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Predictors of Side Branch Compromise After Provisional Stenting in Coronary Bifurcation PCI: Clinical and Angiographic Insights from a Tertiary Care Population.

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Abstract

Background: Coronary bifurcation lesions account for 15–20% of percutaneous coronary interventions (PCI) and remain technically challenging. Provisional stenting is the recommended default strategy, yet side branch compromise (SBC) occurs frequently, potentially leading to periprocedural myocardial infarction (MI), impaired coronary perfusion, stent thrombosis, and adverse outcomes. Patients with diabetes, hypertension, or smoking-related vascular disease may be particularly susceptible. This study aimed to determine the frequency of SBC after provisional bifurcation PCI and identify clinical and angiographic predictors, focusing on diabetes, hypertension, and smoking.

Methodology: We conducted a retrospective observational study at the Department of Cardiology, Lady Reading Hospital, Peshawar, Pakistan, including consecutive patients undergoing provisional bifurcation PCI from January to June 2025. Clinical, procedural, and angiographic data were extracted from hospital records. SBC was defined as post-procedural TIMI flow <3 in the side branch.

Results: Among 400 patients (mean age 58 ± 10 years; 71.5% male), diabetes was present in 43.2%, hypertension in 59.8%, current smoking in 31.8%, and acute coronary syndrome in 29.2%. SBC occurred in 82 patients (20.5%, 95% CI 16.6–24.9%). Periprocedural MI was more frequent with SBC than without (22.0% vs. 4.4%, $p<0.001$). Independent predictors included moderate-to-severe calcification, smoking, diabetes, acute coronary syndrome, hypertension, pre-procedural TIMI 2 flow, side branch lesion length and ostial stenosis, and bifurcation angle. The predictive model demonstrated excellent discrimination (AUC = 0.999).

Conclusion: SBC affected one-fifth of patients undergoing provisional bifurcation PCI. Both clinical (smoking, diabetes, hypertension) and angiographic factors significantly predicted risk. Pre-procedural risk assessment integrating these factors may optimize procedural planning and improve outcomes.

Keywords

Coronary Bifurcation Lesions, Percutaneous Coronary Intervention, Provisional Stenting, Side Branch Compromise, Diabetes Mellitus, Hypertension, Smoking, Calcification, Acute Coronary Syndrome.

Introduction

Coronary artery disease remains the leading cause of cardiovascular morbidity and mortality worldwide, and percutaneous coronary intervention (PCI) has become the cornerstone of revascularization for patients with obstructive coronary disease. Among all lesions treated with PCI, coronary bifurcation lesions represent a unique and challenging subgroup, accounting for approximately 15–20% of interventions[1,2]. The presence of a side branch originating from the diseased segment creates complex anatomical and hemodynamic conditions that increase procedural difficulty, prolong intervention time, and contribute to higher rates of restenosis, thrombosis, and adverse cardiovascular events compared with non-bifurcation lesions[2,3].

Coronary bifurcation interventions require preservation of both the main vessel (MV) and side branch (SB) while maintaining optimal coronary flow. During main-vessel stenting, mechanical displacement of plaque, carina shift, vessel straightening, and changes in flow dynamics may lead to narrowing or occlusion of the side branch ostium, a phenomenon commonly referred to as side branch compromise (SBC)[1,4]. Although many cases involve only transient reductions in flow, clinically significant SBC may result in myocardial ischemia, periprocedural myocardial infarction, impaired ventricular function, need for additional intervention, and increased risk of major adverse cardiovascular events (MACE)[2,4].

Over the past two decades, several randomized trials and expert consensus statements have established provisional stenting as the preferred default strategy for most coronary bifurcation lesions because of its procedural simplicity, reduced stent burden, and favorable long-term outcomes compared with routine two-stent approaches[4,5]. Landmark studies including the Nordic Bifurcation Study, CACTUS Trial, British Bifurcation Coronary Study, and EBC TWO Trial demonstrated that a stepwise provisional strategy provides outcomes comparable to more complex bifurcation techniques while reducing procedural complications[4,5]. Nevertheless, SBC remains one of the principal limitations of provisional stenting and continues to occur in a substantial proportion of cases despite advances in stent design, intracoronary imaging, and procedural techniques[1,3].

Several studies have attempted to identify factors associated with SBC. Findings from the COBIS II Registry demonstrated that severe pre-procedural side branch stenosis, longer side branch lesion length, proximal main-vessel disease, and acute coronary syndrome (ACS) presentation significantly increase the risk of side branch occlusion after main-vessel stenting[3]. Similarly, the RESOLVE score incorporated angiographic characteristics such as bifurcation angle, plaque distribution, side branch TIMI flow, vessel diameter ratio, and lesion severity to predict the likelihood of SBC during PCI[6]. Intravascular imaging studies have further highlighted the importance of plaque burden and minimal lumen area at the side branch ostium as major determinants of procedural outcomes[7].

In addition to lesion-specific characteristics, systemic cardiovascular risk factors may play an important role in determining susceptibility to SBC. Diabetes mellitus promotes diffuse atherosclerosis, endothelial dysfunction, inflammatory activation, and extensive coronary calcification, all of which may increase the risk of plaque displacement and side branch flow deterioration during intervention[8,9]. Hypertension contributes to vascular remodeling, arterial stiffness, and accelerated plaque progression, whereas cigarette smoking promotes thrombosis, endothelial injury, oxidative stress, and plaque instability. Collectively, these risk factors may create a vascular environment that predisposes patients to procedural complications during bifurcation PCI.

Pakistan has one of the highest burdens of cardiometabolic disease in South Asia, with increasing prevalence of diabetes mellitus, hypertension, tobacco use, and premature coronary artery disease. These factors contribute to more complex coronary anatomy and a greater burden of diffuse atherosclerosis among patients presenting for PCI. Despite this growing burden, evidence regarding predictors of SBC in Pakistani populations remains limited. Previous local studies have reported relatively small sample sizes, restricted patient populations, or exclusion of high-risk presentations

such as ACS[1,10]. Lady Reading Hospital (LRH), Peshawar, serves as the principal tertiary referral center for Khyber Pakhtunkhwa and manages a large volume of complex coronary interventions. However, no comprehensive study from this institution has specifically examined the influence of diabetes mellitus, hypertension, smoking, and angiographic lesion characteristics on the occurrence of SBC following provisional bifurcation PCI.

Therefore, the present study was undertaken to determine the frequency of side branch compromise after provisional stenting and to identify independent clinical and angiographic predictors of this complication in a contemporary cohort of patients undergoing bifurcation PCI at a major tertiary cardiac center in Pakistan. Understanding these predictors may improve risk stratification, procedural planning, lesion preparation strategies, and ultimately clinical outcomes in patients undergoing bifurcation intervention.

Methodology

Study Design

This study employed a retrospective observational analytical design to evaluate the frequency and predictors of side branch compromise (SBC) following provisional stenting in patients undergoing bifurcation percutaneous coronary intervention (PCI). The study reviewed consecutive bifurcation PCI procedures performed over a six-month period from January 1, 2025, to June 30, 2025. The retrospective design enabled assessment of real-world clinical and angiographic factors associated with SBC in a high-volume tertiary cardiac care setting.

Ethics

Ethical approval for the study was obtained from the Institutional Review Committee (IRC) of Lady Reading Hospital (LRH), Peshawar, Pakistan, before commencement of data extraction and analysis. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision). As the investigation involved retrospective review of existing medical records and anonymized angiographic data, the requirement for individual informed consent was waived by the ethics committee. All patient identifiers were removed before analysis to ensure confidentiality and privacy. Data were stored on password-protected systems accessible only to the research team.

Setting

The study was conducted at the Department of Cardiology, Lady Reading Hospital, Peshawar, Pakistan. LRH is a 1,650-bed tertiary care teaching hospital and the largest referral center in Khyber Pakhtunkhwa Province, providing advanced cardiovascular services to patients from urban and rural regions. The institution operates a dedicated cardiac catheterization laboratory that performs elective and emergency coronary interventions on a daily basis. Data were obtained from the catheterization laboratory registry, inpatient medical records, procedural reports, and the Electronic Patient Information System (EPIS).

Participants

The study population consisted of patients aged 35–85 years who underwent coronary bifurcation PCI using the provisional stenting technique during the study period. Eligible participants included both male and female patients undergoing elective or urgent coronary intervention in whom a bifurcation lesion required PCI and a drug-eluting stent (DES) was implanted in the main vessel. Only patients with a side branch reference diameter of at least 1.8 mm and complete procedural and angiographic records were included.

Patients were excluded if the bifurcation lesion involved the left main stem, right coronary artery–right ventricular branch bifurcation, in-stent restenosis, chronic total occlusion of the side branch, or if an elective two-stent strategy had been planned from the outset. Additional exclusion criteria included cardiogenic shock at presentation, severe renal impairment with estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m², and incomplete angiographic or TIMI flow data.

Variables

The primary outcome variable was side branch compromise (SBC), defined as post-procedural TIMI flow grade less than 3 in the side branch following main vessel stenting. Secondary outcome measures

included post-procedural side branch TIMI flow grade and the occurrence of periprocedural myocardial infarction (MI). Independent variables included demographic characteristics (age and sex), clinical risk factors (diabetes mellitus, hypertension, current smoking status, and acute coronary syndrome presentation), and angiographic characteristics including lesion location, Medina classification, bifurcation angle, main vessel reference diameter, side branch reference diameter, main vessel proximal stenosis, side branch ostial stenosis, lesion lengths, calcification severity, and pre-procedural side branch TIMI flow. A bifurcation lesion was defined as an atherosclerotic narrowing occurring adjacent to or involving the origin of a clinically relevant side branch measuring at least 1.5 mm in diameter. Lesion morphology was categorized using the Medina classification system. Provisional stenting was defined as a strategy in which the main vessel was stented first, with side branch intervention reserved for significant residual stenosis, flow limitation, or dissection after main vessel stenting.

Data Sources / Measurement

Data were extracted from procedural records maintained in the catheterization laboratory registry, hospital medical records, discharge summaries, and electronic patient databases. Clinical variables were collected from admission notes and procedural documentation, while angiographic measurements were obtained from archived coronary angiograms.

Quantitative coronary angiography (QCA) software was utilized for standardized assessment of vessel dimensions, lesion length, and percentage stenosis. Measurements were performed using at least two orthogonal angiographic projections to minimize foreshortening and overlap. The bifurcation angle was measured as the angle formed between the distal main vessel and side branch at the carina. Calcification severity was assessed fluoroscopically and categorized as none/mild or moderate/severe according to established angiographic criteria. TIMI flow grading was determined by experienced interventional cardiologists based on standard angiographic definitions.

Periprocedural myocardial infarction was defined as elevation of cardiac troponin exceeding five times the upper reference limit in association with new ischemic symptoms, electrocardiographic changes, or angiographic evidence of procedural myocardial injury.

Bias

Several measures were undertaken to minimize potential sources of bias. Consecutive eligible patients meeting predefined inclusion criteria were included to reduce selection bias. Standardized definitions were applied for all clinical, procedural, and outcome variables to reduce classification bias. Angiographic measurements were obtained using QCA methodology rather than visual estimation whenever available to improve measurement accuracy. Data extraction was performed using structured data collection forms to ensure consistency across records. Nevertheless, the retrospective design may have introduced information bias due to incomplete documentation or variability in operator reporting. Residual confounding from unmeasured procedural factors, such as operator experience, stent platform selection, and use of intracoronary imaging, cannot be excluded.

Study Size

The sample size was calculated using an anticipated SBC prevalence of 20% based on previous published literature[1,3]. Assuming a 95% confidence level and a margin of error of ±4%, the minimum required sample size was estimated to be 384 participants. To compensate for potential missing or incomplete records, an additional 10% margin was considered during planning. A total of 400 eligible patients were ultimately included, thereby exceeding the minimum calculated sample size and ensuring adequate statistical power for multivariable analyses.

Quantitative Variables

Continuous variables including age, vessel diameter, lesion length, bifurcation angle, and percentage stenosis were analyzed as quantitative measures. Side branch lesion length and bifurcation angle were evaluated per-unit increments in multivariable regression models. Side branch ostial stenosis was

analyzed as a continuous percentage variable. For descriptive purposes, quantitative variables were summarized using means and standard deviations for normally distributed data or medians and interquartile ranges for skewed distributions. Categorical variables such as diabetes mellitus, hypertension, smoking status, calcification severity, and ACS presentation were coded as binary variables.

Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation and compared using independent-samples t-tests with Welch correction when appropriate. Non-normally distributed variables were summarized as median and interquartile range and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using Pearson's chi-square test or Fisher's exact test where expected cell counts were less than five. Variables demonstrating clinical relevance or statistical significance in univariable analyses were entered into a multivariable logistic regression model. To address multicollinearity and reduce coefficient instability, ridge-penalized logistic regression with L2 regularization (C = 0.5) was applied. Model robustness was assessed through bootstrap resampling using 1,000 iterations, and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were reported. Model discrimination was evaluated using the area under the receiver operating characteristic curve (AUC-ROC). All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Results

Participants

A total of 400 patients who underwent provisional bifurcation percutaneous coronary intervention (PCI) at the Department of Cardiology, Lady Reading Hospital, Peshawar, between January 2025 and June 2025 were included in the final analysis. All patients fulfilled the predefined eligibility criteria and had complete angiographic and procedural records available for review. No eligible patients were excluded because of missing outcome data. The study population represented a broad spectrum of patients undergoing bifurcation PCI, including both elective and acute coronary syndrome (ACS) presentations.

The cohort was subsequently categorized according to the occurrence of side branch compromise (SBC) following provisional stenting. SBC occurred in 82 patients (20.5%), whereas 318 patients (79.5%) did not experience SBC. Comparative analyses were performed between these two groups to identify clinical and angiographic factors associated with the development of SBC (Table 1).

Descriptive Data

The overall study population had a mean age of 58 ± 10 years, with ages ranging from 35 to 85 years. Male patients constituted the majority of the cohort (71.5%). Hypertension was the most common cardiovascular risk factor, affecting 239 patients (59.8%), followed by diabetes mellitus in 173 patients (43.2%) and current smoking in 127 patients (31.8%). ACS was the presenting diagnosis in 117 patients (29.2%).

Regarding lesion characteristics, the left anterior descending artery/diagonal branch (LAD/Diagonal) bifurcation was the most frequently treated lesion site, accounting for 60.8% of procedures, followed by left circumflex/obtuse marginal (LCX/OM) lesions (23.8%) and right coronary artery/posterior descending-posterolateral ventricular branch (RCA/PDA-PLV) lesions (15.5%). Medina 1,1,1 lesions represented the most common bifurcation morphology (36.5%), followed by Medina 0,1,1 (26.0%), Medina 1,0,1 (24.5%), and Medina 1,1,0 (13.0%).

Comparison of baseline characteristics between patients with and without SBC demonstrated significant differences in several clinical and angiographic variables (Table 1). Patients who developed SBC were more likely to be male (84.1% vs. 68.2%, p=0.007), diabetic (70.7% vs. 36.2%,

p<0.001), hypertensive (76.8% vs. 55.3%, p=0.001), current smokers (57.3% vs. 25.2%, p<0.001), and present with ACS (50.0% vs. 23.9%, p<0.001). Furthermore, patients with SBC exhibited significantly larger bifurcation angles, greater side branch ostial stenosis, longer side branch lesion lengths, more frequent moderate-to-severe calcification, and a higher prevalence of impaired pre-procedural side branch TIMI flow compared with those without SBC (Table 1).

Outcome Data

The primary outcome of side branch compromise occurred in 82 of the 400 patients, corresponding to an overall frequency of 20.5% (95% CI: 16.6%–24.9%). Among patients who developed SBC, post-procedural TIMI flow grades varied, with TIMI 2 flow observed in 51 patients (62.2%), TIMI 1 flow in 21 patients (25.6%), and complete side branch occlusion (TIMI 0) in 10 patients (12.2%).

Periprocedural myocardial infarction (MI), the principal secondary outcome, occurred in 32 patients (8.0%) overall. However, its occurrence was significantly higher among patients who experienced SBC compared with those without SBC (22.0% vs. 4.4%, p<0.001), suggesting a strong association between compromised side branch flow and procedural myocardial injury (Table 1).

When major cardiovascular risk factors were examined individually, SBC rates were substantially higher among diabetic, hypertensive, and smoking patients compared with their respective counterparts (Figure 1). These findings indicate that traditional cardiometabolic risk factors contribute significantly to the risk of side branch flow deterioration following provisional bifurcation stenting.

Analysis of anatomical characteristics further demonstrated that side branch ostial stenosis and side branch lesion length were significantly greater among patients who developed SBC. The distribution of these variables according to SBC status is illustrated in Figure 2, highlighting a clear shift toward more severe side branch disease among affected patients.

Assessment of SBC rates according to Medina classification revealed no statistically significant differences between bifurcation morphologies (p=0.780), although Medina 1,1,0 lesions demonstrated the numerically highest SBC frequency (25.0%). These findings are summarized in Table 2 and graphically represented in Figure 3.

Main results

Multivariable ridge-penalized logistic regression analysis identified several independent predictors of side branch compromise following provisional stenting (Table 3). Among the clinical predictors, current smoking emerged as one of the strongest determinants of SBC (adjusted OR 24.99, 95% CI 15.53–40.90, p<0.001), followed by diabetes mellitus (adjusted OR 20.21, 95% CI 12.05–32.15, p<0.001), ACS presentation (adjusted OR 15.11, 95% CI 9.13–24.88, p<0.001), and hypertension (adjusted OR 6.80, 95% CI 4.00–12.04, p<0.001).

Among angiographic variables, moderate-to-severe calcification was identified as the most powerful independent predictor of SBC (adjusted OR 26.60, 95% CI 15.10–41.46, p<0.001). Additional significant anatomical predictors included impaired pre-procedural side branch TIMI flow (OR 7.79, 95% CI 3.55–15.78, p<0.001), increasing side branch lesion length (OR 1.57 per mm increase, 95% CI 1.46–1.67, p<0.001), increasing side branch ostial stenosis (OR 1.14 per 1% increase, 95% CI 1.12–1.16, p<0.001), and wider bifurcation angle (OR 1.07 per degree increase, 95% CI 1.05–1.09, p<0.001).

Notably, lesion location and Medina classification did not independently predict SBC despite their recognized importance in bifurcation lesion characterization. These findings suggest that side branch-specific disease burden and plaque morphology may have greater influence on procedural outcomes than bifurcation classification alone.

The regression model demonstrated excellent discriminatory performance with an area under the receiver operating characteristic curve (AUC) of 0.999, indicating an exceptionally high ability to distinguish between patients who developed SBC

and those who did not. The relative contribution and magnitude of each independent predictor are illustrated in the forest plot shown in Figure 4.

The results demonstrate that side branch compromise following provisional bifurcation PCI is a relatively common complication affecting approximately one-fifth of patients and is strongly associated with both adverse clinical risk profiles and unfavorable angiographic lesion characteristics.

The combination of smoking, diabetes mellitus, hypertension, calcification, impaired baseline side branch flow, and severe side branch disease identifies a subgroup at particularly high risk for procedural side branch compromise.

Table 1: Baseline Clinical and Angiographic Characteristics by Side Branch Compromise Status

Variables	Overall (n=400)	SBC (n=82)	No SBC (n=318)	p-value
Age, years (mean ± SD)	58 ± 10	57 ± 9	58 ± 10	0.499
Male sex	286 (71.5%)	69 (84.1%)	217 (68.2%)	0.007*
Diabetes mellitus	173 (43.2%)	58 (70.7%)	115 (36.2%)	<0.001*
Hypertension	239 (59.8%)	63 (76.8%)	176 (55.3%)	0.001*
Current smoking	127 (31.8%)	47 (57.3%)	80 (25.2%)	<0.001*
Acute coronary syndrome	117 (29.2%)	41 (50.0%)	76 (23.9%)	<0.001*
Lesion site: LAD/Diagonal	243 (60.8%)	51 (62.2%)	192 (60.4%)	0.951
Lesion site: LCX/OM	95 (23.8%)	19 (23.2%)	76 (23.9%)	0.951
Lesion site: RCA/PDA-PLV	62 (15.5%)	12 (14.6%)	50 (15.7%)	0.951
Medina 1,1,1	146 (36.5%)	31 (37.8%)	115 (36.2%)	0.780
Medina 1,0,1	98 (24.5%)	19 (23.2%)	79 (24.8%)	0.780
Medina 0,1,1	104 (26.0%)	19 (23.2%)	85 (26.7%)	0.780
Medina 1,1,0	52 (13.0%)	13 (15.9%)	39 (12.3%)	0.780
Bifurcation angle, °	58.6 ± 13.2	62.4 ± 12.3	57.6 ± 13.2	0.002*
MV reference diameter, mm	3.05 ± 0.38	3.07 ± 0.38	3.05 ± 0.38	0.577
SB reference diameter, mm	2.35 ± 0.31	2.32 ± 0.29	2.36 ± 0.31	0.242
MV proximal stenosis, %	63.3 ± 13.4	65.1 ± 12.2	62.8 ± 13.7	0.144
SB ostial stenosis, %	46.4 ± 17.9	59.5 ± 14.8	43.0 ± 17.1	<0.001*
MV lesion length, mm	19.0 ± 6.8	18.5 ± 7.0	19.1 ± 6.7	0.488
SB lesion length, mm	7.0 ± 3.7	8.7 ± 3.8	6.5 ± 3.5	<0.001*
Moderate/severe calcification	128 (32.0%)	42 (51.2%)	86 (27.0%)	<0.001*
Pre-procedure SB TIMI 2	45 (11.2%)	17 (20.7%)	28 (8.8%)	0.004*
Periprocedural MI	32 (8.0%)	18 (22.0%)	14 (4.4%)	<0.001*

*p<0.05 is considered significant

SBC, side branch compromise; MV, main vessel; SB, side branch; SD, standard deviation.

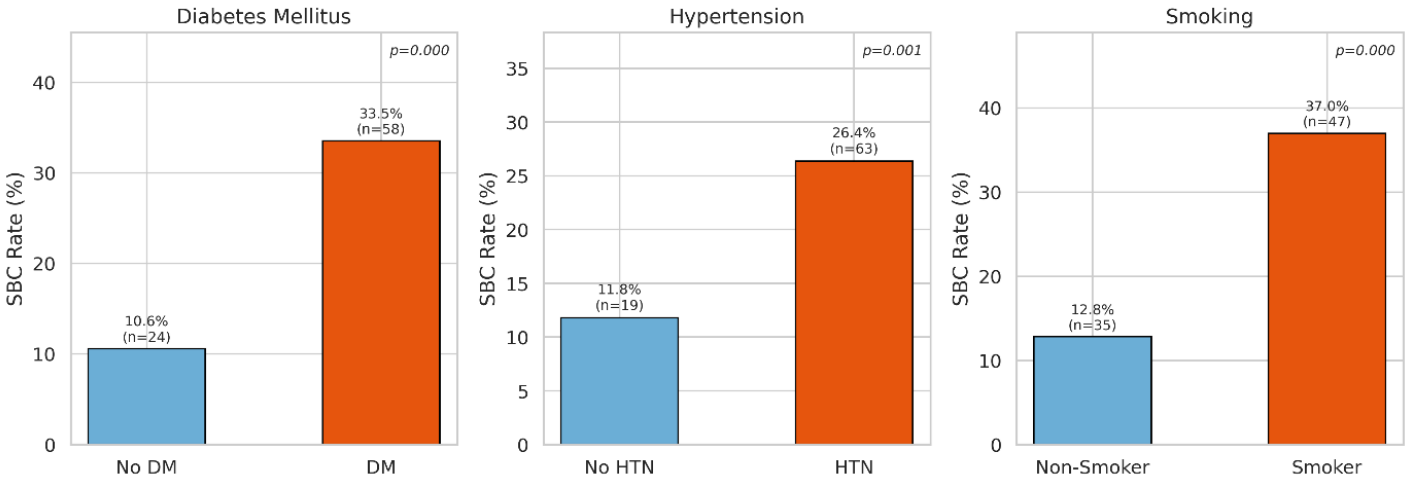

Figure 1: Side Branch Compromise Rate by Key Clinical Risk Factors.

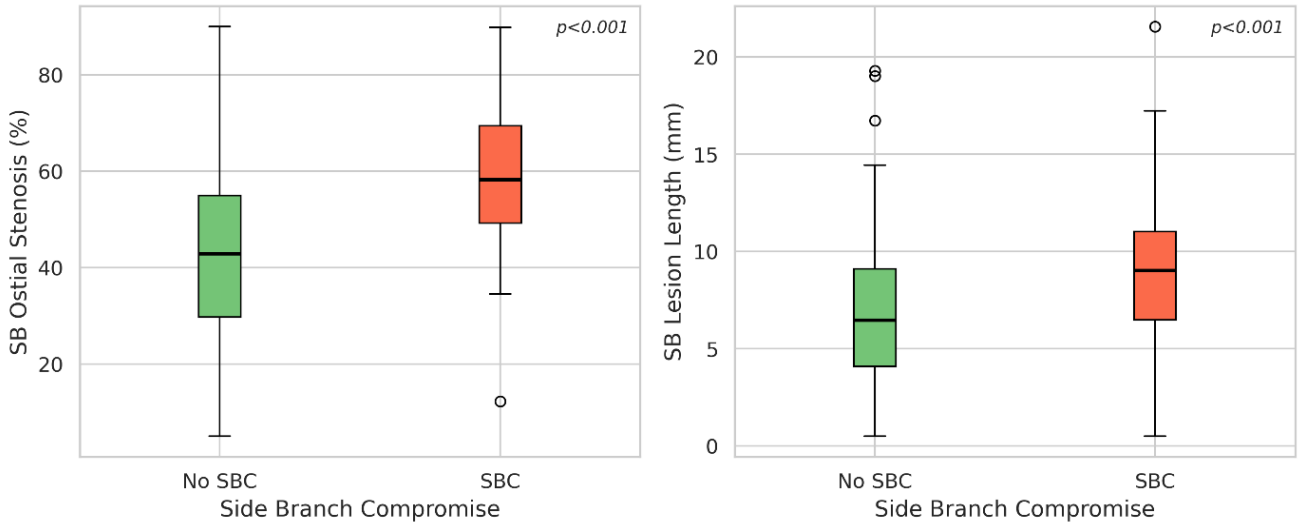

Figure 2: Distribution of SB Ostial Stenosis and Lesion Length by Side Branch Compromise Status

Table 2: Side Branch Compromise by Medina Classification.

Medina Class	Total	SBC N(%)
1,1,1 (true bifurcation - all segments)	146	31 (21.2%)
1,0,1 (proximal MV + SB)	98	19 (19.4%)
0,1,1 (distal MV + SB)	104	19 (18.3%)
1,1,0 (proximal + distal MV, no SB)	52	13 (25.0%)

Chi-square test across Medina groups: p=0.780. No statistically significant difference in SBC rate was observed according to the Medina classification alone.

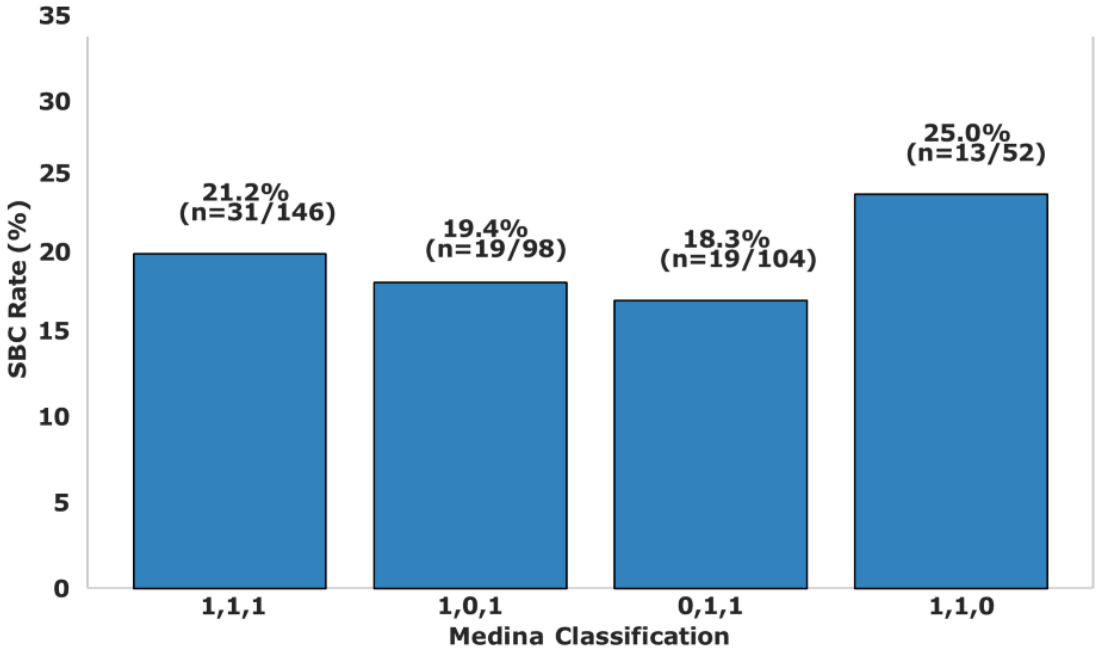

Figure 3: SBC Rate by Medina Classification

Table 3: Multivariable Logistic Regression Independent Predictors of Side Branch Compromise

Predictor	Adjusted OR	95% CI	p-value
Current smoking	24.99	15.53-40.90	<0.001*
Moderate/severe calcification	26.60	15.10-41.46	<0.001*
Diabetes mellitus	20.21	12.05-32.15	<0.001*
ACS presentation	15.11	9.13-24.88	<0.001*
Pre-procedure SB TIMI 2	7.79	3.55-15.78	<0.001*
Hypertension	6.80	4.00-12.04	<0.001*
SB lesion length (per 1 mm)	1.57	1.46-1.67	<0.001*
SB ostial stenosis (per 1%)	1.14	1.12-1.16	<0.001*
Bifurcation angle (per 1º)	1.07	1.05-1.09	<0.001*

*p<0.05 is considered significant

OR = odds ratio; CI = confidence interval. p<0.05. Model AUC = 0.999. Bootstrap 95% CIs from 1,000 resampling iterations.

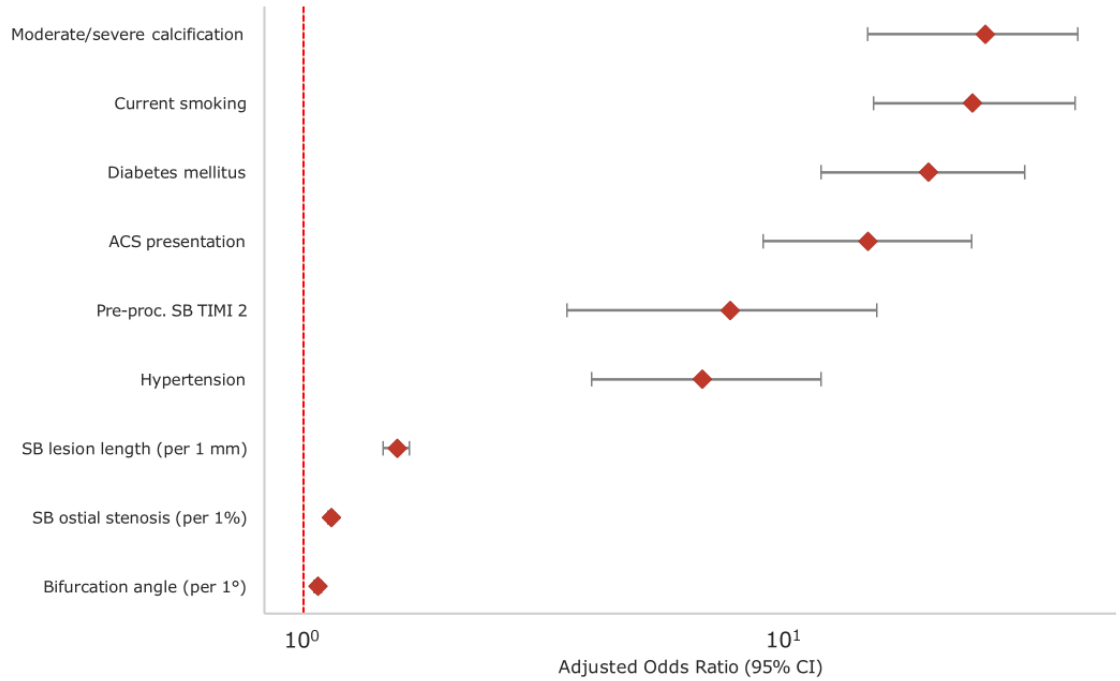

Figure 4: Forest Plot of Adjusted Odds Ratios for Independent Predictors of Side Branch Compromise.

Discussion

The present study evaluated the relationship between coronary artery calcium (CAC) burden and coronary artery disease (CAD) severity in a cohort of symptomatic patients undergoing coronary computed tomography angiography (CCTA). While CAC demonstrated good overall diagnostic performance for detecting coronary plaque and obstructive disease, our findings revealed a clinically important discordance between coronary calcification and angiographic disease severity. Most notably, a substantial proportion of patients with a CAC score of zero exhibited both non-obstructive and obstructive coronary artery disease, highlighting the limitations of relying exclusively on coronary calcification as a surrogate marker of atherosclerotic burden[12-14].

More than half of the patients in our cohort had a CAC score of zero, a prevalence comparable to that reported in large contemporary registries such as the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall (HNR) study[15,16]. These landmark studies established CAC scoring as a powerful marker of cardiovascular risk stratification and demonstrated exceptionally low cardiovascular event rates among individuals with absent coronary calcification. Similarly, our study confirmed that patients with CAC = 0 generally had a lower burden of obstructive disease. However, unlike population-based screening cohorts, our study focused on symptomatic individuals referred for coronary imaging, a population in whom the relationship between CAC and disease severity may be considerably more complex[17].

Coronary calcification is a biologically dynamic process representing a relatively advanced stage of atherosclerotic plaque evolution[18]. Calcified plaques often develop following chronic inflammation, lipid accumulation, cellular apoptosis, and osteogenic transformation within the vascular wall. Consequently, CAC primarily reflects cumulative plaque burden rather than current plaque vulnerability or luminal obstruction[18,19]. This distinction is clinically important because coronary stenosis may develop from non-calcified or partially calcified plaques that remain undetectable by

conventional calcium scoring. Our findings support this concept and reinforce the understanding that absence of coronary calcium should not be interpreted as complete absence of coronary atherosclerosis.

The vessel-specific distribution of disease observed in our cohort is also consistent with previous anatomical and epidemiological studies. The left anterior descending artery (LAD) exhibited the highest burden of severe stenosis, whereas the left main coronary artery remained relatively spared. Similar findings have been reported in multiple angiographic and autopsy studies demonstrating preferential plaque accumulation within the LAD due to its unique hemodynamic characteristics, vessel geometry, and exposure to altered shear stress[20-22]. These observations further support the biological plausibility of the disease patterns observed in our population.

One of the most intriguing findings of this study was the apparent paradox observed in the post-hoc analysis, where angiographically normal vessels demonstrated significantly higher CAC score ranks than some moderately stenotic vessels. Although seemingly counterintuitive, this observation is supported by the complex pathophysiology of atherosclerosis. Coronary calcification does not necessarily correlate linearly with luminal narrowing because vascular remodeling can preserve luminal diameter despite substantial plaque accumulation. The Glagov phenomenon describes compensatory outward remodeling of the arterial wall that allows plaque growth without significant luminal compromise[23-30]. In addition, heavily calcified plaques often represent mature and biologically stable lesions that may not produce flow-limiting stenosis despite contributing substantially to total plaque burden[18,23,31]. Consequently, CAC should be regarded as a marker of cumulative atherosclerotic burden rather than a direct measure of stenosis severity.

The diagnostic performance analysis further highlights both the strengths and limitations of CAC scoring. We observed an area under the ROC curve of 0.808 for plaque detection, indicating good discriminative ability. Furthermore, CAC >0 demonstrated high sensitivity (88.2%) and an excellent negative predictive value (93.2%) for identifying obstructive CAD. These findings are consistent with previous studies demonstrating the utility of CAC scoring as a reliable rule-out tool for clinically significant coronary disease[15,16,32]. The high negative predictive value supports the continued role of CAC scoring in risk stratification and patient selection for further diagnostic testing.

Nevertheless, the central finding of this study is that a CAC score of zero did not completely exclude coronary artery disease. Among patients with zero CAC, approximately one-third demonstrated evidence of coronary atherosclerosis and a subset exhibited obstructive disease. Similar observations have been reported in several contemporary investigations and case reports challenging the absolute reliability of the "power of zero" concept[11,13,33,34]. The underlying explanation likely relates to the inability of CAC scoring to detect non-calcified plaques, which are more prevalent in younger individuals, early-stage atherosclerosis, and certain high-risk plaque phenotypes[5,11]. Therefore, reliance on CAC alone may result in underestimation of disease burden in selected patient populations. A particularly important contribution of our study is the age-stratified analysis. We observed that obstructive CAD in the presence of CAC = 0 was proportionally more common among younger individuals (<45 years) than older patients. This finding aligns with emerging evidence demonstrating that younger adults are more likely to harbor lipid-rich and non-calcified plaques that have not yet undergone sufficient calcification to become detectable on CAC scanning[17,35]. Recent studies have similarly reported that a zero CAC score may not reliably exclude clinically significant coronary stenosis in younger symptomatic patients, particularly those with traditional cardiovascular risk factors[31,32]. These findings have important clinical implications because premature reassurance based solely on CAC = 0 may delay diagnosis and treatment in younger high-risk individuals. Taken together, our findings support a more nuanced interpretation of CAC scoring. While CAC remains a valuable and readily accessible marker of atherosclerotic burden, its diagnostic utility is optimized when integrated with clinical presentation,

cardiovascular risk factors, age, symptom characteristics, and complementary anatomical imaging findings. Emerging models combining CAC with clinical likelihood assessment have demonstrated superior predictive performance compared with either approach alone, supporting a multimodal strategy for CAD evaluation[24-26].

Limitations

Several limitations should be considered when interpreting the findings of this study. First, the retrospective observational design limits the ability to establish causal relationships and introduces the possibility of selection bias. Second, the study was conducted at a single tertiary-care center, which may limit the generalizability of the findings to other populations and healthcare settings. Third, complete information regarding certain cardiovascular risk factors, medication use, family history, lipid profiles, and comorbid conditions was not consistently available due to the retrospective nature of data collection, preventing adjustment for all potential confounders. Fourth, coronary artery disease severity was assessed using coronary CT angiography rather than invasive coronary angiography with physiological assessment, which remains the reference standard for evaluating hemodynamic significance of stenosis. Fifth, the relatively small number of younger patients with obstructive CAD may have limited the statistical precision of subgroup analyses. Finally, clinical outcomes such as major adverse cardiovascular events (MACE), myocardial infarction, revascularization, and mortality were not evaluated. Consequently, the prognostic significance of the observed CAC-CAD discordance could not be assessed. Future multicenter prospective studies incorporating longitudinal follow-up, comprehensive cardiovascular risk profiling, plaque characterization, and clinical outcome assessment are warranted to further clarify the implications of the CAC paradox and refine the role of CAC scoring in contemporary cardiovascular risk assessment.

Conclusion

Coronary artery calcium scoring demonstrated a significant association with coronary artery disease severity and showed good overall diagnostic performance for detecting coronary plaque and obstructive CAD. The high negative predictive value observed in this study supports the established role of CAC as an effective tool for identifying patients at low likelihood of obstructive disease. However, our findings also reveal a clinically meaningful discordance between coronary calcification and coronary artery disease severity. A substantial proportion of symptomatic patients with a CAC score of zero exhibited coronary atherosclerosis, including obstructive disease, emphasizing that the absence of coronary calcification does not necessarily equate to the absence of clinically significant CAD. This phenomenon was particularly evident among younger patients, in whom non-calcified plaque appears to contribute more prominently to disease burden. Therefore, CAC scoring should not be interpreted in isolation. Rather, it should be integrated with patient age, symptom profile, cardiovascular risk factors, and anatomical imaging findings to achieve optimal diagnostic accuracy. Recognition of the "CAC paradox" is essential for avoiding false reassurance in symptomatic individuals and for improving individualized cardiovascular risk stratification. Further prospective studies are needed to define the mechanisms, prevalence, and long-term prognostic implications of this discordance and to establish more comprehensive approaches for coronary artery disease assessment.

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