Cardiology Journal

VIA MEDICA

ORIGINAL ARTICLE

DOI: 10.5603/cj.96228

ISSN 1897–5593
eISSN 1898–018X

Diagnostic value of soluble urokinase-type plasminogen activator receptor in patients with acute coronary syndrome: A systematic review and meta-analysis

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Abstract

Background: *In contemporary clinical practice, there is an increasing need for new clinically relevant biomarkers potentially optimizing management strategies in patients with suspected acute coronary syndrome (ACS). This study aimed to determine the diagnostic utility of soluble urokinase-type plasminogen activator receptor (suPAR) levels in individuals with suspected ACS.*

Methods: *A literature search was performed in Web of Science, PubMed, Scopus, and the Cochrane Central Register of Controlled Trials databases, for studies comparing suPAR levels among patients with and without ACS groups. The methodological quality of the included papers was assessed using the Newcastle-Ottawa Scale. A fixed-effects model was used if $I^2 < 50\%$; otherwise, the random-effects model was performed.*

Results: *Five studies with 3417 participants were included in the meta-analysis. Pooled analysis showed that mean suPAR levels in the ACS group were statistically significantly higher than in the control group (3.56 ± 1.38 vs. 2.78 ± 0.54 ng/mL, respectively; mean difference: 1.04; 95% confidence interval: 0.64–1.44; $I^2 = 99\%$; $p < 0.001$).*

Conclusions: *In the context of ACS, suPAR is a potential biomarker for the early identification of medical conditions in individuals who are being treated in emergency rooms.* (Cardiol J)

Key words: soluble urokinase plasminogen activator receptor, suPAR, acute coronary syndrome, ACS, biomarker, meta-analysis

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Received: 26.06.2023 Accepted: 19.08.2023 Early publication date: 26.09.2023

Introduction

Globally, an estimated 7 million persons are diagnosed with acute coronary syndrome (ACS) yearly [1]. ACS refers to a group of thrombotic coronary artery diseases (CAD) that include unstable angina (UA), myocardial infarction with ST-segment elevation (STEMI), and myocardial infarction without ST-segment elevation (NSTEMI) [2]. The differentiation between STEMI and NSTEMI is crucial in applying appropriate treatment according to guidelines [3–5].

In past decades cardiac troponin (cTn) emerged as a potent and widely used biomarker of myocardial infarction (MI) [6]. Elevated cTn values are still required to diagnose MI according to the Fourth Universal Definition of Myocardial Infarction published in 2018. Moreover, the change (rise or fall) in the cTn level is needed to diagnose the acute nature of MI [7]. Despite the undeniable usefulness of cTn in MI diagnosis, some drawbacks significantly limit its infallibility. First, cTn is a biomarker of myocardial necrosis. Thus, it is elevated in STEMI and NSTEMI but may not be increased in UA patients, who should also be diagnosed with ACS [8]. Next, despite the high sensitivity of cTn, its specificity hovers around 80% because it can also be elevated in other conditions [9]. Last, the increase in cTn levels following MI may be observed even after more than 4 hours [10], significantly limiting early revascularization crucial in STEMI.

The above limitations of cTn advocate the search for novel diagnostic biomarkers of ACS that could complement cTn in the areas where its usefulness is limited, particularly at an early stage of ACS, among patients with renal dysfunctions, and cardiac conditions other than ACS. Extensive research in this field will eventually establish an ACS biomarker mini-panel. Many molecules have been investigated as potential biomarkers in ACS [11]. Heart-type fatty acid-binding protein (H-FABP) was extensively evaluated and gave hope for an early diagnosis of AMI. Nevertheless, a meta-analysis showed that H-FABP had limited usefulness alone [12]. Copeptin is another important biomarker widely studied in terms of AMI diagnosis. It was established to diagnose AMI early after the onset of symptoms, even though cTn was still negative. The most efficient combination of both biomarkers was copeptin and cTn, which had a very high negative predictive value [13, 14]. More recently, microRNAs (miRs) have been comprehensively investigated in various cardiovascular conditions, including ACS [15–17]. Ling et al. [18] demonstrated that patients with ACS had higher levels of miR-21 and miR-126 than healthy controls. MicroRNAs play a diagnostic role; they were established as potential prognostic and treatment-predictive biomarkers in many cardiovascular conditions [19–22].

Another potential diagnostic biomarker in ACS is soluble urokinase plasminogen activator receptor (suPAR) because of its involvement in inflammatory processes essential for plaque formation in ACS [23, 24]. It can be detected in different body fluids, including blood, plasma, serum, urine, and cerebrospinal fluid. suPAR is primarily found in plasma. When collecting blood for suPAR measurement, anticoagulants such as ethylenediaminetetraacetic acid (EDTA), citrate, or heparin are commonly used to prevent clotting and preserve the plasma [25]. suPAR is formed from urokinase plasminogen activator receptor (uPAR), a protein linked to the cell membrane by glycosylphosphatidylinositol, which can be cut off from the cell surface, resulting in the release of a soluble form called soluble urokinase plasminogen activator receptor (suPAR). uPAR is mainly found in immune, endothelial, and smooth muscle cell membranes [26]. Due to the predominant presence of uPAR on immune cells, suPAR may be elevated in conditions with inflammation [27]. suPAR was shown to be associated with different diseases, including the recently widespread coronavirus disease 2019 (COVID-19), in which suPAR levels are elevated and may predict mortality [28]. Importantly, suPAR levels were shown to predict cardiovascular mortality and morbidity as assessed in the general population [29]. suPAR was indicated as a promising prognostic biomarker in emergency patients with ACS (Fig. 1) [30].

Ischemic symptoms, abnormalities on an electrocardiogram, and an increase in blood biomarkers were generally required to make a diagnosis of ACS. However, the symptoms are sometimes rather unusual or absent, and around 33% of patients who arrive at the hospital's emergency department with a MI may not be experiencing chest pains [31]. Similarly, alterations in an electrocardiogram that aid in early diagnosis may be insufficient or completely absent in around 40% of individuals [32]. Furthermore, anomalies in the ST segment may be detected in other cardiac conditions, such as pericarditis, left ventricular hypertrophy, cardiomyopathies, and channelopathies, which may add to difficulties in diagnosis of the illness. As a result of these concerns, we must find the most suitable and reliable biomarker for early diagnosis, prognosis, and classification of ACS patients to enhance the

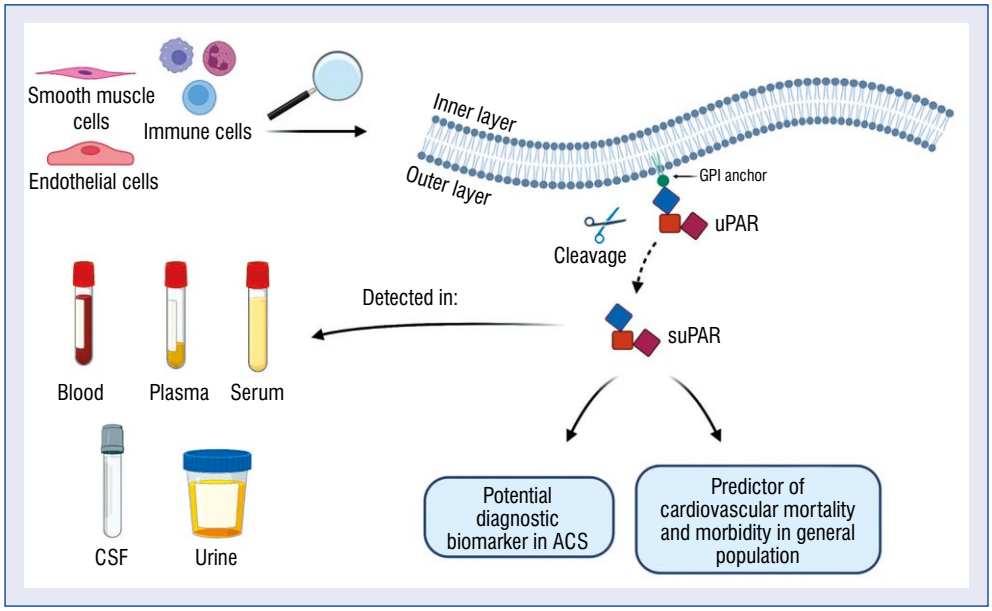

Figure 1. The potential utility of soluble urokinase plasminogen activator receptor (suPAR) in acute coronary syndrome (ACS); CSF — cerebrospinal fluid; GPI — glycosyl-phosphatidylinositol; uPAR — urokinase plasminogen activator receptor.

treatment that these patients get and to ensure the best possible outcome. This systematic review and meta-analysis were conducted to highlight suPAR as a developing ACS biomarker that can be categorized according to its clinical value and function in diagnosing ACS.

Methods

This meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33], and we pre-registered its protocol with PROSPERO (CRD42023431413).

Search strategy and study selection

From January 1st, 2000, to June 16th, 2023, we conducted a comprehensive systematic literature search in the following medical electronic databases: Web of Science, PubMed, Scopus, and the Cochrane Central Register of Controlled Trials, to find papers investigating the diagnostic significance of suPAR in adults with ACS. In addition to the online database search, Google Scholar was employed. A distinct and appropriate search strategy was employed for each source. We were looking for the following terms: "su-PAR" OR "soluble urokinase plasminogen activator receptor" AND "acute coronary syndrome" OR "ACS" OR "STEMI" OR "ST-elevation myocardial infarction" OR "NSTEMI" OR "non-ST-elevation myocardial infarction" OR "myocardial infarction" OR "MI" OR "UA" OR "unstable angina". In addition, we also manually reviewed the reference lists of relevant articles for potential studies. EndNote (version X7; Thomson Reuters) was used to manage the search results. Following an initial search, the duplicate results were deleted.

Two reviewers (M.P. and N.L.B.) independently examined the search criteria and compared the titles and abstracts of the publications found by the databases. The same reviewers then independently examined the full texts of all possibly relevant publications. If there was a disagreement on which literature papers to select, it was resolved with the assistance of another reviewer (L.S.).

Eligibility criteria

All research studies that matched the following criteria were included: (1) cross-sectional or cohort studies; and (2) comparisons of suPAR levels between ACS and control patients. The following were the exclusion criteria: (1) children or pregnant women; (2) reviews; (3) editorials, letters, and conference papers; and (4) non-English-language research.

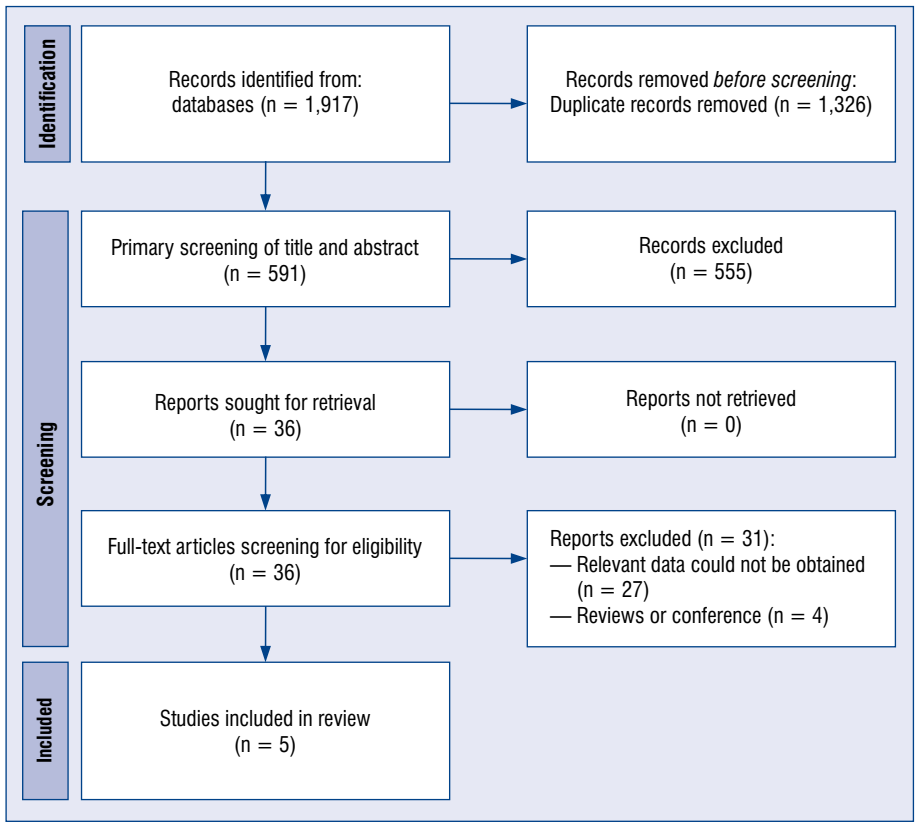

Figure 2. Flowchart detailing selection and screening of the studies included in this review.

Data extraction

Two investigators (M.M. and M.P.) worked separately to choose studies that matched the aforementioned inclusion criteria. Any disagreements were resolved through discussion or referral to a third author (A.N.). Two different writers extracted the data using the standardized form. First author's name, year of publication, research origin, sample size, proportion of male subjects, age, study design, and suPAR levels among study groups were retrieved.

Risk of bias assessment

Five reviewers (M.P., L.S., N.L.B., F.C., and Z.R.) independently assessed the risk of bias in the individual studies. Inconsistencies were resolved through the consensus of all researchers.

First, the methodological quality of the included papers was assessed using the Newcastle-Ottawa Scale (NOS) [34]. The NOS evaluates each publication based on three general criteria: "selection of study groups," "comparability of study groups," and "determination of either the exposure or outcome of interest for case-control or cohort studies," respectively. As a result, NOS can quantify article biases such as selection and information bias. The quality of the papers spans from poor (0–4) to moderate (5–6) to high (7-9), signifying 3 distinct degrees of research quality.

In addition, we performed a sensitivity analysis in which we attempted to eliminate one research study at a time from a meta-analysis, re-estimated the overall effect size, and compared it to the results of the meta-analysis prior to this exclusion. If the results before and after were not significantly different, it showed that a single study had no discernible influence on heterogeneity.

Statistical analysis

To perform a meta-analysis, Review Manager 5.4 (Copenhagen: The Cochrane Collaboration, 2014, Denmark) and Stata version 16 (StataCorp LP, Texas, USA) were used.

To assess suPAR levels, we used mean differences as the effect metric, with 95% confidence intervals (CIs). Hozo's approach was used to determine estimated means and standard deviations when suPAR values were reported as medians with an interquartile range [35]. Cochran's Q statistics and Higgins' index (I^2) were used to calculate

heterogeneity, with 25%, 50%, and 75% representing moderate, substantial, and significant heterogeneity, respectively [36]. The fixed-effects model was used when $I^2 < 50\%$; otherwise, the random-effects model was used. If there were more than 10 trials in a single meta-analysis, Egger's test and funnel plots were employed to analyze possible bias, and funnel plot tests were used for asymmetry to investigate potential publication bias. All p values were calculated using a two-sided test and were defined as < 0.05.

Results

The search method produced 1917 items (Fig. 2). Due to duplication, 1326 papers were discarded, and 591 articles were further excluded following a preliminary evaluation of titles and abstracts, resulting in 36 research papers. Finally, 5 items from Austria, Germany, and Turkey remained [37–41]. The 5 included studies had available data on 3417 patients (1148 with ACS and 2269 in the control group). They were published between 2015 and 2022. The mean age of ACS patients was 63.9 ± ± 5.8 years, compared to 62.6 ± 4.2 years in the non-ACS patient group. The general characteristics of the studies are shown in Table 1. The methodologic quality of the included trials was low, as summarized in Table 1.

All 5 studies reported differences in suPAR values between ACS and non-ACS (control) patients. Pooled analysis showed that mean suPAR levels in the ACS group were 3.56 ± 1.38 ng/mL, compared to 2.78 ± 0.54 ng/ml for the control group (mean differences: 1.04; 95% CI: 0.64–1.44; $I^2 = 99\%$; $p < 0.001$; Fig. 3). The results from the sensitivity analysis did not alter the direction.

Discussion

The meta-analysis showed that the mean suPAR level for the ACS was 3.56 (1.38), and the mean suPAR level for the control group was 2.78 (0.54). The mean difference was 1.04 [0.64, 1.44]. This indicates that the average suPAR level increased after ACS statistically significantly compared to the control group. This fact is rationally explained by the pathomechanisms of ACS. Conducted studies have indicated that suPAR is involved in the pathogenesis of ACS. It is related to inflammation in the endothelium affected by the atherosclerotic process. suPAR also increases macrophage infiltration, leading to an increased pro-inflammatory response in the endothelium. In

Table 1. Baseline characteristics of studies included in the meta-analysis.

Study	Country	Acute coronary syndrome group			Control group			Newcastle-Ottawa Score
		No.	Age	Female sex	No.	Age	Female sex	
Can et al., 2015 [37]	Turkey	55	55.85 ± 11.26	10 (18.2%)	70	54.03 ± 6.89	22 (31.4%)	8
Nikorowitsch et al., 2020 [38]	Germany	626	62.5 ± 2.3	138 (22.0%)	1077	63.3 ± 2.2	230 (21.4%)	9
Schernthaner et al., 2017 [39]	Austria	118	63.5 ± 11.2	32 (27.1%)	76	62.9 ± 9.7	51 (67.1%)	8
Sörensen et al., 2019 [40]	Germany	308	67.5 ± 3.0	101 (32.8%)	1006	62.3 ± 4.2	367 (36.5%)	8
Topf et al., 2022 [41]	Austria	41	70.3 ± 4.3	37 (92.5%)	40	65.3 ± 4.7	38 (92.7%)	8

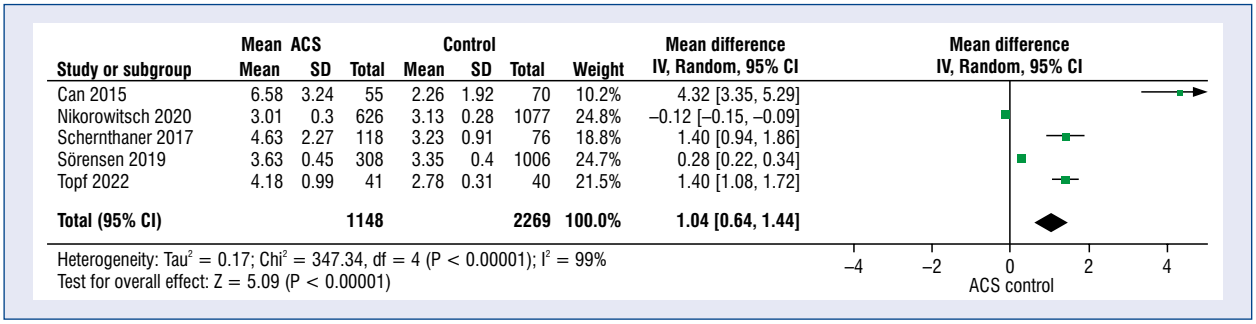

Figure 3. Forest plot of soluble urokinase plasminogen activator receptor (suPAR) values among patients with and without acute coronary syndrome (ACS). The center of each square represents the mean ratio for individual trials, and the corresponding horizontal line stands for the 95% confidence interval (CI). The diamonds represent pooled results; SD — standard difference.

addition, increased infiltration with macrophages promotes the formation of lipid-laden foam cells within plaques.

Moreover, when bound to cells bearing the uPAR receptor, plasminogen activators play a role in promoting fibrinolysis, tissue remodeling, and cell signaling. Consequently, an increase in the inflammatory reaction and an increase in the susceptibility of the atherosclerotic plaque to rupture, deepening its instability, is observed [23]. Based on the ACS pathophysiology, suPAR may be a valuable biomarker in cardiovascular diseases [42, 43].

Soluble urokinase plasminogen activator receptor has been studied as a potentially useful biomarker in patients diagnosed with a first acute MI (AMI) treated with percutaneous coronary intervention, and it is a good predictor of all-cause mortality and cardiovascular mortality [44]. Another analysis indicated that a suPAR level ≥ 3.5 ng/mL is an independent predictor of the risk of MI (hazard ratio [HR]: 3.2, $p < 0.0001$) and cardiovascular death (HR: 2.62; $p < 0.0001$). suPAR predicted not only the occurrence of CAD, but also the suPAR level correlated with the severity of CAD [45]. The suPAR level and advanced echocardiography turned out to be a good stratifier in patients diagnosed with diabetes but without heart disease (preserved left ventricular ejection fraction), allowing the selection of patients requiring intensified medical care [46]. A meta-analysis of patients with chronic kidney disease showed that in this patient population, elevated suPAR levels are also predictive of increased risk of cardiovascular disease ($p < 0.001$; HR: 3.06; 95% CI: 2.21–4.22; $I^2 = 0.0\%$). This prediction makes it possible, similarly to the population of patients with diabetes, to intensify the treatment and isolate the population requiring in-depth cardiological diagnostics [47].

In turn, another study showed a good correlation between the suPAR level and N-terminal-pro-B-type natriuretic peptide (NT-proBNP) concentration (and heart failure), but the suPAR level was not a predictor of atrial fibrillation [48]. An interesting phenomenon is a transient and initial increase in suPAR level after transcatheter aortic valve implantation. This increase is probably related to the implantation procedure itself, which inevitably leads to endothelial damage even with minimally invasive techniques. Although interesting, the increase in the suPAR level observed in this case seems to be of no clinical significance [49]. A recently published meta-analysis of 14,738 patients diagnosed with CAD confirmed that patients with elevated suPAR levels had a significantly higher risk of all-cause mortality (HR: 2.24; 95% CI: 1.97–2.55) and death due to a cardiovascular event (HR: 2.02; 95% CI: 1.58–2.58). Meta-analysis failed to support the predictive power of suPAR for major cardiovascular events (HR: 1.63; 95% CI: 0.86–3.11) [50].

It is worth mentioning that there are some indications in the literature that suPAR is a better predictor than a diagnostic biomarker. Moreover, compared to other markers of inflammation, particularly C-reactive protein, the increase in suPAR level is directly related to endothelial degradation and an increase in endothelial inflammation. In addition, increased C-reactive protein is observed with increasing body mass index or waist circumference. At the same time, the suPAR level is more independent of these indicators, which are also well-known factors in the development of cardiovascular disease. Although this meta-analysis focuses on the diagnostic usefulness of suPAR, given its potential prognostic properties, directions for further research should focus on

the prospective follow-up of patients with ACS over a longer period. The 1-year time horizon adopted most often in publications is too short to determine the relationship between the suPAR level and cardiovascular events and mortality. The longest follow-up period in the studies included in this meta-analysis (3.5 years) is too short. In addition, it is necessary to conduct a study in which the measurement of the suPAR level is repeated periodically, at strictly defined time intervals. The time distance from an acute coronary event should lead to a decrease in suPAR level, especially when intensive treatment is initiated, e.g., optimal doses of statins. Nevertheless, our meta-analysis aimed to assess the diagnostic utility of suPAR.

The limitations of the studies included in this meta-analysis should be briefly summarized. Can et al. [37], in the limitations of their paper, emphasized that the suPAR level was not measured immediately after the onset of symptoms of AMI, and there were no laboratory measurements in the longer follow-up, i.e., after the second day following the coronary event [37]. In comparison, the study presented by Nikorowitsch et al. [38] included a 3.5-year follow-up. It showed that the suPAR level could independently predict cardiovascular death and reinfarction in patients with clinically and hemodynamically confirmed CAD. In addition, the cohort included as many as 1703 patients. A critical methodological limitation of the study was the inclusion of CAD patients requiring coronary angiography. The authors emphasized that there was a large population of patients with CAD who did not require invasive intervention. Therefore, the predictive properties of suPAR in this population are not sufficiently understood currently. Schernthaner et al. [39], in turn, pointed out that their study was from a single center and included a relatively small number of patients. However, it is worth noting that it is still larger than the study presented by Can et al. [37] (194 vs. 125 patients). Clinical parameters (e.g., ejection fraction), as well as other laboratory tests (e.g., NT-proBNP or inflammatory markers), correlated significantly with new biomarkers determined in the study, including the suPAR level [39].

Sörensen et al. [40] indicated that the population included in their study was very heterogeneous. Of the 1314 patients, 1006 were diagnosed as non-AMI. Patients were admitted to the emergency department with symptoms suggestive of AMI; however, in the vast majority (approximately 75.56%), AMI was excluded. Although the average suPAR level in AMI patients vs. non-AMI did not differentiate, the suPAR level was a good predictor of 1-year mortality. The study's authors also emphasized that no other pro-inflammatory markers were determined in the study, so it was impossible to draw conclusions as to whether suPAR is superior to other pro-inflammatory markers in predicting mortality [40]. Topf et al. [41], in turn, focused their study on Takotsubo syndrome, which led to a significant overrepresentation of women in the population of patients with ACS and the control group. This translates into a limited ability to generalize the results [41].

Limitations of the study

The main limitation of our meta-analysis is the small number of included studies. However, considering the inclusion and exclusion criteria and the proposed article selection strategy, all possible papers were included in the study. The I^2 statistic indicates high heterogeneity in the meta-analysis. Nevertheless, it should be noted that the heterogeneity may be overestimated with the small number of included studies. The greatest diversity is observed in the definition of the control group in the studies included in the meta-analysis. However, this problem is typical of observational studies, including cohort studies, where we identify significant difficulties in selecting patients included in the control group.

Conclusions

In the context of ACS, suPAR is a potential biomarker for the early identification of medical conditions in individuals who are being treated in emergency rooms.

Conflict of interest: None declared

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