# **RESEARCH ARTICLE**

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# Incidence and mortality of new-onset glucose disorders in peritoneal dialysis patients in China: a meta-analysis



Yanan Shi, Jiajie Cai, Chunxia Shi, Conghui Liu and Zhongxin Li<sup>\*</sup>

#### **Abstract**

**Background:** Dialysis patients are at high risk of developing glucose metabolism disturbances (GMDs), such as diabetes mellitus (DM), impaired fast glucose (IFG), and impaired glucose tolerance (IGT). However, it is unclear about the incidence of GMDs in Chinese patients with peritoneal dialysis (PD), as well as the influence of new-onset DM (NODM) on the prognosis of PD patients. Therefore, we conducted this meta-analysis to address these issues.

**Methods:** A comprehensive literature search was conducted using PubMed, Embase, Web of Science, SinoMed, and CNKI database for studies that evaluated the incidence of GMDs and mortality in patients with PD. Results were expressed as hazard ratio (HR), risk ratio (RR), or estimate (ES) with 95% confidence intervals (95%Cls).Meta-analysis was performed using a fixed-effects or random-effects model to pool the estimate.

**Results:** Fifteen studies met the inclusion criteria and were included in this meta-analysis. Pooled results showed that, the incidences of NODM, NOIGT, and NOIFG were 12% (95%CI: 9, 15%; P < 0.001), 17% (95%CI: 4, 10%; P < 0.001) and 32% (95%CI: 3, 30%, P < 0.001), respectively. Compared with patients without NODM, PD patients with NODM had an increased risk of mortality (HR = 1.59, 95%CI: 1.28, 1.98; P < 0.001). There was no significant difference in the incidence of NODM between PD and hemodialysis (HD) patients (RR = 1.23, 95%CI: 0.61, 2.51; P = 0.562).

**Conclusion:** Dialysis patients in China had an increased risk of developing GMDs, however, the dialysis modality did not have any significant impact on the incidence of NODM. NODM increased the mortality risk in patients undergoing PD. Thus, physicians should pay attention to the plasma glucose level in patients undergoing dialysis.

Keywords: Diabetes mellitus, Peritoneal dialysis, Glucose metabolism disturbances, Meta-analysis

# Background

New-onset diabetes mellitus (NODM), impaired fast glucose (IFG), and impaired glucose tolerance (IGT) are common complications in chronic kidney disease (CKD) patients undergoing peritoneal dialysis (PD) or hemodialysis (HD) [1–3]. They have been demonstrated to increase the risk of cardiovascular events and death in general population [4, 5], especially in patients receiving

dialysis [1–3]. Dialysis patients with diabetes have a poorer prognosis than those without diabetes [6].

Insulin resistance and concurrent hyperinsulinemia may occur in all the stages of CKD patients, even in patients with normal glomerular filtration rate, irrespective of the type of renal disease [7–9]. The dialysis therapy can partially improve insulin resistance, but not to the normal level [10]. Since glucose is used as the osmotic agents, hyperglycemia is commonly seen in PD patient [11]. This would result in worse survival [11].

Many studies have investigated the association between pre-existing DM at the initiation of dialysis and

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poor survival outcomes among CKD patients who underwent dialysis [12, 13]. However, few studies have reported the prevalence of NODM and its association with survival outcomes in dialysis patients [2, 11, 14]. The incidence of NODM varied greatly across different countries, with 12.7% at 2 years in HD patients in US [14], 4% at 1 year and 21% in 9 years in Taiwan [1]. Woodward et al. [14] collected data from the US Renal Data System, and reported that the prevalence of NODM to be 6% per year in dialysis patients. Whereas, in Asia, a high incidence of hyperglycemia has been observed in Chinese patients in Hong Kong, with a daily exchange of 1.5% glucose dialysate [11]. The incidence of NODM might be overestimated because the competing events were not taken into consideration in the analysis [15]. Moreover, the prevalence of NODM is different across patients undergoing HD or PD. CKD patients who underwent PD are usually younger than those undergoing HD [16-18], and HD patients may have higher risk of developing NODM than PD patients.

The worldwide number of CKD patients who underwent dialysis has been increased in the past decades. Previous studies have revealed that the incidence and prevalence of CKD patients undergoing dialysis are high in Hong Kong and Taiwan, China [11, 19]. Thus, we conducted this meta-analysis to investigate the incidence of GMDs in Chinese dialysis patients, to explore whether dialysis modality is associated with NODM, as well as whether NODM increases the risk of mortality.

# **Methods**

### Search strategy

We performed this meta-analysis in according to the methods of the *Cochrane Handbook for Systematic Reviews of Interventions* [20]. All the results were presented in accordance with the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. Scientific articles published in English or Chinese were searched from Pubmed, Embase, Web of Science, SinoMed (Chinese BioMedical Literature Service System, China), and CNKI (National Knowledge Infrastructure, China). Different retrieval formulas were established according to individual databases. The keywords we used were listed as followings: (diabetes OR new-onset diabetes OR de novo diabetes OR GMD OR IFG OR oral glucose tolerance test OR IGT) AND (dialysis OR PD OR hemodialysis)

.. The bibliographies of the previous reviews and of the included studies were also manually searched to identify other potentially eligible trials.

#### Study inclusion and exclusion criteria

All studies published before January 5, 2020, in English or Chinese language, were considered for inclusion. To

be included, studies must meet the following inclusion criteria: (1) study population: dialysis patients living in China; (2) study design: observational study, cohort study, or case-control studies; (3) outcome: incidence of NOGMD, including NODM, IGT and IFG, survival outcomes in PD patients. Studies were excluded from the final analysis if they did not focus on Chinese patients, or did not provide data of our interest, or published with the following types of study design: reviews, case reports, or policy analysis.

#### Data extraction

Data extraction was performed by two independent investigators. A standardized Excel file was used to extract the following information from each of the included studies: first author's name, year of publication, study design, sample size, patients' baseline characteristics (age, gender, body mass index, and comorbidity), and outcomes. When several publications were from the same trial or population, we only included the latest or most information study in order to avoid the duplication of information.

#### Methodological quality assessment

The methodological quality of each included study was assessed using the modified Newcastle-Ottawa (NOS) scale by two independent investigators [22]. The quality score of each study was given in according to the following three items, patient selection, comparability of the intervention/ control group, and outcome assessment [22]. The total score was 9 points, and higher scores indicated better quality. A study with a NOS scale greater than 5 points was considered to be high quality.

#### Statistical analysis

Before the data were synthesized, heterogeneity was tested by using the Cochrane Q chi-square and  $I^2$ statistic, in which P value < 0.1 or  $I^2 > 50\%$  were defined to have heterogeneity [20]. When substantial heterogeneity was identified, a randomized-effects model (DerSimonian-Laird method) [23] was used; otherwise, a fixed-effects model (Mantel-Haenszelmethod) [24] was preferred to pool the incidence rate and survival rate, as well as the 95% confidence intervals (95%CIs). The incidence rate was calculated with estimate (ES) and 95%CIs; survival rate was a time-to-event variable, thus it was expressed as hazard ratio (HR) with 95%CIs; the comparison between PD and HD in the NODM incidence was calculated with risk ratio (RR) and 95%CIs. In order to detect the potential source of heterogeneity, we performed sensitivity analysis by omitting one study at each turn. Publication bias was assessed by the Begg's [25] and Egger's test [26]. A twotailed *P*-value of less than 0.05 was considered statistically significant, except where otherwise specified. All statistical

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analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA).

#### Result

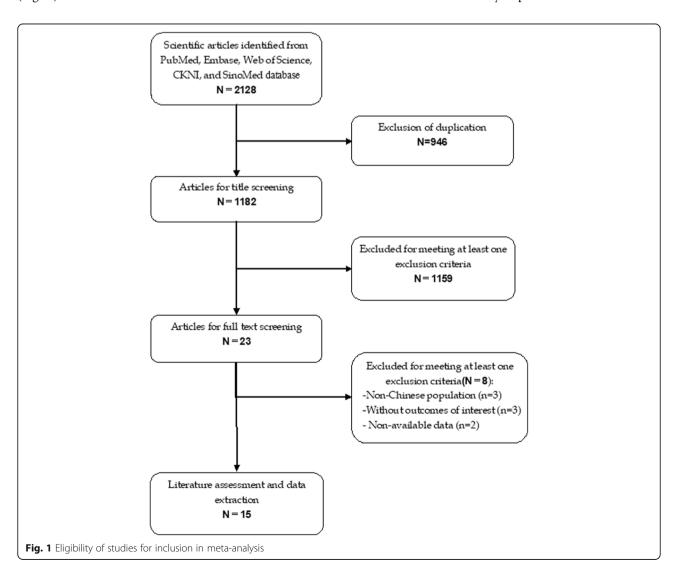
#### Identification of eligible studies

The initial search yielded 2128 publications, of which 946 were excluded because of duplicate records. Then, 1182 publications were left for title/abstract review, and 1159 of them were removed because they were unrelated with our topics, or were reviews and case reports. The remaining 23 studies were reviewed for full-text information, and 8 of them were removed because three studies were not performed in Chinese population; three studies did not provide data of our interest; and two studies had non-available data for analysis. Finally, 15 studies met the inclusion criteria and were included in this meta-analysis [1, 11, 27–39] (Fig. 1).

# Study characteristics and quality assessment

The main characteristics of included studies were presented in Table 1. These studies were published between 2001 and 2019. All the studies were performed with retrospective or prospective cohort design. Eight studies were published in international English journals [1, 11, 27–32], whereas the remaining seven in Chinese journals [33–39]. The sample size varied greatly across the included studies, which ranged from 35 to 26,166. The mean ages of the patients were older than 40 years. Continuous ambulatory PD (CAPD) were applied in six of the included studies [11, 27, 32, 36–38], and the other studies used PD or HD. Based on the NOS for the quality assessment of cohort studies, these studies had a NOS score greater than 5 points, which indicated a high quality.

Incidence of new-onset glucose metabolism disturbance Eight studies [1, 11, 27–32] reported the data of incidence of NOGMDs in dialysis patients. The incidence of



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**Table 1** Baseline characteristics of patients in the trials included in the meta-analysis

| Study         | Study design | Dialysis modality | No. of patients | Male/female  | Age (mean $\pm$ SD, y) | Follow-up (months) | NOS score |
|---------------|--------------|-------------------|-----------------|--------------|------------------------|--------------------|-----------|
| Tien KJ [1]   | Cohort       | PD/HD             | 3346            | 1398/1948    | NA                     | 53.2               | 7         |
|               |              |                   | 22,820          | 10,784/12036 | NA                     |                    |           |
| Szeto CC [11] | Cohort       | CAPD              | 252             | 135/117      | 59 ± 13                | 45.4 ± 26.5        | 6         |
| Yu XF [27]    | Cohort       | CAPD              | 145             | 60/85        | 62 ± 15                | 48                 | 6         |
| Wang IK [28]  | Cohort       | PD/HD             | 6177            | 2665/3512    | 51.0                   | 49.44 ± 34.32      | 8         |
|               |              |                   | 6177            | 2726/3451    | 51.2                   | 52.36 ± 37.2       | 7         |
| Wu PP [29]    | Cohort       | PD/HD             | 2228            | 1096/1132    | 60.29 ± 16.43          | $64.2 \pm 47.04$   | 7         |
|               |              |                   | 8912            | 4384/4528    | 60.29 ± 16.43          | $73.68 \pm 47.4$   |           |
| Dong J [30]   | Cohort       | PD                | 32              | 9/23         | 61 ± 12.5              | 32.4 (12.9–60.8)   | 6         |
|               |              |                   | 580             | 256/324      | 55.2 ± 15.4            |                    |           |
| Chou CY [31]  | Cohort       | PD/HD             | 2548            | 916/1632     | 50.2 ± 14.7            | 70                 | 7         |
|               |              |                   | 10,192          | 3692/6500    | 50.3 ± 14.5            |                    |           |
| Cheng SC [32] | Cohort       | CAPD              | 14              | 5/9          | 46.4 ± 12.0            | 39.9 ± 28.3        | 6         |
|               |              |                   | 21              | 7/14         | $42.4 \pm 9.4$         | $60.5 \pm 37.8$    |           |
| Song ZP [33]  | Cohort       | PD                | 42              | NA           | $60.2 \pm 2.3$         | NA                 | 6         |
|               |              |                   | 42              | NA           | $60.2 \pm 2.3$         |                    |           |
| Yang G [34]   | Cohort       | PD                | 40              | NA           | $58.4 \pm 4.7$         | NA                 | 6         |
|               |              |                   | 42              | NA           | $58.4 \pm 4.7$         |                    |           |
| Ye SH [35]    | Cohort       | PD                | 44              | 24/20        | $60.14 \pm 2.69$       | NA                 | 6         |
|               |              |                   | 44              | 25/19        | 60.78 ± 2.98           |                    |           |
| Peng XY [36]  | Cohort       | CAPD              | 138             | 83/55        | 57 (46–71)             | NA                 | 7         |
|               |              |                   | 69              | 38/31        | 56 (42–71)             |                    |           |
| Xia P [37]    | Cohort       | CAPD/APD          | 442             | 228/214      | 58.4 ± 15.6            | NA                 | 6         |
|               |              |                   | 92              | 53/39        | 56.7 ± 16.0            | NA                 |           |
| Fei JY [38]   | Cohort       | CAPD              | 286             | 148/138      | 58 (13–85)             | 3–120              | 6         |
| Li Y [39]     | Cohort       | PD                | 577             | 280/297      | 58.9 ± 15.5            | NA                 | 6         |

Abbreviation: SD standard deviation, PD Peritoneal dialysis, HD hemodialysis, CAPD continuous ambulatory PD, APD, automated PD

NODM varied from 3.76 to 13.78% across the included studies. Pooled estimate showed that, 12% of patients developed NODM after dialysis (ES = 7, 95%CI: 4, 10%; P < 0.001) (Fig. 2). The test for heterogeneity was significant (I<sup>2</sup> = 98.1%, P < 0.001), thus, we performed sensitivity analysis. When we excluded the trial with outlier [31], the pooled estimate changed a little (ES = 6, 95%CI: 3, 10%; P < 0.001). However, the heterogeneity was still present (I<sup>2</sup> = 97.5%, P < 0.001). We further removed any single study, but the pooled result and heterogeneity did not alter substantially (data not shown).

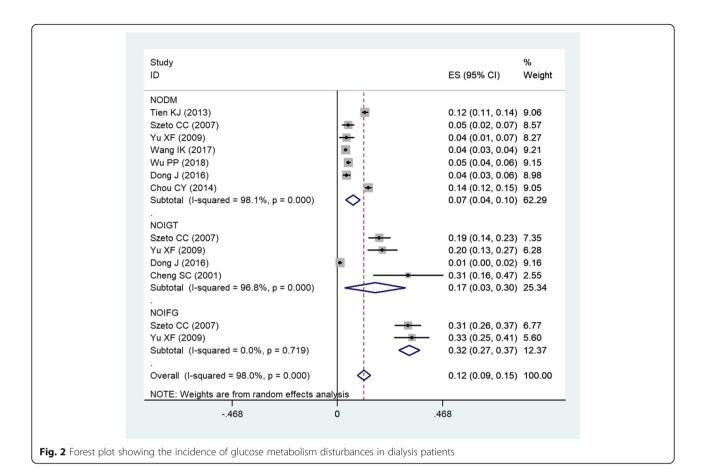
The incidence of NOIGT in dialysis patients varied from 1.14 to 31.43% among the included studies. Pooled results indicated that, the incidence of NOIGT was 17% (ES = 17, 95%CI: 3, 30%; P < 0.001) in patients undergoing dialysis (Fig. 2).

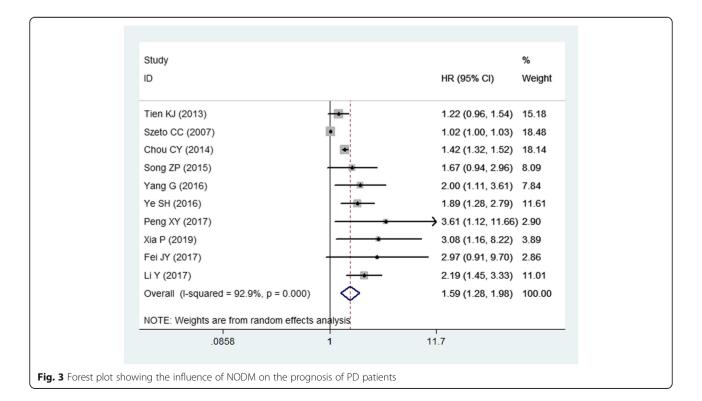
The incidence of NOIFG was almost similar among the included two studies. Pooled results suggested that, 32% of patients developed NOIFG after they received dialysis (ES = 32, 95%CI: 3, 30%, P < 0.001) (Fig. 2).

## Mortality risk and NODM

Ten studies [1, 11, 31, 33–39] reported the data of mortality in dialysis patients. Pooled the results showed that, PD patients who developed NODM had an increased risk of mortality than those without (HR = 1.59, 95%CI: 1.28, 1.98; P < 0.001) (Fig. 3). The test for heterogeneity was significant (I<sup>2</sup> = 92.9%, P < 0.001), thus, we performed sensitivity analysis. When the trial with outlier [36], was removed, the overall estimate did not change substantially (HR = 1.55, 95%CI: 1.25, 1.93; P < 0.001), but the heterogeneity was still present (I<sup>2</sup> = 93.4%, P < 0.001). When we excluded another trial with outlier [11], the summarized data altered slightly (HR = 1.67, 95%CI: 1.39, 2.00; P < 0.001), but the heterogeneity disappeared (I<sup>2</sup> = 47.8%, P = 0.053). This indicated that the

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trial conducted by Szeto cc, et al. [11] contributed to the heterogeneity.

#### Incidence of NODM between PD and HD

Three studies [1, 28, 29] compared the incidence of NODM between PD and HD. Pooled results showed that, PD patients had a similar incidence of NODM with HD patients (RR = 1.23, 95%CI: 0.61, 2.51; P = 0.562) (Fig. 4).

#### **Publication bias**

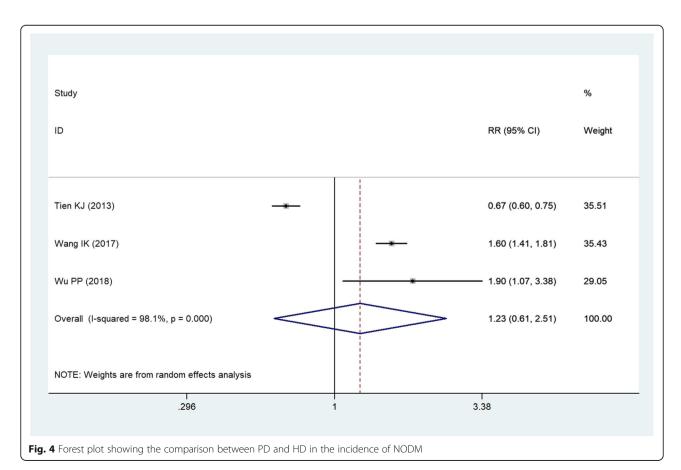
The assessment of publication bias showed that, there was no evidence of significant publication bias by the formal statistical tests (Egg test, P = 0.580; Begg test, P = 0.764).

#### **Discussion**

The present meta-analysis included 15 studies to identify the risk of NOGMDs in Chinese patients undergoing dialysis, and the NODM incidence between PD and HD patients, as well as evaluate the impact of NODM on the survival outcome in PD patients. Our results showed that, the incidence of NODM in Chinese dialysis patients was 7% (95%CI: 4, 10%; P < 0.001). PD patients had similar risk with HD patients of developing NODM (RR =

1.23, 95%CI: 0.61, 2.51; P = 0.562). NODM increased the mortality rate in patients undergoing HD (HR = 1.59, 95%CI: 1.28, 1.98; P < 0.001). Our results were in consistent with the findings of the previous study conducted by Xue C, et al. [40] (Table 2).

The incidence of NODM in dialysis patients varied greatly across different counties and population. Salifu, MO, et al. [41] collected data from the United States Renal Data System (USRDS) from January 2000 to December 2001, and reported the incidence of NODM after HD was 20 per 1000 patient-year, and the prevalence was 7.6% during the 3 years of follow-up [41]. Whereas, in another study which was performed in China Taiwan, the rates of incidence and prevalence in dialysis patients with end-stage renal disease (ESRD) were higher than that in the previous study [1]. In that study, the authors examined the records of ESRD patients from the Taiwan National Health Insurance Research Database between 1999 and 2005 [1]. These patients who underwent dialysis were followed until death, transplant, dialysis withdrawal, or 31 December 2008. The cumulative incidence rate of NODM was 4% at 1 year and 21% at 9 years [1]. The incidence and prevalence of NODM at 10 year was 29 per 1000 patient-years and 12.8%, respectively [1]. Another study



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Table 2 Outcome comparison between this and previous studies

|                                     | Xue C, et al.                | Our study                    |  |
|-------------------------------------|------------------------------|------------------------------|--|
| Number of included studies          | 9                            | 15                           |  |
| Total sample size                   | 13,879                       | 56,390                       |  |
| Population                          | Dialysis patients            | Chinese dialysis patients    |  |
| Incidence of NODM                   | 8% (95%CI: 4, 12%)           | 12% (95%CI: 9, 15%)          |  |
| Incidence of NOIGT                  | 15% (95%CI: 3, 31%)          | 17% (95%Cl: 4, 10%)          |  |
| Incidence of NOIFG                  | 32% (95%CI: 27, 37%)         | 32% (95%CI: 3, 30%)          |  |
| Mortality rate in PD patients       | HR = 1.06, 95%CI: 1.01, 1.44 | HR = 1.59, 95%CI: 1.28, 1.98 |  |
| Incidence of NODM between PD and HD | RR = 0.99, 95%CI: 0.69, 1.40 | RR = 1.23, 95%CI: 0.61, 2.51 |  |

**Abbreviation**: PD Peritoneal dialysis, HD hemodialysis, NODM new-onset diabetes mellitus, NOIFG new-onset impaired fast glucose, NOIGT new-onset impaired glucose tolerance, RR risk ratio, HR hazard ratio, CI confidence intervals

reported that the NODM prevalence in dialysis patients (PD and HD) at 6-year follow-up was 8.5% [13]. This was lower than that in the study of Tien KJ [1], which might be explained by the shorter follow-up period. Other factors may also have an impact on the risk of developing NODM. Woodward et al. [14] reported that, the immunosuppressant agents had great influence on the NODM. In their study, the incidence of NODM in patients who received cyclosporine and tacrolimus ranged from 18 to 30% after the transplant had been performed 2 years [14].

In the present study, we found the risk of developing NODM was not significant different between patients undergoing PD and HD. Our findings were in consistent with that of the previously published studies [1]. Tien KJ, et al. reported that, the incidence of NODM after initiation of dialysis in HD and PD group was 12.80 and 12.20%, respectively [1]. This difference was not significant even after adjustment. However, another study reported a significantly higher incidence of NODM in PD patients than in HD patients. In that study, the incidence of NODM in the two groups was 15.98 and 8.69 per 1000 patient-years, respectively (P < 0.001) [29]. Similarly, Woodward, RS, et al. [14] also reported different incidence of NODM among wait-listed transplanted renal allograft patients. The incremental incidence of NODM was 7.5% for PD patients and 8.2% for HD patients, respectively [14]. This difference might be biased by the confounders, including age, gender, pre-existing comorbidities (hypertension, cardiac disease, and cerebrovascular disease), which had not been adjusted in the data analysis.

Regarding the survival outcome, our study found that, dialysis patients with NODM had a significantly higher mortality rate than those without NODM. Our results were in consistent with the findings in the previous studies. Chou CY, et al. [31] examined the data in Taiwan Renal Registry Database from 1997 to 2005in 2548 PD patients and 10,192 HD patients who had no DM on the initiation of dialysis [31]. Data analysis using

the propensity score matching method suggested that, NODM was associated with a significantly increased risk of mortality (HR = 1.42, 95%CI: 1.32, 1.52; P < 0.001) [31]. Similarly, Salifu, MO et al. [2] found that the mortality rate at the end of 3-year follow-up was significantly higher in NODM patients with HD (49.2%), second highest in patients with pre-existing DM (50.6%) than those without DM (41%) [2]. Tien, KJ, et al. [1] found similar results with the above findings, in which the survival rate was significantly highest in those without DM, moderate in those with NODM, and lowest in those with pre-existing DM. Compared with those without DM, pre-existing DM increased the death risk by 80% (HR = 1.81, 95%CI: 1.75, 1.87); whereas NODM increased the death risk by 10% (HR = 1.10, 95%CI: 1.03, 1.17) [1]. An interesting finding in the Kaplan-Meier survival plot showed that, the survival curves of patients with NODM and without DM began to diverge at 3 years after initiation of dialysis therapy [1]. The authors suggested that, this might reflect the cumulative or delayed damage caused by the increased glucose level [1].

The use of osmotic agents could have an impact on the reduction of GMDs. Icodextrin, derived from cornstarch, is a glucose polymer, which is a commonly used glucose-sparing solution [41]. By using the icodextrin, the ultrafiltration is enhanced and uncontrolled fluid overload is mitigated [42]. This solution has metabolic effects on the glycemic and dyslipidemia control [43-45]. The use of icodextrin may improve the technique and survival in PD patients [46-48]. Wang IK, et al. collected data from Taiwan health insurance database from 2000 to 2010 to assess the effects of icodextrin in reducing the risk of NODM in PD patients [28]. Their results suggested that, among PD patients, the incidence of NODM was significantly lower in icodextrin users than n nonusers (6.22 VS 12.1 per 1000 person-years), with an adjusted HR of 0.66 (95%CI: 0.50, 0.88) [28]. The authors concluded that, icodextrin was effective in reducing the risk of NODM in PD patients.

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There were several potential limitations in this study. First, significant heterogeneity was identified across the included studies. Although sensitivity analysis was performed to explore the potential sources, no valuable information was obtained from the analysis results. However, there were various factors across the included studies, including definition of DM, severity of the ESRD, age of initial dialysis, baseline comorbidity, and the duration of follow-up. These factors might account for the heterogeneity and had impact on the final results. Second, all the included studies were retrospective or prospective cohort studies. Although the cohort studies can reflect the "real-world" and further support the conclusion, cohort data are of course highly prone to selection bias. Third, it would be interesting to compare the influence between pre-existing and new-onset DM on the prognosis of dialysis patients; however, due to the limited data, these data analysis was not performed. Fourth, there were four studies that were derived from the analysis of Taiwan National Health Care Insurance Database with different time periods. However, some of them had the overlap data duration the same period. We have tried to contact the corresponding authors with requests for the original data. However, none of them responded to our request. The overlapped data would result in bias in the data analysis and influence the effect size. Thus, the physicians should interpret our results with caution.

#### Conclusion

The present study confirmed the risk of developing NODM in Chinese patients with dialysis; however, the dialysis modality did not have any significant impact on the incidence of NODM. The development of NODM increased the mortality risk in patients undergoing PD. Thus, physicians should pay attention to the plasma glucose level in patients undergoing dialysis.

#### Abbreviations

CAPD: Continuous ambulatory PD; Cl: Confidence intervals; CKD: Chronic kidney disease; DM: Diabetes mellitus; ES: Estimate; GMD: Glucose metabolism disturbances; HR: Hazard ratio; IFG: Impaired fast glucose; IGT: Impaired glucose tolerance; NODM: New-onset diabetes mellitus; PD: Peritoneal dialysis; RR: Risk ratio

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Not applicable.

#### Authors' contributions

YS and ZL conceived and designed the study. YS, JC, CS and CL were responsible for the collection of data and performing the statistical analysis and manuscript preparation. ZL was responsible for checking the data. All authors were responsible for drafting the manuscript, and read and approved the final version.

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#### Availability of data and materials

All data generated and analysed during this study are included in this published article.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable

#### Competing interests

The authors declare that they have no competing interests.

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