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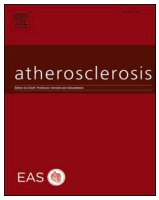

Association of cancer on coronary atherosclerotic burden and plaque rupture: Insights from the BRAVADO study

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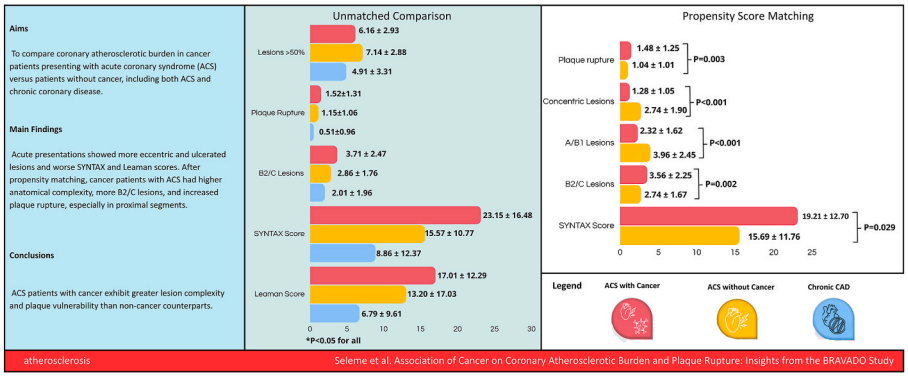
HIGHLIGHTS

- Before matching, cancer ACS patients had fewer lesions but more jeopardized myocardium and B2/C lesions vs. ACSNC.
- Plaque rupture was more frequent in ACS cancer patients than in both chronic CAD and non-cancer ACS groups.
- Matched analysis confirmed greater SYNTAX scores and more complex lesion morphology in cancer patients.
- Plaque rupture in cancer patients occurred more often in proximal segments.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aims: Cardiovascular diseases and cancer represent leading global causes of mortality, sharing common risk factors. However, the specific impact of cancer on atherosclerotic plaque burden and coronary lesion complexity in acute coronary syndrome (ACS) remains understudied. We aim to compare coronary atherosclerotic burden as assessed by coronary angiography in cancer patients with ACS to those without cancer, including ACS and chronic disease.

Methods: This was a multicenter, ambispective observational study conducted between September 2016 and December 2022, involving detailed analysis of clinical records and invasive coronary angiograms. Patients were classified into three cohorts: (1) individuals presenting with acute coronary syndrome (ACS) and a prior history of cancer (ACSC), (2) ACS patients without any history of malignancy (ACSNC), and (3) patients with stable chronic coronary artery disease (CCAD). To reduce confounding, propensity score matching was applied to balance baseline characteristics between the ACSC and ACSNC groups. Comparative assessments focused on the presence of plaque rupture, angiographic complexity, and overall coronary atherosclerotic burden across the three cohorts.

Results: 618 patients were included, comprising 206 individuals each in the ACSC, ACSNC, and CCAD groups. A total of 3752 coronary lesions were analyzed. The most common types of cancer were prostate, hematological, and colorectal cancer. Patients with acute presentation had more eccentric and ulcerated lesions, involving bifurcations, and resulted in worse SYNTAX and Leaman scores when compared to chronic coronary artery disease (p values < 0.01 for all). Post-matching, 234 ACSC and ACSNC patients were compared, revealing higher anatomical complexity in ACSC, evidenced by elevated SYNTAX scores ($p = 0.02$), B2/C lesions ($p < 0.01$), and plaque rupture ($p = 0.03$). ACSC also showed a higher prevalence of plaque rupture in the proximal segments of the vessels ($p < 0.01$).

Conclusion: Among patients with acute coronary syndrome undergoing invasive coronary angiography, those with a history of cancer more frequently exhibited plaque rupture and greater anatomical complexity compared to non-cancer counterparts.

Trial registration: ClinicalTrials.gov Identifier: NCT04222608.

Abbreviations

ACS	acute coronary syndrome
ACSC:	ACS patients with a history of cancer
ACSNC	ACS patients without cancer history
CCAD	chronic coronary syndromes
CAD	coronary artery disease
CVD	cardiovascular diseases
STEMI	ST-segment elevation myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
DM	diabetes mellitus

1. Introduction

Cardiovascular diseases (CVD) and cancer collectively stand as the top global causes of mortality across all age groups. Nevertheless, these pathologies may exhibit an intertwined nature. Cancer and its treatment are strongly linked to coronary artery disease (CAD), representing a critical cause of mortality among cancer survivors [1–3].

CVD and neoplastic diseases are linked by shared risk factors including obesity, smoking, hypertension, and socioeconomic influences [4–9]. Chronic inflammation in cancer patients increases susceptibility to thromboembolic events, which is frequently associated with the pathophysiology of acute coronary syndrome (ACS) [10]. Other prevalent factors among cancer patients, such as anemia, hypoxemia, and hyperviscosity, can act as triggers for ACS by disrupting the balance between oxygen supply and consumption [8,11–13]. Additionally, it has been shown that cancer patients experience a worse prognosis after myocardial infarction compared to non-cancer patients [14]. However, the influence of cancer on atherosclerotic burden and coronary lesion complexity in ACS patients remains inadequately studied.

The present study sought to quantify and contrast the angiographic coronary atherosclerotic burden at the patient level, and angiographic plaque complexity at the lesion level in individuals diagnosed with both cancer and ACS, juxtaposed with cohorts lacking either condition.

2. Methods

2.1. Study design

The present study is part of the BRAvAdO Registry (*BRA*zilian Registry of *A*cute Coronary Syndrome in *O*ncologic Patients, ClinicalTrials.gov Identifier: NCT04222608). The BRAVADO Registry is an ambispective, observational, national multicenter study based on angiographic and clinical data of oncological patients recruited between September 2016 and December 2022. The list of the participants centers can be found in the Supplementary Table 1. The comparison of clinical and angiographic characteristics between the retrospective and prospective cohort can be found in Supplementary Tables 2 and 3

This study received approval from the Ethics Committee at the University of Sao Paulo (95700618.2.1001.0068) and was executed in accordance with the principles of the Declaration of Helsinki.

2.2. Study population

Patients diagnosed with cancer and ACS were consecutively enrolled in the study. Patients without cancer diagnosis and those who presented with ACS or stable coronary artery disease (CAD) were randomly assessed and included in the registry as control groups. The inclusion of control group patients was based on an electronic randomization method, blinded to angiography results (probability sampling).

Patients were divided into three groups [1]: individuals with a history of current or previous oncologic treatment admitted to the hospital for ACS (ACSC) [2]; individuals without a history of oncologic disease but admitted to the hospital for ACS (ACSNC), and [3] patients without a history of oncologic disease undergoing elective outpatient cardiac catheterization (CCAD).

ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA) [15]. The inclusion of patients with chronic CCAD was intended to examine whether acute coronary syndrome in cancer patients results from plaque rupture or other systemic components present in cancer that cause an imbalance between oxygen supply and demand in the myocardium. Furthermore, we conducted a propensity match comparison of angiographic complexity and atherosclerotic burden between the ACSC and ACSNC groups, adjusting for clinical characteristics of both groups.

Inclusion criteria included the absence of contraindications for coronary cineangiography (or percutaneous coronary intervention, when indicated) and a signed written informed consent. Patients were excluded if the cancer diagnosis was non-melanoma skin cancer, bad quality coronary cineangiography, or missing data in the patients' records.

2.3. Angiographic analysis

Coronary segments were divided based on previous published studies [16,17]. Coronary angiographies were independently analyzed by two experienced interventional cardiologists (VS and DC). In case of discrepancy between both, a third interventional cardiologist (CMC) was invited for a final vote. The intraobserver variability for calculation of SYNTAX Score (tertile partitioning), based on reanalyzing 50 cases, indicated a high level of agreement (κ statistic = 0.85; 95% confidence interval [CI], 0.80 – 0.95; $P < 0.001$). The intraobserver variability for identification of complex lesion, based on reanalyzing 323 lesions also indicated a high level of agreement (κ statistic = 0.81; 95% confidence interval [CI], 0.74 – 0.88; $P < 0.001$).

The images were anonymized by a third party and blinded for patients' clinical presentation before angiographic analysis using REDCap electronic data capture tools hosted at redcap.hc.fm.usp.br.

Coronary segments were categorized according to established literature standards [16,17]. The groups were compared at patient and lesion level. For the combination of total atherosclerotic burden and anatomical complexity we used the SYNTAX Score (patient level) [18]. For assessment of the myocardium at risk we used the modified Leaman Score (patient level) [19,20]. Additionally, we assessed and compared the plaque morphologies (lesion level) [21].

The number and location of coronary lesions with obstructions greater than 50% were recorded. Each lesion was classified based on Ambrose's classification **(**Supplementary Fig. 1**)** [19]. This classification divides the lesions into 4 types: concentric (symmetric and smooth narrowing), eccentric type I (asymmetric stenosis with broad neck), eccentric type II (asymmetric stenosis in the form of a convex intraluminal obstruction with a narrow neck) and multiple irregularities (three or more serial, closely spaced narrowing or severe diffuse irregularities within a vessel) [19].

An intraluminal filling defect consistent with thrombus was characterized by an abrupt vessel cutoff with persistent contrast, or an intraluminal filling defect within or near a narrowed region in a vessel, surrounded by homogeneous contrast opacification [22,23]. Plaque ulceration was defined by the presence of contrast and hazy contour beyond the vessel lumen. Plaque irregularity (haziness), defined by irregular margins or overhanging edges. Impaired flow (TIMI flow <3, except lesions characteristic of chronic total occlusion, identified as tapering lesions with multiple fine collaterals) [22,23]. Plaque rupture was defined as lesions presenting %stenosis >50%, associated with at least one of the following characteristics [1]: thrombus [2], ulceration [3], haziness, or [4] TIMI flow less than 3 [22]. In addition to the aforementioned classifications, coronary lesions were also be analyzed according to the ACC/AHA (American College of Cardiology/American Heart Association) classification **(**Supplementary Table 4**)** [24].

2.4. Statistical analysis

Data from the patients' record was transcript into an electronic case report form (CRF) from REDCap (Research Electronic Data Capture). Continuous variables were depicted as median [interquartile range (IQR): 25th–75th percentile], while categorical variables were summarized using absolute and relative frequencies. Statistical analyses were conducted utilizing appropriate methods: the Mann–Whitney *U* test for continuous variables and the Fisher exact test or chi-square ($\chi 2$) test for categorical variables. All statistical tests were two-tailed, and a p-value <0.05 indicates statistical significance. Statistical analyses were performed using IBM SPSS version 20 (Armonk, NY, United States) and R (R Foundation for Statistical Computing, Vienna, Austria).

Since patients with and without cancer have different ACS presentation and epidemiologic characteristics, a propensity score matching (PSM) was used to adjust for confounding variables and compare the coronary artery disease between ACSC and ACSNC individuals. For the creation of the PSM, the dependent variable was the presence of cancer, and all variables of interest were candidates for inclusion in the model. The pairing was performed without substitution, in a 1:1 ratio and with a target caliper of 0.01. The standardized mean difference between the groups before and after pairing was compared to verify the quality of the fit. The variables used in the final pairing model were age, sex, and ACS presentation (STEMI, NSTEMI, UA). Post-hoc power analyses (two-tailed, $\alpha = 0.05$) were conducted for all angiographic variables, computing achieved power and estimated sample sizes for 80% power based on observed effect sizes (Cohen's d or h), mean or proportion differences, and reported p-values.

3. Results

3.1. Patients' characteristics

A total of 618 patients were included in the present work: 206 in the ACSC group, 206 in the ACSNC group, and 206 in the CCAD group. These groups of patients exhibited different baseline characteristics (Table 1 and Fig. 1). The ACSC group had a higher-risk profile, as indicated by higher GRACE scores compared to patients in the ACSNC group. CCAD patients had similar coexisting conditions as ACSC patients, except for better left ventricular function and known CAD (Table 1). The cancer etiology and oncological profile of ASCC patients can be found in the Supplementary Fig. 2 and Supplementary Table 5.

3.2. Coronary lesions

A total of 3752 lesions were assessed, with 1269 in the ACSC group, 1471 in the ACSNC group, and 1012 in the CCAD group. Overall, the ACS groups (ACSC and ACSNC) exhibited a significantly higher atherosclerotic burden across various metrics, including lesions per patient, myocardial at risk (Leaman score), and anatomical complexity (SYNTAX score) (Table 2). Additionally, plaque ruptures were much more frequent in acute patients for all parameters (ulcer, thrombus, haziness, and TIMI flow < III) when compared to the CCAD group (Table 2). The unadjusted comparison of the ACSC and ACSNC groups showed that participants without a history of cancer had more lesions but lower SYNTAX scores. This can be explained by the presence of more B2/C lesions and higher myocardial at risk (Leaman Score) in cancer patients, as seen in Table 2.

3.3. Atherosclerotic burden and plaque rupture in matched ACS groups

Propensity score matching successfully created two comparable groups in terms of clinical characteristics and presentation between the ACSC (n = 117) and ACSNC (n = 117) cohorts (Supplementary Table 6). Coronary anatomical characteristics were reassessed in the acute groups, totaling 1474 lesions (Table 3). While the total number of lesions per patient and myocardial at risk (Leaman Score) showed no significant difference between ACSC and ACSNC groups, cancer patients exhibited higher anatomical complexity (B2/C lesions and SYNTAX score) (Table 3). Plaque rupture was more prevalent in the ACSC group, whereas concentric lesions were more common in the ACSNC group (Table 3). Fig. 2 illustrates the increased density of anatomical complexity (SYNTAX score) and plaque rupture in the ACSC compared to the ACSNC group. Fig. 3 shows the distribution of plaque rupture locations in the ACSC and ACSNC groups, highlighting the higher frequency of plaque rupture in proximal segments observed in the ACSC group.

4. Discussion

The main findings of the present work can be summarized as [1]: there was a higher atherosclerotic burden in ACS groups (ACSC and ACSNC) compared to chronic coronary artery disease (CCAD) patients, accompanied by a greater prevalence of plaque ruptures [2]; unadjusted comparison between ACSC and ACSNC groups highlighted a discrepancy in lesion counts and SYNTAX scores, attributed to a greater prevalence of B2/C lesions and increased myocardial at risk among cancer patients [3]; propensity score matching unveiled higher anatomical complexity and plaque rupture frequency in ACSC patients compared to ACSNC individuals, despite similar total lesion counts and myocardial at risk (**Central Figure**).

The assessment of coronary lesions unravels the complexity of atherosclerotic burden within these groups. Supplementary Table 7 summarizes the metrics of the angiographic analysis. A total of 3752 lesions were evaluated, revealing a pronounced disparity in the atherosclerotic burden between the acute coronary syndrome groups and the CCAD group. This disparity is quantified not only by the number of lesions per patient but also through the nuanced metrics of jeopardy myocardial and anatomical complexity, as reflected in the Leaman and

Table 1
Clinical characteristics.

Clinical Characteristics	ACSC (N = 206)	ACSNC (N = 206)	CCAD (N = 206)	*p- value (overall)*	*p- value (ACSC vs. ACSNC)*	*p- value (ACSC vs. CCAD)*	*p- value (ACNC vs. CCAD)*
Age, years	69.0 ± 10	67.0 ± 9	69.0 ± 9	0.06	0.03	0.60	0.07
Male	136 (66.0)	126 (61.2)	138 (67.0)	0.41	0.37	0.92	0.26
Hypertension	151 (73.3)	143 (69.4)	165 (80.5)	0.03	0.45	0.10	0.01
Diabetes Mellitus	78 (37.9)	86 (41.7)	76 (37.1)	0.58	0.48	0.91	0.37
Dyslipidemia	92 (44.7)	61 (29.6)	99 (48.3)	<0.01	<0.01	0.49	<0.01
Current smoking	31 (15.0)	49 (23.8)	15 (7.3)	<0.01	0.03	0.20	<0.01
Previous PCI	23 (11.2)	33 (16.0)	65 (31.7)	<0.01	0.20	<0.01	<0.01
Previous stroke or TIA	12 (5.8)	11 (5.3)	16 (7.8)	0.55	1.00	0.44	0.33
Previous CABG	13 (6.3)	9 (4.4)	23 (11.3)	<0.03	0.39	0.08	0.01
Known CAD	57 (27.7)	43 (21.0)	169 (82.4)	<0.01	0.14	<0.01	<0.01
Previous MI	46 (22.3)	36 (17.5)	56 (27.3)	0.06	0.27	0.26	0.02
Renal failure				<0.01	<0.01	0.69	<0.01
Requiring dialysis	12 (5.8)	1 (0.5)	12 (5.9)				
Without dialysis	42 (20.4)	25 (12.1)	35 (17.1)				
HIV	6 (2.9)	0 (0)	0 (0)	<0.01	0.03	0.03	-
Use of aspirin in the 7 days preceding admission	52 (25.2)	73 (35.4)	57 (27.8)	0.06	0.03	0.58	0.11
GRACE score, mean and SD	136 ± 36	126 ± 36	N.A.	<0.01	<0.01	N.A.	N.A.
LVEF, mean and SD	50.4 ± 12.4	51 ± 10.7	54.8 ± 14.5	<0.01	0.56	0.02	<0.01
LVEF <50%	80 (42.1)	80 (43.2)	55 (31.1)	0.03	0.84	0.03	0.02
Indication for angiography n (%)							
Elective procedure	0 (0)	0 (0)	206 (100)	<0.01	<0.01	<0.01	<0.01
Low-risk unstable angina	7 (3.3)	0 (0)	0 (0)				
Mod/High Risk unstable angina	36 (17.4)	29 (14.0)	0 (0)				
NSTEMI	120 (58.2)	57 (27.6)	0 (0)				
STEMI	43 (20.8)	120 (58.2)	0 (0)				

ASCC: acute coronary syndrome with history of cancer; ASCNC: acute coronary syndrome with history of cancer; CABG: coronary artery bypass grafting; CCAD: chronic coronary artery disease; MI, myocardial infarction; HIV: human immunodeficiency virus; LVEF: left ventricular ejection fraction; NA: not applicable; PCI: percutaneous coronary intervention; TIA, transient ischemic attack.
Numbers are means ± standard deviation or n (%).

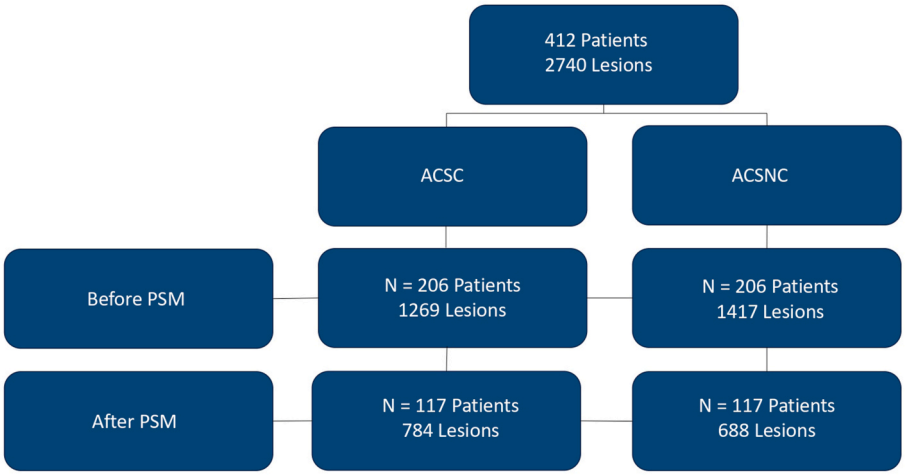

Fig. 1. Flow Chart
Study design and inclusion of patients.
ACSC: acute coronary syndrome with cancer; ACSNC: acute coronary syndrome without cancer; CCAD: chronic coronary artery disease; PSM: propensity score matching.

Table 2
Angiographic characteristics of coronary lesions by study group (N = 3752 lesions).

Angiographic characteristics per patient	ACSC N = 206 (1269 lesions)	ACSNC N = 206 (1471 lesions)	CCAD N = 206 (1012 lesions)	*p- value (overall)*	*p- value (ACSC vs. ACSNC)*	*p- value (ACSC vs. CCAD)*	*p- value (ACNC vs. CCAD)*
Total lesions	6.16 ± 2.93	7.14 ± 2.88	4.91 ± 3.31	<0.01	<0.01	<0.01	<0.01
Plaque rupture	1.52 ± 1.31	1.15 ± 1.06	0.51 ± 0.96	<0.01	<0.01	<0.01	<0.01
Ulcerated lesions	0.10 ± 0.29	0.05 ± 0.22	0.01 ± 0.12	<0.01	0.12	<0.01	0.19
Lesion with thrombus	0.24 ± 0.46	0.36 ± 0.48	0.00 ± 0.00	<0.01	<0.01	<0.01	<0.01
Haziness	0.51 ± 0.59	0.14 ± 0.34	0.07 ± 0.27	<0.01	<0.01	<0.01	0.20
TIMI flow < III	0.67 ± 0.87	0.60 ± 0.79	0.43 ± 0.86	<0.01	0.62	<0.01	0.10
Bifurcations lesions	1.35 ± 1.14	0.94 ± 1.03	0.76 ± 0.95	<0.01	<0.01	<0.01	0.19
Ambrose Classification							
Concentric lesions	1.28 ± 1.04	2.99 ± 1.88	2.06 ± 1.45	<0.01	<0.01	<0.01	<0.01
Eccentric lesions Type I	3.52 ± 2.05	3.10 ± 1.64	2.17 ± 2.08	<0.01	0.07	<0.01	<0.01
Eccentric lesions Type II	1.37 ± 1.42	1.06 ± 1.27	0.67 ± 1.04	<0.01	0.03	<0.01	<0.01
Multiple irregularities	0.01 ± 3.56	0.01 ± 3.53	0.01 ± 3.87	0.82	0.87	0.73	0.71
Graft lesions	0.11 ± 0.56	0.08 ± 0.44	0.08 ± 0.37	0.76	0.80	0.80	1.00
A and B1 lesions	2.26 ± 1.58	4.27 ± 2.33	2.90 ± 2.01	<0.01	<0.01	<0.01	<0.01
B2 and C lesions	3.71 ± 2.47	2.86 ± 1.76	2.01 ± 1.96	<0.01	<0.01	<0.01	<0.01
Intra-stent lesions	0.10 ± 0.40	0.17 ± 0.58	0.14 ± 0.42	0.29	0.27	0.45	0.69
SYNTAX Score	23.15 ± 16.48	15.57 ± 10.77	8.86 ± 12.37	<0.01	<0.01	<0.01	<0.01
Leaman Score	17.01 ± 12.29	13.20 ± 17.03	6.79 ± 9.61	<0.01	0.01	<0.01	<0.01

ASCC: acute coronary syndrome with history of cancer; ASCNC: acute coronary syndrome with history of cancer; CCAD: chronic coronary artery disease; CABG, coronary artery bypass grafting; SD, standard deviation. Numbers are means ± standard deviation or counts (%).

SYNTAX scores. The frequency of plaque ruptures, Ambrose's eccentric lesions type II in acute patients are corroborated by the mechanism of the disease in those patients and pan-arteritis seen in ACS [25,26].

Acute coronary syndrome occurs due to an imbalance between the supply and demand for myocardial oxygen. It can be caused by atherosclerotic plaque thrombosis or non-atherosclerotic factors [27]. Among the non-atherosclerotic causes, several conditions are frequently observed in cancer patients: systemic inflammation, anemia, and infections, which can reduce oxygen supply and increase myocardial demand [5,28–31]. Additionally, cancer therapy may contribute to vasospastic effects, endothelial injury, and acute arterial thrombosis, as well as long-term changes in lipid metabolism leading to premature arteriosclerosis [5,28–31]. Our work questioned whether these systemic and non-atherosclerotic factors in cancer patients could be predominant. However, our work demonstrates that most cancer patients exhibit angiographic patterns distinct from chronic coronary artery disease. The patterns are similar to those observed in acute coronary syndrome without cancer, except that cancer patients show more plaque rupture and a higher burden of coronary artery disease.

The unadjusted comparison between the ACSC and ACSNC groups unveils a paradoxical scenario where the absence of cancer history correlates with a greater number of lesions yet a lower SYNTAX score. This dichotomy is elucidated by the prevalence of B2/C lesions and an elevated myocardial risk in cancer patients, suggesting a nuanced interplay between cancer pathology and coronary lesion characteristics. The presence of more B2/C lesions in the ACSC group indicates a greater anatomical challenge and potentially more complex future interventions [32]. Furthermore, the lower SYNTAX scores in the ACSNC group, despite a higher number of lesions, suggest that these patients may have less complex coronary artery disease, which could influence both short-term and long-term management strategies.

The propensity score matching has enabled the creation of two clinically comparable cohorts within the ACSC and ACSNC groups, facilitating a nuanced analysis of coronary anatomical characteristics. Despite matched clinical presentations, the reassessment of 1474 lesions in these acute groups did not reveal a significant difference in the total number of lesions per patient or myocardial risk, as measured by the Leaman Score. However, a closer examination of anatomical

Table 3
Characteristics of coronary lesions after propensity score matching.

Angiographic characteristics per patient	ACSC N = 117 (784 lesions)	ACSNC N = 117 (688 lesions)	*p* value
Total lesions	6.70 ± 2.51	5.88 ± 2.57	0.29
Plaque rupture	1.48 ± 1.25	1.04 ± 1.01	0.03
Ulcerated lesions	0.11 ± 0.31	0.05 ± 0.22	0.09
Lesion with thrombus	0.30 ± 0.49	0.29 ± 0.45	0.89
Haziness	0.51 ± 0.63	0.16 ± 0.37	<0.01
TIMI flow < III	0.56 ± 0.72	0.53 ± 0.73	0.79
Bifurcations lesions	1.14 ± 0.98	0.97 ± 1.04	0.22
Ambrose Classification			
Concentric lesions	1.28 ± 1.05	2.74 ± 1.90	<0.01
Eccentric lesions Type I	3.32 ± 1.88	2.91 ± 1.56	0.07
Eccentric lesions Type II	1.09 ± 1.26	1.06 ± 1.16	0.87
Multiple irregularities	0.19 ± 1.39	0.01 ± 1.54	0.22
Graft lesions	0.25 ± 0.17	0.04 ± 0.24	0.22
A and B1 lesions	2.32 ± 1.62	3.96 ± 2.45	<0.01
B2 and C lesions	3.56 ± 2.25	2.74 ± 1.67	<0.01
In-stent lesions	0.11 ± 0.43	0.11 ± 0.43	1.00
SYNTAX Score	19.21 ± 12.70	15.69 ± 11.76	0.02
Leaman Score	14.10 ± 9.72	12.31 ± 9.20	0.14

ACSC: acute coronary syndrome with history of cancer; ACSNC: acute coronary syndrome without history of cancer.

complexity, including plaque rupture, B2/C lesions, and SYNTAX score, unveils a higher risk profile in the cancer afflicted ACS cohort. In our power post-hoc analysis (Supplementary Table 9) the differences in plaque rupture and complex lesions (B2/C) achieved high statistical power (84% and 88%, respectively), underscoring the robustness of our findings. Ambrose concentric lesions also reached statistical significance with excellent power (1.00), reflecting a stable morphology, while A/B1 lesions similarly demonstrated strong statistical power. Collectively, these convergent results provide a coherent picture: cancer patients presenting with ACS exhibit a predominance of complex and unstable angiographic features. For the total lesion count, the achieved power was near-optimal (77%). For the *SYNTAX score*, the achieved power was 59%, below the conventional threshold. However, it is important to emphasize that the SYNTAX score is a composite index intrinsically determined by both atherosclerotic burden and lesion complexity—precisely the components for which our analyses showed robust and well-powered differences. In this context, the apparent underpowering of the SYNTAX score should not be interpreted as a limitation of the signal, but rather as a reflection of its broader variance as a summative metric. Indeed, given that the core elements of the score were significantly and robustly different between groups, it is highly likely that a larger sample would only reinforce and consolidate the observed difference in SYNTAX score. Taken together, the post-hoc analyses strengthen our main conclusion: cancer patients present with a distinctly greater angiographic complexity.

Higher coronary complexity in cancer patients may be caused by several interconnected causes. Firstly, endothelial dysfunction and plaque instability can be facilitated by the systemic inflammation linked to cancer, with elevated levels of pro-inflammatory cytokines and acute-phase reactants that may lead to the development of complex coronary lesions [33]. Second, through endothelial degradation and accelerated vascular aging, the side effects of anticancer medicines, such as chemotherapy and radiation therapy, may hasten the course of atherosclerosis and increase plaque vulnerability [5,34,35].

Previous smaller studies have also documented a higher severity of CAD in cancer patients as assessed by the SYNTAX score specially among patients with high inflammation [36,37]. Our study, however, offers additional insights. Firstly, our study is larger in scale and offers a nuanced mapping and frequency analysis of plaque rupture (Table 3 and Fig. 3), its concordance with anatomical complexity (Fig. 2) which provides valuable insights into the underlying mechanisms of CAD in cancer patients. Importantly, we demonstrated that the total atherosclerotic burden and myocardium at risk were similar between the ACSC and ASCNC groups. Differences in lesion-level complexity were responsible for the observed distinctions between the groups.

Coronary plaque rupture or erosion has been widely acknowledged as the primary precipitating factor in ACS [38,39]. It has been demonstrated that although sometimes only one lesion is the culprit for ACS, the syndrome appears to be associated with overall coronary instability [40]. Our study further demonstrates that this instability may be even more pronounced in cancer patients. A better understanding of these factors could guide treatment pathways and necessitate careful cardiovascular monitoring. While cancer treatments offer significant benefits, there is a need for vigilance in managing cardiovascular risks. By comprehending the mechanisms through which cancer therapies exacerbate atherosclerotic disease, clinicians can tailor treatment approaches to

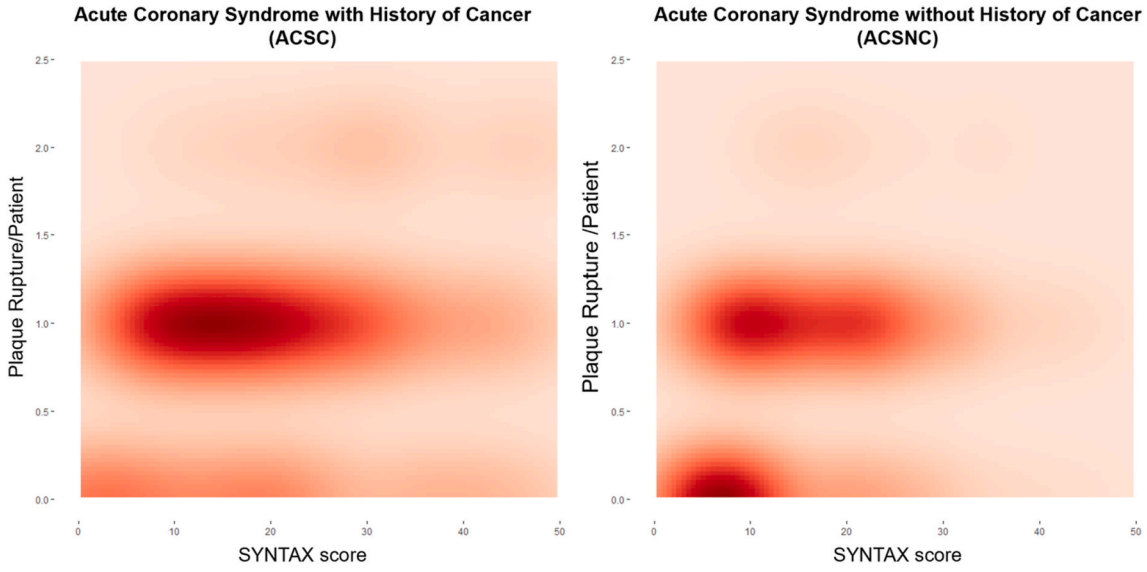

Fig. 2. 2D Density Plot – Comparison Between SYNTAX Score and the Presence of Plaque Rupture
Comparison between SYNTAX Score and the presence of plaque rupture after propensity score matching in A) Acute coronary syndrome with history of cancer (ACSC), and B) acute coronary syndrome without history of cancer (ACSNC). Notice a higher anatomical complexity assessed by the SYNTAX score and a greater presence of complex lesions in the ACSC group.

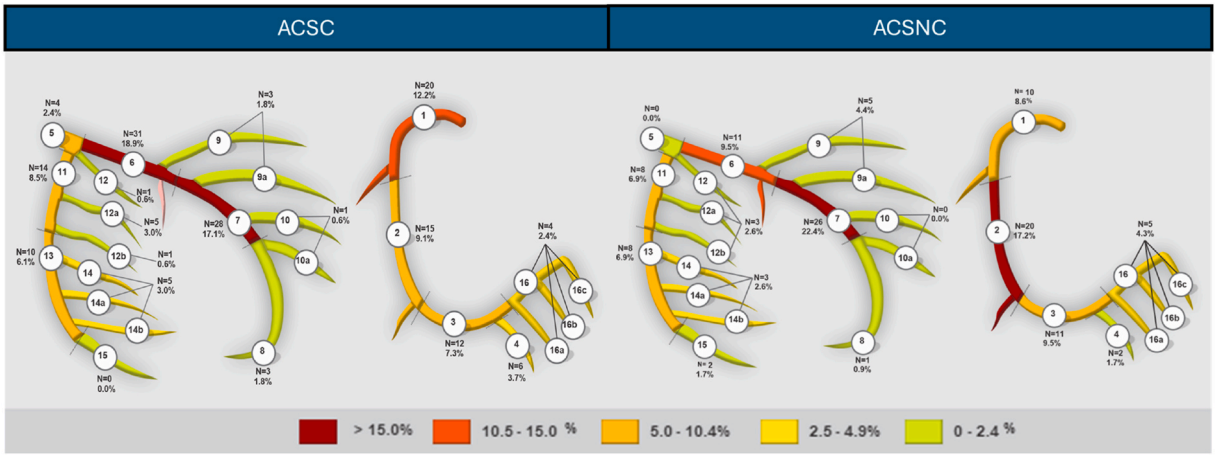

Fig. 3. Location of Plaque Ruptures in the Acute Coronary Syndrome groups
Location of Plaque Ruptures in the ACSC (acute coronary syndrome in cancer patients) and ACSNC (acute coronary syndrome in non-cancer patients) groups after propensity score matching. Notice that 42.1% of plaque rupture in ACSC group were in proximal segments as compared with 25% in ACSNC group ($P < 0.01$). Lesions were divided by absolute number and percentage of lesions.
Central Illustration. Comparative angiographic characteristics of patients with ACS with and without cancer.
Left panel: Unmatched comparison among three groups—ACS with cancer (ACSC), ACS without cancer (ACSNC), and chronic coronary artery disease (CCAD)—showing higher plaque burden, greater anatomical complexity (type B2/C lesions), and elevated SYNTAX and Leaman scores in the ACSC group.
Right panel: After propensity score matching (ACSC vs. ACSNC), patients with cancer continued to exhibit a higher incidence of plaque rupture, more complex lesion morphology (including concentric and B2/C lesions), and greater atherosclerotic burden by SYNTAX score. Notably, plaque rupture was more frequently located in proximal segments among cancer patients (42.1% vs. 25%). Representative coronary segment maps illustrate the distribution and severity of coronary lesions in both groups.

mitigate these risks effectively.

Recent studies have highlighted an increase in the prevalence of cancer among patients presenting with acute myocardial infarction [41]. However, a significant issue arises as cancer patients tend to undergo less invasive diagnostic stratification and receive fewer coronary revascularization procedures [41,42]. The complexities introduced by their oncological status, less frequent guideline-oriented therapeutics alongside the complexity of CAD disease may contribute to worse outcomes following myocardial infarction in cancer patients [14,41].

5. Limitations

The present study has some limitations that deserve mention. As included some retrospective data it may introduce selection bias. As included patients were from tertiary centers, these findings might not be entirely representative of the broader population. However, the BRAvAdO Registry is a multicenter study, data collection and angiographic analysis were centralized with the aim to reduce biases related to local practices and variations in data interpretation. Additionally, our study focused exclusively on patients who underwent invasive coronary angiography. This design choice, while enabling detailed assessment of coronary atherosclerotic burden and plaque morphology, inherently introduces a referral bias. It means that patients with acute coronary syndromes (ACS) who did not undergo catheterization, such as those with Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA) or certain types of Type 2 myocardial infarction, were not included. Consequently, our conclusions regarding plaque rupture and anatomical complexity in cancer patients with ACS are specifically applicable to the population undergoing invasive coronary angiography and may not be generalizable to all ACS presentations in cancer patients.

The characterization of plaques in our study was based on coronary angiography. Without high-resolution intravascular imaging, we could not definitively distinguish plaque rupture from other mechanisms like plaque erosion in vivo. However, coronary angiography remains the gold standard for the diagnosis of acute coronary syndromes.

While propensity score matching was employed to minimize confounding variables between the ACSC and ACSNC groups, it may not fully account for all potential confounders or underlying differences between the two cohorts. Finally, clinical outcomes are not the scope of the present work. Our goal was to provide a comprehensive assessment of CAD in cancer patients. Despite these limitations, our study provides valuable insights into the association between cancer, ACS, and coronary lesion complexity, highlighting the need for optimizing clinical management strategies in this high-risk population.

The present study highlights the intricate link between cancer and coronary artery disease in ACS. Among patients referred for invasive coronary angiography, ACS in cancer patients is predominately linked to plaque rupture, similar to ACS without cancer, but with greater severity and anatomical complexity. The study underscores the higher atherosclerotic burden and increased risk of plaque rupture in these patients compared to those with chronic coronary artery disease, reinforcing the need for tailored management and vigilant monitoring in this high-risk cohort.

6. Conclusion

The present study highlights the intricate link between cancer and coronary artery disease in ACS. Among patients referred for coronary angiography, ACS in cancer patients is predominately linked to plaque rupture, similar to ACS without cancer, but with greater severity and anatomical complexity. These findings reinforce the need for tailored diagnostic approaches and heightened surveillance in this high risk population.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: There are no additional interest conflicts related to the subject discussed in this scientific article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2026.120683.

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