

# Comparative Clinical Implications of Calcified versus Non-Calcified Tissue Protrusion After Coronary Stent Implantation

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**Purpose:** The prognostic implications of calcified versus non-calcified tissue protrusions (TPs) following stent implantation remain undetermined. This study aimed to evaluate the differential clinical outcomes associated with calcified and non-calcified TP morphologies.

**Patients and Methods:** Employing intravascular ultrasound (IVUS), we identified calcified TPs as calcium fragment extrusions permeating the stent struts, while non-calcified TPs were characterized as plaque and/or thrombus extensions through the stent into the arterial lumen. The primary endpoint encompassed target lesion failure (TLF), comprising cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization (TLR), or stent thrombosis, assessed in patients with a follow-up period exceeding one year.

**Results:** Of 1033 patients subjected to pre- and post-intervention IVUS, 62 exhibited calcified TPs (6.0%), and 279 presented non-calcified TPs (27.0%), forming the basis of this analysis. Multivariable linear regression indicated calcified nodules as a significant predictor of calcified TP [Odds Ratio (OR) 2.47; 95% Confidence Interval (CI) 2.33 to 2.62;  $P < 0.001$ ], with ST-segment elevation myocardial infarction emerging as an inverse correlate [OR 0.82; 95% CI 0.73 to 0.93;  $P = 0.004$ ]. Two-year data revealed a higher incidence of TLF in patients with calcified TPs versus their non-calcified counterparts (11.3% vs 2.2%,  $P < 0.001$ ), and a marked increase in clinically driven TLR (9.7% vs 1.4%,  $P < 0.001$ ). Calcified TPs were independently correlated with increased TLF risk in the adjusted model [Hazard Ratio (HR) 2.47; 95% CI 1.17 to 5.16;  $P = 0.027$ ].

**Conclusion:** After drug-eluting stent implantation, IVUS-identified calcified TPs correlate with adverse clinical outcomes compared to non-calcified TP formations.

**Keywords:** percutaneous coronary intervention, intravascular ultrasound, tissue protrusion, prognosis

## Introduction

The introduction of drug-eluting stents (DES) represents a significant advancement in percutaneous coronary intervention (PCI) techniques for managing coronary artery disease. However, postoperative complications such as stent thrombosis and in-stent restenosis (ISR) continue to present substantial clinical challenges.<sup>1</sup> A prevalent issue in post-PCI scenarios is tissue protrusion (TP), which involves the extrusion of coronary lesion constituents (plaque and/or thrombus) through the struts of the stent, detectable via intravascular ultrasound (IVUS).<sup>2-4</sup> This condition is observed in 27–70% of patients treated with DES.<sup>2,5</sup> Despite inconsistencies in earlier IVUS studies regarding the prognostic significance of TP, retrospective analyses have implicated TP in the increased occurrence of adverse coronary events, particularly early in-stent thrombosis.<sup>3,4,6</sup> A notable association has been identified between refractory ISR and the presence of calcified tissue protrusions in patients.<sup>7-10</sup> However, there remains a gap in the comprehensive assessment of the distinct clinical consequences of calcified versus non-calcified TPs, especially considering their prolonged clinical implications. Therefore, this study aims to thoroughly investigate the prevalence, predictive factors, and clinical outcomes associated with both calcified and non-calcified TPs, as identified through post-implantation IVUS analysis.

## Materials and Methods

### Study Design and PCI Protocol

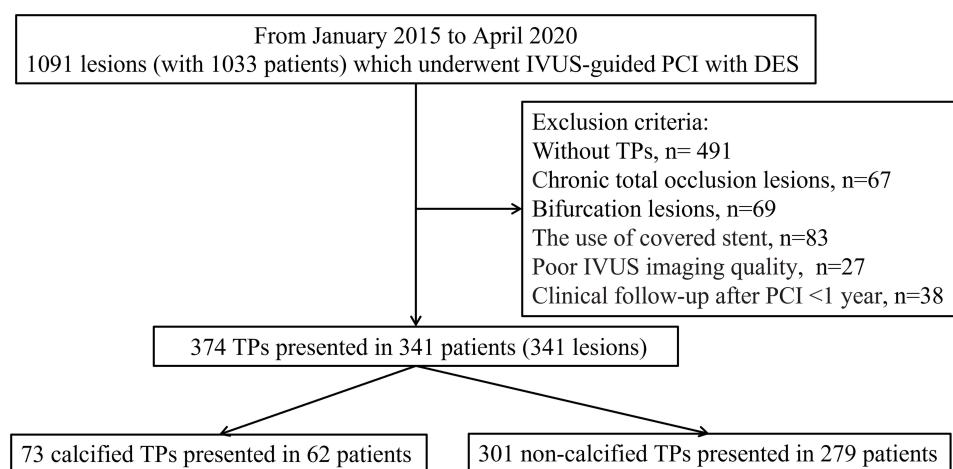
This retrospective, single-center, observational study unfolded at Xiangtan Central Hospital spanning January 2015 to April 2020. Initial and subsequent post-PCI intravascular ultrasound (IVUS) assessments in all the patients were routinely conducted following the successful implementation of drug-eluting stents (DES) in primary PCI procedures. Exclusions encompassed: (1) without TPs, (2) chronic total occlusion lesions, (3) bifurcation lesions, (4) deployment of covered stents, (5) suboptimal IVUS image integrity, and (6) post-PCI clinical follow-ups shorter than one year. PCI methodologies, shaped by operator preference, adhered to prevailing standardized approaches. A minimum of 12 hours prior to PCI, patients were administered a dual antiplatelet primer-300 mg of aspirin, complemented by either 300 mg of clopidogrel or 180 mg of ticagrelor. Commencing with the PCI, intravenous heparin was initiated at 80 IU/kg, sustaining an activated clotting time between 250 and 300 seconds throughout the procedure. Post-PCI management mandated a daily dual antiplatelet regimen for at least 12 months (100 mg aspirin and either 75 mg clopidogrel or 180 mg ticagrelor). Conducted under the ethical tenets of the Declaration of Helsinki, the study secured institutional ethics committee endorsement. All participants provided written, informed consent for the PCI interventions. The study's procedural sequence is delineated in Figure 1.

### Quantitative Coronary Angiographic Analysis

Quantitative coronary angiography of each lesion was facilitated through QAngio XA (Medis, Leiden, the Netherlands). Automated software delineated reference vessel diameter, minimum lumen diameter, percentage diameter stenosis, and lesion length.<sup>11</sup> Calcification manifested as distinct radiopacities within vascular walls at stenotic sites. Coronary perfusion evaluations adhered to Thrombolysis In Myocardial Infarction (TIMI) benchmarks.<sup>12</sup> Multivessel pathology was characterized by a visually confirmed >50% diameter stenosis in no less than two primary epicardial arteries.

### IVUS Imaging and Analysis

Subsequent to the intracoronary introduction of 1–2mg nitroglycerin, IVUS assessments were conducted during pre- or post-DES deployment phases. Data capture utilized the readily accessible QIvus<sup>®</sup> system (Medis, Leiden, the Netherlands) alongside a 40-MHz IVUS array (OptiCross<sup>™</sup>, Boston Scientific, Marlborough, MA, USA). The IVUS catheter retraced from the stent's distal to the target vessel's proximal reference points, propelled at a consistent retraction speed of 0.5 mm/s. Dual cardiologist oversight, blinded to patients' clinical characteristics, complied with standards stipulated by the American College of Cardiology's consensus document on IVUS data handling.<sup>13</sup>



**Figure 1** Study flow.

**Abbreviations:** IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; DES, drug-eluting stents; TP, tissue protrusion.

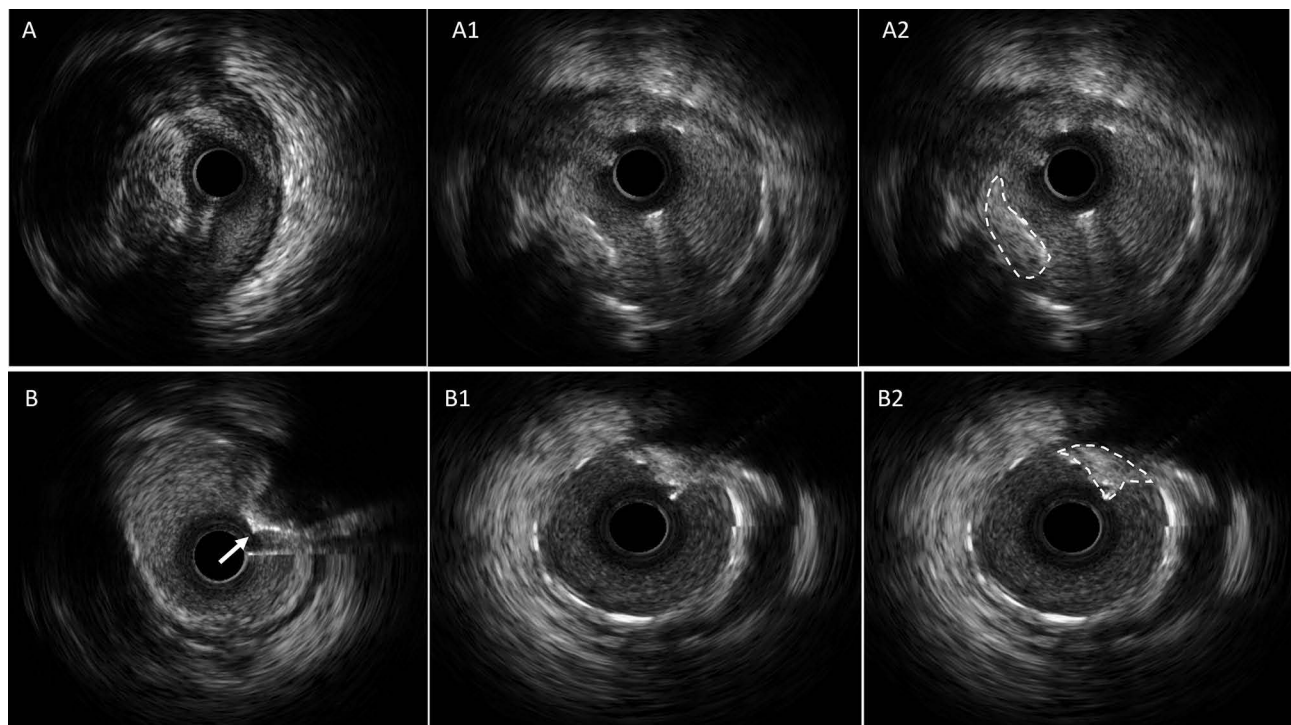
Sequential 1.0 mm intervals underwent quantitative IVUS scrutiny pre- and post-PCI, focusing on external elastic membrane (EEM), lumen, post-PCI stent areas, plaque plus media (EEM minus lumen), and plaque burden (ratio of plaque and media to EEM). Evaluations identified and analyzed the minimal luminal area (MLA) and minimal stent area (MSA) within each implicated lesion and reference segment. Reference segments, positioned 5 mm proximal and distal from each lesion or stent boundary (pre- or post-PCI) and preceding substantial ( $>1.5$  mm diameter) side branches, underwent volumetric IVUS analysis using Simpson's rule, yielding total and normalized volumes (expressed in mm<sup>3</sup>/mm).<sup>5</sup> Plaque rupture presented as luminal-communicating intraplaque cavities capped by residual fibrous fragments.<sup>14</sup> Attenuated plaque, identified by obscured deep arterial echos sans prominent calcification,<sup>14</sup> contrasted with calcified TP, characterized by minute calcific extrusions permeating stent struts;<sup>9</sup> Non-calcified TP involved non-calcified plaque or thrombus breaching stent confines (Figure 2). Assessments extended to TP dimensions and maximal TP expanses. Stent malapposition, indicated by observable blood speckles behind stent struts absent side branch overlay,<sup>3</sup> and edge dissection, evidenced by disruption within or beyond the EEM,<sup>14</sup> underwent diagnostic scrutiny. Consistency in TP diagnostic outcomes demonstrated high intra- and inter-observer agreement ( $\kappa = 0.93$  and  $0.90$ , respectively).

## Clinical Follow-Up and Outcomes

Post-PCI, patients underwent a minimum one-year follow-up. The primary endpoint, target lesion failure (TLF), encompassed cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization (TLR), and stent thrombosis.<sup>15</sup> Verification of clinical incidents entailed comprehensive electronic medical record scrutiny and/or telephonic correspondence.

## Statistical Analysis

Statistical evaluations employed SPSS version 20.0 (IBM Corporation, Armonk, New York). Initial patient assessments focused on individual clinical presentations, with subsequent angiographic and procedural evaluations conducted at both



**Figure 2** Representative intravascular ultrasound images of tissue protrusion before and after percutaneous coronary intervention. (A) Without calcified lesion before stent implantation; A1: Without calcified tissue intrusion through the stent struts into the lumen; A2: Without calcified tissue protrusion was shown as white dotted line. (B) Calcified lesion before stent implantation, white arrowhead indicate calcified nodule; B1: Calcified tissue intrusion through the stent struts into the lumen; B2: Calcified tissue protrusion was shown as white dotted line.

patient and lesion dimensions, culminating in lesion-specific IVUS analysis. Data representation adopted mean±SD or median (interquartile range [IQR]) for continuous metrics, and frequency (%) delineation for categorical data. Normal distribution continuous variables underwent Student's *t*-test analysis, with Fisher's exact test applied to categorical counterparts. Non-normally distributed continuous variables warranted Mann–Whitney testing. Kaplan–Meier methodology charted clinical outcome survival rates, contrasting cases with and without IVUS-identified calcified TP, subject to Log rank testing. Multivariable linear regression assessed the interplay of clinical, angiographic, procedural, and IVUS factors in precipitating calcified TP. Concurrently, the Cox proportional hazards model interrogated the relationship of these variables with TLF. Lesion-centric investigations, acknowledging patient singularity across multiple lesions, necessitated a generalized estimating equation strategy. Statistical materiality was affirmed at a *p*-value threshold of <0.05 for all bidirectional tests.

## Results

From January 2015 to April 2020, 1033 patients presented 1091 lesions, all undergoing IVUS-assisted PCI for de novo native coronary artery defects, with viable pre- and post-PCI IVUS imagery. Of these, 341 lesions from as many patients exhibited 374 TPs, establishing a TP incidence of 31.3% (341/1091) per lesion and 33.0% (341/1033) per patient. Single TPs manifested in 90.3% (308/341) of cases, while 9.7% (33/341) presented dual TPs, consistently of identical TP classification. Comparative analysis ensued between 73 lesions with calcified TPs from 62 patients and 301 lesions with non-calcified TPs from 279 patients.

## Baseline Clinical Characteristics

**Table 1** delineates baseline clinical differentials between patients exhibiting calcified versus non-calcified TP. Patients with calcified TP evidenced elevated chronic kidney disease prevalence (50 vs 39.4%, *p*<0.001) and stable ischemic heart conditions (56.5 vs 32.6%, *p*<0.001), contra a diminished frequency of ST-segment elevation myocardial infarction

**Table 1** Baseline Clinical Characteristics

	Calcified TP (n=62)	Non-Calcified TP (n=279)	P value
Age, yrs	64.0 (55.0–71.0)	64.0 (56.0–71.0)	0.861
Male	41 (66.1)	201 (72.0)	0.290
Current smoking	18(29.0)	103(36.9)	0.396
Hypertension	37(59.7)	167(59.9)	0.997
Diabetes mellitus	18(29.0)	84(30.1)	0.905
Hyperlipidemia	38(61.3)	151(54.1)	0.176
eGFR (mL/ min/1.73 m <sup>2</sup> )	59.4±23.3	76.3±25.7	<0.001
Chronic kidney disease*	31(50.0)	110(39.4)	<0.001
Body mass index, kg/m <sup>2</sup>	28.1 (25.3–31.7)	27.6 (24.9–31.1)	0.521
Previous MI	20(32.3)	81(29.0)	0.214
Previous PCI	23(37.1)	103(36.9)	0.845
Previous CABG	2(3.2)	11(3.9)	0.782
Presenting clinical syndrome			
ST-segment elevation MI	2(3.2)	73(26.2)	<0.001
Non–ST-segment elevation MI	11(17.4)	51(18.3)	0.681
Unstable angina	14(22.6)	66(23.7)	0.545
Stable ischemic heart disease	35(56.5)	91(32.6)	<0.001
Laboratory data			
TC, mg/dL	186.8±42.5	191.4±54.8	0.346
LDL-C, mg/dL	110.1±36.0	119.1±46.5	0.413
HDL-C, mg/dL	45.6±15.0	40.6±15.0	0.514
TG, mg/dL	113.2±79.4	129.2±94.7	0.107

(Continued)

**Table 1** (Continued).

	Calcified TP (n=62)	Non-Calcified TP (n=279)	P value
Creatinine, mg/dL	1.1±1.4	1.1±0.7	0.518
LVEF, %	60.0±11.4	56.4±8.6	0.341
Medication at discharge			
Aspirin	62(100)	279(100)	1
DAPT	62(100)	279(100)	1
Statin	57(91.9)	259(92.8)	0.813
ACEI/ARB	34(54.8)	165(59.1)	0.411
β-Blocker	18(29.0)	80(28.7)	0.902

**Notes:** \*Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> using the Modification of Diet in Renal Disease study equation. Values are mean±SD, median (interquartile range) or n (%).

**Abbreviations:** TP, tissue protrusion; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DAPT, dual-antiplatelet therapy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; TC, total cholesterol; and TG, triglyceride.

(STEMI) (3.2 vs 26.2%,  $p<0.001$ ). Additionally, patients with calcified TP recorded a depressed estimated glomerular filtration rate (eGFR)(59.4±23.3 vs 76.3±25.7 mL/ min/1.73 m<sup>2</sup>,  $p<0.001$ ).

## Angiographic and Procedural Findings

Table 2 reflects the angiographic and procedural discoveries. Calcified TP cases were correlated with heightened calcium presence(42.5 vs 22.6%,  $p<0.001$ ), reduced thrombus incidence(13.4 vs 24.6%,  $p<0.001$ ), and superior baseline TIMI flow (12.3 vs 20.6%,  $p=0.001$ ).

**Table 2** Angiographic and Procedural Findings

	Calcified TP (n=73)	Non-Calcified TP (n=301)	P value
Target coronary artery			0.612
Right	26(35.6)	115(38.2)	
Left anterior descending	35(47.9)	145(48.2)	
Left circumflex	9(12.3)	30(10.0)	
Left main trunk	3(4.1)	11(3.7)	
Multivessel disease	5(6.8)	14(4.7)	0.343
Thrombus	10(13.4)	74(24.6)	<0.001
Calcium	31(42.5)	68(22.6)	<0.001
Lesion length, mm	25.0 (23.5–27.4)	23.8 (22.6–23.9)	0.052
Pre-maximal diameter stenosis,%	86.5 (85.2–87.8)	86.3 (85.8–86.8)	0.821
Post-maximal diameter stenosis, %	0.6 (0.3–1.0)	0.7 (0.5–0.8)	0.902
Pre-PCI TIMI flow grade 0/I	9(12.3)	62(20.6)	0.001
Final PCI TIMI flow grade 3	73(100)	300(99.7)	0.915
Peak CK-MB (IU/l)	234 (145–383)	242 (144–360)	0.674
Second-generation drug-eluting stent*	59(80.8)	251(83.4)	0.193
Total stent length, mm	30.0 (27.9–32.2)	28.0 (27.2–28.7)	0.079
Maximum device diameter#, mm	3.47 (3.40–3.53)	3.42 (3.39–3.44)	0.092
Maximal balloon pressure, atm	16.4 (16.0–16.8)	16.2 (16.0–16.3)	0.329
Reference vessel diameter, mm	3.3 (3.2–3.4)	3.2 (3.2–3.3)	0.136

**Notes:** \*Everolimus-eluting or zotarolimus-eluting stent. #, Device is defined as stent or post-dilating balloon. Values are median (interquartile range) or n (%).

**Abbreviations:** CK-MB, creatine kinase-myocardial band; TIMI, thrombolysis in myocardial infarction; TP, tissue protrusion; PCI, percutaneous coronary intervention.



## IVUS Findings

**Table 3** indicates that of the 374 scrutinized pre-procedural IVUS lesions, those with calcified TP significantly harbored calcified nodules (CN) (79.5 vs 7.6%,  $p<0.001$ ), and conversely, a lower frequency of plaque rupture and attenuated plaque (20.5 vs 36.2%,  $p<0.001$ ; 13.7 vs 31.6%,  $p<0.001$ , respectively) relative to their non-calcified counterparts. Quantitative discernment disclosed a pronounced dense calcium volume in calcified TP lesions [12.3 (11.6–14.0) vs 7.6 (7.0–8.2),  $p<0.001$ ]. **Table 4** notes a higher prevalence of stent malapposition within calcified TP lesions (17.8 vs 10.3%,  $p=0.002$ ), accompanying suboptimal stent expansion and consequentially, diminished post-interventional in-stent MLA, MSA, and average luminal and stent areas, opposed to lesions devoid of calcified TP.

## Predictors of Calcified TP

Utilizing a multivariable linear regression model (**Table 5**), calcified nodules emerged as positive predictors for calcified TP [Odds Ratio (OR) 2.47; 95% Confidence Interval (CI) 2.33 to 2.62;  $P<0.001$ ], contrasted with ST-segment elevation myocardial infarction (STEMI) serving as a negative predictor (OR 0.82; 95% CI 0.73 to 0.93;  $P=0.004$ ).

## Clinical Outcomes

The median follow-up period spanned 2.0 years (interquartile range: 1.4–2.0). **Table 6** encapsulates the post-implantation clinical outcomes. A cumulative TLF rate of 3.8% (13 events) materialized, predominantly propelled by clinically driven TLR (2.9%, 10 events). Both TLF and clinically driven TLR manifested at elevated rates in lesions featuring calcified TP versus those without (11.3 vs 2.2%,  $P<0.001$ ; 9.7 vs 1.4%,  $P<0.001$ , respectively). **Table 7** delineates a multivariate analysis pinpointing significant predictors of target lesion failure, highlighting the presence of calcified tissue protrusion [Hazard Ratio (HR) 2.47; 95% CI 1.17 to 5.16;  $P=0.027$ ] and extensive stent length [Hazard Ratio (HR) 2.43; 95% CI 1.63 to 3.63;  $P=0.001$ ]. **Figure 3** depicts the Kaplan-Meier survival plots for TLF.

**Table 3** Pre-Procedural Intravascular Ultrasound Findings

	Calcified TP (n=73)	Non-Calcified TP (n=301)	P value
Qualitative analysis			
Plaque rupture	15(20.5)	109(36.2)	<0.001
Attenuated plaque	10(13.7)	95(31.6)	<0.001
Calcified nodule	58(79.5)	23(7.6)	<0.001
Quantitative analysis			
Proximal reference luminal area, mm <sup>2</sup>	9.75 ±2.83	9.62 ±2.60	0.219
Distal reference luminal area, mm <sup>2</sup>	7.81 ±2.65	7.67 ±2.29	0.221
Minimal lumen site			
EEM area, mm <sup>2</sup>	14.72 ±4.32	14.68 ±4.21	0.198
Luminal area, mm <sup>2</sup>	2.72 ±1.32	2.68 ±1.29	0.301
Plaque burden, %	75.1 (74.2–77.2)	73.1 (72.3–74.5)	0.332
Remodeling index*	1.04 (9.9–1.09)	0.98 (0.95–1.01)	0.309
Volumetric analysis			
Mean EEM area, mm <sup>3</sup> /mm	14.4 (13.8–15.0)	15.3 (14.9–17.7)	0.404
Mean luminal area, mm <sup>3</sup> /mm	6.2 (6.0–6.4)	6.3 (6.1–6.5)	0.755
Percentage plaque volume, %	61.0 (55.7–67.1)	59.3 (53.1–64.9)	0.413
Percentage necrotic core volume, %	23.4 (22.7–24.0)	24.1 (23.3–25.1)	0.154
Percentage dense calcium volume, %	12.3 (11.6–14.0)	7.6 (7.0–8.2)	<0.001

**Notes:** \*EEM area at the minimal lumen site divided by the average of the proximal and distal reference EEM areas. Values are mean±SD, median (interquartile range) or n (%).

**Abbreviations:** TP, tissue protrusion; EEM, external elastic membrane.

**Table 4** Post-Procedural Intravascular Ultrasound Findings

	Calcified TP (n=73)	Non-Calcified TP (n=301)	P value
Qualitative analysis			
Stent malapposition	13(17.8)	31(10.3)	0.002
Stent edge dissection	4(5.5)	18(6.0)	0.703
Quantitative analysis			
Total stent length, mm	30.0 (27.9–32.2)	28.0 (27.2–28.7)	0.071
In-stent MLA, mm <sup>2</sup>	6.2 (6.1–6.3)	6.6 (6.3–6.9)	0.002
MSA, mm <sup>2</sup>	6.1 (6.0–6.2)	6.5 (6.3–6.8)	<0.001
In-stent mean luminal area, mm <sup>3</sup> /mm	7.9 (7.6–8.0)	8.6 (8.3–8.9)	<0.001
Mean stent area, mm <sup>3</sup> /mm	7.9 (7.8–8.1)	8.5 (8.4–8.7)	<0.001
Stent expansion,* %	69.5 (68.7–70.4)	73.3 (72.0–74.6)	<0.001

**Notes:** Values are n(%) or median (interquartile range). \*, MSA divided by the average of the proximal and distal reference luminal areas.

**Abbreviations:** MLA, minimal luminal area; MSA, minimal stent area.

**Table 5** Multivariate Predictors of Calcified Tissue Protrusion

	Odds Ratio	95% Confidence Interval	p value
Age, per 10 yrs	4.6	−1.3 to 10.6	0.101
Hypertension	14.7	−7.2 to 36.6	0.197
Chronic kidney disease	0.1	−0.7 to 0.9	0.791
ST-segment elevation MI	0.82	0.73–0.93	0.004
Angiographic presence of calcium	6.7	−1.0 to 12.5	0.542
Calcified nodule	2.47	2.33 to 2.62	<0.001
Attenuated plaque	1.28	0.98 to 1.67	0.073

**Abbreviation:** MI, myocardial infarction.

**Table 6** Kaplan–Meier Adverse Cardiac Event Rates

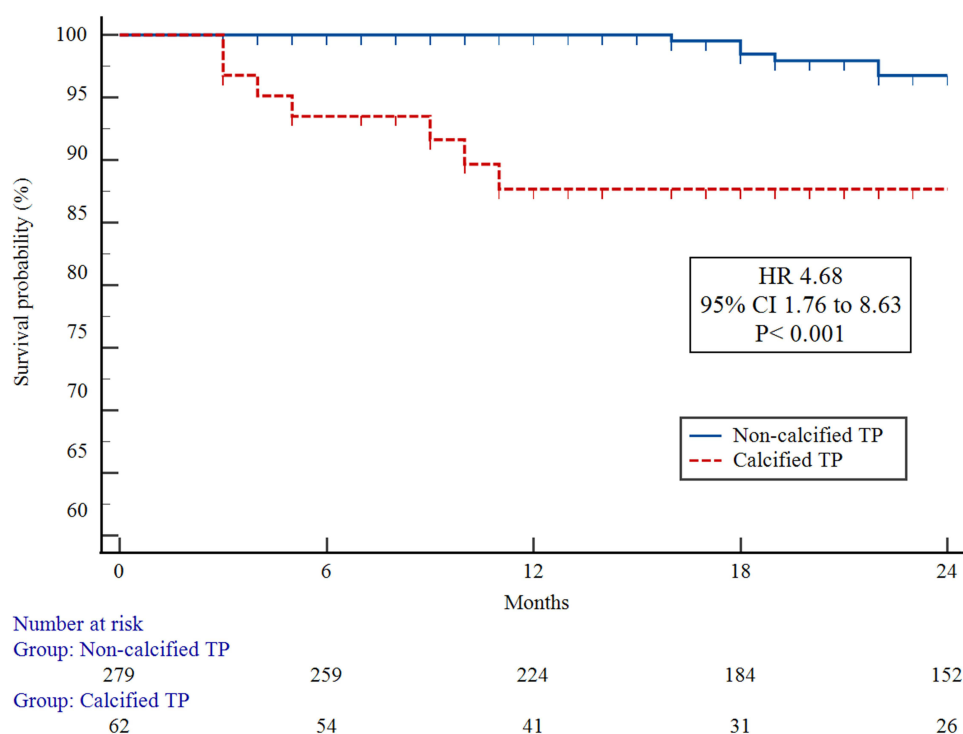
	Calcified TP (n=62)	Non-Calcified TP (n=279)	P value
Target lesion failure	7(11.3)	6(2.2)	<0.001
Clinically driven TLR	6(9.7)	4(1.4)	<0.001
Target vessel myocardial infarction	1(1.6)	4(1.4)	0.711
Cardiac death	0(0)	2(0.72)	0.404
Definite/probable stent thrombosis	0(0)	1(0.36)	0.861

**Note:** Values is n(%).

**Abbreviations:** TLR, target lesion revascularization; TP, tissue protrusion.

**Table 7** Multivariate Predictors of Target Lesion Failure at Follow-Up

	Hazard Ratio	95% Confidence Interval	p value
Age, per 10 years	2.07	1.01 to 4.50	0.068
Diabetes mellitus	1.40	0.68 to 2.89	0.355
Chronic kidney disease	1.59	0.65 to 3.87	0.306
Presence of calcified tissue protrusion	2.47	1.17 to 5.16	0.027
Presence of stent malapposition	1.66	1.02 to 2.72	0.077
Total stent length, per 10 mm	2.43	1.63 to 3.63	0.001



**Figure 3** Kaplan–Meier cumulative incidence curves for target lesion failure.  
**Abbreviations:** HR, hazard ratio; CI, confidence interval; TP, tissue protrusion.

## Discussion

Key insights derived from the current investigation into TP lesions indicate: 1) a discrete prevalence of IVUS-identified calcified TP and non-calcified TP at 6.7% (73/1091) and 27.6% (301/1091) per lesion, respectively; 2) the role of calcified nodules as positive harbingers of calcified TP, opposed by STEMI as a deleterious factor; 3) a pronounced escalation in TLF and clinically driven TLR within the calcified TP cohort relative to its non-calcified counterparts; 4) a direct correlation linking calcified TP and elongated stent length with adverse TLF outcomes. This study is pioneering in its comparative evaluation of clinical repercussions following DES insertion between calcified and non-calcified TP scenarios.

## Prevalence and Composition of TP

Intravascular imaging modalities such as IVUS or OCT frequently identify tissue protrusion subsequent to stent deployment. IVUS studies report TP incidence rates of 5–34.3%,<sup>4,16</sup> while OCT assessments approximate a 90% occurrence post-stent implantation.<sup>17–19</sup> In the present study, TP was detected in 31.3% overall lesions, which was the same as the previous studies. Defined as tissue prolapse between stent struts encroaching into the vascular lumen, the constitutive matter of tissue protrusion is predominantly thrombotic and plaque-derived.<sup>20</sup> Hong et al<sup>21</sup> demonstrated that intracoronary thrombi and necrotic plaque cores can breach stent struts, culminating in TP and the subsequent no-reflow phenomenon post-primary PCI. Coronary angioscopies have revealed a correlation between OCT-identified TP post-stent deployment and the presence of advanced yellow plaque thrombotic activity.<sup>22,23</sup> Calcified nodules represent another prevalent plaque morphology within lesions accompanied by TPs. This study underscored a heightened incidence of calcified nodules within calcified TPs. Specifically, lesions featuring a calcified nodule, absent a calcified sheet, experienced protrusions of fragmented calcified particles through stent struts.<sup>9,24</sup>

## Predictors of TP

TP's emergence has been linked to various determinants including age, body mass index, statin usage, plaque rupture, intracoronary thrombus presence, elevated lipid content, thin-cap fibroatheroma, extensive plaque burden, positive



vascular remodeling, substantial plaque volume, and extended stent implantation durations.<sup>2–4,25</sup> This study identified calcified nodules as a conducive factor for calcified TP, while STEMI served as an inhibitory element. Given the higher incidence of angiographic intracoronary thrombi, augmented necrotic core volumes, plaque burdens, and thin-cap fibroatheromas detected via IVUS in STEMI patients compared to those with non-STEMI or stable angina,<sup>26,27</sup> it is plausible that STEMI patients exhibit a higher frequency of non-calcified TPs. Histopathological examinations suggest that calcified nodules comprise nodular calcifications and fibrin deposits, with their formation linked to eruptive nodular calcifications originating from fragmented calcified plates, accompanied by surrounding fibrin and thrombi.<sup>28–31</sup> This research noted a prevalent occurrence of CN within calcified TPs. Vascular trauma induced by elevated stent or post-dilation balloon pressures could precipitate coronary calcified plate fractures external to the stent, potentially triggering nodular calcification eruptions and subsequent calcified TP genesis. This investigation also highlighted CN's predictive capacity for calcified TP. Despite CN's established association with in-stent restenosis,<sup>8–10</sup> its exact function within the calcified TP formation continuum remains elusive. The recurrent identification of calcified lesions within calcified TP sites, coupled with the routine presence of CN in such lesions, may elucidate the frequent detection of calcified TP in CN-associated calcified regions.

In our quantitative IVUS evaluations, parameters such as EEM area, luminal area, plaque burden, remodeling index at the MSA site, volumetric analysis, and reference luminal area showed no notable disparities between lesions with or without calcified TP, despite challenges in attaining adequate acute gains post-procedure in calcified lesions with calcified TP. Nonetheless, in-stent MLA, MSA, mean luminal and stent areas, along with stent expansion, were markedly reduced in calcified TP lesions compared to non-calcified counterparts. Additionally, stent malapposition prevalence escalated in calcified TP scenarios. Lesions characterized by CN pose a heightened risk for stent underexpansion and malapposition,<sup>32,33</sup> likely attributable to stent deployment in highly calcified regions.

While prior IVUS research posits a contributory role for stent type and design in TP prediction,<sup>34</sup> several studies contradict, citing negligible variations in TP rates across diverse stent types and designs.<sup>3,4,22,35</sup> This study underscores that neither the metal composition nor the structural design of the stent is as critical as the inherent lesion morphology or the rigor of the implantation methodology.

## Outcome of TP

The clinical implications of TP following PCI are contentious. Several studies have indicated a higher incidence of the no-reflow phenomenon during primary PCI in patients with TP, accompanied by elevated post-PCI CK-MB and troponin levels, relative to counterparts without TP.<sup>2–4</sup> TP is also identified as a predisposing factor for subacute, early, and late stent thrombosis.<sup>6,16,36</sup> Okuya et al<sup>37</sup> posited that IVUS-identified TP could serve as a surrogate indicator for poorer clinical outcomes across acute, sub-acute, and late stages in STEMI patients. Conversely, prior IVUS and OCT investigations disclosed no significant correlation between TP and adverse clinical events.<sup>3,4,17,18,22,38</sup>

The present study revealed a pronounced escalation in TLF and clinically driven TLR within the calcified TP cohort relative to the non-calcified group. Corroborating earlier findings, CN is implicated in calcified TP post-DES insertion,<sup>8–10</sup> consistent with our observations. Recent literature underscores the role of eccentric calcified protrusions with irregular contours, as verified through intracoronary imaging, in precipitating early in-stent restenosis following DES insertion.<sup>39,40</sup> This intimates a potential link between immediate post-DES calcified TPs and deteriorated clinical prognoses. Additionally, it is documented that the majority of TPs, typically resolvable during follow-up, eventually facilitate a more expansive lumen post-PCI.<sup>5,17</sup> The subsequent neointimal proliferation within 6–8 months post-DES insertion commonly leads to the disappearance of most TPs,<sup>17,24,41</sup> potentially elucidating the fewer adverse outcomes in non-calcified TP scenarios. Moreover, TP-afflicted patients might necessitate intensified secondary preventive measures (eg, statins,  $\beta$ -blockers, and angiotensin-converting enzyme inhibitors) to optimize long-term prognoses.<sup>42</sup> Consequently, comprehensive studies with larger cohorts are warranted to discern the precise relationship between calcified TP and early or late in-stent restenosis and thrombosis. Interventional cardiologists must remain cognizant of the potential emergence of calcified TPs following DES placement in lesions characterized by calcified nodules.

## Limitations

The current study acknowledges several constraints. Firstly, its single-center, retrospective nature potentially introduces selection bias, as both participant inclusion and IVUS utilization depended on operator preference, possibly diminishing statistical vigor. Secondly, the limited lesion count precludes a precise determination of calcified TPs' incidence, necessitating broader studies for verification. The study's brief duration underscores the need to probe the nexus between these preliminary observations and protracted clinical manifestations through expansive sample analysis. Thirdly, the absence of direct one-to-one correspondence between IVUS observations and histological data is a notable shortfall. Fourthly, compared to OCT, IVUS's lower resolution might contribute to an underestimation of TP, compounded by IVUS's inability - paralleled by OCT<sup>43</sup> - to distinctly characterize histological tissues. Lastly, the study's cross-sectional design did not incorporate follow-up IVUS, limiting longitudinal insights.

## Conclusions

This research indicates a relatively infrequent occurrence of IVUS-identified calcified TP post-DES procedure, particularly in calcified nodule-afflicted lesions. The presence of calcified TP discerned via IVUS correlates with deteriorated clinical prognoses.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

The present research was carried out in accordance with the tenets mentioned in the Helsinki Declaration and was approved by the Ethical Board of Xiangtan Central Hospital (approval number: X20212081). Prior to the commencement of the research, our team obtained written informed consent from each patient.

## Consent for Publication

Not applicable. No individual patient data will be reported.

## Acknowledgment

We are grateful to Bo Chen for their secretarial assistance.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This research received no grants from any funding agency in the public, commercial, or not-for-profit sectors.

## Disclosure

The authors declare that they have no competing interests.

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