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Association of the C-Reactive Protein to Albumin Ratio with the No-Reflow Phenomenon After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

C-Reaktif Protein / Albümin Oranının Perkütan Koroner Girişim Sonrası No-Reflow Fenomeni ile İlişkisi: Sistematik Bir İnceleme ve Meta-Analiz

ABSTRACT

The no-reflow (NR) phenomenon, a complication of percutaneous coronary intervention (PCI), is associated with poor cardiovascular outcomes. Identifying reliable predictors of NR is crucial for risk stratification and improving clinical outcomes. The C-reactive protein (CRP) to albumin ratio (CAR), a marker of systemic inflammation, has been proposed as a potential predictor of NR. This systematic review and meta-analysis aimed to evaluate the relationship between CAR and NR following PCI. A comprehensive literature search was conducted in the Cochrane, Embase, and PubMed databases, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. Studies assessing the predictive value of CAR for NR were included. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity was assessed using Cochrane's Q and I^2 statistics. Four studies comprising a total of 2,068 patients were included. The pooled analysis showed a significant association between elevated CAR and an increased risk of NR (OR: 2.34; 95% CI: 1.19–4.60; P = 0.01; I^2 = 96%). Elevated CAR is associated with an increased risk of NR after PCI, indicating its potential as a prognostic biomarker. However, the high heterogeneity among studies highlights the need for large-scale research to confirm its clinical applicability.

Keywords: C-reactive protein to albumin ratio, meta-analysis, no-reflow phenomenon, percutaneous coronary intervention

ÖZET

Perkütan koroner girişim (PKG) sonrası no-reflow (NR) fenomeni olumsuz kardiyovasküler sonuçlarla ilişkilidir. NR'nin güvenilir öngörücülerini belirlemek, risk sınıflandırması ve klinik sonuçları iyileştirmek için çok önemlidir. Sistemik inflamasyonun bir belirteci olan CRP-albümin oranı (CAO), NR'nin potansiyel bir öngörücüsü olarak önerilmiştir. Bu sistematik inceleme ve meta-analiz, CAO ile PKG sonrası NR oluşumu arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır. PRISMA 2020 yönergelerini izleyerek PubMed, Cochrane ve Embase veri tabanlarında kapsamlı bir literatür araştırması yapıldı. NR için CAO'ın öngörücü değerini değerlendiren çalışmalar dahil edildi. %95 güven aralıkları (GA) ile birleştirilmiş olasılık oranları (OR'ler) rastgele etki modeli kullanılarak hesaplandı. Heterojenlik Cochrane'in Q ve I^2 istatistikleri kullanılarak değerlendirildi. 2.068 hastayı kapsayan dört çalışma dahil edildi. Birleştirilmiş analiz, daha yüksek CAO ile artmış NR riski arasında anlamlı bir ilişki olduğunu gösterdi (OR: 2,34; %95 CI: 1,19–4,60; P = 0,01; I^2 = %96). Yükselmiş CAO'ın PKG'dan sonra NR ile ilişkili olduğunu bulduk, bu da prognostik bir biyobelirteç olarak potansiyel faydasını göstermektedir. Ancak, yüksek heterojenlik, klinik uygulanabilirliğini doğrulamak için büyük ölçekli çalışmalara olan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: CRP-albümin oranı, meta-analiz, no-reflow fenomeni, perkütan koroner girişim

Percutaneous coronary intervention (PCI) is a critical procedure used to treat patients with coronary artery disease (CAD), particularly those experiencing acute coronary syndrome (ACS).[1] However, a significant challenge during PCI is the occurrence of the no-reflow (NR) phenomenon, a condition in which myocardial perfusion fails to recover despite successful coronary artery reperfusion.[2] The NR phenomenon is associated

REVIEW
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with adverse outcomes, including life-threatening arrhythmias, heart failure, prolonged hospital stay, and increased mortality.[3] Identifying reliable predictors of NR could improve patient prognosis and support clinical decision-making.

Recent studies have demonstrated a link between inflammatory markers and the development of NR following PCI.[4-6] Among these markers, the C-reactive protein (CRP) to albumin ratio (CAR) has attracted interest for its ability to reflect systemic inflammation, a key contributor to the pathophysiology of NR.[4,6] Elevated CRP levels, a marker of inflammation, are commonly associated with atherosclerosis and its complications, while lower albumin levels are linked to increased vascular dysfunction and thrombosis.[7,8]

The aim of this systematic review and meta-analysis is to examine the association between the CRP-albumin ratio and the occurrence of NR following PCI. By pooling data from observational studies, we assess whether CAR may serve as an independent predictor of NR in PCI patients and explore its potential role in clinical practice.

Materials and Methods

This systematic review and meta-analysis were conducted and reported in accordance with the guidelines outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement.[9,10] The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42025643272.

Search Strategy

A systematic search was conducted across the Cochrane Library, Embase, and PubMed databases. In addition, the reference list of included studies and relevant systematic reviews were screened to identify any additional eligible studies. The full search strategy for each database is provided in the Supplemental Material. The search was performed up to February 15, 2024.

Eligibility Criteria, Data Extraction, and Study Outcomes

Studies were included in the meta-analysis based on the following eligibility criteria:

1. Observational studies (prospective or retrospective);
2. Studies that compared patients who developed NR after PCI with those who did not;
3. Studies that performed multivariate regression analyses to assess whether CAR was an independent predictor of NR.

Exclusion criteria included studies with overlapping patient populations, conference abstracts, case reports, case series, and studies published in languages other than English.

Three investigators independently conducted the data search, study selection, and data extraction. Any disagreements were resolved by consensus after a thorough review of the full articles and eligibility criteria, in consultation with the senior author.

ABBREVIATIONS

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CAR	C-reactive protein to albumin ratio
CRP	C-reactive protein
LDL	Low-density lipoprotein
MOOSE	the Meta-Analysis of Observational Studies in Epidemiology
NR	No-reflow
NSTEMI	Non-ST-elevation myocardial infarction
CI	Confidence intervals
OR	Odds ratio
PCI	Percutaneous coronary intervention
PRISMA	the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
ROBINS-I	The Risk of Bias in Non-Randomized Studies of Interventions
SCAD	Stable coronary artery disease
STEMI	ST-elevation myocardial infarction
SVG	Saphenous vein graft

Quality Assessment

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was used to assess the risk of bias for each included study.[11] Two independent investigators performed the assessments, and any disagreements were resolved in consultation with the senior author. Sensitivity analyses were conducted using the "leave-one-out" method.

Statistical Analysis

All data analyses were performed in accordance with Cochrane recommendations.[12] Binary endpoints were analyzed using the Mantel-Haenszel method with a random-effects model. The odds ratio (OR) and 95% confidence interval (CI) were used as measures of effect size. All studies analyzed CAR as a continuous variable, and ORs were extracted to reflect changes in outcomes per 1-unit increase in CAR. Heterogeneity was assessed using Cochrane's Q statistic and the Higgins and Thompson I2 statistic. Heterogeneity was considered significant if the P values were less than 0.10 and the I2 value exceeded 25%. Statistical analyses were performed using Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Artificial Intelligence Disclosure

We confirm that no artificial intelligence (AI)-based tools, including chatbots, large language models (LLMs), or image generators, were used in the creation of this meta-analysis.

Results

Study Selection and Baseline Characteristics

As illustrated in Figure 1, the initial search yielded 613 records. After removing duplicates, 11 studies were selected for full-text review. Of these, four studies met the inclusion criteria.[4,6,13,14] A total of 2,068 patients were included across the four studies. Among them, 593 patients (28.7%) were in the NR group, and 1,475 patients (71.3%) were in the non-NR group. Table 1 summarizes

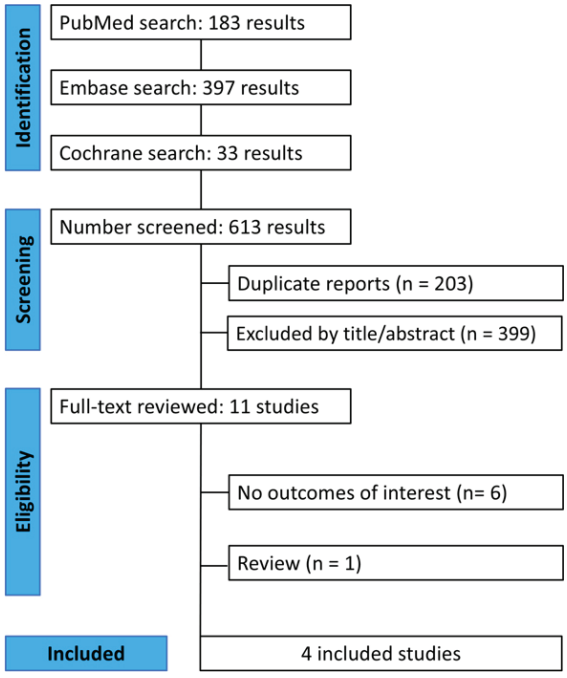

Figure 1. PRISMA flow diagram of study screening and selection.

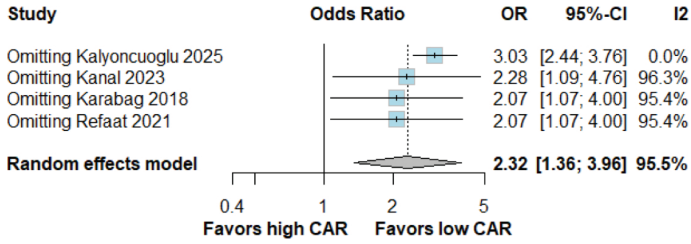

Figure 2. The heterogeneity decreased from I^2 = 95.5% to 0% upon omitting Kanyoncuoglu et al.(13) in the leave-one-out analysis.

the characteristics of the included studies. Two studies enrolled patients presenting with acute ST-elevation myocardial infarction (STEMI),[6,14] one study included patients with non-ST-elevation myocardial infarction (NSTEMI),[13] and one focused on patients undergoing PCI of a saphenous vein graft (SVG).[4]

Quality Assessment

The included studies were assessed as having a moderate overall risk of bias (Appendix 1). In the sensitivity analysis, heterogeneity decreased from I^2 = 95.5% to 0% after omitting the study by Kalyoncuoglu et al.,[13] in 2025 (Figure 2).

Endpoints

A pooled analysis of 593 patients in the NR group and 1,475 in the non-NR group demonstrated a significant association between elevated CAR and the risk of NR in patients undergoing PCI (OR: 2.34; 95% CI: 1.19–4.60; P = 0.01; I2 = 96%) (Figure 3).

Table 1. Baseline Characteristics of Included Studies

Study, Year	Population	No. of Patients, (NR/No NR)	Female, % (NR/No NR)	Age[a], years (NR/No NR)	DM, % (NR/No NR)	HTN, % (NR/No NR)	Current Smoker, % (NR/No NR)	LVEF[a] (NR/No NR)
Kalyoncuoglu et al.,[13] 2025	NSTEMI	30/179	23.3/20.1	56/56	30/27.9	43.3/55.3	50/46.9	47.0/50.1
Kanal et al.,[4] 2023	PCI of SVGb	48/194	21.3/24.4	65.7/65.0	67.3/40.4	73.5/64.6	36.4/30.3	42.0/50.0
Karabag et al.,[6] 2018	Acute STEMI	343/874	20.7/17.6	59/56	29.4/20.5	45.2/38.4	47.5/57.2	41.13/48.90
Refaat et al.,[14] 2021	Acute STEMI	172/228	25.6/31.6	65.21/56.61	69.8/43.9	69.8/43.9	60.5/61.4	42.26/46.37

[a]Mean or median; [b]Includes both acute coronary syndrome and stable coronary artery disease patients. DM, Diabetes Mellitus; HTN, Hypertension; LVEF, Left Ventricular Ejection Fraction; NR, No-Reflow; NSTEMI, Non-ST-Elevation Myocardial Infarction; PCI, Percutaneous Coronary Intervention; STEMI, ST-Elevation Myocardial Infarction; SVG, Saphenous Vein Graft.

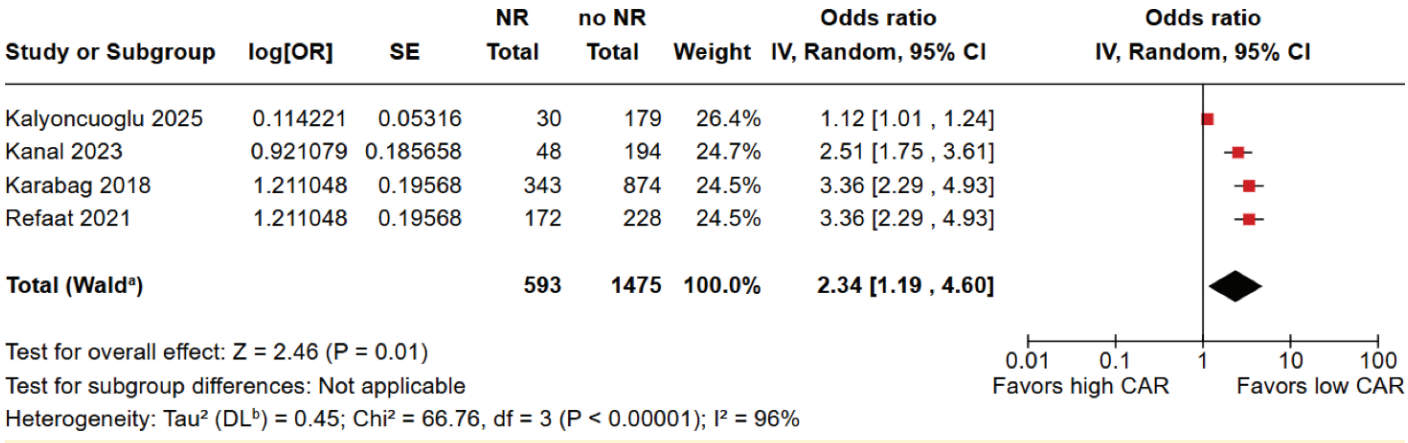

Figure 3. A CRP albumin ratio had a significantly higher rate association of no-reflow in patients undergoing percutaneous coronary intervention.

Discussion

This systematic review and meta-analysis, which included four studies comprising 2,068 patients, compared those who developed NR after PCI to those who did not. The primary finding from the pooled analysis was that a higher CAR was significantly associated with an increased risk of NR in patients undergoing PCI, whereas a lower CAR was associated with a reduced risk.

PCI is a complex procedure, and the NR phenomenon can further complicate clinical outcomes. NR has been linked to adverse events, including an increased risk of malignant arrhythmias, heart failure, and mortality.[1,2,15]

Previous studies suggest that NR occurs more frequently during PCI for ACS compared with elective procedures for stable coronary artery disease (SCAD).[3,16,17] The higher incidence in ACS has been attributed to several factors, including a greater thrombus burden, prolonged ischemia, and more complex lesion morphology—such as ruptured or lipid-rich plaques—which are more common in ACS than in SCAD.[16–19] Given these contributing factors, we aimed to evaluate the overall inflammatory burden in NR versus non-NR populations using the CAR, as ACS typically triggers a significant inflammatory response due to these underlying pathological processes.

Inflammation is a key factor in the progression of atherosclerosis.[20] C-reactive protein, as a biomarker of inflammation, is significantly associated with the advancement of atherosclerotic disease.[7] Research indicates that CRP elevates reactive oxygen species, facilitates the uptake of oxidized low-density lipoprotein (LDL), promotes endothelial dysfunction, and triggers cell apoptosis. Furthermore, it stimulates vascular smooth muscle cell proliferation and increases the likelihood of plaque rupture.[7,21] In contrast, albumin functions as a negative acute-phase protein and serves as an indicator of inflammation severity in critically ill individuals.[22] Decreased serum albumin levels are significantly associated with endothelial dysfunction, increased blood viscosity, and heightened platelet aggregation.[8] Additionally, lower albumin concentrations have been linked to poorer in-hospital outcomes, greater stent restenosis, and more severe CAD.[23,24]

Our meta-analysis revealed that patients who developed NR had significantly higher CAR values compared to those who did not. One potential explanation is that the heightened inflammatory response in these patients results in elevated CRP levels alongside reduced albumin levels. A greater plaque burden may further intensify this inflammatory reaction, contributing to increased lesion complexity, larger occlusions, and more extensive myocardial damage—factors that could further elevate CAR.[25–27] However, no standardized cutoff values currently exist to correlate CAR with the severity of overall disease burden, nor was there consistency in the timing of sample collection in relation to the onset of the event. As a result, definitive risk stratification could not be established.

Limitations

Our study has several limitations. First, all included studies were observational, as no randomized controlled trials (RCTs) on this subject are currently available. Observational studies are inherently more susceptible to various forms of bias, particularly confounding bias, which occurs when the relationship between exposure and outcome is influenced by one or more unmeasured variables. Second, significant heterogeneity was observed across studies. Notably, sensitivity analysis using the leave-one-out method revealed that heterogeneity dropped to zero after excluding the study by Kalyoncuoglu et al.,[13] suggesting that this study was the primary source of variability. Third, there was no standardized protocol for the timing of blood sample collection, which may have influenced the results, particularly given the relatively short half-lives of CRP and albumin. Fourth, we were unable to analyze the association between CAR and clinical outcomes such as cardiac death at follow-up, as these endpoints were not reported in the included studies, except for Kanal et al.[4] Finally, the majority of the included studies were conducted in a single country, which raises concerns regarding the external validity of our findings.

Conclusion

We found that higher CAR levels are associated with an increased risk of NR following PCI, suggesting its potential utility as a prognostic biomarker. These findings indicate that CAR, as a marker of systemic inflammation, may serve as a valuable tool for predicting NR and could support improved risk stratification and clinical decision-making.

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Appendix 1. Risk of bias summary for non-randomized studies (ROBINS-I)

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Kalyoncuoğlu et al.[13] 2025	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Karabağ et al.[6] 2018	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Kanal et al.[4] 2023	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Refaat et al.[14] 2021	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	Moderate

Full search strategy for each database

- PubMed

  ("No-Reflow Phenomenon"[Mesh] OR "no reflow phenomenon" OR "no-reflow" OR "microvascular obstruction") AND ("C-reactive Protein/Albumin " OR "C-reactive protein" OR "C-Reactive Protein"[Mesh] OR "CRP" OR "C-reactive protein to albumin" OR "CAR" OR "CRP Albumin Ratio" OR "Albumins"[Mesh] OR "Albumin")

- Embase

  ('no reflow phenomenon'/exp OR 'no reflow phenomenon' OR 'no-reflow' OR 'microvascular obstruction') AND ('c-reactive protein/albumin' OR 'c-reactive protein' OR 'C reactive protein'/exp OR 'crp' OR 'c-reactive protein to albumin' OR 'car' OR 'crp albumin ratio' OR 'albuminoid'/exp OR 'albumin')

- Cochrane Library

  ("no reflow phenomenon" OR "no-reflow" OR "microvascular obstruction") AND ("C-reactive Protein/Albumin " OR "C-reactive protein" OR "CRP" OR "C-reactive protein to albumin" OR "CAR" OR "CRP Albumin Ratio" OR "Albumin")