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Prognostic impact of galectin-3 in chronic kidney disease patients: a systematic review and meta-analysis

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Abstract

Background Galectin-3 as a β-galactoside-binding lectin, which has served important functions in numerous biological activities including cell growth, apoptosis, pre-mRNA splicing, differentiation, transformation, angiogenesis, inflammation, fibrosis, and host defense, may be used in prediction of clinical outcomes in CKD patients. However, the given results remain debatable and inconclusive. Hence, we performed a comprehensive meta-analysis to clarify the predictive value of galectin-3 in patients with CKD, especially ESRD patients going on dialysis.
Methods PubMed and Embase electronic databases were searched to identify eligible studies reporting the association between galectin-3 and adverse outcomes in CKD patients. We searched the literatures published October 2018 or earlier. We used both fix-effects and random-effects models to calculate the overall effect estimate. An $I^2 > 50\%$ indicates at least moderate statistical heterogeneity. A sensitivity analysis and subgroup analysis were performed to find the origin of heterogeneity.
Results We ultimately enrolled five studies with a total of 5226 patients in this meta-analysis. The result showed that high galectin-3 levels were associated with increased risk of all-cause mortality and cardiovascular (CV) events in CKD patients. For every 1% increased in galectin-3, the risk of all-cause mortality increased by 37.9% (HR 1.379, 95% CI 1.090–1.744). Much more, the risk of CV events in CKD patients was also significantly increased (HR 1.054, 95% CI 1.007–1.102) with no statistical heterogeneity among the studies ($I^2 = 0.0\%$, $p = 0.623$). However, there was no statistical difference between the risk of all-cause mortality and galectin-3 in HD patients (HR 1.171, 95% CI 0.963–1.425).
Conclusions Our meta-analysis suggests that high levels of galectin-3 may increase the risk of all-cause mortality and CV events in CKD patients, however, probably not a sensitive biomarker for outcomes in HD patients. Further studies were warranted to validate our findings.

Keywords Galectin-3 · Chronic kidney disease · Hemodialysis · Mortality · Meta-analysis

Introduction

Chronic kidney disease (CKD) is an increasingly common major health problem worldwide, of which the approximate prevalence is 8–16% [1] and those older than 65 years suffering from CKD nearly are up to 25–35% according to current statistics [2]. Its importance particularly derives from its leading to a serious increase in mortality and morbidity as it progresses toward end-stage renal disease (ESRD) [3]. Mortality rates in patients with ESRD have declined significantly over the past 20 years, but long-term survival remains poor—5-year mean survival for dialysis patients 52.5% (36.7% in patients aged 65–74 years and 20.9% in patients aged ≥ 75 years) [4]. Therefore, the risk stratification of adverse event is an essential component in the management of CKD patients, allowing early identification of high-risk patients and a more aggressive/focused treatment. Inflammation, cardiac remodeling, and fibrosis are potentially important pathways in the pathogenesis of CKD, especially when it comes to dialysis. Although there are numerous classical cardiac biomarkers such as cardiac troponins or natriuretic peptides have been conducive to predict overall and CV

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mortality in CKD patients [5–8]. However, the identification of an optimal biomarker and/or combination of biomarkers still remains a goal to be achieved.

Galectin-3 (Gal-3) belongs to the β-galactoside-binding protein family. It is a ubiquitous protein expressed in epithelial cells, endothelial cells, and macrophages. Even more it plays a role in embryonic development and has the characteristics of promoting fibrosis and inflammation. Recent trials demonstrated that Gal-3 was a significant independent predictor of all-cause mortality, CV events, and left ventricular remodeling in the general population [9, 10]. In addition, Gal-3 acts as a profibrotic agent within the kidney as well and therefore may be involved in progression of CKD [11]. Circulating Gal-3 values are inversely correlated with kidney function, exceeding the reference range by as much as four to fivefold in hemodialysis (HD) patients [12]. In a post hoc analysis of the 4-dimensional study (German Diabetes Mellitus Dialysis), which included 1168 HD patients with diabetes, it revealed that Gal-3 was associated with CV events [12]. However, this correlation provided by a post hoc analysis of a large cohort of diabetic patients raises the question whether the relationship between high Gal-3 levels and adverse outcome is generalizable to other HD populations.

Given that inconsistent results regarding the association between Gal-3 and adverse impacts in CKD patients, we systematically reviewed the current literatures and performed a systematic review and comprehensive meta-analysis to evaluate prognostic value of Gal-3 in CKD patients.

Methods

This meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Search strategies

PubMed and Embase databases were searched by two independent reviewers (TZ and JL) to identify relevant studies that evaluated the association between galectin 3 and clinical outcome in CKD patients up to October 20, 2018. The following search terms were used as follows 'galectin 3' or 'Gal-3' and 'kidney' or 'renal' or 'chronic kidney disease or CKD' or 'end-stage renal disease or ESRD' or 'dialysis' or 'hemodialysis or HD' or 'peritoneal dialysis or PD.' Additionally, a manual search was conducted on the scientific sessions of the American Society of Nephrology, the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and the International Society of Nephrology (ISN) World Congress of Nephrology (WCN) during the past 5 years. And then, titles and abstracts as well as the reference lists of all of the identified reports were examined independently by two researchers mentioned above to determine if a study was suitable for the present meta-analysis.

Inclusion criteria

Studies included in present quantitative analyses should meet the following criteria (1) cohort study or case–control study, Individual case reports, editorials, and review articles were excluded; (2) measured Gal-3 at baseline and documented clinical outcome during follow-up in CKD patients; (3) clearly defined the death events in CKD patients; (4) reported the hazard ratio (HR) or the raw data converted to a HR and the corresponding 95% confidence interval (CI) for Gal-3 levels and adverse outcomes in CKD patients; (5) only studies that included patients with a diagnosis of CKD that is clearly defined and in accordance with current guideline-based definitions were selected. We included published and unpublished studies without language restriction.

Data extraction

Two reviewers (TZ and JL) independently screened the abstracts or titles of the studies from the electronic search to identify all potential eligible studies. Potentially relevant reports were then retrieved as completed manuscripts and assessed for compliance with the inclusion criteria. Relevant data were extracted by two reviewers (TZ and JL) independently from the full text of each identified study using a standardized form. Any uncertainties or discrepancies between the two reviewers were resolved through consensus after rechecking the source data and consultation with the third reviewer (SC). To perform validity analyses, the following information was obtained from each identified article: first author's last name, publication year, country, study design, study population, sample size, participants' age and sex, the proportion of combined diabetes mellitus, duration of follow-up, and end point events.

Quality assessment

To reduce the heterogeneity due to different study designs, the quality of each study was evaluated based on the United States Preventive Task Force [14] and the Evidence-Based Medicine Working Group [15]. A point score system was applied according to the quality of the study. The following characteristics were assessed (1) clear description of inclusion and exclusion criteria; (2) study sample representative for mentioned population; (3) clear description of sample selection; (4) full specification of clinical and demographic variables; (5) follow-up duration more than one year; (6) reporting the loss of follow-up; (7) clear definition of CKD, ESRD, HD, or PD; (8) clear definition of outcomes and outcome assessment; (9) temporality (assessment of Gal-3 at the baseline); and (10) adjustment of possible confounders on the multivariate analysis. We graded the quality as good (≥ 8 criteria), fair (5–7 criteria), and poor (< 5 criteria).

Statistical analysis

We used the metan command in Stata to calculate a summary hazard ratio (HR) for Gal-3 levels and adverse outcomes in CKD patients. To evaluate the heterogeneity across studies, we used I^2 derived from the Chi-square test. An $I^2 > 50\%$ indicates at least moderate statistical heterogeneity. A fixed effects model (the inverse variance method) was used when $I^2 < 50\%$, otherwise the random-effects model (inverse variance heterogeneity method) was used. The sensitivity analysis was done in a random predefined manner after omitting one study at a time and checking the consistency of the overall effect estimate. We also performed subgroup analysis on sample size ($n < 400$ or $n > 400$) and geographic area (Asian or non-Asian). Small-study effects were assessed for each outcome by visual inspection of the funnel plot and an Egger's test [16]. Statistical significance was defined as a 2-tailed p value of 0.05. All statistical analyses were performed using Stata 11 (Stata Corp LP, College Station, TX, USA).

Results

Literature search

A flow diagram of the data search and study selection is presented in Fig. 1. A total of 972 studies were found using our search criteria. We identified 520 duplicate studies, which were discarded. The remaining 452 abstracts were screened further, and we excluded 430 studies, because they were either unrelated, irrelevant, review articles, or editorials. Then full-text studies were then retrieved for detailed evaluation. Of the 22 articles, 17 studies did not meet the inclusion criteria, which were excluded. The remaining five studies [12, 17–20] were included in our meta-analysis.

Description of studies

We included 5 studies [12, 17–20] with a total of 5226 patients. The main features of the studies on the association between Gal-3 and mortality in CKD patients are listed in Table 1. Three studies [12, 17, 20] were conducted in non-Asia, with the exception of two [18, 19] conducted in Asia. All studies were prospective studies. Patients' mean age ranged from 57 to 66 years old. The proportion of male

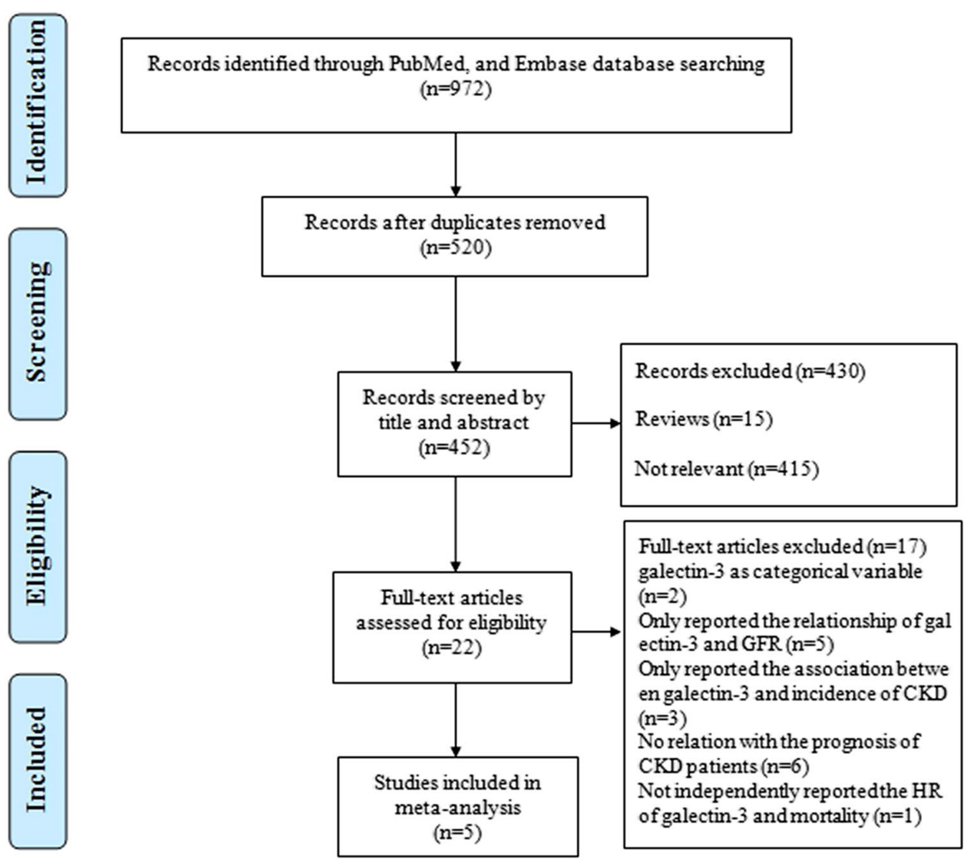

Fig. 1 Flow diagram of the selection process. *HR* hazard ratio; *CKD* chronic kidney disease, *CI* confidence interval

Table 1 Characteristics of the five articles included in the meta-analysis

Author/year	Country	Study design	Study population	Patients total (*n*)	Men (%)	Mean age, (years)	DM (%)	Follow-up (months)	At the end of the event	Quality score
Hogas/2016	Romania	Prospective observational study	HD Patients	88	39.8	57.3 ± 14.4	21.5	22.2	All-cause mortality Death	10
Drechsler/2015	Germany	Prospective study	LURIC-CKD Patients	2578	68.3	62.8 ± 10.5	0	120	All-cause mortality Death due to infection	10
			4D-HD Patients	1168	54	66 ± 8	100	48	CV mortality	
Obokata/2016	Japan	Prospective observational study	HD patients	423	68.8	66 ± 12	45.4	25.2	All-cause mortality Cerebrocardiovascular events	10
Ko/2018	China	Prospective study	HD patients	86	45	60.0 ± 12.6	40.7	53.3	All-cause mortality CV mortality	10
Tuegel/2018	USA	Prospective observational cohort study	CKD patients	883	56	57 ± 15	43	36	All-cause mortality HF events CV events	9

HD hemodialysis, *CKD* chronic kidney diseases, *LURIC* Ludwigshafen Risk and Cardiovascular Health, *4D* German diabetes mellitus dialysis, *CV mortality* cardiovascular mortality, *HF events* heart failure events; *DM* diabetes mellitus, *NM* not mentioned

in the studies ranged between 39.8% and 68.8%, and the mean follow-up periods varied from 22.2 to 120 months. Of the five studies that enrolled patients with CKD, four studies [12, 17–19] comprised patients with HD.

Gal-3 and all-cause mortality, CV events in CKD patients

Five studies [12, 17–20] evaluated the prognostic importance of Gal-3 for all-cause mortality in CKD patients. When pooling data from the studies together, we found that for every 1% increased in Gal-3, the risk of all-cause mortality increased by 37.9% (HR 1.379, 95% CI 1.090–1.744) with statistical heterogeneity among the studies ($I^2=91.8\%$, $p=0.000$) (Fig. 2). Three studies [12, 18, 20] evaluated the prognostic importance of Gal-3 for CV events in CKD patients, CV events risk in CKD patients was significantly increased (HR 1.054, 95% CI 1.007–1.102) with no statistical heterogeneity among the studies ($I^2=0.0\%$, $p=0.623$) (Fig. 2).

Gal-3 and all-cause mortality, CV events in HD patients

In our meta-analysis, data from four studies [12, 17–19] reported the association between Gal-3 and mortality in HD patients. When pooling data from the studies together, we found that there was no statistical difference between Gal-3 and the risk of all-cause mortality in HD patients (HR 1.171, 95% CI 0.963–1.425). Only two studies [12, 17] evaluated the prognostic importance of Gal-3 for CV events in HD patients. There was no statistical difference between Gal-3 and the risk of CV events in HD patients (HR 1.065, 95% CI 0.999–1.135) (Fig. 3).

Sensitivity and subgroup analysis

A sensitivity analysis was performed to find the origin of heterogeneity. After removing the study by Drechsler et al. [12] which was large-scale prospective cohort study, the analysis did not find significant influences on heterogeneity across studies or overall results ($I^2=93.6\%$, $p=0.000$; $z=2.62$, $p=0.009$). Then, we performed a subgroup analyses according to sample size ($n<400$ or $n>400$), geographic area (Asian or non-Asian), we also did not found significant influences on heterogeneity across studies ($n<400$, $I^2=90.6\%$, $p=0.001$, $z=0.96$, $p=0.339$; $n>400$, $I^2=88.3\%$, $p=0.000$, $z=2.27$, $p=0.023$; Asian, $I^2=89.1\%$, $p=0.003$, $z=0.94$, $p=0.349$; non-Asian, $I^2=88.9\%$, $p=0.000$, $z=2.38$, $p=0.017$).

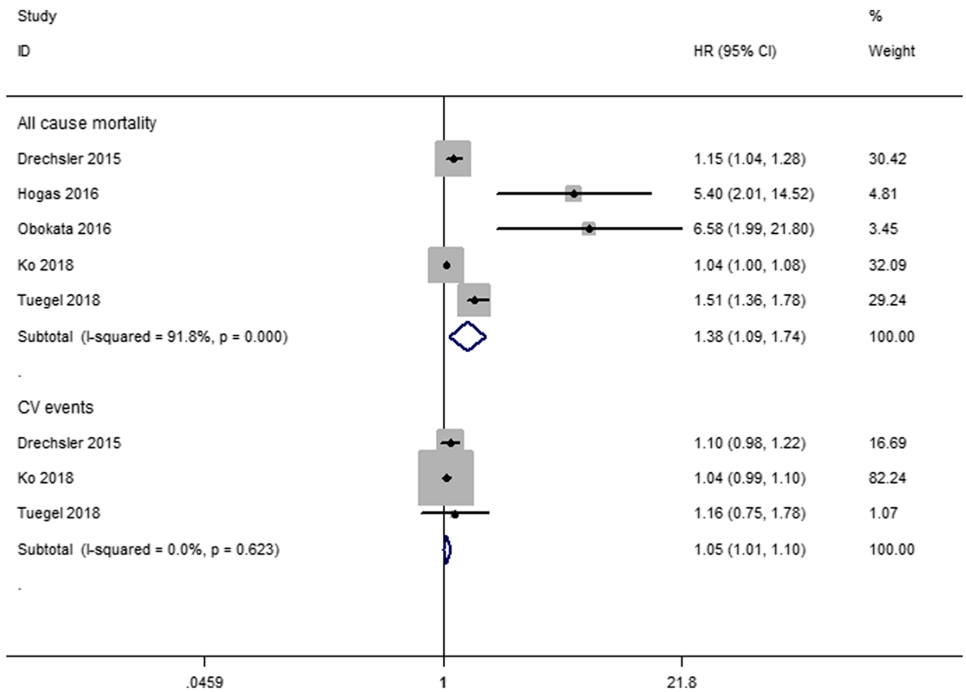

Fig. 2 Forest plot demonstrating the association between galectin-3 and all-cause mortality, CV events in CKD patients

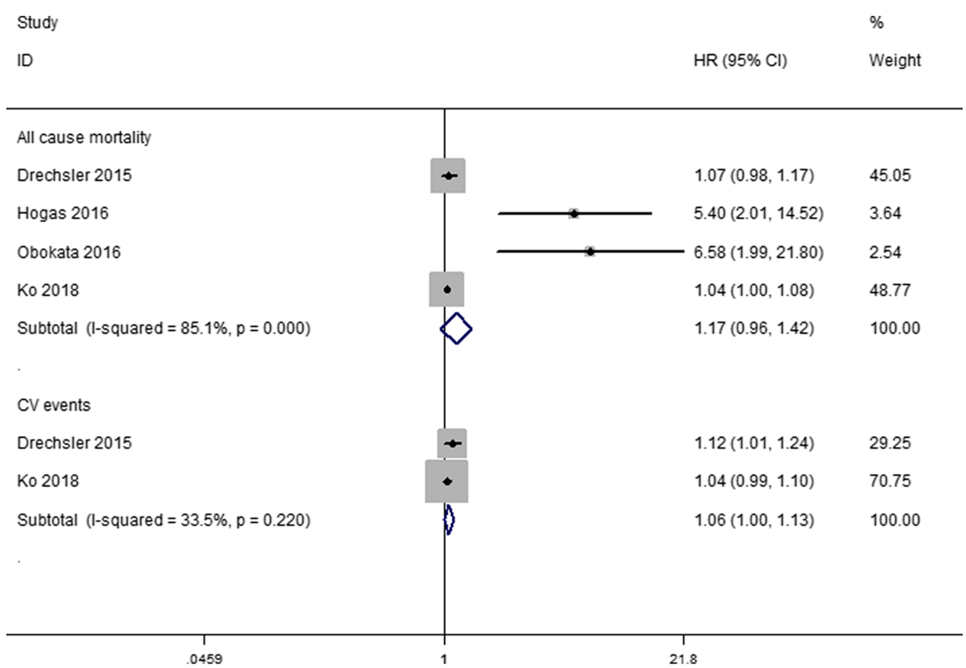

Fig. 3 Forest plot demonstrating the association between galectin-3 and all-cause mortality, CV events in HD patients

Publication bias

We investigated for the potential presence of publication bias through visual inspection of funnel plot asymmetry and by computation of Egger's test. The results of the funnel plot for all-cause mortality in CKD patients were symmetrical, indicating no publication bias (Egger's test: $p = 0.955$) (Fig. 4).

Discussion

Up to date, chronic kidney disease (CKD) of which the prevalence is estimated to be 8–16% worldwide is an increasing public health issue [1]. Over the past decade, there has been a notable decline in the proportion of cardiovascular deaths in CKD patients; however, cardiovascular

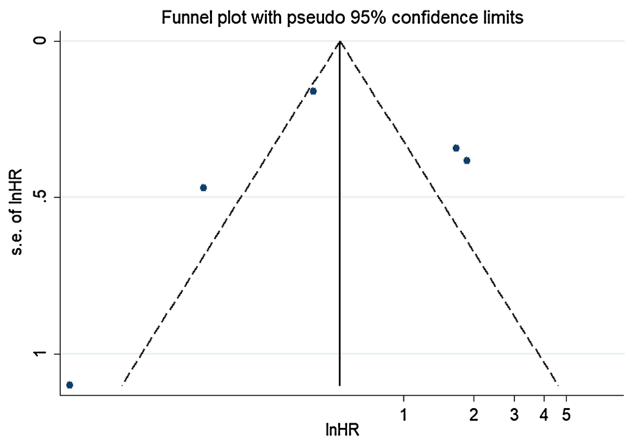

Fig. 4 Funnel plot for the association between galectin-3 and all-cause mortality in CKD patients

disease is still the leading cause of death [21]. Thus, accurate assessment of cardiovascular risk is essential for decision making in daily treatment of CKD patients. Inflammation, cardiac remodeling, and fibrosis may be potentially important pathways in the pathogenesis and prognosis of CKD. As is well known, numerous classical cardiac biomarkers such as cardiac troponins or natriuretic peptides have been conducive to predict overall and CV mortality in patients with CKD [5, 6]. However, the definite role of galectin-3 in CKD patients, especially ESRD patient with dialysis, was remained inconsistent. The identification of an optimal biomarker and/or combination of biomarkers still remains a goal to be achieved. Hence, this meta-analysis was conducted to clarify this debate.

Gal-3, a 29- to 35-kDa protein, is a member of soluble β-galactoside-binding lectins, which is released from human monocytes and macrophages, and also plays important regulatory roles in inflammation, immunity, cancer, atherosclerosis, and diabetes [22–26]. It presents as a ubiquitous localization in the cell, but it can also be secreted to the extracellular space in kidney and in heart [27, 28]. The dual localization of Gal-3 means that Gal-3 exerts multiple functions. It not only regulates cell growth, differentiation, spreading, motility, pro-inflammatory actions [29], but also mediates aldosterone-induced cardiac, vascular, and renal fibrosis [30]. High Gal-3 levels within the myocardium stimulate excessive collagen production [31] and fibroblast activity and accumulation of extracellular matrix. In rat models of myocardial infarction, Gal-3 levels also show a later peak in non-infarcted, remodeling areas [32]. Thus, Gal-3 is a marker of cardiac fibrosis and remodeling. As Gal-3 is also a profibrotic agent in the kidney, it could be considered as a marker of renal fibrosis or inflammation in renal patients [33].

In the past decades, increasing attention has been paid to the association between Gal-3 and adverse outcomes in various clinical conditions, especially for mortality [34]. In this comprehensive meta-analysis involving 5,226 CKD patients from 5 studies, Gal-3 was a remarkably consistent and strong predictor of all-cause mortality and CV events. However, this relationship is not obvious in HD patients. Tang et al. [10] reported that elevated plasma Gal-3 level is correlated with poor kidney function, including lower eGFR. Consistent with this one, Conall et al. [11] also found that higher plasma levels of Gal-3 were associated with rapid decline in eGFR (per 1-SD log-Gal-3; adjusted odds ratio [OR], 1.49; 95% CI, 1.28 to 1.73) based on the analysis report of renal outcome from 2450 samples with a mean follow-up of 10 years. So it needs lager scale studies to further validation the association between Gal-3 and mortality in HD patients.

The current study does have some limitations that should be considered. First, Gal-3 levels were determined using Enzyme-Linked Immunosorbent Assay (ELISA) in all studies, and therefore we can be confident that the values provided are comparable. Second, despite adjusting for multiple risk factors and prevalent diseases, it is possible that there may be residual confounding from conditions and medications not included in the analysis. Third, attempts were made to identify the origin of the high heterogeneity. There are several reasons as to why this may be the case, for example, differing characteristics of the study groups, such as Diabetes; different stages of CKD; different modes of renal replacement therapy; possible variable contributions from confounders such as heart failure and other co-morbid conditions; different follow-up periods; and different geographic area. Fourth, due to provided incompleted data, we did not further to analyze in background therapy, rapid GFR decline or different stages of CKD and different modes of renal replacement therapy. Finally, definition of increased Gal-3 level was not homogeneous among the included studies, and it should move forward a step to study for determining the boundary value of Gal-3 increased.

Conclusion

Gal-3 is a newly recognized and powerful predictor of all-cause mortality and CV events in CKD patients, however, probably not a sensitive biomarker for outcomes in HD patients. It needs further lager scale studies to assess the relationship in HD patients.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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