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Prognostic value of soluble urokinase-type plasminogen activator receptor in coronary artery disease: A meta-analysis

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Abstract

Background: A potential inflammatory biomarker, soluble urokinase-type plasminogen activator receptor (suPAR) has been utilized to assist the prognostic assessment of coronary artery disease (CAD) patients; however, outcomes have been inconsistent. The prognostic relevance of suPAR as a predictor of CAD patient adverse outcomes was therefore examined.

Methods: Research articles published as of 1 January 2022 were retrieved from PubMed, Embase, the Web of Science and the Cochrane Library. All-cause mortality, cardiovascular mortality and other major cardiovascular events (nonfatal myocardial infarction, heart failure or stroke) were analysed as a subset of relevant studies' results. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for each study. The broad EQUATOR guidelines were conformed. Risk of bias was assessed with ROBINS-I tool.

Results: In total, this analysis included nine studies including 14,738 CAD patients. All included studies made a correction for certain potential confounders. However, risk of bias ranged from moderate to critical. When the ROBINS-I tool was used. Patients with CAD that exhibited increased suPAR levels had a substantially higher risk of all-cause mortality (HR = 2.24; 95% CI 1.97–2.55) or cardiovascular mortality (HR = 2.02; 95% CI 1.58–2.58), but not of developing other major cardiovascular events (HR = 1.63; 95% CI 0.86–3.11). Considerable heterogeneity across studies was observed in our meta-analyses, but no significant publication bias was detected.

Conclusion: In patients with coronary disease, suPAR may have prognostic value for both all-cause and cardiovascular mortality but not for other major cardiovascular events.

KEYWORDS
coronary artery disease, meta-analysis, prognosis, soluble urokinase-type plasminogen activator receptor

1 | INTRODUCTION

Patients with coronary artery disease (CAD) have a significantly increased risk of mortality and secondary cardiovascular event incidence, making CAD a major contributor to mortality and morbidity.[1] The ability to reliably predict future cardiac event incidence in CAD patients is essential for their effective care and for the more appropriate allocation of limited healthcare resources. While many prognostic factors have been linked to CAD incidence and associated patient outcomes for use in clinical practice including age and underlying disease, the ability to reliably predict these future disease-related outcomes remains difficult.[2]

Several different biomarkers have been explored as promising tools capable of aiding in the diagnosis and prognostic evaluation of CAD patients. In the circumstances of systemic inflammation and immune system activation, the soluble urokinase-type plasminogen receptor (suPAR) is significantly increased.[3] The release of suPAR into system circulation occurs under conditions of low-grade inflammation owing to the cleavage of cell surface uPAR, which is a connexin expressed on podocytes, smooth muscle cells, endothelial cells and inflammatory cells. Both membrane-bound and soluble uPAR play important roles in the regulation of plasminogen activation pathway activity and integrin-mediated cell signalling that influences proliferative, migratory and adhesive activity. SuPAR is readily detectable in many human biofluids including the blood, urine and ascites, with levels generally remaining consistent throughout the day.[4] Many recent studies have shown higher suPAR levels to be linked with poorer CAD patient outcomes for both individuals affected by stable angina and acute coronary syndrome (ACS).[5] However, these findings are not universal and some controversy remains regarding the prognostic relevance of suPAR in CAD. Accordingly, the present meta-analysis was conducted with the goal of assessing the prognostic utility of suPAR as a predictor of adverse CAD patient outcomes.

2 | METHODS

This meta-analysis followed the rules established by the Meta-Analysis of Observational Studies in Epidemiology,[6] and the search procedure was registered in PROSPERO (CRD42022322354). Reporting of the study conforms to broad EQUATOR guidelines.[7]

2.1 | Literature search

Relevant papers published between 1 January 2022 and the date were systematically searched for in PubMed, Embase, Web of Science and the Cochrane Library using the following search criteria: 'suPAR' OR 'soluble urokinase-type plasminogen activator receptor' AND 'coronary artery disease' OR 'coronary heart disease' OR 'acute coronary syndromes' OR 'myocardial infarction' OR 'anginas'. For full details regarding the database-specific search strategies employed, see Appendix S1.

2.2 | Study selection

Only studies that met the following criteria were included in the analysis: (1) prospective cohort studies; (2) studies of any types of CAD patients (including those with stable angina and acute coronary syndrome); (3) analyses of circulating suPAR levels; and (4) studies reporting at least one of the following outcome endpoints: all-cause mortality, cardiovascular mortality and other major cardiovascular events (OMCE) such as nonfatal myocardial infarction, heart failure and stroke; (5) articles with respective suPAR cut-off thresholds used to group patients into subsets with lowest and highest levels of circulating suPAR together with hazard ratios (HRs) and 95% confidence intervals (CIs) for both of these groups. Research was not included if it: (1) assessed suPAR as a continuous variable; or (2) failed to provide HRs and 95% CIs and these values could not be calculated. If the same cohort was included in more than one study, the article with the larger cohort size was included in this analysis. Figure 1 shows the selection procedure.

2.3 | Data extraction and quality evaluation

Two researchers checked the quality and retrieved data from the studies that met the criteria separately. The use of a third investigator helped reach a consensus and settle any disagreements. Extracted data included the following: first author, publication year, country, study design, mean patient age, the proportion of male patients, sample size, CAD patient type, follow-up duration, outcome determinations, suPAR cut-off value, number of events, multivariate-adjusted HRs and variable adjustment. Study quality was evaluated with the Newcastle–Ottawa scale (NOS), with studies scoring six or more starts being considered of high quality.[8] Bias risk was assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.[9]

2.4 | Statistical analysis

STATA 16.0 was used for all statistical analyses. All-cause mortality, cardiovascular mortality and OMCE incidence

FIGURE 1 Study selection flow chart. Abbreviation: suPAR—soluble urokinase-type plasminogen activator receptor.
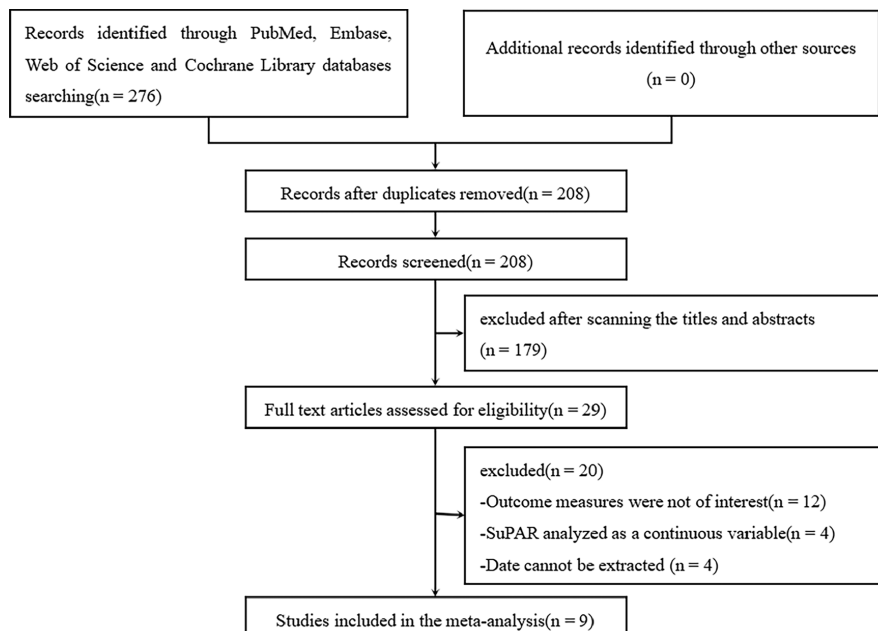
were compared between patients in the highest and lowest suPAR groupings, and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported for each comparison. Both the Cochrane Q test and the I^2 statistic were used to assess the degree of heterogeneity across studies.

Following the identification of heterogeneity ($I^2 > 50\%$ or $p < 0.10$), random-effects models were implemented, whereas fixed-effects models were otherwise utilized. Subgroup analyses were conducted based on the country in which studies were conducted, sample size, CAD type, years of follow-up and C-reactive protein (CRP) adjustment. Sensitivity analyses were conducted via a leave-one-out approach pooled analysis stability. To assess the possibility of publication bias, we employed Egger's test and performed a trim-and-fill analysis if any findings were significant at the $p \le 0.05$ level.

3 | RESULTS

3.1 | Study selection

From the original pool of 208 papers discovered via the literature search, only 29 were considered worthy of a full-text read and 9[10–18] were finally included in this meta-analysis. All studies were considered of high quality, with NOS scores of six stars or higher. However, risk of bias ranged from moderate to critical when the ROBINS-I tool was used. The main study characteristics and quality scores are compiled in Table 1. The details of study quality results were included in Appendix S1. Risks of bias of cohort studies are assessed in Table 2.

3.2 | The association between suPAR levels and all-cause mortality

Eight studies provided all-cause mortality rates.[10–17] The degree of heterogeneity for this outcome was found to be very high ($I^2 = 96.0\%$; $p = 0.000$). When comparing patients in the highest and lowest suPAR categories, the pooled HR for all-cause mortality was 2.24 (95% CI 1.97–2.55). (Figure 2). Sensitivity analyses yielded comparable results, as shown in Appendix S1. As the study conducted by Mehta et al.[10] appeared to be a significant outlier in these analyses, sensitivity analyses were also performed by excluding this study, yielding a reduced pooled HR for all-cause mortality of 1.89 (95% CI 1.39–2.57), suggesting that while this study, which had the largest sample size, somewhat influenced these results, the overall conclusions remained stable. The pooled HR by excluding Mehta (2020) was shown in Appendix S1.

Subgroup analyses were conducted based on country, sample size, CAD patient type, follow-up years and CRP adjustment (Table 3). Higher suPAR levels were consistently related to a higher risk of all-cause mortality regardless of these covariates, as shown by the significant differences between the highest and lowest suPAR patient subgroups.

3.3 | The association between suPAR levels and risk of cardiovascular mortality

The results of four research included cardiovascular mortality as an endpoint.[10,12,15,18] Although considerable heterogeneity was identified for this endpoint ($I^2 = 96.7\%$;

TABLE 1 Main characteristics and quality scores of the included studies

Author/year	Region	Study design	patients	Sample size (% men)	Age (years)	SuPAR cut-off value	Follow-up (years)	Definition of OMCE	Events (No.) HR (95% CI)	Adjustment for variables	NOS score
Eapen 2014	Europe	P	All CAD	2323 (64.0)	63.0±11.9	High vs. Low (≥3.5 vs. <3.5 ng/ml)	2.3	-	All-cause mortality (297) 1.52 (1.13–2.05)	Age, DM, Gensini score, aspirin use, clopidogrel use, acute MI at presentation, LVEF, BMI, hsCRP	6
Sommerer 2019	Germany	P	All CAD	2940 (68.4)	62.7±10.5	Tertiles 3 vs. 1 (≥3010 vs. <2250 pg/ml)	9.9	Nonfatal MI and admission for HF	All-cause mortality (873) 1.25 (1.14–1.38); Cardiovascular mortality (598) 1.22 (1.08–1.37); OMCE (90) 1.48 (0.64–3.43)	Age, sex, lipid lowering therapy, CAD status, BMI, DM, hypertension, smoking, LDL-C, HDL-C, log-triglycerides, eGFR, NT-proBNP, IL-6, CRP	8
Sörensen 2019	Germany	P	ACS	308 (64.4)	64.0 (51.0, 75.0)	Quartiles 4 vs. 1 (>4.8 vs. ≤2.3 ng/ml)	1.0	-	All-cause mortality (29) 6.22 (0.79–49.14)	Age, sex, diabetes, smoking, hyperlipoproteinaemia, SBP, hsT-I	8
Al-Badri 2020	USA	P	All CAD	556 (51.0)	57.0±10.0	High vs. Low (>2523 vs. ≤2523 pg/ml)	6.2	Cardiovascular mortality, myocardial infarction, new-onset HF hospitalization and stroke	All-cause mortality (38) 3.2 (1.8–5.7); OMCE (28) 2.7 (1.4–5.4)	Age, BMI, history of DM, history of hypertension, dyslipidaemia, statin therapy	7
Hodges 2020	Denmark	P	All CAD	1194 (76.9)	63.0±11.0	High vs. Low (>3.5 vs. ≤3.5 ng/ml)	4.2	—	All-cause mortality (177) 1.40 (1.03–1.90)	CRP, TnT, NT-proBNP, age, sex, hypertension, ever smoked, hypercholesterolemia, DM, aspirin use, clopidogrel use, statin use, family history of CAD, BMI, eGFR, number of stenotic vessels and prior MI or CABG	7

TABLE 1 (Continued)

Author/year	Region	Study design	patients	Sample size (% men)	Age (years)	SuPAR cut-off value	Follow-up (years)	Definition of OMCE	Events (No.) HR (95% CI)	Adjustment for variables	NOS score
Mehta 2020	USA	P	All CAD	4184 (63.0)	62.0±10.9	Quartiles 4 vs. 1 (>3929 vs. ≤2275 pg/ml)	5.2	-	All-cause mortality (795) 3.87 (2.93–5.12); Cardiovascular mortality(604) 3.87 (2.93–5.12)	Sex, age, race, DM, current smoking, hypertension, BMI, eGFR, history of CABG, HF, PAD, acute MI at enrolment, revascularization at enrolment and cardiovascular medication use	8
Nikorowitsch 2020	Germany	P	All CAD	1703 (78.4)	64.0 (56.0, 69.0)	Tertiles 3 vs. 1 (≥3.61 vs. <2.53 ng/ml)	3.5	-	Cardiovascular mortality (123) 1.61 (1.07–2.42)	Renal function, CRP, NT-proBNP, hsT-I	6
Peiró 2020	Spain	P	ACS	340 (72.8)	64.9 (55.7, 74.3)	High vs. Low (≥2.6 vs. <2.6 ng/ml)	6.0	Nonfatal MI and admission for HF	All-cause mortality (57) 2.3 (1.2–4.4) OMCE (102) 1.7 (1.1–2.5)	Age, GRACE score, eGFR, cardiac troponin I peak and LVEF <40%	7
Sandø 2020	Denmark	P	ACS	1190 (75.7)	62.0±12.0	Quartiles 4 vs. 1 (≥3.7 vs. <2.4 ng/ml)	3.0	-	All-cause mortality (85) 3.06 (1.94–4.70) Cardiovascular mortality(47) 0.99 (0.18–5.30)	Age, Killip-class ≥2, history of HF, reinfarction	6

Abbreviations: ACS—acute coronary syndromes; BMI—body mass index; CAD—coronary artery disease; CABG—coronary artery bypass grafting; CI—confidence intervals; DM—diabetes mellitus; eGFR—estimated glomerular filtration rate; GRACE score—Global Registry of Acute Coronary Events score; HF—heart failure; HR—hazard ratio; HDL-C—high-density lipoprotein cholesterol; hsCRP—high-sensitivity C-reactive protein; hsT-I—high-sensitivity troponin I; IL-6—interleukin-6; LDL-C—low-density lipoprotein cholesterol; LVEF—left ventricular ejection fraction; MI—myocardial infarction; NOS—Newcastle–Ottawa Scale; NT-proBNP—N-terminal pro-brain natriuretic peptide; OMCE—other major cardiovascular events; P—prospective; PAD—peripheral arterial disease; SBP—systolic blood pressure.

TABLE 2 Risks of bias of cohort studies: ROBINS-I

Study/Bias domain	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result	Overall
Eapen 2014	Critical risk of bias. Not adjusted for sex, diabetes, smoking, etc.	Low risk of bias. Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias. Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias. Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information. No information on which to base a judgement on losses during the study period.	Low risk of bias. Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias. Participants selected from a larger group.	Critical risk of bias
Sommerer 2019	Moderate risk of bias. Adjusted for certain important confounders. But there may still be variables unbalanced.	Low risk of bias. Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias. Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias. Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information. No information on which to base a judgement on losses during the study period.	Low risk of bias. Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias. Participants selected from a larger group.	Moderate risk of bias
Sörensen 2019	Moderate risk of bias. Adjusted for certain important confounders. But there may still be variables unbalanced.	Low risk of bias. Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias. Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias. Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	Low risk of bias. The follow-up rate was 99.8%.	Low risk of bias. Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias. Participants selected from a larger group.	Moderate risk of bias
Al-Badri 2020	Critical risk of bias. Not adjusted for sex, smoking, etc.	Low risk of bias. Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias. Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias. Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information. No information on which to base a judgement on losses during the study period.	Low risk of bias. Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias. Participants selected from a larger group.	Critical risk of bias
Hodges 2020	Moderate risk of bias. Adjusted for certain important confounders. But there may still be variables unbalanced.	Low risk of bias. Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias. Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias. Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information. No information on which to base a judgement on losses during the study period.	Low risk of bias. Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Low risk of bias. All patients admitted to study cohort were analysed.	Moderate risk of bias

TABLE 2 (Continued)

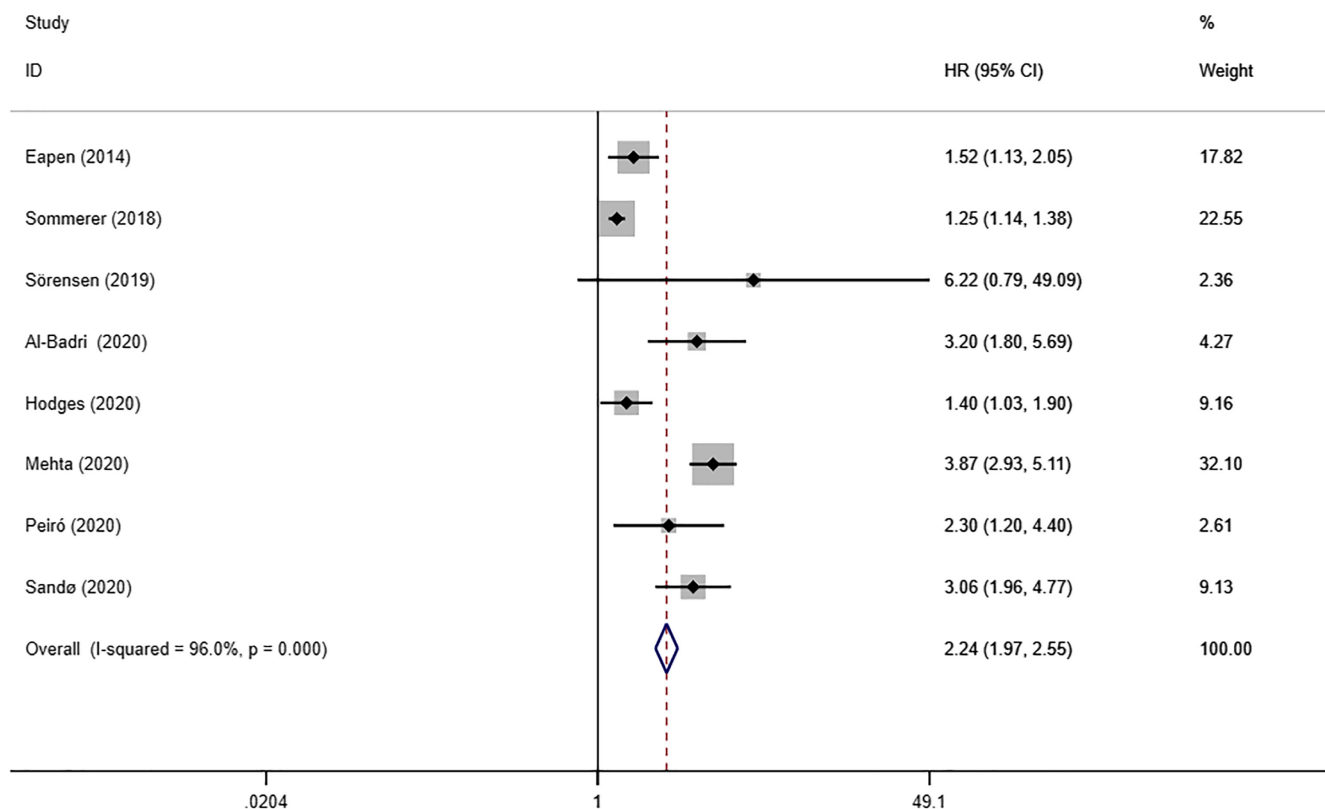| Study/Bias domain	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result	Overall
Mehta 2020	Moderate risk of bias Adjusted for certain important confounders. But there may still be variables unbalanced.	Low risk of bias Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information No information on which to base a judgement on losses during the study period.	Low risk of bias Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias Participants selected from a larger group.	Moderate risk of bias
Nikorowitsch 2020	Critical risk of bias Not adjusted for age, sex, smoking, etc.	Low risk of bias Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information No information on which to base a judgement on losses during the study period.	Low risk of bias Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias Participants selected from a larger group.	Critical risk of bias
Peiró 2020	Critical risk of bias Not adjusted for sex, smoking, etc.	Low risk of bias Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information No information on which to base a judgement on losses during the study period.	Low risk of bias Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Low risk of bias All patients admitted to study cohort were analysed.	Critical risk of bias
Sando 2020	Critical risk of bias Not adjusted for sex, smoking, etc.	Low risk of bias Prospective study; start of follow-up coincide for most participants.	Moderate risk of bias Criteria used to define the exposure were described. However, it is not certain that the exposure information was recorded when the exposure began.	Moderate risk of bias Exposure levels may have changed during the study period, but no correction, for example, multiple measurements, was done.	No information No information on which to base a judgement on losses during the study period.	Low risk of bias Objective outcome assessed could less likely to be influenced by knowledge of the prognostic factor.	Moderate risk of bias Participants selected from a larger group.	Critical risk of bias

Study ID		HR (95% CI)	% Weight
Eapen (2014)		1.52 (1.13, 2.05)	17.82
Sommerer (2018)		1.25 (1.14, 1.38)	22.55
Sörensen (2019)		6.22 (0.79, 49.09)	2.36
Al-Badri (2020)		3.20 (1.80, 5.69)	4.27
Hodges (2020)		1.40 (1.03, 1.90)	9.16
Mehta (2020)		3.87 (2.93, 5.11)	32.10
Peiró (2020)		2.30 (1.20, 4.40)	2.61
Sandø (2020)		3.06 (1.96, 4.77)	9.13
Overall (I-squared = 96.0%, p = 0.000)		2.24 (1.97, 2.55)	100.00

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FIGURE 2 Forest plots for pooled HRs pertaining to CAD patient risk of all-cause mortality

TABLE 3 All-cause mortality subgroup analyses

Subgroup	No. of studies	Pooled HR	95% CI	Heterogeneity between studies
Origin of patients				
Europe	6	1.66	1.44–1.92	$p = 0.000$; $I^2 = 89.0\%$
USA	2	3.78	2.93–4.89	$p = 0.054$; $I^2 = 0.0\%$
Sample size				
≤1000	3	3.46	1.86–6.42	$p = 0.389$; $I^2 = 0.0\%$
>1000	5	2.14	1.88–2.44	$p = 0.000$; $I^2 = 97.4\%$
CAD patient type				
All CAD	5	2.11	1.85–2.40	$p = 0.000$; $I^2 = 97.3\%$
ACS	3	3.27	2.05–5.20	$p = 0.453$; $I^2 = 0.0\%$
Follow-up years				
≤5	4	1.92	1.53–2.41	$P = 0.008$; $I^2 = 74.9\%$
>5	4	2.47	2.11–2.89	$P = 0.000$; $I^2 = 98.5\%$
CRP adjustment				
Yes	3	1.37	1.20–1.56	$p = 0.135$; $I^2 = 50.0\%$
No	5	3.63	2.90–4.55	$p = 0.537$; $I^2 = 0.0\%$

Abbreviations: ACS—acute coronary syndromes; CAD—coronary artery disease; CI—confidence intervals; CRP—C-reactive protein; HR—hazard ratio.

$p = 0.000$), the aggregate hazard ratio (HR) for cardiovascular mortality was 2.02 (95% CI 1.58–2.58) for patients in the highest and lowest suPAR groups (Figure 3). Sensitivity analyses did not reveal any significant change in pooled results, as shown in Appendix S1. When the study conducted by Mehta et al.[10] was excluded, the pooled HR decreased to 1.25 (95% CI 1.11–1.40). The pooled HR by excluding Mehta (2020) was shown in Appendix S1.
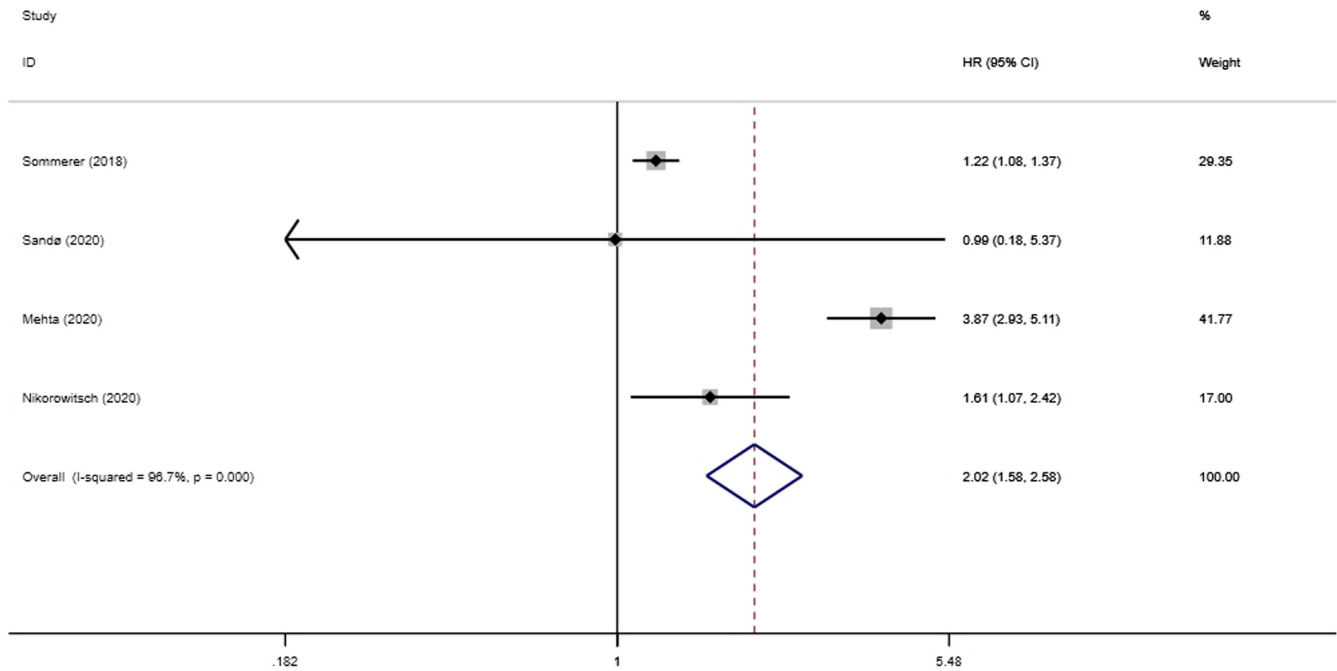
FIGURE 3 Forest plots for pooled HRs pertaining to CAD patient risk of cardiovascular mortality

3.4 | The association between suPAR levels and risk of OMCE incidence

OMCE incidence was reported as a study endpoint in three studies.[11,13,15] Fixed-effects modelling showed that there was no substantial heterogeneity across these trials ($I^2 = 9.8\%$; $p = 0.330$). The combined HR for OMCE incidence was 1.63 (95% CI 0.86–3.11) for comparisons of patients in the highest and lowest suPAR groups (Figure 4).

3.5 | Publication bias analyses

As this study incorporated fewer than 10 publications, funnel plot tests were not conducted. The Egger's test p-value for all three endpoints was greater than 0.05, as shown in Appendix S1, consistent with a lack of any publication bias having affected these results.

4 | DISCUSSION

This study used a meta-analysis approach to investigate whether individuals with coronary artery disease (CAD) who had elevated circulating suPAR levels were more likely to have adverse outcomes. This analysis ultimately included nine prospective observational studies enrolling 14,738 patients. As substantial heterogeneity was observed for certain endpoints, subgroup analyses were performed based on the country of origin, sample size, CAD patient type, years of follow-up and CRP adjustment reported in

these different studies. Higher suPAR levels in individuals with CAD provide value as an independent predictor of both all-cause mortality and cardiovascular mortality, and this association persisted even in these subgroup analyses. Patients in highest suPAR cohort had a 124% and 102% increased risk of all-cause mortality and cardiovascular mortality, respectively, compared to those in the lowest suPAR segment. As such, suPAR offers promise as a prognostic biomarker in CAD patients.

Atherosclerosis is characterized by persistent inflammation,[19] and chronic low-grade inflammatory activity is known to be a risk factor for adverse cardiovascular outcomes.[20] Circulating suPAR levels offer utility as a biomarker of ongoing inflammation in humans and have been reported to be of value as a tool for predicting poor CAD patient prognosis. In one recent review exploring the validity and utility of suPAR as a biomarker in cardiac disease patients, for example, suPAR levels were linked to poor CAD patient prognostic outcomes,[5] although no quantitative analyses were performed. In contrast to this prior review, which was based on a combination of prospective and retrospective data, the present meta-analysis has several advantages. For one, this is the first quantitative assessment of the prognostic utility of suPAR in CAD patients. In addition, only prospective studies were incorporated in these analyses, given that a prospective approach is best suited to the reliable identification and evaluation of biomarkers of interest.

Many different biomarker candidates have been studied in an effort to stratify patients according to their levels of cardiovascular risk. Of these, CRP is perhaps the

best studied. Indeed, CRP is reportedly linked to poorer outcomes in individuals diagnosed with stable coronary disease.[21] Patients in the highest third of the CRP distribution had a 1.97 (95% CI 1.7–2.17) greater pooled relative risk of cardiovascular events, including fatal and nonfatal, compared to those in the lowest third.[22] However, this relative risk fell to 1.19 (95% CI 1.13–1.25) after adjustment for publication bias. Our meta-analysis suggests that suPAR may offer clinical value as a means of assessing the risk of adverse CAD patient outcomes independent of CRP given that higher suPAR levels were associated with rising all-cause mortality rates even in the CRP-corrected patient subgroup (HR = 1.37; 95% CI 1.20–1.56). In contrast to suPAR, CRP has been linked to patients' waist sizes and BMIs, whereas increased suPAR is connected with atherosclerotic plaques and an abnormal urine albumin/creatinine ratio.[23] As such,

both CRP and suPAR may be linked to distinct or overlapping inflammatory processes, ultimately converging in the context of atherogenesis such that both are related to CAD patient risk.

As suPAR cleavage from vascular cells depends on cell surface uPAR profiles, suPAR levels in patient samples are also related to uPAR expression and urokinase-type plasminogen (uPA) secretion. Functionally, uPAR and suPAR exhibit similar extracellular functional roles.[24] A few articles have examined the potential role played by suPAR in the context of CAD pathogenesis. Inflammatory immune cell activation within the coronary arteries can initiate ACS incidence, and in these patients, suPAR levels can serve as a biomarker for the degree of inflammatory activity.[25] The cells that compose the walls of atherosclerotic arteries, including smooth muscle cells (SMCs), endothelial cells and macrophages, can express uPAR on their
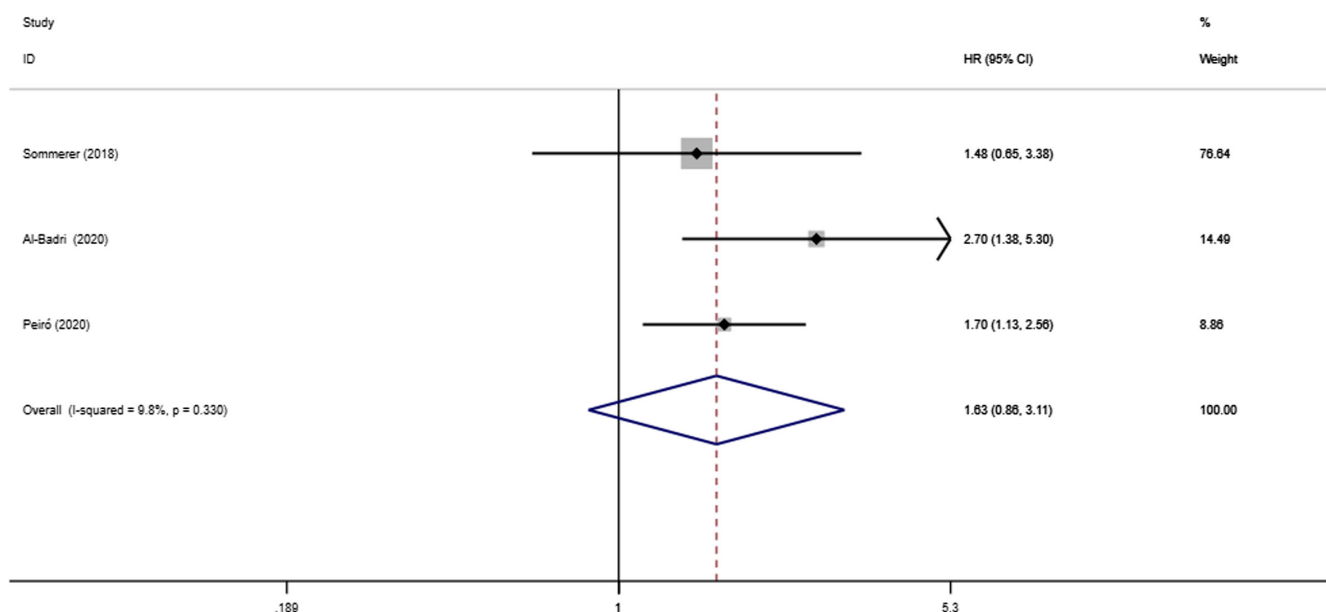

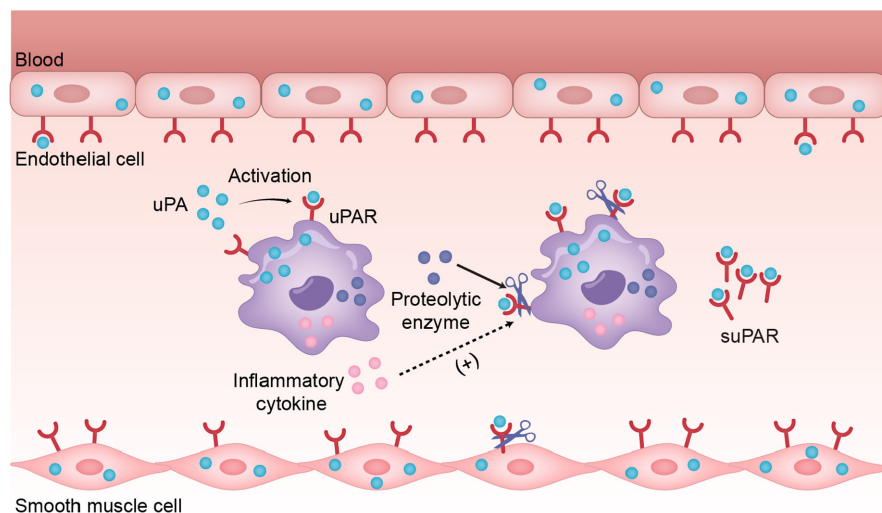**FIGURE 4** Forest plots for pooled HRs pertaining to CAD patient risk of OMCE incidence

FIGURE 5 SuPAR levels reflect the extent of inflammatory activity

surfaces and secrete uPA. Ongoing arterial inflammation can further attract inflammatory macrophages that produce proinflammatory cytokines and proteolytic enzymes capable of cleaving uPAR, thereby increasing circulating suPAR levels and propagating this inflammatory process[26] (Figure 5). Hyperactivation of the uPA-uPAR can cause severe plasmin proteolysis-mediated tissue damage that can be life-threatening in some cases. While minimal levels of uPA expression are evident in vascular walls and cardiac tissue under homeostatic conditions, with plasminogen activator-inhibitor 1 (PAI1) serving to constrain uPA activity, a pronounced rise in uPA expression is evident under atherosclerotic conditions, particularly in infiltrating inflammatory cells. Such uPA overexpression exceeds the inhibitory capacity of PAI1, leading to the activation of uPA-mediated proteolytic activity via binding to uPA that can drive the destruction of collagen and elastic fibres, contributing to an elevated risk of fatal cardiac rupture and/or aneurysmal dilation[27] (Figure 6). Such uPA-uPAR system hyperactivation can also further contribute to atherosclerotic disease progression. During the initial stages of atherosclerosis, monocytes adhere to the activated endothelium, secreting uPA that signals through uPAR to promote cellular activation conducive to the further migration of monocytes to the subendothelial cell layer where they can differentiate into macrophages. The atherogenic activity of macrophages can be further augmented by uPA through increases in NADPH oxidase-dependent oxidative stress and the augmentation of cholesterol biosynthesis, ultimately resulting in lipid accumulation and foam cell formation. The proliferation and migration of vascular SMCs occurs during the advanced stages of atherosclerosis, with the secretion of uPA by intimal macrophages contributing to enhanced uPAR-mediate SMC migration, extracellular matrix adhesion, proliferation and oxidation[24] (Figure 7). However, the specific role that suPAR

FIGURE 6 Plasmin proteolysis resulting from uPA-uPAR system hyperactivation can cause life-threatening tissue damage
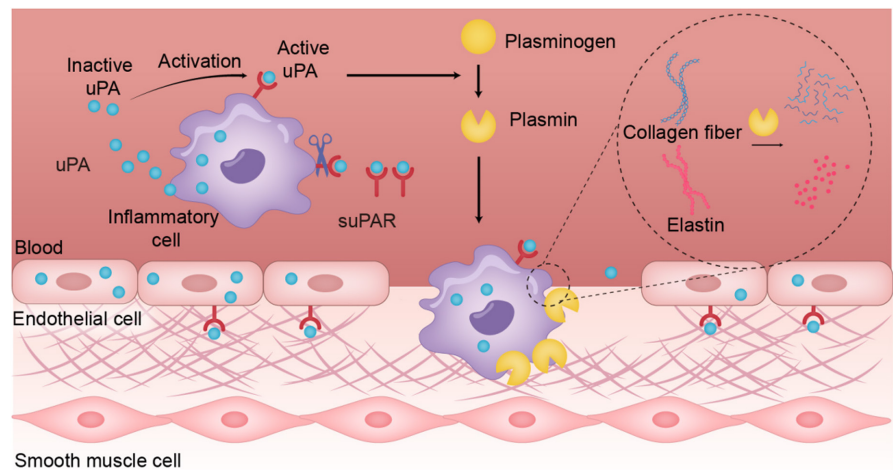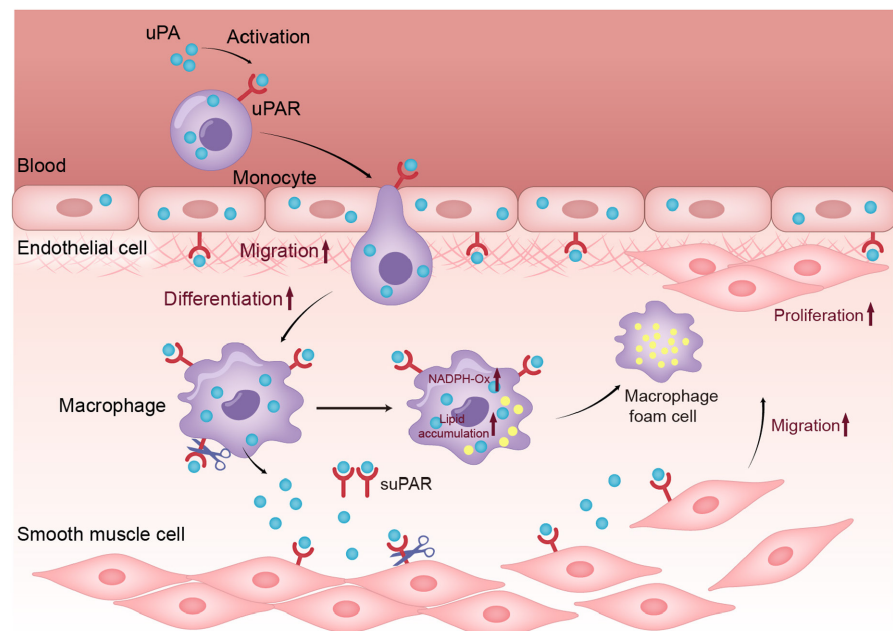

FIGURE 7 Atherosclerotic progression is driven in part by uPA-uPAR system hyperactivation

plays in the context of CAD development warrants further research in an effort to determine whether targeting uPAR or suPAR can improve prognostic outcomes in this patient population.

This meta-analysis is subject to multiple limitations. For one, as all included studies were observational in nature, it is not possible to exclude the potential impact of selection or recall bias on these results. The risk of bias ranged from moderate to critical by ROBINS-I tool, which prevent us to establish a reliable conclusion based upon these findings. Secondly, all studies employed distinct suPAR cut-off threshold values, making it impossible to establish an optimal threshold for further validation. Third, the comprehensiveness of the search can be compromised keeping in mind the following reasons: (1) the truncation was not used in search strategies, (2) the lack of any search protocol for grey literature and (3) the failure to review the reference sections for included studies. Additionally, the number of studies included in the study was limited, especially for the cardiovascular mortality and OMCE outcomes, which might make the conclusions less reliable.

5 | CONCLUSION

In summary, these findings imply that increased suPAR levels are independently associated with an increased risk of both all-cause mortality and cardiovascular mortality in individuals with CAD. However, owing to the limitations outlined above, additional validation will be critical to confirm the findings of this study, particularly for the endpoints exhibiting significant heterogeneity.

AUTHOR CONTRIBUTIONS
Yang Li and Qiang Xiang conceived the analysis. The data were extracted by Yang Li and Yaqun Ding independently. Yinjie Zhao and Yongqing Gui analysed and interpreted the data. Qiang Xiang gave us great guidance throughout the whole process. Yang Li drafted the initial manuscript. Yajing Shen and Qiang Xiang revised the manuscript for important intellectual content.

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CONFLICT OF INTEREST
None.

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SUPPORTING INFORMATION

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