META-ANALYSIS

Prognostic Value of Elevated Plasma Galectin-3 for Renal Adverse Events in Dialysis Patients: A Systematic Review and Meta-Analysis

Huijuan Lu, MD; Jun Shen, BD; Jieqiong Sun, MD; Jia Sun, MD

ABSTRACT

Context • In prognostic research, Galectin-3 (Gal-3) has gained recognition in renal fibrosis and nephrosis for its characteristics of promoting inflammation and fibrosis. High levels of Gal-3 may function as a predictor of adverse outcomes for patients with end-stage renal disease (ESRD).

Objective • The review intended to systematically examine the significance of Gal-3 in the forecast of adverse outcomes for dialysis patients, using a method of evidence-based medicine.

Design • The research team performed a systematic narrative review and meta-analysis by searching the Excerpta Medica Database (EMBASE) and the PubMed, Cochrane, and Web of Science databases for pertinent studies published before June 1, 2022. The search contained both meshes and free terms, such as Galectin 3, Gal-3, renal dialysis, hemodialysis, peritoneal dialysis, HD, and PD.

Setting • The review took place at First People's Hospital of Linping District in Hangzhou, China.

Outcome Measures • The research team used the Newcastle-Ottawa Scale (NOS) for assessment of the quality of the included research. The team created two reports to assess the value of Gal-3 in prediction of risk: (1) one for studies using continuous variables and (2) one for studies using categorical variables, dividing patients into high- and low-level Gal-3 groups with a cut-off value of Gal-3, being Gal-3 < 10.5 ng/mL for the lower tertile, and Gal-3 ≥ 13.4 ng/mL for the higher tertile. The team performed the meta-analysis using Stata 15.0, analyzed publication bias using Egger's test and directly showed it in a funnel plot.

Results • The search found 1061 publications, with eight studies with 5194 participants being included in the current review. For the continuous variables, Gal-3 was associated with all-cause risk of death—Hazard ratio (HR) 1.06, 95%CI 1.01-1.12, and $P = .024$—and cardiovascular (CV) events—HR 1.13, 95%CI 1.07-1.203, and $P = .000$, but no significant correlation existed between Gal-3 and risk of CV mortality—HR 1.07, 95%CI 0.99-1.16, and $P = .091$. For the categorical variables, a high level of Gal-3 was correlated with a high risk of dying, from all causes—HR 2.05, 95%CI 1.50-2.80, and $P = .000$.

Conclusions • Clinicians can use Gal-3 as a standalone forecaster of all-cause mortality and CV events for hemodialysis patients because correlates with these outcomes. Further research is necessary to determine its predictive value for CV mortality. Investigators need to perform further research with a large sample size on the predictive value of Gal-3 for dialysis patients, particularly PD patients, from a variety of ethnic backgrounds to improve the precise treatment for high-risk patients. (*Altern Ther Health Med.* 2023;29(8):86-91)

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End-stage renal disease (ESRD), which has increased in prevalence globally from 2013 to 2022, has emerged as a significant global health issue. Incidence of treated ESRD, although relatively steady in many high-income countries, such as the USA, Northern Europe and other European countries, Japan, and Australia, has been soaring in East and Southeast Asia.[1] This has led to a global economic burden.[2]

Dialysis includes hemodialysis (HD) and peritoneal dialysis (PD). Both are common dialysis methods used routinely for kidney patients as a kidney replacement therapy (KRT) in clinical practice. Hemodialysis represents 69% of KRT and 89% of all dialyses.[3-6] In contrast, PD is usually the first dialysis modality for new kidney failures, and clinicians use it for approximately 11% of dialysis patients.[7]

Despite the wide use of dialysis in clinical practice, the mortality rate for ESRD patients is stubbornly high.[8] Even in the USA, Europe and Japan, with advanced medical treatments, the unadjusted five-year survival of ESRD patients on KRT in 2016 was only 41%, 48%, and 60%, respectively, not to mention people never undergoing KRT due to its high costs.[9]

The mortality rate of ESRD patients not receiving KRT is triple that of those receiving KRT.[10] Leading causes of death include cardiovascular diseases (CVDs), and dialysis patients have a 10-20-fold greater rate of cardiovascular (CV) mortality than the general population.[11] Dialysis-related adverse events (AEs) include CV events, CV mortality, and all-cause death, all of which are important factors influencing the survival prognosis for dialysis patients.

Prognostic Markers

Some research has discovered new predictors. For example, Racki et al and Voroneanu et al found that some traditional biomarkers, such as cardiac troponin, C-reactive protein, and brain natriuretic peptides, can predict the death rate and CV death for individuals in dialysis.[10,11]

Chang et al[12] identified two novel predictors of CVDs, the vascular cell adhesion molecule 1 (VCAM-1), a protein involved in the adhesion and transportation of white blood cells to the stroma during the inflammatory process, and Galectin-3 (Gal-3), a profibrotic mediator in the kidney involved in aldosterone-mediated fibrosis and a member of the lectin galactoside-binding family.[13] In 2014, Chen A et al. showed in their meta-analysis that elevated Gal-3 is associated with higher all-cause mortality and cardiovascular mortality in HF patients. Those researchers found that VCAM-1 can be a standalone CV-mortality risk factor for hemodialysis patients.

Galectin-3

Gal-3 may be a novel prognostic marker for many CVDs, including cardiovascular heart failure (CHF) and coronary artery (CA) disease.[14] Its plasma concentrations elevate before the development of chronic kidney diseases (CKDs).[15,16] The FDA and the American College of Cardiology Foundation/American Heart Association's (ACCF/AHA's) Recommendation for Heart Failure Supervision have indicated that Galectin-3 (Gal-3) may be a predictive factor for heart failure.[17]

Some studies have reported a relationship between the levels of Gal-3 and CVDs in dialysis patients.[18-20]Recent studies have found the association of Gal-3 with all-cause mortality, cardiac death, and cardiovascular composite events in hemodialysis patients. Alouffi et al found an inconsistent prognostic value for GAL-3 and concluded that Gal-3 couldn't be a predictor of CVDs for ESRD patients.[28] Gal3 is not associated with outcome in elderly patients with advanced chronic systolic HF of ischemic etiology when adjusting for NT-proBNP.

Conversely, Wang et al found that serum Gal-3 was a good biomarker for predicting severe abdominal aortic calcification (AAC) and progression for individuals receiving maintenance hemodialysis within 3 years.A prospective cohort who underwent hemodialysis during July 2014 at the Blood Purification Center of Ruijin Hospital were followed up for 3 years. Two AAC assessments were performed: one at baseline and one after the 3-year follow-up period. Serum Gal-3 was detected with quantitative ELISA kits.[21] Voroneanu et al reported that the combination of the levels of Gal-3 and N-terminal pro-brain natriuretic peptide (NTproBNP) could be an effective predictor of mortality rate and CV events in asymptomatic dialysis patients.[22]

According to Zhang et al's systematic review and meta-analysis, people with chronic renal disorders may be more susceptible to all-cause mortality and cardiovascular events when Gal-3 levels are high; however, those researchers found no significant correlation between that level and the prognosis of hemodialysis patients.[23] For hemodialysis patients, four studies in that meta-analysis showed no statistically significant correlation between Gal-3 and all-cause death rates, and the other two studies found no significant correlation between Gal-3 and CV events.

Kim et al found that studies have reported AEs from high levels of Gal-3 inconsistently.[24] Exact prediction of the manifestation of dialysis-related AEs for dialysis patients requires further exploration. Finding an optimum predictor is significant for clinical studies and the treatment of diseases.

Current Study

The present review intended to systematically examine the significance of Gal-3 in the forecast of adverse outcomes for dialysis patients, using a method of evidence-based medicine.

METHODS

Procedures

The review took place at First People's Hospital of Linping District in Hangzhou, China.

Registration. The research team carried out the systematic narrative review and meta-analysis in strict adherence to the Preferred Reporting Items for Review and Meta-analysis (PRISMA) guideline.[25] The PROSPERO 2022 database (https://www.crd.york.ac.uk/prospero/) provides prior registration for use of the method, with CRD = 42022339239 being the current review's PROSPERO registration number.

Search strategy. To conduct the review and meta-analysis, the research team searched the Excerpta Medica Database (EMBASE) and the PubMed, Cochrane, and Web of Science databases for pertinent studies published before June 1, 2022. The search contained both meshes and free terms, such as Galectin 3, Gal-3, renal dialysis, hemodialysis, peritoneal dialysis, HD, and PD.

Inclusion and exclusion criteria. The review included studies if: (1) they had no restrictions on gender or location; (2) the patients were >18 years old; (3) the patients had received clear diagnoses of ESRD and had undergone dialysis, with or without complications; (4) they had reported Gal-3 ranges at baseline and follow-up; (5) they had evaluated all-cause mortality and CV mortality during treatment and at follow-up as well as CV events at follow-up; (6) they were observational studies—case-control studies or cohort studies—in English.

The review included studies if: (1) the outcome measures involved only secondary adverse outcomes, without mortality

data; (2) they were duplicates, case reports, conference summaries, systematic reviews, or animal research, (3) they provided no access to the full text or were without available data; or (4) they provided no HR values or 95% CIs or no original data that the current research team could use to calculate the HR value and 95% CI.

Literature screening and data extraction. Two members of the research team, separately investigated the literature. After deleting duplicates, they read the titles and abstracts to preliminarily exclude ineligible articles. Then they reviewed the full texts of the remaining studies to determine whether to include them. The two researchers discussed and resolved any differences in their selections and requested the assistance of a third member of the research team to make the determination of inclusion if necessary.

Before data extraction, the same two researchers prepared a spreadsheet for the extracted information, which included the first author's name, study's type, sample size, age of participants, dialysis modality, date, country of publication, follow-up duration, and cut-off value for the division between high- and low-level Gal-3. The researchers performed the information extraction independently, and they cross-checked the extracted data after completion of data extraction. If any disagreement occurred, they consulted the third researcher to resolve the issue.

Outcome Measures. The research team used the Newcastle-Ottawa Scale (NOS) for assessment of the quality of the included research. The team created two reports to assess the value of Gal-3 in prediction of risk: (1) one for studies using continuous variables and (2) one for studies using categorical variables, dividing patients into high- and low-level Gal-3 groups with a cut-off value. The team performed the meta-analysis using Stata 15.0.

Quality assessment. The same two researchers independently evaluated the excellence of the qualified retrospective studies using the Newcastle-Ottawa Scale (NOS).[26] The NOS comprises eight items in three domains: selection, comparability, and outcome. It's quality rating varies from 0 to 9, with research possessing a score of 6 or above being rated as being high quality and that with a score of 5 or below being low quality.

Gal-3 groups. For comparison, the cohort was split into tertiles according to levels of Gal-3, being Gal-3 < 10.5 ng/mL for the lower tertile, and Gal-3 ≥ 13.4 ng/mL for the higher tertile.

Gal-3 and mortality. Seven studies,with results in the form of continuous variables, reported the correlation between Gal-3 and all-cause mortality.

Geographical region. The regression analyses examined the differences between the included studies by geographical region—Asian or non-Asian.Cox regression was used to estimate the associations between galectin-3 and death with the use of galectin-3 tertiles and logarithmic transformation.

Publication bias. Analyzed publication bias using Egger's test and directly showed it in a funnel plot.

Statistical Analysis

The research team analyzed the data for the meta-analysis using Stata 15.0 The team: (1) identified the combined effect size using the hazard ratio (HR) with 95% CI; (2) expressed measurement data as means ± standard deviations (SDs); (3) quantified the heterogeneity among the studies as I^2 using Cochran's Q test and Higgins; (4) designated high heterogeneity as $I^2 \geq 50\%$, adopting a random-effects model and exploring the reason for the high heterogeneity using subgroup and sensitivity analyses; (5) designated low heterogeneity as $I^2 < 50\%$ and used the fixed-effects model for analysis; (6) analyzed publication bias using Egger's test and directly showed it in a funnel plot. For the meta-analysis and Egger's test, $P < .05$ indicated significant differences.

Some of the included studies gave a cut-off value for Gal-3 to divide patients into high- and low-level groups, while others reported Gal-3 using continuous variables. Therefore, the team presented the results in two ways.

RESULTS

Literature Screening

Figure 1 depicts the screening procedure. The search retrieved 1061 articles. After removal of 141 duplicates and of 111 studies.809 studies remained. The research team read the titles and abstractsof those articles, and excluded 780 studies. The team tried to obtain full articles for 29 studies, but couldn't retrieve three. The team then reviewed 26 articles for eligibility and excluded 15 because they provided no outcome indicators, 2 because the team was unable to obtain the data, and one because the population wasn't clearly defined. The meta-analysis included eight eligible studies, with 5194 participants.[19,20,27,30-34]

Figure 1. Screening Process Flowchart

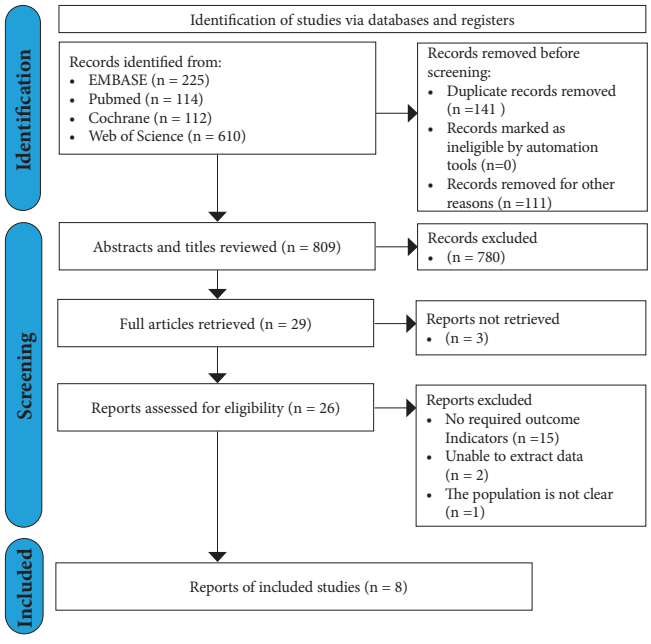
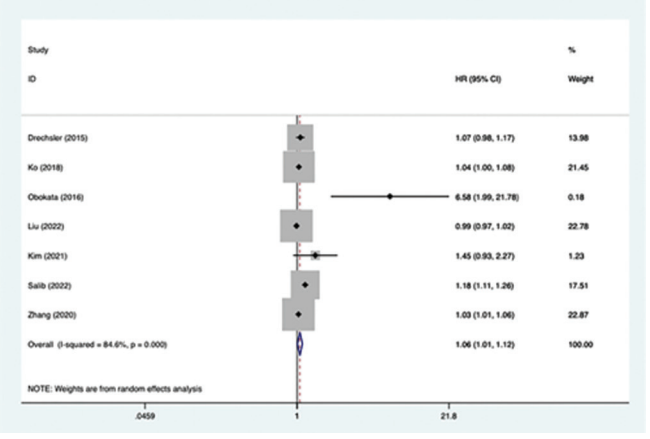


Table 1. Characteristics of the Included Studies

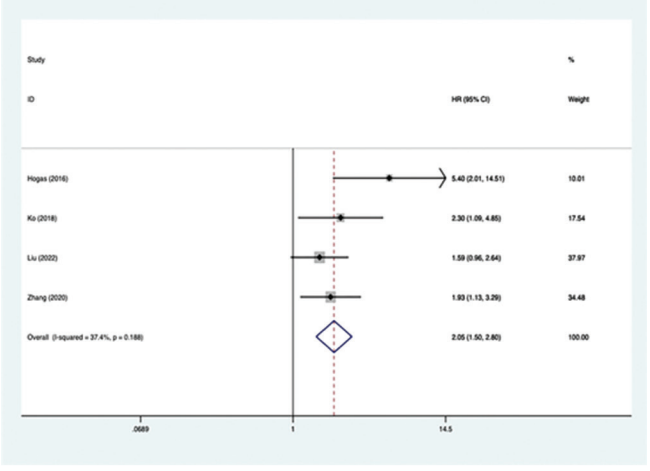
Author, Year	Research Type	Population	Sample Size n (%)	Age, y Mean ± SD	Diabetes n (%)	Hypertension n (%)	Dialysis Time, mos Mean ± SD	Follow-up Time, mos Mean ± SD	Gal-3 High- and Low-dose Partition Values, ng/ml	Single / Multiple Factor(s)	Quality Evaluation
Drechsler, 2015, Germany[30]	Prospective observational study	HD	1168 (100.0) Male: 635 (54.4) Female: 533 (45.6)	66 ± 8	1168 (100)	1036 (88.70)	8.3 ± 6.8	48 ± 3.6	NA	Multiple	9
Hogas, 2016, Romania[20]	Prospective observational study	HD	88 (100.0) Male: 35 (39.8) Female: 53 (60.2)	57.3 ± 14.4	18 (21.50)	71 (80.60)	58.7 ± 38.7	22.2 ± 4.7	23.73	Multiple	8
Ko, 2018, China[31]	Prospective cohort study	HD	86 (100.0) Male: 38 (44.2) Female: 48 (55.8)	59.9 ± 14	35 (40.7)	39 (45.3)	61.2 ± 53.2	53. 3± 6.2	29.5	Multiple	8
Obokata, 2016, Japan[19]	Prospective observational study	HD	423 (100.0) Male: 291 (68.8) Female: 132 (31.2)	66 ± 12	197 (46.6)	358 (84.6)	69.6 ± 87.6	25.2 ± 4.8	8.1, 15.2	Multiple	9
Liu, 2022, China[34]	Prospective cohort study	HD	506 (100.0) Male: 270 (53.4) Female: 236 (46.6)	58 ± 14	NA	NA	51 ± 38.5	60	8.65	Single	8
Kim, 2021, Korea[27]	Prospective observational study	HD	296 (100.0) Male: 157 (53.0) Female: 139 (47.0)	57 ± 13	231 (45.6)	256 (86.5)	48.5 ± 42.8	37.8 ± 13.9	35.27	Multiple	9
Salib, 2022, France[33]	Prospective observational study	HD or hemofiltration	2343 (100.0) Male: 1455 (62.1) Female: 888 (37.9)	64 ± 11	605 (25.8)	NA	34.8 ± 38.4	45.6	11.2, 56.3, 78, 228	Multiple	9
Zhang, 2020, China[32]	Prospective observational study	HD	284 (100.0) Male: 165 (58.1) Female: 119 (41.9)	61 ± 12.4	36 (12.68)	238 (83.8)	90	31	30.5	Single	8

Figure 2. Association of Gal-3 with All-cause Mortality Risk for Dialysis Patients



Note: P = .024, indicating that Gal-3 was associated with a significant risk of all-cause death

Figure 3. Correlation of a High level of Gal-3 With a High Risk of All-cause Mortality



Note: P = .024, indicating that high levels of Gal-3 were significantly related to a high risk of death from all causes

Study's Characteristics and Caliber

Table 1 summarizes the characteristics and designs of the eight eligible studies. Unfortunately, no studies included research on the correlation between plasma Gal-3 and PD because clinicians commonly use it for individuals with new-onset renal failure.

The mean age of participants ranged from 57.3 ± 14.4 to 66 ± 12 years, and the mean follow-up time ranged between 22.2 ± 4.7 and 60 months. Three studies were from China,[31,32,34] one study was from Germany,[23] one was from Romania,[18] one was from the Republic of Korea,[27] one was from Japan,[19] and one was from France.[33] The NOS showed that the overall quality was high, either 8 or 9.

Gal-3 and Risk

Gal-3 and all-cause mortality. Seven studies,[19,27,30-34] with results in the form of continuous variables, reported the correlation between Gal-3 and all-cause mortality (Figure 2). The heterogeneity was high at I^2 = 84.6% and P = .000. The random effects model showed that Gal-3 was associated with a significant risk of all-cause death, with HR 1.06, 95%CI 1.01-1.12, and P = .024.

The heterogeneity was low at I^2 = 37.4% and P = .188 for four studies, with results in the form of categorical variables (Figure 3).[20,31,32,34] A fixed-effects model provided a Gal-3 cut-off value to classify patients into high- and low-level groups. High levels of Gal-3 were significantly related to a high risk of death from all causes, with HR 2.05, 95%CI 1.50-2.80, and P = .000.

Gal-3 and CV mortality. The heterogeneity was high at I2= 3.9% and p=0.002 for three studies with results in the form of continuous variables (Figure 4).[31,33,34] The random-effects model showed no significant correlation between Gal-3 and CV mortality, with HR 1.07, 95%CI 0.99-1.16, and P = .091.

Gal-3 and CV events. The heterogeneity was low for three studies, with results in the form of continuous variables, with I^2 = 0 and P = .433 (Figure 5).[27,30,32] The fixed-effect model

Figure 4. Correlation Between Gal-3 and CV Mortality in Dialysis Patients. No significant correlation existed.

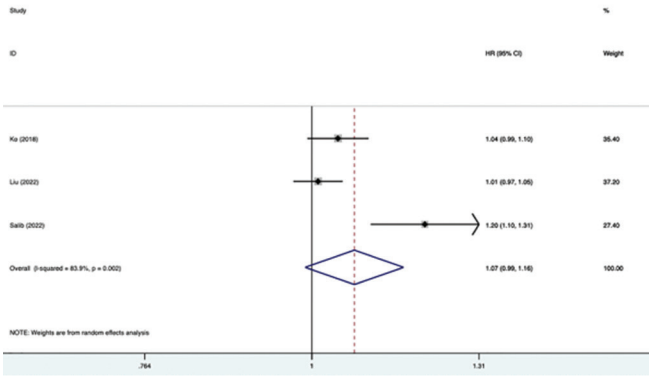
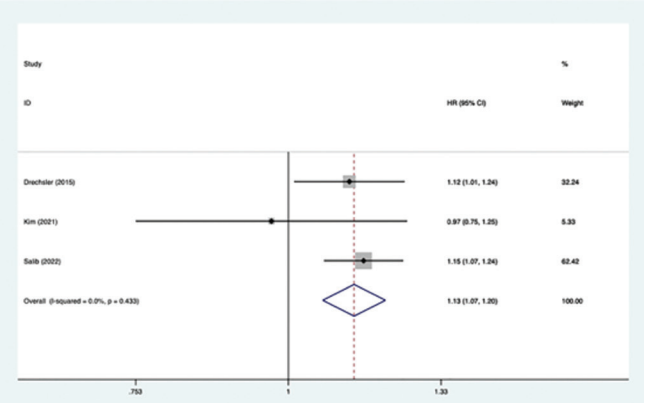


Figure 5. Association of Gal-3 With a High Risk of a CV Event



Note: $P = .024$, indicating that Gal-3 was significantly associated with a high risk of CV events

showed that Gal-3 was significantly associated with a high risk of CV events, with HR 1.13, 95%CI1.07-1.203, and $P = .000$.

Subgroup Analysis

For the correlation between Gal-3 and all-cause death as well as CVmortality, continuous variables were tested for normal distribution by means of the Kolmogorov-Smironov test and are described as mean ± SD for normally distributed variables and median (interquartile range [IQR]) for variables with skewed distribution. statistical heterogeneity existed among the studies that provided results in the form of continuous variables. The regression analyses examined the differences between the included studies by geographical region—Asian or non-Asian. The analyses indicated that geographical region had no significant impact on the heterogeneity among studies—multifactor: $I^2 = 82.0\%$ and $P = .000$; single factor: $I^2 = 79.8\%$ and $P = .026$; Asian: $I^2 = 78.3\%$ and $P = .001$; and non-Asian: $I^2 = 67.6\%$ and $P = .079$.

Publication Bias

A funnel plot directly demonstrated publication bias for the correlation between GAL-3 and all-cause death, as assessed using Egger's test. Publication bias occurred ($P = .043$) in the analysis of continuous variables, and therefore, the research team further analyzed the funnel plot using the cut-and-fill method. After the research team added three studies to the model, the funnel plot became symmetrical and the combined effect size was $P = .416$. However, no publication bias occurred ($P = .052$) for the high- and low-level analysis of Gal-3 groups, as classified by a cutoff value.

DISCUSSION

The current meta-analysis revealed that a high level of Gal-3 was linked with all-cause mortality and CV events but not CV mortality for individuals receiving hemodialysis. Regarding the analysis for the categorical variables, high-level Gal-3 was significantly associated with a high risk of all-cause death (HR 2.05, 95%CI 1.50-2.80, $P = .000$).

While the current meta-analysis increases data about prognostic factors for dialysis patients, a prediction model with a single factor is still not as helpful as a multivariate one. Hence, in future studies the current research team expects to combine Gal-3 with other predictors, such as VCAM-1, to construct a good prognostic-risk prediction model.

Although the present meta-analysis includes more articles than previous ones, has reported more reliable results, requires authors to follow a standardized process, stating how the entire study collects literature, evaluates according to what standards, selects and synthesizes indicators, and ultimately interprets them, in order to draw what conclusions and ensure that every step of the meta-analysis process is objectively reproducible. and is the first that analyzes data in the form of both continuous and categorical variables, it had some limitations. First, it included only eight studies, a small sample size. Second, the included studies were all observational works, in which numerous confounding factors can affect the stability of the results. Also, the current study didn't extensively address small sample sizes, variations in Galectin-3 measurement techniques, and potential confounders in the included studies. Third, the present study aimed to detect the correlation between Gal-3 and adverse outcomes in dialysis patients but failed to involve research about PD patients because that kind of research is novel and limited in quantity. Subsequently, more original studies on PD patients are needed.

CONCLUSIONS

Clinicians can use Gal-3 as a standalone predictor of all-cause mortality and CV events for hemodialysis patients because it correlates with these outcomes. Further research is necessary to determine its predictive value for CV mortality. Investigators need to perform further research with a large sample size on the predictive value of Gal-3 for dialysis patients, particularly PD patients, from a variety of ethnic backgrounds to improve the precise treatment for high-risk patients.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are available in Table 1, Figures 1-5, and Supplemental Documents 1 and 2.

AUTHORS' DISCLOSURE STATEMENT

The Authors declare that there is no conflict of interest.

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