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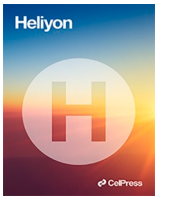

Research article

Association between blood phosphorus level and adverse outcomes in patients with coronary artery disease: A meta-analysis

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ABSTRACT

Objective: The prognostic implication of phosphorus level in patients with coronary artery disease (CAD) remains controversial. We aimed to conduct a meta-analysis to evaluate the prognostic role of blood phosphorus level in CAD patients.

Methods: We searched the PubMed, Web of Science, Scopus, and Embase databases until December 28, 2023, to identify prospective or retrospective longitudinal observational studies that examined the prognostic value of blood phosphorus level in CAD patients. Outcome measures included all-cause or cardiovascular mortality, heart failure, stroke, and major adverse cardiac events (MACEs). The prognostic value of blood phosphorus level was expressed by pooling the fully adjusted hazard ratios (HR) with 95 % confidence intervals (CI) for the hypophosphatemia or hyperphosphatemia compared to the reference normal phosphorus level.

Results: Six studies involving 19,553 CAD patients were included. Meta-analysis showed that the hyperphosphatemia was significantly associated with higher risk of all-cause mortality (HR 1.39; 95 % CI 1.20–1.61), cardiovascular mortality (HR 1.37; 95 % CI 1.22–1.53), heart failure (HR 1.64; 95 % CI 1.44–1.87), and MACEs (HR 1.39; 95 % CI 1.03–1.88) but not stroke (HR 1.23; 95 % CI 0.79–1.92). However, non-significant association was found between hypophosphatemia and all-cause mortality (HR 1.21; 95 % CI 0.98–1.51), cardiovascular mortality (HR 1.07; 95 % CI 0.78–1.45), heart failure (HR 0.87; 95 % CI 0.72–1.05), stroke (HR 1.12; 95 % CI 0.76–1.67), and MACEs (HR 1.16; 95 % CI 0.99–1.36).

Conclusions: Hyperphosphatemia, but not hypophosphatemia independently predicts all-cause mortality, cardiovascular mortality, heart failure, and MACEs in CAD patients.

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Data availability statement

All data included in article or supplemental material.

1. Introduction

Coronary artery disease (CAD), also called coronary heart disease or ischemic heart disease, is characterized by inadequate blood supply to the myocardium due to the narrowing or blockage of the coronary arteries. Despite a decline in deaths from coronary heart disease in recent decades, CAD remains the leading cause of mortality and morbidity worldwide [1]. Patients with CAD face a higher risk of cardiovascular events [2]. Identifying individuals at high risk is crucial for the secondary prevention of CAD. Therefore, the search for additional prognostic factors is still in demand for predicting clinical outcomes.

Phosphorus is an abundant mineral in the human body and plays a pivotal role in gene transcription, cellular signal transduction, bone formation, and enzymes activation [3]. The level of phosphorus in the blood serves as an indicator of phosphate homeostasis [4]. Phosphate homeostasis is primarily regulated by parathyroid hormone, vitamin D, and fibroblast growth factor-23 [5,6]. Abnormal phosphate homeostasis manifests as hypophosphatemia and hyperphosphatemia. Hyperphosphatemia has been identified as a cardiovascular toxin, potentially due to its role in accelerating vascular calcification [7] and inducing endothelial dysfunction [8]. In patients with CAD, higher phosphorus levels have been independently associated with increased plaque burden and adverse plaque composition [9]. These factors collectively contribute to the progression of atherosclerosis and deteriorating cardiovascular health. However, there is ongoing debate surrounding the impact of abnormal phosphorus level on adverse clinical outcomes in CAD patients [10–13].

No prior meta-analysis has been investigated the association between hypophosphatemia, hyperphosphatemia, and adverse prognosis in CAD patients. To address this knowledge gap, we conducted the first meta-analysis to assess the prognostic implication of blood phosphorus level in patients with established CAD.

2. Methods

2.1. Literature search

This study was reported according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses [14]. Two authors independently conducted a literature search using the PubMed, Web of Science, Scopus, and Embase databases, without any language restrictions. Keywords used for literature search included (Supplementary Text S1): ("phosphorus" OR "phosphate" OR "hypophosphatemia" OR "hyperphosphatemia") AND ("coronary artery disease" OR "coronary heart disease" OR "ischemic heart disease" OR "angina" OR "myocardial infarction" OR "acute coronary syndrome") AND ("mortality" OR "death" OR "heart failure" OR "stroke" OR "cardiovascular events"). The last search was conducted on December 28, 2023. In addition to the electronic database search, we manually examined the references of included studies and relevant reviews.

2.2. Study selection

The following criteria were used to select studies for inclusion: 1) participants who had established CAD (stable CAD, acute myocardial infarction, acute coronary syndrome, coronary artery bypass graft surgery, or post-myocardial infarction); 2) abnormal blood level phosphorus or phosphate as exposure; 3) comparison of the hypophosphatemia or hyperphosphatemia with the reference normal phosphorus level; 4) outcomes including all-cause mortality, cardiovascular mortality, heart failure, stroke, or major adverse cardiac events (MACEs) such as cardiovascular death, myocardial infarction, revascularization, heart failure, stroke, graft failure, or revascularization; 5) availability of adjusted risk estimates for at least one measure of the outcomes of interest associated with hypophosphatemia or hyperphosphatemia; and 6) prospective or retrospective longitudinal observational studies as the study design. Exclusion criteria included: 1) participants did not have CAD; 2) the reference was the bottom blood phosphorus level instead of the normal phosphorus level; 3) outcomes were not of interest; or 4) the study was a conference abstract or review article.

2.3. Data extraction and quality assessment

Two independent authors extracted the data using a standardized form. The data abstracted from the eligible studies included the surname of the first author, publication year, study location and design, patient's subtypes, sample sizes, sex distribution, baseline age of patients, blood phosphorus threshold categories, definition of MACEs, follow-up duration, outcome measures, covariates adjusted in the multivariable model, and fully adjusted hazard ratio (HR) with 95 % confidence intervals (CI). The Newcastle Ottawa Scale (NOS) was used by two independent authors to assess the methodological quality of the included studies [15]. The studies were ranked as moderate quality (4–6 points) and high-quality (7 points or more). Disagreements between two authors were settled through discussion with the corresponding author.

2.4. Data analysis

The prognostic value of blood phosphorus was expressed by pooling the fully adjusted HR with 95 % CI for the hypophosphatemia

or hyperphosphatemia compared to the reference normal phosphorus level. Heterogeneity among the studies was evaluated using the Cochrane Q test and I^2 statistic. The presence of significant heterogeneity was defined as a $p < 0.10$ of the Cochrane Q test and/or an I^2 value ≥ 50 %. A random effects model was chosen for all meta-analyses due to evident clinical heterogeneity regarding the thresholds for hypophosphatemia and hyperphosphatemia. To determine the impact of individual studies on the pooled risk estimate, a sensitivity analysis was conducted by removing each study one at a time. If there were at least 5 studies included in the analysis, publication bias was assessed using Begg's test and Egger's test. All meta-analyses were conducted using Stata 12.0 (Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Search results and study characteristic

Briefly, the electronic databases search yielded 1427 potential records. Of which, 770 duplicated records were removed, and 657 articles were reviewed the titles and/or abstracts for possible inclusion. Then, 31 full-text articles were obtained for eligibility evaluation. After application of inclusion and exclusion criteria, 6 studies [10–13,16,17] were included in this meta-analysis (Fig. 1).

The baseline characteristics of the included studies are presented in Table 1. The year of publication was between 2005 and 2022. Two studies [11,17] were prospective cohort designs, whereas the others were retrospective studies. The total number of patients of individual studies ranged from 1663 to 4989 cases, with a total of 19,553 CAD patients. The mean or median age of patients varied from 58.6 to 71.6 years and majority of patients were men (69.1 %–86.2 %). The median/mean length of follow-up ranged from 24 to 65.1 months. All included studies had low risk of bias (7 points or over) according to the NOS criteria (Supplementary Table S1).

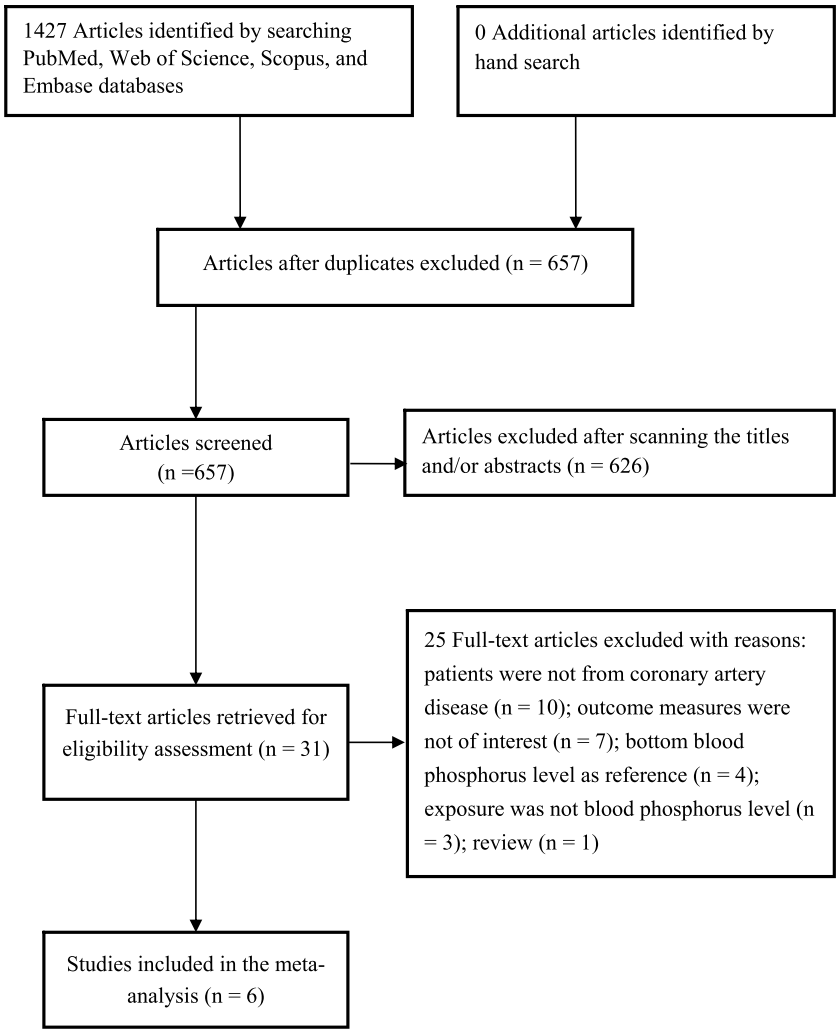

Fig. 1. Flow chart showing the study selection process.

Table 1
Baseline characteristic of the included studies.

Author/ year	Region	Study design	Patients (% male)	Age (years)	Phosphorus threshold (mg/dL)	Definition of MACEs	Outcome measures HR (95 % CI)	Follow-up (months)	Adjusted variables
Tonelli 2005 [10]	USA	R	Post-MI 4127 (86.2)	58.6 ± 9.4	HYPO: ≤2.5 HYPE: ≥4.0 Reference: 2.5–3.4	–	Total death 0.78 (0.40–1.53) HYPO 1.22 (0.95–1.58) HYPE HF 0.77 (0.36–1.65) HYPO 1.43 (0.95–2.14) HYPE	59.7	Age, sex, race, smoking, diabetes, waist-to-hip circumference ratio, fasting glucose, GFR, hemoglobin, serum albumin, aspirin use, LVEF
Aronson 2013 [11]	Israel	P	Acute MI 1663 (78.2)	61.0 ± 12.4	HYPO: <2.50 HYPE: >4.5 Reference: 2.5–3.5	Heart failure, MI, stroke	MACEs 1.04 (0.70–1.55) HYPO 1.73 (1.22–2.45) HYPE Total death 1.24 (0.85–1.80) HYPO 1.75 (1.27–2.40) HYPE Stroke 0.76 (0.44–3.05) HYPO 1.46 (0.61–3.76) HYPE HF 0.99 (0.59–1.66) HYPO 1.79 (1.17–2.73) HYPE	45	Age, sex, eGFR, hemoglobin, previous infarction, hypertension, diabetes, smoking, baseline hemoglobin, serum calcium, STEMI, Killip class, coronary revascularization, LVEF
Park 2019 [12]	Korea	R	CAD undergoing (CABG) 4989 (73.7)	63.1 ± 9.8	HYPO: <2.5 HYPE >4.5 Reference: 2.5–4.5	CV death, graft failure, stroke, MI, revascularization	MACEs 1.27 (0.92–1.75) HYPO 1.07 (0.89–1.28) HYPE Total death 1.76 (1.13–2.76) HYPO 1.10 (0.82–1.47) HYPE CV death 1.03 (0.47–2.26) HYPO 1.18 (0.81–1.73) HYPE Stroke 0.91 (0.46–1.82)	48	Age, sex, diabetes, LVEF, CKD, MI, ACS, left main artery disease, emergent operation, off-pump technique, right internal thoracic arterial graft, right gastroepiploic artery

(*continued on next page*)

Table 1 (*continued*)

Author/ year	Region	Study design	Patients (% male)	Age (years)	Phosphorus threshold (mg/dL)	Definition of MACEs	Outcome measures HR (95 % CI)	Follow-up (months)	Adjusted variables
							HYPO 1.35 (0.63–2.90) HYPE		
Zhu 2019 [13]	China	R	STEMI 1989 (80.8)	60.79 ± 9.8	HYPO: <2.5 HYPE: >4.5 Reference:2.51–3.5	–	Total death 1.19 (0.64–1.54) HYPO 1.46 (1.35–1.83) HYPE	54.6	Age, sex, angulated lesion, CABG, LDL, reference vessel diameter, thyroid disease
Tsai 2021 [16]	Taiwan	R	CAD 2894 (74.4)	71.6 ± 12.2	HYPO: <3.0 HYPE >4.0 Reference: 3.0–3.4	CV death, nonfatal MI or stroke, HF hospitalization	MACEs 1.15 (0.93–1.41) HYPO 1.55 (1.25–1.92) HYPE CV death 1.07 (0.66–1.73) HYPO 1.37 (1.22–1.55) HYPE Stroke 1.47 (0.84–2.57) HYPO 1.03 (0.52–2.05) HYPE HF 1.03 (0.78–1.36) HYPO 1.51 (1.13–2.01) HYPE	65.1	Age, sex, hypertension, diabetes, smoking, eGFR
Cao 2022 [17]	China	P	Acute MI 3891 (69.1)	61 (53–69)	HYPO: ≤3.3[a] HYPE ≥4.2[a] Reference: 3.3–4.2^	–	Total death 1.06 (0.71–1.58) HYPO 1.59 (1.08–2.32) HYPE CV death 1.07 (0.64–1.81) HYPO 1.68 (1.03–2.75) HYPE HF 0.74 (0.58–0.95)[b] HYPO 1.70 (1.44–2.01)[b] HYPE	24	Age, sex, BMI, AMI types, smoking, hypertension, diabetes, MI, PCI, CABG, heart rate, multi-vessel disease, cardiac troponin I, NT-proBNP, eGFR, TC, TG, corrected serum calcium, magnesium

Abbreviations: HR, hazard ratio; CI, confidence intervals; P, prospective; R, retrospective; CV, cardiovascular; HYPE, hyperphosphatemia; HYPO, hypophosphatemia; MACEs, major adverse cardiovascular events; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndromes; CAD, coronary artery disease; CABG, coronary artery bypass grafting; HF, heart failure; BMI, body mass index; LVEF, left ventricular ejection fraction; LDL, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention.

[a] Calculated by 1 mg/dl = 0.3229 mmol/L.

[b] Resuts pooled from subgroups using a random effect model.

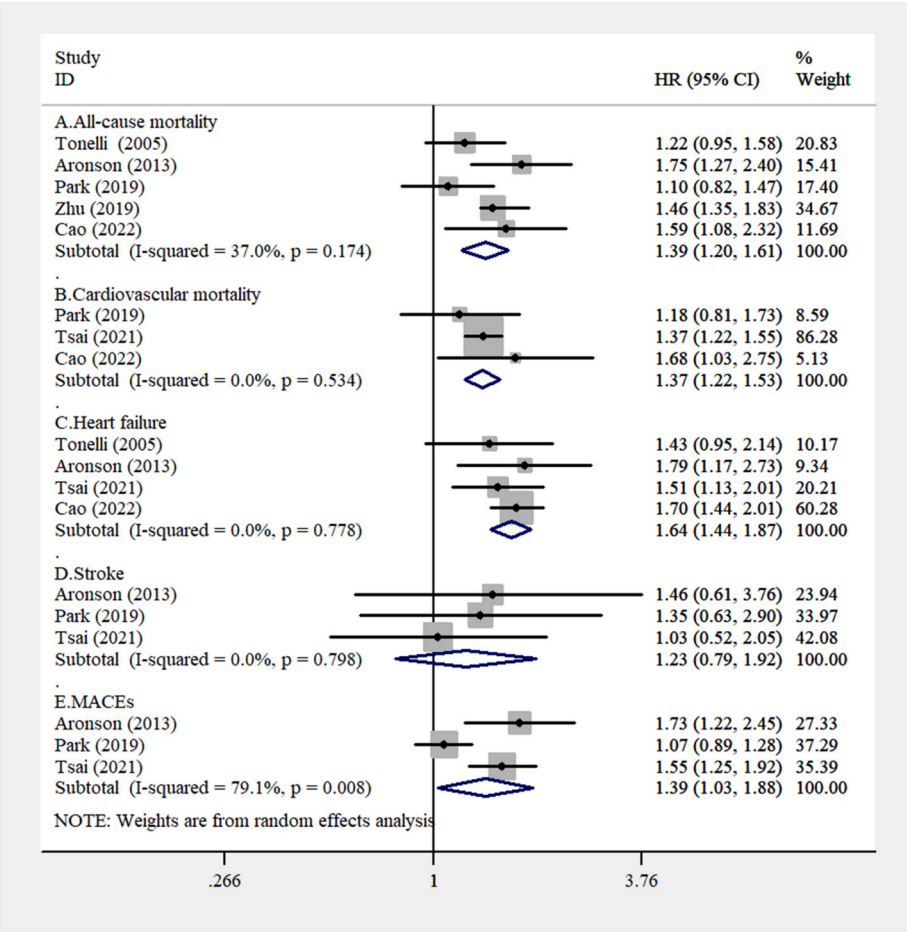

Fig. 2. Forest plots showing the pooled hazard ratios of all-cause mortality (A), cardiovascular mortality (B), heart failure (C), stroke (D), and MACEs (E) for hyperphosphatemia versus the reference normal phosphorus level.

3.2. Association of hyperphosphatemia with adverse outcomes

As shown in Fig. 2, when compared with the reference normal phosphorus level, hyperphosphatemia was significantly associated with an increased risk of all-cause mortality (HR 1.39; 95 % CI 1.20–1.61; $I^2 = 37.0$ %; p = 0.174; Fig. 2A) [10–13,17], cardiovascular mortality (HR 1.37; 95 % CI 1.22–1.53; $I^2 = 0$ %; p = 0.534; Fig. 2B) [12,16,17], heart failure (HR 1.64; 95 % CI 1.44–1.87; $I^2 = 0$ %; p = 0.778; Fig. 2C) [10,11,16,17], and MACEs (HR 1.39; 95 % CI 1.03–1.88; $I^2 = 79.1$ %; p = 0.008; Fig. 2D) [11,12,16], but not stroke (HR 1.23; 95 % CI 0.79–1.92; $I^2 = 0$ %; p = 0.798; Fig. 2E) [11,12,16]. Leave-one-out sensitivity analysis did not significantly alter the originally statistical significance of abovementioned pooling risk estimate. When the analysis was restricted in studies [11,13,17] that enrolled patients with acute myocardial infarction, the pooled HR of all-cause mortality for the hyperphosphatemia was 1.52 (95 % CI 1.33–1.73; $I^2 = 0$ %; p = 0.584). Based on the results of Begg's test (p = 0.806) and Egger's test (p = 0.471), publication bias was not present.

3.3. Association of hypophosphatemia with adverse outcomes

As shown in Fig. 3, when compared with the reference normal phosphorus level, hypophosphatemia was not significantly associated with an increased risk of all-cause mortality (HR 1.21; 95 % CI 0.98–1.51; $I^2 = 16.5$ %; p = 0.310; Fig. 3A) [10–13,17], cardiovascular mortality (HR 1.07; 95 % CI 0.78–1.45; $I^2 = 0$ %; p = 0.997; Fig. 3B) [12,16,17], heart failure (HR 0.87; 95 % CI 0.72–1.05; $I^2 = 11.9$ %; p = 0.333; Fig. 3C) [10,11,16,17], stroke (HR 1.12; 95 % CI 0.76–1.67; $I^2 = 0$ %; p = 0.392; Fig. 3D) [11,12,16], and MACEs (HR 1.16; 95 % CI 0.99–1.36 $I^2 = 0$ %; p = 0.740; Fig. 3E) [11,12,16]. Leave-one-out sensitivity analysis did not significantly alter the originally statistical significance of abovementioned pooling risk estimate. According to the results of Begg's test (p = 1.000) and Egger's test (p = 0.945), publication bias for associations of hypophosphatemia with all-cause mortality was not found.

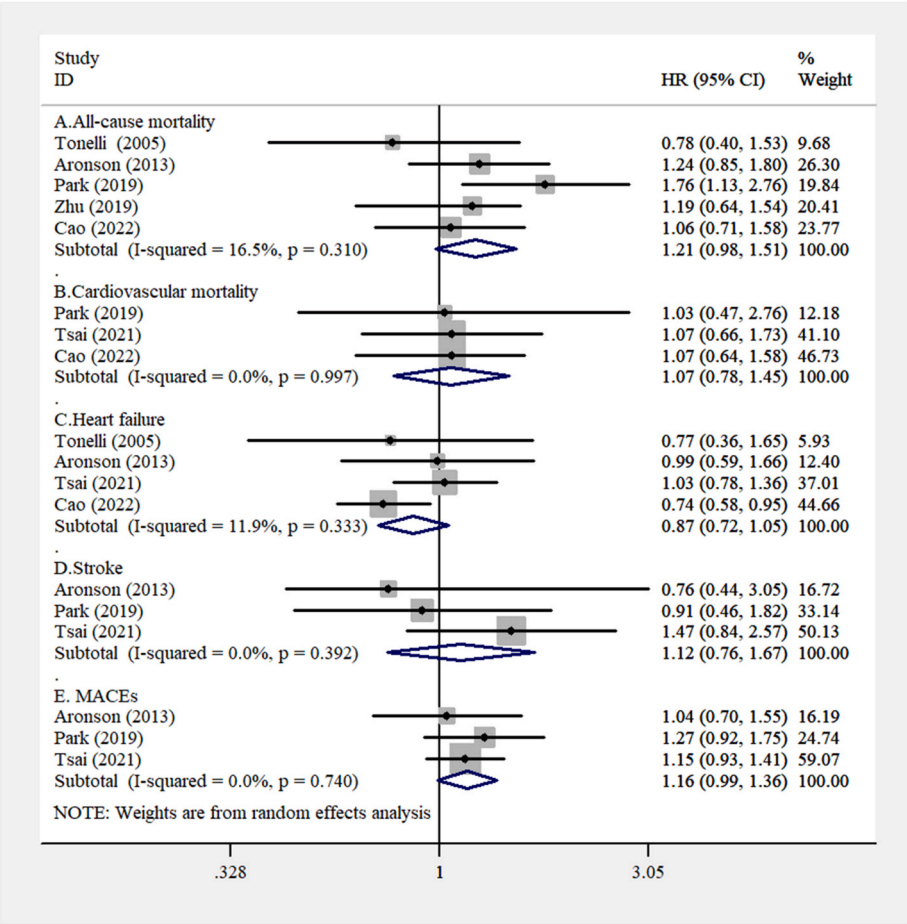

Fig. 3. Forest plots showing the pooled hazard ratios of all-cause mortality (A), cardiovascular mortality (B), heart failure (C), stroke (D), and major adverse cardiac events (E) for hypophosphatemia versus the reference normal phosphorus level.

4. Discussion

This is the first meta-analysis to evaluate the association of blood phosphorus level with adverse outcomes in patients with CAD. The main findings of the current meta-analysis suggested that hyperphosphatemia, but not hypophosphatemia, significantly predicted all-cause mortality, cardiovascular death, heart failure, and MACEs in patients with CAD, even after adjusting for traditional risk factors. When compared to those with the reference normal phosphorus level, CAD patients with hyperphosphatemia had a 39 % higher risk of all-cause mortality, a 37 % higher risk of cardiovascular death, a 64 % higher risk of heart failure, and a 39 % higher risk of MACEs. However, neither hypophosphatemia nor hyperphosphatemia significantly predicted the risk of stroke.

Our study is in accordance with an early meta-analysis that concluded only higher phosphorus level conferred a 20 % higher risk of mortality in dialysis patients, while no significant association was found between lower phosphorus levels and mortality [18]. Another meta-analysis indicated that both very high and very low level of phosphorus were significantly associated with a higher risk for all-cause mortality in patients with end-stage renal disease [19]. The current meta-analysis showed that hyperphosphatemia was significantly associated with an increased risk of all-cause mortality, while hypophosphatemia only exhibited a trend toward increasing mortality risk. The previous and our meta-analysis revealed a non-linear association between blood phosphorus level and mortality risk. Blood phosphorus level associated with unfavorable outcomes may have a J-shaped association, increasing at very low and very high level of phosphorus [16].

CAD involves a wide range of patients. However, it is largely unknown whether the prognostic values of hyperphosphatemia differ between patients with stable CAD and acute myocardial infarction. Our subgroup analysis revealed that the association of hyperphosphatemia with all-cause mortality appeared to be stronger in studies enrolling patients with acute myocardial infarction compared to those including stable CAD patients.

The causes of hypo- and hyperphosphatemia are numerous in humans [20]. Hypophosphatemia often arises from reduced intestinal absorption, increased renal excretion, vitamin D deficiency, or phosphate redistribution. In contrast, chronic hyperphosphatemia is primarily caused by chronic kidney disease, hypoparathyroidism, or excess 1,25-dihydroxyvitamin D.

The mechanisms underlying the relationship between elevated phosphorus levels and CAD outcomes are complex. Several factors may contribute to the adverse effects of hyperphosphatemia in CAD patients. First, elevated phosphorus level can promote coronary artery calcification [21,22], leading to arterial stiffening, reduced elasticity, and impaired blood flow. Second, high phosphorus levels can negatively impact endothelial function [8]. Third, elevated phosphorus can stimulate the release of pro-inflammatory cytokines, resulting in a chronic state of vascular inflammation [23] and exacerbating plaque instability [9]. Fourth, excess of phosphorus level is associated with left ventricular hypertrophy [24], increased carotid intima-media thickness [25], and subclinical coronary atherosclerosis [26], all of which can heighten the risk of adverse cardiovascular events. Finally, dysregulation of parathyroid hormone [18] and fibroblast growth factor 23 [27] due to elevated phosphorus level can disrupt calcium homeostasis, further increasing the risk of cardiovascular complications.

The findings of our meta-analysis have significant clinical implications for future research. Hyperphosphatemia is independently associated with an increased risk of adverse outcomes in patients with CAD. Measuring blood phosphorus levels may enhance risk stratification for CAD. Patients with elevated phosphorus levels should undergo close monitoring and intensive management. Future research is needed to clarify the specific biological mechanisms through which hyperphosphatemia contributes to negative cardiovascular outcomes and to identify optimal phosphorus level thresholds that predict adverse outcomes in CAD patients, taking into account factors such as renal function and other comorbidities. Additionally, randomized controlled trials are necessary to determine whether phosphate-lowering interventions can improve outcomes in CAD patients. Importantly, while hypophosphatemia has not been shown to predict adverse outcomes in CAD patients, understanding its effects and potential clinical significance could be valuable, particularly in specific patient populations.

Several potential limitations should be acknowledged in our meta-analysis. First, this analysis included a relatively small number of eligible studies, which limited our ability to perform subgroup analyses and assess publication bias. Therefore, additional well-designed studies with larger sample sizes are necessary. Second, most of the included studies were retrospective in design, which may introduce potential selection bias. More prospective cohort studies are needed to further validate our findings. Thirdly, the cutoff values for hypophosphatemia and hyperphosphatemia were not consistent across the included studies, making it challenging to apply the results clinically. Future research should utilize standardized thresholds for defining hypo- and hyperphosphatemia to enhance the validity of these findings. Fourth, blood phosphorus level is regulated by vitamin D, parathyroid hormone, and fibroblast growth factor-23. Failure to adjust for these factors may have led to an overestimation of risk. Fifth, significant heterogeneity was observed when pooling the association between hyperphosphatemia and MACEs. This heterogeneity may largely be due to variations in the definitions of MACEs, thresholds for hyperphosphatemia, CAD subtypes, or follow-up durations. Sixth, our ability to detect publication bias for all-cause mortality was limited by the inclusion of fewer studies than the recommended minimum number, and the statistical tests used to detect publication bias are potentially uncertain [28]. Finally, our study was not prospectively registered in the PROSPERO database, which detracts from its overall scientific integrity.

5. Conclusions

Hyperphosphatemia, but not hypophosphatemia, independently predicted all-cause mortality, cardiovascular mortality, heart failure, and MACEs in patients with CAD. Measuring blood phosphorus level may provide valuable prognostic information in these patients.

CRediT authorship contribution statement

Luyu Zhu: Writing – original draft, Visualization, Validation, Resources, Investigation, Formal analysis, Data curation. **Ziyan Liu:** Writing – original draft, Visualization, Validation, Resources, Investigation, Data curation. **Shiqi Zhang:** Writing – original draft, Visualization, Validation, Software, Resources, Investigation, Data curation. **Xiaoyan Wang:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization. **Yu Fan:** Writing – review & editing, Visualization, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38565.

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