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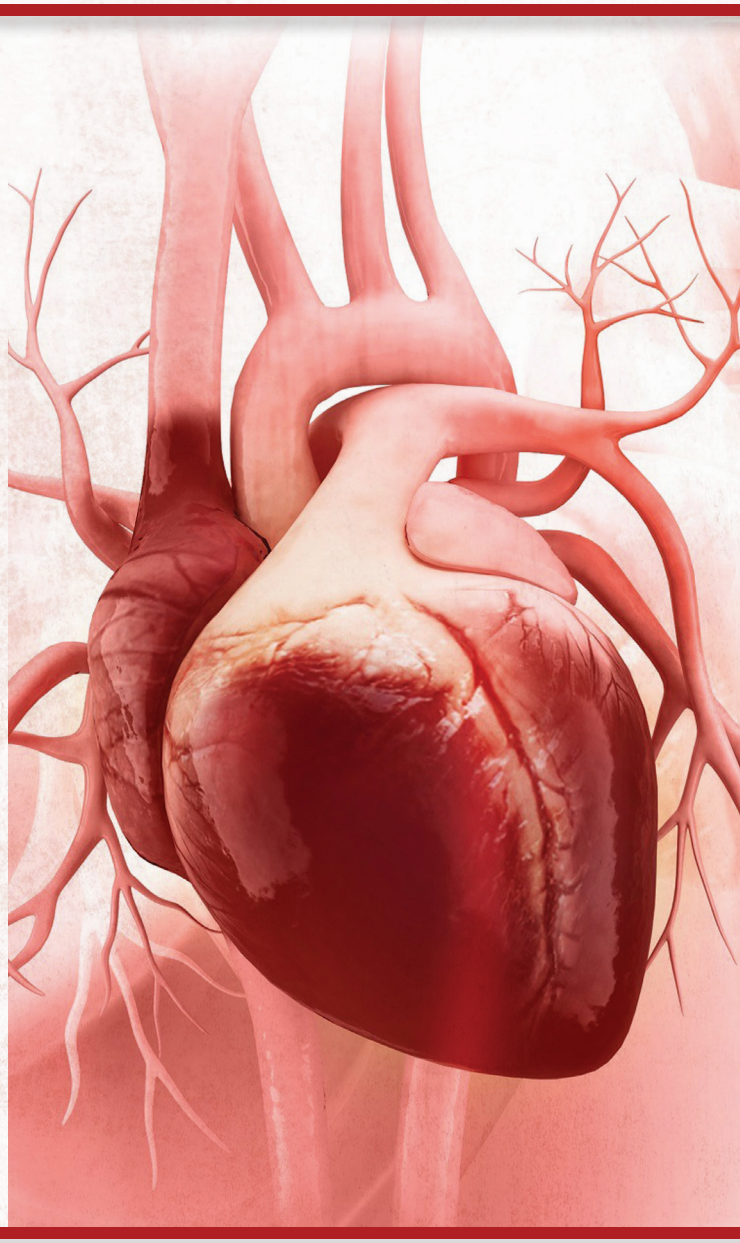

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EDITORIAL

TAVI in Low-Intermediate Surgical Risk Severe Aortic Stenosis in 2025: Clinical Paradigms in a Continuing Evolution

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Transcatheter aortic valve implantation (TAVI) has undergone a remarkable transformation over the past decade, and by 2025 it has expanded firmly beyond the confines of high-risk or inoperable patients. TAVI now stands as an increasingly preferred and compelling therapeutic option in a broad spectrum of patients with severe aortic stenosis (AS), including those with low-intermediate surgical risk. This expansion reflects technological maturation and procedural refinement, together with a growing body of clinical evidence demonstrating that TAVI offers early safety, rapid functional recovery, and high-quality-of-life gains that rival—or surpass—those of surgical aortic valve replacement (SAVR).

Recent systematic reviews and meta-analyses provide a comprehensive synthesis of outcomes in this population. A large 2025 meta-analysis pooling six randomized trials with ≥4 years of follow-up demonstrated no significant difference between TAVI and SAVR in all-cause mortality or disabling stroke in low-intermediate risk patients, although a divergence in mortality favoring SAVR at five years was observed.[1] This finding underscores an emerging dynamic: while early and mid-term outcomes clearly support TAVI, long-term biological valve durability and late-phase event divergence require continued scrutiny, particularly in younger patients with longer life expectancy.

The NOTION-2 trial further refines our understanding by showing that low-risk patients with tricuspid anatomy achieved similar outcomes with TAVI and SAVR at three years, although those with bicuspid valves experienced numerically higher adverse events with TAVI.[2] These results reaffirm that the central role of anatomical assessment—especially in younger and structurally complex patients—remains essential when determining the optimal approach.

Economic analyses published in 2025 add another dimension to this evolving landscape. The United Kingdom and Swedish health-system evaluations concluded that SAPIEN 3 TAVI, despite its higher procedural cost, achieves acceptable cost-effectiveness thresholds in low-risk symptomatic severe AS when gains in quality-adjusted life years and early functional recovery are considered.[3,4] Thus, in carefully selected patients, TAVI represents not only a clinically sound but also an economically rational one.

One of the most important cautionary signals emerges from younger patient populations. Data from the United States Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapy (TVT) registry indicate that patients youger than 65 years represent a small but steadily growing subgroup undergoing TAVI, yet they carry a disproportionately high comorbidity burden and experience significantly worse 1-year mortality and rehospitalization rates compared with those patients aged 65–80 years.[5] These findings underscore the principle that chronological age alone should never be allowed to serve as the dominant factor in clinical decision-making.

Intermediate- and long-term outcomes from major randomized programs were substantially updated in 2025. The 7-year PARTNER 3 results confirmed no significant difference between TAVI and SAVR in the composite endpoint of death, stroke, or valve-related hospitalization, thereby reaffirming the noninferiority of TAVI in low-risk elderly patients.[6] Echocardiographic analyses at five years demonstrated that TAVI provides superior hemodynamics performance—including a higher stroke volume index and lower valvuloarterial impedance—although it remians associated with a higher prevalence of mild aortic regurgitation.[7] Likewise, the five-year findings of Evolut Low-Risk showed mortality and disabling stroke between the two treatments, accompanied by low reintervention rates in both groups.[8] Ten-year follow-up from the NOTION trial additionally suggests that TAVI durability is at least comparable to SAVR in elderly low-risk patients, even as conduction-system injury and paravalvular leak persist as notable concerns.[9]

Real-world experience continues to provide valuable context. Updated 2025 analyses from the TVT Registry demonstrate that carefully selected low-risk patients achieve excellent early outcomes, with <1% 30-day mortality and <5% 1-year mortality, although event rates

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remain slightly higher than those observed in randomized clinical cohorts.[10] These differences likely reflect unmeasured frailty, variations in comorbidity burden, and heterogeneity in center-level experience.

An particularly paradigm-shifting development is the growing evidence supporting earlier intervention. The 2025 EARLY-TAVR trial showed that in asymptomatic severe AS, early TAVI significantly reduced death, stroke, and cardiovascular hospitalization compared with clinical surveillance, despite most surveilled patients eventually undergoing valve replacement.[11] These findings challenge long-standing "watchful waiting" strategies and may redefine treatment thresholds for a substantial proportion of patients.

Taken together, the evidence accumulated by 2025 demonstrates that TAVI is a safe, effective, and clinically advantageous treatment option for many patients with low-intermediate surgical risk severe AS, offering rapid recovery and excellent peri-procedural safety. Nonetheless, persistent considerations—including late-phase mortality divergence, elevated rates of conduction disturbance and paravalvular regurgitation, and ongoing uncertainties in younger cohorts—underscore that TAVI cannot yet be viewed as the universal default for all low-risk patients.

Based on my clinical experience and interpretation of emerging data, I believe that the trajectory of TAVI is unmistakably progressive. The accelerating pace of technological refinement, including next-generation valve platforms, reduced conduction-system trauma, improved commissural alignment, and device designs that preserve future coronary access, strongly suggests that the role of TAVI in low-intermediate risk patients will expand substantially over the next decade. As durability data continue to mature, and as procedural precision improves with modern imaging and artificial intelligence-assisted navigation, TAVI is likely to evolve from "an alternative" to "a predominant first-line therapy" in this population. Thus, the natural trajectory of innovation points toward increasingly frequent TAVI use among low-intermediate risk patients, provided that careful anatomical and clinical selection remains central to decision-making.

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ORIGINAL ARTICLE

Utility of Coronary Computed Tomography Angiography in Complex Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of CTO Studies

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ABSTRACT

Background: Complex percutaneous coronary intervention (PCI) presents technical challenges and elevated procedural risks. Coronary computed tomography angiography (CCTA) is a non-invasive imaging modality that might improve pre-procedural planning and intra-procedural guidance.

Aim: This study evaluates the impact of CCTA-guided PCI compared with standard angiography guidance in complex PCI, with a focus on procedural success, fluoroscopy time, contrast volume, and major adverse cardiac events (MACE).

Study Design: A systematic review and meta-analysis.

Methods: We conducted a systematic search of PubMed/MEDLINE, Embase, Cochrane Library, Scopus, Google Scholar, and ClinicalTrials.gov for studies published between 2014 and 2024. Eligible studies included randomized controlled trials (RCTs) and observational studies comparing CCTA-guided versus angiography-guided PCI in adults. Outcomes were pooled using random-effects meta-analysis. The certainty of evidence was assessed using the GRADE framework.

Results: Five studies (one RCT, four observational; 7,406 participants), all focusing on chronic total occlusion PCI, were included. Meta-analyses revealed no significant differences in procedural success [risk ratio: 0.97, 95% confidence interval (CI): 0.92–1.02], fluoroscopy time [mean difference (MD) +6.0 min, 95% CI: −7.7 to 19.7], or contrast volume (MD −7.0 mL, 95% CI −43.5 to 29.4). MACE rates were also comparable (odds ratio: 1.03, 95% CI: 0.67–1.58). The certainty of evidence was rated as very low due to risk of bias, imprecision, heterogeneity, and limited generalizability.

Conclusion: CCTA-guided PCI is comparable to angiography-guided PCI in terms of procedural success, efficiency, and safety in complex lesions. However, the very low certainty of evidence and reliance on non-randomized studies limit definitive conclusions. High-quality RCTs are required to elucidate the clinical role of CCTA in guiding complex PCI.

Keywords: Cardiovascular, chronic total occlusion (CTO), computed tomography angiography, coronary computed tomography angiography (CCTA), interventional, percutaneous coronary intervention, complex PCI

INTRODUCTION

Despite considerable advances in percutaneous coronary intervention (PCI), complex procedures remain challenging for interventional cardiologists.[1,2] Lesions such as chronic total occlusions (CTOs), bifurcations, heavily calcified vessels, tortuous anatomies, in-stent restenosis, and post–coronary artery bypass grafting PCI are associated with longer procedural times, higher radiation exposure, increased contrast volume, and greater risk of complications, including vessel perforation, dissection, and no-reflow.[2,3-6] These factors contribute to adverse clinical outcomes, including elevated morbidity and mortality.

Coronary computed tomography angiography (CCTA) is a non-invasive imaging modality that provides high-resolution, three-dimensional visualization of coronary anatomy.[2,5] It allows detailed evaluation of lesion morphology, plaque composition, vessel dimensions, and spatial orientation, thereby improving pre-procedural planning.[1,2-8] CCTA can aid catheter and device selection, guide procedural strategy, and potentially enhance procedural efficiency and outcomes.[2,4,5,7,8]

Although evidence suggests potential benefits of CCTA-guided PCI—such as reduced fluoroscopy time, lower contrast volume, and improved procedural success—its use in routine practice remains limited. Barriers include concerns regarding additional radiation exposure, increased contrast load, and the need for specialized equipment and operator expertise.[1,2,5]

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Objective

This systematic review evaluates the utility of CCTA guidance in complex PCI compared with angiography-guided PCI. The primary outcome assessed was procedural success. Secondary outcomes included fluoroscopy time, contrast volume, and major adverse cardiac events (MACE). Additionally, the certainty of evidence for CCTA-guided PCI in complex coronary interventions was assessed using the GRADE framework.

METHODS

Search Strategy

We conducted a systematic search of PubMed/MEDLINE, Embase, Cochrane Library, Scopus, and ClinicalTrials.gov for studies published between 2014 and 2024, limited to English-language articles. There were no restrictions on geographic location or the number of centers. To ensure comprehensive coverage, reference lists of eligible studies and relevant reviews were screened, and authors of conference abstracts were contacted to identify unpublished or ongoing studies.

To capture grey literature and studies potentially missed by conventional databases, Google Scholar was also searched using the keywords "CCTA," "complex PCI," "CTO PCI," "bifurcation PCI," and "graft PCI." For each search, the first 100 results were screened as a pragmatic supplemental approach. We acknowledge that this method might introduce selection bias; therefore, Google Scholar was used solely to complement—not replace—the primary database search strategy.

Study Selection

Two independent reviewers screened titles and abstracts using Covidence, followed by full-text review according to prespecified inclusion criteria. Disagreements were resolved through discussion. Eligible studies included randomized controlled trials (RCTs) and observational studies comparing CCTA-guided PCI with standard angiography-guided PCI in adults undergoing complex PCI. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

Data Extraction

Two reviewers independently extracted study and patient characteristics, intervention details, and outcomes, including procedural success, fluoroscopy time, contrast volume, and MACE. Data were recorded using piloted extraction forms. Discrepancies were resolved by consensus, and study authors were contacted to obtain missing data when necessary.

Risk of Bias Assessment

Risk of bias was independently evaluated by two reviewers. For RCTs, the Cochrane risk of bias 2 (RoB 2) tool was used to assess bias arising from randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For non-RCTs, the risk of bias in non-randomized studies of interventions (ROBINS-I) tool was applied, considering bias due to confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and reporting. Overall risk of bias for each study was determined by the domain with the highest risk.

Measures of Effect

All analyses were performed using Review Manager 5.3. Dichotomous outcomes were summarized as risk ratios (RRs) or odds ratios with 95% confidence intervals (CIs). Continuous outcomes, including fluoroscopy time and contrast volume, were reported as mean differences (MDs) with 95% CIs. When standard deviations were not reported, they were estimated from standard errors or CIs when possible.

Heterogeneity and Reporting Bias

Heterogeneity was evaluated through a visual inspection of forest plots, the chi-square test ($p<0.10$), and the I^2 statistic. I^2 thresholds followed Cochrane recommendations: unimportant (<40%), moderate (30–60%), substantial (50–90%), and considerable (≥75%). Planned subgroup analyses by complex PCI subtype could not be performed because all included studies focused on CTO PCI. Funnel plot assessment was not feasible due to the small number of studies. To minimize reporting bias, broad search strategies across multiple databases were employed.

Data Synthesis

Random-effects meta-analyses were performed using the inverse variance method. Sensitivity analyses were planned to exclude studies at high-risk of bias; however, their utility was limited by study homogeneity and the small number of included trials.

Certainty of Evidence

The certainty of evidence was assessed using the GRADE approach, considering risk of bias, inconsistency, imprecision, and publication bias. Thresholds for clinical significance were defined as a ≥5% difference in procedural success, a ≥5-minute change in fluoroscopy time, a ≥10 mL reduction in contrast volume, and any difference in complications. Overall, the certainty of evidence for all outcomes was rated as very low. A Summary of findings table was generated using GRADEpro, with reasons for downgrading provided in footnotes.

RESULTS

Study Selection and Search Results

Literature search was conducted in September 2024 across multiple databases, including Scopus, MEDLINE, Google Scholar, Embase, and PubMed, yielding 201 (n=132, 25, 17, 15, and 12, respectively) studies. Additional sources, including citation searches (n=16) and grey literature (n=5), contributed 21 more studies. After removing 50 duplicates, 172 unique studies were screened.

Following title and abstract screening, 28 studies were retrieved for full-text evaluation. Of these, 24 full-text articles were assessed for eligibility, and 19 were excluded. Full-text evaluation was performed independently by two reviewers, with discrepancies resolved by consensus. Ultimately, five studies met the inclusion criteria and were included in the analyses. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Study Characteristics

The review included five studies: one RCT and four observational studies (Table 1). Collectively, these studies involved 7,263 patients, with 674 in the CCTA-guided PCI group and 6,589 in the angiography-guided PCI group. The studies were published between 2014 and 2024.

All studies assessed procedural success, fluoroscopy time, contrast volume, and MACE. All included studies focused exclusively on CTO lesions, with no representation of other complex PCI subtypes. Planned subgroup analyses could not be performed due to the lack of studies involving different types of complex PCI.

Excluded Studies

Studies were excluded based on the following criteria: case reports or case series with limited sample size and generalizability; studies with missing data that could not be retrieved; and studies evaluating outcomes different from those predefined, such as comparisons between CCTA-guided PCI and intracoronary-guided PCI rather than angiography-guided PCI. These criteria ensured that only studies assessing the specified outcomes of procedural success, fluoroscopy time, contrast volume, and MACE in the context of CCTA-guided versus angiography-guided PCI were included in the review.

Risk of Bias in Included Studies

The risk of bias was assessed for all included studies. The single RCT demonstrated a low-risk of bias across all domains (RoB 2), whereas the four observational studies exhibited moderate to high-risk of bias according to ROBINS-I. Table 2 summarizes the risk of bias assessments, and Supplementary 1 provides detailed judgments for each study.

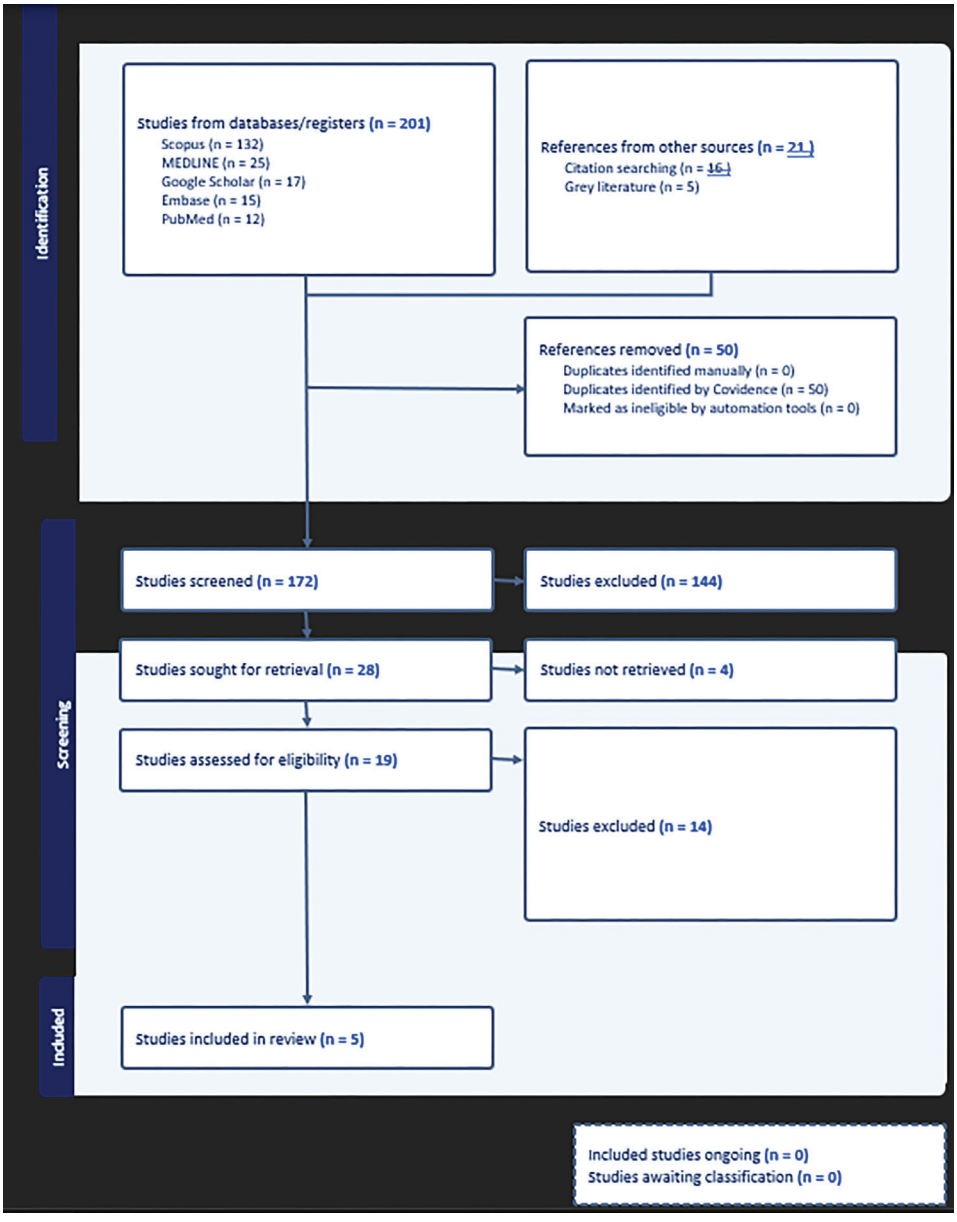

Figure 1. Flow diagram of selecting articles for systematic review

Table 1. Baseline characteristics and outcomes of included studies

Study	Design of the study	Inclusion criteria	Duration	Groups	Patients (n)	Mean age (±SD), years	Main outcomes
Hong et al.[5]	Multicenter, randomized trial	CTO lesions with typical angina or positive functional test for ischemia	1 year	**CTA-guided:** n=200 **Angiographyguided:** n=200	400	62±10 (CTA) 61±11 (Angio)	Higher recanalization success with CTA (94% vs. 84%, p=0.003). Lower antegrade crossing time (44 min vs. 47 min, p=0.042). Benefits primarily in higher J-CTO score cases.
Xenogiannis et al.[9]	Retrospective observational study	CTO lesions undergoing PCI	2018-2019	**CTA Fusion Guidance:** n=27 **Non-CTA Guidance:** n=119	146	66±9 (both groups)	Similar technical success (81% vs. 89%, p=0.279). CTA-guided group had higher lesion complexity (J-CTO score 3.3 vs. 2.7, p=0.009).
Li et al.[10]	Single-center, retrospective observational study	CTO lesions undergoing PCI after CCTA imaging	Retrospective	Success vs. failure outcomes analyzed and compared RECHARGE CCTA score vs. CA based scoring	124 (131 CTO lesions)	54 (IQR: 43–60 years)	Procedural success in 72% of cases. RECHARGECCTA score as effective as catheter-based scoring for predicting success and wire crossing time.
Yu et al.[11]	Multicenter, retrospective observational study	CTO lesions undergoing PCI following CCTA imaging	2007–2015	Single group analyzing procedural success and crossing outcomes Compared CCTA guided scoring system KCCT vs. CA scoring systems for outcomes	643	62 (IQR: 54–70 years)	Procedural success in 74%. KCCT score developed, better prediction than J-CTO or PROGRESS-CTO scores for success and guidewire crossing time.
Simsek et al.[12]	Multicenter, retrospective observational registry study	CTO lesions with TIMI 0 flow ≥3 months	2012–2022	**Preprocedural CCTA:** n=375 **No-CCTA:** n=6659	7,034	64±11 (CCTA) 64±10 (no-CCTA)	Similar procedural success (85% vs. 86%, p=0.329). Higher MACE in CCTA group (3.2% vs. 1.6%, p=0.020). CCTA resolved ambiguity (27%) and identified calcium (18%).

CCTA: Coronary computed tomography angiography, CTO: Chronic total occlusion, PCI: Percutaneous coronary intervention, SD: Standard deviation, IQR: Interquartile range, KCCT: Korea Coronary Calcium Scoring System

Primary Outcome: Procedural Success

Five studies, including one RCT and four observational studies, contributed to this analysis, encompassing a total of 8,311 patients (674 and 6,589 patients in the CCTA-guided and angiography-guided PCI groups, respectively). The forest plot of the meta-analysis (Figure 2) showed a relative risk (RR) of 0.97 (95% CI: 0.92–1.02), indicating no significant difference in procedural success between CCTA-guided and angiography-guided PCI. The risk difference (RD) was −0.03 (95% CI: −0.07 to 0.02), with the CI crossing zero, further suggesting no significant effect.

The minimal important difference (MID) for procedural success was defined as a 5% improvement, a commonly used threshold in PCI studies. The observed difference was below this threshold, and the wide CI crossing 1 indicates uncertainty regarding the direction of effect. Accordingly, the certainty of evidence was downgraded to very low (⨁◯◯◯) due to high-risk of bias, inconsistency, and imprecision.

Using the GRADE framework, the risk of bias was high in the observational studies owing to confounding factors, including lesion complexity, operator expertise, procedural protocols, and variability

Table 2. Summary of risk of bias of included studies

RCTs (RoB 2)						
Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Hong et al.[5]	Low	Low	Low	Low	Low	Low

Non-RCTs (ROBINS-I)								
Study	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	Overall judgment
Xenogiannet al.[9]	High	Low	Low	Low	Moderate	Low	Low	High
Lİ et al.[10]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Yu et al.[11]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Simsek et al.[12]	High	Low	Low	Low	Moderate	Low	Low	High

in center experience and familiarity with CCTA workflows, as well as missing data. The RCT was judged to have a low-risk of bias because of clear randomization and adequate handling of missing data. Given that the majority of included studies were observational, the overall risk of bias was rated as high.

Heterogeneity was evaluated through visual inspection of the forest plot, which showed overlapping CIs, suggesting potential consistency across studies. Moderate statistical heterogeneity was observed (I^2=43%; p=0.23), indicating that variability in study populations and designs had minimal impact on the pooled effect.

Imprecision was assessed by examining the CIs for the RR and RD, which were wide and included the null value, indicating uncertainty about whether the intervention is beneficial or harmful. Because the observed effect did not reach the MID of a 5% increase in procedural success, the evidence was downgraded for imprecision.

Indirectness was not a concern, as the population, intervention, comparison, and outcome (PICO) elements in the included studies were consistent with the review's objectives. Due to the small number of studies, publication bias could not be formally evaluated using a funnel plot; however, an extensive search across multiple databases and additional sources (including grey literature and citation searching) minimized this risk.

Overall, the certainty of evidence for the effect of CCTA-guided PCI on procedural success was rated as very low, indicating that the true effect is highly uncertain.

Secondary Outcomes

Fluoroscopy Time

Four studies, including one RCT and three observational studies, comprising 6,803 patients, contributed to this analysis. The MD in fluoroscopy time was 6.01 minutes longer for CCTA-guided PCI compared with angiography-guided PCI (95% CI: −7.71 to 19.73). The corresponding forest plot is shown in Figure 3. The MID was defined as a 5-minute change. Although the observed increase exceeded this threshold, the wide CI crossing zero and high heterogeneity (I^2=99%) indicated substantial uncertainty in the results.

Risk of bias was moderate in the observational studies due to potential confounders, including lesion complexity and variations in procedural protocols. The RCT was judged to have a low-risk of bias owing to clear randomization and blinding procedures.

Heterogeneity was assessed visually and statistically. Visual inspection revealed partial overlap of CIs, but statistical analysis demonstrated substantial inconsistency (I^2=99%; p<0.001), likely reflecting differences in study design, populations, and procedural protocols. Consequently, the certainty of evidence was downgraded to very low (⨁◯◯◯) due to heterogeneity.

Imprecision was evaluated based on the wide CIs, which included zero, indicating uncertainty regarding the effect. Although the observed increase slightly exceeded the MID, the CIs suggest the possibility of no effect; therefore, the evidence was further downgraded.

Indirectness was not a concern, as the populations and interventions in the included studies were consistent with the review's PICO framework. Due to the small number of studies, publication bias was not formally assessed, but comprehensive searching minimized this risk.

Overall, the certainty of evidence for fluoroscopy time was very low, indicating that the true effect of CCTA-guided PCI on fluoroscopy duration remains highly uncertain.

Contrast Volume

Three studies, including one RCT and two observational studies, involving 6,898 patients, were included in this analysis. The pooled MD in contrast volume was −7.05 mL (95% CI: −43.53 to 29.44), suggesting a slight reduction with CCTA-guided PCI (Figure 4). The MID for contrast volume reduction was set at ≥10 mL; the observed effect did not reach this threshold. The wide CI crossing zero and the high-risk of bias in some studies contributed to substantial uncertainty, resulting in a very low certainty of evidence (⨁◯◯◯) for imprecision and heterogeneity.

Table 3. Summary of findings: CCTA in complex PCI compared to angiography-guided PCI

Patient or population: Health problem or population
Setting:
Intervention: CCTA-guided complex PCI
Comparison: Angiography-guided complex PCI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with angiography-guided complex PCI	Risk with CCTA guided complex PCI				
Procedure success	859 per 1000	833 per 1000 (790 to 876)	RR 0.97 (0.92 to 1.02)	8311 (5 non-randomised studies)	⨁◯◯◯ Very low[a,b,c,d]	CCTA-guided PCI shows a similar likelihood of success compared to angio-guided PCI (RR=0.97, 95% CI: 0.92–1.02) and risk difference: -0.03 (95% CI: -0.07 to 0.02) The evidence is very low certainty about the effect of CCTA in complex PCI on procedure success.
Fluoroscopy time	The mean fluoroscopy Time was 50 minutes	MD 6.01 minutes more (7.71 fewer to 19.73 more)	-	6803 (1 RCT and 1 non-randomised study)	⨁◯◯◯ Very low[e,f,g]	Fluoroscopy time increased slightly with CCTA-guided PCI compared to angiography-guided PCI. The increase was small (6.01 minutes on average), but the evidence is uncertain due to inconsistency (high heterogeneity) and imprecision (wide CI crossing zero). Overall, while there is a trend toward longer fluoroscopy times with CCTA, the evidence quality is low.
Contrast volume	The mean contrast volume was 210 mL	MD 7.05 lower (43.53 lower to 29.44 higher)	-	6898 (1 RCT and 2 non-randomised studies)	⨁◯◯◯ Very low[h,i,j]	The pooled Mean difference of -7.05 mL suggests a slight decrease in contrast volume with CCTA-guided PCI. However, the evidence is very uncertain due to high-risk of bias, inconsistency, and imprecision.
MACE	15 per 1000	15 per 1000 (10 to 23)	OR 1.03 (0.67 to 1.58)	7236 (4 non-randomised studies)	⨁◯◯◯ Very low[k,l,m]	No significant difference in complications between CCTA-guided PCI and angiography-guided PCI. The evidence is very uncertain due to high-risk of bias, inconsistency, and imprecision.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval, MD: Mean difference, OR: Odds ratio, RR: Risk ratio, CCTA: Coronary computed tomography angiography, PCI: Percutaneous coronary intervention, MACE: Major adverse cardiac events
GRADE working group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Mostly non-randomized studies with confounding such as complexity of lesion, operator skills, use of IC imaging. Does not represent other complex lesions, only includes chronic total occlusion (CTO) lesions. [b]Variability in study results, likely due to different populations and procedural protocols, contributed to moderate heterogeneity. [c]Findings primarily apply to CTO PCI and are not generalizable to all types of complex PCI. [d]The pooled risk difference CI crosses 0, indicating no statistically significant effect. Wide CIs reflect imprecision in the estimate of the effect size. [e]High-risk of bias (due to the inclusion of one high-risk study). [f]I^2=99%, indicating significant heterogeneity between the studies. Differences in baseline characteristics and study design likely contribute to the inconsistency. High inconsistency. Downgraded: -1. [g]The CI crosses zero, indicating uncertainty about whether fluoroscopy time increases or decreases with CCTA. The wide CI also reduces confidence in the pooled estimate resulting in imprecise results. [h]Two of the three studies (Simsek and Xenogiannis) have a high-risk of bias due to imbalances in baseline characteristics, small sample sizes, and no statistical adjustments. Downgraded: -1. [i]High heterogeneity indicates significant variability across studies, driven by differences in study designs and results. Downgraded: -1. [j]The confidence interval crosses zero, indicating uncertainty about whether contrast volume increases or decreases. Downgraded: -1. [k]Moderate to high-risk of bias due to confounding and unadjusted observational data. Downgraded: -1. [l]I^2=75%, indicating substantial heterogeneity; Differences in study design (randomized controlled trials vs. observational studies). Variations in baseline characteristics and procedural complexity. Downgraded: -1. [m]CI: 0.67 to 1.58. The CI crosses 1, indicating no significant difference in complications. The wide range of the CI suggests uncertainty. Downgraded: -1

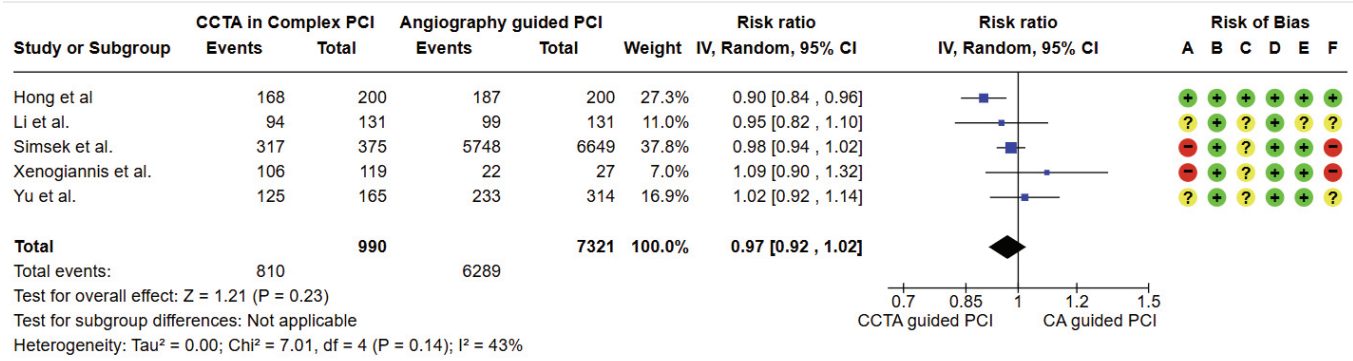

Figure 2. Forest plot for procedure success

CI: Confidence interval, CCTA: Coronary computed tomography angiography, PCI: Percutaneous coronary intervention

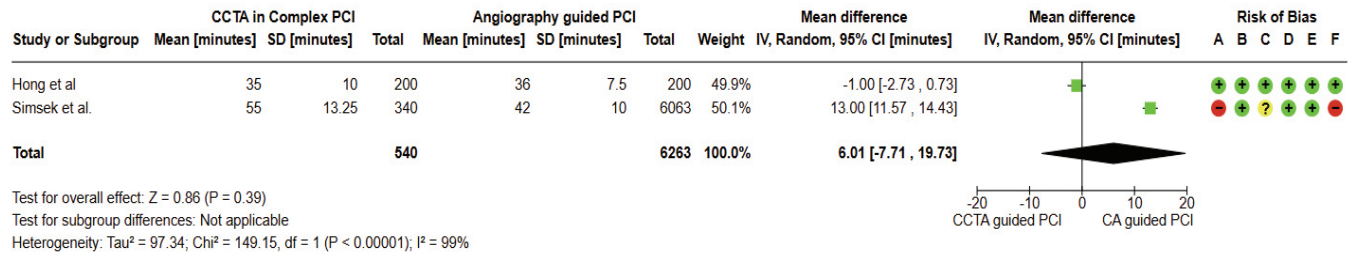

Figure 3. Forest plot for fluoroscopy time

CI: Confidence interval, CCTA: Coronary computed tomography angiography, PCI: Percutaneous coronary intervention, SD: Standard deviation

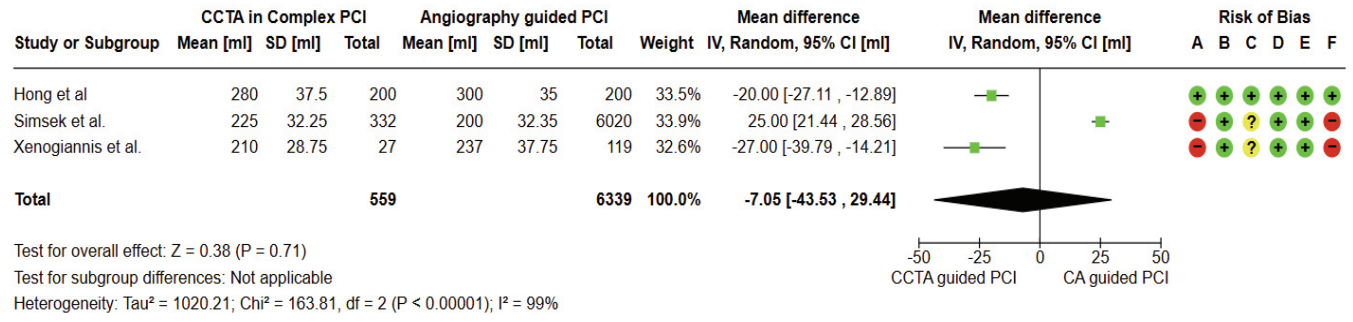

Figure 4. Forest plot for contrast volume

CI: Confidence interval, CCTA: Coronary computed tomography angiography, PCI: Percutaneous coronary intervention, SD: Standard deviation

Risk of bias was high in the observational studies due to potential confounders, such as baseline differences between groups. The RCT was found to have a low-risk of bias, as it was well-conducted and adhered to standard protocols.

Heterogeneity was moderate (I^2=60%; p=0.08), indicating some variability between studies, but not enough to substantially affect the pooled effect. Imprecision remained a concern because the CI included the null value, and the observed effect did not meet the MID.

Indirectness was not a concern, as the PICO elements of the included studies aligned with the review. Publication bias was not formally assessed due to the small number of studies; however, the comprehensive search minimized the risk.

Overall, the certainty of evidence for contrast volume was very low, indicating that the true effect of CCTA-guided PCI on contrast use remains uncertain.

Major Adverse Cardiac Events

Four studies, including one RCT and three observational studies, encompassing 7,236 patients, contributed to this analysis. The pooled OR for MACE was 1.03 (95% CI: 0.67–1.58), indicating no significant difference between CCTA-guided and angiography-guided PCI (Figure 5). The MID for complications was defined as even a single additional event; the observed effect did not reach this threshold.

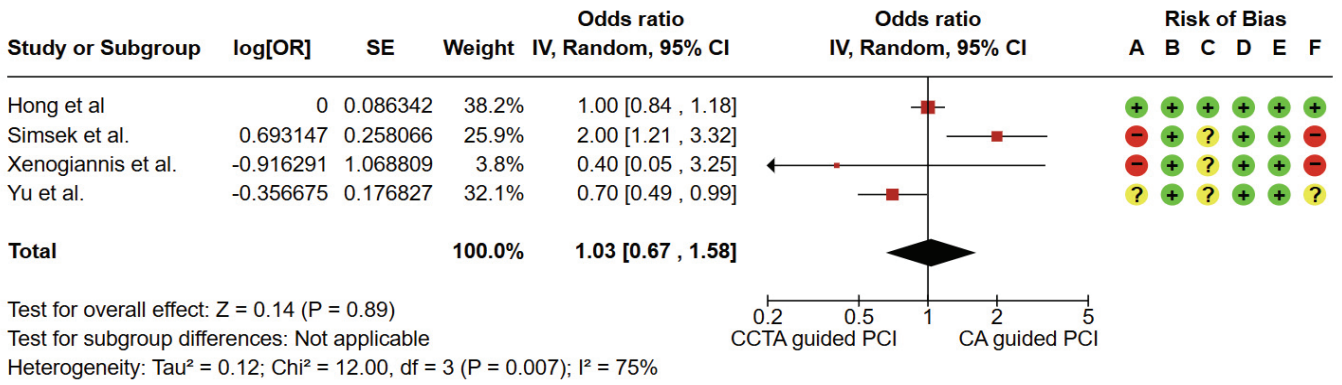

Figure 5. Forest plot for major adverse cardiac events

CI: Confidence interval, CCTA: Coronary computed tomography angiography, PCI: Percutaneous coronary intervention, OR: Odds ratio

Risk of bias was high in the observational studies due to confounding (e.g., baseline differences in patient characteristics) and incomplete outcome reporting. The RCT demonstrated a low-risk of bias due to proper randomization and accounting for confounders.

Substantial heterogeneity was high (I^2=75%; p=0.01), reflecting variability between studies. Wide CIs crossing 1 contributed to uncertainty in the effect estimate. Imprecision and heterogeneity led to downgrading the certainty of evidence to very low (⨁◯◯◯).

Indirectness was not a concern, as populations and interventions were consistent with the review's PICO. Publication bias was not formally evaluated due to the limited number of studies; nevertheless, the comprehensive search strategy minimized the risk of publication bias.

Overall, the certainty of evidence for MACE was very low, indicating that the true effect of CCTA-guided PCI on MACE was highly uncertain. Table 3 shows the summary of findings for different outcomes.

DISCUSSION

Summary of Results and Certainty of Evidence

This systematic review evaluated the utility of CCTA-guided PCI compared with angiography-guided PCI in CTO lesions. Data from five studies, including one RCT and four observational studies, indicated no clinically meaningful differences between the two strategies with respect to procedural success, fluoroscopy time, contrast volume, and MACE.

Using the GRADE framework, the certainty of evidence for all outcomes was rated as very low, primarily due to high-risk of bias, heterogeneity, and imprecision. For procedural success, the evidence was downgraded due to confounding in observational studies and moderate heterogeneity. For secondary outcomes, wide CIs and substantial heterogeneity (I^2 ranging from 43–99%) contributed to very low certainty. Similarly, MACE demonstrated no significant difference, with certainty downgraded because of high-risk of bias, heterogeneity, and imprecision.

Overall, while CCTA-guided PCI may offer advantages in procedural planning for CTO lesions, the current evidence remains insufficient to demonstrate a clear clinical benefit over angiography-guided PCI. High-quality randomized trials are warranted to clarify its role in complex PCI.

Study Limitations

A key limitation of this review is the small number of included studies, resulting in low event rates and imprecision in pooled estimates. The predominance of observational studies, which are susceptible to residual confounding—such as differences in lesion complexity and operator experience—further increased the uncertainty of the evidence.

Heterogeneity across studies, particularly for fluoroscopy time and contrast volume, was another limitation. Variability in patient populations, lesion characteristics, procedural protocols, and real-world differences in operator expertise and familiarity with CCTA workflows likely contributed to this heterogeneity, resulting in imprecision and inconsistency.

Furthermore, although the search strategy encompassed all complex PCI subsets, the included studies focused exclusively on CTO lesions. Consequently, the findings cannot be generalized to other complex PCI types, including multivessel disease, bifurcation lesions, severely calcified lesions requiring atherectomy, or graft interventions, due to insufficient data. Therefore, caution is warranted when extrapolating these results beyond CTO PCI, and further studies are needed to evaluate the utility of CCTA in other complex PCI contexts.

Comparison with Existing Literature

There is a notable gap in systematic reviews specifically evaluating the utility of CCTA in complex PCI procedures compared with angiography-guided PCI across diverse lesion types. Most available studies have focused on CTO procedures, with only one RCT and several observational studies published over the past decade.[5,9-12] Studies investigating CCTA in bifurcation lesions exist; however, these primarily assess outcomes different from those included in the present review.[7,8]

Our findings are consistent with the systematic review by Liang et al.,[4] which examined CCTA-guided PCI in CTOs. They reported that CCTA facilitated pre-procedural planning but had no significant effect on

procedural success or post-procedural MACE. Similarly, Hong et al.[5] reported that CCTA improved procedural planning in CTO cases but did not influence long-term clinical outcomes, particularly MACE. Several studies have explored emerging applications of CCTA in CTO PCI, and an ongoing randomized trial protocol is expected to provide more insight once completed.[13-16]

In contrast, studies examining CCTA in bifurcation PCI, such as those by Wolny et al.[7] and Mohamed et al.,[8] focused on procedural predictors, including side-branch occlusion. While these studies highlight the potential benefits of CCTA in predicting procedural complications, they did not evaluate outcomes such as procedural success or MACE, which were the primary endpoints of our review.

Overall, the current evidence, including our findings and those of Liang et al.,[4] suggests that CCTA may help optimize pre-procedural planning for CTO PCI. However, its impact on clinical outcomes, including MACE and procedural success, remains uncertain.

CONCLUSION

The current evidence on CCTA-guided PCI in CTO lesions is of very low certainty, leaving the clinical benefits over standard angiography—regarding procedural success, fluoroscopy time, contrast use, and MACE—uncertain. While CCTA may facilitate pre-procedural planning and detailed anatomical assessment, the lack of robust clinical outcome data and high heterogeneity across studies limit its routine application in practice.

Although this review aimed to assess complex PCI broadly, the evidence was confined to CTO populations. Therefore, the conclusions cannot be extended to other complex PCI subsets. High-quality RCTs with larger, more homogeneous cohorts are needed to clarify the role of CCTA in complex PCI. Future studies should evaluate procedural efficiency, clinical outcomes, and cost-effectiveness to provide comprehensive guidance on the utility of CCTA in contemporary interventional practice.

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

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Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary 1. Detailed risk of bias table of the included studies

Hong et al.[5] (RCT) - RoB 2 Assessment		
Bias domain	**Risk level**	**Support for judgment**
Randomization process	Low-risk	The study was well-designed with an effective randomization process, ensuring baseline comparability. Allocation methods were described clearly, and there was no evidence of systematic differences between groups.
Deviations from intended interventions	Low-risk	Although the trial was open-label, the outcomes were objective (e.g., procedural success), minimizing the potential impact of unblinding. The study adhered to its protocol and standardized methods, reducing the risk of bias.
Missing outcome data	Low-risk	The missing data was minimal (2.2%), evenly distributed between groups, and unlikely to bias the results. Complete follow-up data was available for most participants, reducing the risk of bias due to attrition.
Measurement of the outcome	Low-risk	The study used objective outcome measures, such as procedural success and TIMI flow grade. While the study was unblinded, the use of objective measures and careful assessment minimized the potential for bias.
Selection of the reported result	Low-risk	The study followed its pre-specified analysis plan and reported all results as outlined in the protocol. There is no indication of selective reporting, ensuring transparency and accuracy in the findings.
Overall judgment	Low-risk	The study was well-designed and carefully conducted, following proper methods such as randomization, consistent procedures, and objective outcome measurements. These factors minimize the risk of bias, resulting in a low overall risk.
Xenogiannis et al.[9] (retrospective observational study) - ROBINS-I assessment		
Bias domain	**Risk level**	**Support for judgment**
Confounding	High-risk	Significant differences between groups (e.g., higher rates of prior failed PCI attempts in the CTA group) were not addressed using statistical adjustments, leading to potential confounding.
Selection of participants	Low-risk	Patients were consecutively selected from the PROGRESS-CTO registry, ensuring comprehensive inclusion.
Classification of interventions	Low-risk	Interventions (CTA fusion-guided vs. non-CTA-guided PCI) were clearly defined and consistently classified.
Deviations from intended interventions	Low-risk	Procedures followed protocol without deviations, and group assignments were inherent to the observational design.
Missing data	Moderate risk	Missing procedural details, such as complete follow-up and patient-level data, may have influenced the analysis.
Measurement of outcomes	Low-risk	Objective outcomes (e.g., procedural success, complications) were reliably measured, minimizing bias.
Selection of the reported result	Low-risk	All pre-specified outcomes were reported transparently without evidence of selective reporting.
Overall judgment	High-risk	The lack of adjustment for baseline imbalances (e.g., prior failed PCI attempts) significantly increases the risk of confounding.
Li et al.[10] (single-center retrospective observational study) - ROBINS-I assessment		
Bias domain	**Risk level**	**Support for judgment**
Confounding	Moderate risk	Potential confounders, such as operator expertise or lesion characteristics, were not statistically adjusted, which could influence the observed outcomes.
Selection of participants	Low-risk	All consecutive patients undergoing CTO PCI were included, ensuring a representative sample and minimizing selection bias.
Classification of interventions	Low-risk	The interventions and outcomes (CCTA-derived RECHARGE scores and procedural success) were clearly defined and consistently applied.
Deviations from intended interventions	Low-risk	No deviations from the intended interventions were observed, as all procedures followed a consistent protocol.
Missing data	Moderate risk	Missing details on predictors, such as lesion complexity, were not fully described, which may have influenced the results.

Measurement of outcomes	Low-risk	Objective outcomes, such as procedural success and guidewire crossing time, were reliably measured with minimal bias.
Selection of the reported result	Low-risk	All pre-specified outcomes were reported without evidence of selective reporting.
Overall judgment	Moderate risk	Despite some limitations due to confounding and missing data, the study design and objective outcome measures support a moderate overall risk of bias.
Yu et al.[11] (multicenter retrospective observational study) - ROBINS-I assessment		
Bias domain	**Risk level**	**Support for judgment**
Confounding	Moderate risk	Although multivariable analysis was conducted, not all operator-related factors (e.g., expertise) were adjusted for, which could influence the observed outcomes.
Selection of participants	Low-risk	All eligible CTO PCI cases with preprocedural CCTA were included, ensuring a representative sample and minimizing selection bias.
Classification of Interventions	Low-risk	The interventions and outcomes (CCTA-derived predictions and guidewire crossing success) were clearly defined and appropriately classified.
Deviations from intended interventions	Low-risk	No deviations from intended procedures were evident, as all CTO PCI procedures followed planned protocols.
Missing data	Moderate risk	Some missing data on lesion-specific characteristics or operator variability were not fully addressed, potentially influencing subgroup analyses.
Measurement of outcomes	Low-risk	Objective metrics, such as guidewire crossing time and procedural success, were reliably assessed and reported.
Selection of the reported result	Low-risk	All pre-specified outcomes, including the development and validation of the KCCT score, were reported transparently.
Overall judgment	Moderate risk	Despite strengths in the design and outcome measurements, residual confounding and missing data contribute to a moderate overall risk of bias.
Simsek et al.[12] (multicenter retrospective observational registry study) - ROBINS-I assessment		
Bias domain	**Risk level**	**Support for judgment**
Confounding	High-risk	The study included a disproportionately smaller number of cases with preprocedural CCTA (375 cases, 5.3%) compared to cases without CCTA (6659 cases). This imbalance could amplify confounding effects, as observed differences in outcomes may be driven by the numerical disparity rather than the intervention itself. Although multivariable regression was used to adjust for some factors (e.g., lesion characteristics), residual confounding (e.g., operator expertise or institutional differences) remains likely.
Selection of participants	Low-risk	All eligible CTO PCI cases from the PROGRESS-CTO registry were included without exclusion, minimizing selection bias.
Classification of interventions	Low-risk	The classification of interventions (CCTA vs. non-CCTA) was clear and consistently applied.
Deviations from intended interventions	Low-risk	No deviations from intended procedures were noted, as the observational design naturally assigned interventions based on clinical practice.
Missing data	Moderate risk	Missing details about the decision-making process for using CCTA and other procedural variables could affect interpretability.
Measurement of outcomes	Low-risk	Objective outcomes (e.g., procedural success, MACE) were reliably measured, minimizing the risk of bias.
Selection of the reported result	Low-risk	All pre-specified outcomes were reported transparently without evidence of selective reporting.
Overall judgment	High-risk	The significant numerical imbalance between the groups (375 vs. 6659 cases) and the residual confounding from unmeasured factors contribute to a high risk of bias.

PCI: Percutaneous coronary intervention, CTO: Chronic total occlusion, ROBINS-I: Risk of bias in non-randomized studies of interventions, CCTA: Coronary computed tomography angiography, MACE: Major adverse cardiac events, TIMI: Thrombolysis in myocardial infarction

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ORIGINAL ARTICLE

Impact of Eosinophil Count on Short-Term Prognosis in Patients with Acute Pulmonary Embolism

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ABSTRACT

Background: Eosinophils, a type of inflammatory cell, have been implicated in thrombosis and proposed as a prognostic marker for various atherosclerotic cardiovascular diseases.

Aim: This study determine the value of an eosinophil count (EOSC) in predicting short-term prognosis in patients with acute pulmonary embolism (APE).

Study Design: Retrospective cohort study.

Methods: In this study, a total of 453 patients who were admitted with APE from September 2015 to July 2020 were retrospectively examined, and their admission complete blood cell counts were measured. The optimal cut-off point for EOSC was determined using receiver operating characteristic analysis. Patients were classified into the low EOSC (≤0.45) and high EOSC (>0.45) groups. Multivariate logistic regression analysis was performed to investigate the independent association between EOSC and early mortality (in-hospital and 30-day) outcomes in patients with APE.

Results: Throughout the hospitalization and 30-day follow-up, a total of 33 deaths (7.3%) occurred. Of the patients who survived, those who died were older and had significantly lower EOSC (p<0.001) but significantly higher white blood cell (WBC) (p<0.001) and platelet (p=0.025) counts. Multivariate regression analyses identified that decreased EOSC (≤0.45) [odds ratio (OR): 4.518; p=0.003], increased WBC count (OR: 1.135; p=0.012), and older age (OR: 1.048; p=0.029) were independently associated with short-term mortality.

Conclusion: A significant correlation was observed between low EOSC and elevated short-term mortality in patients with APE. Thus, blood EOSC can be used in daily clinical practice as a novel marker that correlates with the risk stratification of patients with APE.

Keywords: Eosinophil, mortality, inflammation, thrombus, acute pulmonary embolism

INTRODUCTION

Acute pulmonary embolism (APE) is regarded as the third most prevalent cause of mortality from cardiopulmonary disease, after acute myocardial infarction and stroke.[1,2] The incidence of APE is expected to increase further owing to the enhanced sensitivity of diagnostic imaging, population aging, and the rising prevalence of risk factors such as obesity and cancer linked to venous thromboembolism. Nevertheless, APE mortality rates remain a concern despite the advent of novel diagnostic and therapeutic procedures.[3] Consequently, the early identification of patients at elevated risk of mortality is critical. For this purpose, several risk classification systems have been formulated, including the simplified pulmonary embolism severity index (sPESI), and these indexes comprise several parameters such as blood pressure, echocardiographic evidence of right ventricular dysfunction (RVD), and computed tomography pulmonary angiography.[4] Nevertheless, the need for a reliable indicator that can be accurately and efficiently measured to predict adverse outcomes remains.

Cytokines are produced during inflammation and can trigger blood coagulation.[5] As our knowledge of inflammation and thrombogenesis associated with APE advances, multiple systemic inflammatory index models have been proposed to predict patient prognosis.[6] In this context, C-reactive protein (CRP),[7] D-dimer,[8] platelet count,[9] and white blood cell (WBC)[10] count have been identified as factors associated with APE mortality. These markers exhibit a close relationship between local inflammation and thrombosis within the pulmonary artery.[11] Eosinophils have also been implicated in various inflammatory responses[12] and in the pathogenesis of thrombosis,[13,14] suggesting a close link with APE occurrence. Previous studies have demonstrated that a low eosinophil count (EOSC) is significantly correlated with poor prognosis in various cardiovascular diseases.[15-21]

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However, the association between eosinophils and APE remains to be established. Therefore, this study aimed to examine EOSC's ability to predict the early prognosis (in-hospital or 30-day) of patients with APE.

METHODS

Study Design

This retrospective cohort study included patients with APE admitted between September 2015 and July 2020. Eligible participants were adults aged ≥18 years who presented with clinical signs suggestive of APE, exhibited computed tomography evidence of proximal filling defects involving at least one primary or lobar pulmonary artery, and demonstrated RVD on transthoracic echocardiography or computed tomography. All patients underwent computed tomography pulmonary angiography to confirm the diagnosis of APE. Exclusion criteria: (1) age <18 years; (2) missing EOSC data; (3) time of onset >14 days; (4) sepsis, malignancy, chronic inflammatory conditions, active infection, and use of immunosuppressive therapy at the time of diagnosis of APE.

This study was approved by the Non-Interventional Scientific Research Ethics Committee of Trakya University (approval number: 06/14, date: 01.04.2024).

Data Collection and Definitions

A comprehensive set of baseline demographic and health-related data was retrieved from the hospital's electronic database, including patient age, sex, heart rate, smoking history, presence of diabetes mellitus (DM), and systolic and diastolic blood pressure. The laboratory data collected at admission comprised hemoglobin, WBC count, platelet count, EOSC, serum creatinine, high-sensitivity CRP (hs-CRP), troponins, and D-dimer. All patients were followed up during their hospitalization. The primary endpoint was short-term mortality (in-hospital and 30-day).

Transthoracic echocardiography was performed at the time of hospitalization, and RVD and pulmonary artery systolic pressure were determined by experienced cardiologists.

Statistical Analysis

The distribution of continuous variables was initially evaluated for normality using the Shapiro–Wilk test, supported by visual inspection of Q–Q plots. Variables meeting normality assumptions were summarized as means with standard deviations and compared using the independent-samples t-test. Non-normally distributed variables were described as medians with interquartile ranges and assessed using the Mann–Whitney U test. Categorical variables were presented as counts with percentages and compared using either Pearson's chi-square test or Fisher's exact test, as appropriate. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to determine the optimal cut-off value for EOSC, after which patients were stratified into two groups based on this threshold. Independent prognostic factors for in-hospital mortality were examined using logistic regression. Variables with $p<0.05$ in univariate analyses were entered into multivariate models. The results were expressed as odds ratios (ORs) with 95% confidence intervals. Analyses were conducted using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p<0.05$.

RESULTS

Patient Characteristics

The baseline characteristics of the study participants are summarized in Table 1. This study involved 453 patients with APE. Relative to survivors, patients who died during hospitalization and 30-day follow-up had significantly lower EOSC ($p<0.001$) but significantly higher WBC ($p<0.001$) and platelet ($p=0.025$) counts (Figure 1). A comparative analysis of the two groups revealed that those who died early were older than those who survived. In terms of comorbidities and risk factors, the non-survivor patients had a higher incidence of DM ($p=0.014$) and RVD ($p=0.001$) and a lower incidence of active smoking ($p=0.014$). Patients who met the primary endpoint also had higher systolic pulmonary artery pressure (SPAP) and hs-CRP levels but lower arterial oxygen saturation (SaO_2). However, the other parameters did not differ significantly.

ROC curve analysis showed that admission EOSC had the best predictive value for short-term mortality in the overall APE population, with a sensitivity of 79.5% and a specificity of 72.7% (AUC=0.809, 95% CI: 0.743–0.875; $p<0.001$). The optimal cut-off value for the admission EOSC to identify short-term mortality risk in patients with APE was 0.45 (Figure 2). Based on the optimal cut-off point for EOSC determined using the ROC curve, patients were classified into the low (EOSC ≤0.45) and high (EOSC >0.45) EOSC groups. Compared with patients exhibiting high EOSC, those with low EOSC were older and had significantly higher WBC and D-dimer levels but lower SaO_2 and systolic blood pressure and less active smoking. In addition, hs-CRP, troponin values, and RVD prevalence were higher in the high EOSC group, and the difference was borderline significant ($p=0.051$, 0.067, and 0.066, respectively) (Table 2).

Relationship between EOSC and mortality

Logistic regression analysis was performed to identify independent predictors of in-hospital mortality. A univariate logistic regression found the following as significant risk factors for early mortality: age, DM, active smoking, SaO_2, EOSC ≤0.45, SPAP, RVD, WBC count, platelet count, and hs-CRP. When these confounders were controlled for in multivariate logistic regression, low EOSC (≤0.45) (OR: 4.518; 95% CI: 1.693–12.058; $p=0.003$), older age (OR: 1.048; 95% CI: 1.005-1.092; $p=0.029$), and increased WBC count (OR: 1.135; 95% CI: 1.028 to 1.253; $p=0.012$) were significantly associated with short-term mortality (Table 3).

DISCUSSION

To the best of our knowledge, this study is the first to assess the predictive value of EOSC in APE mortality. The following findings were observed: (1) relative to surviving patients, those who died had lower EOSC levels and higher WBC and platelet counts, and (2) despite adjustment for potential confounders, low EOSC (≤0.45) was an independent predictor of early mortality in patients with APE.

APE is a prevalent cardiovascular disorder that has been associated with elevated morbidity and mortality rates.[1] Consequently, prompt and precise risk assessment at initial diagnosis is necessary to inform treatment decisions and mitigate mortality. APE-induced thrombo-

Table 1. Baseline characteristics of patients with and without in-hospital and 30-day mortality

Variables	Survivor (n=420)	Non-survivor (n=33)	p value
Age, years	63±16	73±9	<0.001
Male gender, n (%)	185 (44%)	18 (54%)	0.243
Diabetes mellitus, n (%)	43 (10%)	8 (24%)	0.014
Active smoker, n (%)	153 (36%)	5 (15%)	0.014
White blood cell count (x109/L)	10.3±3.7	15.2±5.3	<0.001
Platelet count (x109/L)	252±72	282±98	0.025
Hemoglobin (g/dL)	12.4±2.1	12.1±2.1	0.294
Total cholesterol (mg/dL)	173±41	157±40	0.068
Low density lipoprotein cholesterol (mg/dL)	107±36	100±33	0.378
High density lipoprotein cholesterol (mg/dL)	36±12	33±12	0.223
Triglyceride (mg/dL)	118 (89-151)	111 (88-147)	0.784
Creatinine (mg/dL)	0.89 (0.75-1.2)	1.07 (0.92-1.36)	0.105
Eosinophil count (x109/L)	1.6 (0.6-2.8)	0.3 (0.03-0.5)	<0.001
D-dimer (mg/L)	4514(2624-7084)	5343 (2514-8725)	0.199
Peak troponin value (ng/mL)	0.8 (0.07-8.3)	2.4 (0.1-4.6)	0.519
High-sensitivity C-reactive protein (mg/L)	22.7 (7.0-79.8)	46.6 (22.3-100)	0.017
Systolic blood pressure (mmHg)	116±16	111±25	0.106
Diastolic blood pressure (mmHg)	72±12	68±13	0.074
Arterial oxygen saturation (%)	89.2±8.8	81.2±11.6	<0.001
Systolic pulmonary artery pressure (mmHg)	49±16	58±13	0.005
Thrombolytic therapy, n (%)	157 (37%)	14 (42%)	0.565
Right ventricular dysfunction, n (%)	258 (61%)	30 (90%)	0.001

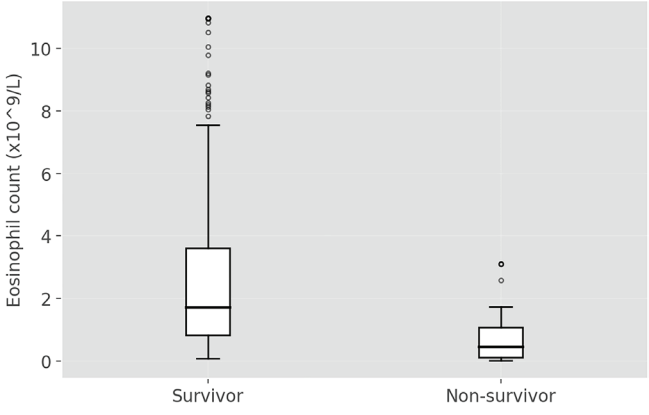

Figure 1. Comparison of eosinophil ratios between the two groups

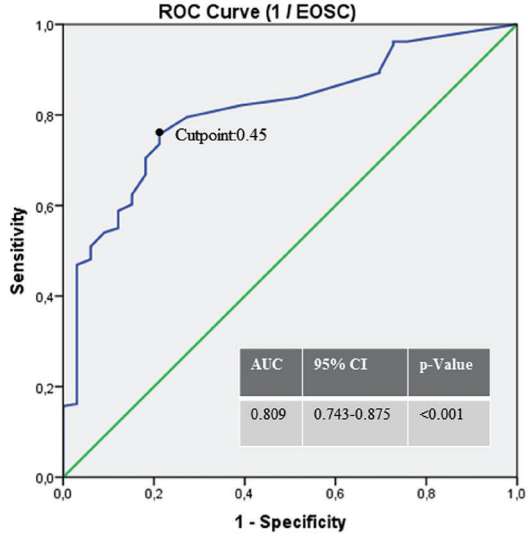

Figure 2. ROC analyses table; cut point values and ROC curves

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, EOSC: Eosinophil count

inflammation plays a vital role in the patient's prognosis. In this regard, several prognostic biomarkers are independent predictors for adverse outcomes in patients with APE.[6,7] Eosinophils are also involved in various inflammatory responses and thrombotic processes.[8-10] Toor et al.[11] examined the prognostic significance of EOSC in patients with coronary artery disease, reporting that elevated preprocedural EOSC levels were associated with enhanced outcomes within the initial 6 months following percutaneous coronary intervention. An earlier study has shown the relevance of eosinopenia and unfavorable outcomes in patients with acute ischemic stroke.[12] Similarly, another retrospective study documented that eosinopenia is a predictor of unfavorable long-term cardiac outcomes in patients with ST-segment elevation myocardial infarction.[13] In addition, a Turkish study of 1,909 patients

Table 2. Baseline characteristics of patients stratified by the optimal cutoff point of EOSC

Variables	High EOSC (>0.45) (n=343)	Low EOSC (≤0.45) (n=110)	p value
Age, years	61±17	69±12	<0.001
Male gender, n (%)	153 (44.6%)	50 (45.5%)	0.912
Diabetes mellitus, n (%)	34 (9.9%)	17 (15.5%)	0.120
Active smoker, n (%)	131 (38.2%)	27 (24.5%)	0.011
White blood cell count (x109/L)	9.8±3.2	13.3±5.2	<0.001
Platelet count (x109/L)	255±75	250±74	0.569
Hemoglobin (g/dL)	12.5±2.2	12.2±2.01	0.218
Total cholesterol (mg/dL)	174±40	166±44	0.102
Low density lipoprotein cholesterol (mg/dL)	108±35	102±38	0.162
High density lipoprotein cholesterol (mg/dL)	36±12	34±13	0.092
Triglyceride (mg/dL)	117 (88-156)	118 (89-136)	0.810
Creatinine (mg/dL)	0.96 (0.88-1.25)	1.13 (0.95-1.34)	0.122
Eosinophil count (x109/L)	2.0 (1.1-3.3)	0.18 (0.08-0.2)	<0.001
D-dimer (mg/L)	4211(2437-6382)	5374 (2807-9938)	0.001
Peak troponin value (ng/mL)	0.8 (0.5-6.0)	2.4 (0.2-18)	0.067
High-sensitivity C-reactive protein (mg/L)	22 (7-75)	41 (7-93)	0.051
Systolic blood pressure (mmHg)	117±16	112±16	0.010
Diastolic blood pressure (mmHg)	72±13	71±11	0.611
Arterial oxygen saturation (%)	90±8	84±11	<0.001
Systolic pulmonary artery pressure (mmHg)	50±17	51±14	0.674
Right ventricular dysfunction, n (%)	210 (61.2%)	78 (70.9%)	0.690

EOSC: Eosinophil count

Table 3. Independent predictors for in-hospital and 30-day acute pulmonary embolism mortality

Variables	Multivariate analysis		
	OR	95% CI	p value
Age	1.048	1.005-1.092	0.029
Diabetes mellitus	1.989	0.663-5.965	0.220
Active smoker	0.553	0.184-1.665	0.292
White blood cell count	1.135	1.028-1.253	0.012
Platelet count	3.538	0.530-23.618	0.192
High sensitivity C-reactive protein	1.006	1.000-1.012	0.057
Systolic pulmonary artery pressure	1.010	0.980-1.041	0.531
Arterial oxygen saturation	0.992	0.949-1.036	0.706
Right ventricular dysfunction	3.350	0.810-13.849	0.095
EOSC ≤0.45	4.518	1.693-12.058	0.003

OR: Odds ratio, CI: Confidence interval, EOSC: Eosinophil count

with acute myocardial infarction found that the rates of in-hospital mortality and major adverse cardiac events were significantly higher among patients with low blood EOSCs than among those with high EOSCs.[14] Furthermore, a study involving 5,287 patients who underwent coronary angiography revealed that patients with myocardial infarction had significantly lower blood EOSCs than those without coronary artery disease.[15] Sincer et al.[16] detected an inverse relationship between blood EOSCs and the severity of acute coronary syndrome subgroups in elderly patients. A more recent study revealed a significant correlation between low eosinophil percentage and elevated mortality rates in patients with acute type A aortic dissection.[17] Furthermore, blood EOSC was identified to be associated with the calcification scores of various arterial segments, ranging from the coronary to the iliac arteries.[18] No published studies have evaluated the link between eosinophils and APE. To our knowledge, this is the first study to demonstrate a correlation between low EOSCs and short-term (in-hospital and 30-day) APE mortality. Reduced circulating eosinophils were associated with a 4.5-fold increase in early mortality. Consequently, EOSC appears to be a more reliable predictor of adverse outcomes in patients with APA as it indicates both inflammation and thrombosis. This ROC cut-off value can be used to extend more careful and intensive care follow-ups in patients presenting with APE and an EOSC of <0.45. Its relationship with the need for thrombolysis can also be examined in future studies.

The blood EOSC can decrease for various reasons. Eosinophilia is often associated with allergic diseases, helminthic infections, eosinophilic

granulomatosis with polyarteritis (Churg–Strauss syndrome), Hodgkin lymphoma, and hypereosinophilic syndrome.[19] Certain pharmacological agents (beta-lactam antibiotics, nitrofurantoin, antiepileptics, and non-steroidal anti-inflammatory drugs) can cause drug-induced eosinophilia via immune-mediated mechanisms.[20] In contrast, glucocorticoids induce eosinopenia by suppressing the release of eosinophils from the bone marrow and increasing the redistribution of circulating cells to tissues.[21] In addition, hypercortisolemic or inflammatory conditions such as acute infections, severe stress, Cushing's syndrome, and sepsis are characterized by a marked decrease in eosinophil levels.[22] Therefore, quantitative assessment of EOSCs holds clinical value as a crucial biological marker in the diagnosis of underlying immunological, infectious, or pharmacological processes.

APE, which is related to chest pain and dyspnea, can trigger acute stress responses that stimulate the release of glucocorticoids, such as cortisol,[23] which can lead to eosinopenia via apoptosis.[24] Furthermore, eosinophils are proinflammatory cells that release large quantities of cytokines, growth factors, and chemokines, thereby enhancing inflammatory reactions.[25] Our data showed a negative correlation between EOSC and WBC count and hs-CRP levels. This observation suggests that a severe inflammatory reaction occurs when EOSC decreases. Multivariate regression analysis indicated that reduced EOSC, together with older age and increased WBC, were independent predictors of APE mortality, even after adjusting for all possible confounding factors. The presence of cytokines and chemokines at the site of a thrombus may lead to an accumulation of eosinophils. This buildup could potentially reduce the number of circulating eosinophils.[26] Another study by Riegger et al.[27] showed that eosinophils are present in all patients with stent thrombosis. Moreover, the presence of aggregated eosinophils in the pulmonary artery may contribute to the development and progression of APE by affecting the inflammatory response and thrombosis. Eosinophils can produce tissue factors and a procoagulant phospholipid surface. These factors activate the prothrombinase complex, generating thrombin and promoting fibrin formation.[28] Furthermore, eosinophils interact with platelets at the thrombus site, resulting in mutual activation. Eosinophils migrate into the thrombi and activate platelets, leading to platelet activation by eosinophils. Therefore, activated platelets may contribute to thrombus formation.[29] In the light of the possible mechanisms mentioned above, we suggest that greater inflammatory response and thrombus burden may explain the more serious clinical condition and, ultimately, increased mortality in patients with APE.

Study Limitations

This study has several potential limitations that must be acknowledged. First, owing to the relatively small sample size and single-center, retrospective nature of the study, some biases are inevitable. Other factors that could cause low or high EOSC, such as asthma, allergic diseases, and medication use, were not considered in this study. Moreover, the relationship between the sPESI index and EOSC in patients with APE was not examined in this study and warrants further investigation. Second, although elevated EOSCs were confirmed at admission in patients with APE, the mechanisms by which eosinophils contribute to the pathogenesis of APE remain undetermined. Thus, further studies are warranted to elucidate the role of eosinophils in APE development.

CONCLUSION

Our data demonstrated that decreased EOSC is a rapid, simple, and inexpensive tool for predicting early prognosis and is significantly associated with increased short-term mortality in patients with APE. Therefore, in daily clinical practice, blood EOSC can be used as a novel marker for risk classification in patients with APE. This finding indicates that eosinophils play a previously unreported dynamic role in the clinical course, and further studies should investigate whether EOSCs can serve as a guide for APE diagnosis and treatment.

Ethics Committee Approval: This study was approved by the Non-Interventional Scientific Research Ethics Committee of Trakya University (approval number: 06/14, date: 01.04.2024).

Informed Consent: Retrospective study.

Authorship Contributions: Concept: M.G., F.K., A.K., Design: M.G., F.K., A.K., Data Collection or Processing: M.G., F.K., U.V., A.K., K.Y., Analysis or Interpretation: M.G., F.K., Literature Search: U.V., A.K., K.Y., Writing: M.G., U.V., A.K., K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

The Relationship Between Acute Kidney Injury and Naples Prognostic Score Following Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: Acute kidney injury (AKI) following transcatheter aortic valve replacement (TAVR) is a common and serious complication that adversely affects patient prognosis and in-hospital mortality rates. Identifying patients at a higher risk before the procedure remains a clinical priority.

Aim: This study aimed to investigate the relationship between AKI and the Naples prognostic score (NPS) in patients undergoing TAVR.

Study Design: This was a retrospective, single-center cohort study.

Methods: A total of 203 patients who underwent TAVR between 2019 and 2024 were retrospectively evaluated in this study. Patients were divided into two groups according to the presence or absence of AKI. Logistic regression analysis was used to determine the independent predictors of AKI, and receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of NPS.

Results: AKI occurred in 39 of the 203 patients (19.2%). A high NPS was significantly more frequent in the AKI group than in the non-AKI group (61.5% vs. 39.6%, p=0.013). Multivariate analysis identified the following as independent predictors of AKI: high NPS [odds ratio (OR): 3.41; 95% confidence interval (CI): 1.08-10.78; p=0.037], lower estimated glomerular filtration rate (OR: 0.87; 95% CI: 0.83-0.92; p<0.001), elevated C-reactive protein (OR: 2.35; 95% CI: 1.49-3.72; p<0.001), higher contrast volume (OR: 1.07; 95% CI: 1.03-1.11; p=0.001), lower ejection fraction (OR: 0.94; 95% CI: 0.90-0.98; p=0.004), and elevated glycated hemoglobin (OR: 2.12; 95% CI: 1.13-4.00; p=0.020). ROC curve analysis showed that an NPS cut-off value of 2.5 predicted AKI with 61.5% sensitivity and 60.4% specificity (area under the curve: 0.635; 95% CI: 0.544-0.726; p=0.009).

Conclusion: The NPS may serve as a practical and easily applicable tool for identifying patients at increased risk of AKI following TAVR. Incorporating NPS into preprocedural risk assessment could improve patient stratification and guide preventive management.

Keywords: Naples prognostic score, transcatheter aortic valve replacement, acute kidney injury

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has introduced significant advancements in severe aortic stenosis treatment, particularly in elderly patients and those at a high surgical risk.[1] However, despite the growing experience, TAVR remains to be associated with various periprocedural complications. Acute kidney injury (AKI) is a key determinant of adverse clinical outcomes.[2] The reported incidence of AKI after TAVR ranges from 10 to 30%, with multiple contributing mechanisms, including contrast-induced nephropathy, hemodynamic instability, systemic inflammation, and embolic events.[3,4] The association between AKI and both short- and long-term mortalities underscores the importance of identifying modifiable risk factors and predictive scoring systems to optimize the patient selection and perioperative management.[5-7]

The Naples prognostic score (NPS) functions as a comprehensive biomarker evaluating the following four key parameters: serum albumin levels reflecting the nutritional status and the anti-inflammatory capacity; total cholesterol (TC) levels representing metabolic balance; absolute lymphocyte count indicating the immune competence; and the neutrophil-to-lymphocyte ratio (NLR) as a systemic inflammation marker. Initially developed and validated in oncology patients, NPS also demonstrates a prognostic value in the field of cardiovascular diseases, depicting strong associations with adverse outcomes in patients undergoing coronary artery bypass grafting (CABG) and those with chronic heart failure.[8,9]

Emerging evidence suggests that systemic inflammatory response and malnutrition play crucial roles in the AKI pathogenesis following cardiovascular interventions. The NPS is not only associated with systemic inflammation and immune-nutritional status but also with endothelial dysfunction and oxidative stress, which are also key contributors to renal injury.[10] Recent studies demonstrated the value of the NPS in AKI prediction following acute coronary syndrome; however, its role in post-TAVR AKI remains unclear.[11]

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This study investigates the relationship between the preprocedural NPS and the AKI incidence following TAVR. It is hypothesized here that a high NPS reflecting a proinflammatory and malnourished state may independently predict AKI development and serve as a novel tool for risk stratification and individualized perioperative management. Clarifying this relationship can contribute to improved patient selection, development of early preventive strategies, and better clinical outcomes in patients undergoing TAVR.

METHODS

Study Population and Design

This retrospective, single-center cohort study involved 203 patients who underwent TAVR between January 2019 and December 2024 for severe symptomatic aortic stenosis. The patients who underwent TAVR and possessed complete preprocedural laboratory data, including serum albumin, TC, monocyte and lymphocyte counts, and serum creatinine levels, were included in this work.

The study population was divided into two subgroups based on AKI occurrence following the procedure: 1) patients who developed AKI; and 2) those who did not. AKI was diagnosed by reviewing the serum creatinine levels recorded in the hospital's electronic medical records. It was then defined as either a ≥0.3 mg/dL absolute increase or a ≥50% relative increase in serum creatinine within 48-72 h after the procedure compared to the baseline.

The patients were excluded from the study if they met any of the following criteria: undergoing multivalvular interventions, receiving chronic hemodialysis or peritoneal dialysis, active severe infections or sepsis, presenting with cardiogenic shock, or uncorrectable anemia.

The clinical characteristics, demographic data, procedural details, and follow-up information were retrospectively collected and evaluated using the hospital's electronic medical record system. The AKI development was evaluated by analyzing the serum creatinine levels at baseline and 48-72 h after the procedure.

The study protocol was approved by the Ethics Committee of University of Health Sciences Türkiye, Koşuyolu High Specialty Training and Research Hospital (decision number: 2025/09/1146; date: 03/06/2025), and it adhered to the ethical principles outlined in the Declaration of Helsinki. Only the anonymized retrospective data were used; hence, an informed consent was not required.

Definition of AKI after TAVR

AKI following TAVR is defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as recommended by the updated consensus report of the Valve Academic Research Consortium-3.[12] Accordingly, AKI is diagnosed if any of the following criteria are met: a serum creatinine increase by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h, an increase to ≥1.5 times the baseline value within 7 days, or a urine output of <0.5 mL/kg/h for at least 6 h. All patients classified into different AKI stages according to the KDIGO criteria were grouped into a single category, called "post-TAVR AKI," to ensure consistency in the statistical analysis.

Preprocedural Assessment and Procedural Technique

The patients diagnosed with symptomatic and severe aortic stenosis evaluated as candidates for TAVR underwent a comprehensive preprocedural assessment. This evaluation included a detailed clinical examination, routine laboratory tests, coronary angiography, transthoracic echocardiography, contrast-enhanced computed tomography angiography for vascular anatomy assessment, and consultations from relevant specialties as necessary. All the collected data were reviewed by a multidisciplinary heart team comprising cardiologists, cardiac surgeons, anesthesiologists, and radiologists to determine the patient eligibility for the procedure.

For the eligible patients, TAVR was electively performed via a percutaneous transfemoral approach. Depending on the patient's clinical condition and institutional protocols, the interventions were performed under either deep sedation or general anesthesia. A temporary pacemaker was inserted via the femoral route as a precaution against rapid ventricular pacing and potential atrioventricular conduction disturbances during the procedure.

Vascular access has been most commonly percutaneously achieved through the right femoral artery. At the end of the procedure, the access sites were closed using Proglide vascular closure devices. Based on anatomical and clinical suitabilities, self-expanding bioprosthetic valves (e.g., CoreValve, Evolut R/Pro, Portico, and ACURATE neo) or balloon-expandable ones (e.g., Edwards SAPIEN XT, S3, and ULTRA) were implanted.

Following the valve deployment, control angiography was performed to exclude aortic regurgitation, paravalvular leak, dissection, and vascular complications. Non-ionic, low-osmolarity contrast agents (i.e., iohexol or iodixanol) were utilized in all the procedures. The volume of contrast administered varied depending on the valve type and the vascular access strategy but was generally maintained within low-to-moderate levels. The renal function parameters were closely monitored both before the contrast administration and at 48-72 h postprocedure.

Postprocedural medical therapy was planned according to the current ESC/EACTS guidelines for the valvular heart disease. Single antiplatelet therapy (i.e., either acetylsalicylic acid or clopidogrel) was initiated in patients without an indication for oral anticoagulation (OAC). Short-term dual antiplatelet therapy was administered for 3-6 months in the selected patients with high thrombotic and low bleeding risks. For patients with an indication for OAC, OAC alone was preferred. Additional antiplatelet agents were not used.

Calculation of the Naples Prognostic Score

The NPS was calculated based on the following four laboratory parameters: serum albumin concentration, TC concentration, NLR, and lymphocyte-to-monocyte ratio (LMR), as previously described in the literature. Scoring was performed as follows: serum albumin <4 mg/dL was assigned with 1 point, while ≥4 g/dL was assigned with 0 points. For the TC, values <180 mg/dL received 1 point, and ≥180 mg/dL received 0 points. An NLR >2.96 was scored as 1 point, whereas values ≤2.96 were scored as 0. Similarly, an LMR ≤4.44 was assigned with 1 point, while >4.44 was assigned with 0 points. Figure 1 illustrates the total NPS score calculated as the sum of these four binary scores.

Statistical Analysis

All the statistical analyses used were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). The continuous variables are expressed as mean±standard deviation or median (interquartile range), while the categorical ones are presented as counts and percentages. The normality was assessed using the Kolmogorov-Smirnov test and a visual inspection of the histograms.

The group comparisons were conducted using independent sample t-tests or Mann-Whitney U tests for the continuous variables and Pearson's chi-square or Fisher's exact tests for the categorical variables. The statistical significance was set at a two-tailed p value <0.05.

A stepwise binary logistic regression analysis was performed to identify the independent predictors of AKI, incorporating variables with p<0.10 in a univariate analysis and those of known clinical relevance. The multicollinearity among the independent variables was assessed using the variance inflation factor (VIF) and tolerance values. Variables with a VIF >5 were considered indicative of a potential multicollinearity and, hence, were excluded or carefully interpreted. The final model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test (p>0.05). The results were reported as odds ratios (OR) with 95% confidence intervals (CI).

To minimize the overfitting risk caused by the limited number of events relative to the number of predictors, the model complexity was restricted and justified by clinical plausibility.

The receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of the NPS and its individual AKI components. The area under the curve (AUC), optimal cut-off value, sensitivity, and specificity are also reported.

Parameter	Threshold Value	Points
Serum albumin(mg/dl)	<4.0 ≥4.0	1 0
Total cholesterol (mg/dl)	≤180 >180	1 0
Neutrophil to lymphocyte ratio	>2.96 ≤2.96	1 0
Lymphocyte to monocyte ratio	≤4.44 >4.44	1 0

Total Score	Risk Category
0-2	Low Naples Prognostic Score
3-4	High Naples Prognostic Score

Figure 1. Cut-off values and calculation of the Naples prognostic score

RESULTS

This study included 203 patients who underwent TAVR and classified according to AKI development. Table 1 summarizes the demographic characteristics of the study cohort. AKI was found to occur in 39 (19.2%) patients. No significant differences existed between the AKI (+) and

Table 1. Comparison of the baseline characteristics by the acute kidney injury status after TAVR

Variable	Total (n=203)	AKI (–) (n=164)	AKI (+) (n=39)	p value
Gender (female)	122 (60.1%)	101 (61.6%)	21 (53.8%)	0.373
Age (years)	80.07±5.70	80.01±5.92	80.23±4.98	0.827
Height (m)	1.617±0.083	1.614±0.082	1.635±0.090	0.153
Weight (kg)	74.83±14.06	74.54±14.19	75.92±13.61	0.581
BMI (kg/m^2)	28.55±5.33	28.58±5.49	28.41±4.73	0.860
Hypertension n%	177 (87.2%)	143 (87.2%)	34 (87.2%)	1.000
Diabetes mellitus n%	84 (41.4%)	61 (37.2%)	23 (59.0%)	0.011
Hyperlipidemia n%	73 (36.0%)	60 (37.0%)	13 (33.3%)	0.672
Chronic kidney disease n%	32 (15.8%)	15 (9.1%)	17 (43.6%)	<0.001
Peripheral artery disease n%	8 (3.9%)	7 (4.3%)	1 (2.7%)	1.000
CABG history n%	37 (18.3%)	30 (18.4%)	7 (19.4%)	0.885
Valve surgery history n%	12 (6.0%)	8 (4.9%)	4 (11.1%)	0.210
PCI history n%	54 (26.7%)	43 (27.2%)	11 (29.7%)	0.756
CAD n%	102 (50.2%)	81 (50.0%)	21 (53.8%)	0.673
Atrial fibrillation n%	60 (29.6%)	44 (26.8%)	16 (41.0%)	0.081
RBBB n%	4 (2.8%)	3 (2.5%)	1 (4.2%)	0.527
LBBB n%	9 (6.4%)	7 (5.9%)	2 (8.3%)	0.650
Naples risk (high) n%	89 (43.8%)	65 (39.6%)	24 (61.5%)	0.013

The continuous variables are given as means and standard deviations or medians and interquartile ranges (25-75th)
BMI: Body mass index, CABG: Coronary artery bypass grafting, PCI: Percutaneous coronary intervention, CAD: Coronary artery disease, RBBB: Right bundle branch block, LBBB: Left bundle branch block, AKI: Acute kidney injury, TAVR: Transcatheter aortic valve replacement

AKI (−) groups in terms of age, sex, body mass index, height, or weight (p>0.05). Likewise, the prevalence of hypertension, hyperlipidemia, prior CABG, previous valve surgery, history of percutaneous coronary intervention, coronary artery disease, and electrocardiogram conduction abnormalities (right or left bundle branch block) was similar between the groups (p>0.05).

In contrast, diabetes mellitus was significantly more common in the AKI (+) group. The prevalence of chronic kidney disease (CKD) was substantially higher among patients who developed AKI (43.6% vs. 9.1%, p<0.001), a finding that highlights the strong association between baseline renal dysfunction and AKI. Although not statistically significant, atrial fibrillation was observed more frequently in the AKI (+) group.

Among the 203 patients, 43.8% (n=89) were classified into the high NPS group. The proportion of patients with high NPS was 39.6% in the non-AKI group and 61.5% in the AKI group, and this difference was statistically significant (p=0.013).

Table 2 shows that several laboratory and clinical parameters significantly differed between groups. The baseline and postoperative creatinine levels and the C-reactive protein (CRP) concentrations were significantly higher in the AKI (+) group (all p<0.001). Conversely, the estimated glomerular filtration rate (eGFR) was markedly lower (p<0.001).

The other notable findings included higher glycated hemoglobin (HbA1c) levels, lower left ventricular ejection fraction (LVEF), and greater contrast volume exposure in the AKI (+) group (all p<0.001). The lymphocyte counts were also significantly reduced in patients with AKI (p=0.044). Although the hemoglobin, hematocrit, and TC levels tended to be lower in the AKI (+) group, the differences were not statistically significant. No significant differences were observed in the white blood cell count, neutrophils, monocytes, total protein, albumin, liver enzymes (i.e., aspartate aminotransferase and alanine aminotransferase), or platelet count between the two groups. The NLR was higher in the AKI (+) group; however, the difference was not statistically significant (4.17±2.17 vs. 3.99±3.53, p=0.770). The LMR was lower in the AKI (+) group, but this difference was also not statistically significant (2.52±1.18 vs. 2.75±1.29, p=0.307).

Table 3 summarizes the results of the univariate and multivariate logistic regression analyses. In the univariate logistic regression analysis, several clinical and procedural variables were significantly

Table 2. Comparison of the laboratory and clinical parameters between the AKI and non-AKI groups

Variable	AKI (−) (n=164)	AKI (+) (n=39)	p value
Hemoglobin g/dL	11.72±2.10	10.99±2.28	0.062
Hematocrit %	36.22±7.11	34.64±4.47	0.089
WBC×10³/µL	7.28±2.22	6.67±1.93	0.119
Platelets/µL	111.097±123.265	133.051±128.658	0.333
Neutrophils×10³/µL	5.11±2.04	4.75±1.70	0.318
Lymphocytes×10³/µL	1.55±0.61	1.33±0.57	0.044
Monocytes×10³/µL	0.62±0.25	0.59±0.25	0.442
Neu/lym ratio	3.99±3.53	4.17±2.17	0.770
Lym/mono ratio	2.75±1.29	2.52±1.18	0.307
Total protein g/L	68.91±9.49	68.23±8.05	0.734
Albumin g/L	39.34±4.66	38.67±5.62	0.440
Total cholesterol mg/dL	187.84±46.77	175.36±46.84	0.136
Creatinine mg/dL	0.97±0.22	1.26±0.19	<0.001
Postop creatinine mg/dL	1.22±0.23	2.01±0.28	<0.001
eGFR mL/min/1.73 m²	64.99±12.70	47.77±9.29	<0.001
CRP mg/L	5.12±1.62	6.61±1.08	<0.001
AST U/L	26.46±21.61	25.84±13.03	0.867
ALT U/L	19.97±26.09	20.01±20.95	0.993
HbA1c %	6.49±0.78	7.11±1.11	<0.001
EF %	57.88±11.03	49.64±14.66	<0.001
Contrast volume mL	74.36±14.62	88.49±13.38	<0.001

The continuous variables are given as means and standard deviations or medians and interquartile ranges (25-75th)
WBC: White blood cell, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HbA1c: Glycated hemoglobin, EF: Ejection fraction, Neu/lym ratio: Neutrophil-to-lymphocyte ratio; Lym/mono ratio: Lymphocyte-to-monocye ratio, AKI: Acute kidney injury, min: Minimum

Table 3. Univariate and multivariate logistic regression analyses of the factors associated with AKI

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Naples risk score (high)	2.44 (1.19-4.99)	0.015	3.41 (1.08-10.78)	0.037
eGFR (mL/min/1.73m²)	0.90 (0.88-0.93)	<0.001	0.87 (0.83-0.92)	<0.001
Contrast volume (mL)	1.06 (1.04-1.09)	<0.001	1.07 (1.03-1.11)	0.001
CRP (mg/dL)	1.91 (1.46-2.49)	<0.001	2.35 (1.49-3.72)	<0.001
LVEF (%)	0.95 (0.93-0.98)	<0.001	0.94 (0.90-0.98)	0.004
HbA1c (%)	2.07 (1.41-3.05)	<0.001	2.12 (1.13-4.00)	0.020
Diabetes mellitus	2.13 (1.05-4.32)	0.036	-	-
Chronic kidney disease	19.93 (8.10-49.01)	<0.001	-	-

AKI: Acute kidney injury, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, EF: Ejection fraction, HbA1c: Glycated hemoglobin, OR: Odds ratio, CI: Confidence interval, LVEF: Left ventricular ejection fraction

associated with the AKI development following TAVR. A high NPS was significantly associated with an increased AKI risk (OR=2.44, 95% CI: 1.19-4.99, p=0.015). Similarly, lower baseline eGFR, higher contrast volume, elevated CRP levels, reduced LVEF, higher HbA1c values, presence of diabetes mellitus, and preexisting CKD were also significantly associated with AKI in the univariate analysis (all p<0.05).

In the multivariate logistic regression model that included variables with clinical relevance and statistical significance in the univariate analysis, the high NPS remained as an independent AKI predictor (OR=3.41, 95% CI: 1.08-10.78, p=0.037). Other independent predictors included lower eGFR (OR=0.87, 95% CI: 0.83-0.92, p<0.001), higher contrast volume (OR=1.07, 95% CI: 1.03-1.11, p=0.001), elevated CRP (OR=2.35, 95% CI: 1.49-3.72, p<0.001), reduced LVEF (OR=0.94, 95% CI: 0.90-0.98, p=0.004), and higher HbA1c (OR=2.12, 95% CI: 1.13-4.00, p=0.020). Notably, despite showing significant associations in the univariate analysis, diabetes mellitus and CKD did not retain statistical significance in the multivariate model likely due to their collinearity with the other covariates.

The ROC curve analysis was performed to assess the predictive ability of the NPS and its components for AKI (Table 4, Figure 2). The NPS demonstrated a moderate predictive ability for AKI, with an AUC of 0.633 (95% CI, 0.542-0.724; p=0.010). Based on the Youden Index, the optimal cut-off value for AKI prediction was 2.5, yielding a sensitivity of 61.5% and a specificity of 60.4%.

None of the individual NPS components, including albumin, TC, NLR, and LMR, showed statistically significant predictive values for AKI (AUCs ranging from 0.415 to 0.556, all p>0.05).

The forest plot in Figure 3 visualizes the discriminative performance of the key clinical and laboratory predictors of AKI. To enhance the interpretability, the OR values were repositioned around a reference value of 1.0, where values >1.0 denote an increased risk, and values <1.0 indicate protective effects.

Among the predictors, HbA1c, contrast volume, CRP, and high NPS were displayed on the right side of the reference line (>1.0), suggesting a significant association with the increased AKI risk.

Table 4. ROC analysis for the NPS score and its components

Predictor	AUC (95% CI)	p value
NPS	0.633 (0.542-0.724)	0.010
Albumin	0.415 (0.313-0.516)	0.098
Total cholesterol	0.415 (0.313-0.514)	0.099
NLR	0.556 (0.451-0.661)	0.276
LMR	0.459 (0.349-0.569)	0.429

ROC: Receiver operating characteristic, NPS: Naples prognostic score, AUC: Area under the curve, CI: Confidence interval, NLR: Neutrophile/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio

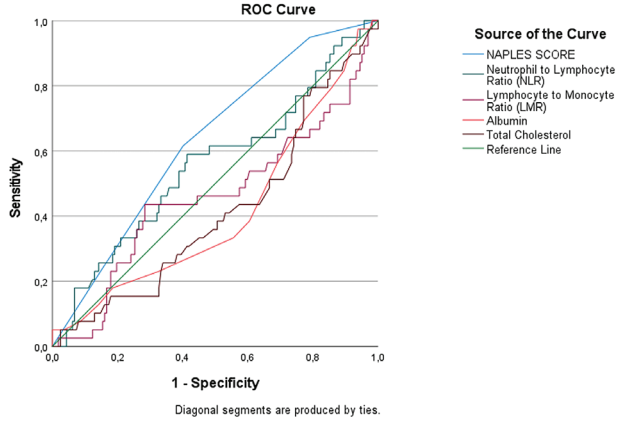

Figure 2. Receiver operating characteristic curve of the Naples prognostic score and its components
ROC: Receiver operating characteristic

Conversely, the eGFR and the LVEF lie to the left of the reference line (<1.0), indicating a protective role.

Both in-hospital and 30-day mortality rates were significantly higher among patients with elevated Naples risk scores and those who developed AKI. A p value <0.05 was considered significant.

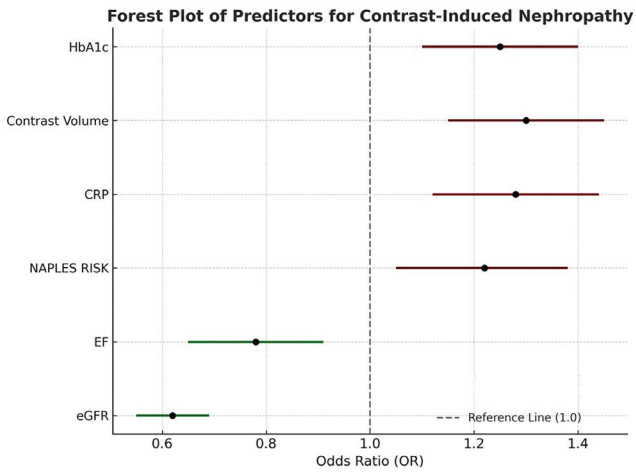

Figure 3. Forest plot illustrating the predictive value of the clinical and laboratory variables for acute kidney injury

CRP: C-reactive protein, EF: Ejection fraction, eGFR: Estimated glomerular filtration rate, HbA1c: Glycated hemoglobin

DISCUSSION

This study demonstrated a significant association between AKI following TAVR and a high NPS. Our findings suggest that the NPS, which is a composite index reflecting the systemic inflammation and nutritional status, may serve as a potential prognostic tool for predicting AKI in patients with cardiovascular disease undergoing TAVR.

Our ROC analysis yielded important insights into the diagnostic utility of the NPS in AKI prediction. The NPS demonstrated a statistically significant discriminative ability (AUC: 0.633, p=0.010), although this value indicated a limited predictive capacity.

The individual components of NPS, namely, serum albumin (AUC: 0.415, p=0.098), TC (AUC: 0.415, p=0.099), NLR (AUC: 0.556, p=0.276), and LMR (AUC, 0.459; p=0.429), did not show statistically significant predictive values for AKI. The AUC values of serum albumin and TC falling below 0.5 particularly suggested a weak and non-directional performance in AKI prediction. These findings support the notion that composite scores incorporating multiple parameters may be more valuable than individual biomarkers in clinical practice.

The analysis of Yelgeç et al.[13] identified the NLR, a key component of the NPS, as a strong predictor of AKI following TAVR. In contrast, although the NLR was higher in patients with AKI in this work, the difference was not statistically significant, suggesting that the NLR may not serve as a universal biomarker for all patient populations, and its predictive value can be influenced by factors like the multifactorial nature of inflammation, sample size, and comorbid conditions. These findings highlight that composite scoring systems combining inflammatory and metabolic parameters may provide a more reliable risk prediction.

The NPS, with its composite structure reflecting both systemic inflammation and nutritional status, has been shown in various studies to possess clinical relevance not only in acute clinical conditions but also across a broader cardio-renal-metabolic spectrum. For instance, in a recent study by Hong et al.[14], the NPS levels were significantly higher in individuals with early-stage CKD than in healthy controls. These also showed a positive correlation with the markers of systemic inflammation and renal dysfunction. These findings suggest that inflammation-based risk-scoring systems may play an increasingly important role in the integrated evaluation of various cardiovascular and renal conditions.

Our study demonstrated that parameters like HbA1c, contrast volume, CRP level, and NPS are significantly associated with AKI development following TAVR. These variables reflect the detrimental impact of metabolic dysregulation, systemic inflammation, malnutrition, and physiological stress induced by the procedure on renal function. In other words, AKI is not only solely related to procedural factors but is also closely linked to systemic pathophysiological processes.[15]

In contrast, cardiorenal reserve indicators, such as a higher eGFR and LVEF, play a protective role against AKI. eGFR and LVEF reductions may lead to diminished renal perfusion, thereby increasing susceptibility to kidney injury. These opposing associations highlight the multifactorial nature of AKI and underscore the importance of considering both local and systemic factors in risk assessments.

In this context, composite scoring systems, such as the NPS, which provide a holistic assessment of the inflammation and nutritional status, may enhance the predictive accuracy when used alongside traditional risk markers. The prognostic value of the NPS has also been demonstrated in various cardiovascular conditions in the recent studies, including acute coronary syndrome, heart failure, aortic stenosis treated with surgical or percutaneous interventions, peripheral artery disease, and pulmonary embolism.[16-18]

Similarly, in a large multicenter cohort from the "Magna Graecia" Registry comprising 1,535 patients, the AKI incidence following TAVR is 15.3%. In this study, several risk scores, including Mehran, WBH, CR4EATME3AD3, and ACEF, were retrospectively evaluated and found to be significantly higher in patients who developed AKI. However, the ROC analyses revealed that these scores had a limited predictive power (AUC ≤0.604). Additionally, the multivariate analysis identified various procedure-related and patient-specific factors (e.g., recent revascularization, use of self-expanding prostheses, atrial fibrillation, low-osmolar contrast media, and blood transfusion) as the independent risk factors for AKI.[19]

These findings suggest that AKI following TAVR represents a complex clinical condition that is shaped by multifactorial cause-and-effect relationships and that the current scoring systems may not always provide sufficient predictive power. Therefore, new and more sensitive risk scores specifically tailored to the TAVR population must be developed.

In light of all these data, easily applicable composite scoring systems, such as the NPS, which integrates markers of inflammation and nutritional status, are believed to contribute to both the general management of cardiovascular diseases and to the prediction of post-TAVR complications. Incorporating these tools into the preprocedural risk stratification can enable an earlier identification of high-risk individuals, a preventive strategy optimization, and the ultimate improvement of patient outcomes.

In this study, as show in Table 5, both the in-hospital and 30-day mortality rates were significantly higher among patients who

developed AKI and those with elevated NPS. Specifically, the in-hospital mortality rate was 35.9% in the AKI (+) group compared to 4.3% in the AKI (−) group (p<0.001). Similarly, the 30-day mortality rate was 20.0% in patients with AKI versus 3.8% in those without AKI (p=0.002). The prevalence of the high NPS was also significantly greater in the AKI (+) group (61.5% vs. 39.6%, p=0.013). These findings, as demonstrated in Table 5, suggest that this scoring system reflecting both inflammation and nutritional deficiency may be associated with poor short-term outcomes after TAVR.

Table 5. Association between AKI, Naples risk score, and mortality outcomes

Variables	AKI (−) (n=164)	AKI (+) (n=39)	p value
High Naples risk score, n (%)	65 (39.6%)	24 (61.5%)	0.013
In-hospital mortality, n (%)	7 (4.3%)	14 (35.9%)	<0.001
30-day mortality, n (%)	6 (3.8%)	5 (20.0%)	0.002

AKI (+): Patients who developed acute kidney injury, and AKI (−): Patients without AKI
AKI: Acute kidney injury

Our findings are consistent with those of previous studies highlighting the prognostic value of the NPS in structural heart interventions. In a prospective study, a high NPS (≥3) was identified as an independent predictor of the 1-year all-cause mortality and major adverse cardiovascular events in patients undergoing TAVR.[20] The authors emphasized that systemic inflammation and malnutrition, which are the core NPS components, are critical contributors to the adverse clinical outcomes following TAVR. Our study supports this relationship, demonstrating that the coexistence of a high NPS and AKI significantly increases the early mortality risk.

The NPS score offers the advantage of reflecting the multifactorial nature of AKI, possibly playing a complementary role in clinical decision-making as a low-cost and easily accessible predictor. However, it should be emphasized that the NPS should ideally be supported by more robust models with a stronger predictive power.

Study Limitations

Our study has several limitations. First, it was designed retrospectively and conducted at a single center, which may have introduced a selection bias and limited the findings' generalizability. The relatively small sample size may have also reduced the statistical power for detecting certain associations, particularly in the subgroup analyses. The exclusion of patients with incomplete data may have also introduced unexpected effects on the study outcomes.

Furthermore, the NPS was assessed only during the preprocedural period without accounting for the dynamic changes in its components over time. The acute alterations in parameters, such as the albumin levels or the lymphocyte counts potentially influenced by dehydration, systemic inflammatory responses, or transient nutritional imbalances, may have affected the stability and the accuracy of the score.

Finally, the prognostic performance of the NPS was not directly compared with the other validated risk prediction tools for AKI, such as the Mehran or ACEF scores. This omission limits the ability of assessing the relative predictive value of the NPS. Future studies comparing the NPS with established AKI risk scores may better elucidate the clinical utility of the NPS.

CONCLUSION

This study finds that the NPS is a potentially significant predictor of AKI after TAVR. However, considering the modest AUC value and the lack of a comparative validation with established risk scores, the prognostic strength of the NPS must be interpreted with caution. Therefore, incorporating the NPS with the other well-known clinical and procedural risk factors may enhance the risk assessment accuracy. Further large-scale multicenter studies are needed to more robustly validate the predictive value of the NPS.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of University of Health Sciences Türkiye, Koşuyolu High Specialty Training and Research Hospital (decision number: 2025/09/1146; date: 03/06/2025), and it adhered to the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions: Concept: Z.E.G., R.Z., Design: Z.E.G., R.Z., Data Collection or Processing: R.B., Analysis or Interpretation: Z.E.G., R.Z., Literature Search: Z.E.G., Writing: Z.E.G., R.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

Effect of Magnesium Levels on the Progression of Contrast-induced Nephropathy in NSTEMI Patients Undergoing PCI

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ABSTRACT

Background: Contrast-induced nephropathy (CIN) is the most common cause of hospital-acquired acute renal failure. The increased use of contrast media in diagnostic and interventional cardiac catheterization procedures and the increased frequency of these procedures have made CIN a common problem in clinical cardiology practice.

Aim: The aim of our study was to understand the role of magnesium (Mg^{2+}) levels in patients who developed CIN after non-ST elevation myocardial infarction (NSTEMI).

Study Design: The study was conducted retrospectively and a total of 4,324 patients who applied to the cardiology clinic with NSTEMI were included in the study.

Methods: This retrospective single-center study included 4,003 NSTEMI patients undergoing percutaneous coronary intervention (PCI). Patients with systemic inflammatory or rheumatologic diseases, hematologic disorders, renal or hepatic failure, infection, malignancy, or prior thrombolytic therapy were excluded. CIN was defined as an increase in serum creatinine ≥25% or ≥0.5 mg/dL within 48-72 hours after contrast exposure. Statistical analyses were performed using SPSS 26.0. Logistic regression identified independent predictors, and receiver operating characteristic (ROC) analysis determined the optimal magnesium cut-off for CIN prediction.

Results: CIN occurred in 1,062 patients (26.5%). Patients who developed CIN were older and had higher rates of diabetes mellitus, lower systolic blood pressure, and lower left ventricular ejection fraction. Serum magnesium levels were significantly lower in patients with CIN. ROC analysis identified an Mg^{2+} cut-off of 2.13 mg/dL [area under the curve=0.745, 95% confidence interval (CI): 0.681-0.809, p<0.001; sensitivity 78%, specificity 76%]. In multivariate analysis, age, diabetes, systolic blood pressure, preprocedural creatinine, estimated glomerular filtration rate, and Mg^{2+} <2.13 mg/dL (OR=2.02, 95% CI: 1.71-2.31, p<0.001) were independent predictors of CIN.

Conclusion: Low magnesium levels are independently associated with an increased risk of CIN in NSTEMI patients undergoing PCI. Routine assessment of Mg^{2+} before contrast exposure may help identify high-risk patients and improve prevention strategies.

Keywords: Magnesium, non-ST elevation myocardial infarction, contrast induced nephropathy

INTRODUCTION

Contrast-induced nephropathy (CIN), which is most often a reversible form of acute kidney injury, is a major complication of the coronary angiography (CAG) and percutaneous coronary procedures that is linked to adverse clinical outcomes.[1] Even when percutaneous revascularization is technically successful, the CIN occurrence in these patients has consistently been associated with prolonged hospitalization alongside higher mortality and morbidity rates.[2] Multiple determinants have been implicated in the CIN risk, including the type and the dose of the administered contrast, concurrent use of nephrotoxic medications, systemic inflammation, diabetes mellitus (DM), pre-existing renal impairment, heart failure (HF), advanced age, reduced hemoglobin concentrations, and female sex.[3] Coronary artery disease (CAD) is the most prevalent cardiovascular disorder that carries substantial mortality and morbidity. CAD may clinically manifest as silent ischemia, stable or unstable angina pectoris, acute myocardial infarction, HF, or even sudden cardiac death. When atherosclerosis underlies the presentation, CAD frequently appears as acute coronary syndrome (ACS). In contemporary practice, ACS is categorized into three groups based on the initial electrocardiogram and biochemical markers: ST-elevation myocardial infarction (STEMI); non-STEMI (NSTEMI), in which myocardial injury is verified by elevated damage markers despite no ST elevation; and unstable angina. For patients diagnosed with ACS, early therapy—thrombolytics in the coronary care setting and/or percutaneous coronary intervention (PCI) in the catheterization laboratory—is implemented to promptly restore patency and blood flow in a coronary artery that is acutely occluded by thrombus. PCI has markedly improved ACS management by reducing ischemic complications and improving survival; nevertheless, the

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intraprocedural use of contrast agents heightens the likelihood of CIN characterized by an acute deterioration in the renal function.[4] The CIN pathophysiology remains incompletely clarified. Proposed mechanisms include perturbations in renal hemodynamics, injury mediated by oxygen-derived free radicals, direct tubular cytotoxicity of the contrast medium,[5] and vasoconstriction within the renal microvasculature.

The most widely used CIN definition is a serum creatinine increase exceeding 25% over baseline or an absolute rise greater than 0.5 mg/dL above the baseline level.[6] Clinically, CIN is considered an acute kidney injury typically emerging within 5-7 days after intravenous contrast exposure and cannot be explained by alternative etiologies;[7] however, the more severe CIN forms—those with a higher probability of requiring hemodialysis—most often present within the first 48 h following the procedure. There is broad expert agreement on the importance of adequate hydration and the avoidance of hypovolemia prior to contrast administration. In addition, several pharmacologic strategies have also been investigated in the literature for CIN prevention, including N-acetylcysteine,[8] theophylline,[9] fenoldopam,[10] sodium bicarbonate,[11] and ascorbic acid.[12] Among these, sodium bicarbonate did not demonstrate superiority over iso-osmolar saline infusion,[13] while the other agents have generally shown, at best, a marginal adjunctive efficacy when added to optimal hydration. The rationale for a magnesium-mediated protective effect in CIN draws on the following observations: CIN appears more frequent among patients with hypomagnesemia;[14] combining magnesium supplementation with N-acetylcysteine confers protection against post-ischemic acute renal failure;[15] and hypomagnesemia is implicated in the pathobiology of chronic cyclosporine nephropathy.[16] On the basis of these magnesium-related data in the CIN context, we sought to examine the association between the serum magnesium levels and the CIN development among patients with NSTEMI undergoing PCI.

METHODS

Study Design and Population

This retrospective, observational analysis included a total of 4,324 patients managed between August 2020 and August 2024. Due to insufficient or missing data, 321 individuals were excluded, leaving 4,003 patients for the final evaluation. Cases that were considered eligible were those who presented to the emergency department with an NSTEMI diagnosis and subsequently underwent CAG. Within this cohort, the patients were monitored for the CIN occurrence, and those who developed CIN were identified and assessed. A written informed consent was obtained from all the participants. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Tokat Gaziosmanpaşa University Hospital (decision number: 25-MOBAEK-136; date: 24.04.2025). The study received no financial support from any institution or organization. Artificial intelligence-supported technologies, such as large language models, chatbots, or image generators, were not employed in the generation, processing, or analysis of the study data.

The serum magnesium levels were measured in patients with NSTEMI. Their relationship with the CIN development was also examined. The NSTEMI diagnosis was established according to the European Society of Cardiology Guideline criteria.[17] The patients were excluded if they received thrombolytic therapy prior to the invasive procedure, if an invasive procedure was not performed within 12 h of the symptom onset; or if they had systemic inflammatory or rheumatologic disease, storage disease, anemia, malignancy, were younger than 18 years, had any hematologic disease, including acute or chronic stroke, advanced renal and/or hepatic failure, a history of acute or chronic infection, blood transfusion within the prior 3 months, severe valvular disease, or prior valve surgery.

Laboratory Parameters and Demographic Data

The biochemical parameters were obtained using a Beckman Coulter LH-750 hematology analyzer (Beckman Coulter, Inc., Fullerton, California). All the blood samples were collected after an overnight fast with patients in a sitting or supine position. Routine laboratory tests, including serum magnesium, were drawn immediately prior to the PCI procedure. DM was considered as a fasting plasma glucose level >125 mg/dL, HbA1c >6.5%, or ongoing use of antidiabetic therapy (oral agents/insulin). The patients were considered to have hyperlipidemia if their total cholesterol and low-density lipoprotein cholesterol exceeded 200 mg/dL and 100 mg/dL, respectively, or if they used lipid-lowering medications. Hypertension (HT) was considered as the use of antihypertensive drugs or a systolic/diastolic blood pressure >140/90 mmHg. Individuals who smoked within the previous 6 months were classified as smokers. Serum creatinine was measured on hospital admission and again 48 to 72 h after exposure to the contrast agent. CIN was defined as a creatinine increase of >0.5 mg/dL or a ≥25% rise within 48 h following PCI.

Echocardiography, Coronary Angiography, and Risk Scoring

Prior to CAG, all patients underwent transthoracic echocardiography using the Vivid E7 (GE Vingmed Ultrasound) system with an MS5 (1.5-4.5 MHz) probe. The left ventricular ejection fraction (LVEF) was calculated using the Simpson method. All CAG and PCI procedures were performed on the Xper Allura FD-10 C-arm detector system (Philips Medical Systems International B.V., Best, Netherlands). The standard Judkins technique with a 6 Fr catheter was employed in all cases using either femoral or radial access. The procedure duration and the total volume of contrast administered were recorded. The PCI procedures were performed by two experienced interventional cardiologists. For each patient, the MEHRAN risk score (MRS) was calculated, incorporating eight clinical and procedural variables: age >75 years, hypotension, congestive HF, intra-aortic balloon pump, serum creatinine, DM, anemia, and contrast volume. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula.

Statistical Analysis

All analyses and figure generation were executed in SPSS v26.0 (SPSS Inc., Chicago, IL, USA). For continuous measures, the distributional properties were evaluated both by formal testing with the Kolmogorov-Smirnov test and by a visual inspection of the histograms and quantile-quantile (Q-Q) plots. Based on these assessments, the continuous variables are described as mean±standard deviation when approximately normal or as median with interquartile range,

otherwise. The between-group contrasts used Student's t-test or the Mann-Whitney U test as appropriate. The categorical data were reported as counts and percentages and compared using Pearson's chi-square (χ^2) test. We identified the optimal cut-point of Mg^{2+} for predicting CIN by performing a receiver operating characteristic (ROC) analysis. The resulting threshold was then applied to dichotomize the Mg^{2+} levels. The CIN associations were first screened via univariable logistic regression. The variables meeting the significance criterion ($p<0.05$) were subsequently retained in a multivariable logistic regression model. The effect estimates are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). To aid the interpretation of the binary endpoint across the Mg^{2+} strata, we additionally plotted a stratified incidence graph and a model-based predicted-probability curve from the logistic regression. A two-sided $p<0.05$ was taken to denote the statistical significance throughout.

RESULTS

A total of 4,003 patients were included in the analysis. CIN was observed to develop in 1,062 individuals (26.53%). Table 1 summarizes the cohort's demographic, clinical, laboratory characteristics, and medications. The between-group comparisons demonstrated significant differences in age, DM, LVEF, systolic blood pressure, and MRS. In the laboratory profile, the preprocedural and postprocedural creatinine, hemoglobin and hematocrit, troponin, C-reactive protein, and Mg^{2+} levels were all statistically significant.

Among patients with NSTEMI, the ROC analysis identified an Mg^{2+} cut-off of 2.13 mg/dL with an area under the curve of 0.745 (95% CI 0.681-0.809, $p<0.001$), a sensitivity of 78%, and a specificity of 76% (Figure 1). In the multivariate logistic regression model, age, DM, systolic blood pressure, MRS, preprocedural creatinine, eGFR, and Mg^{2+} <2.13 mg/dL emerged as the independent predictors of CIN in the myocardial infarction population (OR: 2.019, 95% CI: 1.712-2.310, $p<0.001$; Table 2). Table 3 presents the CIN incidence distribution across the Mg^{2+} strata.

The graphical analyses in Figure 2 depict the association between the Mg^{2+} concentration and the CIN among 4,003 NSTEMI patients undergoing PCI. Figure 2a presents that 730 out of 1,920 (38%) patients with Mg^{2+} <2.13 mg/dL developed CIN, whereas 332 of 2,083 (17%)

Table 1. Baseline demographic, hematological, and angiographic characteristics, and medications of patients according to the presence or absence of contrast-induced nephropathy (CIN)

Variable	No-CIN (n=2941)	CIN (n=1062)	p
Age (mean±SD)	66.49±8.7	69.91±8.91	**0.003**
Gender (female, n%)	1323 (44.98)	477 (44.91)	0.883
BMI (mean±SD)	28.19±5.70	29.01±3.89	0.207
DM (n%)	1176 (39.98)	456 (42.93)	**0.013**
HT (n%)	1030 (35.02)	371 (34.93)	0.119
HL (n%)	852 (28.96)	297 (27.96)	0.503
COPD (n%)	529 (17.98)	192 (18.07)	0.294
Current smoker (n%)	1211 (41.17)	432 (40.67)	0.179
Previous myocardial infarction (n%)	812 (27.60)	290 (27.30)	0.209
HF (n%)	1128 (38.35)	413 (38.88)	0.228
LVEF (%)	50.21±5.78	47.54±6.33	**0.010**
Systolic blood pressure (mmHG)	112.20±15.36	83.69±10.30	**<0.001**
MEHRAN score	4.92±1.03	11.41±3.79	**<0.001**
Hematological results			
Pre-precedural creatinine (mg/dL)	0.95±0.23	1.23±0.43	**0.015**
Pre-precedural eGFR (mL/dk/1.73 m^2)	85.41±11.23	68.52±10.47	**<0.001**
Post-precedural creatinine (mg/dL)	1.02±0.47	1.84±0.70	**<0.001**
Post-precedural eGFR (mL/dk/1.73 m^2)	83.25±10.9	45.11±11.36	**<0.001**
Hemoglobin (g/dL)	12.28±3.79	9.56±3.41	**0.022**
Hematocrit value	40.11±5.39	33.40±5.71	**<0.001**
Platelet (x10^3/µL)	412.20±35.79	413.70±36.71	0.059
Total cholesterol (mg/dL)	218.20±19.44	221.70±18.61	0.843
LDL cholesterol (mg/dL)	128.36±15.3	129.28±14.8	0.597

Table 1. Continued

Variable	No-CIN (n=2941)	CIN (n=1062)	p
ALT (U/L)	41.23±9.3	42.13±8.52	0.491
AST (U/L)	31.57±8.20	32.47±7.90	0.145
Sodium (mmol/L)	134.41±8.70	135.09±7.07	0.555
Potassium(mmol/L)	4.57±1.08	4.45±1.12	0.637
Magnesium (mg/dL)	2.5±1.12	1.83±0.42	**<0.001**
CRP (mg/L)	13.54±3.54	25.47±5.31	**<0.001**
Troponin (ng/mL)	452.12±30.47	469.09±28.41	**0.035**
Coronary angiography procedure results			
LAD (n%)	882 (29.98)	318 (29.94)	0.761
LCX (n%)	891 (30.29)	323 (30.41)	0.593
RCA (n%)	1171 (39.81)	421 (39.62)	0.509
Amount of contrast medium (mL)	126.31±21.30	125.33±23.27	0.712
Procedure time (min)	42.20±10.41	41.39±9.39	0.831
TIMI flow grade	2.49±0.12	2.01±0.04	**<0.001**
Medications			
ACE inh/ARB (n%)	1852 (62.87)	659 (62.05)	0.887
Beta-blocker (n%)	1458 (49.57)	530 (49.90)	0.795
Statin medication (n%)	863 (29.34)	312 (29.37)	0.437
Antiagregan medication (n%)	896 (30.46)	329 (30.97)	0.913

ALT: Alanin aminotransferaz, AST: Aspartat aminotransferaz, LDL: Light density lipoprotein, TSH: Thyroid stimulating hormone, T4: Thyroxine, CRP: C-reactive protein, WBC: White blood cell, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme blocker, ARB: Angiotensin receptor blocker, SS: Syntaks score, DM. Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, HF: Heart failure, LVEF: Left ventricular ejection fraction, eGFR: Estimated glomerular filtration rate, LAD: Left antrior desending artery, LCX: Circumflex artery, RCA: Right coronary artery, TIMI: Thrombolysis score in myocardial infarction, SD: standard deviation, CIN: contrast-induced nephropathy

Table 2. Univariate and multivariate regression analysis to identify independent predictors in contrast nephropathy patients

Variable	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age	1.156 (1.022-1.309)	0.018	1.221 (1.045-1.427)	0.011
Diabetes mellitus	1.342 (1.101-1.621)	0.007	1.287 (1.041-1.556)	0.019
LVEF (%)	1.052 (0.821-1.311)	0.321	0.893 (0.711-1.122)	0.274
Systolic blood pressure (mmHg)	1.189 (1.041-1.387)	0.014	1.165 (1.031-1.349)	0.021
MEHRAN score	1.952 (1.049-2.579)	0.021	1.876 (1.120-2.449)	0.008
Pre-procedural creatinine (mg/dL)	1.341 (1.112-1.615)	0.002	1.297 (1.076-1.559)	0.005
Pre-procedural eGFR (mL/min/1.73 m²)	1.298 (1.087-1.489)	0.009	1.244 (1.041-1.482)	0.017
Post-procedural creatinine (mg/dL)	1.118 (0.945-1.326)	0.172	1.083 (0.881-1.297)	0.282
Post-procedural eGFR (mL/min/1.73 m²)	1.097 (0.841-1.325)	0.411	1.061 (0.792-1.289)	0.503
Hemoglobin (g/dL)	1.032 (0.813-1.249)	0.672	0.943 (0.712-1.189)	0.461
Hematocrit value	1.153 (0.907-1.419)	0.247	1.098 (0.833-1.317)	0.391
CRP (mg/L)	1.221 (0.991-1.497)	0.061	1.093 (0.884-1.345)	0.337
Troponin (ng/mL)	1.137 (0.989-1.307)	0.071	0.913 (0.711-1.201)	0.511
TIMI flow grade	1.179 (0.974-1.417)	0.091	0.926 (0.742-1.165)	0.497
Magnesium <2.13 (mg/dL)	2.236 (1.821-2.419)	<0.001	2.019 (1.712-2.310)	<0.001

LVEF: Left ventricular ejection fraction, CRP: C-reactive protein, TIMI: Thrombolysis score in myocardial infarction, CI: Confidence interval, eGFR: Estimated glomerular filtration rate

Table 3. Relationship between magnesium levels and CIN development

Magnesium group	CIN (+) patients	CIN (-) patients	Total	CIN incidence
Mg <2.13 mg/dL	730	1190	1920	38%
Mg ≥2.13 mg/dL	332	1751	2083	17%
Total	1062	2941	4003	26.5%

CIN: Contrast-induced nephropathy

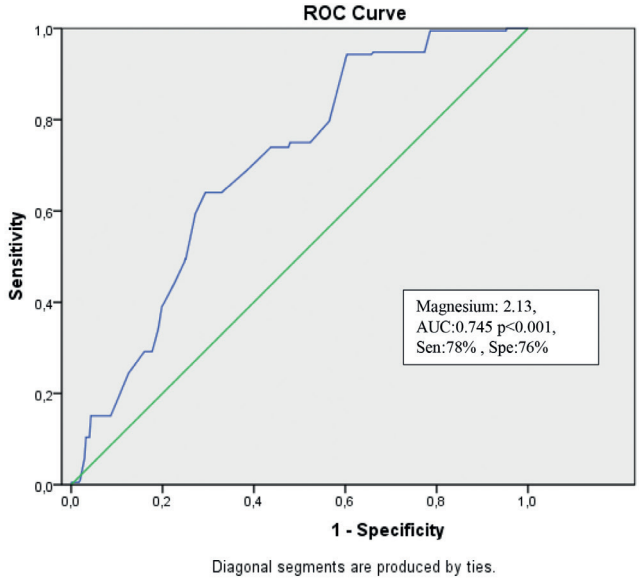

Figure 1. ROC curve showing magnesium levels in patients with non-STEMI CIN
ROC: Receiver operating characteristic, non-STEMI: Non-ST-elevation myocardial infarction, CIN: Contrast-induced nephropathy, AUC: Area under the curve

patients with Mg^{2+} ≥2.13 mg/dL experienced it. In Figure 2b, the logistic regression-derived probability curve demonstrates an inverse relationship between the Mg^{2+} level and the CIN risk, depicting a pronounced increase in the predicted probability below the 2.13 mg/dL threshold (red dashed line). The shaded green band represents a 95% CI.

DISCUSSION

We observed a robust association between the lower serum Mg^{2+} and the CIN development in this cohort of NSTEMI patients who underwent CAG and PCI. Beyond magnesium, several preprocedural clinical and biochemical characteristics were linked to the CIN risk, including reduced eGFR, lower systolic blood pressure, and higher creatinine concentrations before the procedure. Together, these findings underscore a multifactorial substrate for CIN in the NSTEMI population.

Pathobiologically, CIN reflects the interplay of intrarenal vasoconstriction, enhanced reactive oxygen species generation, and direct tubular injury.[18] Moreover, the abrupt vasoconstrictive response and the ensuing decline in the renal blood flow that follow contrast administration further catalyze the renal damage.[19] While the estimated CIN risk in the general population is approximately

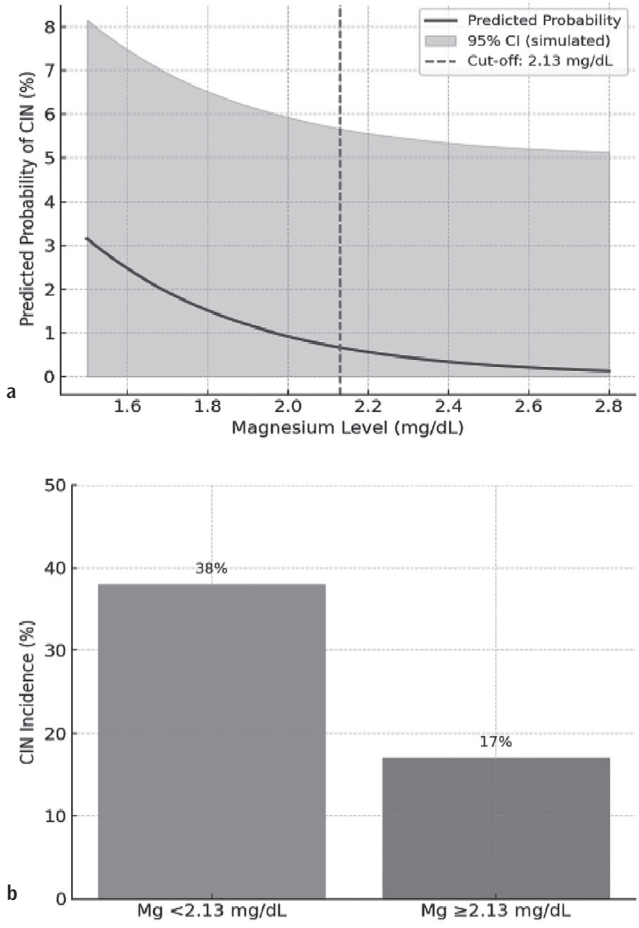

Figure 2. Relationship between magnesium levels and CIN development. (a) Stratified incidence of CIN by magnesium levels. Stratified incidence of CIN by magnesium levels. CIN occurred in 38% (730/1920) of patients with Mg <2.13 mg/dL and in 17% (332/2083) with Mg 22.13 mg/dL. (b) Predicted probability of CIN by magnesium level (logistic regression). Logistic regression curve showing predicted probability of CIN according to magnesium level. CIN risk increased sharply below 2.13 mg/dL (red dashed line, 95% CI shown in green).
CIN: Contrast-induced nephropathy, CI: Confidence interval

0.6-2.3%,[20] the incidence in patients undergoing PCI rises to roughly 15-35%.[21] Clinically, CIN is associated with longer hospitalization, higher mortality, and chronic renal failure.[7] It is also linked to an increase in major adverse cardiovascular events.[22] Consequently, current preventive practice emphasizes adequate hydration, iso-osmolar contrast selection, and intravenous isotonic saline. Although N-acetylcysteine can reduce the CIN occurrence, it does not appear to

influence hard outcomes like mortality or dialysis requirement.[23] From a mechanistic standpoint, magnesium is indispensable for cellular homeostasis and functions as a cofactor in a wide array of enzymatic reactions.[24] The experimental and clinical observations we obtained indicated that Mg^{2+} can dampen the macrophage activation and exert anti-inflammatory effects by lowering cytokines, such as interleukin (IL)-1β, IL-6, and IL-10,[25] while also mitigating the oxidative stress.[26] Therefore, hypomagnesemia is a plausible pathogenic contributor that promotes oxidative injury, reactive oxygen species accumulation, and endothelial dysfunction, all of which can facilitate the CIN evolution.

The pleiotropic vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic actions of magnesium suggest a protective role spanning both the cardiovascular and renal systems.[27] Consistent with this, prior literature has connected low Mg^{2+} with a greater cardiovascular risk[28] and with conditions like atherosclerosis, HT, insulin resistance, metabolic syndrome, and osteoporosis.[29] In the kidney, magnesium may prevent or reverse injury that is induced by nephrotoxic agents.[26,30] Among individuals with diabetic nephropathy, lower plasma Mg^{2+} is associated with a faster renal function decline and progression to end-stage renal disease.[31]The clinical data specific to the CIN prevention further support a role for magnesium. Firouzi et al.[32] reported that prophylactic magnesium reduced CIN in primary PCI patients, whereas Demirtola et al.[33] demonstrated a significant negative correlation existing between serum Mg^{2+} and CIN occurrence. Our results are in alignment with these observations and extend them by demonstrating—in a large NSTEMI cohort undergoing PCI—that low preprocedural Mg^{2+} is independently associated with a subsequent CIN risk, positioning Mg^{2+} as a potentially modifiable biomarker for risk stratification and targeted prevention.

Patients presenting with ACS are frequently hemodynamically unstable.[34] This instability can impair renal perfusion and limit the implementation of an adequate prophylactic hydration.[35] The urgency of CAG and the frequent need for diuretics may exacerbate medullary ischemia.[36,37] In our dataset, the systolic blood pressure was indeed significantly lower among patients who developed CIN, and this is consistent with these hemodynamic considerations.

From a practical perspective, the serum Mg^{2+} measurement is inexpensive, rapid, and universally available in hospital laboratories. Therefore, incorporating a routine pre-PCI Mg^{2+} assessment may offer a simple, low-cost means of identifying patients at a heightened risk. Furthermore, the magnesium supplementation in those with low levels can represent a feasible preventive strategy; nevertheless, prospective randomized trials are needed to establish the optimal dosing protocols and determine causality with greater certainty.

Study Limitations

This study has several limitations. First, its single-center, retrospective design restricts generalizability. Second, its retrospective nature did not allow us to fully control for all the potential confounders. Specifically, detailed information on the hydration status before and after the contrast exposure, use of nephrotoxic drugs, exact type and volume of contrast administered, and concomitant medications (e.g., ACE inhibitors and statins) were not systematically available. Each of these factors may materially affect the CIN risk and should be carefully captured in the future work. Additionally, we were also unable to evaluate other renal pathologies (e.g., proteinuria) that might have influenced the baseline renal function. To enhance the precision and the external validity of these findings, multicenter prospective studies incorporating a comprehensive assessment of these parameters are warranted.

CONCLUSION

This study demonstrates that the Mg^{+2} level is an important CIN determinant in patients with NSTEMI undergoing PCI. Considering the Mg^{+2} evaluation—and, where appropriate, preprocedural magnesium treatment—may be beneficial for the CIN prevention, particularly in individuals with low Mg^{+2} values.

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Tokat Gaziosmanpaşa University Hospital (decision number: 25-MOBAEK-136; date: 24.04.2025).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices: S.E.Ö., G.G.T., Concept: S.E.Ö., Design: S.E.Ö., Data Collection or Processing: S.E.Ö., Ç.Z., K.K., Analysis or Interpretation: S.E.Ö., Literature Search: S.E.Ö., Writing: S.E.Ö., G.G.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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INTERVENTIONAL CARDIOLOGY PERSPECTIVES

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CASE REPORT

Simultaneous Thrombotic Involvement of LAD and RCA in Combined ST-segment Elevation Myocardial Infarction: A Rare Clinical Entity

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ABSTRACT

Simultaneous acute thromboses in both the left and right coronary arteries (RCAs) are uncommon. A 39-year-old male presented with chest pain and was admitted to the hospital. Electrocardiography (ECG) revealed ST-segment elevation in both the inferior and anterior leads. Due to the presence of ST-segment elevation myocardial infarction, emergency coronary angiography was performed. The angiogram demonstrated a complete occlusion in the proximal left anterior descending artery and a critical thrombotic lesion in the RCA. Both lesions were treated with stent placement. Acute coronary syndromes can present with varying ECG patterns, and simultaneous ST-segment elevations in the anterior and inferior leads are rarely observed. This report describes a case of combined acute coronary syndrome.

Keywords: Acute coronary syndrome, simultaneous infarction, concomitant coronary occlusion

INTRODUCTION

In clinical settings, the occurrence of simultaneous thrombotic lesions in both the right and left coronary arteries is uncommon. In anterior myocardial infarction (MI), ST-segment elevation is typically seen in the anterior leads, with reciprocal ST-segment depression usually appearing in the inferior leads. Similar cases have been documented in the literature,[1,2] suggesting that concurrent ST-segment elevations may result from variations along the left anterior descending (LAD) artery pathway. We report a case involving simultaneous anterior and inferior ST-segment elevation MI (STEMI), caused by a complete acute occlusion of the LAD and a significant thrombotic lesion in the right coronary artery (RCA).

CASE REPORT

A 39-year-old male presented to the emergency department with severe chest pain that began 1 h before arrival. He was an active smoker with a history of hypertension, but no known coronary artery disease or diabetes. On admission, his vital signs were as follows: blood pressure 90/65 mmHg, heart rate 75 bpm, respiratory rate 22 breaths/min, and oxygen saturation 93% on room air. Physical examination showed normal heart sounds without murmurs or additional sounds, clear lung fields bilaterally, and no peripheral edema. Electrocardiography (ECG) revealed normal sinus rhythm at 70 bpm and ST-segment elevation in both the inferior and anterior leads (Figure 1). A diagnosis of STEMI was made, and the patient was admitted to the coronary intensive care unit (ICU). His Killip class was II, indicating mild heart failure without signs of cardiogenic shock. Despite borderline hypotension (blood pressure 90/65 mmHg), the patient did not meet the criteria for cardiogenic shock, as there was no sustained hypotension, marked tachycardia, altered consciousness, or evidence of severe end-organ hypoperfusion. He was promptly given loading doses of aspirin (300 mg), clopidogrel (600 mg), and intravenous unfractionated heparin (5000 U) before undergoing urgent coronary angiography without thrombolytic therapy.

Emergency coronary angiography was performed based on the diagnosis of simultaneous acute inferior and anterior MI. The angiogram revealed complete occlusion in the proximal LAD artery and a significant lesion in the RCA (Figure 2). The RCA lesion was severe but not fully occlusive and did not show obvious signs of plaque rupture or thrombus on angiography. Stenting was performed on both lesions using drug-eluting stents, resulting in optimal angiographic outcomes and TIMI-3 flow restoration in both the LAD and RCA. After complete revascularization, the patient was monitored in the coronary ICU with stable hemodynamic status. Following successful revascularization of the LAD occlusion, the patient experienced immediate relief from chest pain, and his hemodynamic parameters significantly improved, with blood pressure rising from 90/65 mmHg to 110/70 mmHg, heart

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rate increasing to 76, respiratory rate decreasing to 18 breaths/min, and oxygen saturation improving to 94%. A followup ECG immediately after revascularization showed marked resolution of ST-segment elevations in both the anterior and inferior leads. Post-procedure therapy in the ICU included aspirin 100 mg/day, clopidogrel 75 mg/day, atorvastatin 80 mg/day, pantoprazole 40 mg/day, and enoxaparin 60 mg twice daily. Beta-blockers and ACE inhibitors were initially withheld due to borderline hypotension. Intravenous hydration was initiated to address the borderline hypotension, leading to improved blood pressure and clinical stability.

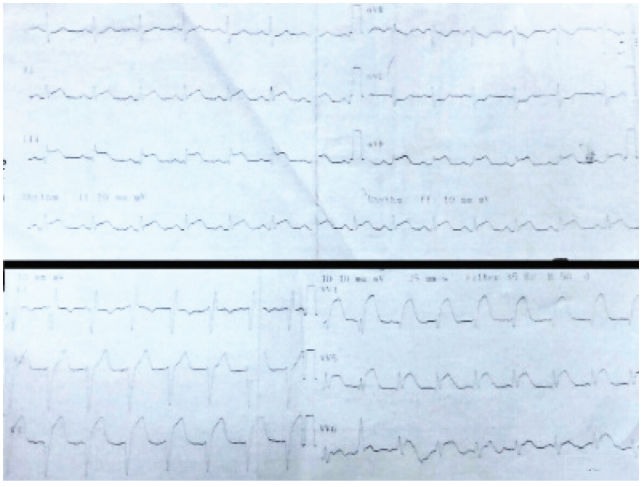

Figure 1. Admission ECG showing simultaneous ST-segment elevations in the anterior (V1-V4) and inferior leads (II, III, aVF), indicating acute myocardial infarction affecting both the LAD and RCA territories

ECG: Electrocardiography, LAD: Left anterior descending, RCA: Right coronary artery

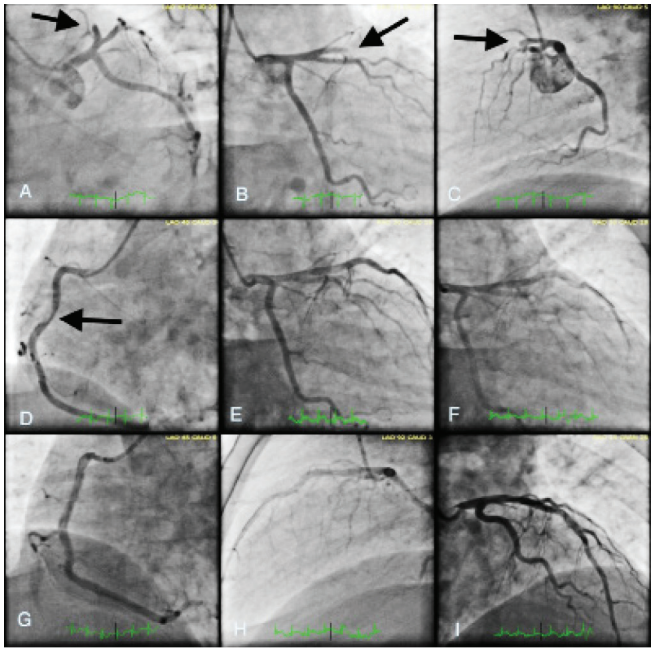

Figure 2. A, B, C, D) Coronary angiographic images taken during acute STEMI presentation. A, B, C) Show total occlusion (indicated by black arrows) in the proximal LAD artery. D) Shows a significant thrombotic lesion (indicated by black arrows) in the mid-segment of the RCA. E, F, G, H, I) Postprocedural coronary angiography images following successful percutaneous coronary intervention and complete revascularization

STEMI: ST-segment elevation myocardial infarction, LAD: Left anterior descending, RCA: Right coronary artery

DISCUSSION

Acute simultaneous coronary occlusion (ASCO) is a rare condition in clinical practice. STEMI typically results from a single epicardial coronary artery occlusion or thrombotic lesion, causing ST-segment elevation in the corresponding ECG leads and reciprocal ST-segment depression in opposite leads. However, simultaneous ST-segment elevations in both the anterior and inferior leads are unusual in acute coronary syndromes. These combined anterior and inferior ST-segment elevations present diagnostic challenges, requiring careful differentiation from conditions such as pericarditis, diffuse myocarditis, and acute aortic dissection. The relatively young age of our patient emphasizes the need to recognize early-onset coronary artery disease, especially in smokers or those with multiple cardiovascular risk factors. According to literature case series, the incidence of ASCO is around 2.5%.[3,4] While the exact mechanism of ASCO is not fully understood, it has been linked to several factors, including the abuse of vasoactive agents, hypercoagulable states, and coronary vasospasm.[5-7] In rare cases, left ventricular thrombi have also been implicated.[8]

Some studies suggest that simultaneous plaque ruptures in different coronary arteries, along with thrombosis due to hemodynamic instability, may contribute to ASCO.[9] Although commonly observed, our patient did not develop cardiogenic shock. In a case series by Pollak et al.,[4] 23% of patients experienced ventricular arrhythmias, and 36% developed cardiogenic shock. Similarly, a review by Mahmoud et al.[6] found that cardiogenic shock and sudden cardiac death occurred in approximately 40-50% of cases. The RCA and LAD are the most commonly affected coronary arteries in ASCO, with the most frequent ECG finding being simultaneous ST-segment elevations in the anterior and inferior leads.[4]

Although isolated lesions in a superdominant LAD can rarely present with both anterior and inferior ST-segment elevations, our patient also had significant RCA stenosis. Therefore, we interpreted the ECG findings as indicating simultaneous ischemia in both LAD and RCA territories. Our patient's history did not reveal drug abuse or underlying hypercoagulable conditions, and no triggers for vasospasm were identified. This case highlights that prompt and complete revascularization of multiple culprit lesions can significantly improve clinical outcomes, prevent progression to cardiogenic shock, and reduce myocardial damage.

Further prospective studies are needed to better understand the pathophysiology of ASCO and to establish optimal management strategies, ultimately improving clinical outcomes.

Conclusion

Acute coronary syndromes can present atypical ECG findings. Simultaneous ST-segment elevations in the anterior and inferior leads are rare but clinically significant. Revascularization of all affected

lesions should be prioritized, as this rare condition has a high risk of cardiogenic shock. Early and complete revascularization can help minimize total myocardial damage and improve patient outcomes.

Informed Consent: Written informed consent was obtained from the patient for publication.

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INTERVENTIONAL CARDIOLOGY PERSPECTIVES

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CASE REPORT

Left Internal Mammary Artery-pulmonary Artery Fistula after CABG: Successful Closure Using a Modified Balloon Technique

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ABSTRACT

Fistulas between arteries and veins may be either congenital or acquired, and their management typically depends on the presenting symptoms. While initial treatments were surgical, advancements in both technology and clinical expertise have facilitated the adoption of less invasive percutaneous catheter-based approaches. In this report, we detailed a technique we employed to close a fistula that developed between the left internal mammary artery and the pulmonary artery following bypass surgery. The method involved cutting a coronary balloon under sterile conditions, which led to thrombosis as a result of retrograde blood filling.

Keywords: Fistula, coronary artery bypass grafting, pulmonary artery

INTRODUCTION

Fistulas between the internal mammary artery (IMA) and the pulmonary artery (PA) are relatively uncommon.[1] These fistulas may be congenital, acquired, or iatrogenic in origin. Acquired fistulas are generally associated with inflammation, infection, or neoplastic processes, whereas iatrogenic fistulas most often result from surgical trauma. Patients with congenital or acquired fistulas typically present with symptoms such as hemoptysis, dyspnea, chest murmur with trill, and chest pain. In iatrogenic cases, recurring angina due to steal syndrome may be detected incidentally, either with hemoptysis or in the absence of symptoms.[2] In our case, the patient was asymptomatic regarding the fistula and was incidentally diagnosed with an inferior myocardial infarction (MI) related to the right coronary artery (RCA). A fistula between the left IMA (LIMA) and the PA was identified during coronary angiography.

CASE REPORT

A 64-year-old male patient had undergone coronary artery bypass grafting (CABG) surgery 11 years prior. He presented to our clinic with a diagnosis of inferior MI and subsequently underwent emergency percutaneous coronary intervention (PCI) of the RCA. Imaging revealed a 99% occlusion of the left anterior descending artery (LAD), a fistula extending from the proximal segment of the LIMA to the PA, and minimal distal flow (Figure 1).

Transthoracic echocardiography and thoracic computed tomography confirmed the presence of a fistula originating from the LIMA to the PA. Considering the angiographic visibility of the fistula and the risk of reduced myocardial perfusion secondary to the coronary steal phenomenon, closure of the fistula was considered appropriate. In this report, we describe a novel technique for closing a LIMA-to-PA fistula that developed after coronary bypass surgery.

This innovative technique entails cutting a coronary balloon under sterile conditions, resulting in intraluminal thrombosis due to retrograde blood entry against the natural direction of flow. The patient, who was admitted with acute coronary syndrome, was found to have a fistula between the LIMA and the PA during the initial angiographic evaluation. A total occlusion of the RCA was treated with two PCIs, using 3 × 23-mm and 3.5 × 28-mm stents. Postdilation was performed with a 3.5 × 20-mm noncompliant balloon to ensure complete vessel patency. Three days later, predilation of the native LAD was carried out using a 2.5 × 15-mm balloon. A 7-F internal mammary catheter was introduced into the LIMA using a guiding catheter, and a 0.014-inch floppy wire was advanced. A 1.5 × 10-mm balloon was cut and mounted onto the wire, with the cut surface positioned against the direction of flow. After inflation to 4 atm for 30 seconds, the balloon was deflated, and its distal shaft was severed. The balloon was then separated into two parts (the main shaft and distal segment), which were reloaded separately onto the wire in a configuration that created a parachute effect. This assembly was guided to the target site,

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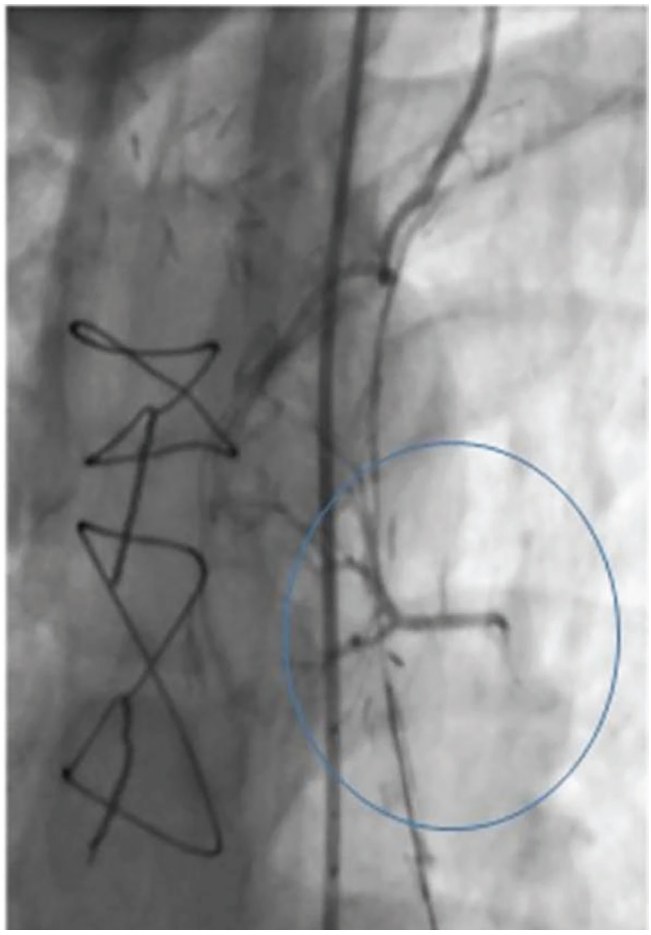

Figure 1. Imaging of the left coronary system and grafts revealed 99% occlusion of the left anterior descending artery. A fistula was also noted originating from the proximal portion of the left internal mammary artery to the pulmonary artery, with minimal distal flow observed

where the cut balloon was partially deployed. The proximal shaft was secured against the bronchial artery to allow controlled release. Owing to the one-way arterial flow, the device expanded slightly and became lodged at the fistula site. The wire was carefully withdrawn, leaving the embolic balloon components in place. Five minutes after deployment, angiography confirmed reduced flow to TIMI grade 1 and decreased fistulization. The procedure concluded without complications (Figures 2-4).

DISCUSSION

Fistulas between the LIMA and the PA are uncommon vascular anomalies. According to a study by Madu et al.[3], the incidence of PA fistulas following CABG procedures involving the LIMA was 0.67% among 595 cases. Similarly, Guler et al.[4] reported a LIMA-PA fistula incidence of 0.93% (5 out of 537 patients) based on follow-up angiography after CABG. They noted that the true prevalence in the general population might be underestimated due to typically asymptomatic nature of these fistulas. Furthermore, such fistulas are generally identified between 2 and 5 years postoperatively.[5]

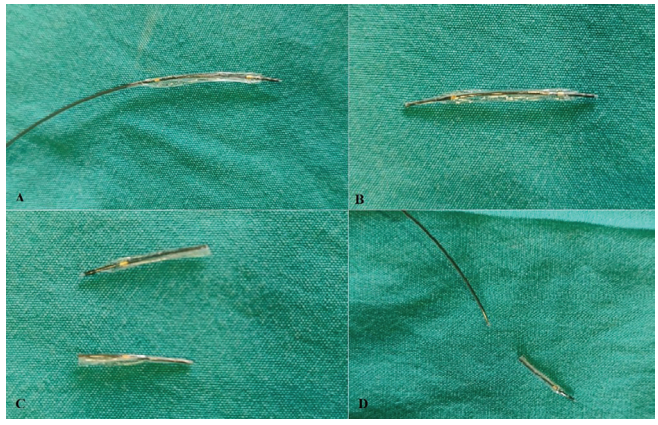

Figure 2. (A) The balloon was inflated to 4 atm pressure. B) After 30 seconds, the balloon was deflated and detached by cutting from the distal shaft. C) The balloon was then cut in half. D) The main shaft and the distal segment of the balloon were prepared separately and loaded onto the floppy wire with the cut surface facing against the direction of flow (parachute effect)

Figure 3. The main shaft and the cut distal portion of the balloon were mounted on a 0.14-inch wire for navigation to the target artery

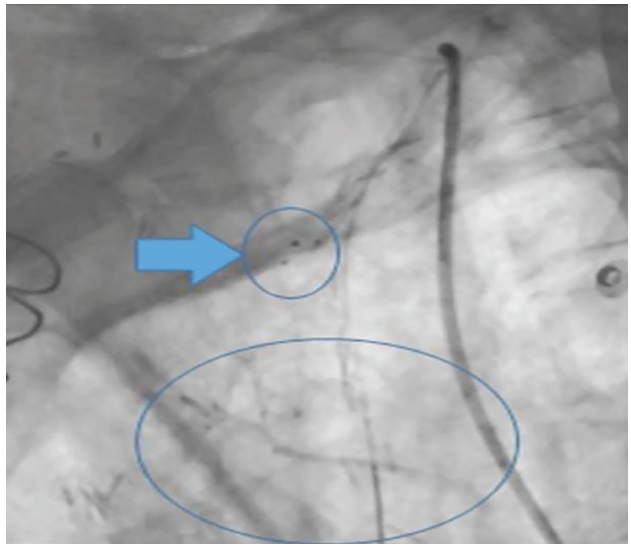

Figure 4. Post deployment imaging showed that blood flow in the fistulized side branch of the left internal mammary artery was reduced by approximately 90%

While most of these fistulas are asymptomatic, symptomatic cases present with angina, dyspnea, hemoptysis, and an intrathoracic murmur.[6,7] Management strategies include medical observation with symptomatic relief, catheter-based interventions, embolization using coils or glue, balloon occlusion, and surgical repair.[8]

Angina is the most frequently reported symptom, primarily due to the steal phenomenon, in which the lower pressure within the PA diverts coronary blood flow, resulting in myocardial ischemia.[9] When determining a treatment approach, clinicians should assess the severity of symptoms. Although there is broad consensus regarding intervention indications, many authors highlight the importance of hemodynamic assessment using various diagnostic tools.

For instance, Reis et al.[10] recommended the use of intravenous Doppler ultrasound and angiography to assess the functional significance of LIMA-LAD fistulas in patients after bypass surgery. Similarly, Nielson and Kang[11] employed myocardial perfusion scintigraphy followed by conventional angiography to identify ischemic regions in symptomatic individuals.

In asymptomatic cases, conventional angiography is generally considered adequate for diagnosis, particularly within the first 2-5 years following CABG. Abbott et al.[12] reported the successful closure of a LIMA-PA fistula using a polytetrafluoroethylene-coated stent. Although the stent remained patent and the fistula was closed after the procedure, the patient subsequently died due to multiple organ failure. With the advent of intravascular adhesive agents, glue embolization of the fistulous tract has become an additional therapeutic option, though it presents a higher risk of unintended embolization.

In a technique similar to ours, Jagadeesan et al.[13] employed a balloon to occlude the fistulous tract, injected adhesive into the distal segment, and kept the balloon inflated until the material solidified, after which the device was withdrawn. Carminati et al.[14] also used a coronary balloon to assess the fistula's morphology and assist in determining the appropriate closure strategy. Furthermore, Pop et al.[15] reported, for the first time, the use of temporary balloon protection of the vein of Labbé during embolization of a dural arteriovenous fistula to preserve cortical venous drainage.

In our clinic, we have applied this method in several patients presenting with massive hemoptysis after high-risk thoracic surgery for lung cancer.[16] At that time, instead of bisecting the balloon, we chose to cut it at the shaft and position the distal portion within the fistulous side branch to induce thrombosis. Due to the emergency nature of the cases and the unavailability of coils or alternative devices, the procedure was successfully carried out using a coronary balloon.

CONCLUSION

After the patients had stabilized, we refined the procedure by cutting the balloon in half and allowing the blood to fill the cut tip in a direction opposite to flow, thereby creating a parachute effect that helped occupy the lumen of the fistulized vessel. Our short-term outcomes were highly successful. We recommend this technique as it can be performed in any angiography laboratory using standard equipment, and it is both cost-effective and simple to execute once the operator is familiar with the method.

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and any related images.

Presented in: This study was presented as a poster at the 30th National Applied Interventional Cardiology Congress in 2023 and included in the congress proceedings.

Authorship Contributions: Surgical and Medical Practices - Ö.I., H.R.N., R.B., A.S.Y., M.N.D., Concept - Ö.I., H.R.N., R.B., A.S.Y., M.N.D., Design -Ö.I., H.R.N., R.B., A.S.Y., M.N.D., Data Collection or Processing - Ö.I., H.R.N., R.B., A.S.Y., M.N.D., Analysis or Interpretation: Ö.I., H.R.N., R.B., A.S.Y., M.N.D., Literature Search - Ö.I., H.R.N., R.B., A.S.Y., M.N.D., Writing:Ö.I., H.R.N., R.B., A.S.Y., M.N.D.

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CLINICAL IMAGE

RAC Sign Detected in Transthoracic Echocardiography in a Patient with Acute Anterior Myocardial Infarction

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Keywords: Acute myocardial infarction, coronary artery anomalies, RAC sign

Initially described in 2018, as a transthoracic echocardiographic (TTE) finding, the retro-aortic anomalous coronary artery (RAC) sign is characterized by the appearance of a distinctly echogenic tubular structure on an echocardiogram, located on the atrial side of the atrioventricular (AV) groove.[1] With an estimated prevalence of about 0.39%, the most prevalent anomaly is the anomalous origin of the left circumflex coronary artery (LCx) from the right sinus of Valsalva.[2] A 66-year-old female was admitted to our cardiology department with crushing, substernal chest pain. An electrocardiography revealed a sinus rhythm and T-wave inversions in the precordial derivations. TTE demonstrated regional hypokinesia in the anterior and apical segments of the left ventricle. The four-chamber apical views indicated a tubular structure with hyperechoic walls along the atrial aspect of the AV groove. A variant of the RAC sign involves the LCx (Figure 1). Researchers have recently characterized this observation as the RAC sign on TTE.[1] Medical treatment was initiated, and the patient was immediately transferred to the catheter laboratory. Coronary angiography (Figure 2) demonstrated a complete occlusion of the left anterior descending (LAD) artery distal to the diagonal 1 branch. As anticipated, the LCx was not visualized within the left coronary system. The right coronary artery was normal, and the LCx was found to originate from a separate ostium situated adjacent to the right aortic sinus (Figure 3). Subsequently, the LAD total occlusion was successfully traversed using a floppy guide wire. Balloon angioplasty was performed, followed by successful deployment of a drug-eluting stent at the lesion site. No procedural complications were observed at the conclusion of the intervention. After the patient's condition stabilized, a multislice computed tomography (MSCT) cardiac angiography was performed to delineate the LCx course. MSCT coronary angiography revealed an anatomical variant of the left circumflex artery. The artery originated from the right coronary cusp, coursed posterior to the aorta within the left AV groove, and terminated at the lateral wall of the left ventricle (Figure 4). The patient was discharged without any adverse cardiac events.

A retro-aortic course of the coronary artery is generally considered a benign anatomic variant; however, cases of cardiovascular events, including myocardial infarction and sudden cardiac death, have been reported in literature.[3-5] This echocardiographic sign (RAC) is strongly associated with the detection of retro-aortic coronary anomalies on cardiac CT imaging.[1] Given its high specificity (93.9%), cardiologists can reliably document its presence on TTE as a strong indicator of an anomalous coronary artery in echocardiography reports.[1,3] The clinical significance of the RAC sign remains uncertain.[6] Cases of iatrogenic occlusion of the abnormal LCx due to inadvertent suture placement have been reported, particularly during valve surgeries, which are frequently performed in the current clinical practice.[7] Some authors have even advocated routine coronary angiography in all patients undergoing aortic valve surgery, regardless of age, to detect this anomaly and facilitate a well-planned, multi-step surgical approach.[8] Over the past decade, with the advent of percutaneous bioprosthetic aortic valve implantation [transcatheter aortic valve implantation (TAVI), transcatheter aortic valve replacement], the risk of compression of the aberrant LCx by the bioprosthetic valve has become a recognized concern. Only a few cases of TAVI involving an anomalous LCx artery have been reported.[9,10] Some operators have utilized protected coronary catheters with a guideliner to prevent TAVI-related complications involving compression of the anomalous LCx.[10] The level of the retro-aortic course of the anomalous LCx may serve as a predictor of coronary compression during TAVI procedures. Interventional cardiologists should remain vigilant for coronary artery anomalies to minimize procedural delays and reduce additional radiation exposure.

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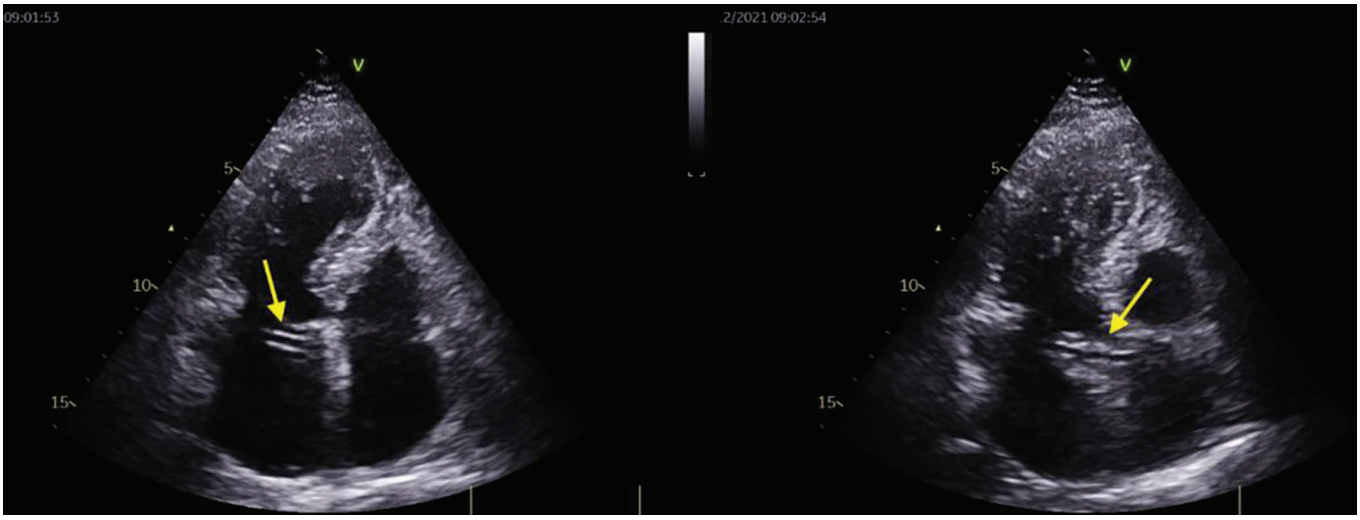

Figure 1. Transthoracic echocardiographic demonstrating the retro-aortic anomalous coronary artery sign (yellow arrow) in a typical apical four-chamber view

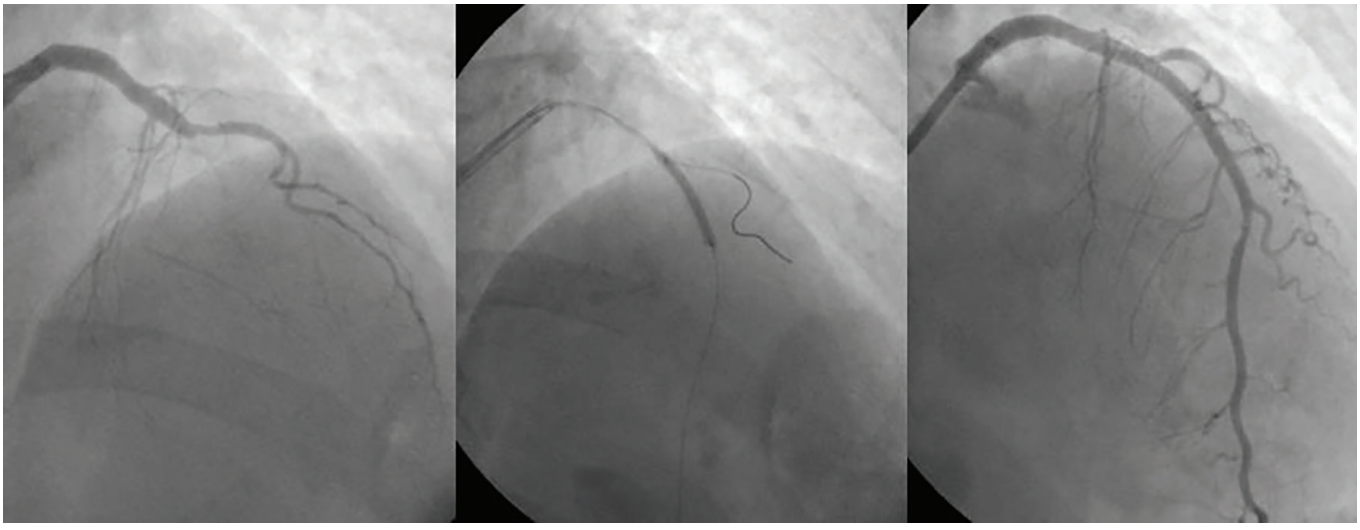

Figure 2. Coronary angiography (apical view) showing complete occlusion of the left anterior descending artery distal to the diagonal 1 branch. The lesion was successfully traversed using a floppy guidewire, followed by balloon angioplasty and stent deployment. As expected, the left circumflex coronary artery was not visualized within the left coronary system

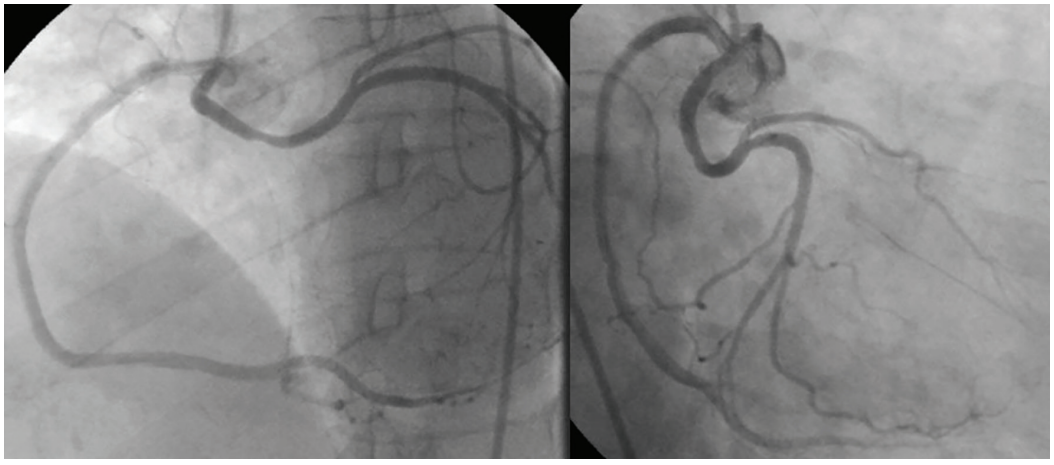

Figure 3. The retro-aortic anomalous coronary artery appeared normal. The left circumflex coronary artery was found to originate from a separate ostium located adjacent to the right aortic sinus

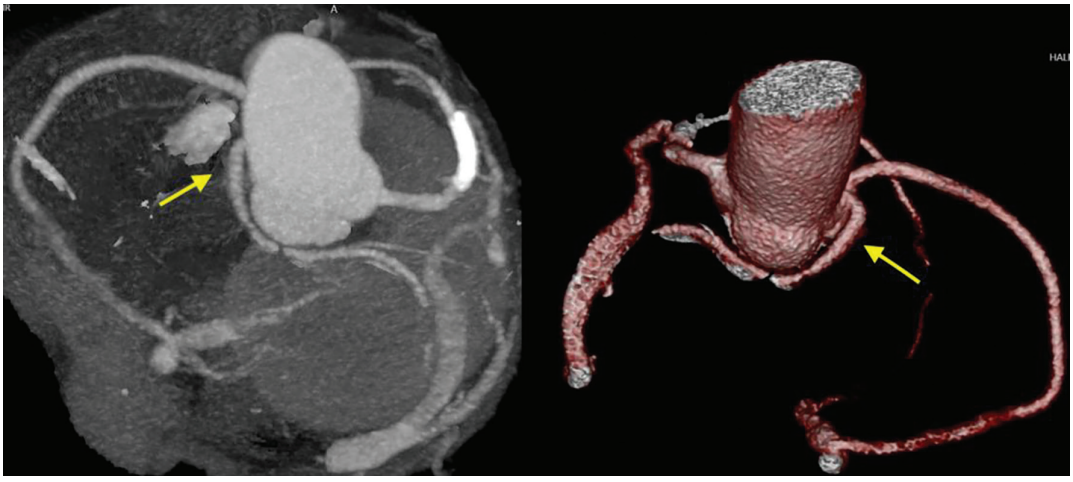

Figure 4. Multislice computed tomography coronary angiography revealed an anatomical variant of the left circumflex coronary artery, originating from the right coronary cusp and coursing posterior to the aorta within the left atrioventricular groove

Informed Consent: Written informed consent was obtained from the patient.

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