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Original Article

The role of osteopontin, KIM-1, and fetuin-A as prognostic markers for cardiovascular disease in patients with chronic kidney disease: A systematic review and meta-analysis

[El papel de la osteopontina, KIM-1 y fetuina-A como marcadores pronósticos de enfermedades cardiovasculares en pacientes con enfermedad renal crónica: Una revisión sistemática y un meta-análisis]

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Abstract

Context: Chronic kidney disease (CKD) is often related to cardiovascular disease (CVD) as a consequence of the progressive nature of the disease. The role of osteopontin (OPN), kidney injury molecule-1 (KIM-1), and fetuin-A in predicting the risk of developing CVD in CKD patients has not been definitively established.

Aims: To evaluate their prospective use in predicting cardiovascular events in patients with chronic kidney disease (CKD).

Methods: A systematic literature search was conducted following the PRISMA 2020 guidelines on databases recorded from February to December 2023. The concentration of each marker was then presented in pooled standardized mean difference (SMD) and hazard ratio (HR). The subgroup analysis was performed by considering factors such as age and geographical location.

Results: Thirty-one studies with a total population of 14,445 were included. Increased OPN levels were significantly associated with CVD events in CKD patients (pooled SMD = 3.47, 95% CI 1.65-5.31, p = 0.0002), while changes in KIM-1 and fetuin-A levels were not significantly affected. Increased levels of OPN were also found to significantly increase CVD risk (pooled HR = 1.38 (95% CI 1.13-1.68, p = 0.001), but not with KIM-1 and fetuin-A (pooled HR KIM-1 = 1.09, p = 0.44; pooled HR fetuin-A = 1.22, p = 0.08). With the exception of the fetuin-A marker, no discernible changes were found during a sensitivity analysis.

Conclusions: Increased OPN level demonstrated a significant and considerable effect on the risk of developing CVD in CKD patients, implying its potential as a prognostic marker. After sensitivity analysis, decreased fetuin-A levels are also correlated with CVD occurrence in CKD patients.

Keywords: cardiovascular disease; chronic kidney disease; fetuin-A; KIM-1; osteopontin.

Resumen

Contexto: *Helminthostachys zeylanica* (L.) Hook., es una planta que se ha utilizado tradicionalmente en Asia como medicina. Su follaje se utiliza tanto con fines medicinales como consumido como verdura, mientras que los rizomas se han empleado históricamente para tratar una variedad de afecciones, incluidas las enfermedades infecciosas.

Objetivos: Dilucidar el perfil fitoquímico de *H. zeylanica* y evaluar su potencial antibacteriano mediante análisis metabolómico no dirigido.

Métodos: Se extrajeron varias partes de la planta mediante la técnica de maceración y, a continuación, se evaluó la actividad antibacteriana mediante el método de difusión en disco de Kirby-Bauer. Luego, se determinaron la concentración mínima inhibitoria (CMI) y la concentración mínima bactericida (CMB). El análisis fitoquímico se realizó mediante LC-HRMS. Se utilizaron análisis multivariados, incluidos PCA y PLS-DA, para explorar las variaciones en los perfiles de metabolitos y su asociación con la actividad antibacteriana.

Resultados: Los resultados mostraron que los extractos de *H. zeylanica* tenían una actividad antibacteriana moderada, particularmente contra ciertas bacterias Gram-positivas, aunque su eficacia fue generalmente menor en comparación con el antibiótico estándar cloranfenicol. El perfil metabolómico reveló firmas metabólicas distintas para cada parte de la planta, enfatizando así los ambientes fitoquímicos únicos. Además, nuestros hallazgos sugieren que *H. zeylanica* contiene compuestos bioactivos con propiedades antibacterianas selectivas. Sin embargo, su efectividad general, particularmente contra bacterias Gram-negativas, es limitada en comparación con los antibióticos convencionales.

Conclusiones: Este estudio no solo contribuye a la comprensión farmacológica de *H. zeylanica*, sino que también enfatiza la importancia del análisis metabolómico integral para determinar el potencial terapéutico de las plantas medicinales.

Palabras Clave: actividad antibacteriana; *Helminthostachys zeylanica*; LC-HRMS; metabolómica; metabolitos secundarios.

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Abbreviations: CKD: Chronic kidney disease; CVD: Cardiovascular disease; HR: Hazard ratio; KIM-1: Kidney injury molecule-1; OPN: Osteopontin; SMD: Standardized mean difference.

INTRODUCTION

The high incidence of global chronic kidney disease (CKD) cases has now become a concern for global health. Chronic kidney disease is defined by the Kidney Disease Improving Global Outcomes (KDIGO) as a functional and structural kidney disorder characterized by a glomerular filtration rate of less than 60 mL/minute per 1.73 m^2 for a period exceeding three months (Stevens et al., 2024). In the United States, the prevalence of CKD was found to be 14.8% of the general population from 2013 to 2016 (United States Renal Data System, 2018). Despite major clinical advances in CKD, the mortality rate among patients with CKD remains quite high and contributes significantly to world mortality. From 1990 until 2017, the mortality rate of CKD has significantly increased, reaching a 41.5% rise (Kovesdy, 2022). As a consequence, CKD has been the 12th leading cause of death globally (World Health Organization, 2021).

One of the primary contributors behind CKD patient's mortality is cardiovascular disease (CVD) (Jankowski et al., 2021). Cardiovascular diseases have been responsible for 40-50% of mortality in patients with advanced CKD (Thompson et al., 2015). The mechanisms involve several mediators excreted from impaired kidneys, which could alter vascular calcification, inflammation, and damage cardiovascular apparatus (Jankowski et al., 2021). This could potentially worsen the clinical outcomes of CKD patients and hence require extra attention. Therefore, clinicians are currently attempting to develop a new predictive method to detect CVD risk in patients with CKD. The use of biomarkers as diagnostic and prognostic modalities has now become a promising method due to its non-invasive procedures (Medić et al., 2015).

Osteopontin (OPN), kidney injury molecule-1 (KIM-1), and fetuin-A are markers of vascular calcification and renal injury that are currently extensively studied to understand their roles in the diagnosis and prognosis of a disease. Both vascular calcification and renal injury are believed to depict the progression of CVD in CKD (Laffin and Bakris, 2021).

Osteopontin, a phosphorylated glycoprotein, regulates mineralization and has been linked to the many pathologies of renal and vascular diseases (Paloian and Giachelli, 2014). Kidney injury molecule-1 is a type I transmembrane protein that is now widely recognized for its role in detecting kidney injury (De Silva et al., 2016). The significant association between KIM-1 levels and the risk of CVD, such as chronic heart failure, has also been investigated by several studies (Carlsson et al., 2014; Damman et al., 2010). Fetuin-A, a serum glycoprotein in the liver, has also been reported to correlate with various pathological mechanisms of CVDs, such as atherosclerosis (Chao et al., 2017). While previous studies have investigated the roles of OPN, KIM-1, and fetuin-A, their prognostic significance for cardiovascular events in CKD patients remains inconsistent. These inconsistencies may stem from variations in study designs, populations, and analytical methods. Therefore, this study aims to address the inconsistent findings in the role of OPN, KIM-1, and fetuin-A as prognostic markers for cardiovascular events in CKD patients by performing a comprehensive systematic review and meta-analysis to derive more robust and reliable conclusions. The findings could guide clinicians in risk stratification and management of CKD patients at high risk of cardiovascular events.

MATERIAL AND METHODS

Review methodology

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Page et al., 2021) through a literature search across various databases from February to December 2023. The review question included in this study is: "In patients with chronic kidney disease, how do OPN, KIM-1, and fetuin-A levels compare to standard prognostic tools in predicting the risk of cardiovascular events?". Registration on the International Prospective Register of Systematic Reviews (PROSPERO) was carried out to prevent the risk of study duplication (CRD42022357894). Three authors (YW, BSW, and V) were involved in the literature search, study selection, quality assessment, and data extraction process. Any discrepancies in the selection of studies will be discussed by involving all authors to reach a consensus.

Information sources and search strategy

A literature search was conducted through electronic databases such as PubMed, Scopus, Web of Science, ScienceDirect, EBSCO/CINAHL, ProQuest, and Preprints (Medrxiv and Bioxriv) using Medical Subject Heading Terms (MeSH) for keywords: "Osteopontin" or "OPN" or "Sialoprotein 1" or "Secreted Phosphoprotein 1" or "Uropontin", "KIM-1" or "Kidney injury molecule-1" or "TIMD1" or "hepatitis A virus receptor" or "HAV cellular receptor" or "TIM-1",

"Fetuin-A" or "AHSG" or "α2-Heremans Schmid glycoprotein" and "cardiovascular disease" OR "Cardiovascular" and "chronic kidney diseases" or "chronic renal insufficiency" or "chronic renal diseases" or "chronic renal failure" or "chronic kidney failure". The search was conducted using Boolean operators "AND" and "OR". Complete search strategy is demonstrated in supplementary Table S1.

Eligibility criteria

The included studies were initially screened based on the title and abstract of the articles. Screening was conducted by reviewing the entire content of the article if the full-text article was obtained. The inclusion criteria for this study were: 1) population: adult patients (≥ 18 years) with CKD; 2) index and comparison: studies presenting the measurement results of serum/plasma/urine OPN, KIM-1, and/or fetuin-A levels between patients with and without CVD; 3) cohort, case-control, or cross-sectional study designs; 4) outcome: studies containing mean and SD data, data supporting mean and SD calculations, or studies containing hazard ratio (HR) and 95% confidence intervals values; and 5) full-text availability of the article. Articles were excluded if they met the following criteria: 1) case series, case report, review, clinical trial study designs; 2) studies that did not present the required data; 3) duplicated studies.

Data extraction

The extracted data included the first author's name, publication year, sample size, age of the study population, study location, concentrations of OPN, KIM-1, fetuin-A markers, specimen, the number of CKD patients with and without CVD, study design, mean values, SD, or HR. This information was then organized into a data extraction table.

Study of risk of bias assessment

The quality assessment of the studies was conducted using the Newcastle-Ottawa Scale (NOS), a method used to analyse the quality of non-randomized observational studies (such as cohort, case-control, and cross-sectional studies) included in systematic reviews and/or meta-analyses (Modesti et al., 2016; Wells et al., 2021).

Effect measures and statistical analysis

The meta-analysis was conducted by collecting data on pooled standardized mean difference (SMD) and pooled HR from each included study. The effect of the marker level changes toward CVD occurrence is presented as a standard mean difference. Standard mean difference values between 0.2-0.5 are considered to have a small effect, 0.5-0.8 have a moderate effect, and more than 0.8 have a strong/large effect (Andrade, 2020). Meta-analysis using hazard ratio calculations was conducted to illustrate how often an event occurs compared to the reference group over a specific period (Higgins et al., 2019). Analysis with hazard ratio is widely used in various prognostic studies to measure the occurrence of a disease event.

To calculate the standardized mean difference, the mean and standard deviation values were obtained for each marker. For studies that did not provide these values, alternative data, including median (m), the upper limit (a), and lower limit (b) of marker concentrations, was required to determine mean and standard deviation values using the formula outlined by Hozo et al. (2005). The extracted hazard ratio values were adjusted hazard ratios (aHR), meaning HR values were adjusted by eliminating various covariates and analyzed based on significance values of $p<0.05$ and a 95% confidence interval (CI).

Heterogeneity tests among studies were conducted using the Q-test and I^2 test. A Cochrane Q-test with a significant p-value ($p<0.10$) indicates heterogeneity among studies. The choice of the analysis model was based on the value of this heterogeneity. A random-effects model was performed when the I^2 test yielded a value of >50% and the Q-test was significant ($p<0.1$) (Xia et al., 2014). Otherwise, a fixed-effect model was used. Statistical analyses were performed using Review Manager 5.4 (The Cochrane Collaboration, Oxford, UK) and STATA version 16.0 software (Stata Corporation, College Station, TX, USA).

Subgroup analysis was conducted to explore possible causes of heterogeneity and only performed on groups with a sufficient number of studies. Subgroup analysis was conducted on two variables: age dan geographical location. Assessment of publication bias was performed quantitatively with Egger's test if ≥10 studies were involved. Publication bias is indicated if the results of Egger's test show $p<0.05$ (indicating significant publication bias). Sensitivity analysis was carried out by excluding studies with potential bias (NOS <7), followed by a reanalysis to assess the consistency of results.

RESULTS

Search results and study selection

The study search was conducted on five major databases, namely PubMed, Scopus, Web of Science, CINAHL, and ProQuest, and it screened 3,097 studies. Additionally, studies were also searched in other type of sources, including preprints, such as Medrxiv and Biorxiv. Screening of studies was carried out until several studies were excluded for various reasons,

including inappropriate populations, irrelevant methods, different markers and outcomes, lack of outcome values, and non-English articles. This process resulted in the inclusion of 31 studies (Fig. 1).

Study characteristics

The characteristics of the included studies with overall CVD clinical outcomes are summarized in Table 1. All included studies comprised of 14,445 patients in total. Based on the type of marker used, there were six studies using OPN, six studies using KIM-1, and 21 studies using fetuin-A. In terms of measurement types, 26 studies had computable standardized mean difference values, and 10 studies provided hazard ratio measurements. There were 21 studies with a mean age below 60 years old. One study by Meneghini et al. (2013) did not provide age data for the population. Specific chronic kidney disease patient groups related to a particular comorbidity were reported in only one study (Azoz et al., 2022), which involved patients with diabetes mellitus. The population in this study was also diverse, with a distribution across Asia (11 studies), Europe (10 studies), America (five studies), Australia (one study), Africa (three studies), and multicenter (one study).

Risk of bias in studies

The assessment of the quality of all included studies is summarized in supplementary material (Tables S2-S4). The results indicate that 13 cohort studies had good quality (scores 7-9), and four cohort studies had a high risk of bias (scores 4-6) due to selection bias. In case-control studies, one study had a high risk of bias, and two other studies were of good quality. In cross-sectional studies, 11 studies were categorized as "very good studies".

Statistical analysis

A meta-analysis using the SMD measurement effect was used to depict the effect of marker level changes on the occurrence of CVD in CKD patients. For the OPN marker, the meta-analysis was conducted on five studies with a total of 2,648 samples (Fig. 2A). The results indicate that the increase in OPN levels had a significant effect on CVD occurrence in CKD patients (SMD = 3.47, 95% CI = 1.65-5.31, $p<0.0002$). However, it indicated high heterogeneity ($I^2 = 99\%$). The analysis of the KIM-1 marker involved only two studies. An increase in KIM-1 levels did not have a significant effect on CVD in patients with CKD (SMD = 1.02, 95% CI = -0.50-2.55, p = 0.19). The random effect model is used in the analysis due to its high heterogeneity ($I^2 = 97\%$) (Fig. 2B).

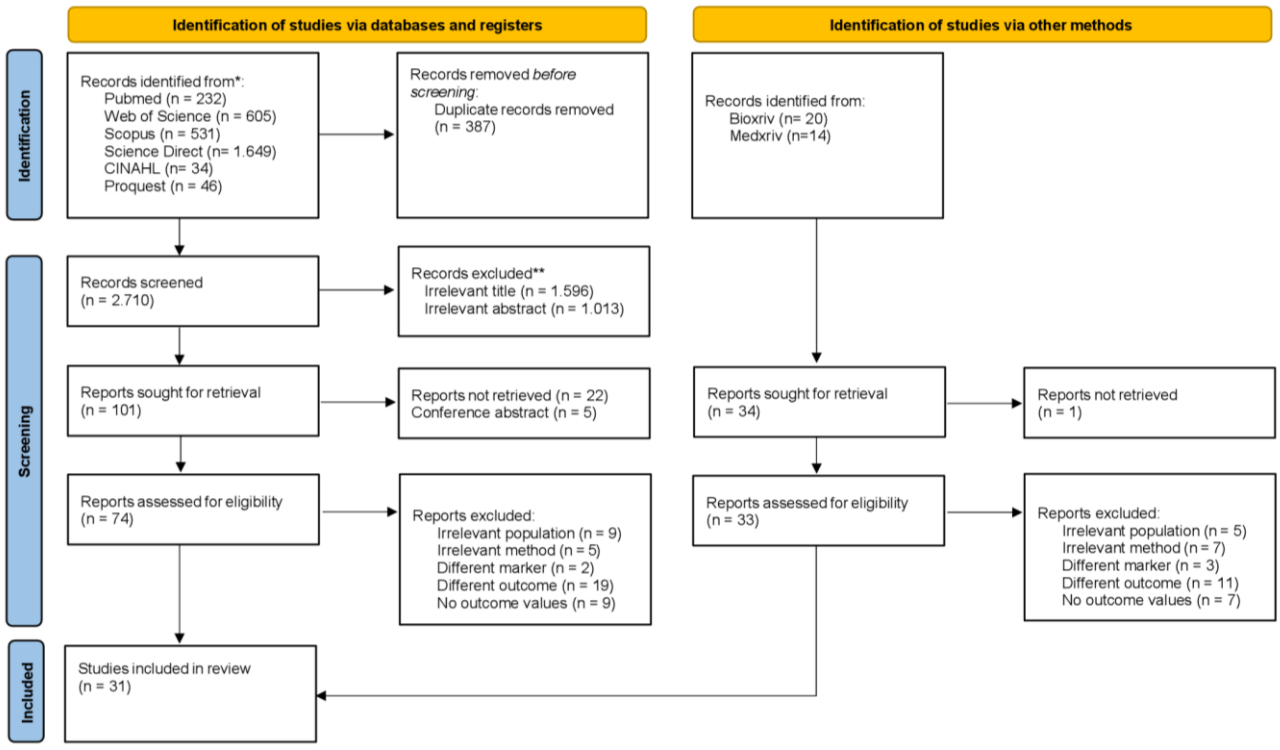

Figure 1. PRISMA 2020 flow diagram template for systematic reviews.

The grey boxes should only be completed if applicable; otherwise, they should be removed from the flow diagram. Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information. Page et al. (2021) at https://journals.plos.org/plosmedicine/article/figure?id=10.1371/journal.pmed.1003583.g001

Table 1. Characteristics of Included studies.

Author (Year)	Study design	Study location	Age*	Total sample (female)	Sample size		Comorbidities	Marker	Specimen type	Outcome value of CVD	Outcome value of non-CVD	Measurements unit	Hazard ratio (HR) 95% CI
					CVD	Non-CVD				Mean ± SD*	Mean ± SD*		
Kocyigit et al. (2015)	Cross-sectional	Turkey	33.1 ± 11.7	89 (34)	51	14	N/A	Fetuin-A	Serum	272 ± 56	236 ± 36	µg/mL	-
	Cross-sectional	Turkey	33.1 ± 11.7	89 (34)	24	14	N/A	Fetuin-A	Serum	238 ± 44	236 ± 36	µg/mL	-
El-Shehaby et al. (2010)	Cross-sectional	Egypt	43.0 ± 11.1	70 (34)	50	20	N/A	Fetuin-A	Serum	0.308 ± 0.132	0.53 ± 0.13	g/L	-
Gan et al. (2021)	Cross-sectional	China	52.27 ± 14.52	75	32	43	N/A	Fetuin-A	Serum	0. 44 ± 0.11	0.52 ± 0.11	g/L	-
Vassallo et al. (2019)	Prospective cohort	United States	71.45 ± 2.95	112 (38)	76	36	N/A	KIM-1	Plasma	-	-	-	1.02 (0.83-1.26)
Maharem et al. (2013)	Case-control	Egypt	47.67 ± 11.65	57 (34)	19	38	N/A	Fetuin-A	Serum	0.27 ± 0.15	0.22 ± 0.12	g/L	-
Ramirez-Sandoval et al. (2016)	Cross-sectional	Mexico	39.74 ± 6.04	76 (43)	19	57	N/A	OPN	Serum	25.53 ± 8.34	15.59 ± 6.41	ng/mL	-
McMillan et al. (2018)	Cross-sectional	United States	63.76 ± 9.55	90 (45)	33	57	N/A	KIM-1	Plasma	0.92 ± 0.28	0.58 ± 0.11	ng/mL	-
Meneghini et al. (2013)	Prospective cohort	Italia	-	107 (52)	66	41	N/A	Fetuin-A	Serum	0.31 ± 0.08	0.32 ± 0.1	g/L	-
Coen et al. (2006)	Cross-sectional	Italia	59.41 ± 12.93	132 (45)	119	13	N/A	Fetuin-A	Serum	0.31 ± 0.1	0.38 ± 0.07	g/L	-
Ma et al. (2022)	Case-control	China	57.1 ± 12.72	162 (77)	69	93	N/A	Fetuin-A	Serum	197.53 ± 26.11	210.43 ± 29.54	µg/mL	-
Jung et al. (2010)	Prospective cohort	South Korea	50.4 ± 13.5	67 (30)	21	46	N/A	Fetuin-A	Serum	0.31 ± 0.1	0.35 ± 0.06	g/L	-

Table 1. Characteristics of Included studies (continued...)

Author (Year)	Study design	Study location	Age*	Total sample (female)	Sample size		Comorbidities	Marker	Specimen type	Outcome value of CVD	Outcome value of non-CVD	Measurements unit	Hazard ratio (HR) 95% CI
					CVD	Non-CVD				Mean ± SD*	Mean ± SD*		
Chen et al. (2014)	Prospective cohort	Taiwan	59 ± 12	388 (201)	131	257	N/A	Fetuin-A	Serum	-	-	-	0.9 (0.81-0.99)
Alderson et al. (2016a)	Prospective cohort	Great Brittain	63.8 ± 14.1	463 (177)	108	355	N/A	Fetuin-A	Serum	-	-	-	1.001 (0.99-1.01)
Wang et al. (2008)	Prospective cohort	China	56 ± 12	231 (133)	57	174	N/A	Fetuin-A	Serum	0.29 ± 0.06	0.32 ± 0.07	g/L	1.61 (1.03-2.51)
Wang et al. (2009)	Prospective cohort	China	55.5 ± 16.3	231 (113)	89	142	N/A	Fetuin-A	Serum	-	-	-	2.83 (1.84-4.35)
Stenvinkel et al. (2005)	Prospective cohort	Sweden	52 ± 1	258 (97)	90	168	N/A	Fetuin-A	Serum	0.22 ± 0.14	0.25 ± 0.17	g/L	-
Forné et al. (2019)	Prospective cohort	Spain	59.19 ± 2.89	1366 (584)	73	1293	N/A	OPN	Serum	24.96 ± 6.78	13.23 ± 2.64	ng/mL	1.33 (1.07-1.66)
Azoz et al. (2022)	Case-control	Egypt	57.54 ± 7.24	70 (20)	31	39	Diabetes Melitus	OPN	Serum	177.16 ± 6.06	74.85 ± 8.28	ng/mL	-
Jasani et al. (2018)	Cross-sectional	India	48.5 ± 12.8	100 (53)	60	40	N/A	Fetuin-A	Serum	0.26 ± 0.2	0.56 ± 0.2	g/L	-
Chen et al. (2016)	Prospective cohort	Taiwan	59 ± 13	685 (51)	365	320	N/A	Fetuin-A	Serum	0.41 ± 0.08	0.61 ± 0.1	g/L	-
Moe et al. (2005)	Prospective cohort	United States	49 ± 13	49 (19)	35	14	N/A	Fetuin-A	Serum	0.51 ± 0.04	0.45 ± 0.15	g/L	-
Honda et al. (2006)	Prospective cohort	Sweden	54 ± 12	176 (62)	60	116	N/A	Fetuin-A	Serum	0.26 ± 0.18	0.21 ± 0.13	g/dL	-
Smith et al. (2013)	Cross-sectional	Australia	68 ± 17.34	48	6	36	N/A	Fetuin-A	Serum	0.16 ± 0.07	0.16 ± 0.07	g/L	-
Feldreich et al. (2020)	Prospective cohort	Sweden	71 ± 6.4	1316 (842)	-	-	N/A	KIM-1	Plasma	-	-	-	1.42 (1.23-1.65)

Table 1. Characteristics of Included studies (continued...)

Author (Year)	Study design	Study location	Age*	Total sample (female)	Sample size		Comorbidities	Marker	Specimen type	Outcome value of CVD	Outcome value of non-CVD	Measurements unit	Hazard ratio (HR) 95% CI
					CVD	Non-CVD				Mean ± SD*	Mean ± SD*		
Alderson et al. (2016b)	Prospective cohort	Great Brittain	64.5 ± 14.7	1982 (747)	-	-	N/A	KIM-1	Plasma	-	-	-	1.05 (0.85-1.3)
Sevinc et al. (2021)	Cross-sectional	Turkey	46.8 ± 10.3	92 (49)	50	42	N/A	Fetuin-A	Serum	78.4 ± 24.9	91.3 ± 16.7	ng/mL	-
Jotwani et al. (2019)	Prospective cohort	United States	72	2377 (959)	-	-	N/A	KIM-1	Urine	-	-	-	0.93 (0.86-1.02)
Ulutas et al. (2018)	Cross-sectional	Turkey	58.3 ± 15.7	93 (49)	45	48	N/A	OPN	Serum	5.4 ± 3.6	5.5 ± 3.5	ng/mL	-
	Cross sectional	Turkey	58.3 ± 15.7	93 (49)	45	48	N/A	OPN	Serum	651.5 ± 188.3	694.3 ± 214.7	ng/mL	-
Lee et al. (2019)	Prospective Cohort	Multicenter	73.12 ± 9.07	2376 (959)	306	2070	N/A	KIM-1	Urine	889.6 ± 227.03	841.67 ± 170.85	pg/mL	-
Bozic et al. (2018)	Prospective Cohort	Spain	61.93 ± 2.77	1043 (386)	95	948	N/A	OPN	Blood	25.15 ± 8.16	20.51 ± 4.43	ng/mL	1.65 (1.02-2.65)
Cottone et al. (2007)	Cross sectional	Italia	57 ± 16	64 (28)	30	34	N/A	Fetuin-A	Blood	0.49 ± 0.2	0.64 ± 0.24	g/L	-

Table 2. Summary of the findings results for markers related to CVD occurrence in patients with CKD before sensitivity analysis, along with the results of Egger's test calculation

Measurement effect	Group	Total study	SMD or HR	95% CI	I^2 (%)	P- value	Egger's test	Z score
SMD	OPN	5	3.47	1.65 – 5.31	99	0-0002*	<0.0001**	4.55
	KIM-1	2	1.02	-0.50 – 2.55	97	0.19	<0.0001**	5.91
	Fetuin-A	19	-0.42	-0.86 – (0.02)	96	0.06	0.2010	1.28
HR	OPN	2	1,38	1.13– 1.68	0	0.001*	0.4693	0.72
	KIM-1	4	1.09	0.88 – 1.35	88	0.44	0.3958	0.85
	Fetuin-A	4	1.22	0.97 – 1.52	90	0.08	0.0028**	2.99

*p<0.05 means statistically significant results. **p<0.05 means a significant risk of bias. SMD: standardized mean difference; HR: hazard ratio.

Table 3. Sensitivity analysis results on the three prognostic markers.

Measurement effect	Group	Total study	SMD or HR	95% CI	I^2 (%)	P-value
SMD	OPN	5	3.47	1.65-5.31	99	0.0002*
	KIM-1	2	1.02	-0.50-2.55	97	0.19
	Fetuin-A	15	-0.41	(-0.70)-(-0.12)	84	0.006*
HR	OPN	2	1.38	1.13-1.68	0	0.001*
	KIM-1	4	1.09	0.88-1.35	88	0.44
	Fetuin-A	3	1.62	0.84-3.13	93	0.15

*p<0.05 means statistically significant results. **p<0.05 means a significant risk of bias. SMD: standardized mean difference; HR: hazard ratio.

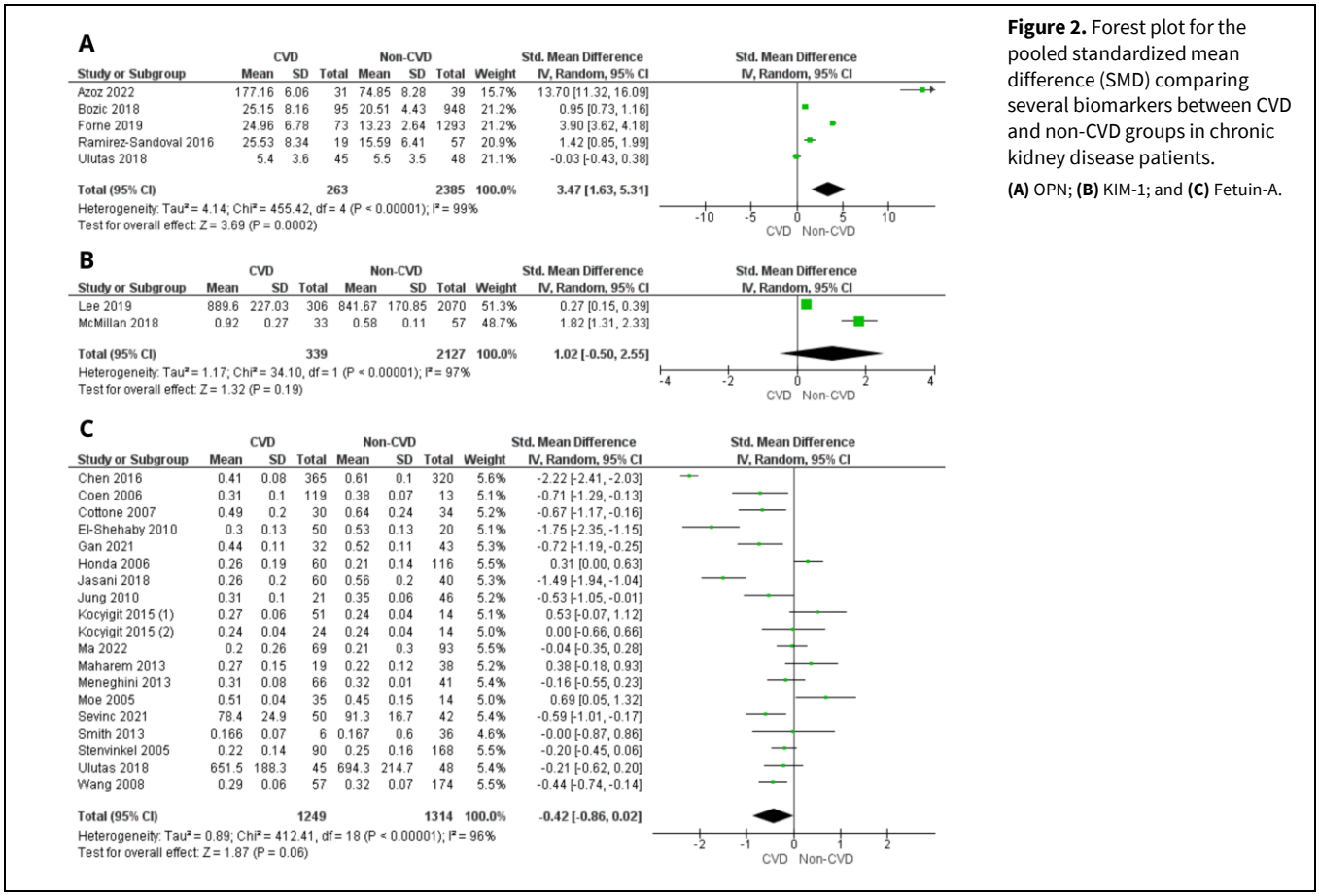

Figure 2. Forest plot for the pooled standardized mean difference (SMD) comparing several biomarkers between CVD and non-CVD groups in chronic kidney disease patients.

(A) OPN; **(B)** KIM-1; and **(C)** Fetuin-A.

Additionally, in 19 analysed studies, we found that the decrease in fetuin-A levels was not significantly associated with CVD in patients with CKD (SMD = -0.42, 95% CI = -0.86 – 0.02, p = 0.06, I^2 = 96%) (Fig. 2C). Subgroup analysis was conducted based on age and geographic location variables only on the fetuin-A marker due to a sufficient number of studies to conduct analysis. Based on the age group, the population group with a mean age <60 years showed no significance between the decrease in fetuin-A levels and CVD in CKD patients. Analysis for the elderly group could not be performed due to limited study (supplemental material Fig. S1). Based on the study regions, none of the regions showed a significant relationship between changes in fetuin-A levels and CVD, while the test for subgroup difference also depicted a nonsignificant p = 0.06 (supplemental material Fig. S2). Therefore, geographical location did not seem to play a role in CVD in patients with CKD.

The increase in OPN marker levels in chronic kidney disease patients indeed showed a significant 38% increase in the risk of CVD compared to normal with low heterogeneity (HR = 1.38, 95% CI = 1.09-1.64, p = 0.001). Unfortunately, only two studies were included in this analysis (Fig. 3A). Meta-analysis of the KIM-1 marker (Fig. 3B) also indicated that an increase in the marker levels did not significantly increase the risk of CVD with a high level of heterogeneity (HR = 1.09, 95% CI = 0.88-1.35, p = 0.44, I^2 = 88%). A decrease in fetuin-A levels was also not correlated to an increased risk of CVD (HR = 1.22, 95% CI = 0.97-1.52, p = 0.08) (Fig. 3C).

Publication bias and sensitivity analysis

Assessment of potential publication bias was performed using quantitative approaches (Egger's test), especially in study groups involving more than ten studies. In this study, the assessment of publication bias Egger's test could only be conducted on one study group, the group that analysed the changes in fetuin-A concentration toward CVD with the SMD measurement effect. Egger's test value indicates no risk of bias (Z = 1.28; p = 0.2010).A sensitivity analysis of the findings from the previous analysis was conducted by excluding studies with potential bias or moderate to low quality (with NOS QS score <7). Subsequently, SMD and HR values were re-evaluated to examine the consistency of results after excluding studies with potential bias. The comparison of results before and after sensitivity analysis is presented in Tables 2-3. Sensitivity analysis indicates a significant change in the group of studies measuring the fetuin-A marker concerning CVD, shifting from nonsignificant to significant (p = 0.006).

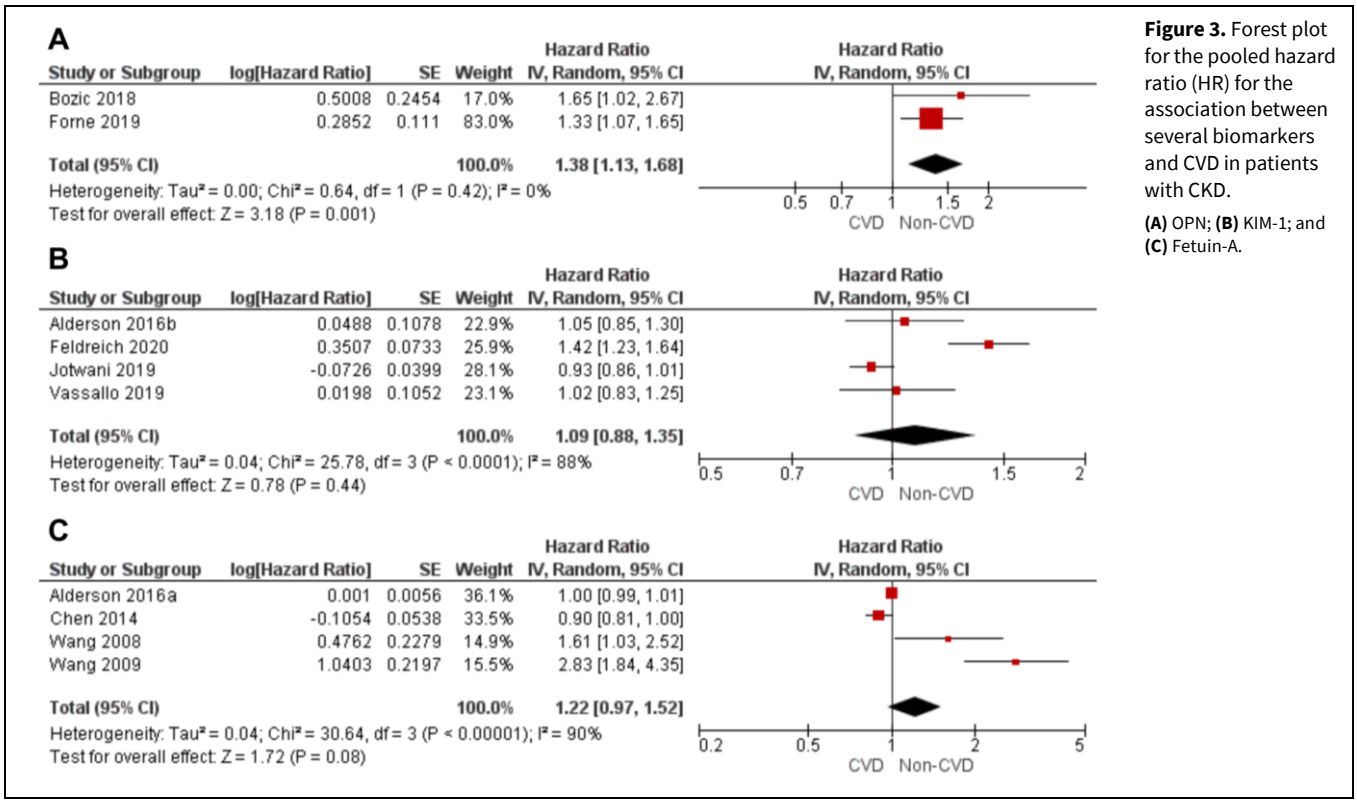

Figure 3. Forest plot for the pooled hazard ratio (HR) for the association between several biomarkers and CVD in patients with CKD.
(A) OPN; **(B)** KIM-1; and **(C)** Fetuin-A.

DISCUSSION

The risk of developing CVD in patients with CKD is presented by the three markers used in this study. The effect of changes in the levels of the three markers on the increased incidence of CVD in CKD patients is depicted through the SMD values according to the previously mentioned range. Meanwhile, the predictive strength evaluation of the three markers in predicting the increased incidence of CVD is assessed using HR. The results indicate the significant and substantial potential of the OPN as a marker for CVD (SMD = 3.47). Further analysis to measure the prognostic strength of OPN shows that CVD events increases by up to 38% in CKD patients with elevated OPN levels.

This finding is consistent with previous studies demonstrating a positive correlation between OPN and various triggers of CVD, such as atherosclerosis-related diseases and vascular calcification (Chaitanya et al., 2018; Shirakawa and Sano, 2021). The role of OPN in CVD is known through its action in regulating vascular calcification. Acute increases in OPN have protective effects, such as wound healing and neovascularization. However, chronic increases in OPN can indicate a higher risk of CVD (Bjerre et al., 2013; Shirakawa et al., 2018). Additionally, OPN is known to play a role in the development of atherosclerotic plaques and dystrophic calcification (Wolak, 2014). Vascular endothelial growth factor (VEGF) and vascular permeability factor (VPF) are cytokines that play a role in angiogenesis (Icer and Gezmen-Karadag, 2018). The presence of these cytokines also triggers an increase in the expression of αvβ3 and OPN as ligands on the endothelial cell surface. This leads to increased migration of endothelial cells in the intima, causing narrowing of the arterial lumen. The same process occurs in vascular calcification. OPN levels are significantly higher in patients with calcified valve disease compared to non-calcified valves (Waller et al., 2010). Intriguingly, OPN plays a dual role in the vascular calcification process, which could either be an inducer or inhibitor of vascular calcification. A study by Speer et al. (2005) showed that vascular smooth muscle cells with deleted OPN-expressing genes exhibited a significantly higher incidence of vascular calcification. Therefore, increased OPN levels can be correlated with atherosclerosis, which often underlies CVD (Waller et al., 2010).

Kidney injury molecule-1 was not found to have a significant effect on CVD in this study. A meta-analysis of hazard ratios yielded similar results, indicating that an increase in KIM-1 levels had no significant association with CVD. The majority of KIM-1 is generally expressed by the kidney's proximal tubule cells (Wasung et al., 2015). Under physiological conditions, the expression of KIM-1 is maintained at low levels and changes linearly with age (Pennemans et al., 2013). An increase in KIM-1 levels will occur if cardiovascular abnormalities underlie the renal abnormalities in patients. This condition is known as cardiorenal syndrome type 1 (acute) and type 2 (chronic) (Uduman, 2018). In patients with myocardial infarction affecting cardiac pump function, it will result in decreased perfusion to various organs (including the kidneys) and hypotension. This leads to hypoxia and renal injury, causing damage to kidney tubule cells and the release of KIM-1 into the tubule lumen (Medić et al., 2015).

A study by Sarnak et al. (2014) also showed the same results, where an increase in urine KIM-1 levels was not significantly associated with the occurrence of CVD. This is further supported by previous studies stating that an increase in KIM-1 levels is not significantly associated with the onset of acute decompensated heart failure (Grodin et al., 2015). Moreover, despite earlier studies suggesting that KIM-1 has the potential to depict CVD in CKD patients, the prognostic strength of KIM-1 is not as robust as other markers such as NGAL (Dupont et al., 2012).

Fetuin-A emerged as the most frequently encountered marker during the screening phase of studies in the compilation of this meta-analysis. Decreased fetuin-A levels were found to be non-significant in terms of CVD occurrence among CKD patients. A more in-depth analysis to assess the prognostic strength of fetuin-A revealed that there's no significant increase in the risk of CVD in chronic kidney disease patients with decreased fetuin-A levels. This finding needs further examination, considering the potential publication bias in the included studies. Four previously included studies have a high potential for bias, which could alter the actual results. However, sensitivity analysis reveals a significant change in the group of studies examining the fetuin-A marker in relation to cardiovascular disease (CVD). Decreased fetuin-A levels are found to be associated with increased CVD in CKD patients with a small effect (low SMD value), suggesting its potential as a prognostic marker. According to the subgroup analysis, the relationship between geographical location and age and the expected clinical outcomes showed no significant correlation. This suggests that both age and geographical location are not considerable factors influencing the biomarker's properties.

Fetuin-A is capable of inhibiting vascular calcium-phosphate deposition by forming a fetuin-mineral complex. Thus, a decrease in fetuin-A impacts the risk of worsening cardiovascular function due to the lack of factors involved in vascular calcification inhibition (Mori et al., 2012). A study by Talib et al. (2012) shows

that fetuin-A levels in hemodialysis patients correlate with diastolic heart dysfunction. Another study by Laughlin et al. (2012) indicates that low fetuin-A levels significantly predict cardiovascular disease-related mortality in patients without diabetes. The reduction in fetuin-A levels is also associated with malnutrition, inflammation, atherosclerosis, and calcification (MIAC) in chronic kidney disease (CKD) patients (Mutluay et al., 2019). This suggests that fetuin-A still has the potential to depict cardiovascular disease in CKD patients.

Strengths and limitations

Based on our literature search, there has been no systematic review and meta-analysis comprehensively addressing the prognostic value of OPN, KIM-1, and fetuin-A on the occurrence of CVD in patients with CKD within a single study. However, this study has several limitations. First, the three markers used have varying numbers of studies in this meta-analysis. Second, the study has not been able to identify the threshold/cut-off levels of markers that may be potential indicators of the risk of CVD. The data in this study mainly focus on how significant the effect of changes in marker levels is on the expected events. Third, although most studies have good quality (NOS ≥7), some studies are still reported to have potential bias. However, we attempted to re-evaluate the study results by conducting a sensitivity analysis, excluding studies with potential bias (NOS <7). Fourth, this study still has high heterogeneity, which can be influenced by various factors, such as differences in sample characteristics, disease groups and comorbidities, and CKD severity, among others.

With the various limitations of this study, we provide several recommendations. Although the overall population involved in this study was relatively large, this population was not evenly distributed across the non-CVD group. Research involving a larger and more evenly distributed number of studies is recommended to compare the potential of the three markers. Further research to determine the threshold concentrations for each marker regarding the expected clinical outcomes is needed to assist clinicians in determining the prognosis of patients with CKD.

CONCLUSION

Osteopontin has a significant and substantial effect on CVD in patients with CKD, making it a potential prognostic marker. It was also found that OPN also demonstrated increases in the risk of developing CVD by 38% in patients with CKD. When sensitivity analysis is conducted, a decrease in fetuin-A levels demonstrates a significant impact on the occurrence of CVD, indicating its potential use as a prognostic marker. However, more high-quality studies are required to support the findings presented in this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Welliam Y	Witarto BS	Visuddho V	Susilo H	Wungu CDK	Budiarto RM	Multazam CECZ
Concepts or ideas	x	x	x	x			
Design	x	x	x	x			
Definition of intellectual content				x			
Literature search	x	x	x	x			
Experimental studies	x			x			
Data acquisition	x	x	x				
Data analysis	x			x			
Statistical analysis	x	x					
Manuscript preparation	x			x			
Manuscript editing	x	x					x
Manuscript review	x	x	x	x	x	x	x

Citation Format: Welliam Y, Witarto BS, Visuddho V, Susilo H, Wungu CDK, Budiarto RM, Multazam CECZ (2025) The role of osteopontin, KIM-1, and fetuin-A as prognostic markers for cardiovascular disease in patients with chronic kidney disease: A systematic review and meta-analysis. J Pharm Pharmacogn Res 13(4): 1128–1146. https://doi.org/10.56499/jppres24.2174_13.4.1128

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Supplementary Data

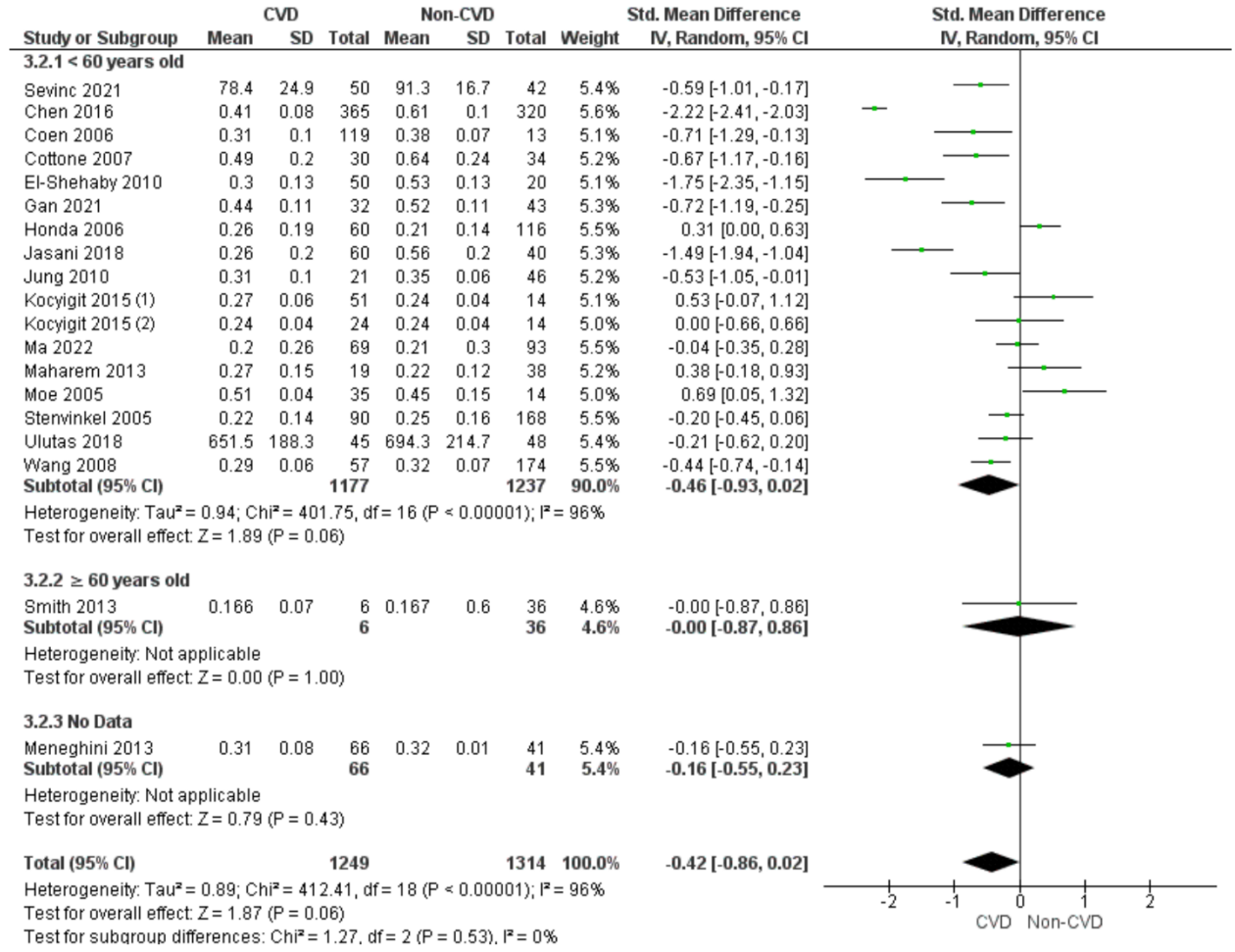

Figure S1. Subgroup analysis results based on age: (1) < 60 years and (2) ≥ 60 years, that analyze fetuin-A level changes toward cardiovascular disease (CVD) occurrence in chronic kidney disease patients.

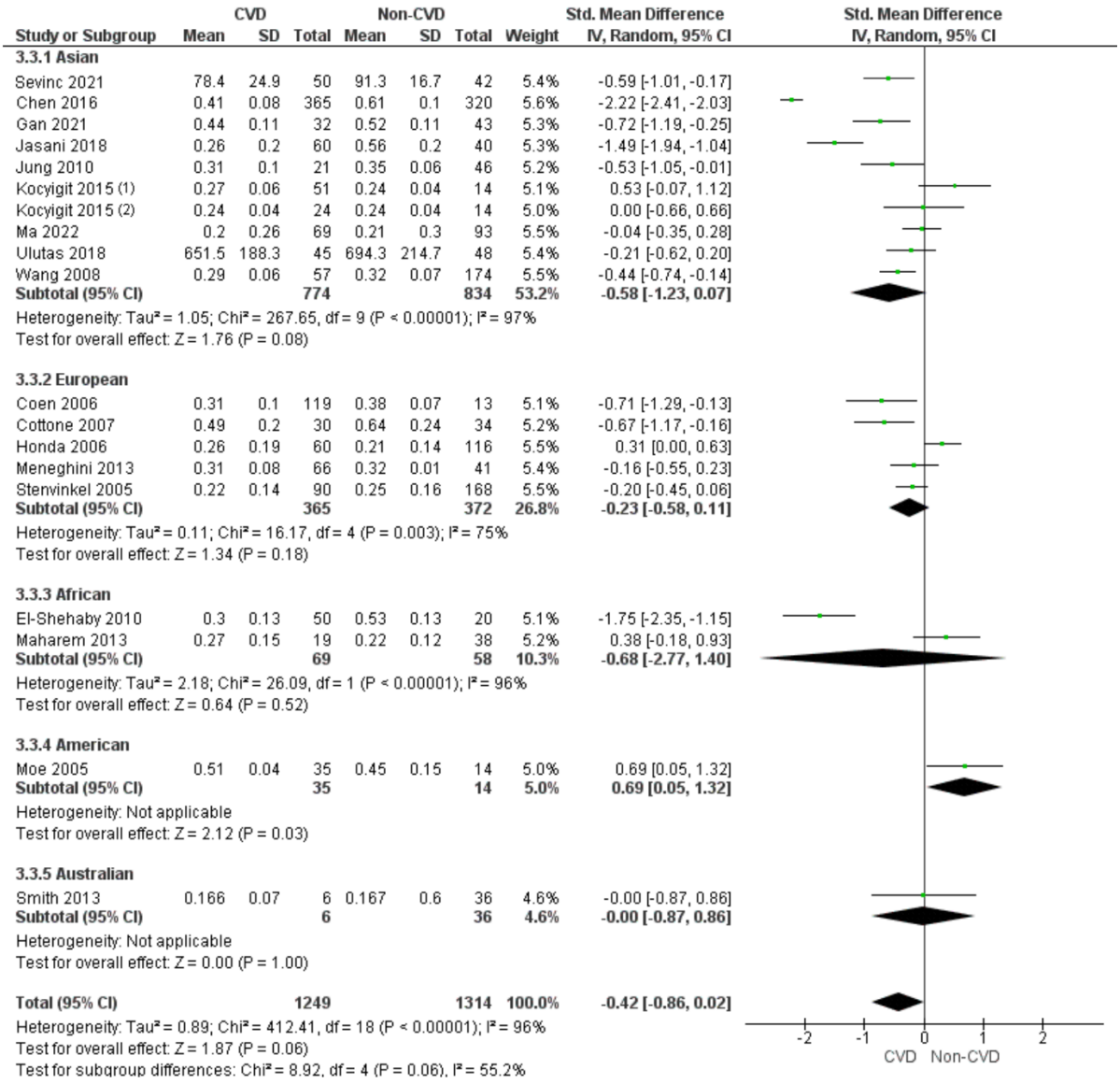

Figure S2. Subgroup analysis results based on geographical location that analyze fetuin-A level changes toward cardiovascular disease (CVD) occurrence in chronic kidney disease patients.

Table S1. Search strategy.

DATABASE	KEYWORDS	
PubMed	#1	"Osteopontin" OR "OPN" OR "Sialoprotein 1" OR "Secreted Phosphoprotein 1" OR "Uropontin OR
	#2	"KIM-1" OR "Kidney injury molecule-1" OR "TIMD1" OR "hepatitis A virus receptor" OR "HAV cellular receptor" OR "TIM-1"
	#3	"Fetuin-A" OR "AHSG" OR "α2-Heremans Schmid glycoprotein"
	#4	"Cardiovascular disease" OR "Cardiovascular"
	#5	"chronic kidney diseases" OR "chronic renal insufficiency" OR "chronic renal diseases" OR "chronic renal failure" OR "chronic kidney failure"
	#6	(#1 OR #2 OR #3) AND #4 AND #5
Web of Science	#1	Osteopontin OR OPN OR Sialoprotein 1 OR Secreted Phosphoprotein 1 OR Uropontin OR
	#2	KIM-1 OR Kidney injury molecule-1 OR TIMD1 OR hepatitis A virus receptor OR HAV cellular receptor

		OR TIM-1
	#3	Fetuin-A OR AHSG OR α2-Heremans Schmid glycoprotein
	#4	Cardiovascular disease OR Cardiovascular
	#5	chronic kidney diseases OR chronic renal insufficiency OR chronic renal diseases OR chronic renal failure OR chronic kidney failure
	#6	(#1 OR #2 OR #3) AND #4 AND #5
Scopus	#1	“Osteopontin” OR “OPN” OR “Sialoprotein 1” OR “Secreted Phosphoprotein 1” OR “Uropontin OR
	#2	“KIM-1” OR “Kidney injury molecule-1” OR “TIMD1” OR “hepatitis A virus receptor” OR “HAV cellular receptor” OR “TIM-1”
	#3	“Fetuin-A” OR “AHSG” OR “α2-Heremans Schmid glycoprotein”
	#4	“Cardiovascular disease” OR “Cardiovascular”
	#5	“chronic kidney diseases” OR “chronic renal insufficiency” OR “chronic renal diseases” OR “chronic renal failure” OR “chronic kidney failure”
	#6	(#1 OR #2 OR #3) AND #4 AND #5
Science Direct	#1	“Osteopontin” OR “OPN” OR “KIM-1” OR “Kidney injury molecule-1” OR “TIM-1” OR “Fetuin-A”
	#2	“Cardiovascular disease” OR “Cardiovascular”
	#3	“chronic kidney diseases”
CINAHL	#1	“Osteopontin” OR “OPN” OR “Sialoprotein 1” OR “Secreted Phosphoprotein 1” OR “Uropontin OR
	#2	“KIM-1” OR “Kidney injury molecule-1” OR “TIMD1” OR “hepatitis A virus receptor” OR “HAV cellular receptor” OR “TIM-1”
	#3	“Fetuin-A” OR “AHSG” OR “α2-Heremans Schmid glycoprotein”
	#4	“Cardiovascular disease” OR “Cardiovascular”
	#5	“chronic kidney diseases” OR “chronic renal insufficiency” OR “chronic renal diseases” OR “chronic renal failure” OR “chronic kidney failure”
	#6	(#1 OR #2 OR #3) AND #4 AND #5
Proquest	#1	“Osteopontin” OR “OPN” OR “Sialoprotein 1” OR “Secreted Phosphoprotein 1” OR “Uropontin OR
	#2	“KIM-1” OR “Kidney injury molecule-1” OR “TIMD1” OR “hepatitis A virus receptor” OR “HAV cellular receptor” OR “TIM-1”
	#3	“Fetuin-A” OR “AHSG” OR “α2-Heremans Schmid glycoprotein”
	#4	“Cardiovascular disease” OR “Cardiovascular”
	#5	“chronic kidney diseases” OR “chronic renal insufficiency” OR “chronic renal diseases” OR “chronic renal failure” OR “chronic kidney failure”
	#6	(#1 OR #2 OR #3) AND #4 AND #5
Bioxriv	#1	Osteopontin OR Kidney injury molecule-1 OR Fetuin-A
	#2	Cardiovascular disease
	#3	Chronic kidney disease
	#4	#1 AND #2 AND #3
Medxriv	#1	Osteopontin OR Kidney injury molecule-1 OR Fetuin-A
	#2	Cardiovascular disease
	#3	Chronic kidney disease
	#4	#1 AND #2 AND #3

Table S2. Quality assessment of cohort studies using Newcastle Ottawa Scale (NOS) assessment.

	Selection				Comparability	Outcome			
Author (Year)	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**NOS score**
Vassallo (2019)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Meneghini (2013)	☆	☆	☆	-	-	☆	☆	☆	6
Jung (2010)	☆	☆	☆	-	☆	☆	☆	☆	7
Chen (2014)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Alderson (2016a)	☆	☆	☆	-	☆	-	-	☆	5
Wang (2008)	☆	☆	☆	-	☆☆	☆	-	☆	7
Wang (2009)	☆	☆	☆	-	☆☆	☆	☆	☆	8
Stenvinkel (2005)	☆	☆	☆	-	☆☆	☆	-	☆	7
Forne (2019)	☆	☆	☆	-	☆☆	☆	☆	☆	8
Chen (2016)	☆	☆	☆	-	☆☆	☆	-	-	6
Moe (2005)	☆	☆	☆	☆	-	☆	-	-	5
Honda (2006)	☆	☆	☆	-	☆☆	☆	-	☆	7
Feldreich (2020)	☆	☆	☆	-	☆☆	☆	☆	☆	8
Alderson (2016b)	☆	☆	☆	☆	☆☆	☆	-	☆	8
Jotwani (2019)	☆	☆	☆	-	☆☆	☆	-	☆	7
Lee (2019)	☆	☆	☆	-	☆☆	☆	-	☆	7
Bozic (2018)	☆	☆	☆	-	☆☆	☆	-	☆	7

Total maximum score is 9. A study with score from 7-9, has high quality, 4-6, high risk, and 0-3 very high risk of bias.

Table S3. Quality assessment of case-control studies using Newcastle Ottawa Scale (NOS) assessment.

	Selection				Comparability	Outcome			
Author (Year)	**Is the case definition adequate?**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response**	**NOS score**
Maharem (2013)	☆	☆	☆	☆	☆	☆	☆	-	8
Ma (2022)	☆	☆	-	☆	-	☆	☆	☆	6
Azoz (2022)	☆	☆	☆	-	☆	☆	☆	☆	7

Total maximum score is 9. A study with score from 7-9, has high quality, 4-6, high risk, and 0-3 very high risk of bias.

Table S4. Quality assessment of cross-sectional studies using Newcastle Ottawa Scale (NOS) assessment.

Author (Year)	Selection				Comparability	Outcome		NOS score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of subjects in different outcome groups on the basis of design or analysis.	Assessment of outcome	Statistical test	
Kocyigit (2015)	☆	☆	☆	☆☆	-	☆	☆	7
El-Shehaby (2010)	☆	☆	☆	☆☆	-	☆	☆	7
Gan (2021)	☆	-	☆	☆☆	☆☆	☆☆	☆	9
Ramirez (2016)	☆	☆	-	☆☆	-	☆☆	☆	7
McMillan (2018)	☆	☆	☆	☆☆	-	☆☆	☆	8
Coen (2006)	☆	☆	-	☆☆	-	☆☆	☆	7
Jasani (2018)	☆	☆	☆	☆☆	-	☆☆	☆	8
Smith (2013)	☆	-	☆	☆☆	-	☆☆	☆	7
Sevinc (2021)	☆	☆	☆	☆☆	-	☆☆	☆	8
Ulutas (2018)	☆	-	-	☆☆	☆☆	☆☆	☆	8
Cottone (2007)	☆	-	☆	☆☆	☆☆	☆☆	☆	9

Total maximum score is 8. A study with score from 7-8, belong to good studies, 5-6 satisfactory studies, and 0-4 unsatisfactory studies.