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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 Xue<sup>1,2</sup>, Chun-li Lu<sup>2</sup>, Xin-yan Jin<sup>2</sup>, Xue-han Liu<sup>2</sup>, MinYang<sup>3</sup>, Xiao-qin Wang<sup>4</sup>, Hong Cheng<sup>4</sup>, Jun Yuan<sup>4</sup>, Qiang Liu<sup>4</sup>, Ruo-xiang Zheng<sup>2</sup>, and Jian-ping Liu<sup>2\*</sup>

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

<sup>2</sup> Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

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

<sup>4</sup> Department of nephrology, Hubei provincial hospital of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

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

**Email addresses:** Xue Xue (xue025004138@163.com); Chun-li Lu (annyzheni@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@hbtc.edu.cn); Qiang Liu (leonjordan23@sina.com); Ruo-xiang Zheng (zhengruox@

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

24 **\*Corresponding**

25 Jian-ping Liu\*

26 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine,

27 Beijing, 100029, China. E-mail: Liujp@bucm.edu.cn

28 Telephone number: 13718004410.

29 **Word count of full text:** 3469.

31 **Abstract**

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

35 **Design** A systematic review of observational studies.

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

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

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

1  
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3  
4 45 SUA category was significantly higher than lowest for all-cause (1 study; 1287  
5  
6 46 participants; HR 1.79; 95%CI 1.17-2.75) and CV mortality (1 study; 1287 participants;  
7  
8  
9 47 HR 2.63; 95%CI 1.62-4.27). And an increase of 1mg/dl in SUA level was associated  
10  
11 48 with an 16% increased risk of all-cause mortality (1 study; 1287 participants; HR 1.16;  
12  
13 49 95%CI 1.03-1.32) and 34% increased CV mortality risk (1 study; 1287 participants;  
14  
15 50 HR 1.34; 95%CI 1.16-1.55). While, in retrospective cohort studies, highest SUA  
16  
17 51 category was not found to elevate all-cause (5 studies; 4570 participants; HR 1.09;  
18  
19 52 95%CI 0.70-1.70) and CV mortality (3 studies; 3748 participants; HR 1.00; 95%CI  
20  
21 53 0.44-2.31) compared with lowest. And there was also no increase in all-cause (8 studies;  
22  
23 54 11541 participants; HR 0.94; 95%CI 0.88-1.02) and CV mortality (3 studies; 7427  
24  
25 55 participants; HR 0.90; 95%CI 0.76-1.06) with every 1mg/dl increase in SUA level.  
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34  
35 56 **Conclusions** Results of prospective cohort study and retrospective cohort studies were  
36  
37 57 inconsistent. Consequently, prospective, multicenter, long term follow-up studies are  
38  
39 58 required in future to confirm association of SUA and mortality in PD patients.

40  
41 59 **Trial registration number** International Platform of Registered Systematic Review and  
42  
43 60 Meta-analysis Protocols (INPLASY.COM) registration number:202140020.  
44

#### 45 61 **Strengths and limitations of this study**

46  
47  
48 62 This is the first systematic review of observational studies exploring the correlation  
49  
50 63 between SUA level and mortality in PD patients.

51  
52  
53 64 We used critical systematic review and subgroup analysis to describe the results, and  
54  
55 65 proposed future research direction.

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57  
58 66 In spite of many important confounding factors had been adjusted in the studies,  
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67 residual and unknown confounding still can not be excluded entirely.

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

## 70 **Introduction**

71 End-stage renal disease (ESRD) is one of the major diseases affecting human health,  
72 which causes enormous pressure and burden on medical care and society. Peritoneal  
73 dialysis (PD), as one of the effective alternative treatments for ESRD, has many  
74 features, such as stable hemodynamics, protection of residual renal function (RRF),  
75 good removal of middle molecular toxins, low risk of infectious disease infection,  
76 health economics advantage and home treatment [1]. Currently, PD has been widely  
77 used all over the world. Epidemiological survey results showed that as of 2013, the  
78 total number of people receiving peritoneal dialysis worldwide reached approximately  
79 220,000 [2]. Of concern, patients with ESRD treated with dialysis still have a high  
80 mortality rate [3]. Therefore, the identification of potential risk factors that can be  
81 intervened is still an important topic in the field of PD, which is of great significance  
82 for improving the prognosis of patients and increasing the quality of life.

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

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4 89 between SUA level and risk of death among dialysis patients. For hemodialysis  
5  
6 90 population, many studies have confirmed that hypouricemia significantly increased the  
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8  
9 91 mortality of maintenance hemodialysis patients [10-12]. Nevertheless, SUA's role for  
10  
11 92 all-cause and CV mortality in PD patients has been controversial. One study in PD  
12  
13 93 patients indicated that elevated SUA level was an independent risk factor for all-cause  
14  
15 94 and CV mortality in men treated with PD [13]. The result of another study showed that  
16  
17 95 the prognostic value of SUA in all-cause and CV mortality was weak in PD patients  
18  
19 96 [14]. Whereas hyperuricemia was found to predict lower risk of all-cause mortality in  
20  
21 97 PD patients with lower relative appendicular skeletal muscle in another study [15]. In  
22  
23 98 short, results regarding the effect of SUA on the prognosis of PD patients appeared to  
24  
25 99 be inconsistent.

30  
31  
32 100 At present, there is a lack of systematic reviews on the relationship between SUA,  
33  
34 101 all-cause and CV mortality in PD population. We hypothesized that there may be exist  
35  
36 102 independent correlation between elevated SUA level and mortality in participants with  
37  
38 103 PD. Thus, we systematically analyze available studies to determine whether the  
39  
40 104 hypothesis was right.

## 45 105 **Methods**

### 48 106 **Protocol and registration**

49  
50 107 Methods of this review were specified in advance and documented in International  
51  
52 108 Platform of Registered Systematic Review and Meta-analysis Protocols  
53  
54 109 (INPLASY.COM). (**Registration number:202140020**). The content of this review  
55  
56 110 was reported according to the guidelines of "Meta-analysis of Observational Studies in  
57  
58  
59  
60



1  
2  
3  
4 111 Epidemiology guidelines” (MOOSE) [16].  
5

6 112 **Eligibility criteria**  
7

8  
9 113 ***Types of studies***  
10

11 114 Cohort studies and case-control studies were identified.  
12

13  
14 115 ***Participants***  
15

16 116 All participants who had received PD for more than 3 months. There was no restriction  
17  
18 117 on the type of PD, including continuous ambulatory PD, intermittent PD, automated  
19  
20  
21  
22 118 PD, continuous cyclic PD and tidal PD.  
23

24  
25 119 ***Exposure factor***  
26

27 120 Hyperuricemia in PD population was the exposure factor of this study. Either  
28  
29 121 categorization according to baseline SUA level or time-average SUA concentration  
30  
31  
32 122 was acceptable. Definition of hyperuricemia and the categorization for the SUA level  
33  
34  
35 123 was based on the definition in each included article respectively.  
36

37  
38 124 ***Outcome***  
39

40 125 Primary outcome: all-cause mortality. The death was determined by the hospital  
41  
42 126 medical record and death certificate.  
43

44  
45 127 Secondary outcome: CV mortality. The definition of “CV events”: coronary  
46  
47  
48 128 events (myocardial infarction, unstable angina), cardio myopathy, cardiac arrest,  
49  
50  
51 129 cardiac dysrhythmia, congestive heart failure, ischemic brain injury, cerebrovascular  
52  
53 130 accident and peripheral vascular disease. The cause of death was determined through  
54  
55  
56 131 medical history, hospital medical records and death certificates.  
57

58  
59 132 ***Exclusion criteria***  
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4 133 (1) Hazard ratio (HR) and its corresponding 95% confidence interval (CI) (or other data  
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6 134 to calculate them) of all-cause or CV mortality for 1mg/dl change in SUA level, or for  
7  
8  
9 135 the highest versus lowest SUA category or the lowest versus highest category could not  
10  
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12 136 be obtained from the original article; (2) Cohort studies with a total sample size of less  
13  
14 137 than 100 participants; (3) If studies originated from the same series of cohort samples,  
15  
16  
17 138 or part of the cohort samples were published repeatedly, only the literature with the  
18  
19  
20 139 largest sample size and the longest follow-up could be included, and the rest of the  
21  
22 140 literature need to be excluded.

#### 23 24 25 141 **Search strategy**

26  
27 142 Two authors (X.X. and H.C.) searched the following Chinese and English databases  
28  
29  
30 143 from their inception to 15<sup>th</sup> January 2021. Chinese databases included China National  
31  
32 144 Knowledge Infrastructure (CNKI), SinoMed, Chinese Science and Technology Journal  
33  
34  
35 145 Database (VIP), and Wan Fang Database. English databases included PubMed,  
36  
37  
38 146 EMBASE, the Cochrane Library, and Web of Science. Trial registers including Clinical  
39  
40  
41 147 Trials. gov and the World Health Organization International Clinical Trials Registry  
42  
43  
44 148 Platform were also searched. Additionally, related reviews, conference papers,  
45  
46  
47 149 references lists and gray literatures also were searched manually to minimize the  
48  
49  
50 150 missed detection rate. No language or publication type was imposed, published  
51  
52  
53 151 abstracts were also considered. If there was a lack of information in the retrieved  
54  
55  
56 152 literature, it was necessary to contact the author via email to obtain the missing data to  
57  
58  
59 153 ensure that literatures could be included in a comprehensive way. Taking “PubMed” as  
60  
154 an example, the retrieval strategy was as follows: (“Uric Acid” [Mesh] OR “Uric Acid”

1  
2  
3  
4 155 OR “serum uric acid”) AND (“Mortality” [Mesh] OR “Mortality”) AND ( “Peritoneal  
5  
6 156 Dialysis” [Mesh] OR “Peritoneal Dialysis” OR “PD” OR “continuous ambulatory PD”  
7  
8  
9 157 OR “CAPD” OR “intermittent PD” OR “IPD” OR “automated PD” OR “APD” OR  
10  
11  
12 158 “continuous cyclic PD” OR “CCPD” OR “tidal PD” OR “TPD”).

### 14 159 **Studies selection and data extraction**

16  
17 160 The titles and the abstracts were screened first, then the full-text versions were checked  
18  
19 161 according to inclusion and exclusion criteria. Two authors (X.X. and Q.L.) examined  
20  
21  
22 162 the full text to identify the eligible trials independently. We made a data extraction  
23  
24  
25 163 sheet in advance. Two authors (X.X. and H.C.) extracted data independently.  
26  
27 164 Disagreements of studies selection and data extraction were resolved by consulting  
28  
29  
30 165 corresponding author JP Liu. Information was extracted from each included trial on:  
31  
32  
33 166 first author, publication year, age, gender, study design, dialysis duration, sample size,  
34  
35 167 study location, center, length of follow up, categories according to serum uric acid,  
36  
37  
38 168 comparison, adjustments, adjusted HR (95%CI).

### 39 40 41 169 **Methodological quality assessment**

42  
43 170 The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality  
44  
45 171 of observational studies [17]. NOS allocated a maximum of 9 points for quality of  
46  
47  
48 172 selection, comparability, and outcome of study population. Two authors (X.X. and J.Y.)  
49  
50  
51 173 assessed and validated the quality of included studies independently. Any  
52  
53 174 disagreements were resolved by discussion with corresponding author JP Liu. Overall  
54  
55  
56 175 study quality scores were defined as poor (0–3), fair (4–6), or good (7–9).

### 57 58 59 176 **Statistical analysis**

1  
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3  
4 177 SUA was analyzed not only as a categorical variable, but also as a continuous variable  
5  
6 178 in the included studies. The statistical analysis for the overall association between SUA  
7  
8  
9 179 levels and death risk (all-cause and CV mortality) were based on random effects model  
10  
11 180 and on comparisons of highest versus lowest category of SUA level, or by increase of  
12  
13  
14 181 1mg/dl. HR and 95% CI were used as effect indicators. HR and corresponding 95% CI  
15  
16  
17 182 of each study were transformed to their natural logarithm (lnHR, lnCI and lnUCI), and  
18  
19  
20 183 overall HR and its 95% CI was calculated by exponentiation of the pooled lnHR, lnCI  
21  
22 184 and lnUCI.

23  
24  
25 185 If data of cases, person-years, and HR and 95% CI for each category were  
26  
27 186 available in included studies, then a dose-response analysis would be performed to  
28  
29  
30 187 further explore the relationship between SUA and mortality. The potential non-linearity  
31  
32  
33 188 association was examined by modeling SUA levels using restricted cubic splines with  
34  
35 189 three knots at 25, 50, and 75% of the distribution. We assigned the median or middle  
36  
37  
38 190 point of the upper and lower boundaries in each category as the corresponding dose to  
39  
40  
41 191 the related HR for each study. In case of  $P$  value  $> 0.05$ , the linear regression model  
42  
43 192 should be considered.

44  
45 193 square ( $I^2$ ) was applied to test the statistical heterogeneity among studies (Higgins  
46  
47  
48 194 and Thompson, 2003) [19]. When  $I^2 > 85\%$ , we believed that the results could not be  
49  
50  
51 195 pooled. Data not suitable for statistical pooling were synthesized qualitatively. To  
52  
53  
54 196 explore the source of heterogeneity among studies, subgroup analyses were conducted  
55  
56 197 according to study design, study location, publication years, adjustment for sex,  
57  
58  
59 198 adjustment for DM and adjustment for albumin. Additionally, the meta-regression  
60

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4 199 analysis was also performed to detect potential heterogeneity based on the above  
5  
6 200 variables when about 10 studies were included. Sensitivity analysis was performed with  
7  
8  
9 201 removing one study at a time to explore the robustness of results if data were available.  
10  
11 202 The possibility of publication bias was detected by funnel plots and Egger's test if there  
12  
13  
14 203 were about 10 studies. STATA16.0 software (StataCorp, College Station, Texas, 77845  
15  
16  
17 204 USA) was used for data analysis.

### 205 **Patient and Public Involvement statement**

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

## 208 **Results**

### 209 **Search results**

210 Two hundred and forty-two relevant citations were retrieved. After scanning the full  
211 texts, five literatures were excluded. We excluded cohort samples of the same series  
212 [13,15,20], only the studies with the largest sample size and the longest follow-up time  
213 were included [21,22]. Besides, we excluded a published abstract [23], due to its total  
214 sample size of entire cohort was only 60 participants. And another study was excluded  
215 due to whose pooled effect estimation were reported as odds ratio (OR) with 95% CI  
216 [24]. Finally, fourteen literatures were eligible for this review. Details of search and  
217 selection process were illustrated in Fig.1.

### 218 **Characteristic of included trials**

219 A total of fourteen literatures involving 24031 participants were included [14,21,22,25-  
220 35]. The included studies were all cohort studies, including prospective and

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

### 223 **Methodological quality of included studies**

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

### 235 **Primary outcome**

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

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

1  
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4 243 In retrospective cohort studies, five studies with 4570 patients reported HR and  
5  
6 244 95% CI of all-cause mortality for the highest versus the lowest SUA category  
7  
8  
9 245 [14,28,29,33,34]. The highest SUA category was not found to elevate all-cause  
10  
11 246 mortality (HR 1.09; 95% CI 0.70-1.70; Fig.2) compared with the lowest category of  
12  
13  
14 247 PD patients.

15  
16  
17 248 HR and corresponding 95% CI were reported in three retrospective cohort studies  
18  
19 249 for the lowest versus the highest SUA category [26,27,31]. Among them, the data of  
20  
21 250 one of the articles [27] was supplemented by the corresponding author Changxiu via e-  
22  
23 251 mail. The pooled HR was 1.52 (95%CI 0.79-2.89), with heterogeneity of  $I^2=32.8\%$ .

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

253 Only one prospective study with 1287 PD patients reported HR and 95% CI of all-  
24  
25 254 cause mortality for 1mg/dl increase in SUA level [21]. And pooled result showed that  
26  
27 255 for every 1mg/dl increase in SUA level, risk of all-cause death increased by 16% (HR  
28  
29 256 1.16; 95%CI 1.03-1.32; Fig.3).

30  
31 257 In retrospective cohort studies, eight studies with 11541 PD patients reported HR  
32  
33 258 and 95% CI of all-cause mortality for 1mg/dl increase in SUA level [14,22,27-  
34  
35 259 30,33,35]. When the unit of SUA concentration in the literature was different, 60  $\mu$   
36  
37 260 mol/l was approximately equal to 1mg/dl. In short, each 1mg/dl increase in SUA level  
38  
39 261 didn't appear to significantly increase the risk of all-cause mortality in PD population  
40  
41 262 (HR 0.94; 95% CI 0.88-1.02; Fig.3).

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

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

1  
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3  
4 265 of outcomes of the entire cohort population, we were unable to obtain the number of  
5  
6 266 all-cause and CV deaths and person-years in each category. Despite we tried our best  
7  
8  
9 267 to contact authors by email or phone in order to acquire necessary data for non-linearity  
10  
11  
12 268 test, only one auther responded and provided relevant data [27]. At last, dose-response  
13  
14  
15 269 analysis failed.

## 17 270 **Secondary outcome**

### 19 271 *Association of serum uric acid in categories with cardiovascular mortality*

22 272 One prospective cohort study with 1287 patients reported HR and 95% CI of CV  
23  
24 273 mortality for the highest SUA category compared with the lowest [21]. Pooled result  
25  
26  
27 274 of HR in the highest versus the lowest category was 2.63 (95% CI 1.62-4.27). (eFigure1  
28  
29  
30 275 in the [Supplement](#))

32 276 Three retrospective cohort studies with 3748 patients reported HR and 95% CI of  
33  
34  
35 277 CV mortality for the highest versus the lowest SUA category [14,28,29]. And the  
36  
37  
38 278 highest SUA category was not found to increase CV mortality (HR 1.00; 95% CI 0.44-  
39  
40  
41 279 2.31) compared with the lowest category of PD patients (eFigure1 in the [Supplement](#)).

### 43 280 *Association of serum uric acid per 1mg/dl increase with cardiovascular mortality*

45 281 One prospective cohort study with 1287 patients reported HR and 95% CI of CV  
46  
47  
48 282 mortality for 1mg/dl increase in SUA level [21]. And an increase of 1mg/dl in SUA  
49  
50  
51 283 level was associated with an 34% increased risk of CV mortality (HR 1.34; 95%CI  
52  
53  
54 284 1.16-1.55; eFigure2 in the [Supplement](#)).

56 285 Three retrospective cohort studies with 7427 patients reported HR and 95% CI of  
57  
58  
59 286 CV mortality for 1mg/dl increase in SUA level [14,29,35]. By meta-analysis, each 1  
60



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2  
3  
4 287 mg/dl increase in SUA level didn't appear to significantly increase the risk of CV death  
5  
6 288 in PD population (HR 0.90; 95% CI 0.76-1.06; eFigure2 in the [Supplement](#)).

8  
9 289 **Additional analysis**

10  
11 290 ***Subgroup analysis and meta-regression***

12  
13  
14 291 We explored the source of heterogeneity for subgroup analysis and meta-regression.  
15  
16 292 Subgroup analysis only included literatures which were on comparisons of the highest  
17  
18 293 versus the lowest category of SUA level, or by change of 1mg/dl increase. The pooled  
19  
20 294 HR (95% CI) and I<sup>2</sup> of subgroup analysis for association of SUA with all-cause and  
21  
22 295 CV mortality were presented in Table 2a and Table 2b, respectively.

23  
24  
25  
26  
27 296 As mentioned before, whether SUA was a categorical variable or a continuous  
28  
29 297 variable, results of prospective cohort studies differed from those of retrospective  
30  
31 298 studies. Besides, combined with the results of subgroup analysis, when SUA was  
32  
33 299 estimated as a categorical variable, association of higher SUA level with increased all-  
34  
35 300 cause and CV mortality was significant in studies of mainland in China, but not in the  
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37 301 rest of the locations. SUA as a continuous variable, relationship of higher CV mortality  
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39 302 for 1 mg/dl increase in SUA level was significant in studies of mainland China, but not  
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41 303 in the rest of the locations. Furthermore, we analyzed the relevant studies published in  
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43 304 the past ten years, and results of studies completed during 2011-2016 were different  
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45 305 from the results during 2017-2021 period.

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48 306 In addition, in studies of association between SUA (as a continuous variable) and  
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50 307 all-cause mortality, study design, study location, publication years, adjusted for sex and  
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52 308 DM were the heterogeneous sources by meta-regression (Table 2a).

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4 309 ***Test of Publication bias***  
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6 310 The funnel plots and Egger's test ( $t=1.07, p=0.309$ ) indicated that there was no obvious  
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9 311 publication bias of studies for association of all-cause mortality and SUA level per  
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11 312 1mg/dl increase. The funnel plot was presented in eFigure3 in the [Supplement](#).  
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14 313 ***Sensitivity analysis***  
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17 314 In retrospective cohort studies, primary outcome showed that there was no significant  
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19 315 effect on the pooled HR values of other studies with one study removed at a time. The  
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22 316 above indicated that the results were robust.  
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25 317 **Discussion**  
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27 318 **Principal findings and comparison with prior reviews**  
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30 319 For PD population, previous original studies indicated inconsistent relationship  
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32 320 between SUA and mortality. After searching systematically, we found that there were  
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35 321 some meta-analyses of investigating the correlation between SUA and mortality in  
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37 322 different population [36-39], however, we have not yet found one only for PD patients.  
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40 323 A systematic review published in 2016 showed that elevated SUA level was  
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42 324 significantly associated with the risk of death in patients with CKD, including dialysis  
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44 325 and non-dialysis subjects [40]. Subgroup analysis of this review demonstrated that  
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46 326 hyperuricemia was an independent predictor for mortality in PD population, while, this  
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48 327 predictive value was not found in the hemodialysis (HD) population. Only 1  
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51 328 prospective cohort study and 2 retrospective cohort studies were included in PD  
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54 329 subgroup. In our study, we included a total of 14 cohort studies, of which 2 were  
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56 330 prospective studies and 12 were retrospective studies. Quality of all studies was good  
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4 331 by NOS assessment. Only one prospective cohort study suggested that regardless of  
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6 332 whether SUA was estimated as a continuous or a categorical variable, elevated SUA  
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9 333 level was significantly associated with increased risk of all-cause and CV mortality in  
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11 334 PD patients. Whereas, no significant associations between them in retrospective study.  
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14 335 Considering that only one prospective study [21] was included in analysis, so the result  
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17 336 should be interpreted with caution.

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19 337 Although the detrimental effect of SUA is obvious, which is an endothelial toxin  
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22 338 and plays a role in endothelial dysfunction [41], as a powerful free radical scavenger in  
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25 339 human at the same time, SUA may be expected to offer a number of benefits within the  
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27 340 CV system in PD patients [42,43]. Besides, the problem of protein loss and malnutrition  
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30 341 is prominent in PD population [44]. “Malnutrition-inflammation complex syndrome  
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32 342 (MICS)” is believed to be the main cause of high rate of CV atherosclerotic disease and  
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35 343 increased mortality and hospitalization in HD patients [45,46]. The underlying  
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37 344 mechanism of MICS may also be present in PD patients. As a nutritional marker ,  
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40 345 SUA might be involved in the MICS axis. The pooled result of the retrospective studies  
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43 346 did not find that elevated SUA was associated with increased risk of mortality, perhaps  
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46 347 related to complex interaction mechanisms. Further investigations are warranted to  
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48 348 clarify the precise mechanisms.

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50 349 In addition, heterogeneous among included studies was generally high. The  
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53 350 different study location was one of the main sources of heterogeneity among studies by  
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56 351 meta-regression test. Subgroup analysis results further suggested that hyperuricemia  
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58 352 was associated with a high risk of CV death in the PD population in mainland China.  
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4 353 As a result, the correlation between the SUA level and the risk of death in different  
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6 354 regions needs to be explored and verified by prospective studies in future.  
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### 9 355 **Implications further research**

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11 356 Since the results of prospective and retrospective cohort studies were inconsistent, and  
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13 357 different regions of the study seemed to produce different result. Therefore, prospective,  
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15 358 multicenter, long term follow-up studies are required in future to explore the correlation  
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17 359 between SUA level and the risk of death in different regions, as well as to determine  
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19 360 the range of SUA concentrations which can reduce mortality and improve prognosis in  
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21 361 PD patients.  
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27 362 Additionally, since PD patients often suffered from underlying diseases and  
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29 363 complex conditions. Therefore, confounding factors must be adjusted comprehensively  
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31 364 in observational study to explore the relationship between etiology and prognosis in  
32  
33 365 future. For PD population, the following confounding factors should be considered to  
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35 366 make the conclusion more convincing. Such as: traditional independent risk factors of  
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37 367 CV events (age, gender, total lipoprotein cholesterol, low or high density lipoprotein  
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39 368 cholesterol, hypertension, diabetes, smoking [47]), history of CV, emotion status,  
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41 369 residual renal function, the related parameters of PD, the parameters of nutritional  
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43 370 status, use of diuretic and lower UA agents and so forth.  
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51 371 Besides, necessary information should be reported in detail in study report. Not  
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53 372 only can readers become more familiar with the details of the study, but also can  
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55 373 conveniently carry out secondary research and avoid waste of research resources.  
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### 58 374 **Conclusions**

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4 375 The results of the prospective and retrospective cohort studies were inconsistent. Only  
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6 376 one prospective cohort study showed that elevated SUA level was significantly  
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9 377 associated with increased risk of all-cause and CV mortality in PD patients.  
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12 378 Nevertheless, pooled result of retrospective cohort studies did not appear to indicate a  
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15 379 prominent association. So it is necessary to use SUA-lowering agents with caution for  
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17 380 PD patients in clinics. And prospective, multicenter, long term follow-up studies are  
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19  
20 381 needed in future to investigate the correlation between SUA level and the risk of death  
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22  
23 382 in different regions, as well as to explore the range of SUA concentration associated  
24  
25 383 with the lowest mortality in PD patients.

26  
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32  
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34 390 Registration: XX, CLL, XYJ and XHL. Acquisition, analysis, or interpretation of data:  
35 391 XX, HC, QL, JY, and JPL. Drafting of the manuscript: XX, XHL, CLL, XYJ and RXZ.  
36 392 Statistical analysis: MY, XX and XQW. Critical revision of the manuscript: XQW and  
37 393 JPL. Supervision: JPL.

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39  
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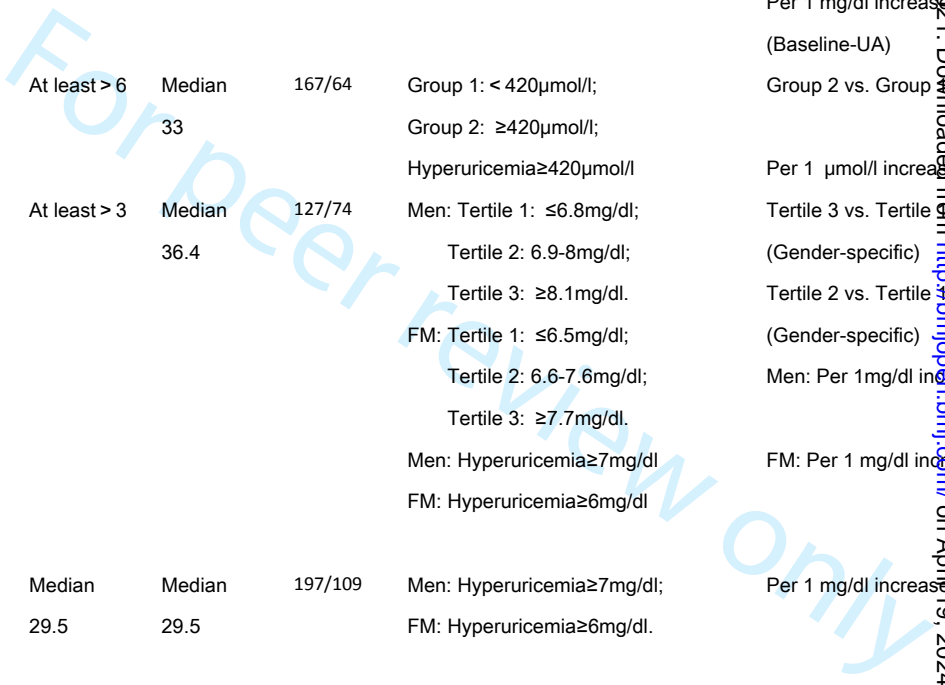


508 **Table 1** Characteristics of included studies

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 3 vs. Group	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 (Gender-specific) Tertile 2 vs. Tertile (Gender-specific) Per 1 mg/dl increase	Age, RRF, Hb, Alb, phosphate, LDLC, CRP, history 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)
Xu 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 (DM: Gender specific) Tertile 3 vs. Tertile (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	Age, sex, BMI, SBP, Ca, P,	ACM: 1.478(0.602-3.627)

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4											
5	[36]	Korea	-center			43.9		Group 2: TA-UA≥5.5 mg/dl.			Alb, TC, DM, SGA.
6	ChangWX2018	China:	RCS/	55.2±14.9	171/300	At least > 3	22.6±15.9	AC 44	Group1: TA-UA < 6mg/dL;	Group 3 vs. Group	Sex, age, DM, CVD history, ACM: 4.69(1.24-17.72)
7		Mainlan	Single						Group2: TA-UA 6–8mg/dL;	Group 1 vs. Group	RRF, BMI, SBP, Hb, Alb, BUN, ACM: 3.24(1.25-8.39)
8		d							Group3: TA-UA ≥8mg/dL.	Group 1 vs. Group	SCr, Na, K, CO2, Ca, P, LDL- ACM: 0.603 (0.158-2.309)
9										Per 1 mg/dl increase	C, CRP, RASi, diuretic. ACM: 0.86(0.67-1.12)
10										(Baseline-UA)	
11										Group 2 vs. Group	Age, Scr, P, Alb, BG, iPTH, ACM: 1.572(1.155-2.141)
12	ZhangQL2018	China:	RCS/	Median 51	557/1063	At least > 6	Median	167/64	Group 1: < 420µmol/l;		history of DM, DBP, Charlson CVM: 1.734(1.033-2.912)
13		Mainlan	Single				33		Group 2: ≥420µmol/l;		score. ACM: 1.002(1.001-1.004)
14		d							Hyperuricemia≥420µmol/l	Per 1 µmol/l increase	
15											Age, sex, BMI, pre-dialysis ACM: 0.4(0.24-0.68)
16	Lai,KJ 2018	China:	RCS/	53.5±15.3	237/492	At least > 3	Median	127/74	Men: Tertile 1: ≤6.8mg/dl;	Tertile 3 vs. Tertile	
17		Taiwan	Single				36.4		Tertile 2: 6.9-8mg/dl;	(Gender-specific)	status, smoking, present CVM: 0.4(0.2-0.81)
18									Tertile 3: ≥8.1mg/dl.	Tertile 2 vs. Tertile	medications, comorbidities of ACM: 1.06(0.7-1.58)
19									FM: Tertile 1: ≤6.5mg/dl;	(Gender-specific)	CVD, hyper-tension, DM, CVM: 1.04(0.62-1.77)
20									Tertile 2: 6.6-7.6mg/dl;	Men: Per 1mg/dl increase	Charlson score, PD related ACM: 0.84(0.69-0.9)
21									Tertile 3: ≥7.7mg/dl.		parameters, Kt/v, BUN, Scr, CVM: 0.79(0.61-1.01)
22									Men: Hyperuricemia≥7mg/dl	FM: Per 1 mg/dl increase	GPT, WBC, ALP, Alb, Hb, ACM: 0.57(0.44-0.73)
23									FM: Hyperuricemia≥6mg/dl		ferritin, TC, TG, Ca, P, iPTH, CVM: 0.6(0.41-0.87)
24											transferrin saturation.
25											Sex., BMI, hypertension , ACM: 0.773(0.62-0.97)
26	Yang FY 2018	China:	RCS/	51.8±14.4	232/487	Median	Median	197/109	Men: Hyperuricemia≥7mg/dl;	Per 1 mg/dl increase	dialysis duration, eGFR, Kt/v, LDL-C, iPTH.
27		Mainlan	Single			29.5	29.5		FM: Hyperuricemia≥6mg/dl.		
28		d									
29	ChangWX2019	China:	RCS/	18–80	150/309	At least > 3	NR	AC 50	Group 1: SUA decliner;	Group 1 vs. Group	Gender, age, BMI, SBP, Hb, ACM: 2.23(1.13-4.40)
30		Mainlan	Single						Group 2: SUA non-decliner.		Na, K, Cl, BUN, Scr, CO2, Ca, P, Alb, TG, FBG, CRP, RRF, PET type, Kt/V, DM, use of CCB, RASi , diuretic , β-
31		d							(“SUA decliner” and “SUA non - decliner” according to run - in and longitudinal changes in the follow-up)		
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Mainlan	Single	42	Tertile 2: 384-460µmol/l;	Tertile 1 vs. Tertile	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)

509 **Abbreviations:** AC: All-cause; ACM: All-cause mortality; CV: Cardiovascular; CVM: Cardiovascular mortality; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; RCS:  
 510 Retrospective cohort study; PCS: Prospective cohort study; vs.: versus; Alb: Serum albumin; DM: Diabetes mellitus; NDM: Non diabetes mellitus; HN: Hypertensive nephropathy; RRF: Residual  
 511 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  
 512 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  
 513 cholesterol; HDL-C: High density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; FM:  
 514 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;  
 515 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:  
 516 Alkaline phosphate; eGFR: estimated glomerular filtration rate; FBG: Fasting blood glucose; FPG: Fasting plasma glucose; PET: Peritoneal equilibration test; CCB: Calcium blocker; NLR: Neutrophil  
 517 to lymphocyte ratio; ECW/TBW: Extracellular water/Total body water; ASMI: Appendicular skeletal muscle mass index; ESA: Erythropoiesis stimulating agents; 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 <sup>2</sup> )	No. of study	Sample size	HR (95%CI)	Heterogeneity (I <sup>2</sup> )	Meta-regression (P value)
Study design									<i>P</i> =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									<i>P</i> =0.000
China—mainland	4	4683	1.57(1.26-1.96)	21.1%	7	7594	1.04(0.97-1.11)	73.0%	
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)	-	<i>P</i> =0.002
Publication years									<i>P</i> =0.017
2011—2016	2	3480	1.53(1.08-2.18)	48.9%	2	3480	1.12(1.01-1.24)	37.9%	
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									<i>P</i> =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									<i>P</i> =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									<i>P</i> =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									<i>P</i> =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%
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519 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; I<sup>2</sup>: I-square; No.: Number.

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520 **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 <sup>2</sup> )	No. of study	Sample size	HR (95%CI)	Heterogeneity (I <sup>2</sup> )
<b>Study design</b>								
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	7442	0.90(0.76-1.06)	70.2%
<b>Study location</b>								
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)	474	1.00(0.91-1.10)	-
<b>Publication years</b>								
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	5231	0.82(0.62-1.08)	77.7%
<b>No. of center</b>								
Single center	3	2842	1.49(0.66-3.38)	84.7%	2	1770	1.06(0.80-1.39)	80.3%
Multicenter	1	2193	1.35(0.74-2.46)	-	2	693	1.01(0.93-1.09)	0.0%
<b>Adjusted for sex</b>								
Yes	3	3972	1.39(0.60-3.24)	84.4%	4	8711	1.05(0.90-1.23)	74.0%
No	1	1063	1.73(1.03-2.91)	-	0	0	-	-
<b>Adjusted for diabetes mellitus</b>								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8711	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	-	-
<b>Adjusted for serum albumin</b>								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8711	1.05(0.90-1.23)	74.0%

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521	No	0	0	-	-	0	0	-	-
	<b>Abbreviations:</b>	HR:	Hazard ratio;	CI:	Confidence interval;	I <sup>2</sup> :	I-square;	No.:	Number.

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## 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)

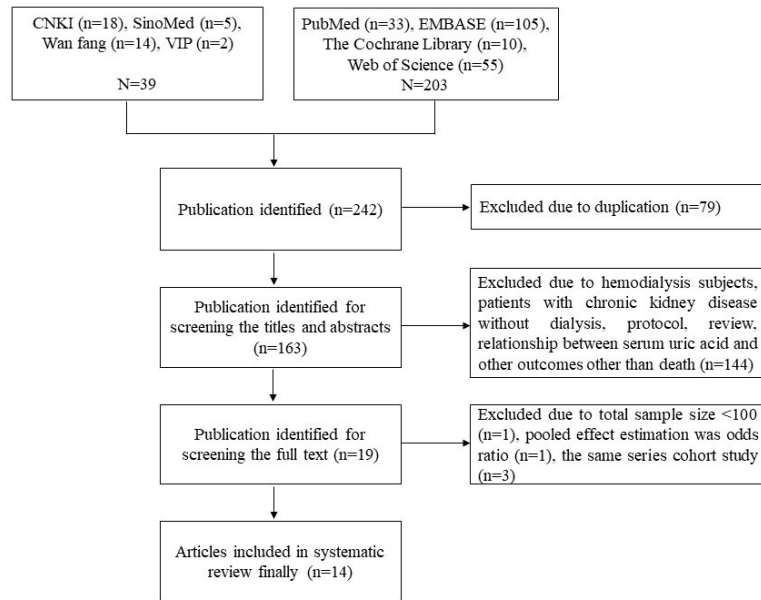


Fig.1 Flow diagram of study search and selection.

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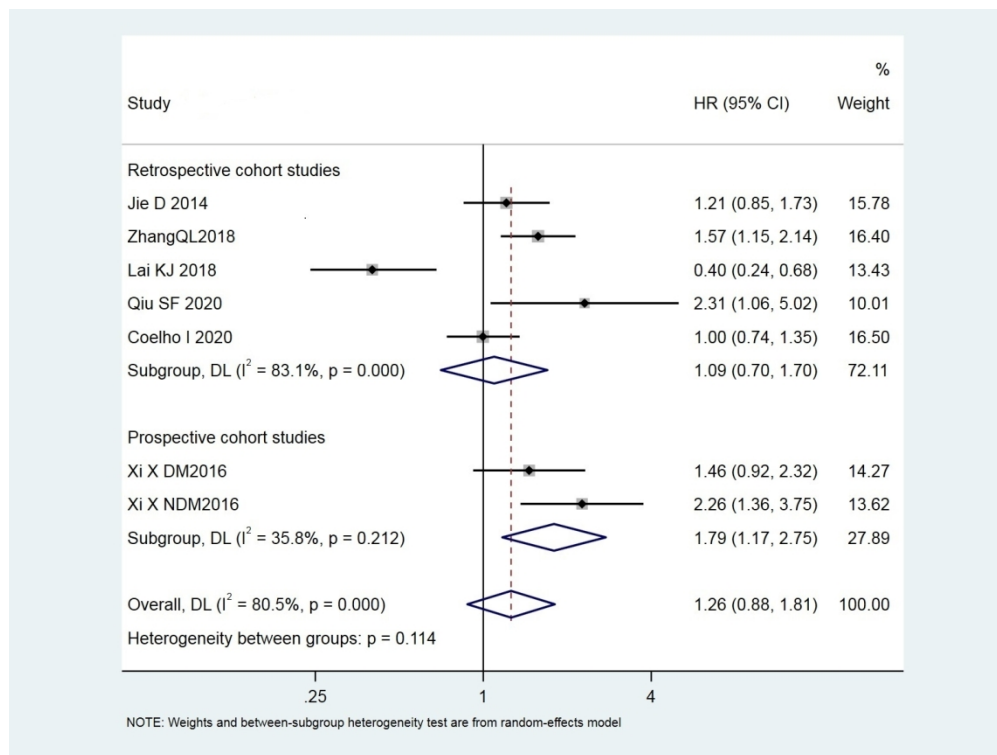


Fig.2 Forest plot and pooled HR for association of SUA in categories (the highest SUA category versus the lowest) with all-cause mortality in PD patients  
 Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

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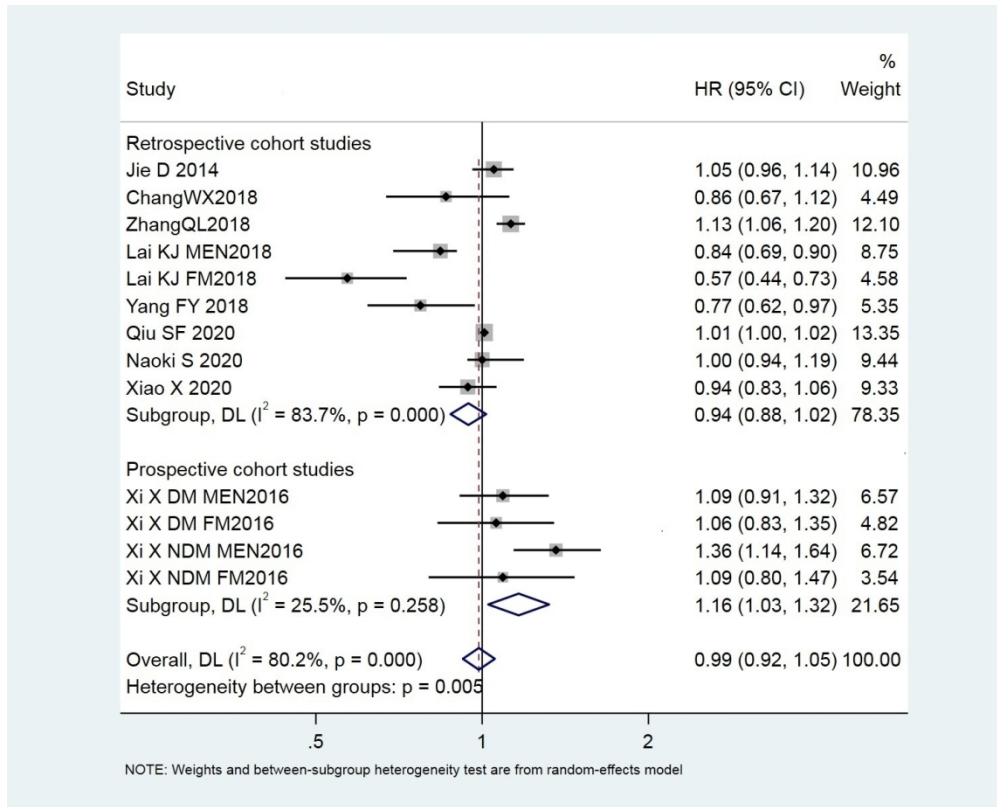
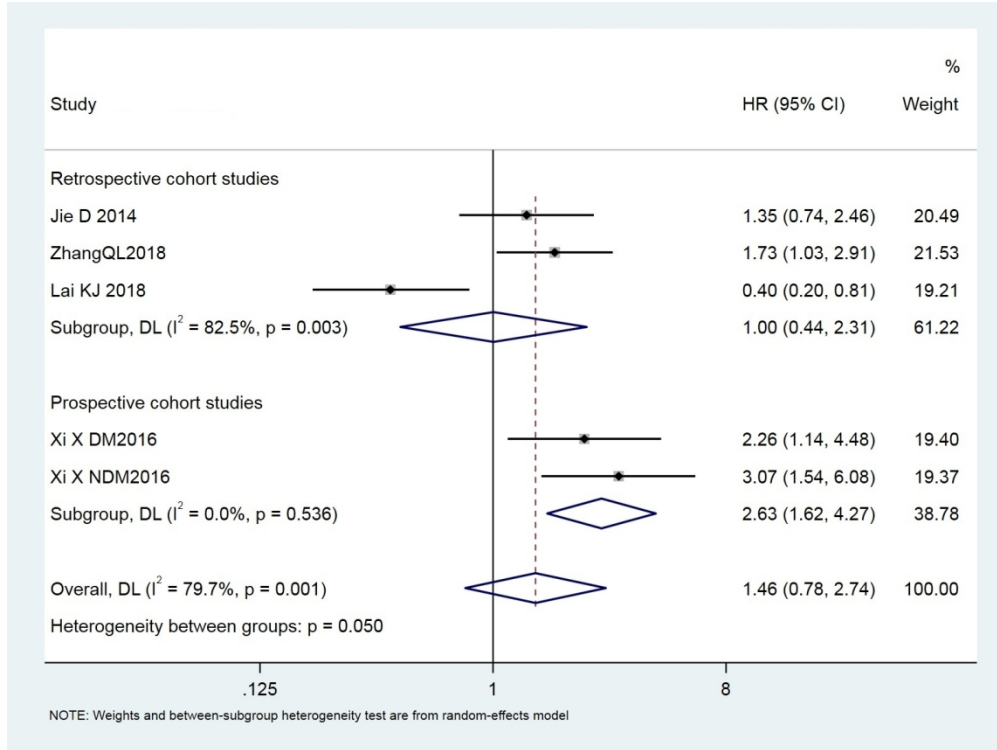


Fig.3 Forest plot and pooled HR for association of SUA per 1mg/dl increase with all-cause mortality in PD patients.

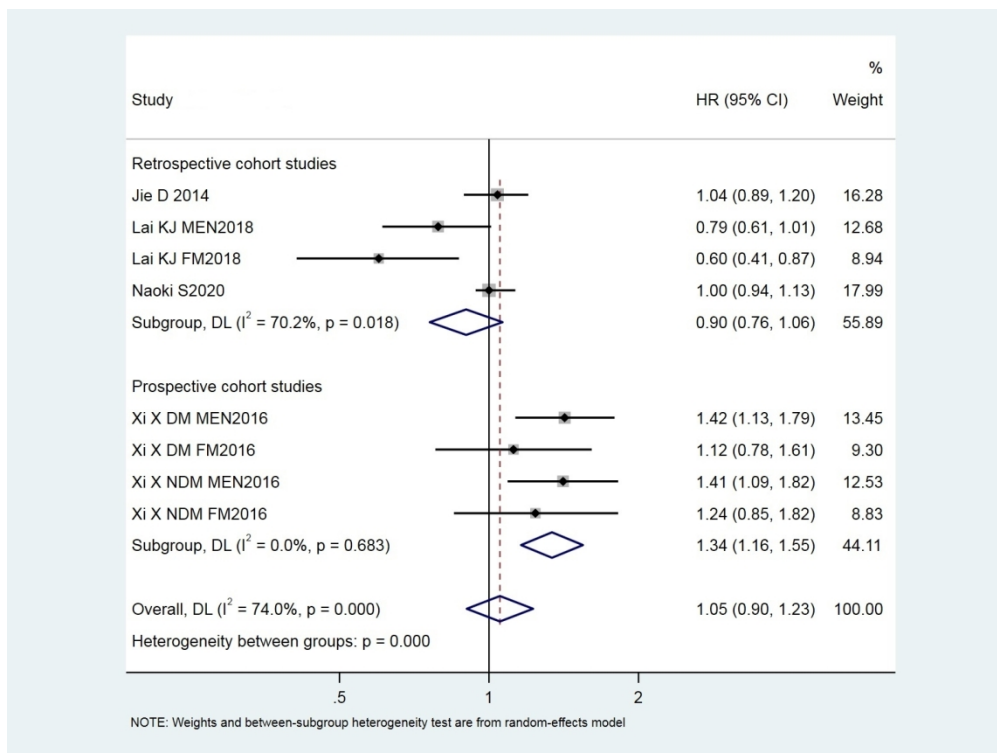
Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis.

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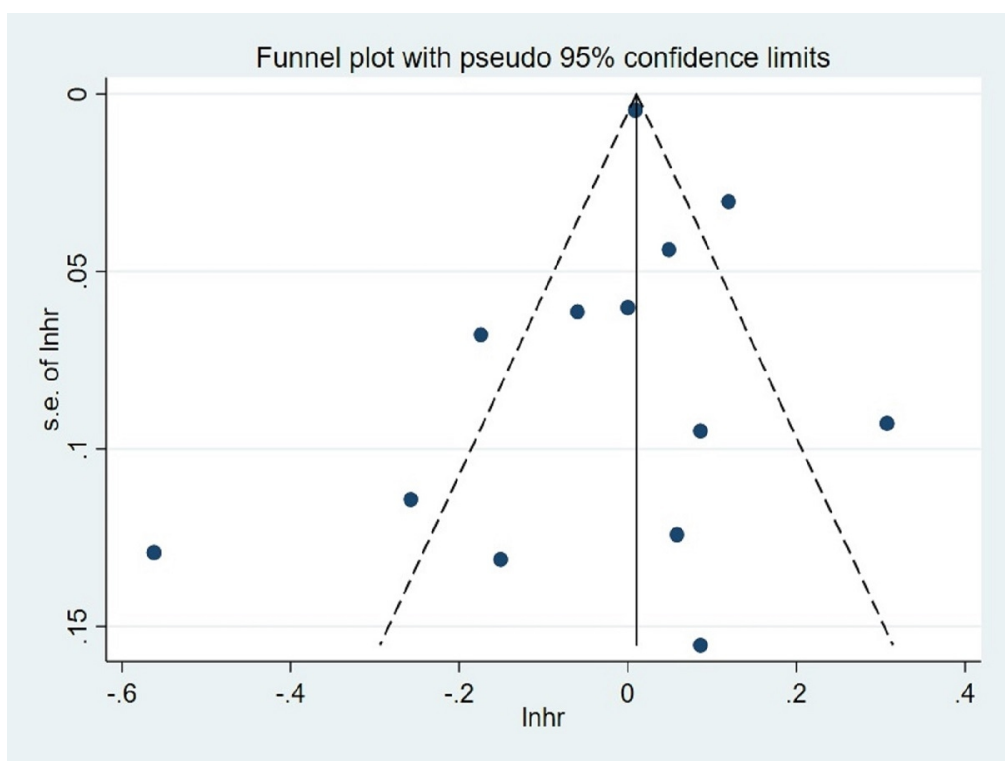
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**eTable 1** Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)

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



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

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

Checklist Item	Answer
<b>Reporting of background should include</b>	
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
<b>Reporting of search strategy should include</b>	
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
<b>Reporting of methods should include</b>	
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

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

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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
<b>Reporting of results should include</b>	
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
<b>Reporting of discussion should include</b>	
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
<b>Reporting of conclusions should include</b>	
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.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052274.R1
Article Type:	Original research
Date Submitted by the Author:	19-Aug-2021
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 Robinson, Nicola; London South Bank University, Liu, Jian-Ping; Beijing University of Chinese Medicine, Centre for Evidence-Based Chinese Medicine
<b>Primary Subject Heading</b>:	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 Xue<sup>1,2</sup>, Chun-li Lu<sup>2</sup>, Xin-yan Jin<sup>2</sup>, Xue-han Liu<sup>2</sup>, MinYang<sup>3</sup>, Xiao-qin Wang<sup>4</sup>, Hong Cheng<sup>4</sup>, Jun Yuan<sup>4</sup>, Qiang Liu<sup>4</sup>, Ruo-xiang Zheng<sup>2</sup>, Nicola Robinson<sup>2,5</sup>, and Jian-ping Liu<sup>2\*</sup>

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

<sup>2</sup> Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

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

<sup>4</sup> Department of Nephrology, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

<sup>5</sup> 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@

1  
2  
3  
4 23 hotmail.com); Hong Cheng (chenghong@hbhtcm.com); Jun Yuan (yjun\_92@  
5  
6 24 hbtcn.edu.cn); Qiang Liu (leonjordan23@sina.com); Ruo-xiang Zheng (zhengruox@  
7  
8  
9 25 foxmail.com); Nicola Robinson (nicky.robinson@lsbu.ac.uk); Jian-ping Liu  
10  
11  
12 26 (Liujp@bucm.edu.cn).

13  
14 27 **\*Corresponding**

15  
16  
17 28 Jian-ping Liu\*

18  
19 29 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine,  
20  
21  
22 30 Beijing, 100029, China. E-mail: Liujp@bucm.edu.cn

23  
24  
25 31 Telephone number: 13718004410.

26  
27 32 **Word count of full text:** 4105.

28  
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31  
32 34 **Abstract**

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35 35 **Objectives** To analyze the relationship between serum uric acid (SUA), all-cause  
36  
37 36 mortality and cardiovascular (CV) mortality in peritoneal dialysis (PD) patients to  
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40 37 inform clinical practice and future research.

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43 38 **Design** A systematic review of observational studies.

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45 39 **Data sources** PubMed, Embase, Web of Science, the Cochrane Library, CNKI,  
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48 40 SinoMed, VIP and Wan Fang electronic databases were searched from their inception  
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51 41 to January 2021 for cohort and case-control studies reporting SUA and mortality in PD  
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54 42 patients.

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56 43 **Methods** Effect estimates were presented as hazard ratios (HR) with 95% confidence  
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58  
59 44 intervals (CI) in a meta-analysis using STATA 16.0. Data not suitable for pooling were  
60

45 synthesized qualitatively.

46 **Results** Fourteen cohort studies with 24031 patients were included. No case-control  
47 studies were identified. For prospective cohort studies, pooled results for the highest  
48 SUA category was significantly greater than the lowest for all-cause (1 study; 1287  
49 participants; HR 1.79; 95%CI 1.17-2.75) and CV mortality (1 study; 1287 participants;  
50 HR 2.63; 95%CI 1.62-4.27). An increase of 1mg/dl in SUA level was associated with  
51 a 16% increased risk of all-cause mortality (1 study; 1287 participants; HR 1.16; 95%CI  
52 1.03-1.32) and 34% increased CV mortality risk (1 study; 1287 participants; HR 1.34;  
53 95%CI 1.16-1.55). For retrospective cohort studies, the highest SUA category did not  
54 demonstrate an elevated all-cause mortality (5 studies; 4570 participants; HR 1.09;  
55 95%CI 0.70-1.70) or CV mortality (3 studies; 3748 participants; HR 1.00; 95%CI 0.44-  
56 2.31) compared with the lowest SUA category. Additionally, there was no increase in  
57 all-cause mortality (8 studies; 11541 participants; HR 0.94; 95%CI 0.88-1.02) or CV  
58 mortality (3 studies; 7427 participants; HR 0.90; 95%CI 0.76-1.06) for every 1mg/dl  
59 increase in SUA level.

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

### 63 **Strengths and limitations of this study**

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



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

68 ▶ Of the included studies, eleven were conducted in China, two in other Asian countries  
69 and one in Europe, this limits the generalizability of our results.

70 ▶ Dose-response relationship could not be determined from these data.

## 71 **Introduction**

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

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

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4 89 hemodialysis population, hypouricemia significantly increased mortality [10-12].  
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6 90 Nevertheless, the role of SUA in all-cause and CV mortality in PD patients has been  
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8  
9 91 controversial. An elevated SUA level has been shown to be an independent risk factor  
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11 92 for all-cause and CV mortality in men treated with PD [13]. Another study showed that  
12  
13 93 the prognostic value of SUA in all-cause and CV mortality was weak in PD patients  
14  
15 94 [14]. Hyperuricemia has also been found to predict lower risk of all-cause mortality in  
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17 95 PD patients with lower relative appendicular skeletal muscle [15]. In short, the effect  
18  
19 96 of SUA on the prognosis of PD patients appears to be inconsistent.  
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25 97 Currently, systematic reviews on the relationship between SUA, all-cause and CV  
26  
27 98 mortality in the PD population are lacking. We hypothesized that there may be an  
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29 99 independent correlation between elevated SUA level and mortality in participants with  
30  
31 100 PD. Thus, we systematically analyzed available studies to determine whether this  
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33 101 hypothesis could be confirmed.  
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## 38 102 **Methods**

39  
40 103 The methods in this review were specified in advance. The review was reported  
41  
42 104 according to the “Meta-analysis of Observational Studies in Epidemiology guidelines”  
43  
44 105 (MOOSE) [16].  
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46  
47

### 48 106 **Eligibility criteria**

#### 49 107 *Types of studies*

50  
51 108 Cohort and case-control studies were identified.  
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#### 55 109 *Participants*

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57 110 Participants had to receive PD for more than 3 months. There was no restriction on the  
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4 111 type of PD, including continuous ambulatory PD, intermittent PD, automated PD,  
5  
6 112 continuous cyclic PD and tidal PD.  
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9 113 **Exposure factor**

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11 114 Hyperuricemia in PD population was the exposure factor in this study. Either  
12  
13 115 categorization according to baseline SUA level or time-average SUA concentration  
14  
15 116 was acceptable. Definition of hyperuricemia and the categorization for the SUA level  
16  
17 117 was based on the definition reported in each included article.  
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22 118 **Outcome**

23  
24 119 The primary outcome was all-cause mortality and death was determined by the hospital  
25  
26 120 medical record or death certificate.  
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29

30 121 The secondary outcome was CV mortality, defined as a “CV events”: coronary  
31  
32 122 events (myocardial infarction, unstable angina), cardio myopathy, cardiac arrest,  
33  
34 123 cardiac dysrhythmia, congestive heart failure, ischemic brain injury, cerebrovascular  
35  
36 124 accident and peripheral vascular disease. The cause of death was determined through  
37  
38 125 medical history, hospital medical records or death certificates.  
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43 126 **Exclusion criteria**

44  
45 127 (1) Unable to obtain the following information from the original article. Hazard ratio  
46  
47 128 (HR) and its corresponding 95% confidence interval (CI) (or other data required in  
48  
49 129 order perform the calculation) for all-cause or CV mortality for 1mg/dl change in SUA  
50  
51 130 level, or for the highest versus lowest SUA category or the lowest versus highest  
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53 131 category; (2) Cohort studies with a total sample size of less than 100 participants; (3)  
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55 132 Studies originating from the same cohort sample, or part of a cohort sample that had  
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4 133 been previously published. Only the literature which reported the largest sample size  
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7 134 and the longest follow-up could be included.  
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### 9 135 **Search strategy**

10  
11 136 Two authors (X.X. and H.C.) searched the following Chinese and English databases  
12  
13  
14 137 from their inception to 15<sup>th</sup> January 2021. Chinese databases included China National  
15  
16  
17 138 Knowledge Infrastructure (CNKI), SinoMed, Chinese Science and Technology Journal  
18  
19  
20 139 Database (VIP), and Wan Fang Database. English databases included PubMed,  
21  
22  
23 140 EMBASE, the Cochrane Library, and Web of Science. Trial registers including Clinical  
24  
25 141 Trials. gov and the World Health Organization International Clinical Trials Registry  
26  
27 142 Platform were also searched. Additionally, related reviews, conference papers,  
28  
29  
30 143 references lists and gray literatures were also searched manually. No language or  
31  
32  
33 144 publication type was imposed, published abstracts were also considered. If the retrieved  
34  
35  
36 145 literature had missing information, it was necessary to contact the author via email to  
37  
38 146 obtain the data to ensure that literature could be included. Taking “PubMed” as an  
39  
40  
41 147 example, the searching strategy was as follows: (“Uric Acid”[Mesh] OR “Uric Acid”  
42  
43 148 [Title/Abstract] OR “serum uric acid”[Title/Abstract]) AND (“Mortality”[Mesh] OR  
44  
45  
46 149 “Mortality”[Title/Abstract]) AND ( “ Peritoneal Dialysis”[Mesh] OR “Peritoneal  
47  
48 150 Dialysis”[Title/Abstract] OR “PD”[Title/Abstract] OR “continuous ambulatory PD”  
49  
50  
51 151 [Title/Abstract] OR “CAPD”[Title/Abstract] OR “intermittent PD”[Title/Abstract] OR  
52  
53 152 “IPD”[Title/Abstract] OR “automated PD”[Title/Abstract] OR “APD”[Title/Abstract]  
54  
55  
56 153 OR “continuous cyclic PD”[Title/Abstract] OR “CCPD”[Title/Abstract] OR “tidal  
57  
58 154 PD”[Title/Abstract] OR “TPD”[Title/Abstract]). The searching strategies for other  
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4 155 databases are presented in eTable1 in the Supplement.  
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6  
7 156 **Studies selection and data extraction**  
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9 157 The titles and the abstracts were initially screened, then the full-text versions were  
10  
11 158 checked according to the inclusion and exclusion criteria. Two authors (X.X. and Q.L.)  
12  
13  
14 159 examined the full text to identify the eligible studies independently. Two authors (X.X.  
15  
16  
17 160 and H.C.) extracted data independently and entered information into a data extraction  
18  
19  
20 161 sheet. Disagreements on study selection and data extraction were resolved by  
21  
22 162 consulting corresponding author JP Liu. The following information was extracted from  
23  
24  
25 163 each included study: first author, publication year, age, gender, study design, dialysis  
26  
27 164 duration, sample size, study location, center, length of follow up, categories according  
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30 165 to SUA, comparison, adjustments, and adjusted HR (95%CI).  
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33 166 **Methodological quality assessment**  
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35 167 The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to appraise the  
36  
37 168 quality of observational studies [17]. NOS allocates a maximum of 9 points for quality  
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39  
40 169 of selection, comparability, and outcome of study population. Two authors (X.X. and  
41  
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43 170 X.Y.J.) appraised the quality of included studies independently. Any disagreements  
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46 171 were resolved by discussion with corresponding author JP Liu. Overall study quality  
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48 172 scores were defined as poor (0–3), fair (4–6), or good (7–9).  
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51 173 **Statistical analysis**  
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53 174 SUA was analyzed not only as a categorical variable, but also as a continuous variable  
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56 175 in the included studies. The statistical analysis for the overall relationship between SUA  
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58 176 level and death risk (all-cause and CV mortality) were based on the random effects  
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4 177 model and on comparisons of the highest versus the lowest category of SUA level, or  
5  
6 178 by increase of 1mg/dl. HR and 95% CI were used as effect indicators. HR and  
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9 179 corresponding 95% CI of each study were transformed to their natural logarithm (lnHR,  
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12 180 lnICI and lnUCI), and overall HR and its 95% CI was calculated by exponentiation of  
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14  
15 181 the pooled lnHR, lnICI and lnUCI.

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17 182 If data on cases, person-years, and HR and 95% CI for each category were  
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20 183 available in the included studies, then a dose-response analysis would be performed to  
21  
22 184 further explore the relationship between SUA and mortality. The potential non-linearity  
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25 185 association was examined by modeling SUA levels using restricted cubic splines with  
26  
27 186 three knots at 25, 50, and 75% of the distribution. We assigned the median or middle  
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30 187 point of the upper and lower boundaries in each category as the corresponding dose to  
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32  
33 188 the related HR for each study. In general, if there is a dose-response relationship  
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35 189 between SUA and mortality, and  $P$  value for non-linear  $< 0.05$ , non-linear regression  
36  
37  
38 190 model should be considered. When the  $P$  value was close to the critical value of 0.05,  
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40  
41 191 both linear and non-linear models needed to be fitted.

42  
43 192 The square ( $I^2$ ) was applied to test the statistical heterogeneity among studies  
44  
45  
46 193 (Higgins and Thompson, 2003) [18]. When  $I^2 > 85\%$ , we believed that the results could  
47  
48  
49 194 not be pooled. Data not suitable for statistical pooling were synthesized qualitatively.  
50  
51 195 To explore the source of heterogeneity among studies, subgroup analyses were  
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54 196 conducted according to study design, study location, publication years, adjustment for  
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56 197 sex, adjustment for DM and adjustment for albumin. Additionally, the meta-regression  
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59 198 analysis was also performed to detect potential heterogeneity based on the above  
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4 199 variables when about 10 studies were included. Sensitivity analysis was performed  
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6 200 removing one study at a time to explore the robustness of results if data were available.  
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8  
9 201 The possibility of publication bias was detected by funnel plots and Egger's test if there  
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11 202 were about 10 studies. STATA16.0 software (StataCorp, College Station, Texas, 77845  
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13  
14 203 USA) was used for data analysis.

#### 17 204 **Patient and Public Involvement statement**

18  
19 205 Patients or the public WERE NOT involved in the design, or conduct, or reporting, or  
20  
21  
22 206 dissemination plans of our study.

### 25 207 **Results**

#### 27 208 **Search results**

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30 209 Two hundred and forty-two relevant citations were retrieved. After scanning the full  
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32 210 texts, five articles were excluded. Cohort samples from the same study were excluded  
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35 211 [13,15,19], and only the studies with the largest sample size and the longest follow-up  
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37 212 time were included [20,21]. In addition, a published abstract was excluded, because the  
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40 213 total sample size of the entire cohort was only 60 participants [22]. Another study was  
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42 214 excluded due to its pooled effect estimation which was reported as an odds ratio (OR)  
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45 215 with 95% CI [23]. Finally, fourteen studies were eligible for this review. Details of the  
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48 216 search and selection process are illustrated in Fig.1.

#### 51 217 **Characteristic of included trials**

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53 218 A total of fourteen studies consisting of 24031 participants were included [14,20,21,24-  
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55  
56 219 34]. All were cohort studies, including prospective and retrospective studies. The main  
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58 220 characteristics of included studies are given in Table 1 and Table2.  
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## 221 **Methodological quality of included studies**

222 The overall quality of included studies was good with a mean NOS score of 7.57 (range  
223 7–9). All studies scored greater than or equal to 7 (eTable2 in the Supplement). In terms  
224 of "comparability", the most important confounding factors that required adjustment  
225 were: estimated glomerular filtration rate (eGFR) or serum creatinine (Scr) or urinary  
226 volume (UV) or residual renal function (RRF). The above indicators can reflect the  
227 patient's current residual renal function status. In addition, according to the literature  
228 and clinical observations, other confounding factors needing adjustment should include  
229 gender, age, diabetes history, cardiovascular disease (CVD) history, Kt/v (urea  
230 clearance index, representing dialysis adequacy), use of UA-lowering drugs, and serum  
231 albumin (representing nutritional status).

## 232 **Primary outcome**

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

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

240 In retrospective cohort studies, five studies with 4570 patients reported HR and  
241 95% CI of all-cause mortality for the highest versus the lowest SUA category  
242 [14,27,28,32,33]. All cause mortality (HR 1.09; 95% CI 0.70-1.70; Fig.2) was not



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4 243 significantly elevated compared with the lowest category of PD patients.  
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6 244 HR and corresponding 95% CI were reported in three retrospective cohort studies  
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9 245 for the lowest versus the highest SUA category [25,26,30]. Among them, the data from  
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11  
12 246 one article [26] was supplemented by the corresponding author via e-mail. The pooled  
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14  
15 247 HR was 1.52 (95%CI 0.79-2.89), with heterogeneity of  $I^2=32.8\%$ .

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17 248 ***Relationship between serum uric acid per 1mg/dl increase and all-cause mortality***

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19 249 Only one prospective study with 1287 PD patients reported HR and 95% CI of all-  
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22 250 cause mortality for every 1mg/dl increase in SUA level [20]. The pooled result showed  
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25 251 that for every 1mg/dl increase in SUA level, risk of all-cause death increased by 16%  
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28 252 (HR 1.16; 95%CI 1.03-1.32; Fig.3).

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30 253 For the retrospective cohort studies, eight studies with 11541 PD patients reported  
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33 254 HR and 95% CI of all-cause mortality for every 1mg/dl increase in SUA level  
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36 255 [14,21,26-29,32,34]. When the units of SUA concentration in the literature were  
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38  
39 256 different,  $60 \mu \text{mol/l}$  was approximately equal to 1mg/dl. In short, each 1mg/dl increase  
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42 257 in SUA level did not appear to significantly increase the risk of all-cause mortality in  
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45 258 the PD population (HR 0.94; 95% CI 0.88-1.02; Fig.3).

46 259 ***Dose-response relationship between serum uric acid and all-cause mortality***

47  
48 260 Most of the included studies [14,20,21,25,27,29,30,32-34] only reported the number of  
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51 261 outcomes for the entire cohort population. It was not possible to obtain the number of  
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54 262 all-cause and CV deaths and person-years for each category. We tried our best to  
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57 263 contact authors by email or phone in order to acquire the necessary data for the non-  
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60 264 linearity test, only one author responded and provided relevant data [26]. A dose-

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4 265 response analysis was not possible.  
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7 266 **Secondary outcome**

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9 267 ***Relationship between serum uric acid by categories and cardiovascular mortality***

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11 268 One prospective cohort study with 1287 patients reported HR and 95% CI of CV  
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13 269 mortality for the highest SUA category compared with the lowest [20]. The pooled  
14  
15 270 result of HR comparing the highest versus the lowest category was 2.63 (95% CI 1.62-  
16  
17 271 4.27). (Fig.4).  
18  
19  
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21  
22 272 Three retrospective cohort studies with 3748 patients reported HR and 95% CI of  
23  
24 273 CV mortality for the highest versus the lowest SUA category [14,27,28]. The highest  
25  
26 274 SUA category was no more in terms of elevated CV mortality (HR 1.00; 95% CI 0.44-  
27  
28 275 2.31) compared with the lowest category of PD patients. (Fig.4).  
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31  
32 276 ***Relationship between serum uric acid per 1mg/dl increase and cardiovascular mortality***

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34 277 One prospective cohort study with 1287 patients reported HR and 95% CI of CV  
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36 278 mortality for per 1mg/dl increase in SUA level [20]. An increase of each 1mg/dl in  
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38 279 SUA level was associated with a 34% increased risk of CV mortality (HR 1.34; 95%CI  
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40 280 1.16-1.55). (Fig.5).  
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45 281 Three retrospective cohort studies with 7427 patients reported HR and 95% CI of  
46  
47 282 CV mortality per 1mg/dl increase in SUA level [14,28,34]. Meta-analysis showed that  
48  
49 283 each 1 mg/dl increase in SUA level did not appear to significantly increase the risk of  
50  
51 284 CV death in PD population (HR 0.90; 95% CI 0.76-1.06). (Fig.5).  
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55  
56 285 **Additional analysis**

57  
58 286 ***Subgroup analysis and meta-regression***  
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4 287 We explored the source of heterogeneity through subgroup analysis and meta-  
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6 288 regression. Subgroup analysis only included literature which compared the highest  
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9 289 versus the lowest category of SUA level, or explored a change of 1mg/dl increase. The  
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11  
12 290 pooled HR (95% CI) and  $I^2$  of subgroup analysis of the relationship between SUA and  
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15 291 all-cause and CV mortality are presented in Table 3 and Table 4, respectively.

16  
17 292 As mentioned before, whether SUA was a categorical variable or a continuous  
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20 293 variable, the results of the prospective cohort study differed from those of retrospective  
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23 294 studies. Besides, combined with the results of subgroup analysis, when SUA was  
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26 295 estimated as a categorical variable, the association of higher SUA level with increased  
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29 296 all-cause and CV mortality was significant in studies from mainland China, but not in  
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32 297 other countries. SUA as a continuous variable showed that the relationship of higher  
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35 298 CV mortality for 1 mg/dl increase in SUA level was significant in studies from  
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38 299 mainland China, but not elsewhere. Furthermore, we analyzed the relevant studies  
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41 300 published in the past ten years, and results of studies completed during 2011-2016 were  
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44 301 different from the results during 2017-2021 period.

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46 302 In addition, in studies of the relationship between SUA (as a continuous variable)  
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48  
49 303 and all-cause mortality, study design, study location, publication years, adjusted for sex  
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51  
52 304 and DM were heterogeneous by meta-regression (Table 3).

#### 53 305 ***Test of Publication bias***

54  
55 306 Funnel plots and Egger's test ( $t=1.07$ ,  $p=0.309$ ) indicated there was no obvious  
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57  
58 307 publication bias of studies for the relationship between all-cause mortality and SUA  
59  
60 308 level per 1mg/dl increase. The funnel plot is presented in eFigure1 in the Supplement.

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4 309 ***Sensitivity analysis***  
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6 310 In retrospective cohort studies, results of primary outcome showed there was no  
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9 311 significant effect on the pooled HR values of other studies with one study removed at  
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12 312 a time. The above indicated the results were robust.  
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14 313 **Discussion**

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17 314 **Principal findings and comparison with prior reviews**

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19 315 For PD population, previous original studies indicated inconsistent relationship  
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22 316 between SUA and mortality. After searching systematically, we found that there were  
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24  
25 317 some meta-analyses investigating the correlation between SUA and mortality in  
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27  
28 318 different populations [35-38], however, we have not yet found a review only of PD  
29  
30 319 patients. A systematic review published in 2016 showed that elevated SUA level was  
31  
32 320 significantly associated with the risk of death in patients with CKD, including dialysis  
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35 321 and non-dialysis subjects [39]. Subgroup analysis in this review demonstrated that  
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38 322 hyperuricemia was an independent predictor for mortality in PD population, while, this  
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40 323 predictive value was not found in the hemodialysis (HD) population. As only 1  
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43 324 prospective cohort study and 2 retrospective cohort studies were included in the  
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46 325 subgroup analysis, results should be interpreted with caution.

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48 326 In our study, we included a total of 14 cohort studies, of which 2 were prospective  
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51 327 studies and 12 were retrospective studies. There was no obvious publication bias of  
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54 328 studies according to funnel plots and Egger's test. Researchers can not control the  
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56 329 process of data accumulation in retrospective cohort studies, but researchers can  
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59 330 directly acquire relevant data on exposure and outcome according to the study design  
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4 331 in prospective studies, so the risk of bias is small. Thus, instead of pooling results of  
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6 332 the two studies, we reported them individually. Only one prospective cohort study  
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9 333 suggested that regardless of whether SUA was estimated as a continuous or a  
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11 334 categorical variable, elevated SUA level was significantly associated with increased  
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14 335 risk of all-cause and CV mortality in PD patients. Whereas, there was no significant  
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17 336 associations between them in the retrospective studies. Below we have attempted to  
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20 337 discuss the inconsistency of the results from the aspects of participants, exposure,  
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22 338 comparability and outcomes.

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25 339 First of all, the prospective cohort study clearly indicated that participants on PD  
26  
27 340 were consecutively enrolled. It is well known that consecutive recruitment is very  
28  
29  
30 341 important to reduce selection bias. While, in some retrospective studies, the process of  
31  
32 342 enrollment was not detailed. The follow-up of the participants was also a prominent  
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34  
35 343 issue, including the duration and adequacy of follow-up and the rate of loss to follow-  
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38 344 up. In a prospective study, effective measures can be taken to reduce the loss to follow-  
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40 345 up rate to avoid bias. The rate of loss to follow-up in a prospective study by Xia X et  
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43 346 al. (2016) was only 3.5% [20], but in some retrospective cohorts, the adequacy and lost  
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46 347 follow-up rates were not reported.

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48 348 Second, hyperuricemia in the PD population was the exposure factor of this study.  
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51 349 Both prospective and retrospective cohort studies, the definition of hyperuricemia and  
52  
53 350 the categorization for the SUA level was based on the definition provided in each  
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56 351 included article. It should be noted that in retrospective multi-center studies, the  
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59 352 measurement methods of SUA may not be uniform across centers. This may lead to  
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4 353 measurement bias and have a slight impact on results.  
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6 354 Third, control of the most important and other confounding factors is very  
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9 355 important for the comparability between the groups. The most important confounding  
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11  
12 356 factors included indicators that can reflect the patient's current residual renal function  
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14  
15 357 status. Other confounding factors need to be adjusted and should include gender, age,  
16  
17 358 diabetes history, CVD history, Kt/v, use of UA-lowering drugs, and serum albumin.  
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19 359 Most of the studies did not adjust for all potential risk factors. For example, the  
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21  
22 360 prospective study of Xia X et al. (2016) lacked adjustment for the confounding factor  
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25 361 Kt/v [20]. Therefore, we can not exclude the potential impact of these uncontrolled  
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28 362 confounding factors.

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30 363 Regarding the outcomes, the definition of all-cause and cardiovascular death was  
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32  
33 364 clear. However, the handling of patients transferring to hemodialysis therapy, loss to  
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36 365 follow-up, and renal transplantation was different for prospective and retrospective  
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39 366 studies. The above information from patients was used as censoring data for survival  
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42 367 analysis in the prospective study [20]. Whereas, in some retrospective studies, they  
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45 368 were directly excluded from the study [32]. This may affect the results and lead to  
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48 369 inconsistencies between the prospective and retrospective studies. Although the risk of  
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51 370 bias in the design type of prospective study was relatively small, the interpretation of  
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54 371 the results should still be cautious due to the limited quality and quantity of prospective  
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57 372 study.

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59 373 SUA, known for its detrimental effect, is an endothelial toxin and plays a role in  
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374 endothelial dysfunction [40]. However, as a powerful free radical scavenger in human

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4 375 at the same time, SUA may be expected to offer a number of benefits within the CV  
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6 376 system in PD patients [41,42]. Besides, the problem of protein loss and malnutrition is  
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9 377 prominent in PD population [43]. “Malnutrition-inflammation complex syndrome  
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11 378 (MICS)” is believed to be the main cause of the high rate of CV atherosclerotic disease  
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14 379 and increased mortality and hospitalization in HD patients [44,45]. The underlying  
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17 380 mechanism of MICS may also be present in PD patients. As a nutritional marker, SUA  
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20 381 might be involved in the MICS axis. Therefore, the relationship between SUA and  
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22 382 mortality in PD patients is a complex proposition. Taking into account the feature of  
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25 383 SUA itself, we hypothesize that both extremely low and high SUA level may increase  
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27 384 the risk of death. In our study, we also would like to explore the dose-response  
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30 385 relationship between SUA level and mortality in PD population, but in the end the  
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32 386 analysis to explore a dose-response relationship was impossible due to insufficient data.  
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35 387 Further investigations are warranted to clarify this relationship and explore the range of  
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38 388 SUA concentration associated with the lowest mortality in the PD patients.

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40 389 Moreover, in addition to different study designs, different study location was also  
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43 390 one of the main sources of heterogeneity among studies according to the meta-  
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46 391 regression test. Subgroup analysis results further suggested hyperuricemia was  
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48 392 associated with a high risk of CV death in PD population only in mainland China. As a  
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51 393 result, the relationship between SUA level and the risk of death in different regions  
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54 394 needs to be explored and verified by prospective studies in future.

### 395 **Implications further research**

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58 396 Since the results of prospective and retrospective cohort studies were inconsistent, and  
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4 397 the different regions seemed to lead to different results, prospective, multicenter, long  
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6 398 term follow-up studies are required in future. It is important to explore the relationship  
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9 399 between SUA level and the risk of death in different regions, as well as to determine  
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11 400 the range of SUA concentrations which can reduce mortality and improve prognosis in  
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14 401 the PD patients.

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17 402 Additionally, since PD patients often suffer from underlying diseases and complex  
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19 403 conditions, adjustment is required for confounding factors to explore the relationship  
20  
21 404 between these factors and prognosis. For the PD population, the following confounding  
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23 405 factors should be considered to make the evidence more compelling. Such as:  
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25 406 traditional independent risk factors of CV events (age, gender, total lipoprotein  
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27 407 cholesterol, low or high density lipoprotein cholesterol, hypertension, diabetes,  
28  
29 408 smoking [46]), history of CV, emotion status, residual renal function, the related  
30  
31 409 parameters of PD, the parameters of nutritional status, use of diuretic and lower UA  
32  
33 410 agents etc.

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35 411 Comprehensive information should be reported in detail in the study report so that  
36  
37 412 readers can become more familiar with the details of the study, and can conduct  
38  
39 413 secondary research to avoid wasting research resources.

#### 40 414 **Study limitations**

41  
42 415 There were several limitations in this review. Systematic reviews of observational  
43  
44 416 studies can provide a higher level of evidence, but they also have methodological  
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46 417 limitations. For example, the included original studies may differ in their design, data  
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48 418 collection methods, and definitions of exposure, confounding factors and outcomes.  
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4 419 These differences may have a slight influence on the true effect size. Second, in this  
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6 420 review, the included studies were mainly from Asian populations (only one from  
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9 421 Europe), and the generalizability of the results was limited. Third, in spite of many  
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11 422 important confounding factors that to be adjusted in the studies, residual and unknown  
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13  
14 423 confounding factors can not be entirely excluded. Fourth, the duration of follow up in  
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17 424 all studies was less than 5 years. It is difficult to determine long-term impact of elevated  
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19 425 SUA level on mortality. Finally, some necessary data was not obtained, and the  
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22 426 exploration of dose-response relationship could not be conducted, but will need to be  
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24  
25 427 determined in future studies.

## 428 **Conclusions**

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

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3 444 Registration: XX, CLL, XYJ and XHL. Acquisition, analysis, or interpretation of data:  
4 445 XX, HC, QL, JY, and JPL. Drafting of the manuscript: XX, XHL, CLL, XYJ and RXZ.  
5 446 Statistical analysis: MY, XX and XQW. Critical revision of the manuscript: XQW, NR  
6 447 and JPL. Supervision: JPL.

7  
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13 453 **Competing interests** None.

14 454 **Provenance and peer review** Not commissioned; externally peer reviewed.

15 455 **Data sharing statement** The datasets used for meta-analyses are available from the  
16 456 corresponding author on reasonable request.

17 457

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## Ethics approval statement

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6 564 Dear editors,  
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10 566 Our study was to systematically evaluate the relationship between serum uric acid,  
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12 567 all-cause and cardiovascular mortality in peritoneal dialysis patients based on the  
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14 568 observational studies that have been published. As the nature of the study, ethics  
15  
16 569 approval is not applicable for this study.  
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21 57022  
23 571 With best regards,  
2425  
26 572 Yours sincerely,  
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29 573 (Corresponding author)  
3031 574 Jian-ping Liu,  
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34 575 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese  
3536 576 Medicine, Beijing, 100029, China  
3738 577 E-mail: LiuJP@bucm.edu.cn  
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578 **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 3 vs. Group	Age, Alb, DM, HN, RRF , phosphate , Log CRP	ACM: 1.15(0.20-2.57) ACM: 2.96(1.29-6.80)
Ji 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 (Gender-specific) Tertile 2 vs. Tertile (Gender-specific) Per 1 mg/dl increase	Age, RRF, Hb, Alb, phosphate, LDLC, CRP, history 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)
Xu 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 (DM: Gender specific) Tertile 3 vs. Tertile (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).
Junjin 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	Age, sex, BMI, SBP, Ca, P, Alb, TC, DM, SGA.	ACM: 1.478(0.602-3.627)
ChangWX2018 [39]	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 1 vs. Group 1 vs. Group	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)

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5									Per 1 mg/dl increase (Baseline-UA)	P, LDL-C, CRP, RASI, diuretic.	ACM: 0.86(0.67-1.12)	
6	Zhang QL 2018	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	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)
7												
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10	Lai KJ 2018	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 (Gender-specific) Tertile 2 vs. Tertile (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)
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20	Yang FY 2018	China: Mainland	RCS/ Single	51.8±14.4	232/487	Median	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)
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24 579 **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  
 25 580 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:  
 26 581 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;  
 27 582 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;  
 28 583 Na: Serum sodium; K: Serum potassium; Cl: Serum chlorine; CO2: Venous carbon dioxide; LDL-C: Low density lipoprotein cholesterol; RASI: Renin-angiotensin system inhibitor; BG: Blood glucose; iPTH: intact parathyroid hormone;  
 29 584 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:  
 30 585 Triglyceride.

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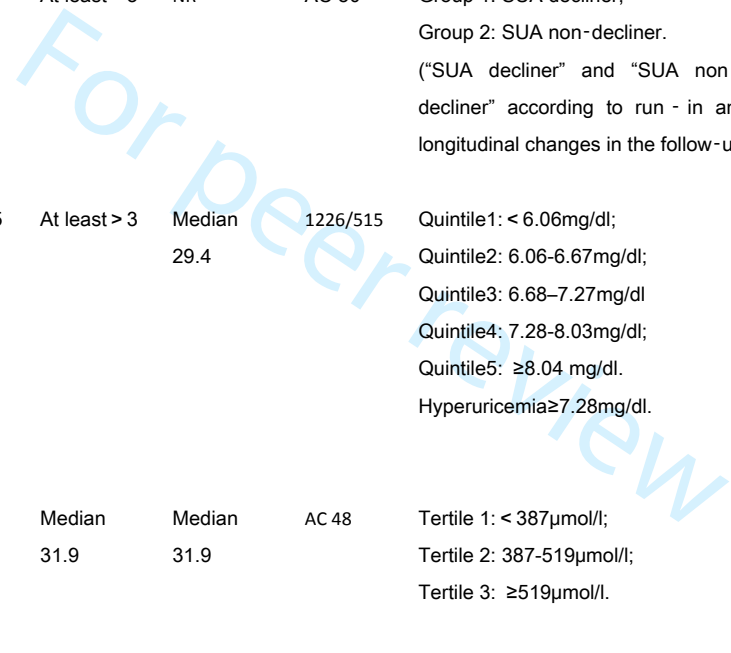
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586 **Table 2** Characteristics of included studies (2019-2020 years)

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)
Qiang WX 2019 [10]	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 [18]	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 [27]	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 2 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)
Correia I 2020 [32]	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)
Nakaki S 2020 [34]	Japan	RCS/multicenter	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 2 Group 2 vs. Group 3 Group 3 vs. Group 4 Group 4 vs. Group 5 Group 5 vs. Group 1	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)

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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 10µmol/l increase	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)
[22]	Mainland	Single			42		Tertile 2: 384-460µmol/l;	Tertile 1 vs. Tertile 2	eGFR, DBP, use of diuretic	ACM: 0.993(0.598-1.651)
							Tertile 3: > 460µmol/l.	Per 1µmol/l increase	and LUA, Hb, Alb, TC.	ACM: 0.999(0.997-1.001)

587 **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  
588 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:  
589 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  
590 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  
591 agents; 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 <sup>2</sup> )	No. of study	Sample size	HR (95%CI)	Heterogeneity (I <sup>2</sup> )	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; I<sup>2</sup>: I-square; No.: Number.

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594 **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 <sup>2</sup> )	No. of study	Sample size	HR (95%CI)	Heterogeneity (I <sup>2</sup> )
<b>Study design</b>								
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	7448	0.90(0.76-1.06)	70.2%
<b>Study location</b>								
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)	474	1.00(0.91-1.10)	-
<b>Publication years</b>								
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	525	0.82(0.62-1.08)	77.7%
<b>No. of center</b>								
Single center	3	2842	1.49(0.66-3.38)	84.7%	2	1770	1.06(0.80-1.39)	80.3%
Multicenter	1	2193	1.35(0.74-2.46)	-	2	693	1.01(0.93-1.09)	0.0%
<b>Adjusted for sex</b>								
Yes	3	3972	1.39(0.60-3.24)	84.4%	4	8711	1.05(0.90-1.23)	74.0%
No	1	1063	1.73(1.03-2.91)	-	0	0	-	-
<b>Adjusted for diabetes mellitus</b>								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8711	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	-	-
<b>Adjusted for serum albumin</b>								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8711	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	-	-

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

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5 596 **Figure legends**  
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8 **Fig.1** Flow diagram of study search and selection.  
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11 **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  
12

13 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.  
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16 **Fig.3** Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.  
17

18 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis.  
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21 **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.  
22

23 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.  
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26 **Fig.5** Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.  
27

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

32 **eFigure 1.** Funnel plot for relationship between serum uric acid level per 1mg/dl increase and all-cause mortality in peritoneal dialysis patients.  
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35 **eTable 1.** Searching strategies for electronic databases  
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38 **eTable 2.** Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)  
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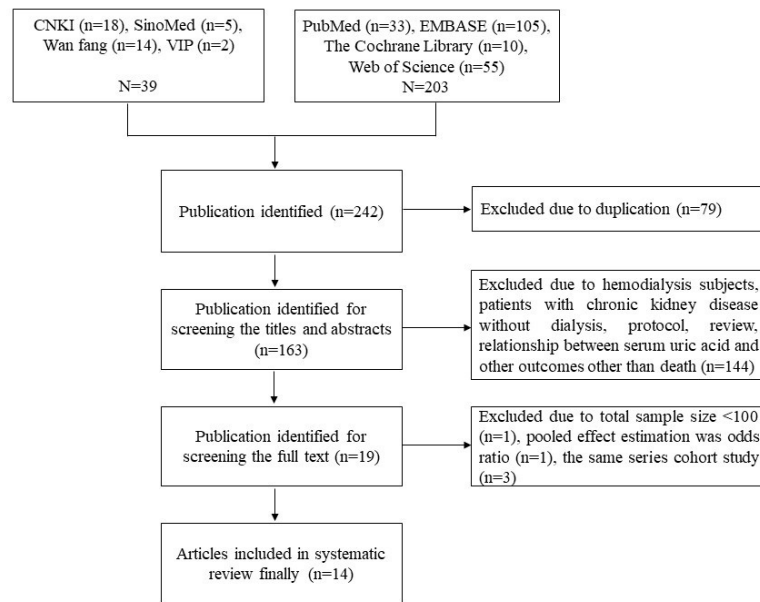


Fig.1 Flow diagram of study search and selection.

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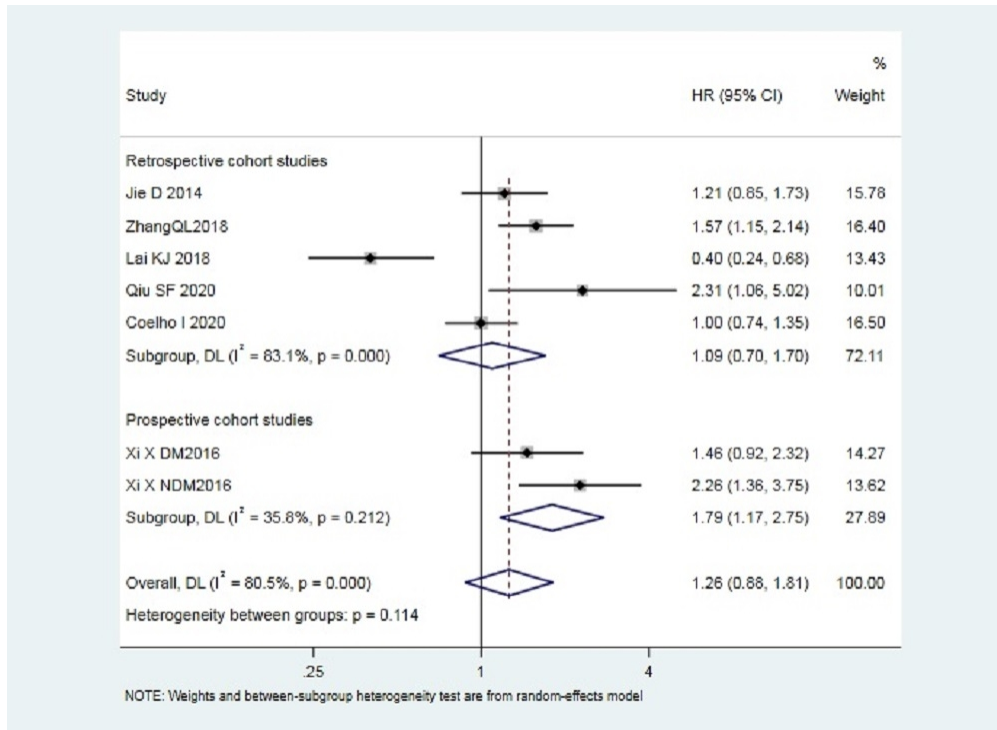


Fig.2 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and all-cause mortality in PD patients  
 Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

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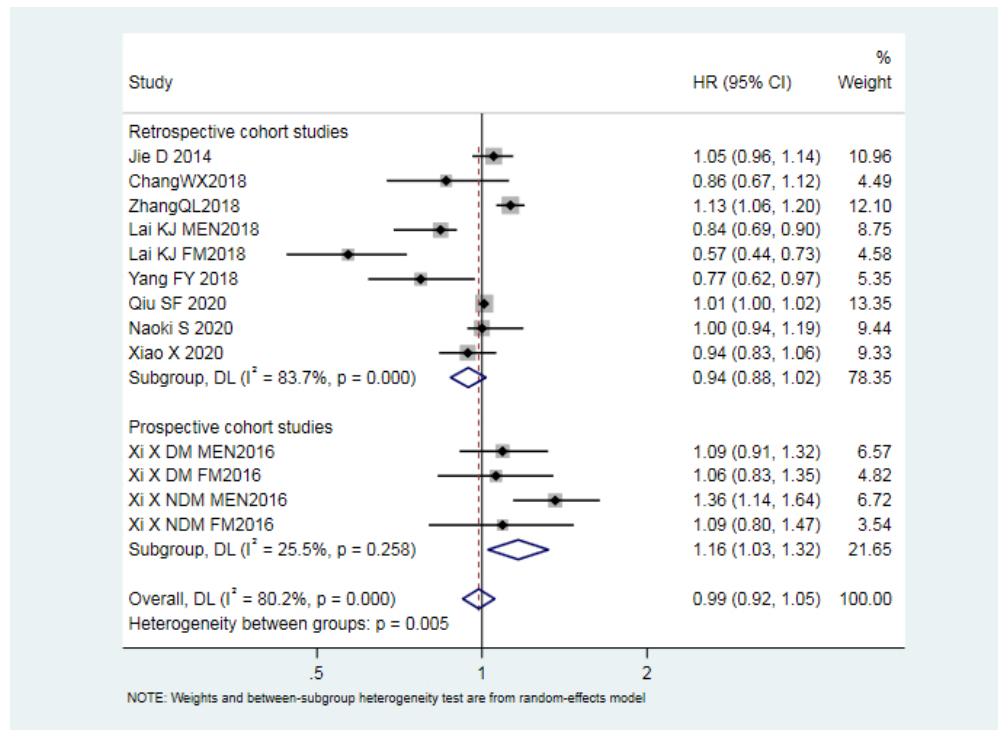


Fig.3 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.

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

371x270mm (47 x 47 DPI)

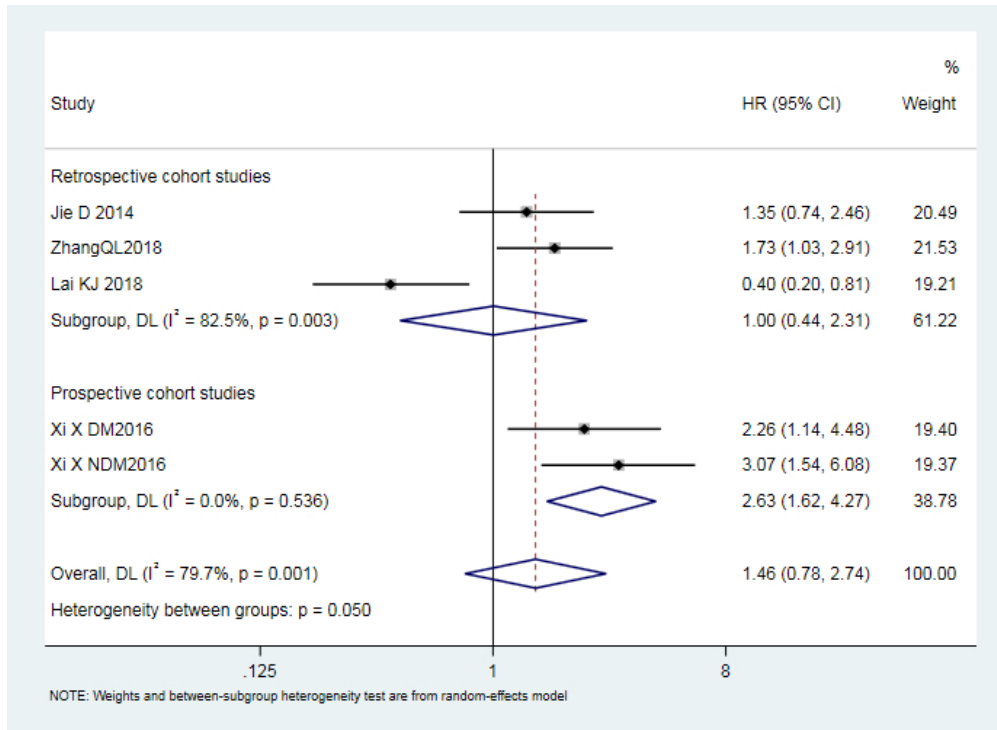


Fig.4 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and cardiovascular mortality in PD patients. Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

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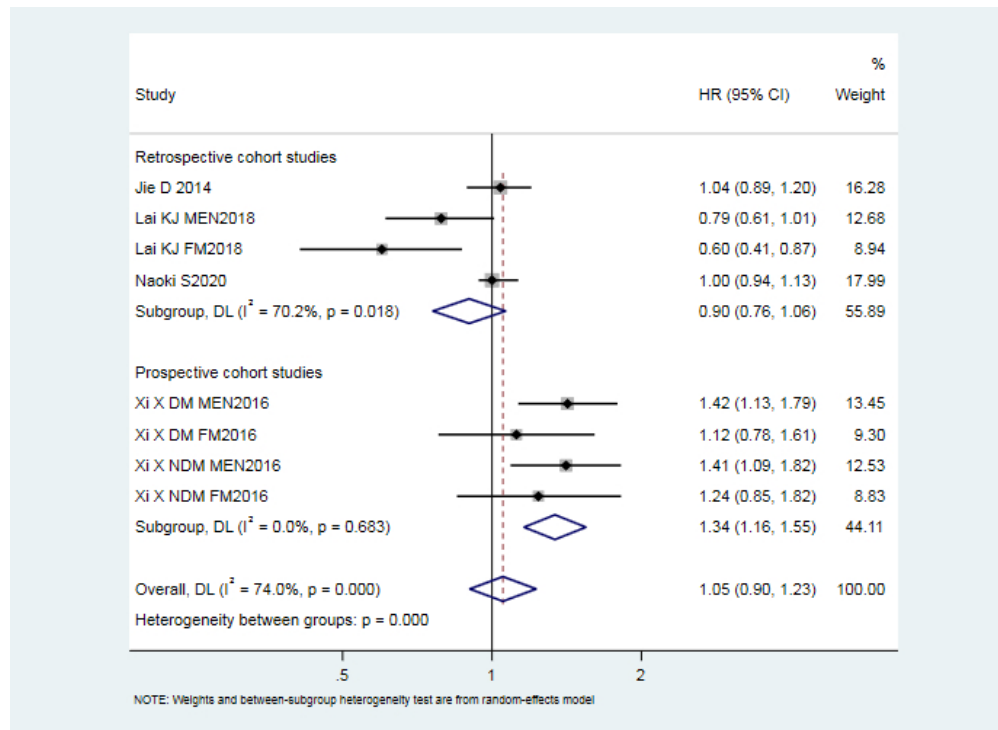
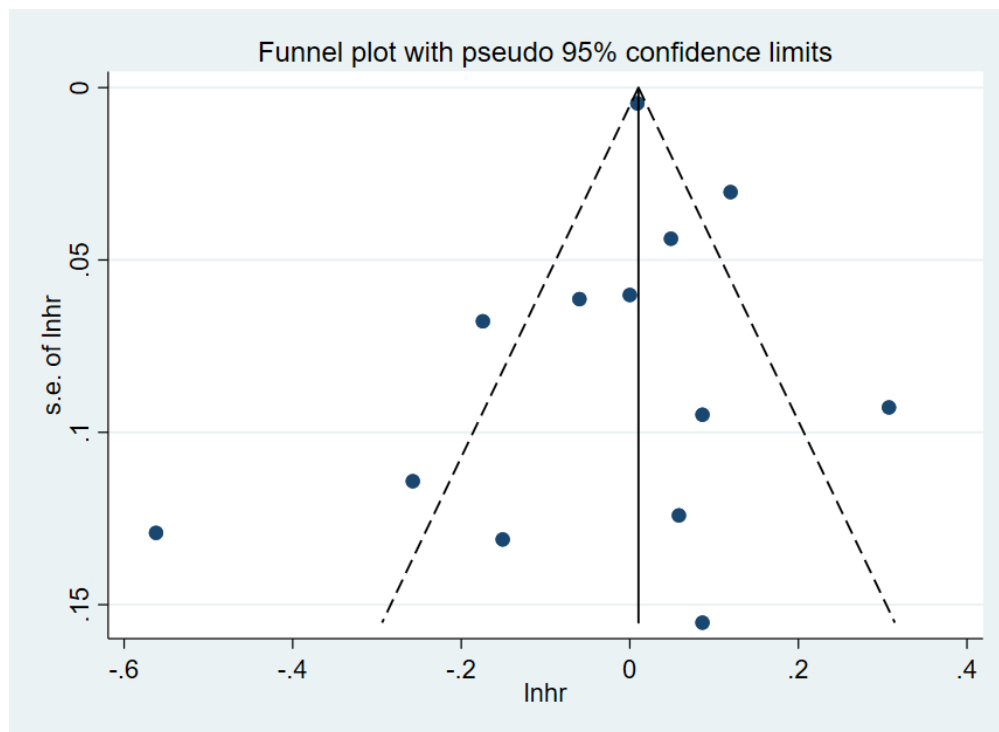


Fig.5 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.

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

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**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

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CNKI, SinoMed,  
VIP, Wan Fang

#2. siwanglv (mortality,死亡率)  
#3. fumotouxu (peritoneal dialysis,腹膜透析) OR lianxuxingfeiwochuangfumotouxu (continuous ambulatory peritoneal dialysis,连续性非卧床腹膜透析) OR zidonghuafumotouxu (automated peritoneal dialysis,自动化腹膜透析)  
#4. #1 AND #2 AND # 3

SinoMed:5  
VIP:2  
WanFang:14

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**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
<b>Reporting of background should include</b>	
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; Page 5-6, Line 109-112
<b>Reporting of search strategy should include</b>	
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, Line 146-155
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
<b>Reporting of methods should include</b>	
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
<b>Reporting of results should include</b>	
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
<b>Reporting of discussion should include</b>	
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
<b>Reporting of conclusions should include</b>	
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

26 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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# BMJ Open

## 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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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 Xue<sup>1,2</sup>, Chun-li Lu<sup>2</sup>, Xin-yan Jin<sup>2</sup>, Xue-han Liu<sup>2</sup>, MinYang<sup>3</sup>, Xiao-qin Wang<sup>4</sup>, Hong Cheng<sup>4</sup>, Jun Yuan<sup>4</sup>, Qiang Liu<sup>4</sup>, Ruo-xiang Zheng<sup>2</sup>, Nicola Robinson<sup>2,5</sup>, and Jian-ping Liu<sup>2\*</sup>

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

<sup>2</sup> Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

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

<sup>4</sup> Department of Nephrology, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, 430061, China

<sup>5</sup> 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@

1  
2  
3  
4 23 hotmail.com); Hong Cheng (chenghong@hbhtcm.com); Jun Yuan (yjun\_92@  
5  
6 24 hbtcn.edu.cn); Qiang Liu (leonjordan23@sina.com); Ruo-xiang Zheng (zhengruox@  
7  
8  
9 25 foxmail.com); Nicola Robinson (nicky.robinson@lsbu.ac.uk); Jian-ping Liu  
10  
11  
12 26 (Liujp@bucm.edu.cn).

13  
14 27 **\*Corresponding**

15  
16  
17 28 Jian-ping Liu\*

18  
19 29 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine,  
20  
21  
22 30 Beijing, 100029, China. E-mail: Liujp@bucm.edu.cn

23  
24  
25 31 Telephone number: 13718004410.

26  
27 32 **Word count of full text:** 4105.

28  
29  
30 33

31  
32 34 **Abstract**

33  
34  
35 35 **Objectives** To analyze the relationship between serum uric acid (SUA), all-cause and  
36  
37 36 cardiovascular (CV) mortality in peritoneal dialysis (PD) patients to inform clinical  
38  
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40 37 practice and future research.

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42  
43 38 **Design** A systematic review of observational studies.

44  
45 39 **Data sources** PubMed, Embase, Web of Science, the Cochrane Library, CNKI,  
46  
47  
48 40 SinoMed, VIP and Wan Fang databases were searched from their inception to January  
49  
50  
51 41 2021 for cohort and case-control studies reporting SUA and mortality in PD patients.

52  
53 42 **Methods** The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to  
54  
55  
56 43 appraise quality of cohort and case-control studies. Effect estimates were presented as  
57  
58  
59 44 hazard ratios (HR) with 95% confidence intervals (CI) in a meta-analysis using STATA  
60

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3  
4 16.0. Data not suitable for pooling were synthesized qualitatively.  
5

6  
7 **Results** Fourteen cohort studies with 24031 patients were included. No case-control  
8  
9 studies were identified. For prospective cohort studies, pooled results for the highest  
10  
11 SUA category was significantly greater than the lowest for all-cause (1 study; 1287  
12  
13 participants; HR 1.79; 95%CI 1.17-2.75) and CV mortality (1 study; 1287 participants;  
14  
15 HR 2.63; 1.62-4.27). An increase of 1mg/dl in SUA level was associated with a 16%  
16  
17 increased risk of all-cause mortality (1 study; 1287 participants; HR 1.16; 1.03-1.32)  
18  
19 and 34% increased CV mortality risk (1 study; 1287 participants; HR 1.34; 1.16-1.55).  
20  
21 For retrospective cohort studies, the highest SUA category did not demonstrate an  
22  
23 elevated all-cause (5 studies; 4570 participants; HR 1.09; 0.70-1.70) or CV mortality  
24  
25 (3 studies; 3748 participants; HR 1.00; 0.44-2.31) compared with the lowest SUA  
26  
27 category. Additionally, there was no increase in all-cause (8 studies; 11541 participants;  
28  
29 HR 0.94; 0.88-1.02) or CV mortality (3 studies; 7427 participants; HR 0.90; 0.76-1.06)  
30  
31 for every 1mg/dl increase in SUA level.  
32  
33  
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39

40 **Conclusions** Results of prospective and retrospective cohort studies were inconsistent.  
41  
42 Consequently, prospective, multi-center, long-term follow-up studies are required to  
43  
44 confirm the relationship between SUA and mortality in PD patients.  
45  
46

#### 47 **Strengths and limitations of this study**

- 48  
49  
50  
51 ▶ This is the first systematic review of observational studies which has explored the  
52  
53 relationship between SUA level and mortality in PD patients.  
54  
55  
56 ▶ We used critical appraisal of included studies and subgroup analysis to present the  
57  
58 results, and proposed future research directions based on the results.  
59  
60

- 1  
2  
3  
4 67 ▶ Of the included studies, eleven were conducted in China, two in other Asian countries  
5  
6  
7 68 and one in Europe, this limits the generalizability of our results.  
8  
9 69 ▶ Dose-response relationship could not be determined from these data.  
10

## 11 70 **Introduction**

12  
13  
14 71 End-stage renal disease (ESRD) is one of the major diseases affecting human health,  
15  
16  
17 72 and causes enormous pressure and burden on medical care and society. One of the  
18  
19  
20 73 effective treatments for ESRD is peritoneal dialysis (PD) which is characterized by  
21  
22  
23 74 enabling stable hemodynamics, protecting residual renal function (RRF), and  
24  
25  
26 75 demonstrates good removal of middle molecular toxins, and is associated with a low  
27  
28  
29 76 risk of infection, and can be delivered at home [1]. Currently, PD is widely used  
30  
31  
32 77 globally. The total number of people receiving PD worldwide in 2013 reached  
33  
34  
35 78 approximately 220,000 [2]. Of concern is that patients with ESRD treated with dialysis  
36  
37  
38 79 still have high mortality [3]. The identification of potential risk factors has great  
39  
40  
41 80 significance if patients' prognosis and quality of life is to be improved.

42  
43 81 Uric acid (UA) is the final product of purine nucleotide metabolism in humans.  
44  
45  
46 82 Previous studies have demonstrated that elevated serum uric acid (SUA) is closely  
47  
48  
49 83 related to the increased risk of hypertension, peripheral arterial disease, cardiovascular  
50  
51  
52 84 (CV) event and chronic kidney disease (CKD) in the general population [4-7]. Higher  
53  
54  
55 85 SUA levels also appear to be an independent risk factor for all-cause and CV mortality  
56  
57  
58 86 in CKD subjects [8,9]. However, there have been conflicting results about the  
59  
60  
61 87 relationship between SUA level and risk of death among dialysis patients. In the  
62  
63  
64 88 hemodialysis population, hypouricemia significantly increased mortality [10-12].

1  
2  
3  
4 89 Nevertheless, the role of SUA in all-cause and CV mortality in PD patients has been  
5  
6 90 controversial. An elevated SUA level has been shown to be an independent risk factor  
7  
8  
9 91 for all-cause and CV mortality in men treated with PD [13]. Another study showed that  
10  
11 92 the prognostic value of SUA in all-cause and CV mortality was weak in PD patients  
12  
13  
14 93 [14]. Hyperuricemia has also been found to predict lower risk of all-cause mortality in  
15  
16  
17 94 PD patients with lower relative appendicular skeletal muscle [15]. In short, the effect  
18  
19 95 of SUA on the prognosis of PD patients appears to be inconsistent.

20  
21  
22 96 Currently, systematic reviews on the relationship between SUA, all-cause and CV  
23  
24 97 mortality in the PD population are lacking. We hypothesized that there may be an  
25  
26  
27 98 independent correlation between elevated SUA level and mortality in participants with  
28  
29  
30 99 PD. Thus, we systematically analyzed available studies to determine whether this  
31  
32  
33 100 hypothesis could be confirmed.

## 34 35 101 **Methods**

36  
37  
38 102 The methods in this review were specified in advance. The review was reported  
39  
40 103 according to the “Meta-analysis of Observational Studies in Epidemiology guidelines”  
41  
42  
43 104 (MOOSE) [16].

## 44 45 105 **Eligibility criteria**

### 46 47 106 *Types of studies*

48  
49  
50 107 Cohort and case-control studies were identified.

### 51 52 108 *Participants*

53  
54  
55 109 Participants had to receive PD for more than 3 months. There was no restriction on the  
56  
57  
58 110 type of PD, including continuous ambulatory PD, intermittent PD, automated PD,  
59  
60

1  
2  
3  
4 111 continuous cyclic PD and tidal PD.  
5

6 112 **Exposure factor**  
7

8  
9 113 Hyperuricemia in PD population was the exposure factor in this study. Either  
10  
11 114 categorization according to baseline SUA level or time-average SUA concentration  
12  
13  
14 115 was acceptable. Definition of hyperuricemia and the categorization for the SUA level  
15  
16  
17 116 was based on the definition reported in each included article.  
18

19 117 **Outcome**  
20

21  
22 118 The primary outcome was all-cause mortality and death was determined by the hospital  
23  
24 119 medical record or death certificate.  
25

26  
27 120 The secondary outcome was CV mortality, defined as a “CV events”: coronary  
28  
29 121 events (myocardial infarction, unstable angina), cardio myopathy, cardiac arrest,  
30  
31 122 cardiac dysrhythmia, congestive heart failure, ischemic brain injury, cerebrovascular  
32  
33 123 accident and peripheral vascular disease. The cause of death was determined through  
34  
35 124 medical history, hospital medical records or death certificates.  
36  
37  
38

39  
40 125 **Exclusion criteria**  
41

42  
43 126 (1) Unable to obtain the following information from the original article. Hazard ratio  
44  
45 127 (HR) and its corresponding 95% confidence interval (CI) (or other data required in  
46  
47 128 order perform the calculation) for all-cause or CV mortality for 1mg/dl change in SUA  
48  
49 129 level, or for the highest versus lowest SUA category or the lowest versus highest  
50  
51 130 category; (2) Cohort studies with a total sample size of less than 100 participants; (3)  
52  
53 131 Studies originating from the same cohort sample, or part of a cohort sample that had  
54  
55  
56 132 been previously published. Only the literature which reported the largest sample size  
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58  
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4 133 and the longest follow-up could be included.  
5

6  
7 134 **Search strategy**  
8

9 135 Two authors (X.X. and H.C.) searched the following Chinese and English databases  
10  
11 136 from their inception to 15<sup>th</sup> January 2021. Chinese databases included China National  
12  
13 137 Knowledge Infrastructure (CNKI), SinoMed, Chinese Science and Technology Journal  
14  
15 138 Database (VIP), and Wan Fang Database. English databases included PubMed,  
16  
17 139 EMBASE, the Cochrane Library, and Web of Science. Trial registers including Clinical  
18  
19 140 Trials. gov and the World Health Organization International Clinical Trials Registry  
20  
21 141 Platform were also searched. Additionally, related reviews, conference papers,  
22  
23 142 references lists and gray literatures were also searched manually. No language or  
24  
25 143 publication type was imposed, published abstracts were also considered. If the retrieved  
26  
27 144 literature had missing information, it was necessary to contact the author via email to  
28  
29 145 obtain the data to ensure that literature could be included. Taking “PubMed” as an  
30  
31 146 example, the searching strategy was as follows: (“Uric Acid”[Mesh] OR “Uric Acid”  
32  
33 147 [Title/Abstract] OR “serum uric acid”[Title/Abstract]) AND (“Mortality”[Mesh] OR  
34  
35 148 “Mortality”[Title/Abstract]) AND ( “ Peritoneal Dialysis”[Mesh] OR “Peritoneal  
36  
37 149 Dialysis”[Title/Abstract] OR “PD”[Title/Abstract] OR “continuous ambulatory PD”  
38  
39 150 [Title/Abstract] OR “CAPD”[Title/Abstract] OR “intermittent PD”[Title/Abstract] OR  
40  
41 151 “IPD”[Title/Abstract] OR “automated PD”[Title/Abstract] OR “APD”[Title/Abstract]  
42  
43 152 OR “continuous cyclic PD”[Title/Abstract] OR “CCPD”[Title/Abstract] OR “tidal  
44  
45 153 PD”[Title/Abstract] OR “TPD”[Title/Abstract]). The searching strategies for other  
46  
47 154 databases are presented in eTable1 in the Supplement.  
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49  
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## 155 **Studies selection and data extraction**

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

## 165 **Methodological quality assessment**

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

## 172 **Statistical analysis**

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

1  
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3  
4 177 by increase of 1mg/dl. HR and 95% CI were used as effect indicators. HR and  
5  
6 178 corresponding 95% CI of each study were transformed to their natural logarithm (lnHR,  
7  
8  
9 179 lnICI and lnUCI), and overall HR and its 95% CI was calculated by exponentiation of  
10  
11  
12 180 the pooled lnHR, lnICI and lnUCI.

13  
14 181 If data on cases, person-years, and HR and 95% CI for each category were  
15  
16 182 available in the included studies, then a dose-response analysis would be performed to  
17  
18  
19 183 further explore the relationship between SUA and mortality. The potential non-linearity  
20  
21  
22 184 association was examined by modeling SUA levels using restricted cubic splines with  
23  
24  
25 185 three knots at 25, 50, and 75% of the distribution. We assigned the median or middle  
26  
27  
28 186 point of the upper and lower boundaries in each category as the corresponding dose to  
29  
30  
31 187 the related HR for each study. In general, if there is a dose-response relationship  
32  
33  
34 188 between SUA and mortality, and  $P$  value for non-linear  $< 0.05$ , non-linear regression  
35  
36  
37 189 model should be considered. When the  $P$  value was close to the critical value of 0.05,  
38  
39  
40 190 both linear and non-linear models needed to be fitted.

41  
42 191 The square ( $I^2$ ) was applied to test the statistical heterogeneity among studies  
43  
44 192 (Higgins and Thompson, 2003) [18]. When  $I^2 > 85\%$ , we believed that the results could  
45  
46 193 not be pooled. Data not suitable for statistical pooling were synthesized qualitatively.  
47  
48  
49 194 To explore the source of heterogeneity among studies, subgroup analyses were  
50  
51  
52 195 conducted according to study design, study location, publication years, adjustment for  
53  
54  
55 196 sex, adjustment for DM and adjustment for albumin. Additionally, the meta-regression  
56  
57  
58 197 analysis was also performed to detect potential heterogeneity based on the above  
59  
60 198 variables when about 10 studies were included. Sensitivity analysis was performed

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4 199 removing one study at a time to explore the robustness of results if data were available.

5  
6 200 The possibility of publication bias was detected by funnel plots and Egger's test if there  
7  
8  
9 201 were about 10 studies. STATA16.0 software (StataCorp, College Station, Texas, 77845  
10  
11 202 USA) was used for data analysis.

### 12 13 14 203 **Patient and Public Involvement statement**

15  
16  
17 204 Patients or the public WERE NOT involved in the design, or conduct, or reporting, or  
18  
19 205 dissemination plans of our study.

## 20 206 **Results**

### 21 207 **Search results**

22  
23  
24  
25  
26  
27 208 Two hundred and forty-two relevant citations were retrieved. After scanning the full  
28  
29 209 texts, five articles were excluded. Cohort samples from the same study were excluded  
30  
31 210 [13,15,19], and only the studies with the largest sample size and the longest follow-up  
32  
33 211 time were included [20,21]. In addition, a published abstract was excluded, because the  
34  
35 212 total sample size of the entire cohort was only 60 participants [22]. Another study was  
36  
37 213 excluded due to its pooled effect estimation which was reported as an odds ratio (OR)  
38  
39 214 with 95% CI [23]. Finally, fourteen studies were eligible for this review. Details of the  
40  
41 215 search and selection process are illustrated in Fig.1.

### 42 216 **Characteristic of included trials**

43  
44  
45  
46  
47 217 A total of fourteen studies consisting of 24031 participants were included [14,20,21,24-  
48  
49 218 34]. All were cohort studies, including prospective and retrospective studies. The main  
50  
51 219 characteristics of included studies are given in Table 1 and Table2.

### 52 220 **Methodological quality of included studies**

1  
2  
3  
4 221 The overall quality of included studies was good with a mean NOS score of 7.57 (range  
5  
6 222 7–9). All studies scored greater than or equal to 7 (eTable2 in the Supplement). In terms  
7  
8  
9 223 of "comparability", the most important confounding factors that required adjustment  
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11  
12 224 were: estimated glomerular filtration rate (eGFR) or serum creatinine (Scr) or urinary  
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14 225 volume (UV) or residual renal function (RRF). The above indicators can reflect the  
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17 226 patient's current residual renal function status. In addition, according to the literature  
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20 227 and clinical observations, other confounding factors needing adjustment should include  
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22 228 gender, age, diabetes history, cardiovascular disease (CVD) history, Kt/v (urea  
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24 229 clearance index, representing dialysis adequacy), use of UA-lowering drugs, and serum  
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26  
27 230 albumin (representing nutritional status).

### 231 **Primary outcome**

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

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

239 In retrospective cohort studies, five studies with 4570 patients reported HR and  
240 95% CI of all-cause mortality for the highest versus the lowest SUA category  
241 [14,27,28,32,33]. All cause mortality (HR 1.09; 95% CI 0.70-1.70; Fig.2) was not  
242 significantly elevated compared with the lowest category of PD patients.

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4 243 HR and corresponding 95% CI were reported in three retrospective cohort studies  
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6 244 for the lowest versus the highest SUA category [25,26,30]. Among them, the data from  
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9 245 one article [26] was supplemented by the corresponding author via e-mail. The pooled  
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11  
12 246 HR was 1.52 (95%CI 0.79-2.89), with heterogeneity of  $I^2=32.8\%$ .

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14 247 ***Relationship between serum uric acid per 1mg/dl increase and all-cause mortality***

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16  
17 248 Only one prospective study with 1287 PD patients reported HR and 95% CI of all-  
18  
19 249 cause mortality for every 1mg/dl increase in SUA level [20]. The pooled result showed  
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22 250 that for every 1mg/dl increase in SUA level, risk of all-cause death increased by 16%  
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24  
25 251 (HR 1.16; 95%CI 1.03-1.32; Fig.3).

26  
27 252 For the retrospective cohort studies, eight studies with 11541 PD patients reported  
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29  
30 253 HR and 95% CI of all-cause mortality for every 1mg/dl increase in SUA level  
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33 254 [14,21,26-29,32,34]. When the units of SUA concentration in the literature were  
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36 255 different, 60  $\mu$  mol/l was approximately equal to 1mg/dl. In short, each 1mg/dl increase  
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38 256 in SUA level did not appear to significantly increase the risk of all-cause mortality in  
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40 257 the PD population (HR 0.94; 95% CI 0.88-1.02; Fig.3).

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43 258 ***Dose-response relationship between serum uric acid and all-cause mortality***

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45 259 Most of the included studies [14,20,21,25,27,29,30,32-34] only reported the number of  
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47  
48 260 outcomes for the entire cohort population. It was not possible to obtain the number of  
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50  
51 261 all-cause and CV deaths and person-years for each category. We tried our best to  
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54 262 contact authors by email or phone in order to acquire the necessary data for the non-  
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56 263 linearity test, only one author responded and provided relevant data [26]. A dose-  
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58  
59 264 response analysis was not possible.

## 265 **Secondary outcome**

### 266 ***Relationship between serum uric acid by categories and cardiovascular mortality***

267 One prospective cohort study with 1287 patients reported HR and 95% CI of CV  
268 mortality for the highest SUA category compared with the lowest [20]. The pooled  
269 result of HR comparing the highest versus the lowest category was 2.63 (95% CI 1.62-  
270 4.27). (Fig.4).

271 Three retrospective cohort studies with 3748 patients reported HR and 95% CI of  
272 CV mortality for the highest versus the lowest SUA category [14,27,28]. The highest  
273 SUA category was no more in terms of elevated CV mortality (HR 1.00; 95% CI 0.44-  
274 2.31) compared with the lowest category of PD patients. (Fig.4).

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

276 One prospective cohort study with 1287 patients reported HR and 95% CI of CV  
277 mortality for per 1mg/dl increase in SUA level [20]. An increase of each 1mg/dl in  
278 SUA level was associated with a 34% increased risk of CV mortality (HR 1.34; 95%CI  
279 1.16-1.55). (Fig.5).

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

## 284 **Additional analysis**

### 285 ***Subgroup analysis and meta-regression***

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

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4 287 regression. Subgroup analysis only included literature which compared the highest  
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6 288 versus the lowest category of SUA level, or explored a change of 1mg/dl increase. The  
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9 289 pooled HR (95% CI) and I<sup>2</sup> of subgroup analysis of the relationship between SUA and  
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11 290 all-cause and CV mortality are presented in Table 3 and Table 4, respectively.

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14 291 As mentioned before, whether SUA was a categorical variable or a continuous  
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16 292 variable, the results of the prospective cohort study differed from those of retrospective  
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18 293 studies. Besides, combined with the results of subgroup analysis, when SUA was  
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20 294 estimated as a categorical variable, the association of higher SUA level with increased  
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22 295 all-cause and CV mortality was significant in studies from mainland China, but not in  
23  
24 296 other countries. SUA as a continuous variable showed that the relationship of higher  
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26 297 CV mortality for 1 mg/dl increase in SUA level was significant in studies from  
27  
28 298 mainland China, but not elsewhere. Furthermore, we analyzed the relevant studies  
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30 299 published in the past ten years, and results of studies completed during 2011-2016 were  
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32 300 different from the results during 2017-2021 period.

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35 301 In addition, in studies of the relationship between SUA (as a continuous variable)  
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37 302 and all-cause mortality, study design, study location, publication years, adjusted for sex  
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39 303 and DM were heterogeneous by meta-regression (Table 3).

#### 304 ***Test of Publication bias***

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

#### 308 ***Sensitivity analysis***

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4 309 In retrospective cohort studies, results of primary outcome showed there was no  
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6 310 significant effect on the pooled HR values of other studies with one study removed at  
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9 311 a time. The above indicated the results were robust.

## 312 **Discussion**

### 313 **Principal findings and comparison with prior reviews**

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

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



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4 331 the two studies, we reported them individually. Only one prospective cohort study  
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6 332 suggested that regardless of whether SUA was estimated as a continuous or a  
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9 333 categorical variable, elevated SUA level was significantly associated with increased  
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11 334 risk of all-cause and CV mortality in PD patients. Whereas, there was no significant  
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14 335 associations between them in the retrospective studies. Below we have attempted to  
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17 336 discuss the inconsistency of the results from the aspects of participants, exposure,  
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20 337 comparability and outcomes.

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22 338 First of all, the prospective cohort study clearly indicated that participants on PD  
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24 339 were consecutively enrolled. It is well known that consecutive recruitment is very  
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27 340 important to reduce selection bias. While, in some retrospective studies, the process of  
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30 341 enrollment was not detailed. The follow-up of the participants was also a prominent  
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33 342 issue, including the duration and adequacy of follow-up and the rate of loss to follow-  
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36 343 up. In a prospective study, effective measures can be taken to reduce the loss to follow-  
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38  
39 344 up rate to avoid bias. The rate of loss to follow-up in a prospective study by Xia X et  
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41 345 al. (2016) was only 3.5% [20], but in some retrospective cohorts, the adequacy and lost  
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43 346 follow-up rates were not reported.

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45 347 Second, hyperuricemia in the PD population was the exposure factor of this study.  
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48 348 Both prospective and retrospective cohort studies, the definition of hyperuricemia and  
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51 349 the categorization for the SUA level was based on the definition provided in each  
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54 350 included article. It should be noted that in retrospective multi-center studies, the  
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57 351 measurement methods of SUA may not be uniform across centers. This may lead to  
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59 352 measurement bias and have a slight impact on results.  
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4 353 Third, control of the most important and other confounding factors is very  
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6 354 important for the comparability between the groups. The most important confounding  
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9 355 factors included indicators that can reflect the patient's current residual renal function  
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12 356 status. Other confounding factors need to be adjusted and should include gender, age,  
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14 357 diabetes history, CVD history, Kt/v, use of UA-lowering drugs, and serum albumin.  
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17 358 Most of the studies did not adjust for all potential risk factors. For example, the  
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20 359 prospective study of Xia X et al. (2016) lacked adjustment for the confounding factor  
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22 360 Kt/v [20]. Therefore, we can not exclude the potential impact of these uncontrolled  
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24  
25 361 confounding factors.

26  
27 362 Regarding the outcomes, the definition of all-cause and cardiovascular death was  
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29  
30 363 clear. However, the handling of patients transferring to hemodialysis therapy, loss to  
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33 364 follow-up, and renal transplantation was different for prospective and retrospective  
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36 365 studies. The above information from patients was used as censoring data for survival  
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38 366 analysis in the prospective study [20]. Whereas, in some retrospective studies, they  
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41 367 were directly excluded from the study [32]. This may affect the results and lead to  
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44 368 inconsistencies between the prospective and retrospective studies. Although the risk of  
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47 369 bias in the design type of prospective study was relatively small, the interpretation of  
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50 370 the results should still be cautious due to the limited quality and quantity of prospective  
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53 371 study.

54 372 SUA, known for its detrimental effect, is an endothelial toxin and plays a role in  
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56 373 endothelial dysfunction [40]. However, as a powerful free radical scavenger in human  
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59 374 at the same time, SUA may be expected to offer a number of benefits within the CV  
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4 375 system in PD patients [41,42]. Besides, the problem of protein loss and malnutrition is  
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6 376 prominent in PD population [43]. “Malnutrition-inflammation complex syndrome  
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9 377 (MICS)” is believed to be the main cause of the high rate of CV atherosclerotic disease  
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11 378 and increased mortality and hospitalization in HD patients [44,45]. The underlying  
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14 379 mechanism of MICS may also be present in PD patients. As a nutritional marker, SUA  
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16 380 might be involved in the MICS axis. Therefore, the relationship between SUA and  
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19 381 mortality in PD patients is a complex proposition. Taking into account the feature of  
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22 382 SUA itself, we hypothesize that both extremely low and high SUA level may increase  
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24 383 the risk of death. In our study, we also would like to explore the dose-response  
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27 384 relationship between SUA level and mortality in PD population, but in the end the  
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30 385 analysis to explore a dose-response relationship was impossible due to insufficient data.  
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33 386 Further investigations are warranted to clarify this relationship and explore the range of  
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35 387 SUA concentration associated with the lowest mortality in the PD patients.

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38 388 Moreover, in addition to different study designs, different study location was also  
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40 389 one of the main sources of heterogeneity among studies according to the meta-  
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43 390 regression test. Subgroup analysis results further suggested hyperuricemia was  
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45 391 associated with a high risk of CV death in PD population only in mainland China. As a  
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48 392 result, the relationship between SUA level and the risk of death in different regions  
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51 393 needs to be explored and verified by prospective studies in future.

#### 394 **Implications further research**

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56 395 Since the results of prospective and retrospective cohort studies were inconsistent, and  
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59 396 the different regions seemed to lead to different results, prospective, multicenter, long  
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4 397 term follow-up studies are required in future. It is important to explore the relationship  
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6 398 between SUA level and the risk of death in different regions, as well as to determine  
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9 399 the range of SUA concentrations which can reduce mortality and improve prognosis in  
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12 400 the PD patients.

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14 401 Additionally, since PD patients often suffer from underlying diseases and complex  
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17 402 conditions, adjustment is required for confounding factors to explore the relationship  
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20 403 between these factors and prognosis. For the PD population, the following confounding  
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23 404 factors should be considered to make the evidence more compelling. Such as:  
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25 405 traditional independent risk factors of CV events (age, gender, total lipoprotein  
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27 406 cholesterol, low or high density lipoprotein cholesterol, hypertension, diabetes,  
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29  
30 407 smoking [46]), history of CV, emotion status, residual renal function, the related  
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33 408 parameters of PD, the parameters of nutritional status, use of diuretic and lower UA  
34  
35 409 agents etc.

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38 410 Comprehensive information should be reported in detail in the study report so that  
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41 411 readers can become more familiar with the details of the study, and can conduct  
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43 412 secondary research to avoid wasting research resources.

### 44 45 413 **Study limitations**

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48 414 There were several limitations in this review. Systematic reviews of observational  
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51 415 studies can provide a higher level of evidence, but they also have methodological  
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53 416 limitations. For example, the included original studies may differ in their design, data  
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56 417 collection methods, and definitions of exposure, confounding factors and outcomes.  
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59 418 These differences may have a slight influence on the true effect size. Second, in this  
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4 419 review, the included studies were mainly from Asian populations (only one from  
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6 420 Europe), and the generalizability of the results was limited. Third, in spite of many  
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9 421 important confounding factors that to be adjusted in the studies, residual and unknown  
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11 422 confounding factors can not be entirely excluded. Fourth, the duration of follow up in  
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14 423 all studies was less than 5 years. It is difficult to determine long-term impact of elevated  
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17 424 SUA level on mortality. Finally, some necessary data was not obtained, and the  
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19 425 exploration of dose-response relationship could not be conducted, but will need to be  
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21  
22 426 determined in future studies.

## 427 **Conclusions**

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

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444 Registration: XX, CLL, XYJ and XHL. Acquisition, analysis, or interpretation of data:

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4 445 XX, HC, QL, JY, and JPL. Drafting of the manuscript: XX, XHL, CLL, XYJ and RXZ.  
5 446 Statistical analysis: MY, XX and XQW. Critical revision of the manuscript: XQW, NR  
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17 458 corresponding author on reasonable request.

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## Ethics approval statement

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566 Dear editors,

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568 Our study was to systematically evaluate the relationship between serum uric acid,

569 all-cause and cardiovascular mortality in peritoneal dialysis patients based on the

570 observational studies that have been published. As the nature of the study, ethics

571 approval is not applicable for this study.

572

573 With best regards,

574 Yours sincerely,

575 (Corresponding author)

576 Jian-ping Liu,

577 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese

578 Medicine, Beijing, 100029, China

579 E-mail: LiuJP@bucm.edu.cn

580 **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 3 vs. Group	Age, Alb, DM, HN, RRF , phosphate , Log CRP	ACM: 1.15(0.20-2.57) ACM: 2.96(1.29-6.80)
Ji 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 (Gender-specific) Tertile 2 vs. Tertile (Gender-specific) Per 1 mg/dl increase	Age, RRF, Hb, Alb, phosphate, LDLC, CRP, history 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)
Xu 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 (DM: Gender specific) Tertile 3 vs. Tertile (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	Age, sex, BMI, SBP, Ca, P, Alb, TC, DM, SGA.	ACM: 1.478(0.602-3.627)
ChangWX2018 [39]	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 1 vs. Group 1 vs. Group	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)

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5									Per 1 mg/dl increase (Baseline-UA)	P, LDL-C, CRP, RASI, diuretic.	ACM: 0.86(0.67-1.12)		
6									Group 2 vs. Group	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)		
7	Zhang QL 2018	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	Per 1 µmol/l 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)	
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10	Lai KJ 2018	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 (Gender-specific) Tertile 2 vs. Tertile (Gender-specific) Men: Per 1mg/dl increase FM: Per 1 mg/dl increase	Sex., BMI, hypertension , dialysis duration, eGFR, Kt/v, LDL-C, iPTH.	ACM: 0.773(0.62-0.97)	
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20	Yang FY 2018	China: Mainland	RCS/ Single	51.8±14.4	232/487	Median	Median 29.5	197/109	Men: Hyperuricemia≥7mg/dl; FM: Hyperuricemia≥6mg/dl.	Per 1 mg/dl increase			
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24 581 **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  
 25 582 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:  
 26 583 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;  
 27 584 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;  
 28 585 Na: Serum sodium; K: Serum potassium; Cl: Serum chlorine; CO2: Venous carbon dioxide; LDL-C: Low density lipoprotein cholesterol; RASI: Renin-angiotensin system inhibitor; BG: Blood glucose; iPTH: intact parathyroid hormone;  
 29 586 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:  
 30 587 Triglyceride.

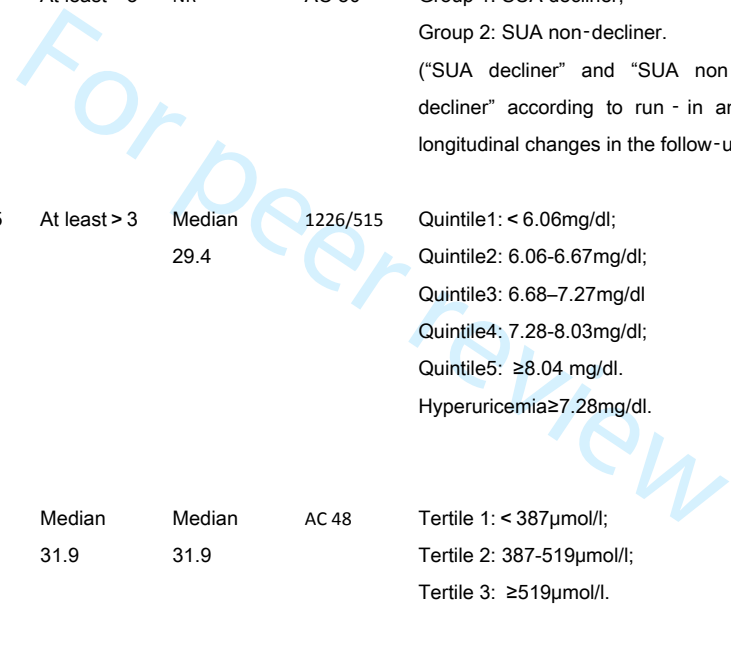
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588 **Table 2** Characteristics of included studies (2019-2020 years)

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)
Qiang WX 2019 [10]	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 [18]	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 [27]	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 2 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)
Correia I 2020 [32]	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)
Nakaki S 2020 [34]	Japan	RCS/multicenter	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 2 Group 2 vs. Group 3 Group 3 vs. Group 4 Group 4 vs. Group 5	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)

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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 10µmol/l increase	ACM: 1.00(0.99-1.02)
		CVM: 1.00(0.98-1.03)
Tertile 1: < 384µmol/l;	Tertile 3 vs. Tertile 1	ACM: 0.924(0.547-1.727)
Tertile 2: 384-460µmol/l;	Tertile 1 vs. Tertile 2	ACM: 0.993(0.598-1.651)
Tertile 3: > 460µmol/l.	Per 1µmol/l increase	ACM: 0.999(0.997-1.001)

China: RCS/	47.0±15.2	1269/2124	At least > 3	Median	554/275	Age, sex, DM , CVD , BMI ,
Mainland	Single			42		eGFR, DBP, use of diuretic
						and LUA, Hb, Alb, TC.

**589 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  
**590** 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:  
**591** 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  
**592** 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  
**593** agents; LUA: lower uric acid agent; UV: Urinary volume; eGFR: estimated glomerular filtration rate; DBP: Diastolic blood pressure; TC: Total cholesterol.

594 **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 <sup>2</sup> )	No. of study	Sample size	HR (95%CI)	Heterogeneity (I <sup>2</sup> )	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%	

595 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; I<sup>2</sup>: I-square; No.: Number.

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596 **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 <sup>2</sup> )	No. of study	Sample size	HR (95%CI)	Heterogeneity (I <sup>2</sup> )
<b>Study design</b>								
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	7448	0.90(0.76-1.06)	70.2%
<b>Study location</b>								
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)	474	1.00(0.91-1.10)	-
<b>Publication years</b>								
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	525	0.82(0.62-1.08)	77.7%
<b>No. of center</b>								
Single center	3	2842	1.49(0.66-3.38)	84.7%	2	1770	1.06(0.80-1.39)	80.3%
Multicenter	1	2193	1.35(0.74-2.46)	-	2	693	1.01(0.93-1.09)	0.0%
<b>Adjusted for sex</b>								
Yes	3	3972	1.39(0.60-3.24)	84.4%	4	8711	1.05(0.90-1.23)	74.0%
No	1	1063	1.73(1.03-2.91)	-	0	0	-	-
<b>Adjusted for diabetes mellitus</b>								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8711	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	-	-
<b>Adjusted for serum albumin</b>								
Yes	4	5035	1.46(0.78-2.74)	79.7%	4	8711	1.05(0.90-1.23)	74.0%
No	0	0	-	-	0	0	-	-

597 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; I<sup>2</sup>: I-square; No.: Number.

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5 598 **Figure legends**  
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8 **Fig.1** Flow diagram of study search and selection.  
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11 **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

12 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.  
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15 **Fig.3** Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.

16 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; DM: Diabetes mellitus; NDM: Non-diabetes mellitus; FM: Female; PD: Peritoneal dialysis.  
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19 **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.

20 **Abbreviations:** HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.  
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23 **Fig.5** Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.

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

28 **eFigure 1.** Funnel plot for relationship between serum uric acid level per 1mg/dl increase and all-cause mortality in peritoneal dialysis patients.  
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31 **eTable 1.** Searching strategies for electronic databases  
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34 **eTable 2.** Methodological quality assessment of the cohort studies utilizing the Newcastle-Ottawa Scale (NOS)  
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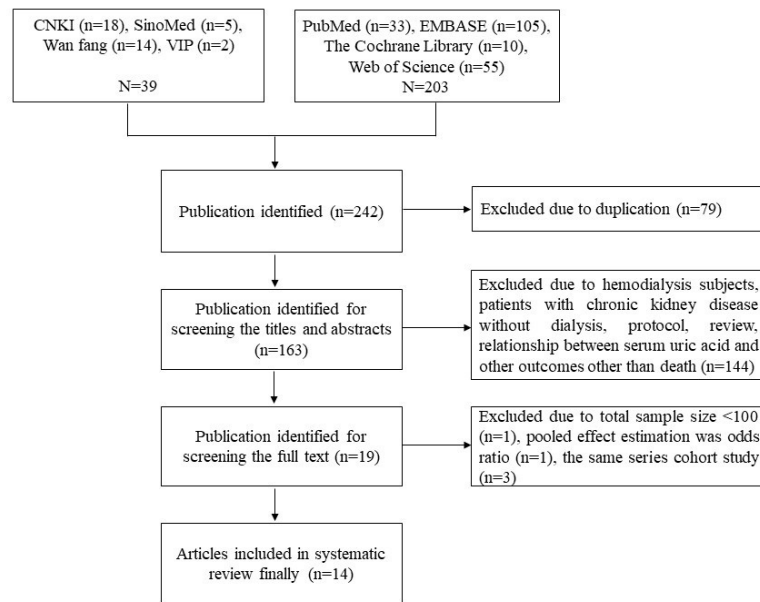


Fig.1 Flow diagram of study search and selection.

93x76mm (300 x 300 DPI)

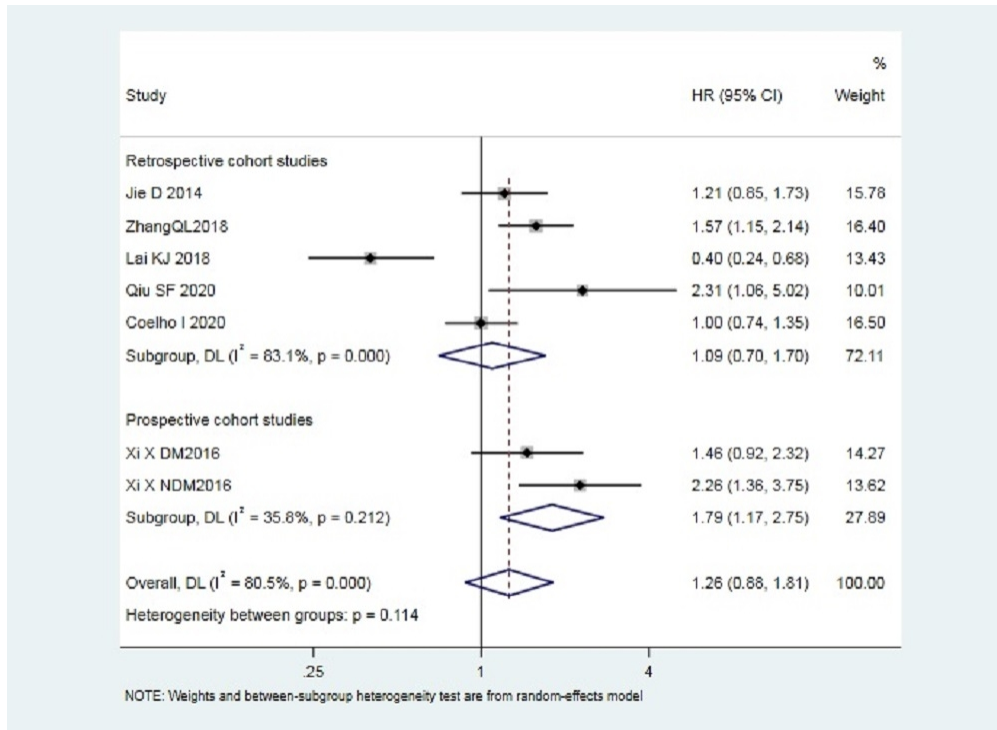


Fig.2 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and all-cause mortality in PD patients  
 Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

211x154mm (120 x 120 DPI)

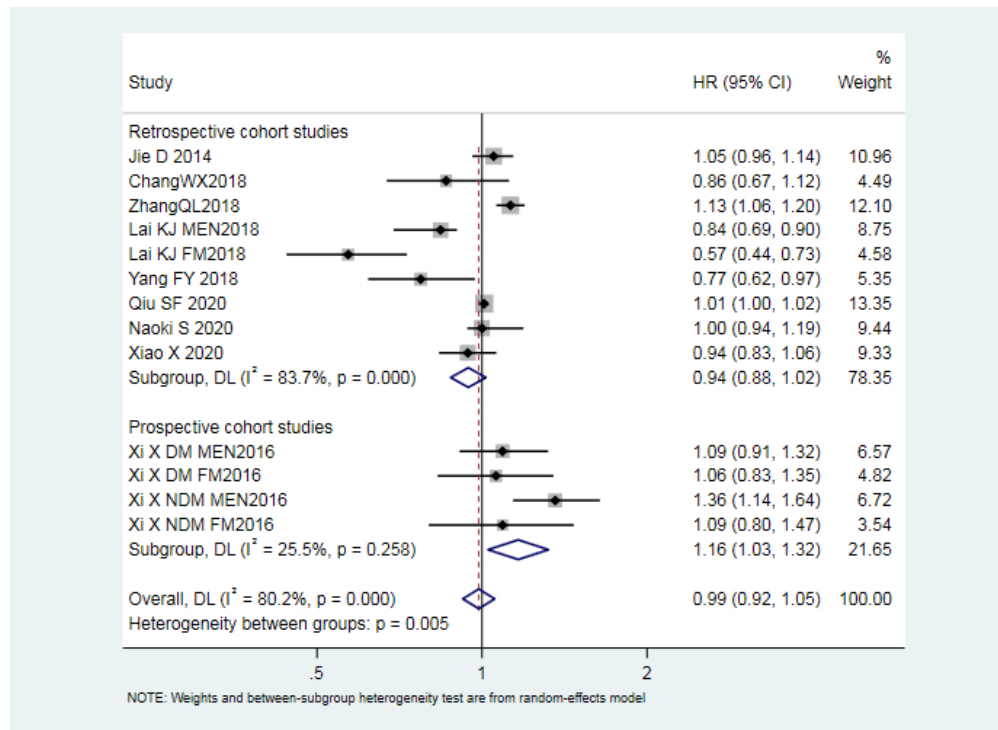


Fig.3 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and all-cause mortality in PD patients.

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

371x270mm (47 x 47 DPI)

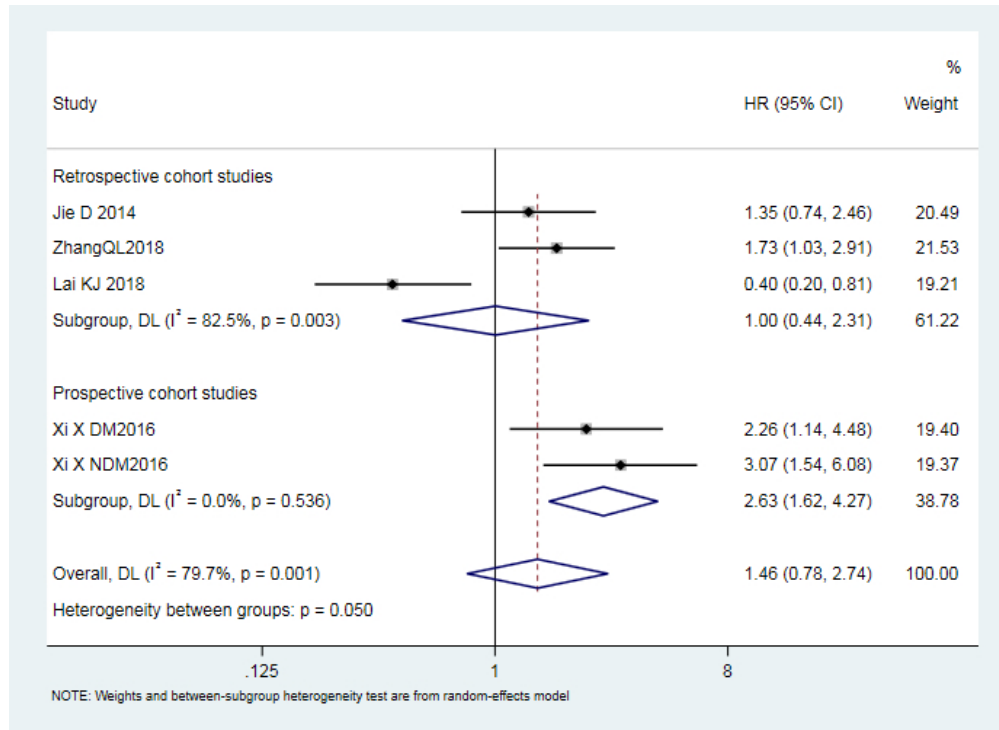


Fig.4 Forest plot and pooled HR for relationship between SUA by categories (the highest SUA category versus the lowest) and cardiovascular mortality in PD patients. Abbreviations: HR: Hazard ratio; CI: Confidence interval; SUA: Serum uric acid; PD: Peritoneal dialysis.

371x270mm (47 x 47 DPI)

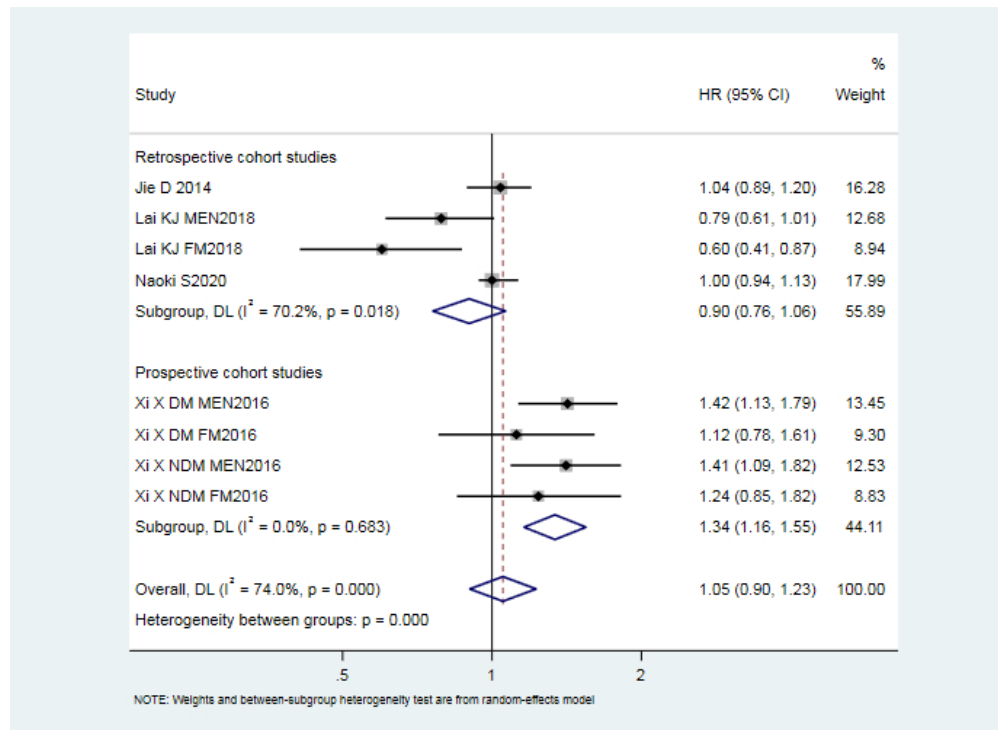
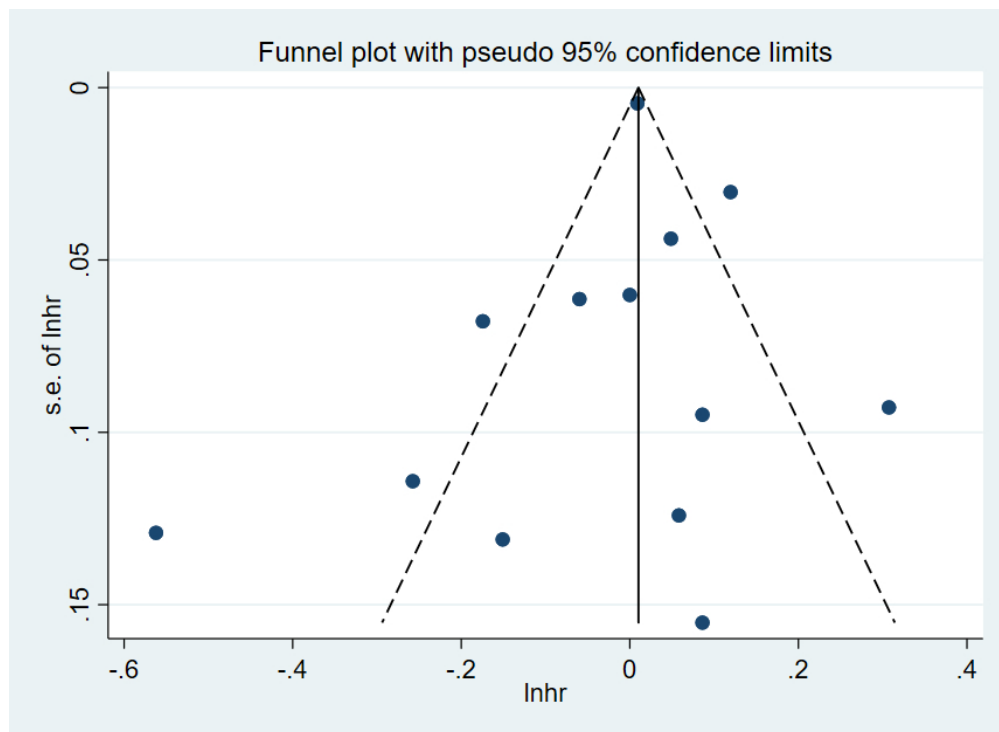


Fig.5 Forest plot and pooled HR for relationship between SUA per 1mg/dl increase and cardiovascular mortality in PD patients.

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

371x270mm (47 x 47 DPI)



301x219mm (72 x 72 DPI)

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**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

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CNKI, SinoMed,  
VIP, Wan Fang

#2. siwanglv (mortality,死亡率)  
#3. fumotouxu (peritoneal dialysis,腹膜透析) OR lianxuxingfeiwochuangfumotouxu (continuous ambulatory peritoneal dialysis,连续性非卧床腹膜透析) OR zidonghuafumotouxu (automated peritoneal dialysis,自动化腹膜透析)  
#4. #1 AND #2 AND # 3

SinoMed:5  
VIP:2  
WanFang:14

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For peer review only



**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
<b>Reporting of background should include</b>	
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; Page 5-6, Line 109-112
<b>Reporting of search strategy should include</b>	
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, Line 146-155
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
<b>Reporting of methods should include</b>	
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
<b>Reporting of results should include</b>	
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
<b>Reporting of discussion should include</b>	
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
<b>Reporting of conclusions should include</b>	
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

26 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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