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ORIGINAL ARTICLE

Cancer patients with acute coronary syndrome have non-superior bleeding risk compared to patients with similar characteristics – a propensity score analysis from the ProACS registry

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Abstract
Introduction: The management of acute coronary syndrome (ACS) in malignancy is challenging due to higher bleeding risk.
Methods: We analyzed patients with cancer (active or in the previous five years) prospectively included in the ProACS registry between 2010 and 2019. Our aim was to assess safety (major bleeding, primary endpoint) and secondary efficacy endpoints (in-hospital mortality and combined in-hospital mortality, reinfarction and ischemic stroke) of ACS treatment. Propensity score matching analysis (1:1) was further performed to better understand predictors of outcomes.
Results: We found 934 (5%) cancer patients out of a total of 18 845 patients with ACS. Cancer patients had more events: major bleeding (2.9% vs. 1.5%), in-hospital mortality (5.8% vs. 3.4%) and the combined endpoint (7.4% vs. 4.9%). The primary endpoint was related to cancer diagnosis (OR 1.97), previous bleeding (OR 7.09), hemoglobin level (OR 4.94), atrial fibrillation (OR 3.50), oral anticoagulation (OR 3.67) and renal dysfunction. Mortality and the combined secondary endpoint were associated with lower use of invasive coronary angiography and antiplatelet and neurohormonal blocker therapy. After propensity score matching (350 patients), there were no statistically significant differences in endpoints between the populations.

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Conclusion: Bleeding risk was not significant higher in the cancer population compared to patients with similar characteristics, nor were mortality or ischemic risk. The presence of cancer should not preclude simultaneous ACS treatment.

PALAVRAS-CHAVE
Oncologia;
Síndrome coronária aguda;
Hemorragia;
Cárdio-oncologia

Doentes oncológicos com síndrome coronária aguda não têm maior risco hemorrágico quando comparados com doentes com características similares – Uma análise de emparelhamento de *score* de propensão do Registo ProACS

Resumo
Introdução: A abordagem da síndrome coronária aguda (SCA) na doença oncológica é desafiante dado o seu elevado risco hemorrágico.
Métodos: Análise de doentes com doença oncológica (ativo ou nos cinco anos prévios) incluídos prospetivamente no registo ProACS, entre 2010 e 2019. Os autores avaliaram a segurança (hemorragia *major* – objetivo primário) e eficácia (mortalidade intra-hospitalar; reenfarte e acidente vascular cerebral isquémico – objetivo secundário composto) do tratamento da SCA. Uma análise de emparelhamento de *score* de propensão (1:1) foi realizada para avaliar os preditores dos resultados.
Resultados: Avaliámos 934 (5%) doentes oncológicos de um total de 18 845 doentes com SCA. Os doentes com cancro tiveram mais eventos: hemorragia *major* (2,9% *versus* 1,5%), mortalidade intra-hospitalar (5,8% *versus* 3,4%) e objetivo secundário composto (7,4% *versus* 4,9%). O objetivo primário relacionou-se com o diagnóstico de cancro (OR 1,97), hemorragia prévia (OR 7,09), nível de hemoglobina (OR 4,94), fibrilhação auricular (OR 3,50), anticoagulação oral (OR 3,67) e disfunção renal. A mortalidade e o objetivo secundário composto associaram-se a uma menor realização de coronariografia invasiva e utilização de terapêutica antiagregante ou de bloqueio neuro-hormonal. Após análise de emparelhamento de *score* de propensão (350 doentes), não se verificaram diferenças estatisticamente significativas entre as populações relativamente aos objetivos propostos.
Conclusão: O risco hemorrágico não é significativamente superior na população oncológica quando comparado com doentes com características similares, assim como o risco isquémico e de mortalidade. O diagnóstico de cancro não deve impedir o tratamento contemporâneo da SCA.

Introduction

Cardiovascular disease and cancer are the two leading causes of death in Portugal and worldwide.[1,2] Advances in cancer treatment in recent decades have led to improvements in life expectancy for these patients, but also to an increase in the burden of cardiovascular disease, with the risk of developing an acute coronary syndrome (ACS) at least double that of the general population.[3–5] Observational studies have shown that cancer at various stages may be observed in up to 15% of patients with ACS.[6–8]

The association between cancer and ACS is complex and multifactorial. There are several shared risk factors in the etiopathogenesis of coronary artery disease and cancer, such as older age, male gender, smoking, diabetes and obesity.[9] Malignancy itself is associated with a hypercoagulable and prothrombotic state which promotes oxidative stress and progression of atherosclerosis.[10] Also, cancer treatment (chemotherapy and radiotherapy) have additional cardiotoxic effects, increasing the risk of arterial thrombosis and vasospasm.[11]

Cancer patients are furthermore at twofold higher risk of bleeding,[12] and it is well known that bleeding in ACS is associated with higher risk of mortality.[13] Management of ACS in this population is challenging due to older age, frailty, presence of anemia, thrombocytopenia and coagulopathy, nutritional deficiencies, tumor and metastasis bleeding risk, vascular effects of chemotherapy and radiation therapy, delayed stent endothelization, prevalent use of anticoagulation for venous thromboembolism or atrial fibrillation, more frequent renal and hepatic dysfunction and probability of interruption of antiplatelet therapy in the event of urgent surgery, biopsy or re-initiation of cancer therapy.[7,8,14,15] The new European non-ST-elevation myocardial infarction (NSTEMI) guidelines recognized these issues and considered the presence of active cancer as a major

criterion at the time of percutaneous coronary interventions (PCI) for high bleeding risk.[16] Concerns about bleeding risk may contribute to suboptimal use of invasive diagnostic and treatment strategies and evidence-based recommended medication in this population, which in turn appears to increase both short- and long-term mortality.[14,17,18]

Randomized controlled trials assessing the efficacy and safety of ACS treatment have excluded cancer patients and observational studies have shown varying results in terms of outcomes.[19–21] The aim of the present study was to assess the safety and efficacy of ACS treatment strategies in cancer patients, analyzing data from a multicenter registry of contemporary patients treated in a European country.

Methods

Patient population and study protocol

We analyzed consecutive patients prospectively included in the Portuguese Registry of Acute Coronary Syndromes (ProACS) between October 2010 and September 2019. The study population was grouped according to the presence or absence of a cancer diagnosis, defined as active cancer or cancer in remission (if diagnosed in the previous five years).

ProACS is a continuous and prospective observational registry, promoted by the Portuguese Society of Cardiology and coordinated by the National Center for Data Collection in Cardiology (CNCDC). Each participating cardiology department voluntarily and consecutively includes patients admitted to the hospital for an ACS (ST-elevation myocardial infarction [STEMI], NSTEMI and unstable angina) according to symptoms, electrocardiography and biomarkers of myocardial necrosis. Patients with myocardial infarction type 4 and 5 (after revascularization procedures) and type 2 are excluded from the registry. Patients with an ACS but with uninterpretable electrocardiogram (complete left bundle branch block or pacemaker rhythm) are classified as having undetermined myocardial infarction.

The following data are included in the registry: demographics, baseline characteristics, laboratory and clinical evolution, pharmacological and invasive interventions, and vital status at discharge. The registry complies with data protection legislation and data are validated in two steps: automated validation at the time the data are entered, and at completion of patient data inclusion by the investigator. The ProACS registry is approved by the Portuguese Data Protection Authority and is registered at clinicaltrials.gov (N CT 01642329).

Endpoints

The primary endpoint (safety) was major bleeding, defined as intracranial bleeding or bleeding that caused substantial hemodynamic compromise requiring treatment (GUSTO bleeding classification[22]).

Secondary endpoints (efficacy) were in-hospital mortality and a combined endpoint of in-hospital mortality, reinfarction and ischemic stroke. Reinfarction was defined as recurrence of chest pain (or equivalent) after resolution of the initial symptoms, with duration greater than 20 min, accompanied by electrocardiographic changes and a new rise in biomarkers of myocardial necrosis compared to the previous value (a rise in creatinine kinase MB $\times 2$ baseline or >50% of previous value and/or rise in >20% of previous troponin value). Ischemic stroke was defined as new-onset focal neurologic deficits without signs of bleeding on cranial computed tomography.

The covariables of interest were age, atrial fibrillation, previous chronic kidney disease, previous bleeding, STEMI, Killip class, left ventricular ejection fraction (LVEF), left main disease, hemoglobin and creatinine levels, brain natriuretic peptide, platelet count <150 000/mm^3, antiplatelet therapy (single or dual), oral anticoagulation, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, invasive coronary angiography (ICA) and PCI.

Statistical analysis

All patients with correctly entered data in ProACS between October 2010 and September 2019 were included.

Characteristics were summarized as percentages for categorical variables, as means and standard deviations for continuous variables when normality was verified by the Kolmogorov-Smirnov test, and as medians and interquartile ranges when normality was not verified.

Comparisons between groups (with and without cancer) were made with the Student's t test, the Mann-Whitney U test, or the chi-square test, as appropriate.

Univariate logistic regression analysis was used to assess the association between variables and endpoints. Significant single-variable prognosticators were subsequently included in multivariate logistic regression analysis.

Propensity-score matching (1:1; match tolerance 0.000002) was further performed to adjust for the potential bias due to differences between the study groups. Univariate and multivariate logistic regression analysis was repeated after propensity-score matching to assess the association between variables and endpoints.

For all analyses, a value of $p<0.05$ was considered significant. IBM SPSS statistical software (version 24) was used for all statistical analysis.

Results

At total of 18 845 consecutive ACS patients were included in the present study, of whom 934 (5%) had a diagnosis of cancer. Baseline characteristics of both populations are presented in Table 1.

Compared to patients without malignancy, cancer patients were older, fewer were male and fewer were active smokers, but they had more cardiovascular risk factors such as hypertension and diabetes, and more previous history of myocardial infarction, PCI, heart failure, atrial fibrillation and bleeding events. The cancer group also had more comorbidities, including chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease and dementia. Mean hemoglobin was significantly lower in cancer patients.

In terms of ACS, both groups most frequently had NSTEMI or unstable angina (54% in cancer patients vs. 51%), followed by STEMI (41% vs. 45%) and undetermined myocardial infarction (5% vs. 4%). Cancer patients less often presented with

Table 1 Main characteristics of the study population.

Variable	Overall population			Propensity score matching		
	With cancer (n=934)	Without cancer (n=17 911)	p	With cancer (n=350)	Without cancer (n=350)	p
Male gender, %	69.5	73.0	0.018	72.0	77.7	0.081
Age, years	73±11	66±14	<0.001	69±11	69±12	0.941
Median follow-up time, days	5 (3-8)	4 (3-6)	<0.001	4 (3-7)	4 (3-6)	0.076
Active smoking, %	16.0	30.1	<0.001	24.3	28.3	0.229
Hypertension, %	74.1	68.3	<0.001	70.9	74.9	0.234
Diabetes, %	34.4	30.7	0.018	33.7	30.0	0.292
Dyslipidemia, %	54.8	57.0	0.207	56.1	54.7	0.714
Previous ACS, %	23.6	18.7	<0.001	19.7	22.6	0.355
Previous PCI, %	16.1	13.5	0.026	15.1	17.1	0.472
Previous heart failure, %	9.4	5.7	<0.001	6.3	8.6	0.249
Previous stroke, %	8.6	7.4	0.172	8.9	10.3	0.989
Renal impairment, %	10.8	5.7	<0.001	6.9	6.0	0.644
COPD, %	7.6	5.0	<0.001	6.9	5.7	0.533
Dementia, %	3.1	1.8	0.005	1.4	1.7	0.761
Previous bleeding, %	4.4	1.7	<0.001	1.1	1.1	1.000
STEMI, %	40.9	45.3	0.009	41.1	42.9	0.646
Killip class >I, %	20.5	15.5	<0.001	17.7	13.1	0.094
Chest pain on admission, %	88.0	91.0	0.006	88.8	91.4	0.249
Atrial fibrillation, %	10.0	6.9	<0.001	7.7	8.6	0.678
Mean hemoglobin at admission, mg/dl	12.9±2.1	13.8±1.9	<0.001	13.3±2	13.7±1.9	0.003
Minimum hemoglobin during hospitalization, mg/dl	11.5 ±2.0	12.6±2.0	<0.001	12.1 ±2.0	12.6±1.9	0.003
Platelet count <150 000/mm^3, %	13.4	11.2	0.055	10.7	12.4	0.488
Mean LVEF, %	49±12	51±12	<0.001	49±12	51±12	0.194
ICA, %	78.5	88.3	<0.001	88.3	86.3	0.427
PCI, %	59.4	68.8	<0.001	66.9	67.4	0.872
Stent implantation, %	94.2	94.7	0.628	93.4	94.6	0.584
CABG surgery or planned, %	6.3	7.4	0.226	7.4	9.4	0.341
>50% stenosis, %						
Left main	11.3	7.4	<0.001	8.4	5.6	0.178
One-vessel disease	37.9	42.3	0.026	44.4	40.7	0.347
Hospital treatment, %						
Aspirin	97.4	98.3	0.037	99.1	98.6	0.458
$P2Y_{12}$ inhibitors	90.8	93.3	0.004	94.3	90.3	0.047
Clopidogrel	77.1	75.3	0.386	75.7	75.8	0.977
Ticagrelor	22.1	26.9	0.004	26.0	24.4	0.656
Prasugrel	0.0	0.1	1.0	0.0	0.0	—
Single APT	10.1	7.2	0.003	6.0	9.4	0.184
Dual APT	89.1	92.2	0.003	93.3	91.9	0.514
OAC	4.8	3.6	0.049	5.7	3.1	0.098
NOAC	1.3	1.02	0.600	1.4	0.9	0.494
Parenteral anticoagulation[a]	86.9	85.5	0.231	87.4	84.5	0.276
Beta-blockers	77.3	80.8	0.009	81.4	80.0	0.632
ACE inhibitors or ARBs	82.3	85.8	0.006	85.7	86.9	0.649
Statins	92.7	94.5	0.020	93.4	94.6	0.524

ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; APT: antiplatelet therapy; ARBs: angiotensin receptor blockers; CABG: coronary artery bypass grafting; BNP: brain natriuretic peptide; COPD: chronic obstructive pulmonary disease; ICA: invasive coronary angiography; LVEF: left ventricular ejection fraction; NOAC: novel oral anticoagulant; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

[a] Unfractionated heparin, enoxaparin, fondaparinux or bivalirudin.

Table 2 Primary and secondary endpoints in the overall population and after propensity score matching analysis.

	Overall population			Propensity score matching		
	Endpoint	Without cancer	p	Cancer	Without cancer	p
Major bleeding, %	2.9	1.5	<0.001	1.7	0.9	0.505
In-hospital mortality, %	5.8	3.4	<0.001	4.0	3.1	0.541
Reinfarction, %	1.6	1.0	0.073	1.4	1.7	0.761
Ischemic stroke, %	0.4	0.7	0.270	2.0	2.6	0.613
In-hospital mortality, reinfarction and ischemic stroke, %	7.4	4.9	<0.001	5.4	5.1	0.866

chest pain and more often with symptoms and signs of heart failure (Killip class >1).

During hospitalization, cancer patients had lower LVEF and less often underwent ICA and PCI, even if they had more severe coronary anatomy. When PCI was performed, there were no significant differences in rates of balloon angioplasty between groups (5.8% vs. 5.3%), while the cancer group had higher rates of bare-metal stent implantation (23.3% vs. 18.6%, odds ratio [OR] 1.33, p=0.0003).

Regarding the endpoints, cancer patients had more events: major bleeding (2.9% vs. 1.5%, p<0.001), in-hospital mortality (5.8% vs. 3.4%, p<0.001) and the combined endpoint of in-hospital mortality, reinfarction and ischemic stroke (7.4% vs. 4.9%, p<0.001) (Table 2). Cancer was an independent predictor of major bleeding events (OR 1.97; 95% confidence interval [CI] 1.36-2.88, p<0.001) and cancer patients with the primary endpoint (n=27) had significantly higher in-hospital mortality (22.2% vs. 5.3%, OR 5.1; 95% CI 1.92-13.26, p=0.003), lower baseline hemoglobin levels (11.9±2.6 g/dl vs. 12.9±2.1 g/dl, p=0.032) and a trend to lower platelet count (16.7% vs. 13.3%, p=0.051). Aspirin, $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) and dual antiplatelet therapy (DAPT) were less frequently prescribed in these patients. Four patients (15%) with the primary endpoint were on oral anticoagulants: three with vitamin K antagonists (VKAs) (9% of VKA users) and one with a non-vitamin K antagonist oral anticoagulant (NOAC) (8% of NOAC users).

In the cancer group (n=934), the primary endpoint was associated with a previous bleeding event, hemoglobin at admission, atrial fibrillation, higher creatinine level during hospitalization and oral anticoagulation. In the multivariate analysis, previous bleeding events and atrial fibrillation were independent predictors of the primary endpoint (Table 3).

Cancer was also an independent predictor of in-hospital mortality (OR 1.73; 95% CI 1.30-2.30, p<0.001). Patients who died were older (79±9 vs. 72±11 years, p<0.001) and had more thrombocytopenia (26.5% vs. 12.6%, p=0.006), anemia (minimum hemoglobin 10.8±2 vs. 11.6±2 g/dl, p=0.014), renal impairment (23.1% vs. 10.1%, p=0.003), STEMI (61.1% vs. 39.7%, p=0.002) and atrial fibrillation (20.4% vs. 9.4%, p=0.009) and lower LVEF (38±13% vs. 50±12%, p<0.001). In the univariate analysis on cancer patients, mortality was associated with lower prescription of neurohormonal blockers and antiplatelet therapy – no antiplatelet treatment (OR 10.29), single antiplatelet treatment (OR 2.15) – and less frequent ICA (OR 0.23) and PCI (OR 0.49). There was also a trend for less radial access use (p=0.068) and more frequent left main disease as culprit lesion (12.5 vs. 3.1%, p=0.043). We found no association between anticoagulation treatment (oral or parenteral) or type of percutaneous treatment (balloon vs. stent implantation) and in-hospital mortality. In the multivariate analysis, STEMI, LVEF<40%, thrombocytopenia, chronic kidney disease, no ACE inhibitor therapy and no use of ICA were independent predictors of in-hospital mortality (Table 3).

Sixty-nine (7.4%) cancer patients reached the secondary combined endpoint (in-hospital mortality, reinfarction and ischemic stroke). This group less often received antiplatelet therapy (none [4.3 vs. 0.6%], single [17.4 vs. 9.5%] or dual [78.3 vs. 89.9%]) and neurohormonal blocker therapy (53.6 vs. 85.8%, p<0.001) and less frequently underwent ICA (54% vs. 80.5%, p<0.001), and there was a trend to less PCI (49% vs. 60%, p=0.074). We found no differences in anticoagulant prescription rate or type of percutaneous treatment in patients who reached the secondary combined endpoint. In the multivariate analysis, STEMI, LVEF <40%, Killip class >I, thrombocytopenia, creatinine >2 mg/dl, no ACE inhibitor therapy and no use of ICA were independent predictors of the combined secondary endpoint (Table 3).

Propensity score analysis

Because the study groups were significantly different, we performed a propensity score matching analysis including baseline characteristics, LVEF and use of ICA (Table 1 and Supplementary Table 1). After homogenizing the populations, there were no statistically significant differences between patients with and without cancer regarding the primary (1.7% vs. 0.9%, p=0.505) and secondary endpoints (in-hospital mortality: 4% vs. 3.1%, p=0.861; combined endpoint: 5.4% vs. 5.1.%, p=0.866) (Table 2).

There was a very small number of major bleeding events in the paired cancer population (n=6), and for this reason, primary endpoint predictors were not assessed due to low statistical power. The results of the analysis for predictors of the secondary endpoints in the paired cancer population are presented in Table 4.

Thrombocytopenia was a consistent predictor of the secondary endpoints in both univariate and multivariate analysis. STEMI, Killip class >I and creatinine >2 mg/dl during hospitalization also predicted endpoints in multivariate analysis. In the paired population, we found no statistically

Table 3 Univariate and multivariate analysis of primary and secondary endpoints in the overall cancer population (n=934).

Variable	p	OR	95% CI
Primary endpoint: major bleeding			
Univariate analysis			
Previous bleeding	<0.001	7.09	2.69-18.71
Atrial fibrillation	0.011	3.50	1.43-8.56
Hemoglobin<10 g/dl	0.002	4.94	1.99-12.28
Creatinine>2 mg/dl	0.029	2.93	1.14-7.52
Oral anticoagulation	0.037	3.67	1.21-11.11
Multivariate analysis			
Previous bleeding	<0.001	8.83	3.13-24.94
Atrial fibrillation	0.002	4.32	1.68-11.10
Secondary endpoint: in-hospital mortality			
Univariate analysis			
Age>75 years	<0.001	2.87	1.56-5.28
Atrial fibrillation	0.009	2.47	1.23-4.98
STEMI	0.002	2.39	1.36-4.20
Killip class>I	<0.001	5.14	2.93-9.02
LVEF<40%	<0.001	3.83	2.00-7.34
Left main disease	0.043	2.77	1.06-7.21
Hemoglobin>12 g/dl	0.009	0.36	0.16-0.80
Creatinine>2 mg/dl	<0.001	4.37	2.25-8.49
BNP>400 pg/ml	0.019	3.11	1.15-8.39
Platelet count<150 000/mm^3	0.006	2.51	1.28-4.89
No APT	<0.001	10.29	2.39-44.28
Single APT	<0.001	2.15	1.05-4.44
Dual APT	<0.001	0.35	0.18-0.69
Beta-blockers	<0.001	0.18	0.10-0.31
ACE inhibitors	<0.001	0.12	0.07-0.22
PCI	0.009	0.49	0.28-0.85
ICA	<0.001	0.23	0.13-0.40
Multivariate analysis			
LVEF<40%	<0.001	6.34	2.95-13.63
STEMI	<0.001	5.20	2.21-12.23
Chronic renal disease	0.003	3.88	1.58-9.53
Platelet count<150 000/mm^3	0.009	3.37	1.35-8.41
ACE inhibitors	<0.001	0.16	0.08-0.35
ICA	<0.001	0.20	0.09-0.43
Secondary endpoint: combined in-hospital mortality, reinfarction and ischemic stroke			
Univariate analysis			
Age>75 years	<0.001	2.37	1.40-3.99
Atrial fibrillation	0.034	2.02	1.04-3.93
STEMI	0.002	2.25	1.37-3.71
Killip class >I	<0.001	3.84	2.32-6.36
LVEF <40%	0.001	2.63	1.42-4.87
Left main disease	0.026	4.29	1.36-13.54
Hemoglobin >12 g/dl	0.013	0.45	0.23-0.86
Creatinine >2 mg/dl	<0.001	3.76	2.06-6.85
BNP>400 pg/mL	0.007	3.34	1.33-8.35
Platelet count <150 000/mm^3	<0.001	2.86	1.66-4.91
No ATP	<0.001	7.82	1.83-33.43
Single APT	<0.001	2.01	1.04-3.90
Dual APT	<0.001	0.40	0.22-0.74
ACE inhibitors	<0.001	0.19	0.12-0.32
Beta-blockers	<0.001	0.28	0.17-0.47
ICA	<0.001	0.28	0.17-0.46

Table 3 (*Continued*)

Variable	p	OR	95% CI
Multivariate analysis			
STEMI	<0.001	3.74	1.84-7.62
LVEF<40%	0.009	2.54	1.26-5.09
Killip class>I	0.030	2.21	1.08-4.52
Platelet count<150 000/mm^3	0.003	3.29	1.50-7.21
Creatinine>2 mg/dl	0.002	3.11	1.53-6.30
ACE inhibitors	0.008	0.40	0.20-0.79
ICA	<0.001	0.24	0.12-0.48

ACE: angiotensin-converting enzyme; APT: antiplatelet therapy; BNP: brain natriuretic peptide; CI: confidence interval; ICA: invasive coronary angiography; LVEF: left ventricular ejection fraction; OR: odds ratio; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

Table 4 Univariate and multivariate analysis of secondary endpoints in the matched population (n=350).

Variable	p	OR	95% CI
Secondary endpoint: in-hospital mortality			
Univariate analysis			
LVEF<30%	0.015	7.83	1.91-31.12
STEMI	0.019	3.77	1.16-12.26
Killip class>I	0.023	3.75	1.25-11.23
Platelet count<150 000/mm^3	0.049	3.67	1.08-12.41
Creatinine>2 mg/dl	0.017	2.77	0.58-13.37
Hemoglobin>12 g/dl	0.021	0.18	0.04-0.84
Beta-blockers	0.006	0.21	0.07-0.62
ACE inhibitors	0.008	0.20	0.07-0.61
Multivariate analysis			
STEMI	0.010	5.81	1.51-22.31
Killip class>I	0.024	4.03	1.21-13.49
Platelet count<150 000/mm^3	0.011	6.18	1.52-25.09
Beta-blockers	0.006	0.19	0.06-0.63
Secondary endpoint: combined in-hospital mortality, reinfarction and ischemic stroke			
Univariate analysis			
LVEF<30%	0.036	5.30	1.34-20.90
STEMI	0.013	3.31	1.23-8.92
Creatinine>2 mg/dl	<0.001	3.76	2.06-6.85
Platelet count<150 000/mm^3	0.048	2.28	1.22-4.24
Hemoglobin>12 g/dl	<0.001	0.40	0.22-0.74
ACE inhibitors	0.040	0.33	0.12-0.92
Multivariate analysis			
Platelet count <150 000/mm^3	0.019	4.59	1.28-16.39
Creatinine >2 mg/dl	0.024	4.34	1.21-15.52

ACE: angiotensin-converting enzyme; CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

significant differences regarding antiplatelet and anticoagulant prescription, use of ICA or PCI.

Discussion

Our study confirmed that cancer patients represent a non-negligible group in the ACS population (5%) and that they have a worse prognosis during hospitalization for ACS, including more major bleeding and ischemic events and higher mortality.

Several factors may be responsible for this increased risk of events. Firstly, and similar to previously published results,[23,24] cancer patients were older and had more comorbidities and more severe coronary artery disease. Although the proportion of patients undergoing thoracic radiation therapy is unknown, the high incidence of left main disease in our cohort could be related to previous radiotherapy.[25] Presentation may be more atypical, due to radiotherapy- and chemotherapy-related neurotoxicity, which can affect the ability to feel pain and also due to the frequent use of opioids and other analgesics.[26] In addition, cancer patients

have lower cardiac reserve, related to previous myocardial infarction, PCI and heart failure at presentation.[20] Our propensity score analysis is in line with this hypothesis, because homogenization in terms of baseline characteristics blurs the differences in endpoints.

In our overall population, major bleeding events were associated with increased mortality and cancer diagnosis. A previous study also demonstrated that more than half of noncardiac deaths in cancer patients were due to bleeding events.[20] Bleeding events were associated with previous predisposition to bleeds and hemoglobin level, use of oral anticoagulation, atrial fibrillation and renal impairment. However, bleeding risk was not significantly higher compared to patients with similar characteristics, specifically previous bleeding history, oral anticoagulation, atrial fibrillation and diagnosis of chronic kidney disease. In the paired populations, only mean hemoglobin level was significantly lower in patients with cancer. However, mean hemoglobin level at admission and during hospitalization was still above 12 g/dl. Other studies have shown that lower hemoglobin at admission could predict severe bleeding.[24,27] In a substudy of the BleeMACS registry, hemoglobin <11 g/dl was the strongest predictor of severe spontaneous bleeding at one year after ACS.[24] However, in our overall population, a previous bleeding episode was the most powerful multivariate predictor of the primary endpoint during hospitalization.

Moreover, it has been reported that cancer and its treatment contribute to an increase of at least 1.8% in the prevalence of atrial fibrillation,[28] due to comorbidities, anticancer treatment, and cancer-associated factors such as dehydration and inflammation.[6] Decisions about whether to initiate or maintain anticoagulation therapy, and which anticoagulant to choose, are complex because scores such as CHA_2DS_2-VASc, HAS-BLED and HEMORR2HAGES do not take into consideration the additional risks conferred by malignancy, BleeMACS being the only score that includes cancer as a risk factor.[12,28–30] Also, no randomized trials have been conducted specifically assessing oral anticoagulants use in cancer patients with atrial fibrillation. However, secondary analyses of the novel oral anticoagulant (NOAC) trials in patients with or without a history of cancer or in those who developed cancer after enrollment showed that NOACs are at least as effective and safe as warfarin in this subgroup.[31–33] On the other hand, the use of VKAs in the cancer population can be more challenging than NOACs, because of the former's more frequent interactions with chemotherapy, antibiotics, analgesics and other commonly prescribed drugs.[34,35] Consequently, the International Society on Thrombosis and Haemostasis recommends that NOACs should be considered as the first choice in cancer patients, especially in those with a favorable prognosis (except for luminal gastrointestinal cancers or active gastrointestinal mucosal abnormalities).[28]

In our study, oral anticoagulation – mainly with VKAs – was independently associated with major bleeding events. However, we found no difference between the proportion of patients on VKA and NOAC therapy (9% vs. 8%, p=0.94) who suffered major bleeding. Hence, NOAC therapy appears to be as safe as VKAs in our population. Regarding parental anticoagulation, in our registry it is not specified for how long and at what dosage it was prescribed. We can assume that, since atrial fibrillation was also associated with major bleeding, cancer patients with this arrhythmia probably received more aggressive anticoagulation therapy, including parenteral anticoagulants. Decisions on triple therapy (anticoagulation and DAPT) in cancer patients with ACS and atrial fibrillation should be individualized and it should mostly be reserved for patients with good functional status and favorable prognosis, with low bleeding risk and without major risk factors (such as previous bleeding or anemia).[6,34] Since we do not know the degree of anticoagulation of patients on parenteral therapy, we did not perform a subanalysis regarding triple therapy.

More patients in the cancer groups had the secondary combined endpoint, mainly with increased mortality. However, mortality risk and ischemic events were not significantly higher than in patients with similar characteristics after propensity score matching. As expected, in our population predictors of the secondary endpoints were STEMI, Killip class >I, reduced left ventricular ejection fraction and renal failure. Other identified predictors that merit particular consideration were the presence of thrombocytopenia, no prescription of neurohormonal blockers and antiplatelet therapy, and also no invasive procedures (ICA and PCI). A platelet count <100 000/mm^3 is estimated to be present in 10-25% of patients with cancer.[34] Thrombocytopenia was not an independent predictor of bleeding in our population, in line with a study of cancer patients with ACS and chronic thrombocytopenia,[36] but it was consistently associated with mortality and ischemic events. In patients with thrombocytopenia, the risk of bleeding varies and may depend on the underlying cause of thrombocytopenia; clinical experience suggests that platelet function rather than platelet count is the determinant factor.[36] Another study has postulated the 'platelet paradox' of coronary thrombosis in thrombocytopenic patients, in whom aspirin therapy was associated with significantly improved seven-day survival after ACS without a significant increase in bleeding complications.[37] Previous studies also demonstrated that concerns about bleeding may prompt interventional cardiologists to defer invasive approaches or PCI and prescription of aspirin, more potent platelet inhibition with ticagrelor or prasugrel or DAPT, leading to higher mortality.[3,15,17,26,38–41] On the other hand, when the invasive strategy is not postponed, cancer patients could have the same long-term cardiac mortality as the general population, although with higher noncardiac mortality due to cancer itself.[20] Our results after propensity score matching are in agreement with these findings: the matched cancer population had similar rates of aspirin prescription, DAPT, ICA and PCI, and no difference in mortality was observed between patients with and without cancer.

Expert consensus recommends the use of stents, preferably newer-generation drug-eluting stents (which may have lower rates of stent thrombosis), avoiding bifurcation and overlapping stents in patients with cancer.[42] Our data showed that in cancer patients undergoing PCI, drug-eluting stents were more often used, without significant differences in outcomes according to the type of stent. The use of intravascular ultrasound or optical coherence tomography is also recommended to ensure adequate stent expansion, apposition and lack of edge dissection,[42] but this information was not retrieved in our registry. A minority of our cancer patients underwent balloon angioplasty only (5.8%), which

may be preferred, for example, if PCI is necessary in patients awaiting cancer surgery.[42]

Cancer patients were also less likely to be prescribed optimal medical therapy, such as ACE inhibitors, beta-blockers or statins. In our study, patients who did not receive ACE inhibitors more often presented with hypotension and more severely impaired renal function, which may explain their worse short-term prognosis. However, long-term data in cancer patients show that optimal medical therapy in this population can reduce cardiovascular mortality at one year after ACS.[6,18]

Our findings indicate that all patients with a current or prior history of cancer should be treated as a high-risk group using an integrative approach, addressing both cardiac and noncardiac aspects.

Study limitations

The ProACS multicenter registry is based on voluntary contributions from the participating cardiology centers, and for this reason, we cannot completely ensure consecutive inclusion of patients. Also, patients who were admitted to non-cardiology departments were not included, and patients with other significant comorbidities such as cancer would be more likely to be admitted to a non-cardiological department. Similarly to other registries, some patients were excluded due to missing data; in our case, 2276 patients were excluded due to lack of information regarding cancer status.

An important limitation is that there are no data regarding type of cancer, staging, cancer therapy (chemotherapy and radiotherapy) or how many patients had active cancer at the time of ACS diagnosis. These are significant determinants of outcomes including in-hospital mortality and bleeding. However, it was not possible to address this information in our study, or cause of in-hospital death and the exact timing of the primary endpoint, because these data were not pre-specified in the collected variables. Long-term outcome after hospital discharge was also not assessed, because it was missing in more than 30% of patients, although this was not the focus of our study. It was also not possible to study the implications of parental anticoagulation in detail, because specific information regarding dosage and duration was unavailable.

We performed a propensity score matching analysis to reduce the risk of bias and group imbalance. However, these can only be totally overcome with randomization. Moreover, after pairing, there is a reduction in comorbidities that are related to major bleeding, and consequently in the rate of major bleeding in both populations.

Conclusion

The management of ACS in patients with cancer is particularly challenging due to higher bleeding and mortality risks. In our study, major bleeding events were mainly related to previous bleeding predisposition and atrial fibrillation, associated with anticoagulation strategy. On the other hand, in-hospital mortality, reinfarction and ischemic stroke were associated with lower use of ICA and antiplatelet and neurohormonal blocker therapy.

After propensity score matching in terms of baseline characteristics and use of invasive procedures, major bleeding, mortality and ischemic risks were not significantly higher in cancer patients. These findings indicate that the presence of cancer should not limit the effective and safe treatment of ACS, but rather lead to a particularly rigorous assessment of bleeding and thrombotic risk, regarding both pharmacological and interventional decisions.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2021.04.010.

References

1. Saúde DGS. Plataforma da Mortalidade [online]; 2020. Available from: https://app.powerbi.com/view?r=eyJrIjoiOGRhNjdjYzgtOGZmNy00NDZjLWI1YTctNWQyNzRiMDg3NzJiIiwidCI6IjQyOTc3ZjkwLWE1NjItNDk1OS04ZjJjLTE4NDE2NjI1Zjc2NiIsImMiOjh9&mnredir=1&lnc=6047AAAAAAAAAAAAAAAAAAAA [accessed 17.04.20].
2. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392:1736–88.
3. Pothineni NV, Shah NN, Rochlani Y, et al. Temporal trends and outcomes of acute myocardial infarction in patients with cancer. Ann Transl Med. 2017;5:482.
4. Navi B, Reiner A, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. J Am Coll Cardiol. 2017;22:926–38.
5. Guha A, Dey AK, Jneid H, et al. Acute coronary syndromes in cancer patients: the differences of ACS in cancer patients and the general population are discussed. Eur Heart J. 2019;40:1487–90.
6. Banasiak W, Zymliński R, Undas A. Optimal management of cancer patients with acute coronary syndrome. Pol Arch Intern Med. 2018;30:244–53.
7. Potts J, Iliescu C, Lopez Mattei J, et al. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. Eur Heart J. 2019 Jun;40:1790–800.
8. Roule V, Verdier L, Blanchart K, et al. Systematic review and meta-analysis of the prognostic impact of cancer among patients with acute coronary syndrome and/or percutaneous coronary intervention. BMC Cardiovasc Disord. 2020;20:38.

9. Koene R, Prizment A, Blaes A, et al. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133:1104–14.
10. Yetis Sayin B, Oto MA. Acute coronary syndrome in cancer patients. Am J Cardiovasc Drugs. 2018;18:361–72.
11. Zamorano J, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology. Eur Heart J. 2016;37:2768–801.
12. Shah S, Norby F, Datta Y, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv. 2018;13:200–9.
13. Eikelboom J, Mehta S, Anand S, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006;114:774–82.
14. Al-Hawwas M, Tsitlakidou D, Gupta N, et al. Acute coronary syndrome management in cancer patients. Curr Oncol Rep. 2018;22:78.
15. Park J, Guo W, Al-Hijji M, et al. Acute coronary syndromes in patients with active hematologic malignancies – incidence, management, and outcomes. Int J Cardiol. 2019;15: 6–12.
16. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42:1289–367.
17. Donisan T, Balanescu D, Palaskas N, et al. Cardiac interventional procedures in cardio-oncology patients. Cardiol Clin. 2019;37:469–86.
18. Iannaccone MD, Ascenzo F, De Filippo O, et al. Optimal medical therapy in patients with malignancy undergoing percutaneous coronary intervention for acute coronary syndrome: a BleeMACS sub-study. Am J Cardiovasc Drugs. 2017;17:61–71.
19. Quintana R, Monlezun D, Davogustto G, et al. Outcomes following percutaneous coronary intervention in patients with cancer. Int J Cardiol. 2020;300:106–12.
20. Wang F, Gulati R, Lennon R, et al. Cancer history portends worse acute and long-term noncardiac (but not cardiac) mortality after primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. Mayo Clin Proc. 2016;91:1680–92.
21. Landes U, Kornowski R, Bental T, et al. Long-term outcomes after percutaneous coronary interventions in cancer survivors. Coron Artery Dis. 2017;28:5–10.
22. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329:673–82.
23. Bharadwaj A, Swamy P, Mamas M. Outcomes of percutaneous coronary interventions in cancer patients. Expert Rev Cardiovasc Ther. 2020;18:25–32.
24. Iannaccone M, D'Ascenzo F, Vadalà P, et al. Prevalence and outcome of patients with cancer and acute coronary syndrome undergoing percutaneous coronary intervention: a BleeMACS substudy. Eur Heart J Acute Cardiovasc Care. 2018;7: 631–8.
25. Desai MY, Jellis LCJ, Kotecha R, et al. Radiation-associated cardiac disease – a practical approach to diagnosis and management. JACC Cardiovasc Imag. 2018;11:1132–49.
26. Yusuf S, Daraban N, Abbasi N, et al. Treatment and outcomes of acute coronary syndrome in the cancer population. Clin Cardiol. 2012;35:443–50.
27. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation. 2019;140:240–61.
28. Delluc A, Wang T, Yap E, et al. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH. J Thromb Haemost. 2019;17:1247–52.
29. Raposeiras-Roubín S, Faxén J, Íñiguez-Romo A, et al. Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: the BleeMACS score. Int J Cardiol. 2018;254:10–5.
30. Mosarla R, Vaduganathan M, Qamar A, et al. Anticoagulation strategies in patients with cancer: jacc review topic of the week. J Am Coll Cardiol. 2019;73:1336–49.
31. Chen S, Hellkamp A, Becker R, et al. Efficacy and safety of rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation and a history of cancer: observations from ROCKET AF. Eur Heart J Qual Care Clin Outcomes. 2019;5:145–52.
32. Melloni C, Dunning A, Granger C, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE Trial. Am J Med. 2017;130:1440–8.
33. Fanola C, Ruff C, Murphy S, et al. Efficacy and safety of edoxaban in patients with active malignancy and atrial fibrillation: analysis of the ENGAGE AF – TIMI 48 Trial. J Am Heart Assoc. 2018;7:e008987.
34. Undas A, Drabik L, Non-vitamin K. antagonist oral anticoagulants in cancer patients with atrial fibrillation. Anatol J Cardiol. 2020;23:10–8.
35. Deng Y, Tong Y, Deng Y, et al. Antagonist oral anticoagulants versus warfarin in patients with cancer and atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc. 2019;8:e012540.
36. Iliescu C, Balanescu D, Donisan T, et al. Safety of diagnostic and therapeutic cardiac catheterization in cancer patients with acute coronary syndrome and chronic thrombocytopenia. Am J Cardiol. 2018;122:1465–70.
37. Sarkiss M, Yusuf S, Warneke C, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. Cancer. 2007;109:621–7.
38. Styczkiewicz K, Styczkiewicz M, Myćka M, et al. Clinical presentation and treatment of acute coronary syndrome as well as 1-year survival of patients hospitalized due to cancer: a 7-year experience of a nonacademic center. Medicine (Baltimore). 2020;99:e18972.
39. Velders M, Boden H, Hofma SH, et al. Elevation myocardial infarction in patients with cancer treated with primary percutaneous coronary intervention. Am J Cardiol. 2013;112:1867–72.
40. Nabiałek-Trojanowska I, Dąbrowska-Kugacka A, Lewicka-Potocka Z, et al. Acute coronary syndrome in patients undergoing anticancer therapies: a single-center, controlled case study. Adv Clin Exp Med. 2019;28:1667–73.
41. Cordero A, López-Palop R, Carrillo P, et al. Prevalence and postdischarge incidence of malignancies in patients with acute coronary syndrome. Rev Esp Cardiol (Engl Ed). 2018;71:267–73.
42. Iliescu C, Grines C, Herrmann J, et al. SCAI Expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologıa Intervencionista. Catheter Cardiovasc Interv. 2016;87:E202–23.