



REVIEW

Impact of Diabetes on Long-Term Outcomes After Percutaneous Intervention for Coronary Bifurcation Lesions: A Systematic Review and Meta-analysis

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Abstract

Introduction Percutaneous coronary intervention (PCI) in coronary bifurcation lesions is technically complex and associated with higher adverse event rates. Diabetes mellitus (DM) worsens outcomes through diffuse atherosclerosis and a prothrombotic, proinflammatory state, even with drug-eluting stents. However, the specific impact of DM on bifurcation PCI outcomes remains unclear. This study aims to evaluate the effect of DM on long-term clinical outcomes after PCI for coronary bifurcation lesions through a systematic review and meta-analysis.

Methods We conducted a systematic review and meta-analysis following PRISMA guidelines (PROSPERO-registered). PubMed, Cochrane, Web of Science, and Scopus were searched through August 2025. Observational studies comparing the clinical impact of diabetes mellitus in patients with coronary bifurcation lesions were eligible if they reported mortality, myocardial infarction (MI), or bleeding. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using random-effects models.

Results Five retrospective studies and one prospective study comprising 12,494 patients undergoing percutaneous coronary intervention (PCI) for coronary bifurcation lesions (involving both left main and non-left main locations) were included, with diabetes prevalence ranging from 33% to 50%. Across all follow-up periods, diabetes was consistently associated with worse outcomes. Diabetic patients had significantly higher risks of MACE from 9 months to 2 years (RR range 1.73–1.92) and increased myocardial infarction rates up to 5 years (RR range 1.90–2.16). Diabetes was also associated with higher cardiac mortality at 9 months (RR 1.96) and increased target lesion revascularization from 9 months to 2 years (RR range 1.61–1.82). No significant association was observed between diabetes and stent thrombosis.

Conclusion In patients undergoing PCI for coronary bifurcation lesions, diabetes mellitus is associated with significantly worse long-term clinical outcomes, including higher rates of MACE, myocardial infarction and repeat revascularization. Despite contemporary drug-eluting stent use, diabetic patients remain at increased ischemic risk, underscoring the need for tailored revascularization strategies and optimized metabolic and procedural management in this high-risk population.

Keywords Diabetes mellitus · Bifurcation lesions · Meta-analysis

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Introduction

Percutaneous coronary intervention (PCI) is a minimally invasive procedure used to restore coronary blood flow in obstructions through techniques such as catheterization, balloon inflation, stent implantation, or atherectomy. Although effective, it may present complications such as in-stent restenosis and acute thrombosis, whose incidence is lower with the use of drug-eluting stents. Anatomical conditions, such as coronary bifurcations (CB), and metabolic conditions such as diabetes mellitus (DM), can compromise the success of PCI [1, 2].

CB are the division of a coronary vessel into two branches, main and side, being significant when the side branch has a diameter greater than or equal to 2.25 mm, which allows stent implantation. They are vulnerable anatomical and hemodynamic points, in which flow bifurcation and arterial wall conformation promote turbulence, low shear stress, and thus a greater propensity for endothelial injury and atherosclerotic plaques. The MEDINA system standardizes the description of the compromised anatomical pattern through a numerical coding. PCI in CB presents a higher rate of procedural and long-term complications even with drug-eluting stents, especially in left main coronary bifurcations. Routine use of glycoprotein IIb/IIIa inhibitors may reduce acute stent thrombosis, but studies on their efficacy in more complex patients, such as those with DM, are still lacking [2].

DM is a metabolic disease recognized as one of the main independent risk factors for atherosclerotic cardiovascular disease. Strict glycemic control since diagnosis, with glycated hemoglobin below 7%, significantly reduces macrovascular outcomes, with benefits proportional to its reduction. In addition to frequently coexisting with hypertension, dyslipidemia, and obesity, DM promotes metabolic and inflammatory changes that accelerate atherogenesis. Mechanisms such as insulin resistance, endothelial dysfunction, activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, associated with oxidative stress and chronic inflammation, create a prothrombotic and proinflammatory environment. Furthermore, mediators such as microRNAs, epithelial sodium channels, and SGLT2 cotransporters explain the worst cardiovascular outcomes observed in people with diabetes [3, 4].

The difficulty faced by the diabetic patient lies not only in clinical management, but also in interventions during cardiovascular events. DM is associated with more diffuse, calcified, and multifocal atherosclerosis, which hinders complete revascularization by PCI; therefore, this technique is not considered the first-choice strategy in patients with DM even with the use of drug-eluting stents, with coronary artery bypass grafting (CABG) being the standard instead.

In addition, the inflammatory and prothrombotic milieu characteristic of DM further favors endothelial dysfunction and hyperproliferation of smooth muscle cells, increasing the risk of restenosis and stent thrombosis [5].

Although evidence has already been published on the impact of DM in patients undergoing PCI, data regarding its specific effect on coronary bifurcation PCIs are still limited. This is due to the anatomical heterogeneity of these lesions, which often require individualized approaches according to the characteristics of each patient and the bifurcation involved. Clinical trials that compared outcomes between diabetic patients undergoing PCI or CABG demonstrated similar mortality between procedures, regardless of the presence of diabetes, although management and long-term outcomes remain challenging in this population [6, 7].

Therefore, the present study aims to evaluate the impact of diabetes mellitus on long-term clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) for the treatment of coronary bifurcation lesions through a systematic review and meta-analysis of comparative studies.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [8] and the MOOSE recommendations for meta-analyses of observational studies [9], provided in Supplementary Table 1. Methodological decisions were additionally informed by Cochrane Handbook for Systematic Reviews of Interventions, Version 6.4, Chap. 24 – Reviews of exposure–outcome associations [10]. The protocol was prospectively registered in the PROSPERO database (CRD420251268922).

Eligibility Criteria

We included studies enrolling adult patients undergoing percutaneous coronary intervention for coronary bifurcation lesions — either left main or non-left main — in which clinical outcomes were reported separately for patients with and without diabetes mellitus at the index procedure. Eligible designs comprised randomized trials, prospective or retrospective comparative cohorts, and registries, provided that at least one prespecified long-term outcome was available with a minimum follow-up of 9 months. When multiple time points were reported, data from the longest follow-up (typically around 1, 3, or 5 years) were extracted. The primary endpoint of this study was Major Adverse Cardiovascular Events (MACE), accepted according to each individual study's protocolized definition. We recognized a degree of definitional heterogeneity across the included

cohorts; specifically, while the majority of studies reported traditional MACE composite endpoints (including combinations of death, myocardial infarction, and repeat revascularization), certain cohorts (Lim et al. and Watanabe et al.) reported Target Lesion Failure (TLF). Pooling these endpoints under a broader definition of major adverse composite events is clinically justified because both composites serve as standard, structurally parallel surrogates for overall ischemic and safety failures in coronary interventions. Both track the most critical hard clinical events (cardiac death and vessel-specific myocardial infarction) combined with repeat revascularization drive, thereby capturing the overall clinical burden of disease progression.

Studies were excluded if diabetes-stratified outcomes were not available, if relevant clinical data could not be extracted, or if the design corresponded to case reports, narrative reviews, conference abstracts without full text, or non-comparative registries. To reduce procedural heterogeneity, only drug-eluting stent cohorts were eligible for quantitative synthesis. When studies reported separate strata for drug-eluting and bare-metal stents, only drug-eluting stent data were included; studies reporting exclusively bare-metal stent outcomes or mixed stent cohorts without stratification were excluded. For overlapping publications, the dataset with the most complete and updated follow-up was retained.

Information Sources and Search Strategy

A comprehensive search of PubMed, Scopus, Web of Science and the Cochrane Library was performed from database inception through the date of the final search. Reference lists of eligible articles and relevant reviews were screened manually to identify additional studies. No restrictions were placed on language or publication date.

The PubMed search syntax was: (“diabetes mellitus” OR diabetes OR “type 2 diabetes” OR T2DM OR “insulin treated” OR “insulin dependent”) AND (“percutaneous coronary intervention” OR PCI OR stent* OR “drug eluting stent*” OR “drug-eluting stent*” OR DES) AND (bifurcat* OR “coronary bifurcation” OR “bifurcation lesion*” OR Medina OR “left main” OR LMCA). Search strategies were adapted to the indexing structure of each database, with complete syntaxes provided in Supplementary Table 2.

Selection Process

Two reviewers (B.I & J.S) independently screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Disagreements were resolved through discussion or consultation with a third reviewer (R.S-M). No automation tools or machine-learning algorithms were used during screening.

Data Collection Process

Data extraction was performed independently by two reviewers (B.I & V.O) using a standardized, pilot-tested form. Extracted variables included study design, enrolment period, sample size, definitions of diabetes mellitus, baseline clinical and angiographic characteristics, lesion complexity, procedural details, duration and completeness of follow-up, and all prespecified outcomes by diabetes status. When necessary, corresponding authors were contacted for clarification. In cases of overlapping reports, the study with the most complete follow-up dataset was used.

For studies reporting Kaplan–Meier survival curves without explicit event counts, time-to-event data were extracted using WebPlotDigitizer (version 5.2) and reconstructed according to the method proposed by Guyot et al. 2012 [11]. Coordinates of survival curves for diabetic and non-diabetic patients were digitized from high-resolution images at prespecified landmark times and calibrated using reported numbers at risk. To evaluate the chronological progression of clinical risk, cumulative event rates were extracted at multiple sequential time points (9 months, 1 year, 1.5 years, and 2 years). We explicitly acknowledge that these interval time points are statistically non-independent, as they represent cumulative event proportions reconstructed from overlapping patient horizons within the same study cohorts. For the primary pooled analyses of overall clinical endpoints, the maximum available follow-up period from each included study was utilized. This validated approach enabled consistent derivation of cumulative event proportions when only graphical survival information was available.

Risk of Bias Assessment

Because the comparison of diabetic and non-diabetic patients represents a non-randomized exposure contrast, all studies were evaluated using the ROBINS-I tool [12], including those originally designed as non-randomized trials. Two reviewers (R.S-M & V.O) independently assessed each domain—confounding, participant selection, exposure classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting—with discrepancies resolved through consensus.

Statistical Analysis

All statistical analyses were performed in R (version 4.5.2; R Foundation for Statistical Computing) using the *meta* package. For each endpoint, risk ratios with corresponding 95% confidence intervals were calculated comparing diabetic with non-diabetic patients. Random-effects models

based on the DerSimonian–Laird estimator were applied, with effect sizes pooled on the log scale and subsequently back-transformed for interpretation.

Between-study heterogeneity was assessed through Cochran's Q statistic, the between-study variance (τ^2), and the I^2 statistic. Forest plots were generated to display study-specific and pooled estimates. To examine the influence of each individual study on the overall effect, leave-one-out analyses were performed by iteratively removing each study and recalculating the pooled risk ratio. Potential sources of heterogeneity were further explored using Baujat plots, which identify the relative contribution of each study to overall heterogeneity and to the pooled effect estimation.

Potential publication bias was initially considered using visual inspection of funnel plots and Egger's regression test. However, given that fewer than 10 studies were available for pooling across all clinical outcomes, formal statistical testing for publication bias was deemed underpowered and unreliable according to current methodological guidelines. Consequently, quantitative assessment of publication bias was omitted from the primary analysis to prevent misleading interpretations, and a qualitative approach regarding the comprehensive nature of our literature search was preferred.

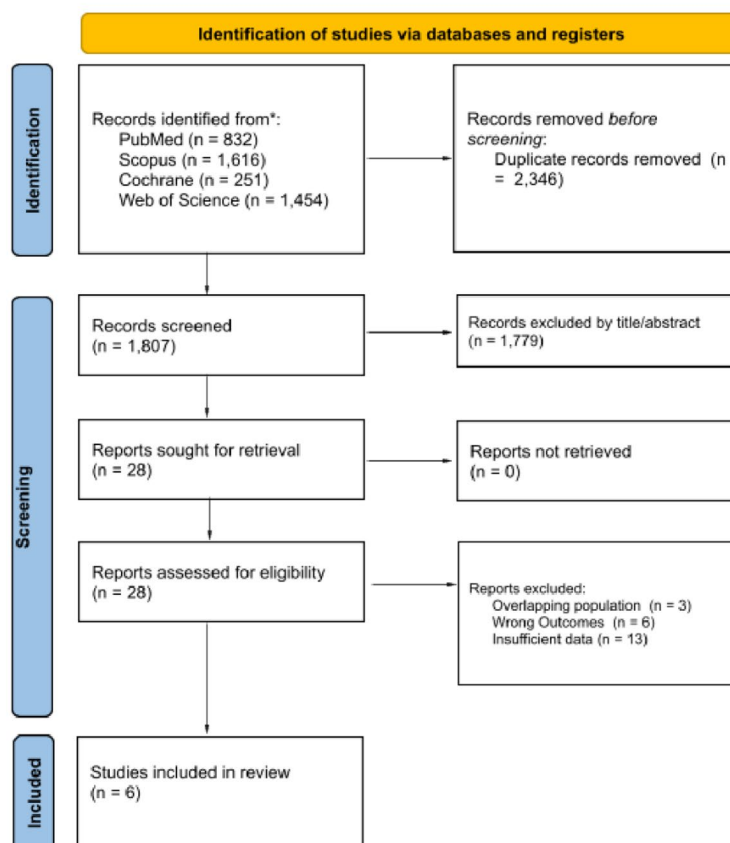
Results

Study Selection and Characteristics

The initial systematic database search yielded a total of 4,153 records (PubMed: 832, Scopus: 1,616, Cochrane: 251, and Web of Science: 1,454). After the removal of 2,346 duplicate records, 1,807 unique citations underwent rigorous title and abstract screening. Of these, 1,779 records were excluded for not meeting the predefined eligibility criteria. The remaining 28 reports were sought for retrieval and assessed through full-text evaluation. A total of 22 studies were subsequently excluded due to overlapping populations ($n = 3$), wrong outcomes ($n = 6$), or insufficient data ($n = 13$). Ultimately, 6 cohort studies (1 prospective and 5 retrospective) met all inclusion criteria and were comprehensive enough to be included in the final qualitative and quantitative meta-analysis (Fig. 1). Ultimately, 6 studies (5 retrospectives and 1 prospective) met the inclusion criteria and were incorporated into the final analysis [13–18]. Table 1 summarizes six studies, mostly retrospective (5/6), including 12,494 patients undergoing coronary bifurcation PCI. As detailed in Table 1, the included cohorts represented a mixture of bifurcation locations; the majority of

Fig. 1 PRISMA Flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Study

* True bifurcation defined as Medina 1,1,1; 1,0,1; or 0,1,1

Abbreviations: ADA, American Diabetes Association; BF, bifurcation; BMS, bare-metal stent; DES, drug-eluting stent; DM, diabetes mellitus; FKB, final kissing balloon; HbA1c, glycated hemoglobin A1c; IQR, interquartile range; IVUS, intravascular ultra-

cohorts were predominantly non-left main lesions (with left main coronary artery [LMCA] bifurcation distribution ranging from approximately 11% to 39%), while one study focused exclusively on left main bifurcations. The diabetes prevalence ranged from 33% to 50% (100–1,834 DM patients per study). Populations were predominantly male (68–84%) with similar mean age in DM vs. non-DM (generally mid-60s to early-70s). Diabetes was defined by physician diagnosis/treatment ($\pm$ HbA1c > 6.5%) or WHO/ADA criteria. Primary endpoints were mainly composite ischemic outcomes (MACE or TLF), with follow-up from 9 to 53 months. Most studies used DES (often 2nd-generation), with one early cohort including 1st-generation DES and BMS; reporting of IVUS/FKB and bifurcation complexity varied across studies.

Outcomes

Major Adverse Cardiovascular Events (MACE)

Across follow-up periods, diabetes was consistently associated with a higher risk of MACE. At 9 months, four studies including 9,844 patients (3,068 with diabetes and 6,776 without diabetes) reported MACE outcomes. The pooled random-effects model showed a 73% increased risk of 9-month MACE in the diabetic population (RR 1.73; 95% CI 1.47–2.03; $p < 0.001$), with low heterogeneity ($I^2 = 10.7\%$; $p = 0.339$) as shown in Fig. 2A. All studies demonstrated a directionally consistent increased risk among patients with diabetes.

At 1 year, three studies, comprising 9,543 patients (2,968 with diabetes; 6,575 without diabetes), reported MACE events. Diabetes was associated with an 89% increased risk of 1-year MACE (RR 1.89; 95% CI 1.45–2.47; $p < 0.001$) as shown in Fig. 2B, although heterogeneity was substantial ($I^2 = 74.5\%$; $p = 0.019$). At 1.5 years, the same three studies ($n = 9,543$) reported mid-term outcomes. The pooled analysis demonstrated a 78% increased risk (RR 1.78; 95% CI 1.56–2.03; $p < 0.001$) shown in Fig. 2C, with low heterogeneity ($I^2 = 28.2\%$; $p = 0.248$). At 2 years, diabetes continued to be associated with higher MACE risk across the same three studies ($n = 9,543$ patients). The pooled random-effects model showed that diabetes nearly doubled the 2-year MACE risk (RR 1.92; 95% CI 1.69–2.17; $p < 0.001$) shown in Fig. 2D, with low-to-moderate heterogeneity ($I^2 = 30.2\%$; $p = 0.238$).

Myocardial Infarction (MI)

Diabetes was strongly and consistently associated with higher rates of myocardial infarction across all follow-up durations. At 9 months, four studies ($n = 7,181$) showed a

significantly increased risk of MI among diabetic patients (RR 1.90; 95% CI 1.33–2.72), with no heterogeneity ($I^2 = 0.0\%$) shown in Fig. 3A. At 1 year, three studies ($n = 6,880$) reported MI outcomes. Diabetes was associated with more than a twofold increase in MI (RR 2.16; 95% CI 1.57–2.96; $I^2 = 0.0\%$) shown in Fig. 3B. At 1.5 years, across the same three studies ($n = 6,880$), diabetic individuals continued to show a significantly elevated risk of MI (RR 2.10; 95% CI 1.59–2.78; $I^2 = 0.0\%$) shown in Fig. 3C. Again, all studies showed a uniform direction of association. At 2 years, the excess ischemic risk persisted (RR 2.10; 95% CI 1.59–2.78), with no evidence of heterogeneity ($I^2 = 0.0\%$) shown in Fig. 3D, and consistent findings across all studies. At 5 years, long-term follow-up from three studies ($n = 3,085$) demonstrated that diabetes remained a significant predictor of MI (RR 1.93; 95% CI 1.11–3.35) shown in Fig. 3E. Moderate heterogeneity was observed ($I^2 = 45.9\%$).

Cardiac Death

Three studies ($n = 6,390$) reported 9-month cardiac mortality. Diabetes was associated with a significantly higher risk of cardiac death, with a pooled risk ratio of 1.96 (95% CI 1.06–3.63; $p = 0.033$) shown in Fig. 4. Heterogeneity was absent ($I^2 = 0\%$; $p = 0.717$), indicating consistent findings across all studies.

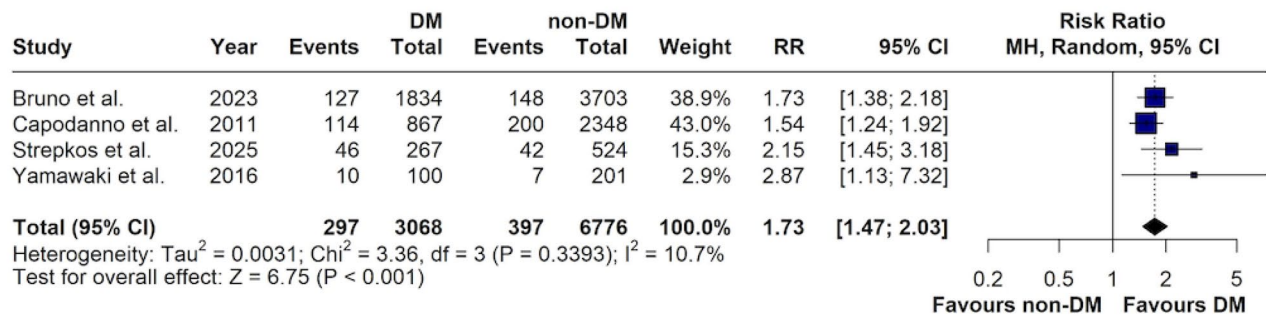
Stent Thrombosis (ST)

Stent thrombosis at 9 months was evaluated in three studies ($n = 6,390$). The pooled analysis did not show a statistically significant association (RR 1.49; 95% CI 0.91–2.45; $p = 0.112$) shown in Fig. 5A. There was no heterogeneity ($I^2 = 0\%$).

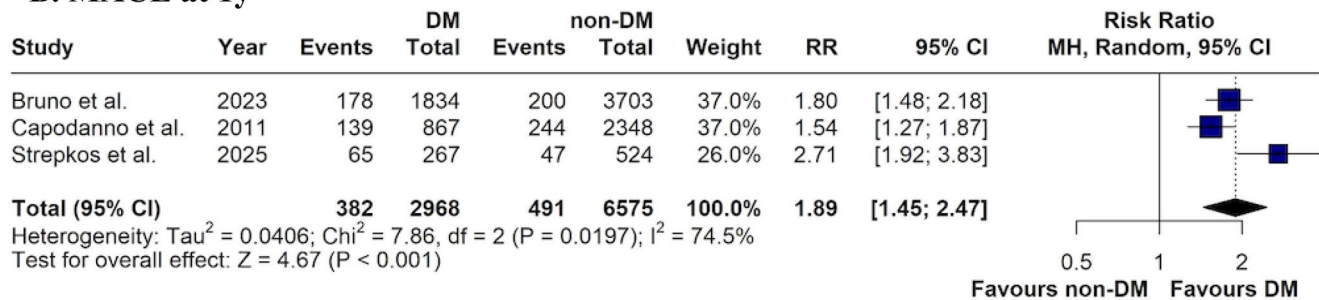
Target Lesion Revascularization (TLR)

At 9 months, four studies ($n = 8,132$) reported TLR outcomes. Diabetes was associated with a significantly elevated risk, the pooled model showed a 71% increased TLR risk (RR 1.71; 95% CI 1.22–2.41; $p = 0.002$) shown in Fig. 6A, with no heterogeneity ($I^2 = 0\%$). At 1 year, three studies ($n = 7,831$) reported TLR rates. Diabetes was associated with a significantly higher 1-year TLR risk (RR 1.82; 95% CI 1.39–2.38; $p < 0.001$) shown in Fig. 6B, with no heterogeneity ($I^2 = 0\%$). At 1.5 years, the same three studies ($n = 7,831$), the pooled analysis showed a significantly increased risk (RR 1.61; 95% CI 1.29–2.02; $p < 0.001$) shown in Fig. 6C, with no heterogeneity ($I^2 = 0\%$). At 2 years, three studies ($n = 7,831$) again demonstrated consistently higher TLR rates in diabetes, with a 77% higher risk of TLR (RR 1.77; 95% CI 1.43–2.17; $p < 0.001$) shown in Fig. 6D, with no detectable heterogeneity ($I^2 = 0\%$).

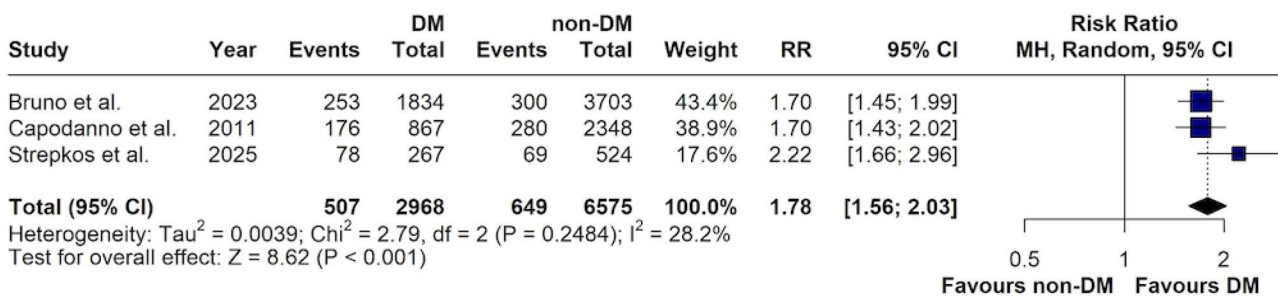
A. MACE at 9 months



B. MACE at 1y



C. MACE at 1.5y



D. MACE at 2y

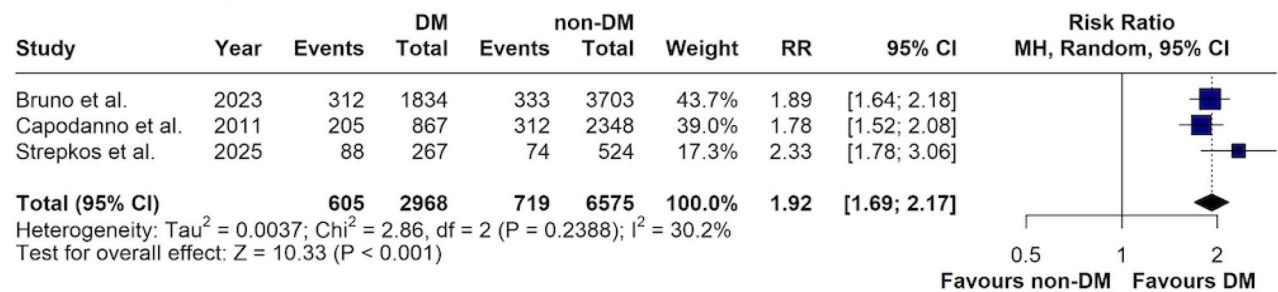


Fig. 2 Meta-analysis of Major Adverse Cardiovascular Events (MACE)

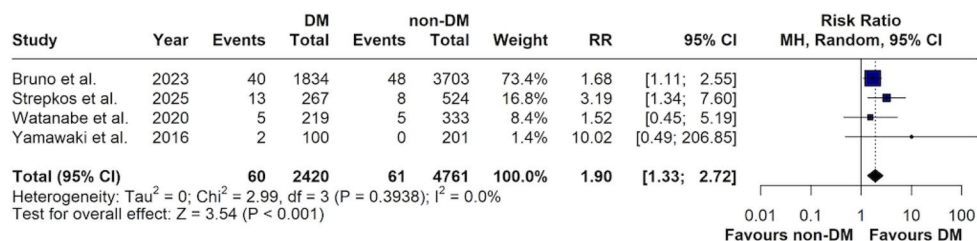
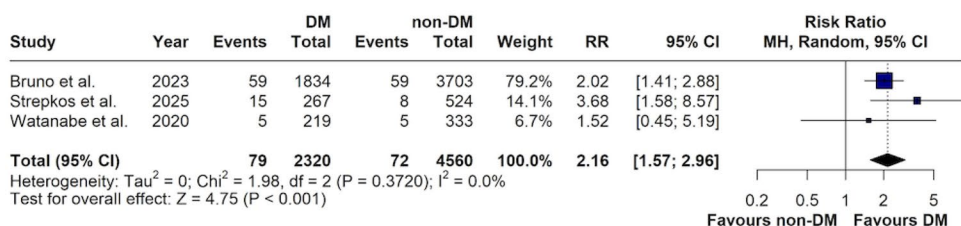
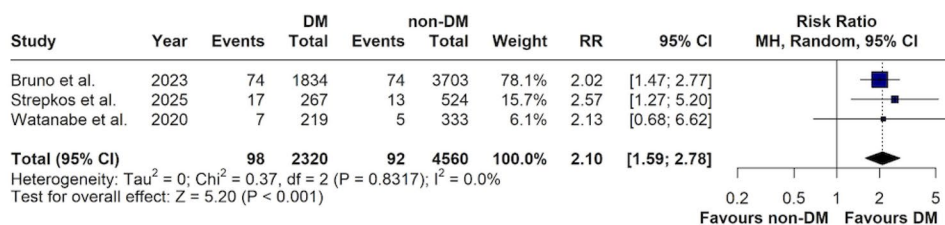
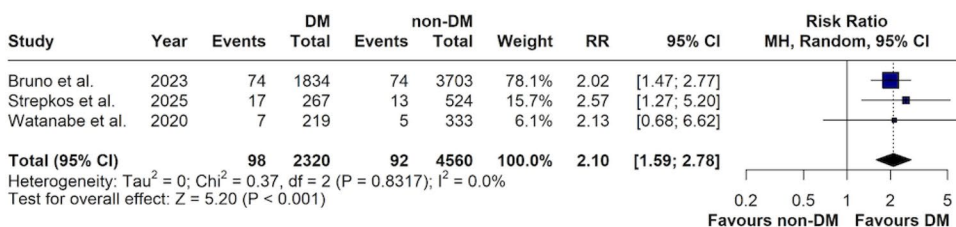
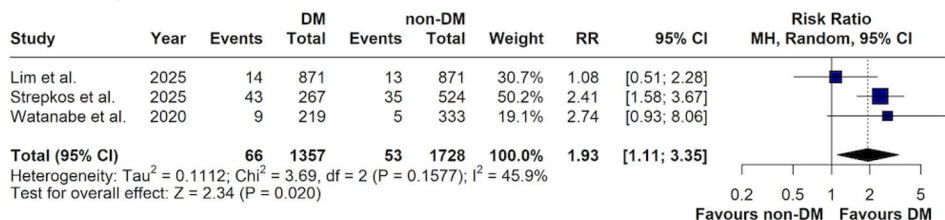
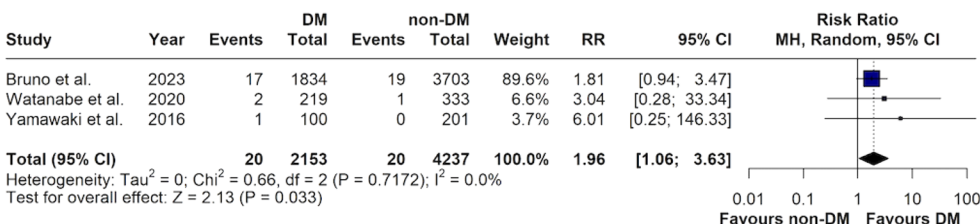
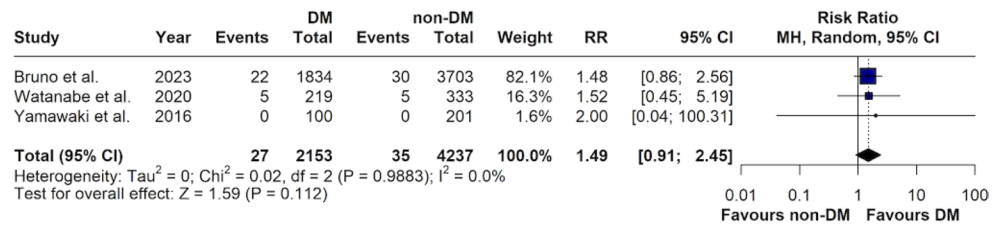
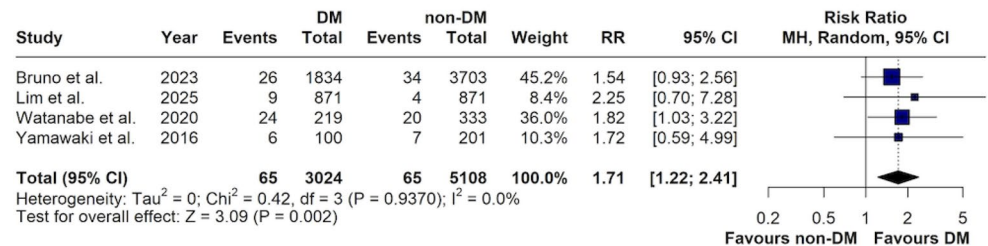
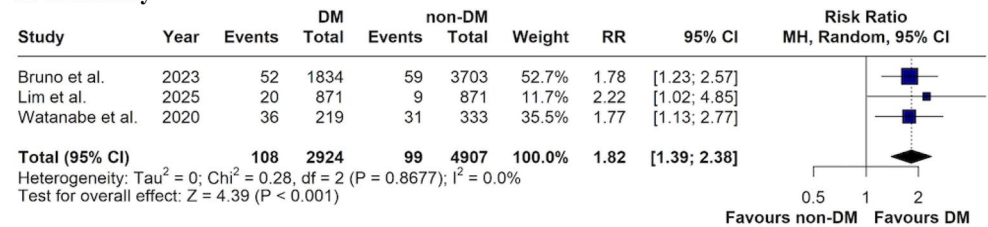
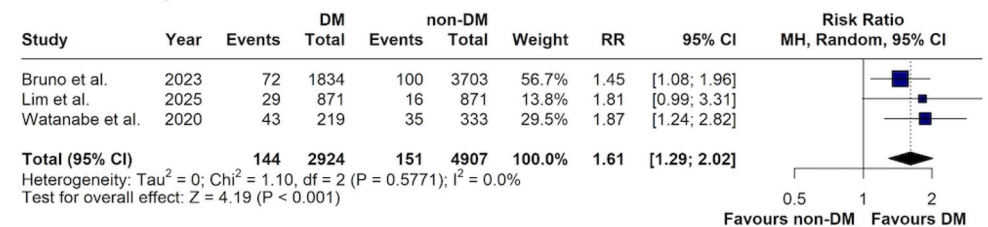
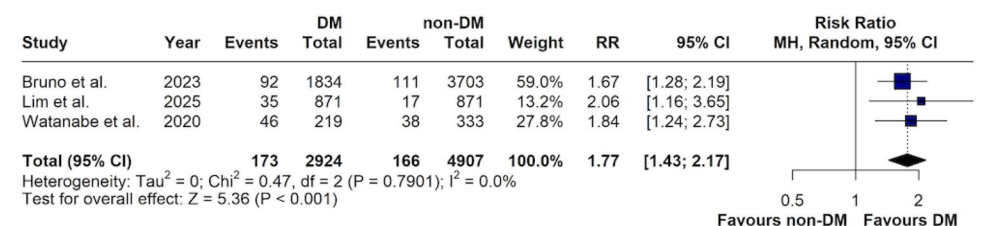
Fig. 3 Meta-analysis of Myocardial Infarction (MI)**A. MI at 9 months****B. MI at 1y****C. MI at 1.5y****D. MI at 2y****E. MI at 5y****Fig. 4** Meta-analysis of Cardiac Death. **A** Cardiac Death at 9 months

Fig. 5 Meta-analysis of Stent Thrombosis. **A.** Stent Thrombosis at 9 months**Fig. 6** Meta-analysis of Target Lesion Revascularization (TLR)**A. TLR at 9 months****B. TLR at 1y****C. TLR at 1.5y****D. TLR at 2y****Sensitivity Analysis****Major Adverse Cardiovascular Events (MACE) Sensitivity Analysis**

Across all timepoints, sensitivity analyses indicated robust and internally consistent findings for MACE, with no evidence of small-study effects or publication bias based on generally symmetric funnel plots. At 9 months, results were

highly stable with low heterogeneity (I^2 0–10.7%); leave-one-out estimates ranged from RR 1.66–1.87, consistent with the pooled effect (RR 1.73, 95% CI 1.47–2.03), with Capodanno et al. contributing most to heterogeneity/influence and Bruno and Yamawaki minimally. At 1 year, heterogeneity was substantial (I^2 74.5%), driven mainly by Capodanno and Strepkos, yet the direction and magnitude remained consistent (RR 1.89, 95% CI 1.45–2.47); excluding Strepkos markedly reduced heterogeneity (I^2 16.3%).

At 1.5 years, estimates remained stable (RR 1.78, 95% CI 1.56–2.03; I^2 28.2%), and at 2 years the pooled effect persisted (RR 1.92, 95% CI 1.69–2.17; I^2 30.2%) despite differential study influence. Overall, pooled results consistently suggested a higher MACE risk among diabetic patients (Figure S1–S4).

Myocardial Infarction (MI) Sensitivity Analysis

Sensitivity analyses for myocardial infarction (MI) consistently supported a stable association between diabetes and higher MI risk across follow-up periods, with no clear evidence of small-study effects based on generally symmetric funnel plots. At 9 months, results were highly robust: heterogeneity was negligible, leave-one-out estimates ranged from RR 1.72–2.68, and the pooled effect remained consistent (RR 1.90, 95% CI 1.33–2.72), with Strepkos contributing most to heterogeneity and Bruno showing minimal influence. At 1 year, the pooled estimate remained stable (leave-one-out RR 1.98–2.66), with Strepkos again driving heterogeneity and Bruno exerting the greatest influence on the effect size, while Watanabe contributed little. At 1.5 years, findings were similarly stable (leave-one-out RR 2.03–2.44) and closely matched the primary estimate (RR 2.10, 95% CI 1.59–2.78), with heterogeneity largely attributable to Strepkos. At 5 years, stability was moderate: Lim and Strepkos contributed most to heterogeneity (Lim most influential on effect size), but leave-one-out analyses remained directionally consistent with the pooled result (RR 1.93, 95% CI 1.11–3.35; I^2 = 45.9%) despite variations in I^2 when individual studies were omitted (Figure S5–S8).

Cardiac Death Sensitivity Analysis

Sensitivity analyses demonstrated that the 9-month cardiac death findings were robust. The Baujat plot showed that Bruno et al. exerted the greatest overall influence on the pooled estimate, whereas Yamawaki et al. contributed the most to statistical heterogeneity. Watanabe et al. showed very limited contribution to either dimension. The funnel plot was symmetric and revealed no signs of small-study effects or publication bias, with all studies falling within the expected confidence boundaries. Leave-one-out testing further supported the stability of the results: sequential omission of individual studies produced risk ratios between 1.87 and 3.89, all with confidence intervals overlapping the primary pooled estimate (RR 1.96). Although removing Bruno et al. widened the confidence interval because of decreased precision, the direction and magnitude of the effect remained consistent (Figure S9).

Stent Thrombosis Sensitivity Analysis

The 9-month stent thrombosis findings were highly stable. The Baujat plot showed minimal heterogeneity across studies; Yamawaki et al. contributed slightly more but still exerted negligible influence on the pooled effect. Funnel plot assessment did not reveal asymmetry. Leave-one-out analyses yielded RRs between 1.49 and 1.56, all overlapping with the primary pooled estimate (RR 1.49, 95% CI 0.91–2.45, I^2 = 0%). These findings indicate a robust and nonsignificant association (Figure S10).

TLR Sensitivity Analysis

Across follow-up intervals, sensitivity analyses for target lesion revascularization (TLR) demonstrated high robustness and no evidence of small-study effects, with consistently symmetric funnel plots and negligible heterogeneity (I^2 = 0% throughout). At 9 months, results were highly stable (leave-one-out RR 1.65–1.86) and remained aligned with the pooled estimate (RR 1.71); Bruno et al. most influenced effect size, while Lim et al. contributed most to heterogeneity, with Watanabe and Yamawaki showing minimal influence. At 1 year (~4,300 patients), diabetes was consistently associated with higher TLR risk (RR 1.82, 95% CI 1.39–2.38), and omitting any study did not materially change estimates (RRs 1.77–1.87), with Lim contributing the most in Baujat diagnostics. At 1.5 years, findings remained highly stable (leave-one-out RR 1.52–1.85) and overlapped with the pooled effect (RR 1.61, 95% CI 1.29–2.02), with Bruno exerting the greatest influence but minimal impact on heterogeneity. At 2 years, robustness persisted (leave-one-out RR 1.52–1.85) with a stable pooled estimate (RR 1.77, 95% CI 1.43–2.17); Watanabe contributed most to heterogeneity, followed by Lim, while Bruno had the least influence. Overall, diabetes was consistently associated with higher TLR risk across timepoints (Figure S11–S14).

Quality Assessment

Overall, five studies were judged to have moderate risk of bias (Bruno 2023; Capodanno 2011; Lim 2025; Strepkos 2025; Watanabe 2020), largely driven by bias due to confounding (D1), rated moderate in all five and, in Watanabe 2020, an additional moderate risk in participant selection (D2). Most other domains were consistently rated low risk, including classification of interventions (D3), deviations from intended interventions (D4), missing data (D5), and outcome measurement (D6). Selection of the reported result (D7) was rated moderate in Capodanno 2011 and Strepkos 2025. Yamawaki 2016 was rated at serious overall risk of bias due to a serious confounding risk (D1), while remaining

domains were low risk (Figure S15). Due to the small number of included studies per endpoint ($n < 10$), formal evaluation of publication bias via funnel plots and Egger's testing was not performed, as these methods lack sufficient statistical power to detect asymmetry in small meta-analyses.

Discussion

In this systematic review and meta-analysis of 1 prospective and 5 retrospective studies including 12,494 patients, we assessed the long-term impact of diabetes mellitus on clinical outcomes after PCI for the treatment of coronary bifurcation lesions. Our results reinforce what is frequently observed in clinical practice: DM was associated with a greater risk of MACE and myocardial infarction across all follow-up durations and was also linked to an increased risk of cardiac death and target lesion revascularizations. However, there was no statistically significant difference in stent thrombosis between the two groups. Sensitivity analysis confirmed the robustness of our findings, as leave-one-out testing consistently aligned with the pooled estimates.

As mentioned in the introduction, despite being more invasive, CABG is often preferred over PCI for coronary revascularization in patients with DM, due to their higher baseline risk [1, 19]. Prior studies reported lower cardiac and all-cause mortality with CABG compared to PCI, highlighting the overall disease complexity in this population. [1, 19, 20] However, a long-term analysis from the SYNTAXES study 10-year follow-up revealed that diabetes itself determines a worse prognosis, regardless of the revascularization strategy [7]. Still, in practice, many diabetic patients undergo PCI, including for the treatment of coronary bifurcation lesions. In this population, as CB lesions are inherently high-risk, PCI represents additional complexity, thereby amplifying the likelihood of adverse events [2, 12–14].

Regarding major clinical endpoints, our results suggest that DM was associated with higher rates of MACE, myocardial infarction and cardiac death. These findings are consistent with other studies that show that diabetes is a significant predictor of adverse outcomes in patients undergoing PCI, especially those related to ischemic events and cardiac mortality [8, 21]. This reinforces the higher complexity of coronary artery disease in diabetic patients, due to the inflammatory and prothrombotic milieu characteristics of this metabolic condition. In addition, previous literature also demonstrates that bifurcation PCI is inherently more complex and is associated with worse cardiac outcomes compared with non-bifurcation PCI [2, 21–23].

Not surprisingly, we observed a regular increase in TLR risk among diabetic patients, across all follow-up durations. This finding was shown in previous evidence which

demonstrates that bifurcation PCI is linked to higher rates of restenosis. [24, 25] Diabetes further contributes to this outcome through mechanisms such as endothelial dysfunction and neointimal hyperplasia. Both characteristics enhance restenosis susceptibility [1, 26].

In contrast, the higher risk of stent thrombosis amongst diabetic patients did not reach statistical significance. This likely reflects the low event rate. Even so, the limited number of studies contributing to this endpoint (3/6) results in a smaller sample size. This variation inherently diminishes the statistical power of the pooled estimates for specific endpoints. Over the last years, overall ST rates are low, occurring in less than 1% of patients [27–29]. This can be explained by advances in antithrombotic therapy and the widespread use of second-generation DES. As a result, larger sample sizes may be needed to reach statistical differences. Still, multiple factors are involved in the physiopathology of ST beyond diabetes and its severe endothelial dysfunction alone, such as nonadherence to dual antiplatelet therapy, insufficient neointimal coverage and residual target-lesion thrombus [30]. Interestingly, although diabetes is a well-established risk factor for ST, the available data from our meta-analysis was insufficient to demonstrate a statistically significant association.

Overall, these findings show that diabetes is not only a risk factor for cardiovascular events, but also a strong predictor of major adverse cardiovascular outcomes in patients undergoing PCI for the treatment of coronary bifurcation lesions. Therefore, given the worse clinical outcomes, diabetic patients undergoing bifurcation PCI may benefit from coordinated longitudinal follow-up and specialized care.

Limitations

There are several limitations to this study. All six studies included cohorts, 5 of which were retrospective. They are inherently susceptible to selection bias and residual confounding. Moreover, 5 studies presented a moderate risk of bias, predominantly driven by bias due to confounding (D1). Most of the other domains were consistently graded low risk. One study (Yamawaki 2016) was rated at serious overall risk of bias, due to a major confounding risk (D1). This can compromise internal validity. Additionally, sample sizes varied across outcomes, given that not all studies provided data to every clinical endpoint. As a result, pooled estimates based on fewer studies are more vulnerable to bias, and may present reduced statistical power. Follow-up duration varied across the studies, ranging from 9 to 53 months. That could underestimate late events in studies with shorter follow-up.

Furthermore, the evaluation of clinical outcomes across multiple sequential interval time points (from 9 months to 2 years) relies on cumulative data extracted from the same baseline study populations and Kaplan–Meier curves. Consequently, these intermediate time points do not constitute independent replications, and their highly concordant risk estimates and low heterogeneity ($I^2=0\%$) are a direct reflection of this statistical overlap. Nonetheless, this longitudinal tracking approach allowed us to confirm that the clinical disadvantage associated with diabetes manifests early and persists continuously over time. Another important limitation is the presence of definitional heterogeneity within our pooled primary outcome. The precise components of MACE varied across studies, and notably, the cohorts by Lim et al. and Watanabe et al. reported TLF rather than MACE. Although these composites share key clinical elements (such as cardiac death and target-vessel ischemic events), mixing MACE and TLF introduces an inherent conceptual variation. While our statistical heterogeneity was remarkably low ($I^2=0\%$), this mathematical consistency does not eliminate the underlying variations in definitions, and these findings should be interpreted with the understanding that the primary endpoint represents a broader composite of major adverse ischemic events. Additionally, due to the limited number of studies included per endpoint (fewer than 10 cohorts), formal assessments of publication bias, such as Egger's testing and funnel plot asymmetry evaluation, could not be reliably interpreted or applied. The small sample size of studies inherently limits the statistical power to detect publication bias, meaning that its presence cannot be definitively ruled out, which mandates a cautious interpretation of the overall completeness of the available literature. Another major methodological limitation is that our pooled risk ratios (RRs) are based on crude, unadjusted event counts rather than multivariable-adjusted hazard ratios (HRs). Because diabetic and non-diabetic patients differ substantially at baseline regarding clinical and angiographic risk factors, pooling crude data is inherently susceptible to residual confounding and selection bias. Although several included studies individually calculated adjusted effect estimates, a pooled meta-analysis of adjusted estimates was not feasible due to the substantial heterogeneity in the specific covariates adjusted for across trials, as well as inconsistent reporting of adjusted parameters at matching interval time points. To mitigate this risk, we rigorously evaluated the domain of baseline confounding using the ROBINS-I tool, and our findings should be interpreted as an overall macro-level representation of crude clinical risk differences. Lastly, stent type varied across studies, with some using second-generation DES, and others using first-generation DES and BVS, which could have influenced restenosis and stent thrombosis outcomes.

Conclusion

Diabetes mellitus is associated with significantly worse long-term outcomes after PCI for coronary bifurcation lesions, including higher rates of MACE, myocardial infarction and repeat revascularization, despite contemporary drug-eluting stent use. These findings highlight the persistent high ischemic risk in diabetic patients and underscore the need for optimized, individualized revascularization strategies in this population.

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Author Contributions R.S.-M. (Ricardo F.O. Suruagy-Motta) served as the lead investigator, performed all statistical analyses in R, conducted sensitivity analyses, acted as the third reviewer for study selection, and performed the risk of bias assessment. B.M.I. (Bruno Marçola Ishizuka) independently screened titles and abstracts for study selection and performed the data extraction. V.A.O. (Victor Arthur Ohannesian) performed data extraction and conducted the risk of bias assessment using the ROBINS-I tool. J.A.S. (Júlia Agra Silva) independently screened titles and abstracts for the study selection process. D.R. (Diego Rajchenberg), V.O.D. (Viviane de Oliveira Dantas), E.L.O.P. (Eduarda Lima Ornelas Pinto), N.P.A. (Nathália Pires Abeyá), E.M.F. (Evandro Martins Filho), L.A. (Lorenzo Azzalini), and S.K. (Sant Kumar) contributed to the critical revision of the manuscript for important intellectual content and the final drafting of the discussion and conclusion.

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Declarations

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