: TA-UA<5.5 mg/dl; Group 2: TA-UA≥5.5 mg/dl.	Group 1 vs. Group 2	Age, sex, BMI, SBP, Ca, P, Alb, TC, DM, SGA.	ACM: 1.478(0.602-3.627)
ChangWX2018 [26]	China: Mainland	RCS/ Single	55.2±14.9	171/300	At least > 3	22.6±15.9	AC 44	Group1: TA-UA < 6mg/dL; Group2: TA-UA 6–8mg/dL; Group3: TA-UA ≥8mg/dL.	Group 3 vs. Group 2 Group 1 vs. Group 2 Group 1 vs. Group 3	Sex, age, DM, CVD history, RRF, BMI, SBP, Hb, Alb, BUN, SCr, Na, K, CO2, Ca,	ACM: 4.69(1.24-17.72) ACM: 3.24(1.25-8.39) ACM: 0.603 (0.158-2.309)

									Per 1 mg/dl increase (Baseline-UA)	P, LDL-C, CRP, RASi, diuretic.	ACM: 0.86(0.67-1.12)
ZhangQL2018 [27]	China: Mainland	RCS/ Single	Median 51	557/1063	At least > 6	Median 33	167/64	Group 1: < 420μmol/l; Group 2: ≥420μmol/l; Hyperuricemia≥420μmol/l	Group 2 vs. Group 1 Per 1 μmol/l increase	Age, Scr, P, Alb, BG, iPTH, history of DM, DBP, Charlson score.	ACM: 1.572(1.155-2.141) CVM: 1.734(1.033-2.912) ACM: 1.002(1.001-1.004)
Lai KJ 2018 [28]	China: Taiwan	RCS/ Single	53.5±15.3	237/492	At least > 3	Median 36.4	127/74	Men: Tertile 1: ≤6.8mg/dl; Tertile 2: 6.9-8mg/dl; Tertile 3: ≥8.1mg/dl. FM: Tertile 1: ≤6.5mg/dl; Tertile 2: 6.6-7.6mg/dl; Tertile 3: ≥7.7mg/dl.	Tertile 3 vs. Tertile 1 (Gender-specific) Tertile 2 vs. Tertile 1 (Gender-specific) Men: Per 1mg/dl increase	Age, sex, BMI, pre-dialysis status, smoking, present medications, comorbidities of CVD, hyper-tension, DM, Charlson score, PD related parameters, Kt/v, BUN, Scr, GPT, WBC, ALP, Alb, Hb, ferritin, TC, TG, Ca, P, iPTH, transferrin saturation.	ACM: 0.4(0.24-0.68) CVM: 0.4(0.2-0.81) ACM: 1.06(0.7-1.58) CVM: 1.04(0.62-1.77) ACM: 0.84(0.69-0.9) CVM: 0.79(0.61-1.01) ACM: 0.57(0.44-0.73) CVM: 0.6(0.41-0.87)
Yang FY 2018 [29]	China: Mainland	RCS/ Single	51.8±14.4	232/487	Median 29.5	Median 29.5	197/109	Men: Hyperuricemia≥7mg/dl; FM: Hyperuricemia≥6mg/dl.	Men: Hyperuricemia≥7mg/dl FM: Per 1 mg/dl increase	Sex,, BMI, hypertension , dialysis duration, eGFR, Kt/v, LDL-C, iPTH.	ACM: 0.773(0.62-0.97)

Abbreviations: AC: All-cause; ACM: All-cause mortality; CV: Cardiovascular; CVM: Cardiovascular mortality; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; RCS: Retrospective cohort study; PCS: Prospective cohort study; vs.: versus; Alb: Serum albumin; DM: Diabetes mellitus; NDM: Non diabetes mellitus; HN: Hypertensive nephropathy; RRF: Residual renal function; CRP: C-reactive protein; Hb:Hemoglobin; BMI: Body mass index; SUA: Serum uric acid; Scr: Serum creatinine; MAP: Mean arterial pressure; P: Serum phosphorus; HDL-C: High density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; FM: Female; NR:Not reported; TA-UA: Time average-uric acid; SBP: Systolic blood pressure; Ca: Serum calcium; TC: Total cholesterol; SGA: Subjective global assessment; BUN: Blood urea nitrogen; Na: Serum sodium; K: Serum potassium; Cl: Serum chlorine; CO2: Venous carbon dioxide; LDL-C: Low density lipoprotein cholesterol; RASi: Renin-angiotensinsystem inhibitor; BG: Blood glucose; iPTH: intact parathyroid hormone; DBP: Diastolic blood pressure; PD: Peritoneal dialysis; eGFR: estimated glomerular filtration rate; Kt/v: Urea clearance index; GPT: Glutamic-pyruvic transaminase; WBC: White blood cell counts; ALP: Alkaline phosphate; TG: Triglyceride.

586 **Table 2** Characteristics of included studies (2019-2020 years)

Study ID	Study location (Region)	Study design/ Center	Age (years)	Male/ Total Sample(n)	Dialysis duration (months)	Follow-up (months)	Deaths AC/CV (n)	Definition of hyperuricemia or categories according to serum uric acid	Comparison	Adjustments	Adjusted HR (95%CI)
ChangWX2019 [30]	China: Mainland	RCS/ Single	18—80	150/309	At least > 3	NR	AC 50	Group 1: SUA decliner; Group 2: SUA non-decliner. ("SUA decliner" and "SUA non-decliner" according to run-in and longitudinal changes in the follow-up)	Group 1 vs. Group 2	Gender, age, BMI, SBP, Hb, Na, K, Cl, BUN, Scr, CO2, Ca, P, Alb, TG, FBG, CRP, RRF, PET type, Kt/V, DM, use of CCB, RASi , diuretic , β-blocker.	ACM: 2.23(1.13-4.40)
Xiang SL 2019 [38]	China: Mainland	RCS/ 98centers	52.5±14.6	5163/9405	At least > 3	Median 29.4	1226/515	Quintile1: < 6.06mg/dl; Quintile2: 6.06-6.67mg/dl; Quintile3: 6.68–7.27mg/dl Quintile4: 7.28-8.03mg/dl; Quintile5: ≥8.04 mg/dl. Hyperuricemia≥7.28mg/dl.	Quintile5 vs. Quintile3 Quintile4 vs. Quintile3 Quintile2 vs. Quintile3 Quintile1 vs. Quintile3	Age, sex, BMI, DM, CVD, RRF, Hb, Alb, K, Na, P, Ca, iPTH, Scr, FPG.	ACM: 1.482(1.187-1.849) CVM: 1.144(0.786-1.665) ACM: 1.335(1.073-1.662) CVM: 1.146(0.796-1.648) ACM: 1.160(0.938-1.434) CVM: 1.311(0.932-1.843) ACM: 1.162(0.945-1.427) CVM: 1.166(0.820-1.657)
Gu SF 2020 [32]	China: Mainland	RCS/ Single	44—65	63/140	Median 31.9	Median 31.9	AC 48	Tertile 1: < 387μmol/l; Tertile 2: 387-519μmol/l; Tertile 3: ≥519μmol/l.	Tertile 3 vs. Tertile 1 Tertile 2 vs. Tertile 1 Per 20μmo/l increase	Gender, age, DM , hypertension, CVD, BMI, K, ESA, RRF , use of diuretic and LUA.	ACM: 2.308(1.062-5.017) ACM: 0.959(0.423-2.174) ACM: 1.003(1.00-1.005)
Coelho I 2020 [33]	Portugal	RCS/ Single	60.2±14.6	407/682	At least > 3	31.4±25.6	NR	Group 1: below median; Group 2: above median.	Group 2 vs. Group 1	Age, comorbidities, DM and baseline RRF.	ACM: 0.997(0.74-1.35)
Naoki S 2020 [34]	Japan	RCS/mult-icenter	63±14	2916/4742	Median 28	Deadline : the end of 2012	AC 379	Group 1: < 5.0mg dl; Group 2: 5.0- < 5.5mg dl; Group 3: 5.5- < 6.0mg dl; Group 4: 6.0- < 6.5mg dl; Group 5: 6.5- < 7.0mg dl;	Group 1 vs. Group 3 Group 2 vs. Group 3 Group 3 vs. Group 3 Group 4 vs. Group 3 Group 5 vs. Group 3	Age, gender, BMI ,UV ,dialysis duration, under-lying disease, comorbid disease, medication and laboratory data.	ACM: 1.80(1.13-2.86) ACM: 1.43(0.88-2.32) ACM: 1.22(0.75-1.98) ACM: 1.37(0.86-2.20) ACM: 1.54(0.75-2.49)

									Group 6: 7.0- < 7.5mg dl;	Group 7 vs. Group 6		ACM: 1.58(0.94-2.63)
									Group 7: 7.5- < 8.0mg dl;	Group 8 vs. Group 6		ACM: 1.88(1.06-3.35)
									Group 8: 8.0- < 8.5mg dl;	Group 9 vs. Group 6		ACM: 1.93(1.15-3.24)
									Group 9: ≥8.5mg dl;	Per 10μmo/l increase		ACM: 1.00(0.99-1.02)
												CVM: 1.00(0.98-1.03)
Xiao X 2020 [22]	China: Mainland	RCS/ Single	47.0±15.2	1269/2124	At least > 3	Median 42	554/275	Tertile 1: < 384μmol/l; Tertile 2: 384-460μmol/l; Tertile 3: > 460μmol/l.	Tertile 3 vs. Tertile 1	Per 1μmol/l increase	Age, sex, DM , CVD , BMI , eGFR, DBP, use of diuretic and LUA, Hb, Alb, TC.	ACM: 0.924(0.547-1.727) ACM: 0.993(0.598-1.651) ACM: 0.999(0.997-1.001)

Abbreviations: AC: All-cause; ACM: All-cause mortality; CV: Cardiovascular; CVM: Cardiovascular mortality; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; RCS: Retrospective cohort study; PCS: Prospective cohort study; NR:Not reported; SUA: Serum uric acid; vs.: versus; BMI: Body mass index; SBP: Systolic blood pressure; Hb:Hemoglobin; Na: Serum sodium; K: Serum potassium; Cl: Serum chlorine; BUN: Blood urea nitrogen; Scr: Serum creatinine; CO2: Venous carbon dioxide; Ca: Serum calcium; P: Serum phosphorus; Alb: Serum albumin; TG: Triglyceride; FBG: Fasting blood glucose; CRP: C-reactive protein; RRF: Residual renal function; PET: Peritoneal equilibration test; Kt/v: Urea clearance index; DM: Diabetes mellitus; CCB: Calcium blocker; RASi: Renin-angiotensinsystem inhibitor; iPTH: intact parathyroid hormone; FPG: Fasting plasma glucose; ESA: Erythropoiesis stimulating agentts; LUA: lower uric acid agent; UV: Urinary volume; eGFR: estimated glomerular filtration rate; DBP: Diastolic blood pressure; TC: Total cholesterol.

592 **Table 3** Subgroup analyses of the relationship between serum uric acid and all-cause mortality

	Serum uric acid (categorical variable)				Serum uric acid (continuous variable)				
	No. of study	Sample size	HR (95%CI)	Heterogeneity(I^2)	No. of study	Sample size	HR (95%CI)	Heterogeneity (I^2)	Meta-regression (*P* value)
Study design									*P*=0.007
Prospective cohort study	1	1287	1.79(1.17-2.75)	35.8%	1	1287	1.16(1.03-1.32)	25.5%	
Retrospective cohort study	5	4570	1.09(0.70-1.70)	83.1%	8	11541	0.94(0.88-1.02)	83.7%	
Study location									
China—mainland	4	4683	1.57(1.26-1.96)	21.1%	7	7594	1.04(0.97-1.11)	73.0%	*P*<0.001
China—Taiwan	1	492	0.40(0.24-0.68)	-	1	492	0.70(0.48-1.03)	85.9%	
Other	1 (Portugal)	682	1.00(0.74-1.35)	-	1 (Japan)	4742	1.00(0.89-1.13)	-	*P*=0.002
Publication years									
2011—2016	2	3480	1.53(1.08-2.18)	48.9%	2	3480	1.12(1.01-1.24)	37.9%	*P*=0.017
2017—2021	4	2377	1.07(0.59-1.93)	87.3%	7	9348	0.92(0.84-1.01)	85.5%	
No. of center									*P*=0.539
Single center	5	3664	1.27(0.82-1.98)	83.7%	7	5893	0.97(0.89-1.06)	83.3%	
Multicenter	1	2193	1.21(0.85-1.73)	-	2	6935	1.03(0.96-1.11)	0%	
Adjusted for sex									*P*<0.001
Yes	4	4112	1.27(0.72-2.26)	84.9%	8	11765	0.97(0.90-1.04)	76.7%	
No	2	1745	1.25(0.80-1.95)	76.7%	1	1063	1.13(1.06-1.20)	_	
Adjusted for diabetes mellitus									*P*=0.019
Yes	6	5857	1.26(0.88-1.81)	80.5%	8	12341	1.00(0.94-1.07)	80.0%	
No	0	0	-	-	1	487	0.77(0.62-0.97)	-	
Adjusted for serum albumin									*P*=0.108
Yes	4	5035	1.22(0.76-1.96)	84.7%	7	12201	0.99(0.90-1.09)	81.0%	
No	2	822	1.40(0.62-3.14)	74.4%	2	627	0.90(0.70-1.17)	81.6%	

593 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; I2: I-square; No.: Number.

Table 4 Subgroup analyses of the relationship between serum uric acid and cardiovascular mortality

	Serum uric acid (categorical variable)				Serum uric acid (continuous variable)			
	No. of study	Sample size	HR (95%CI)	Heterogeneity(I^2)	No. of study	Sample size	HR (95%CI)	Heterogeneity (I^2)
Study design								
Prospective cohort study	1	1287	2.63(1.62-4.27)	0.0%	1	1287	1.34(1.16-1.55)	0.0%
Retrospective cohort study	3	3748	1.00(0.44-2.31)	82.5%	3	7427	0.90(0.76-1.06)	70.2%
Study location								
China—mainland	3	4543	1.93(1.39-2.68)	13.9%	2	3480	1.22(1.05-1.43)	44.6%
China—Taiwan	1	492	0.40(0.20-0.80)	-	1	492	0.71(0.55-0.93)	29.5%
Other					1 (Japan)	4742	1.00(0.91-1.10)	-
Publication years								
2011—2016	2	3480	2.06(1.27-3.34)	38.7%	2	3480	1.22(1.05-1.43)	44.6%
2017—2021	2	1555	0.85(0.20-3.57)	90.8%	2	5234	0.82(0.62-1.08)	77.7%
No. of center								
Single center	3	2842	1.49(0.66-3.38)	84.7%	2	1749	1.06(0.80-1.39)	80.3%
Multicenter	1	2193	1.35(0.74-2.46)	-	2	6965	1.01(0.93-1.09)	0.0%
Adjusted for sex								
Yes	3	3972	1.39(0.60-3.24)	84.4%	4	8714	1.05(0.90-1.23)	74.0%
No	1	1063	1.73(1.03-2.91)	-	0	0	_	_
Adjusted for diabetes mellitus								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8714	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	_	-
Adjusted for serum albumin								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8714	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	_	-

Abbreviations: HR: Hazard ratio; CI: Confidence interval; I2: I-square; No.: Number.

Figure legends

Fig.1 Flow diagram of study search and selection.

Fig.2 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and all-cause mortality in PD patients

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis**.**

Fig.3 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis**.**

Fig.4 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and cardiovascular mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis**.**

Fig.5 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis**.**

Supplement legends

eFigure 1. Funnel plot for relationship between serum uric acid level per 1mg/dl increase and all-cause mortality in peritoneal dialysis patients.

eTable 1. Searching strategies for electronic databases

eTable 2. Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

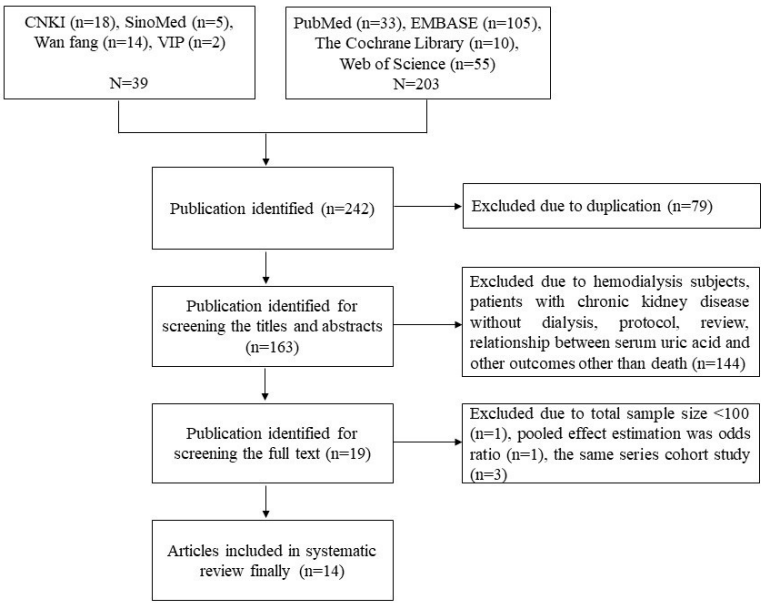

Fig.1 Flow diagram of study search and selection.

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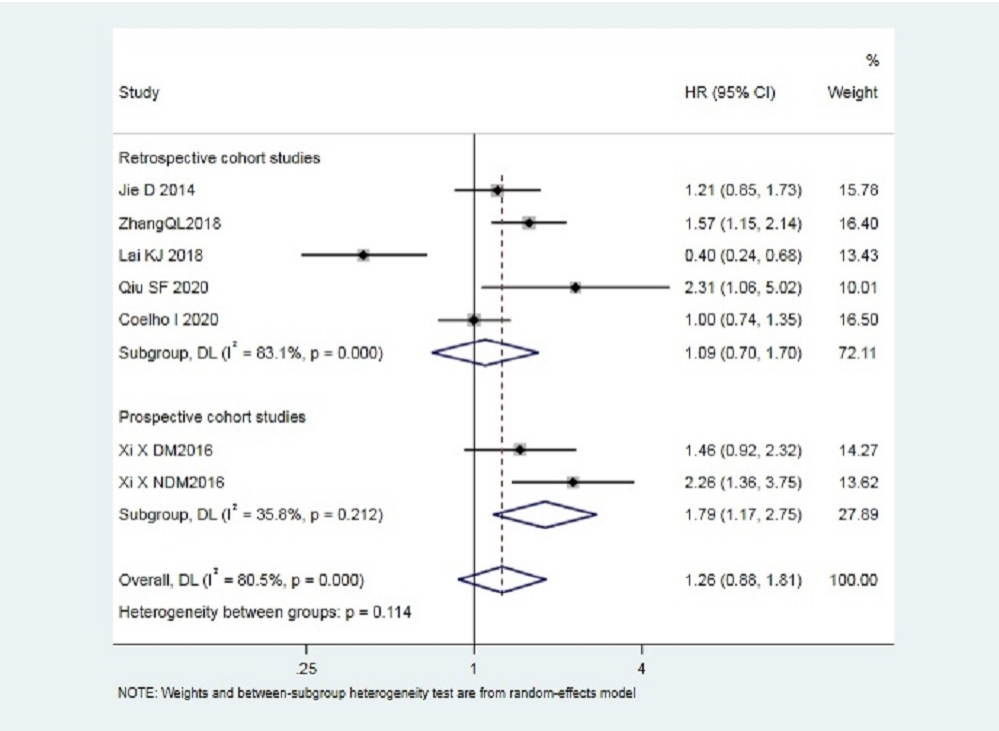

Fig.2 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and all-cause mortality in PD patients
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

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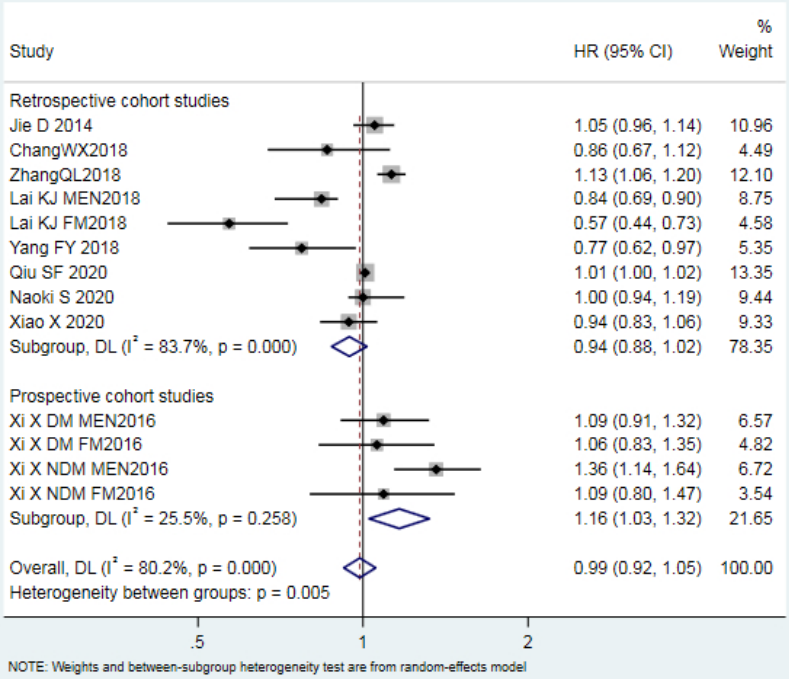


Fig.3 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Famale; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)

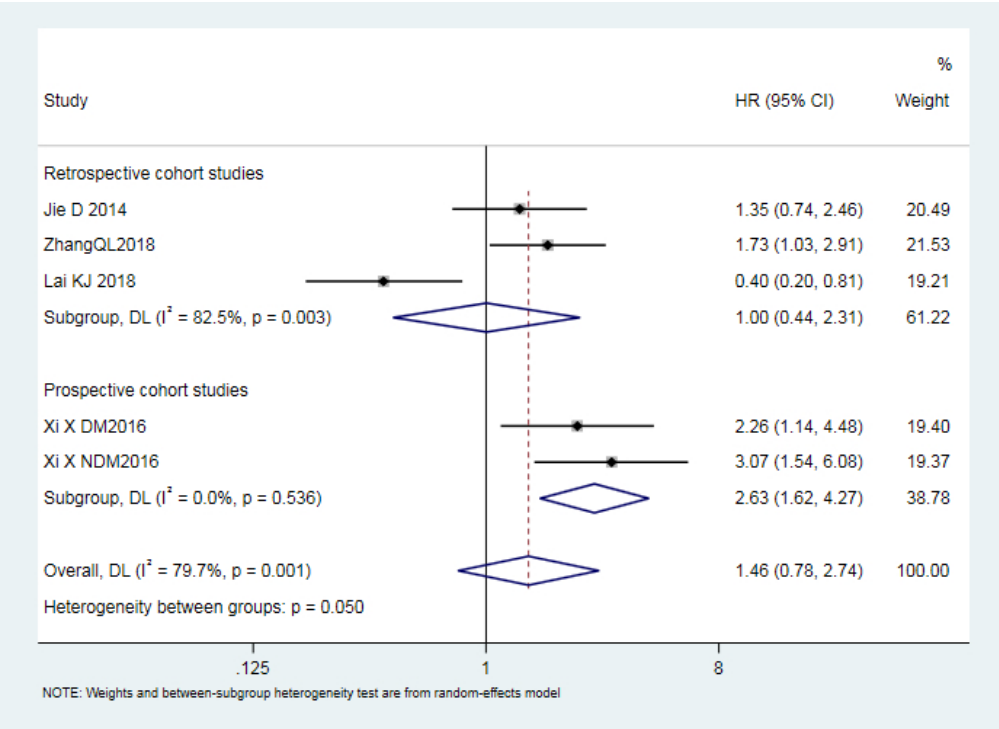


Fig.4 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and cardiovascular mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)

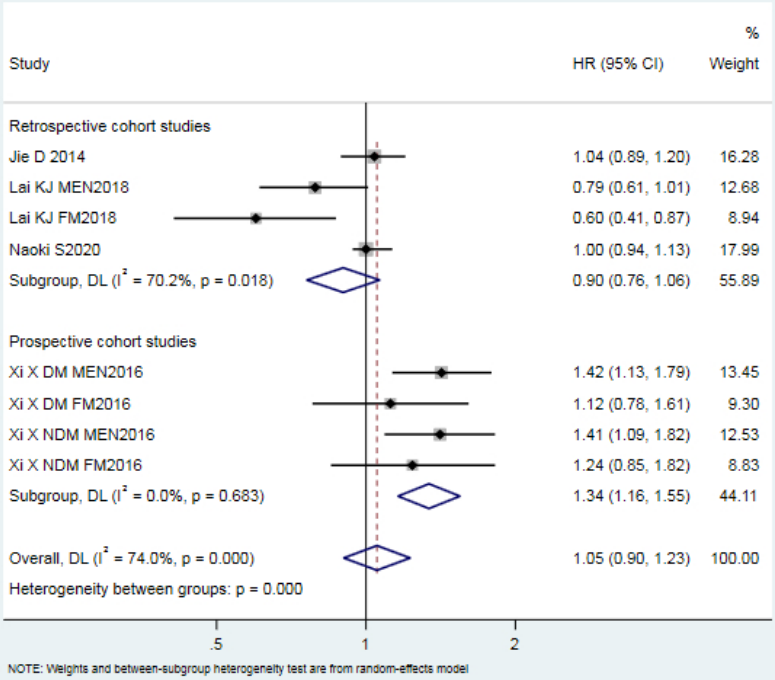
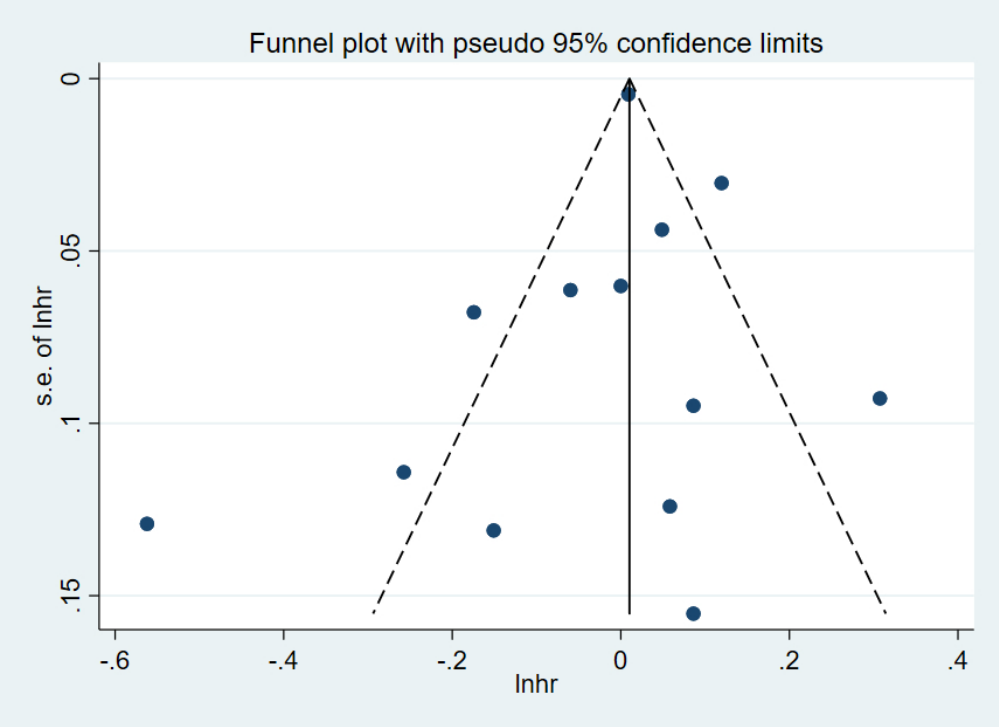


Fig.5 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Famale; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)



301x219mm (72 x 72 DPI)

eTable 1 Searching strategies for electronic databases

Databases	Searching strategies	Results (n)
PubMed	#1. Uric Acid [Mesh] OR Uric Acid [Title/Abstract] OR serum uric acid [Title/Abstract] #2. Mortality [Mesh] OR Mortality [Title/Abstract] #3. Peritoneal Dialysis [Mesh] OR Peritoneal Dialysis [Title/Abstract] OR PD [Title/Abstract] OR continuous ambulatory PD [Title/Abstract] OR CAPD [Title/Abstract] OR intermittent PD [Title/Abstract] OR IPD [Title/Abstract] OR automated PD [Title/Abstract] OR APD [Title/Abstract] OR continuous cyclic PD [Title/Abstract] OR CCPD [Title/Abstract] OR tidal PD [Title/Abstract] OR TPD [Title/Abstract] #4. #1 AND #2 AND # 3	33
The Cochrane library	#1. Uric Acid [Title/Abstract/Keywords] OR serum uric acid [Title/Abstract/Keywords] #2. Mortality [Title/Abstract/Keywords] #3. Peritoneal Dialysis [Title/Abstract/Keywords] OR PD [Title/Abstract/Keywords] OR continuous ambulatory PD [Title/Abstract/Keywords] OR CAPD [Title/Abstract/Keywords] OR intermittent PD [Title/Abstract/Keywords] OR IPD [Title/Abstract/Keywords] OR automated PD [Title/Abstract/Keywords] OR APD [Title/Abstract/Keywords] OR continuous cyclic PD [Title/Abstract/Keywords] OR CCPD [Title/Abstract/Keywords] OR tidal PD [Title/Abstract/Keywords] OR TPD [Title/Abstract/Keywords] #4. #1 AND #2 AND # 3	10
EMBASE	#1. (Uric Acid OR serum uric acid).ab,ti #2. (Mortality).ab,ti #3. (Peritoneal Dialysis OR PD OR continuous ambulatory PD OR CAPD OR intermittent PD OR IPD OR automated PD OR APD OR continuous cyclic PD OR CCPD OR tidal PD OR TPD).ab,ti #4. #1 AND #2 AND # 3	105
Web of Science	#1. Uric Acid OR serum uric acid [Topic] #2. Mortality [Topic] #3. Peritoneal Dialysis OR PD OR continuous ambulatory PD OR CAPD OR intermittent PD OR IPD OR automated PD OR APD OR continuous cyclic PD OR CCPD OR tidal PD OR TPD [Topic] #4. #1 AND #2 AND # 3	55
Chinese databases:	#1. niaosuan (uric acid,尿酸) OR xueniaosuan (serum uric acid,血尿酸)	CNKI:18

CNKI, SinoMed, VIP, Wan Fang	#2. siwanglv (mortality,死亡率) #3. fumotouxi (peritoneal dialysis,腹膜透析) OR lianxuxingfeiwochuangfumotouxi (continuous ambulatory peritoneal dialysis,连续性非卧床腹膜透析) OR zidonghuafumotouxi (automated peritoneal dialysis,自动化腹膜透析) #4. #1 AND #2 AND # 3	SinoMed:5 VIP:2 WanFang:14

eTable 2 Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

Study ID	Selection				Comparability	Outcome			Total score
	Representativeness of exposed group	Representativeness of non-exposed group	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of groups on the basis of design or analysis	Assessment of outcome	Follow up long enough	Adequacy of follow-up of groups	
Sheng F 2013[25]	☆	☆	☆	☆	☆	☆	☆	-	7
Jie D 2014[14]	☆	☆	☆	☆	☆	☆	☆	☆	8
Xi X 2016[21]	☆	☆	☆	☆	☆	☆	☆	☆	8
Eunjin B2016[26]	☆	☆	☆	☆	-	☆	☆	☆	7
ChangWX2018[27]	☆	☆	☆	☆	☆	☆	☆	☆	8
ZhangQL2018[28]	☆	☆	☆	☆	☆	☆	☆	-	7
Lai KJ 2018[29]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yang FY 2018 [30]	☆	☆	☆	☆	☆	☆	☆	-	7
ChangWX2019[31]	☆	☆	☆	☆	☆	☆	☆	-	7
Xiang SL 2019[32]	☆	☆	☆	☆	☆	☆	☆	☆	8
Qiu SF 2020[33]	☆	☆	☆	☆	☆	☆	☆	-	7
Coelho I 2020[34]	☆	☆	☆	☆	☆	☆	☆	-	7
Naoki S 2020[35]	☆	☆	☆	☆	☆	☆	☆	☆	8
Xiao X 2020[22]	☆	☆	☆	☆	☆	☆	☆	☆	8

MOOSE Checklist——A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Checklist Item	Answer
Reporting of background should include	
Problem definition	Page 5, Line 97-98
Hypothesis statement	Page 5, Line 98-100
Description of study outcome(s)	Page 5, Line 99-100; Page 6, Line 119-125
Type of exposure or intervention used	Page 5, Line 99-100; Page 6, Line 113-117
Type of study designs used	Page 5, Line 108
Study population	Page 5, Line 98-100; Page5-6, Line 109-112
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	Page 7, Line 136
Search strategy, including time period included in the synthesis and keywords	Page 7, Line 137-139, Page 7-8, Line146-155
Effort to include all available studies, including contact with authors	Page 7, Line 144-146
Databases and registries searched	Page 7, Line 140-143
Search software used, name and version, including special features used (eg, explosion)	Page 7-8, Line 146-155
Use of hand searching (eg, reference lists of obtained articles)	Page 7, Line 142-143
List of citations located and those excluded, including justification	Page 6-7, Line 127-134; Page 10, Line 209-216
Method of addressing articles published in languages other than English	Page 7, Line 143-144
Method of handling abstracts and unpublished studies	Page 7, Line 143-144
Description of any contact with authors	Page 7, Line 144-146
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Page 8, Line 157-165
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Page 8, Line 162-165
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Page 8, Line 167-172
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Page 8, Line 168-169; Page 11, Line 223-231
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 8-10, Line 174-203
Assessment of heterogeneity	Page 9-10, Line 197-199
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 8-10, Line 174-203

MOOSE Checklist——A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Provision of appropriate tables and graphics	Page 7-8, Line 154-155
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Page 10, Line 215-216 Fig.1
Table giving descriptive information for each study included	Page 10, Line 219-220 Table 1,2
Results of sensitivity testing (eg, subgroup analysis)	Page 13-14, Line 285-304
Indication of statistical uncertainty of findings	Page 15, Line 309-312
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Page 15, Line 327-328
Justification for exclusion (eg, exclusion of non–English-language citations)	Page 10, Line 209-216
Assessment of quality of included studies	Page 16-17, Line 339-372
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Page 20, Line 429-433
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review	Page 20, Line 429
Guidelines for future research	Page 20, Line 433-437
Disclosure of funding source	Page 21, Line 448-452

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.

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Relationship between serum uric acid, all-cause mortality and cardiovascular mortality in peritoneal dialysis patients: systematic review and meta-analysis of cohort studies

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Title Page

Title: Relationship between serum uric acid, all-cause mortality and cardiovascular mortality in peritoneal dialysis patients: systematic review and meta-analysis of cohort studies

Authors： Xue Xue1,2, Chun-li Lu2, Xin-yan Jin2, Xue-han Liu2, MinYang3, Xiao-qin Wang4, Hong Cheng4, Jun Yuan4, Qiang Liu4, Ruo-xiang Zheng2, Nicola Robinson2,5, and Jian-ping Liu2*

1 The First Clinical College and Affiliated Hospital, Hubei University of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

2 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

3 Basic Medical School and Affiliated Hospital, Hubei University of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

4 Department of Nephrology, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

5 Institute of Health and Social Care, London South Bank University, 103 Borough Road, London SE1 0AA, UK

Key words： serum uric acid, all-cause mortality, cardiovascular mortality, peritoneal dialysis, systematic review.

Email addresses: Xue Xue (xue025004138@163.com); Chun-li Lu (annyzhenni@163.com); Xin-yan Jin (20170941260@bucm.edu.cn); Xue-han Liu (xuehan_liu@foxmail.com); MinYang (1750096103@qq.com); Xiao-qin Wang (wangxiao773@

hotmail.com); Hong Cheng (chenghong@hbhtcm.com); Jun Yuan (yjun_92@hbtcm.edu.cn); Qiang Liu (leonjordan23@sina.com); Ruo-xiang Zheng (zhengruox@foxmail.com); Nicola Robinson (nicky.robinson@lsbu.ac.uk); Jian-ping Liu (Liujp@bucm.edu.cn).

***Corresponding**

Jian-ping Liu*

Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China. E-mail: Liujp@bucm.edu.cn

Telephone number: 13718004410.

Word count of full text： 4105.

Abstract

Objectives To analyze the relationship between serum uric acid (SUA), all-cause and cardiovascular (CV) mortality in peritoneal dialysis (PD) patients to inform clinical practice and future research.

Design A systematic review of observational studies.

Data sources PubMed, Embase, Web of Science, the Cochrane Library, CNKI, SinoMed, VIP and Wan Fang databases were searched from their inception to January 2021 for cohort and case-control studies reporting SUA and mortality in PD patients.

Methods The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to appraise quality of cohort and case-control studies. Effect estimates were presented as hazard ratios (HR) with 95% confidence intervals (CI) in a meta-analysis using STATA

16.0. Data not suitable for pooling were synthesized qualitatively.

Results Fourteen cohort studies with 24031 patients were included. No case-control studies were identified. For prospective cohort studies, pooled results for the highest SUA category was significantly greater than the lowest for all-cause (1 study; 1287 participants; HR 1.79; 95%CI 1.17-2.75) and CV mortality (1 study; 1287 participants; HR 2.63; 1.62-4.27). An increase of 1mg/dl in SUA level was associated with a 16% increased risk of all-cause mortality (1 study; 1287 participants; HR 1.16; 1.03-1.32) and 34% increased CV mortality risk (1 study; 1287 participants; HR 1.34; 1.16-1.55). For retrospective cohort studies, the highest SUA category did not demonstrate an elevated all-cause (5 studies; 4570 participants; HR 1.09; 0.70-1.70) or CV mortality (3 studies; 3748 participants; HR 1.00; 0.44-2.31) compared with the lowest SUA category. Additionally, there was no increase in all-cause (8 studies; 11541 participants; HR 0.94; 0.88-1.02) or CV mortality (3 studies; 7427 participants; HR 0.90; 0.76-1.06) for every 1mg/dl increase in SUA level.

Conclusions Results of prospective and retrospective cohort studies were inconsistent. Consequently, prospective, multi-center, long-term follow-up studies are required to confirm the relationship between SUA and mortality in PD patients.

Strengths and limitations of this study

- This is the first systematic review of observational studies which has explored the relationship between SUA level and mortality in PD patients.
- We used critical appraisal of included studies and subgroup analysis to present the results, and proposed future research directions based on the results.

- Of the included studies, eleven were conducted in China, two in other Asian countries and one in Europe, this limits the generalizability of our results.
- Dose-response relationship could not be determined from these data.

Introduction

End-stage renal disease (ESRD) is one of the major diseases affecting human health, and causes enormous pressure and burden on medical care and society. One of the effective treatments for ESRD is peritoneal dialysis (PD) which is characterized by enabling stable hemodynamics, protecting residual renal function (RRF), and demonstrates good removal of middle molecular toxins, and is associated with a low risk of infection, and can be delivered at home [1]. Currently, PD is widely used globally. The total number of people receiving PD worldwide in 2013 reached approximately 220,000 [2]. Of concern is that patients with ESRD treated with dialysis still have high mortality [3]. The identification of potential risk factors has great significance if patients' prognosis and quality of life is to be improved.

Uric acid (UA) is the final product of purine nucleotide metabolism in humans. Previous studies have demonstrated that elevated serum uric acid (SUA) is closely related to the increased risk of hypertension, peripheral arterial disease, cardiovascular (CV) event and chronic kidney disease (CKD) in the general population [4-7]. Higher SUA levels also appear to be an independent risk factor for all-cause and CV mortality in CKD subjects [8,9]. However， there have been conflicting results about the relationship between SUA level and risk of death among dialysis patients. In the hemodialysis population, hypouricemia significantly increased mortality [10-12].

Nevertheless, the role of SUA in all-cause and CV mortality in PD patients has been controversial. An elevated SUA level has been shown to be an independent risk factor for all-cause and CV mortality in men treated with PD [13]. Another study showed that the prognostic value of SUA in all-cause and CV mortality was weak in PD patients [14]. Hyperuricemia has also been found to predict lower risk of all-cause mortality in PD patients with lower relative appendicular skeletal muscle [15]. In short, the effect of SUA on the prognosis of PD patients appears to be inconsistent.

Currently, systematic reviews on the relationship between SUA, all-cause and CV mortality in the PD population are lacking. We hypothesized that there may be an independent correlation between elevated SUA level and mortality in participants with PD. Thus, we systematically analyzed available studies to determine whether this hypothesis could be confirmed.

Methods

The methods in this review were specified in advance. The review was reported according to the "Meta-analysis of Observational Studies in Epidemiology guidelines" (MOOSE) [16].

Eligibility criteria

Types of studies

Cohort and case-control studies were identified.

Participants

Participants had to receive PD for more than 3 months. There was no restriction on the type of PD, including continuous ambulatory PD, intermittent PD, automated PD,

continuous cyclic PD and tidal PD.

Exposure factor

Hyperuricemia in PD population was the exposure factor in this study. Either categorization according to baseline SUA level or time-average SUA concentration was acceptable. Definition of hyperuricemia and the categorization for the SUA level was based on the definition reported in each included article.

Outcome

The primary outcome was all-cause mortality and death was determined by the hospital medical record or death certificate.

The secondary outcome was CV mortality, defined as a "CV events": coronary events (myocardial infarction, unstable angina), cardio myopathy, cardiac arrest, cardiac dysrhythmia, congestive heart failure, ischemic brain injury, cerebrovascular accident and peripheral vascular disease. The cause of death was determined through medical history, hospital medical records or death certificates.

Exclusion criteria

(1) Unable to obtain the following information from the original article. Hazard ratio (HR) and its corresponding 95% confidence interval (CI) (or other data required in order perform the calculation) for all-cause or CV mortality for 1mg/dl change in SUA level, or for the highest versus lowest SUA category or the lowest versus highest category; (2) Cohort studies with a total sample size of less than 100 participants; (3) Studies originating from the same cohort sample, or part of a cohort sample that had been previously published. Only the literature which reported the largest sample size

and the longest follow-up could be included.

Search strategy

Two authors (X.X. and H.C.) searched the following Chinese and English databases from their inception to 15th January 2021. Chinese databases included China National Knowledge Infrastructure (CNKI), SinoMed, Chinese Science and Technology Journal Database (VIP), and Wan Fang Database. English databases included PubMed, EMBASE, the Cochrane Library, and Web of Science. Trial registers including Clinical Trials. gov and the World Health Organization International Clinical Trials Registry Platform were also searched. Additionally, related reviews, conference papers, references lists and gray literatures were also searched manually. No language or publication type was imposed, published abstracts were also considered. If the retrieved literature had missing information, it was necessary to contact the author via email to obtain the data to ensure that literature could be included. Taking "PubMed" as an example, the searching strategy was as follows: ("Uric Acid"[Mesh] OR "Uric Acid" [Title/Abstract] OR "serum uric acid"[Title/Abstract]) AND ("Mortality"[Mesh] OR "Mortality"[Title/Abstract]) AND (" Peritoneal Dialysis"[Mesh] OR "Peritoneal Dialysis"[Title/Abstract] OR "PD"[Title/Abstract] OR "continuous ambulatory PD" [Title/Abstract] OR "CAPD"[Title/Abstract] OR "intermittent PD"[Title/Abstract] OR "IPD"[Title/Abstract] OR "automated PD"[Title/Abstract] OR "APD"[Title/Abstract] OR "continuous cyclic PD"[Title/Abstract] OR "CCPD"[Title/Abstract] OR "tidal PD"[Title/Abstract] OR "TPD"[Title/Abstract]). The searching strategies for other databases are presented in eTable1 in the Supplement.

Studies selection and data extraction

The titles and the abstracts were initially screened, then the full-text versions were checked according to the inclusion and exclusion criteria. Two authors (X.X. and Q.L.) examined the full text to identify the eligible studies independently. Two authors (X.X. and H.C.) extracted data independently and entered information into a data extraction sheet. Disagreements on study selection and data extraction were resolved by consulting corresponding author JP Liu. The following information was extracted from each included study: first author, publication year, age, gender, study design, dialysis duration, sample size, study location, center, length of follow up, categories according to SUA, comparison, adjustments, and adjusted HR (95%CI).

Methodological quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to appraise the quality of observational studies [17]. NOS allocates a maximum of 9 points for quality of selection, comparability, and outcome of study population. Two authors (X.X. and X.Y.J.) appraised the quality of included studies independently. Any disagreements were resolved by discussion with corresponding author JP Liu. Overall study quality scores were defined as poor (0–3), fair (4–6), or good (7–9).

Statistical analysis

SUA was analyzed not only as a categorical variable, but also as a continuous variable in the included studies. The statistical analysis for the overall relationship between SUA level and death risk (all-cause and CV mortality) were based on the random effects model and on comparisons of the highest versus the lowest category of SUA level, or

by increase of 1mg/dl. HR and 95% CI were used as effect indicators. HR and corresponding 95% CI of each study were transformed to their natural logarithm (lnHR, lnlCI and lnUCI), and overall HR and its 95% CI was calculated by exponentiation of the pooled lnHR, lnlCI and lnUCI.

If data on cases, person-years, and HR and 95% CI for each category were available in the included studies, then a dose-response analysis would be performed to further explore the relationship between SUA and mortality. The potential non-linearity association was examined by modeling SUA levels using restricted cubic splines with three knots at 25, 50, and 75% of the distribution. We assigned the median or middle point of the upper and lower boundaries in each category as the corresponding dose to the related HR for each study. In general, if there is a dose-response relationship between SUA and mortality, and *P* value for non-linear < 0.05, non-linear regression model should be considered. When the *P* value was close to the critical value of 0.05, both linear and non-linear models needed to be fitted.

The square (I^2) was applied to test the statistical heterogeneity among studies (Higgins and Thompson, 2003) [18]. When $I^2 > 85\%$, we believed that the results could not be pooled. Data not suitable for statistical pooling were synthesized qualitatively. To explore the source of heterogeneity among studies, subgroup analyses were conducted according to study design, study location, publication years, adjustment for sex, adjustment for DM and adjustment for albumin. Additionally, the meta-regression analysis was also performed to detect potential heterogeneity based on the above variables when about 10 studies were included. Sensitivity analysis was performed

removing one study at a time to explore the robustness of results if data were available. The possibility of publication bias was detected by funnel plots and Egger's test if there were about 10 studies. STATA16.0 software (StataCorp, College Station, Texas, 77845 USA) was used for data analysis.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our study.

Results

Search results

Two hundred and forty-two relevant citations were retrieved. After scanning the full texts, five articles were excluded. Cohort samples from the same study were excluded [13,15,19], and only the studies with the largest sample size and the longest follow-up time were included [20,21]. In addition, a published abstract was excluded, because the total sample size of the entire cohort was only 60 participants [22]. Another study was excluded due to its pooled effect estimation which was reported as an odds ratio (OR) with 95% CI [23]. Finally, fourteen studies were eligible for this review. Details of the search and selection process are illustrated in Fig.1.

Characteristic of included trials

A total of fourteen studies consisting of 24031 participants were included [14,20,21,24-34]. All were cohort studies, including prospective and retrospective studies. The main characteristics of included studies are given in Table 1 and Table2.

Methodological quality of included studies

The overall quality of included studies was good with a mean NOS score of 7.57 (range 7–9). All studies scored greater than or equal to 7 (eTable2 in the Supplement). In terms of "comparability", the most important confounding factors that required adjustment were: estimated glomerular filtration rate (eGFR) or serum creatinine (Scr) or urinary volume (UV) or residual renal function (RRF). The above indicators can reflect the patient's current residual renal function status. In addition, according to the literature and clinical observations, other confounding factors needing adjustment should include gender, age, diabetes history, cardiovascular disease (CVD) history, Kt/v (urea clearance index, representing dialysis adequacy), use of UA-lowering drugs, and serum albumin (representing nutritional status).

Primary outcome

Relationship between serum uric acid by categories and all-cause mortality

In order to reduce the heterogeneity of methodology, we discussed the results according to different study designs. For prospective cohort studies, the summary HR and 95% CI of all-cause mortality for the highest SUA category compared with the lowest category came from one study which included 1287 patients [20]. As presented in Fig.2, the pooled result of the highest SUA category was significantly higher than the lowest for all-cause mortality (HR 1.79; 95% CI 1.17-2.75).

In retrospective cohort studies, five studies with 4570 patients reported HR and 95% CI of all-cause mortality for the highest versus the lowest SUA category [14,27,28,32,33]. All cause mortality (HR 1.09; 95% CI 0.70-1.70; Fig.2) was not significantly elevated compared with the lowest category of PD patients.

HR and corresponding 95% CI were reported in three retrospective cohort studies for the lowest versus the highest SUA category [25,26,30]. Among them, the data from one article [26] was supplemented by the corresponding author via e-mail. The pooled HR was 1.52 (95%CI 0.79-2.89), with heterogeneity of I^2=32.8%.

Relationship between serum uric acid per 1mg/dl increase and all-cause mortality

Only one prospective study with 1287 PD patients reported HR and 95% CI of all-cause mortality for every 1mg/dl increase in SUA level [20]. The pooled result showed that for every 1mg/dl increase in SUA level, risk of all-cause death increased by 16% (HR 1.16; 95%CI 1.03-1.32; Fig.3).

For the retrospective cohort studies, eight studies with 11541 PD patients reported HR and 95% CI of all-cause mortality for every 1mg/dl increase in SUA level [14,21,26-29,32,34]. When the units of SUA concentration in the literature were different, 60 μ mol/l was approximately equal to 1mg/dl. In short, each 1mg/dl increase in SUA level did not appear to significantly increase the risk of all-cause mortality in the PD population (HR 0.94; 95% CI 0.88-1.02; Fig.3).

Dose-response relationship between serum uric acid and all-cause mortality

Most of the included studies [14,20,21,25,27,29,30,32-34] only reported the number of outcomes for the entire cohort population. It was not possible to obtain the number of all-cause and CV deaths and person-years for each category. We tried our best to contact authors by email or phone in order to acquire the necessary data for the non-linearity test, only one author responded and provided relevant data [26]. A dose-response analysis was not possible.

Secondary outcome

Relationship between serum uric acid by categories and cardiovascular mortality

One prospective cohort study with 1287 patients reported HR and 95% CI of CV mortality for the highest SUA category compared with the lowest [20]. The pooled result of HR comparing the highest versus the lowest category was 2.63 (95% CI 1.62-4.27). (Fig.4).

Three retrospective cohort studies with 3748 patients reported HR and 95% CI of CV mortality for the highest versus the lowest SUA category [14,27,28]. The highest SUA category was no more in terms of elevated CV mortality (HR 1.00; 95% CI 0.44-2.31) compared with the lowest category of PD patients. (Fig.4).

Relationship between serum uric acid per 1mg/dl increase and cardiovascular mortality

One prospective cohort study with 1287 patients reported HR and 95% CI of CV mortality for per 1mg/dl increase in SUA level [20]. An increase of each 1mg/dl in SUA level was associated with a 34% increased risk of CV mortality (HR 1.34; 95%CI 1.16-1.55). (Fig.5).

Three retrospective cohort studies with 7427 patients reported HR and 95% CI of CV mortality per1mg/dl increase in SUA level [14,28,34]. Meta-analysis showed that each 1 mg/dl increase in SUA level did not appear to significantly increase the risk of CV death in PD population (HR 0.90; 95% CI 0.76-1.06). (Fig.5).

Additional analysis

Subgroup analysis and meta-regression

We explored the source of heterogeneity through subgroup analysis and meta-

regression. Subgroup analysis only included literature which compared the highest versus the lowest category of SUA level, or explored a change of 1mg/dl increase. The pooled HR (95% CI) and I^2 of subgroup analysis of the relationship between SUA and all-cause and CV mortality are presented in Table 3 and Table 4, respectively.

As mentioned before, whether SUA was a categorical variable or a continuous variable, the results of the prospective cohort study differed from those of retrospective studies. Besides, combined with the results of subgroup analysis, when SUA was estimated as a categorical variable, the association of higher SUA level with increased all-cause and CV mortality was significant in studies from mainland China, but not in other countries. SUA as a continuous variable showed that the relationship of higher CV mortality for 1 mg/dl increase in SUA level was significant in studies from mainland China, but not elsewhere. Furthermore, we analyzed the relevant studies published in the past ten years, and results of studies completed during 2011-2016 were different from the results during 2017-2021 period.

In addition, in studies of the relationship between SUA (as a continuous variable) and all-cause mortality, study design, study location, publication years, adjusted for sex and DM were heterogeneous by meta-regression (Table 3).

Test of Publication bias

Funnel plots and Egger's test (t=1.07, p=0.309) indicated there was no obvious publication bias of studies for the relationship between all-cause mortality and SUA level per 1mg/dl increase. The funnel plot is presented in eFigure1 in the Supplement.

Sensitivity analysis

In retrospective cohort studies, results of primary outcome showed there was no significant effect on the pooled HR values of other studies with one study removed at a time. The above indicated the results were robust.

Discussion

Principal findings and comparison with prior reviews

For PD population, previous original studies indicated inconsistent relationship between SUA and mortality. After searching systematically, we found that there were some meta-analyses investigating the correlation between SUA and mortality in different populations [35-38], however, we have not yet found a review only of PD patients. A systematic review published in 2016 showed that elevated SUA level was significantly associated with the risk of death in patients with CKD, including dialysis and non-dialysis subjects [39]. Subgroup analysis in this review demonstrated that hyperuricemia was an independent predictor for mortality in PD population, while, this predictive value was not found in the hemodialysis (HD) population. As only 1 prospective cohort study and 2 retrospective cohort studies were included in the subgroup analysis, results should be interpreted with caution.

In our study, we included a total of 14 cohort studies, of which 2 were prospective studies and 12 were retrospective studies. There was no obvious publication bias of studies according to funnel plots and Egger's test. Researchers can not control the process of data accumulation in retrospective cohort studies, but researchers can directly acquire relevant data on exposure and outcome according to the study design in prospective studies, so the risk of bias is small. Thus, instead of pooling results of

the two studies, we reported them individually. Only one prospective cohort study suggested that regardless of whether SUA was estimated as a continuous or a categorical variable, elevated SUA level was significantly associated with increased risk of all-cause and CV mortality in PD patients. Whereas, there was no significant associations between them in the retrospective studies. Below we have attempted to discuss the inconsistency of the results from the aspects of participants, exposure, comparability and outcomes.

First of all, the prospective cohort study clearly indicated that participants on PD were consecutively enrolled. It is well known that consecutive recruitment is very important to reduce selection bias. While, in some retrospective studies, the process of enrollment was not detailed. The follow-up of the participants was also a prominent issue, including the duration and adequacy of follow-up and the rate of loss to follow-up. In a prospective study, effective measures can be taken to reduce the loss to follow-up rate to avoid bias. The rate of loss to follow-up in a prospective study by Xia X et al. (2016) was only 3.5% [20], but in some retrospective cohorts, the adequacy and lost follow-up rates were not reported.

Second, hyperuricemia in the PD population was the exposure factor of this study. Both prospective and retrospective cohort studies, the definition of hyperuricemia and the categorization for the SUA level was based on the definition provided in each included article. It should be noted that in retrospective multi-center studies, the measurement methods of SUA may not be uniform across centers. This may lead to measurement bias and have a slight impact on results.

Third, control of the most important and other confounding factors is very important for the comparability between the groups. The most important confounding factors included indicators that can reflect the patient's current residual renal function status. Other confounding factors need to be adjusted and should include gender, age, diabetes history, CVD history, Kt/v, use of UA-lowering drugs, and serum albumin. Most of the studies did not adjust for all potential risk factors. For example, the prospective study of Xia X et al. (2016) lacked adjustment for the confounding factor Kt/v [20]. Therefore, we can not exclude the potential impact of these uncontrolled confounding factors.

Regarding the outcomes, the definition of all-cause and cardiovascular death was clear. However, the handling of patients transferring to hemodialysis therapy, loss to follow-up, and renal transplantation was different for prospective and retrospective studies. The above information from patients was used as censoring data for survival analysis in the prospective study [20]. Whereas, in some retrospective studies, they were directly excluded from the study [32]. This may affect the results and lead to inconsistencies between the prospective and retrospective studies. Although the risk of bias in the design type of prospective study was relatively small, the interpretation of the results should still be cautious due to the limited quality and quantity of prospective study.

SUA, known for its detrimental effect, is an endothelial toxin and plays a role in endothelial dysfunction [40]. However, as a powerful free radical scavenger in human at the same time, SUA may be expected to offer a number of benefits within the CV

system in PD patients [41,42]. Besides, the problem of protein loss and malnutrition is prominent in PD population [43]. "Malnutrition-inflammation complex syndrome (MICS)" is believed to be the main cause of the high rate of CV atherosclerotic disease and increased mortality and hospitalization in HD patients [44,45]. The underlying mechanism of MICS may also be present in PD patients. As a nutritional marker，SUA might be involved in the MICS axis. Therefore, the relationship between SUA and mortality in PD patients is a complex proposition. Taking into account the feature of SUA itself, we hypothesize that both extremely low and high SUA level may increase the risk of death. In our study, we also would like to explore the dose-response relationship between SUA level and mortality in PD population, but in the end the analysis to explore a dose-response relationship was impossible due to insufficient data. Further investigations are warranted to clarify this relationship and explore the range of SUA concentration associated with the lowest mortality in the PD patients.

Moreover, in addition to different study designs, different study location was also one of the main sources of heterogeneity among studies according to the meta-regression test. Subgroup analysis results further suggested hyperuricemia was associated with a high risk of CV death in PD population only in mainland China. As a result, the relationship between SUA level and the risk of death in different regions needs to be explored and verified by prospective studies in future.

Implications further research

Since the results of prospective and retrospective cohort studies were inconsistent, and the different regions seemed to lead to different results, prospective, multicenter, long

term follow-up studies are required in future. It is important to explore the relationship between SUA level and the risk of death in different regions, as well as to determine the range of SUA concentrations which can reduce mortality and improve prognosis in the PD patients.

Additionally, since PD patients often suffer from underlying diseases and complex conditions, adjustment is required for confounding factors to explore the relationship between these factors and prognosis. For the PD population, the following confounding factors should be considered to make the evidence more compelling. Such as: traditional independent risk factors of CV events (age, gender, total lipoprotein cholesterol, low or high density lipoprotein cholesterol, hypertension, diabetes, smoking [46]), history of CV, emotion status, residual renal function, the related parameters of PD, the parameters of nutritional status, use of diuretic and lower UA agents etc.

Comprehensive information should be reported in detail in the study report so that readers can become more familiar with the details of the study, and can conduct secondary research to avoid wasting research resources.

Study limitations

There were several limitations in this review. Systematic reviews of observational studies can provide a higher level of evidence, but they also have methodological limitations. For example, the included original studies may differ in their design, data collection methods, and definitions of exposure, confounding factors and outcomes. These differences may have a slight influence on the true effect size. Second, in this

review, the included studies were mainly from Asian populations (only one from Europe), and the generalizability of the results was limited. Third, in spite of many important confounding factors that to be adjusted in the studies, residual and unknown confounding factors can not be entirely excluded. Fourth, the duration of follow up in all studies was less than 5 years. It is difficult to determine long-term impact of elevated SUA level on mortality. Finally, some necessary data was not obtained, and the exploration of dose-response relationship could not be conducted, but will need to be determined in future studies.

Conclusions

The results from the prospective and retrospective cohort studies were inconsistent. Only one prospective cohort study showed that elevated SUA level was significantly associated with increased risk of all-cause and CV mortality in PD patients. Nevertheless, the pooled result of retrospective cohort studies did not appear to indicate a prominent association. So it is necessary to use SUA-lowering agents with caution for PD patients in clinics. International prospective, multicenter, long term follow-up studies are needed in the future to investigate the relationship between SUA level and the risk of death, and to explore the range of SUA concentrations associated with the lowest mortality in the PD patients.

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XX, HC, QL, JY, and JPL. Drafting of the manuscript: XX, XHL, CLL, XYJ and RXZ. Statistical analysis: MY, XX and XQW. Critical revision of the manuscript: XQW, NR and JPL. Supervision: JPL.

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Ethics approval statement

Dear editors,

Our study was to systematically evaluate the relationship between serum uric acid, all-cause and cardiovascular mortality in peritoneal dialysis patients based on the observational studies that have been published. As the nature of the study, ethics approval is not applicable for this study.

With best regards,

Yours sincerely,

(Corresponding author)

Jian-ping Liu,

Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

E-mail: LiuJP@bucm.edu.cn

Table 1 Characteristics of included studies (2013-2018 years)

Study ID	Study location (Region)	Study design/ Center	Age (years)	Male/ Total Sample(n)	Dialysis duration (months)	Follow-up (months)	Deaths AC/CV (n)	Definition of hyperuricemia or categories according to serum uric acid	Comparison	Adjustments	Adjusted HR (95%CI)
Sheng F 2013 [24]	China: Mainland	RCS/ Single	54.1±17.4	98/156	31.3±17.5	31.3±17.5	41/23	Group 1:≤7.0mg/dl; Group 2: 7.0-10.0 mg/dl; Group 3: ≥10.0 mg/dl.	Group 1 vs. Group 2 Group 3 vs. Group 2	Age, Alb, DM, HN, RRF , phosphate , Log CRP	ACM: 1.15(0.20-2.57) ACM: 2.96(1.29-6.80)
Jie D 2014 [14]	China: Mainland	RCS/ 7 centers	58.1±15.5	1078/2193	At least > 3	Median 26.5	586/231	Men: Tertile 1: 2.09-5.79mg/dl; Tertile 2: 5.80-7.38 mg/dl; Tertile 3: 7.39-16.7 mg/dl. FM: Tertile 1: 1.74-5.37mg/dl; Tertile 2: 5.38-6.65 mg/dl; Tertile 3: 6.66-8.08 mg/dl.	Tertile 3 vs. Tertile 2 (Gender-specific) Tertile 2 vs. Tertile 1 (Gender-specific) Per 1 mg/dl increase	Age, RRF, Hb, Alb, phosphate, LDLC, CRP, histroy of CVD and DM, BMI, MAP, center size, gender adjusted only SUA as continuous variable.	ACM: 1.21(0.85-1.73) CVM: 1.35(0.74-2.46) ACM: 1.23(0.90-1.70) CVM: 1.29(0.75-2.23) ACM: 1.05(0.96-1.14) CVM: 1.04(0.89-1.20)
Xin X 2016 [20]	China: Mainland	PCS/ Single	47.6±15.0	757/1287	At least > 3	Median 30.7	231/126	Men: Tertile 1: < 6.46mg/dl; (DM)Tertile 2: 6.46-7.38 mg/dl; Tertile 3: ≥7.38 mg/dl. Men: Tertile 1: < 7.00mg/dl; (NDM)Tertile2: 7.70-7.89mg/dl; Tertile 3: ≥7.89 mg/dl. FM: Tertile 1: < 5.89mg/dl; (DM)Tertile 2: 5.89-7.09 mg/dl ; Tertile 3: ≥7.09 mg/dl. FM: Tertile 1: < 6.46mg/dl; (NDM)Tertile2: 6.46-7.48mg/dl; Tertile 3: ≥7.48 mg/dl.	Tertile 3 vs. Tertile 1 (DM: Gender specific) Tertile 3 vs. Tertile 1 (NDM: Gender specific) Per 1 mg/dl increase	Age, gender, BMI, history of CVD and hypertension, Hb, Alb, Scr, P, HDL-C; RRF, log-transformed Hs-CRP, glycated Hb, use of allopurinol and ACEI or ARB.	ACM: 1.46(0.92-2.32) CVM: 2.26(1.14-4.48) ACM: 2.26(1.36-3.75) CVM: 3.07(1.54-6.08) ACM (DM, MEN):1.09(0.91-1.32); ACM (DM, FM):1.06(0.83-1.35); ACM(NDM, MEN):1.36(1.14-1.64); ACM (NDM, FM):1.09(0.80-1.47); CVM (DM, MEN):1.42(1.13-1.79); CVM (DM, FM):1.12(0.78-1.61); CVM(NDM, MEN):1.41(1.09-1.82); CVM (NDM, FM):1.24(0.85-1.82).
Eunjin B2016 [25]	South Korea	PCS/mult -icenter	NR	NR/651	At least > 3	Median 43.9	AC 106	Group 1: TA-UA<5.5 mg/dl; Group 2: TA-UA≥5.5 mg/dl.	Group 1 vs. Group 2	Age, sex, BMI, SBP, Ca, P, Alb, TC, DM, SGA.	ACM: 1.478(0.602-3.627)
ChangWX2018 [26]	China: Mainland	RCS/ Single	55.2±14.9	171/300	At least > 3	22.6±15.9	AC 44	Group1: TA-UA < 6mg/dL; Group2: TA-UA 6–8mg/dL; Group3: TA-UA ≥8mg/dL.	Group 3 vs. Group 2 Group 1 vs. Group 2 Group 1 vs. Group 3	Sex, age, DM, CVD history, RRF, BMI, SBP, Hb, Alb, BUN, SCr, Na, K, CO2, Ca,	ACM: 4.69(1.24-17.72) ACM: 3.24(1.25-8.39) ACM: 0.603 (0.158-2.309)

									Per 1 mg/dl increase (Baseline-UA)	P, LDL-C, CRP, RASi, diuretic.	ACM: 0.86(0.67-1.12)
ZhangQL2018 [27]	China: Mainland	RCS/ Single	Median 51	557/1063	At least > 6	Median 33	167/64	Group 1: < 420μmol/l; Group 2: ≥420μmol/l; Hyperuricemia≥420μmol/l	Group 2 vs. Group 1 Per 1 μmol/l increase	Age, Scr, P, Alb, BG, iPTH, history of DM, DBP, Charlson score.	ACM: 1.572(1.155-2.141) CVM: 1.734(1.033-2.912) ACM: 1.002(1.001-1.004)
Lai KJ 2018 [28]	China: Taiwan	RCS/ Single	53.5±15.3	237/492	At least > 3	Median 36.4	127/74	Men: Tertile 1: ≤6.8mg/dl; Tertile 2: 6.9-8mg/dl; Tertile 3: ≥8.1mg/dl. FM: Tertile 1: ≤6.5mg/dl; Tertile 2: 6.6-7.6mg/dl; Tertile 3: ≥7.7mg/dl. Men: Hyperuricemia≥7mg/dl FM: Hyperuricemia≥6mg/dl	Tertile 3 vs. Tertile 1 (Gender-specific) Tertile 2 vs. Tertile 1 (Gender-specific) Men: Per 1mg/dl increase FM: Per 1 mg/dl increase	Age, sex, BMI, pre-dialysis status, smoking, present medications, comorbidities of CVD, hyper-tension, DM, Charlson score, PD related parameters, Kt/v, BUN, Scr, GPT, WBC, ALP, Alb, Hb, ferritin, TC, TG, Ca, P, iPTH, transferrin saturation.	ACM: 0.4(0.24-0.68) CVM: 0.4(0.2-0.81) ACM: 1.06(0.7-1.58) CVM: 1.04(0.62-1.77) ACM: 0.84(0.69-0.9) CVM: 0.79(0.61-1.01) ACM: 0.57(0.44-0.73) CVM: 0.6(0.41-0.87)
Yang FY 2018 [29]	China: Mainland	RCS/ Single	51.8±14.4	232/487	Median 29.5	Median 29.5	197/109	Men: Hyperuricemia≥7mg/dl; FM: Hyperuricemia≥6mg/dl.	Per 1 mg/dl increase	Sex,, BMI, hypertension , dialysis duration, eGFR, Kt/v, LDL-C, iPTH.	ACM: 0.773(0.62-0.97)

Abbreviations: AC: All-cause; ACM: All-cause mortality; CV: Cardiovascular; CVM: Cardiovascular mortality; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; RCS: Retrospective cohort study; PCS: Prospective cohort study; vs.: versus; Alb: Serum albumin; DM: Diabetes mellitus; NDM: Non diabetes mellitus; HN: Hypertensive nephropathy; RRF: Residual renal function; CRP: C-reactive protein; Hb:Hemoglobin; BMI: Body mass index; SUA: Serum uric acid; Scr: Serum creatinine; MAP: Mean arterial pressure; P: Serum phosphorus; HDL-C: High density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; FM: Female; NR:Not reported; TA-UA: Time average-uric acid; SBP: Systolic blood pressure; Ca: Serum calcium; TC: Total cholesterol; SGA: Subjective global assessment; BUN: Blood urea nitrogen; Na: Serum sodium; K: Serum potassium; Cl: Serum chlorine; CO2: Venous carbon dioxide; LDL-C: Low density lipoprotein cholesterol; RASi: Renin-angiotensinsystem inhibitor; BG: Blood glucose; iPTH: intact parathyroid hormone; DBP: Diastolic blood pressure; PD: Peritoneal dialysis; eGFR: estimated glomerular filtration rate; Kt/v: Urea clearance index; GPT: Glutamic-pyruvic transaminase; WBC: White blood cell counts; ALP: Alkaline phosphate; TG: Triglyceride.

588 **Table 2** Characteristics of included studies (2019-2020 years)

Study ID	Study location (Region)	Study design/ Center	Age (years)	Male/ Total Sample(n)	Dialysis duration (months)	Follow-up (months)	Deaths AC/CV (n)	Definition of hyperuricemia or categories according to serum uric acid	Comparison	Adjustments	Adjusted HR (95%CI)
ChangWX2019 [30]	China: Mainland	RCS/ Single	18—80	150/309	At least > 3	NR	AC 50	Group 1: SUA decliner; Group 2: SUA non-decliner. ("SUA decliner" and "SUA non-decliner" according to run-in and longitudinal changes in the follow-up)	Group 1 vs. Group 2	Gender, age, BMI, SBP, Hb, Na, K, Cl, BUN, Scr, CO2, Ca, P, Alb, TG, FBG, CRP, RRF, PET type, Kt/V, DM, use of CCB, RASi , diuretic , β-blocker.	ACM: 2.23(1.13-4.40)
Xiang SL 2019 [38]	China: Mainland	RCS/ 98centers	52.5±14.6	5163/9405	At least > 3	Median 29.4	1226/515	Quintile1: < 6.06mg/dl; Quintile2: 6.06-6.67mg/dl; Quintile3: 6.68–7.27mg/dl Quintile4: 7.28-8.03mg/dl; Quintile5: ≥8.04 mg/dl. Hyperuricemia≥7.28mg/dl.	Quintile5 vs. Quintile3 Quintile4 vs. Quintile3 Quintile2 vs. Quintile3 Quintile1 vs. Quintile3	Age, sex, BMI, DM, CVD, RRF, Hb, Alb, K, Na, P, Ca, iPTH, Scr, FPG.	ACM: 1.482(1.187-1.849) CVM: 1.144(0.786-1.665) ACM: 1.335(1.073-1.662) CVM: 1.146(0.796-1.648) ACM: 1.160(0.938-1.434) CVM: 1.311(0.932-1.843) ACM: 1.162(0.945-1.427) CVM: 1.166(0.820-1.657)
Gu SF 2020 [32]	China: Mainland	RCS/ Single	44—65	63/140	Median 31.9	Median 31.9	AC 48	Tertile 1: < 387μmol/l; Tertile 2: 387-519μmol/l; Tertile 3: ≥519μmol/l.	Tertile 3 vs. Tertile 1 Tertile 2 vs. Tertile 1 Per 20μmo/l increase	Gender, age, DM , hypertension, CVD, BMI, K, ESA, RRF , use of diuretic and LUA.	ACM: 2.308(1.062-5.017) ACM: 0.959(0.423-2.174) ACM: 1.003(1.00-1.005)
Coelho I 2020 [33]	Portugal	RCS/ Single	60.2±14.6	407/682	At least > 3	31.4±25.6	NR	Group 1: below median; Group 2: above median.	Group 2 vs. Group 1	Age, comorbidities, DM and baseline RRF.	ACM: 0.997(0.74-1.35)
Naoki S 2020 [34]	Japan	RCS/mult-icenter	63±14	2916/4742	Median 28	Deadline : the end of 2012	AC 379	Group 1: < 5.0mg dl; Group 2: 5.0- < 5.5mg dl; Group 3: 5.5- < 6.0mg dl; Group 4: 6.0- < 6.5mg dl; Group 5: 6.5- < 7.0mg dl;	Group 1 vs. Group 3 Group 2 vs. Group 3 Group 3 vs. Group 3 Group 4 vs. Group 3 Group 5 vs. Group 3	Age, gender, BMI ,UV ,dialysis duration, under-lying disease, comorbid disease, medication and laboratory data.	ACM: 1.80(1.13-2.86) ACM: 1.43(0.88-2.32) ACM: 1.22(0.75-1.98) ACM: 1.37(0.86-2.20) ACM: 1.54(0.75-2.49)

									Group 6: 7.0- < 7.5mg dl;	Group 7 vs. Group 6		ACM: 1.58(0.94-2.63)
									Group 7: 7.5- < 8.0mg dl;	Group 8 vs. Group 6		ACM: 1.88(1.06-3.35)
									Group 8: 8.0- < 8.5mg dl;	Group 9 vs. Group 6		ACM: 1.93(1.15-3.24)
									Group 9: ≥8.5mg dl;	Per 10μmo/l increase		ACM: 1.00(0.99-1.02)
												CVM: 1.00(0.98-1.03)
Xiao X 2020 [22]	China: Mainland	RCS/ Single	47.0±15.2	1269/2124	At least > 3	Median 42	554/275	Tertile 1: < 384μmol/l; Tertile 2: 384-460μmol/l; Tertile 3: > 460μmol/l.	Tertile 3 vs. Tertile 1	Per 1μmol/l increase	Age, sex, DM , CVD , BMI , eGFR, DBP, use of diuretic and LUA, Hb, Alb, TC.	ACM: 0.924(0.547-1.727) ACM: 0.993(0.598-1.651) ACM: 0.999(0.997-1.001)

Abbreviations: AC: All-cause; ACM: All-cause mortality; CV: Cardiovascular; CVM: Cardiovascular mortality; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; RCS: Retrospective cohort study; PCS: Prospective cohort study; NR:Not reported; SUA: Serum uric acid; vs.: versus; BMI: Body mass index; SBP: Systolic blood pressure; Hb:Hemoglobin; Na: Serum sodium; K: Serum potassium; Cl: Serum chlorine; BUN: Blood urea nitrogen; Scr: Serum creatinine; CO2: Venous carbon dioxide; Ca: Serum calcium; P: Serum phosphorus; Alb: Serum albumin; TG: Triglyceride; FBG: Fasting blood glucose; CRP: C-reactive protein; RRF: Residual renal function; PET: Peritoneal equilibration test; Kt/v: Urea clearance index; DM: Diabetes mellitus; CCB: Calcium blocker; RASi: Renin-angiotensinsystem inhibitor; iPTH: intact parathyroid hormone; FPG: Fasting plasma glucose; ESA: Erythropoiesis stimulating agentts; LUA: lower uric acid agent; UV: Urinary volume; eGFR: estimated glomerular filtration rate; DBP: Diastolic blood pressure; TC: Total cholesterol.

Table 3 Subgroup analyses of the relationship between serum uric acid and all-cause mortality

	Serum uric acid (categorical variable)				Serum uric acid (continuous variable)				
	No. of study	Sample size	HR (95%CI)	Heterogeneity(I^2)	No. of study	Sample size	HR (95%CI)	Heterogeneity (I^2)	Meta-regression (*P* value)
Study design									*P*=0.007
Prospective cohort study	1	1287	1.79(1.17-2.75)	35.8%	1	1287	1.16(1.03-1.32)	25.5%	
Retrospective cohort study	5	4570	1.09(0.70-1.70)	83.1%	8	11541	0.94(0.88-1.02)	83.7%	
Study location									
China—mainland	4	4683	1.57(1.26-1.96)	21.1%	7	7594	1.04(0.97-1.11)	73.0%	*P*<0.001
China—Taiwan	1	492	0.40(0.24-0.68)	-	1	492	0.70(0.48-1.03)	85.9%	
Other	1 (Portugal)	682	1.00(0.74-1.35)	-	1 (Japan)	4742	1.00(0.89-1.13)	-	*P*=0.002
Publication years									
2011—2016	2	3480	1.53(1.08-2.18)	48.9%	2	3480	1.12(1.01-1.24)	37.9%	*P*=0.017
2017—2021	4	2377	1.07(0.59-1.93)	87.3%	7	9348	0.92(0.84-1.01)	85.5%	
No. of center									*P*=0.539
Single center	5	3664	1.27(0.82-1.98)	83.7%	7	5893	0.97(0.89-1.06)	83.3%	
Multicenter	1	2193	1.21(0.85-1.73)	-	2	6935	1.03(0.96-1.11)	0%	
Adjusted for sex									*P*<0.001
Yes	4	4112	1.27(0.72-2.26)	84.9%	8	11765	0.97(0.90-1.04)	76.7%	
No	2	1745	1.25(0.80-1.95)	76.7%	1	1063	1.13(1.06-1.20)	_	
Adjusted for diabetes mellitus									*P*=0.019
Yes	6	5857	1.26(0.88-1.81)	80.5%	8	12341	1.00(0.94-1.07)	80.0%	
No	0	0	-	-	1	487	0.77(0.62-0.97)	-	
Adjusted for serum albumin									*P*=0.108
Yes	4	5035	1.22(0.76-1.96)	84.7%	7	12201	0.99(0.90-1.09)	81.0%	
No	2	822	1.40(0.62-3.14)	74.4%	2	627	0.90(0.70-1.17)	81.6%	

Abbreviations: HR: Hazard ratio; CI: Confidence interval; I2: I-square; No.: Number.

Table 4 Subgroup analyses of the relationship between serum uric acid and cardiovascular mortality

	Serum uric acid (categorical variable)				Serum uric acid (continuous variable)			
	No. of study	Sample size	HR (95%CI)	Heterogeneity(I^2)	No. of study	Sample size	HR (95%CI)	Heterogeneity (I^2)
Study design								
Prospective cohort study	1	1287	2.63(1.62-4.27)	0.0%	1	1287	1.34(1.16-1.55)	0.0%
Retrospective cohort study	3	3748	1.00(0.44-2.31)	82.5%	3	7427	0.90(0.76-1.06)	70.2%
Study location								
China—mainland	3	4543	1.93(1.39-2.68)	13.9%	2	3480	1.22(1.05-1.43)	44.6%
China—Taiwan	1	492	0.40(0.20-0.80)	-	1	492	0.71(0.55-0.93)	29.5%
Other					1 (Japan)	4742	1.00(0.91-1.10)	-
Publication years								
2011—2016	2	3480	2.06(1.27-3.34)	38.7%	2	3480	1.22(1.05-1.43)	44.6%
2017—2021	2	1555	0.85(0.20-3.57)	90.8%	2	5234	0.82(0.62-1.08)	77.7%
No. of center								
Single center	3	2842	1.49(0.66-3.38)	84.7%	2	1749	1.06(0.80-1.39)	80.3%
Multicenter	1	2193	1.35(0.74-2.46)	-	2	6965	1.01(0.93-1.09)	0.0%
Adjusted for sex								
Yes	3	3972	1.39(0.60-3.24)	84.4%	4	8714	1.05(0.90-1.23)	74.0%
No	1	1063	1.73(1.03-2.91)	-	0	0	_	_
Adjusted for diabetes mellitus								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8714	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	_	-
Adjusted for serum albumin								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8714	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	_	-

Abbreviations: HR: Hazard ratio; CI: Confidence interval; I2: I-square; No.: Number.

Figure legends

Fig.1 Flow diagram of study search and selection.

Fig.2 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and all-cause mortality in PD patients

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis**.**

Fig.3 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis**.**

Fig.4 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and cardiovascular mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis**.**

Fig.5 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.

Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis**.**

Supplement legends

eFigure 1. Funnel plot for relationship between serum uric acid level per 1mg/dl increase and all-cause mortality in peritoneal dialysis patients.

eTable 1. Searching strategies for electronic databases

eTable 2. Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

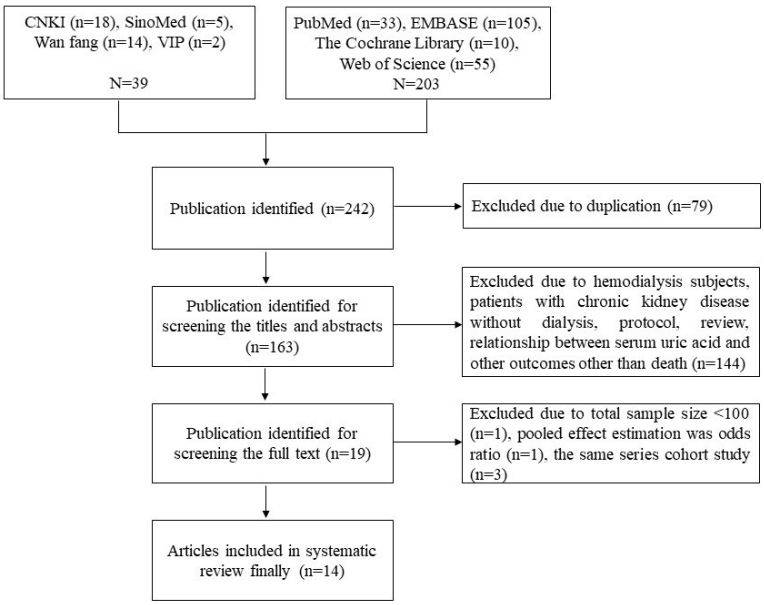

Fig.1 Flow diagram of study search and selection.

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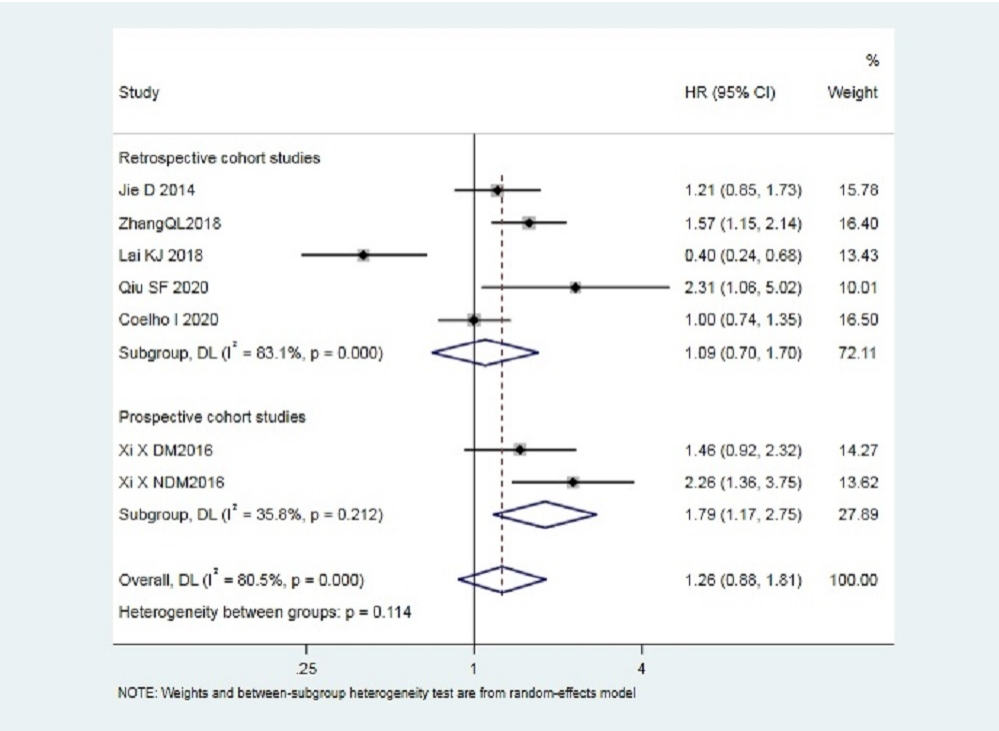

Fig.2 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and all-cause mortality in PD patients
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

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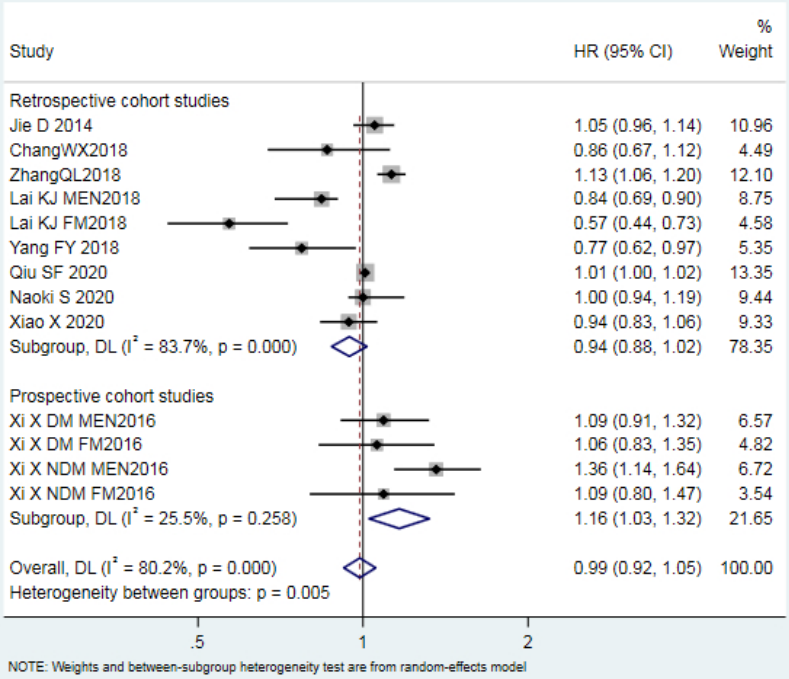


Fig.3 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Famale; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)

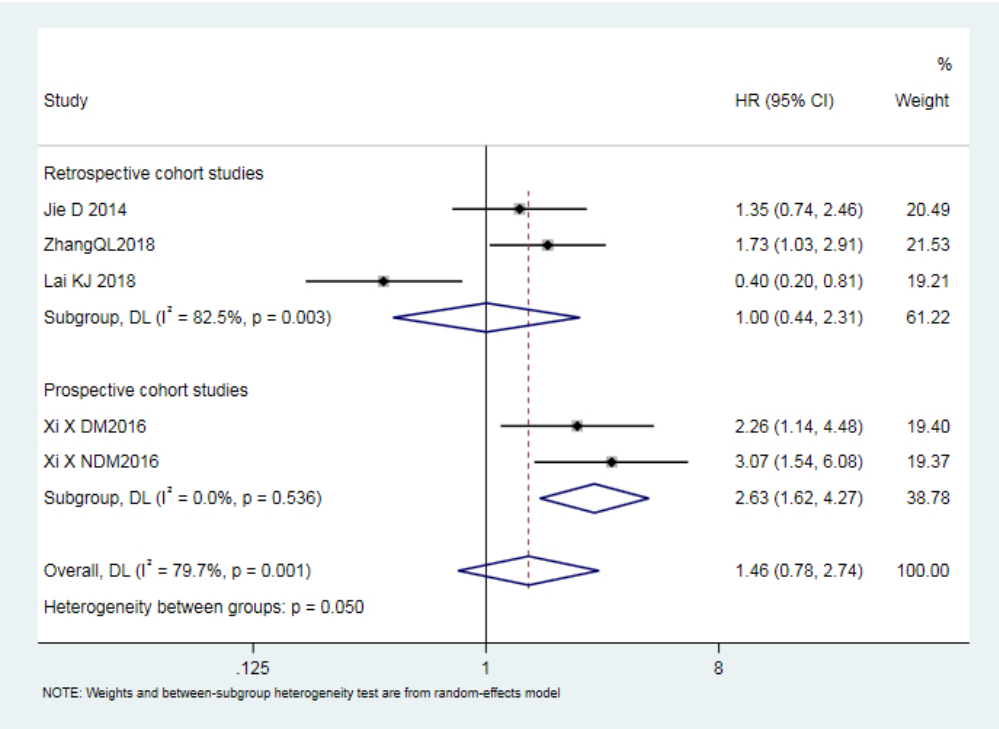


Fig.4 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and cardiovascular mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)

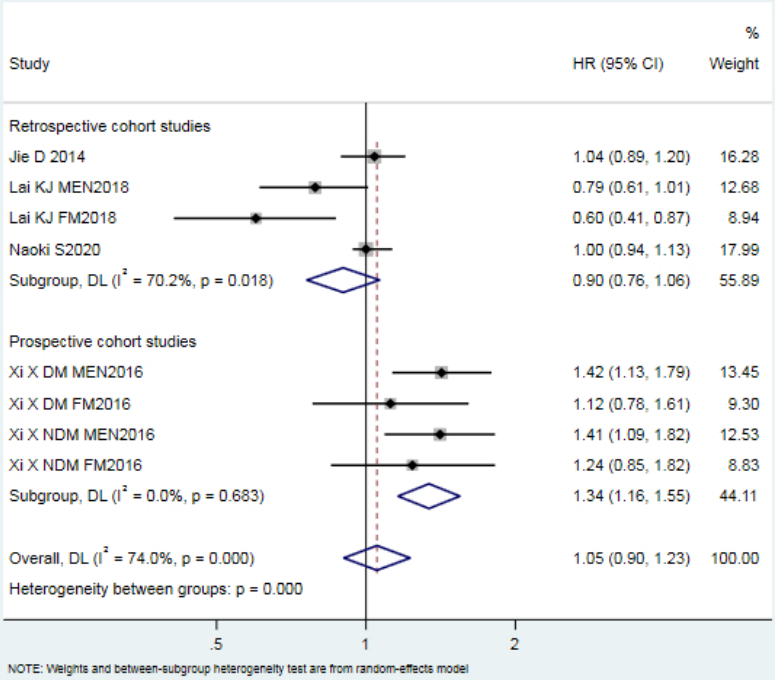
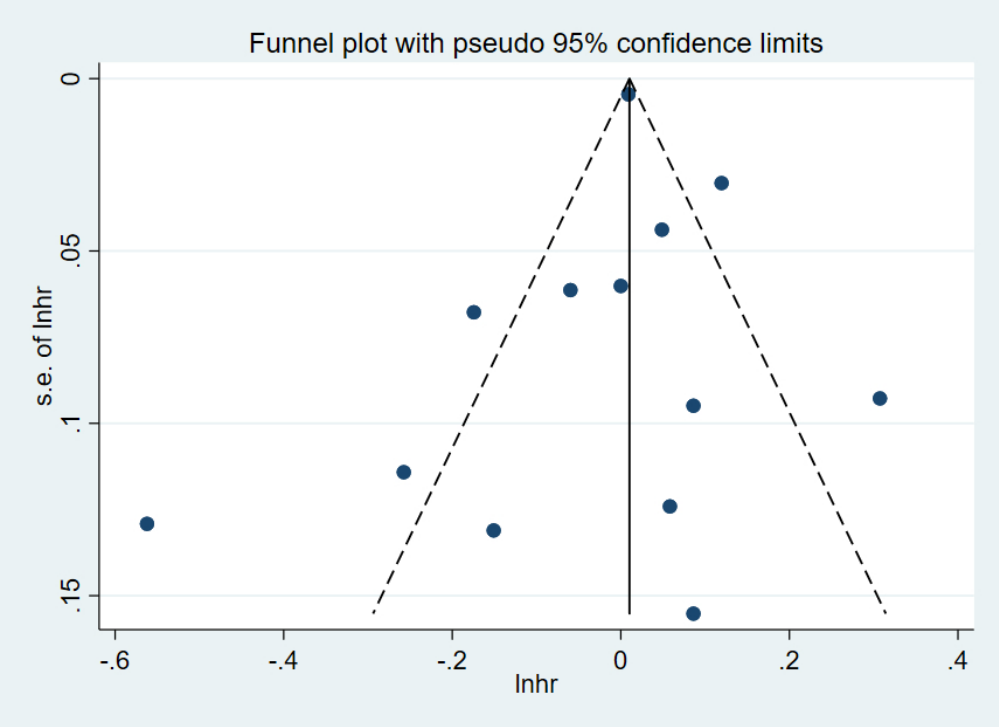


Fig.5 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Famale; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)



301x219mm (72 x 72 DPI)

eTable 1 Searching strategies for electronic databases

Databases	Searching strategies	Results (n)
PubMed	#1. Uric Acid [Mesh] OR Uric Acid [Title/Abstract] OR serum uric acid [Title/Abstract] #2. Mortality [Mesh] OR Mortality [Title/Abstract] #3. Peritoneal Dialysis [Mesh] OR Peritoneal Dialysis [Title/Abstract] OR PD [Title/Abstract] OR continuous ambulatory PD [Title/Abstract] OR CAPD [Title/Abstract] OR intermittent PD [Title/Abstract] OR IPD [Title/Abstract] OR automated PD [Title/Abstract] OR APD [Title/Abstract] OR continuous cyclic PD [Title/Abstract] OR CCPD [Title/Abstract] OR tidal PD [Title/Abstract] OR TPD [Title/Abstract] #4. #1 AND #2 AND # 3	33
The Cochrane library	#1. Uric Acid [Title/Abstract/Keywords] OR serum uric acid [Title/Abstract/Keywords] #2. Mortality [Title/Abstract/Keywords] #3. Peritoneal Dialysis [Title/Abstract/Keywords] OR PD [Title/Abstract/Keywords] OR continuous ambulatory PD [Title/Abstract/Keywords] OR CAPD [Title/Abstract/Keywords] OR intermittent PD [Title/Abstract/Keywords] OR IPD [Title/Abstract/Keywords] OR automated PD [Title/Abstract/Keywords] OR APD [Title/Abstract/Keywords] OR continuous cyclic PD [Title/Abstract/Keywords] OR CCPD [Title/Abstract/Keywords] OR tidal PD [Title/Abstract/Keywords] OR TPD [Title/Abstract/Keywords] #4. #1 AND #2 AND # 3	10
EMBASE	#1. (Uric Acid OR serum uric acid).ab,ti #2. (Mortality).ab,ti #3. (Peritoneal Dialysis OR PD OR continuous ambulatory PD OR CAPD OR intermittent PD OR IPD OR automated PD OR APD OR continuous cyclic PD OR CCPD OR tidal PD OR TPD).ab,ti #4. #1 AND #2 AND # 3	105
Web of Science	#1. Uric Acid OR serum uric acid [Topic] #2. Mortality [Topic] #3. Peritoneal Dialysis OR PD OR continuous ambulatory PD OR CAPD OR intermittent PD OR IPD OR automated PD OR APD OR continuous cyclic PD OR CCPD OR tidal PD OR TPD [Topic] #4. #1 AND #2 AND # 3	55
Chinese databases:	#1. niaosuan (uric acid,尿酸) OR xueniaosuan (serum uric acid,血尿酸)	CNKI:18

CNKI, SinoMed, VIP, Wan Fang	#2. siwanglv (mortality,死亡率) #3. fumotouxi (peritoneal dialysis,腹膜透析) OR lianxuxingfeiwochuangfumotouxi (continuous ambulatory peritoneal dialysis,连续性非卧床腹膜透析) OR zidonghuafumotouxi (automated peritoneal dialysis,自动化腹膜透析) #4. #1 AND #2 AND # 3	SinoMed:5 VIP:2 WanFang:14

eTable 2 Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

Study ID	Selection				Comparability	Outcome			Total score
	Representativeness of exposed group	Representativeness of non-exposed group	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of groups on the basis of design or analysis	Assessment of outcome	Follow up long enough	Adequacy of follow-up of groups	
Sheng F 2013[25]	☆	☆	☆	☆	☆	☆	☆	-	7
Jie D 2014[14]	☆	☆	☆	☆	☆	☆	☆	☆	8
Xi X 2016[21]	☆	☆	☆	☆	☆	☆	☆	☆	8
Eunjin B2016[26]	☆	☆	☆	☆	-	☆	☆	☆	7
ChangWX2018[27]	☆	☆	☆	☆	☆	☆	☆	☆	8
ZhangQL2018[28]	☆	☆	☆	☆	☆	☆	☆	-	7
Lai KJ 2018[29]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yang FY 2018 [30]	☆	☆	☆	☆	☆	☆	☆	-	7
ChangWX2019[31]	☆	☆	☆	☆	☆	☆	☆	-	7
Xiang SL 2019[32]	☆	☆	☆	☆	☆	☆	☆	☆	8
Qiu SF 2020[33]	☆	☆	☆	☆	☆	☆	☆	-	7
Coelho I 2020[34]	☆	☆	☆	☆	☆	☆	☆	-	7
Naoki S 2020[35]	☆	☆	☆	☆	☆	☆	☆	☆	8
Xiao X 2020[22]	☆	☆	☆	☆	☆	☆	☆	☆	8

MOOSE Checklist——A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Checklist Item	Answer
Reporting of background should include	
Problem definition	Page 5, Line 97-98
Hypothesis statement	Page 5, Line 98-100
Description of study outcome(s)	Page 5, Line 99-100; Page 6, Line 119-125
Type of exposure or intervention used	Page 5, Line 99-100; Page 6, Line 113-117
Type of study designs used	Page 5, Line 108
Study population	Page 5, Line 98-100; Page5-6, Line 109-112
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	Page 7, Line 136
Search strategy, including time period included in the synthesis and keywords	Page 7, Line 137-139, Page 7-8, Line146-155
Effort to include all available studies, including contact with authors	Page 7, Line 144-146
Databases and registries searched	Page 7, Line 140-143
Search software used, name and version, including special features used (eg, explosion)	Page 7-8, Line 146-155
Use of hand searching (eg, reference lists of obtained articles)	Page 7, Line 142-143
List of citations located and those excluded, including justification	Page 6-7, Line 127-134; Page 10, Line 209-216
Method of addressing articles published in languages other than English	Page 7, Line 143-144
Method of handling abstracts and unpublished studies	Page 7, Line 143-144
Description of any contact with authors	Page 7, Line 144-146
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Page 8, Line 157-165
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Page 8, Line 162-165
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Page 8, Line 167-172
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Page 8, Line 168-169; Page 11, Line 223-231
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 8-10, Line 174-203
Assessment of heterogeneity	Page 9-10, Line 197-199
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 8-10, Line 174-203

MOOSE Checklist——A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Provision of appropriate tables and graphics	Page 7-8, Line 154-155
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Page 10, Line 215-216 Fig.1
Table giving descriptive information for each study included	Page 10, Line 219-220 Table 1,2
Results of sensitivity testing (eg, subgroup analysis)	Page 13-14, Line 285-304
Indication of statistical uncertainty of findings	Page 15, Line 309-312
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Page 15, Line 327-328
Justification for exclusion (eg, exclusion of non–English-language citations)	Page 10, Line 209-216
Assessment of quality of included studies	Page 16-17, Line 339-372
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Page 20, Line 429-433
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review	Page 20, Line 429
Guidelines for future research	Page 20, Line 433-437
Disclosure of funding source	Page 21, Line 448-452

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.