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ORIGINAL ARTICLE

Acute ischaemic stroke in active cancer versus non-cancer patients: stroke characteristics, mechanisms and clinical outcomes

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Abstract

Background and purpose: Demographics, clinical characteristics, stroke mechanisms and long-term outcomes were compared between acute ischaemic stroke (AIS) patients with active cancer (AC) versus non-cancer patients.

Methods: Using data from 2003 to 2021 in the Acute STroke Registry and Analysis of Lausanne, a retrospective cohort study was performed comparing patients with AC, including previously known and newly diagnosed cancers, with non-cancer patients. Patients with inactive cancer were excluded. Outcomes were the modified Rankin Scale (mRS) score at 3 months, death and cerebrovascular recurrences at 12 months before and after propensity score matching.

Results: Amongst 6686 patients with AIS, 1065 (15.9%) had a history of cancer. After excluding 700 (10.4%) patients with inactive cancer, there were 365 (5.5%) patients with AC and 5621 (84%) non-cancer AIS patients. Amongst AC patients, 154 (42.2%) strokes were classified as cancer related. In multivariable analysis, patients with AC were older (adjusted odds ratio [aOR] 1.02, 95% confidence interval [CI] 1.00–1.03), had fewer vascular risk factors and were 48% less likely to receive reperfusion therapies (aOR 0.52, 95% CI 0.35–0.76). Three-month mRS scores were not different in AC patients (aOR 2.18, 95% CI 0.96–5.00). At 12 months, death (adjusted hazard ratio 1.91, 95% CI 1.50–2.43) and risk of cerebrovascular recurrence (sub-distribution hazard ratio 1.68, 95% CI 1.22–2.31) before and after propensity score matching were higher in AC patients.

Conclusions: In a large institutional registry spanning nearly two decades, AIS patients with AC had less past cerebrovascular disease but a higher 1-year risk of subsequent death and cerebrovascular recurrence compared to non-cancer patients. Antithrombotic medications at discharge may reduce this risk in AC patients.

KEYWORDS
antithrombotics, cancer, cerebrovascular recurrences, ischaemic stroke, mortality

INTRODUCTION

Between 4% and 20% of patients with acute ischaemic stroke (AIS) have comorbid cancer [1–3]. Systemic cancer increases the risk of stroke [4] and this risk varies depending on age, cancer type, stage and time from diagnosis [5, 6]. Stroke characteristics in patients with active cancer (AC) are distinct from those of non-cancer (NC) patients, such as additional survival benefits from statins, more frequent multiterritorial lesions and cryptogenic aetiology in AC patients [7–9].

Cryptogenic mechanisms account for approximately 50% of strokes in cancer patients and predict poor survival, particularly when hypercoagulability is detected [10]. If cryptogenic stroke and hypercoagulability are associated with increased cancer-related mortality, it is also of interest to investigate whether other presumably less frequent cancer-related mechanisms can be identified in these patients. Examples include nonbacterial thrombotic endocarditis (also a manifestation of hypercoagulability), tumour embolism and oncological treatments, such as prothrombotic effects, cardiotoxicity of cancer therapies or vasculopathy due to radiotherapy [11]. Unfortunately, most published studies lack data on the potential effects of cancer therapeutics and do not consider mechanisms other than nonspecific hypercoagulability.

Previous research found that concomitant cancer in AIS patients may increase the risk of early clinical deterioration, mortality and stroke recurrence [12–14]. This risk of recurrence is estimated to be between two- and three-fold higher in the short term [15–17] and the mortality rate ranges from 17% to 64% at 3 or 6 months after AIS [18–22]. However, these studies were relatively small and most of them did not include patients with a new diagnosis of cancer at the time of the stroke or shortly afterwards, which account for between 28% and 42% of AIS patients with AC [23, 24]. In addition, these studies provided outcome data only up to 6 months after AIS. Since the survival of cancer patients in the last two decades is increasing [25], exploring potential predictors of long-term outcomes after AIS in this population seems crucial.

Aims

In this retrospective cohort quality-control study from our institution, the aim was to delineate the clinical characteristics, stroke mechanisms, medium-term disability and its predictors, long-term mortality and cerebrovascular recurrence in AIS patients with AC compared with NC.

METHODS

Database description

A retrospective cohort study was performed using the Acute STroke Registry and Analysis of Lausanne (ASTRAL) of the University Hospital of Lausanne. ASTRAL is a single-centre cohort registry of consecutive patients (≥16 years) of all AIS admitted to the stroke unit and/or intensive care unit within 24 h of last known well time [26]. The database is approved by our institutional review board as a clinical and research registry. All data are derived from routine clinical and radiological management.

Study population, laboratory, radiological and clinical data

All patients in the ASTRAL registry from January 2003 to December 2021 were included. The study populations of interest were patients with AC, including both newly diagnosed and known AC patients, and patients without a history of cancer (NC). AC was defined as cancer diagnosed within the previous 6 months (excluding nonmelanoma skin cancer, benign meningioma and myelodysplastic syndrome); recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; and haematological cancers that were not in complete remission [27]. Newly diagnosed cancer referred to patients with cancer identified during the admission for the index stroke, within the following 12 months or during the inpatient work-up for suspected cancer complicated by in-hospital stroke, as defined in an our previous study [24]. Inactive cancer (IC) was defined as patients lacking any trace of malignancy on appropriate radiological and biological testing during at least 6 months of follow-up and receiving no active treatment. These patients were excluded from the analysis. In cases of multiple cancers (e.g., one active and one inactive), patients were classified according to the most active tumour (i.e., most advanced stage, active treatment). Cancer was classified based on anatomopathological results; when not available, classification was based on the most likely diagnosis according to clinical and radiological findings. All other patients not meeting the AC or IC criteria were included in the NC group. For both study groups of interest, AC and the control group NC, demographic, clinical, laboratory, radiological and outcome data were extracted.

Acute laboratory data included basic laboratory blood tests (comprehensive metabolic panel, blood count, coagulation factors, lipid profile) measured within 24 h of stroke onset. The decision to assess hypercoagulability biomarkers (i.e., D-dimers and fibrin monomers) was up to the treating physician and was not available for all patients. Regarding neuroradiological variables, the presence was assessed of silent (subacute or chronic) ischaemic lesions and symptomatic haemorrhagic transformation between 0 and 7 days after onset according to the European Cooperative Acute Stroke Study (ECASS) II definition [28]. Multiterritorial strokes were defined as multiple acute infarctions clinically and/or radiologically either in the bilateral anterior circulation or in both the anterior and posterior circulations. Variables of interest with more than 20% missing data (such as fibrin monomers and D-dimers) were not used for statistical analysis.

Stroke mechanisms

Stroke subtypes were categorized according to the TOAST trial classification system [29] with the following specific mechanisms added: dissection of supracardiac arteries, multiple simultaneous causes and undetermined aetiology. Patients with patent foramen ovale (embolic stroke of undetermined source [ESUS] plus a RoPE score ≥ 7 [30]) were grouped with the cardioembolic mechanism.

Then, within the category of other determined/rare causes, a distinction was made between (i) cancer-related causes—detailing when present alone or with concurrent conventional stroke aetiologies (such as atherosclerosis, cardioembolism, lacunar infarcts)—and (ii) other rare causes, as recently defined by Vicino et al. [31]. The latter group includes these entities: vasculitis (not infectious), non-neoplastic hypercoagulability, vasculopathy/malformation (non-inflammatory), haemodynamic cause, vasospasm, pregnancy/delivery related, migrainous, peri-intervention ≤24 h diagnostic, peri-intervention ≤24 h therapeutic, drugs/medication related, rare cardiac or infectious endocarditis, genetic cause, other and infectious/parainfectious [31].

Based on the available literature [32], clinical experience and multidisciplinary discussion with haematologists, oncologists and pharmacologist consultants at our institution, three major cancer-related categories of mechanism were defined: (i) cancer associated, (ii) cancer therapy related and (iii) cancer diagnostic procedure related. For the second category, cancer drugs were considered with at least a moderate level of evidence for association with ischaemic stroke as a potential stroke mechanism according to a recent publication [33]. For the drugs not included in this review, a search was performed for potential associations with cerebrovascular events using various sources of information, including summaries of product characteristics [34], Micromedex, PubMed and Meyler's Side Effects of Drugs [35]. Cancer drugs were considered prothrombotic, applying the same criteria used in this recent review [33]. Additional details about attributing AIS to the underlying oncological disease are listed in Table S1.

Regarding AIS patients with AC and two potentially concomitant cancer-related mechanisms as defined after an initial round of chart review, these cases were collectively reassessed by two vascular neurologists, an oncologist and a pharmacologist until agreement was reached on the most likely mechanism.

Medium- and long-term outcome measures and cerebrovascular recurrence

The medium- and long-term outcome measures were (i) functional outcome at 90 days assessed with the modified Rankin Scale (mRS) score, (ii) death over the 12 months and (iii) stroke and transient ischaemic attack (TIA) recurrences over the 12 months. Recurrence was defined as ischaemic or haemorrhagic cerebrovascular events, including TIAs and retinal events, as defined previously [17].

See Data S1 for information on the definition of cancer-related stroke mechanisms, statistics and ethical considerations.

RESULTS

Baseline characteristics

From 2003 to 2021, 1065 (15.9%) out of 6686 patients with AIS registered in ASTRAL had a history of cancer. Excluding 700 patients (10.4%) with IC, there were 365 (5.5%) AIS patients with AC and 5621 (84.1%) NC patients. The AC patients consisted of 260 patients with known AC (71.2%) and 105 (28.8%) with newly diagnosed cancer. Median age of the overall (AC and NC) population was 73.8 (interquartile range 21.5), and 2647 (44%) were women (Table 1).

In unadjusted results, median age was similar in both groups, but AC patients were more often males (Table 1). On acute brain imaging, patients with AC had more multiterritorial and posterior circulation lesions and slightly more silent brain infarcts. Regarding biological and laboratory parameters, patients with AC had higher levels of neutrophil-to-lymphocyte ratio, C-reactive protein and total cholesterol, lower haemoglobin level, platelet count and prothrombin time activity. Workflow metrics of reperfusion therapies were similar, but AC patients received less intravenous thrombolysis (IVT) or bridging therapy (23% AC vs. 34% NC). Although AC patients more often had a change in treatment goals (enlisted palliative care) during the AIS hospitalization than NC patients did (21% AC vs. 10% NC), they were more likely to receive anticoagulation at discharge (31% AC vs. 26% NC). Conversely, AC patients less frequently received lipid-lowering and antiplatelet therapy after hospitalization.

The most represented tumours in the AC group were gastrointestinal (27%), lung (23%) and genitourinary tumours (21%) (Table 2). The frequency of metastatic disease was 59%, of which 8% showed brain metastasis. Overall, 35% of AC patients received an AC treatment, including chemotherapy (18%), hormonotherapy (6.9%), immunotherapy (2.6%), radiotherapy (1.5%) and surgery during hospitalization (3%) or a combination of therapies (3%).

In multivariable analysis, patients with AC were older and more often male compared to NC patients (Table 3). Notably, AC patients were 48% less likely to receive IVT (± endovascular treatment, EVT) (adjusted odds ratio [aOR] 0.52, 95% confidence interval [CI] 0.35–0.76), and they presented more multiterritorial and posterior circulation strokes and less often traditional vascular risk factors such as heart valvulopathy. They also had lower systolic blood pressure, creatinine and haemoglobin levels and a higher neutrophil-to-lymphocyte ratio.

Stroke mechanisms

Stroke mechanisms were different between the two groups. Overall, 179/361 AC patients (50% vs. 59% NC) presented conventional aetiologies such as atherosclerosis, cardioembolism, dissection or

TABLE 1 Baseline demographic, clinical, laboratory and radiological characteristics.

		Cancer presence		
	Total population	Active cancer (AC)	Non-cancer (NC)	
Variable	*N* = 5986	*N* = 365	*N* = 5621	*p*
Age	73.8 (61.3, 82.8)	74.2 (63.6, 80.6)	73.8 (60.9, 82.9)	0.642
Female sex	2647/5986 (44%)	141/365 (39%)	2506/5621 (45%)	**0.026**
mRS pre-stroke	0 (0, 2)	1 (0, 2)	0 (0, 1)	**<0.001**
NIHSS at admission	6.0 (3.0, 14.0)	6.0 (3.0, 15.0)	6.0 (3.0, 14.0)	0.070
Medical history[a]				
Hypertension	4319/5986 (72%)	267/365 (73%)	4052/5621 (72%)	0.660
Previous stroke/TIA	1610/5944 (27%)	108/362 (30%)	1502/5582 (27%)	0.225
Diabetes mellitus	1140/5982 (19%)	74/365 (20%)	1066/5617 (19%)	0.541
Dyslipidaemia	4465/5974 (75%)	251/364 (69%)	4214/5610 (75%)	**0.009**
Smoking	1407/5947 (24%)	97/360 (27%)	1310/5587 (23%)	0.130
Atrial fibrillation	1733/5982 (29%)	94/364 (26%)	1639/5618 (29%)	0.172
Coronary disease	1110/5975 (19%)	72/362 (20%)	1038/5613 (18%)	0.508
Peripheral arteriopathy	388/5954 (7%)	34/363 (9%)	354/5591 (6%)	**0.023**
Cardiac valvulopathy	236/5981 (4%)	6/365 (2%)	230/5616 (4%)	**0.020**
Ejection fraction <35%	320/5986 (5%)	13/365 (4%)	307/5621 (6%)	0.118
Alcohol addiction	616/5959 (10%)	45/362 (12%)	571/5597 (10%)	0.177
Psychosis and depression	797/5986 (13%)	45/365 (12%)	752/5621 (13%)	0.567
BMI	25.0 (23.0, 28.0)	24.0 (22.0, 27.0)	25.0 (23.0, 28.0)	**<0.001**
Medication at stroke onset				
Antiplatelet therapy	2163/5986 (36%)	125/365 (34%)	2038/5621 (36%)	0.438
Anticoagulation	787/5942 (13%)	70/360 (19%)	717/5582 (13%)	**<0.001**
Lipid-lowering therapy	1740/5971 (29%)	102/362 (28%)	1638/5609 (29%)	0.677
Antihypertensives	3423/5961 (57%)	184/363 (51%)	3239/5598 (58%)	**0.007**
Radiological features				
Silent infarcts[b]	1355/4504 (30%)	91/253 (36%)	1264/4251 (30%)	**0.036**
Symptomatic haemorrhagic transformation 0–7 days[c]	136/5660 (2%)	8/334 (2%)	128/5326 (2%)	>0.9
Posterior circulation territory	1470/5854 (25%)	51/358 (14%)	1419/5496 (26%)	**<0.001**
Multiple territories	196/4374 (5%)	31/273 (11%)	165/4101 (4%)	**<0.001**
Biological values				
Temperature at admission	36.3 (36.0, 36.7)	36.4 (36.0, 36.8)	36.3 (36.0, 36.7)	**0.012**
Mean blood pressure				
Systolic	150.0 (133.0, 169.0)	143.0 (129.0, 160.0)	151.0 (134.0, 170.0)	**<0.001**
Laboratory results				
Blood glucose levels (mmol/L)	6.6 (5.7, 8.0)	6.7 (5.8, 8.1)	6.6 (5.7, 8.0)	0.302
C-reactive protein levels (mg/dL)	4.0 (1, 10)	13.0 (5, 41)	3.0 (1, 9)	**<0.001**
Haemoglobin level (g/L)	139 (126, 149)	124.0 (105.2, 140)	139.0 (128, 150)	**<0.001**
White blood cell count (g/L)	8.2 (6.7, 10.4)	8.2 (6.2, 10.9)	8.2 (6.7, 10.4)	0.434
Platelet count (g/L)	227 (188.0, 275)	221.5 (164.2, 285)	228.0 (189, 274)	**0.036**
NLR	3.5 (2.1, 6.2)	5.5 (2.9, 9.1)	3.4 (2.1, 6.0)	**<0.001**
PT (% activity)	100.0 (85.0, 100.0)	90.0 (75.0, 100.0)	100.0 (85.0, 100.0)	**<0.001**
Monomers[d]	60/350 (17%)	42/165 (25%)	18/185 (10%)	
Total cholesterol (mmol/L)	4.8 (4.0, 5.8)	4.6 (3.8, 5.5)	4.9 (4.0, 5.8)	**<0.001**
Acute creatinine (μmol/L)	86.0 (73.0, 103.0)	83.0 (69.0, 105.8)	86.0 (73.0, 103.0)	0.129

TABLE 1 (Continued)

Variable	Total population	Cancer presence		
		Active cancer (AC)	Non-cancer (NC)	
	N = 5986	*N* = 365	*N* = 5621	*p*
Intervention type[e]				
IVT (± EVT)	1994/5984 (33%)	83/365 (23%)	1911/5619 (34%)	**<0.001**
EVT (± IVT)	1005/5984 (17%)	66/365 (18%)	939/5619 (17%)	0.497
Timing (min)				
Onset-to-door	196.0 (85, 586)	179.0 (74, 512)	196.0 (86, 589)	0.073
Onset-to-needle	145.0 (105, 205)	148.0 (110, 206)	145.0 (105, 205)	0.450
Onset-to-groin	255.0 (185, 400)	257.0 (188.2, 415)	255.0 (185, 400)	0.748
Medication at hospital discharge				
Lipid-lowering therapy	4316/5967 (72%)	227/363 (63%)	4089/5604 (73%)	**<0.001**
Anticoagulation	1546/5961 (26%)	111/363 (31%)	1435/5598 (26%)	**0.037**
Antiplatelet therapy	3901/5703 (68%)	191/353 (54%)	3710/5350 (69%)	**<0.001**
Goals of care				
Palliative care	626/5938 (11%)	74/358 (21%)	552/5580 (10%)	**<0.001**

Note: Continuous and ordinal variables are expressed as median (with interquartile range, IQR), and categorical variables as absolute counts (with percentage).Bold values represent $P < 0.05$.

Abbreviations: BMI, body mass index; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; TIA, transient ischaemic attack.

[a]Vascular risk factors are considered present if current or past.

[b]On any imaging.

[c]According to European Cooperative Acute Stroke Study (ECASS) II definition.

[d]Monomers are expressed as increased/within normal range, as per institutional laboratory results. Monomers were missing in 200/365 (54.8%) of AC patients; therefore, no *p* value was calculated. The number and proportion of other missing values can be detected from the absolute counts in the table.

[e]IVT (± EVT) refers to the proportion of patients treated with intravenous thrombolysis alone or followed by endovascular treatment. EVT (± IVT) refers to the patients treated with endovascular thrombectomy alone or preceded by intravenous thrombolysis.

multiple causes, 28% (vs. 4%) had a rare cause only and 16% (vs. 26%) were of undetermined mechanism (Table 4). Amongst rare causes of stroke, 154/365 (42%) AC patients presented an identifiable cancer-associated, cancer therapy or diagnostic-procedure-related cause only or concomitant with conventional mechanisms. These cancer-related mechanisms are defined in Table S1.

Medium- and long-term outcomes

In multivariable analysis, having an AC was not associated with a shift in the mRS score towards a worse outcome at 3 months before (aOR 2.18, 95% CI 0.96–5.00) (Figure 1 and Table S2) and after propensity score matching (PM) (aOR 1.34, 95% CI 0.78–2.31) (Tables S2 and 5). About 43% of AC patients regained functional independence (mRS 0–2) at 90 days (Table S3).

Risk of death at 12 months was higher in AC than in NC patients before (adjusted hazard ratio 1.91, 95% CI 1.50–2.43) and after PM (aHR 1.62, 95% CI 1.14–2.30) (Figure 2a, Tables 5 and S4). Antiplatelet (aHR 0.41, 95% CI 0.27–0.61) and anticoagulation therapies at discharge (aHR 0.42, 95% CI 0.27–0.64) seemed protective although this may reflect confounding by indication (Table S4). The cause of death within 12 months was more often non-vascular in the AC group (54% vs. 14%), presumably mostly due to the underlying oncological disease (but could not be ascertained for each patient) (Table S5). Regarding withdrawal of care for AC patients, 25/74 (33.8%) died for a non-vascular cause (probably cancer related).

Active cancer patients had an increased risk of cerebrovascular recurrence compared with NC patients before (aHR 1.72, 95% CI 1.25–2.37) and after PM (aHR 1.93, 95% CI 1.02–3.66) and adjustments for potential confounders, including secondary prevention therapies at discharge (e.g., antiplatelets, anticoagulation and statins) (Tables 5 and S6). This risk remained increased (sub-distribution HR [sHR] 1.68, 95% CI 1.22–2.31) also when analysing death from any cause as a competing risk (Figure 2b and Table S7). In the AC group, patients receiving antithrombotic medications at discharge had reduced risk of cerebrovascular recurrences compared with untreated patients (sHR 0.42, 95% CI 0.22–0.81) (Figure 3).

DISCUSSION

In a large retrospective cohort study in a single centre over 18 years, it was found that an estimated 5.5% of patients with AIS had AC.

TABLE 2 Cancer-related characteristics.

Variable	Active cancer (AC) (*N* = 365)
Type of cancer[a]	
Gastrointestinal	99/365 (27%)
Lung	83/365 (23%)
Genitourinary	76/365 (21%)
Breast and gynaecological	50/365 (14%)
Haematological	38/365 (10%)
Other[b]	9/365 (2.5%)
Melanoma	7/365 (1.9%)
Primary brain	7/365 (1.9%)
Metastatic cancer, WHO stage IV	182/311 (59%)
Active brain metastasis	29/359 (8.1%)
Cancer relapse or progression	63/360 (18%)
Active treatment[c]	
Chemotherapy	66/363 (18%)
Hormonotherapy	25/363 (6.9%)
Radiotherapy head/neck/mediastinum	5/363 (1.5%)
Immunotherapy	9/363 (2.6%)
Surgery during hospitalization	11/363 (3%)
Combination therapy[d]	11/363 (3%)
No active treatment	236/363 (65%)

Abbreviation: WHO, World Health Organization.

[a]Total sum and percentages are >365 (100%) because some patients presented more than one AC.

[b]Sarcomas, and unknown primary tumours because of missing histopathology.

[c]Active treatment as defined in the methods involved AC patients only except for one case with newly diagnosed cancer who was hospitalized for cancer work-up and treatment and had an in-hospital stroke 3 days after starting platinum-based chemotherapy.

[d]Chemoimmunotherapy (7), chemoradiotherapy (3); hormone and radiotherapy (1).

Compared with NC patients, AC patients were older and more often male. They had fewer conventional vascular risk factors, more multiterritorial strokes and more laboratory abnormalities. AC patients were 48% less likely to receive IVT or bridging therapy. Regarding stroke mechanisms, these were cancer related (attributed to the cancer itself or in addition to conventional stroke causes) in 42% of AC patients. Although AC patients did not show a higher disability at 1 month after AIS, mortality and risk of recurrent cerebrovascular events were different between study groups. AC patients presented a two-fold higher risk of death at 12 months. In addition, having an AC was a major predictor of cerebrovascular recurrence at 12 months even after adjusting for secondary preventive strategies at discharge and PM. Finally, antithrombotic therapies may reduce cerebrovascular recurrence in the AC population.

The clinical characteristics of AIS patients with AC in our study align with previous smaller studies [8,21,22,36]. Compared with NC patients, AC patients in our cohort were older and had fewer traditional vascular risk factors, such as heart valvulopathy. Similarly, other studies reported age ≥ 65, absence of atrial fibrillation and dyslipidaemia as being associated with an AC [8,21,36]. Although no differences were found in time metrics of AIS care between the two groups, AC patients were 56% less likely to receive IVT or bridging therapy (pure EVT rates were not different). These results align with previous clinical studies on AIS patients with cancer [18,20,37]. Increased anticoagulation use, perceived higher bleeding risk, higher pre-stroke disability, shorter life expectancy, more frequent comorbidities in AC patients and conservative indications by American guidelines for some tumour types (known gastrointestinal or intra-axial brain tumours) may explain this difference [38]. European guidelines do state, however, that other non-metastatic oncological patients are likely to have a similar relative benefit from IVT as non-oncological patients [39].

A novel and detailed categorization of potential cancer-related stroke mechanisms was used (defined in Table S1) based on data from other authors [11,40] and pathophysiological considerations. It was found that 42% of patients with AC have a stroke mechanism attributed to underlying cancer or cancer therapy/diagnostic procedures alone or in addition to concurrent conventional AIS aetiologies, such as atherosclerosis, cardioembolism and small vessel disease. Many prior studies have used a more rigid stroke classification system, whereby strokes suspected to be from cancer-mediated hypercoagulability based on high-risk cancer types, abnormal coagulation markers and/or multiterritory infarcts were classified as cryptogenic rather than cancer related. As a result, the percentage of cryptogenic strokes in previous studies [8,41,42], which ranged from 31% to 51%, was substantially lower in our cohort (16%).

Previous studies highlighted a worse functional outcome at 3 months in AIS patients with AC treated with reperfusion therapies compared with NC patients [13, 21] with functional independence (mRS 0–2) at 3 months ranging between 23% and 47% [13, 18–21]. It was found that 43% of AC patients achieve functional independence at 3 months (vs. 60% in the NC group), but adjusted and PM analysis do not show differences in functional outcomes (Figure 1 and Table S2). This may be partly explained by differences in the definition of AC compared to previous studies. Most of these investigations used a heterogeneous definition of AC, with some including newly diagnosed cancer patients within 6 months of the AIS [21]—a distinct subset of patients who may have different risks, pathophysiology and outcomes [24]—and others excluding them [20] or including any past cancer [18]. Alternatively, the potential negative effect on medium-term disability could be limited to more aggressive cancer types (e.g., advanced lung or breast cancers) or the proportion of AC patients not initiating or resuming cancer treatments after AIS. Future studies powered to answer these questions could provide further results.

Acute ischaemic stroke patients with AC exhibit a high mortality rate of 17%–64% at either 3 or 6 months compared with NC and IC patients [18-22,43]. In our study, AC patients had a death rate of 59%, equating to a two-fold higher risk of death (aHR 1.91, 95% CI 1.50–2.43) compared to NC patients after adjusting for

TABLE 3 Unadjusted and adjusted analysis of demographic, clinical, radiological and laboratory variables comparing AIS patients with active cancer (AC) versus non-cancer patients (NC) (dependent variable AC [yes/no]).

	Univariable		Multivariable	
Independent variable	**aOR (95% CI)**	***p***	**aOR (95% CI)**	***p***
Age ≥ 16 years (per 10 years)	1.01 (1.00, 1.01)	0.091	1.02 (1.00, 1.03)	**0.037**
Sex (ref. female)	0.78 (0.63, 0.97)	**0.027**	0.44 (0.30, 0.63)	**<0.001**
IVT (± EVT)	0.57 (0.44, 0.73)	**<0.001**	0.52 (0.35, 0.76)	**<0.001**
EVT (± IVT)	1.10 (0.83, 1.44)	0.497	1.03 (0.64, 1.62)	0.898
Posterior circulation territory	0.48 (0.35, 0.64)	**<0.001**	0.57 (0.37, 0.85)	**0.007**
Multiterritorial stroke	3.06 (2.01, 4.52)	**<0.001**	2.07 (1.12, 3.62)	**0.014**
Previous stroke/TIA	1.15 (0.91, 1.45)	0.225	1.12 (0.79, 1.57)	0.507
Hypertension	1.05 (0.83, 1.34)	0.660	1.20 (0.80, 1.81)	0.381
Diabetes mellitus	1.09 (0.83, 1.41)	0.541	0.82 (0.52, 1.26)	0.373
Dyslipidaemia	0.74 (0.59, 0.93)	**0.009**	0.90 (0.62, 1.32)	0.576
Smoking	1.20 (0.94, 1.53)	0.131	1.19 (0.79, 1.77)	0.405
Atrial fibrillation	0.85 (0.66, 1.07)	0.173	0.70 (0.47, 1.04)	0.079
Coronary disease	1.09 (0.83, 1.42)	0.508	0.82 (0.54, 1.23)	0.341
Prosthetic valves	0.39 (0.15, 0.81)	**0.025**	0.28 (0.09, 0.69)	**0.012**
Ejection fraction < 35%	0.64 (0.35, 1.08)	0.121	0.50 (0.19, 1.11)	0.120
Peripheral arteriopathy	1.53 (1.04, 2.18)	**0.024**	0.99 (0.55, 1.71)	0.984
Alcohol addiction	1.25 (0.89, 1.71)	0.178	1.26 (0.76, 2.01)	0.357
Psychosis or depression	0.91 (0.65, 1.24)	0.567	0.85 (0.53, 1.31)	0.473
NIHSS at admission	1.00 (0.99, 1.02)	0.559	0.99 (0.96, 1.02)	0.487
mRS pre-stroke	1.30 (1.19, 1.42)	**<0.001**	1.08 (0.93, 1.26)	0.308
Temperature at admission	1.30 (1.10, 1.53)	**0.002**	1.08 (0.86, 1.37)	0.508
Systolic blood pressure (per 1 mmHg)	0.99 (0.98, 0.99)	**<0.001**	0.99 (0.98, 1.00)	**0.008**
Blood glucose levels (mmol/L)	1.05 (0.72, 1.51)	0.779	0.96 (0.52, 1.73)	0.885
Creatinine levels (μmol/L)	0.77 (0.53, 1.09)	0.142	0.60 (0.36, 0.98)	**0.046**
NLR	1.64 (1.43, 1.87)	**<0.001**	1.44 (1.16, 1.77)	**<0.001**
Platelet count (g/L)	0.55 (0.41, 0.74)	**<0.001**	0.67 (0.44, 1.01)	0.055
Hemoglobin level (g/L)	0.02 (0.01, 0.03)	**<0.001**	0.02 (0.01, 0.05)	**<0.001**
Prothrombin time (% activity)	0.81 (0.61, 1.10)	0.154	0.88 (0.54, 1.48)	0.611

Abbreviations: AIS, acute ischaemic stroke; aOR, adjusted odds ratio; CI, confidence interval; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; TIA, transient ischaemic attack.Bold values represent $P < 0.05$.

confounders and PM (aHR 1.62, 95% CI 1.14–2.30). Non-vascular causes of death were significantly higher in the AC group (54%) compared with the NC group (14%) (Table S5). Although specific data on the precise causes of death are lacking, this excess mortality could be from cancer-related causes. Hypercoagulability in AC patients (as previously defined by D-dimer levels above the median value) has been associated with a reduced 1-year survival, and reduced D-dimer levels with anticoagulation may be associated with improved survival [10]. Systematic data on D-dimer levels were lacking, but both anticoagulant and antiplatelet therapies at discharge seemed to play a protective role in our cohort, although this may reflect confounding from indication bias (i.e., physicians less often prescribed antithrombotic therapy to patients who they viewed as more likely to die) (Table S4).

In our cohort, 1-year cerebrovascular recurrence rates were approximately twice as common in the AC group (17% AC vs. 7.6% NC). Previous studies reported a similar AIS recurrence rate at 6 and 12 months ranging from 13% to 16% with AC and adenocarcinoma as independent predictors of recurrence [16,44]. Verschoof et al. [20] recently highlighted an increased recurrence rate at 3 months (4% vs. 1% in NC patients) in 124 cancer patients treated with EVT, which is lower than in our cohort. A longer time interval from the index stroke and a slightly different definition of cerebrovascular recurrence (inclusion of haemorrhagic strokes and TIAs in our case) may account for this variation. In our AC cohort, it was found that antithrombotic therapies at discharge may prevent recurrent cerebrovascular events over 12 months (Figure 3). Although confounding by indication cannot be ruled out, these results align with a recent

TABLE 4 Stroke mechanisms.

Variable	Total population N = 5986	Cancer presence	
		Active cancer (AC) N = 365	Non-cancer (NC) N = 5621
Modified TOAST mechanisms			
Atherosclerotic, cardiac including PFO, dissection and multiple causes (including concomitant rare)	3447/5895 (58.5%)	179/361 (50%)	3268/5534 (59.1%)[a]
Lacunar	603/5895 (10.2%)	20/361 (5.4%)	583/5534 (10.5%)
Rare causes only	341/5895 (5.8%)	103/361 (28.4%)	238/5534 (4.3%)
Undetermined	1504/5895 (25.5%)	59/361 (16.2%)	1445/5534 (26.1%)
TOAST rare mechanisms			
Rare cancer related only or with conventional mechanisms (Table S1)	154/5986 (2.6%)	154/365 (42.2%)	0/5621 (0%)
Other rare[b]	220/5986 (3.7%)	6/365 (1.6%)	238/5621 (4.3%)
Non-rare mechanisms only	5612/5986 (93.7%)	205/365 (56.2%)	5383/5621 (95.7%)

Abbreviations: PFO, patent foramen ovale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

[a]Missing data on four AC and 87 NC patients in the 'Modified TOAST mechanisms' grouping.

[b]Defined in Methods, Stroke mechanisms.

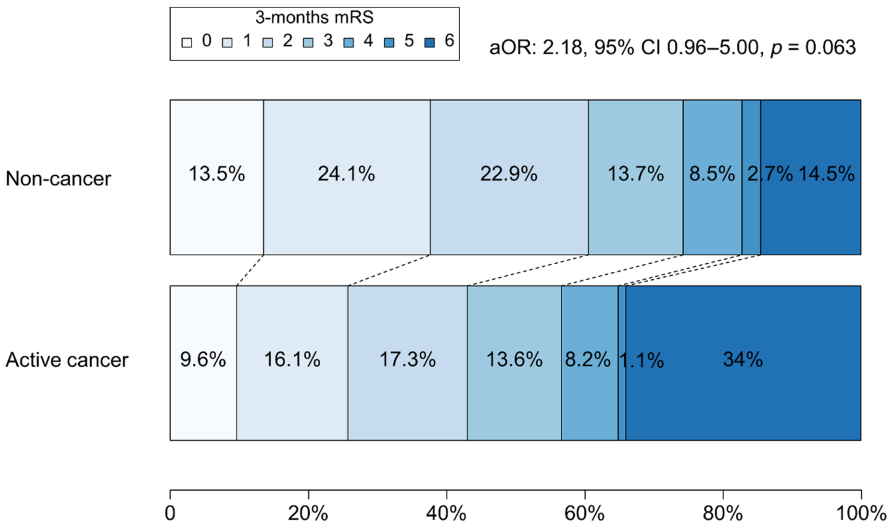

FIGURE 1 Modified Rankin Scale score shift at 3 months in active cancer (AC) versus non-cancer (NC) patients with acute ischaemic stroke (AIS) before propensity score matching. Comparison by ordinal logistic regression showed non-significant effect of having AC in AIS patients compared with NC and is expressed as an adjusted common odds ratio aOR (aOR 2.18, 95% CI 0.96–5.00, $p = 0.063$).

TABLE 5 Unadjusted, adjusted and propensity-matched outcome measures.

Analysis	Unadjusted 3-month mRS shift OR (95% CI)	Adjusted[a] 3-month mRS shift aOR (95% CI)	Unadjusted 12-month mortality HR (95% CI)	Adjusted 12-month mortality aHR (95% CI)	Unadjusted 12-month recurrence[b] HR (95% CI)	Adjusted 12-month recurrence[b] aHR (95% CI)
Before PM	**2.17 (1.78–2.65)**[c]	2.18 (0.96, 5.00)	**3.12 (2.65–3.67)**	**1.91 (1.50–2.43)**	**2.53 (1.94–3.31)**	**1.72 (1.25–2.37)**
After PM	1.35 (0.96, 1.88)	1.34 (0.78, 2.31)	**1.75 (1.37, 2.23)**	**1.62 (1.14, 2.30)**	**2.38 (1.32, 4.28)**	**1.93 (1.02, 3.66)**

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; HR, hazard ratio; mRS, modified Rankin Scale; OR, odds ratio; PM, propensity score matching.

[a]See supplement for adjustments (Tables S2, S4 and S6).

[b]Cerebrovascular recurrence as defined in Methods, Medium- and long-term outcome measures and cerebrovascular recurrence.

[c]Bold odds and hazard ratios are statistically significant. See supplementary tables for *p* values (Tables S2, S4 and S6).

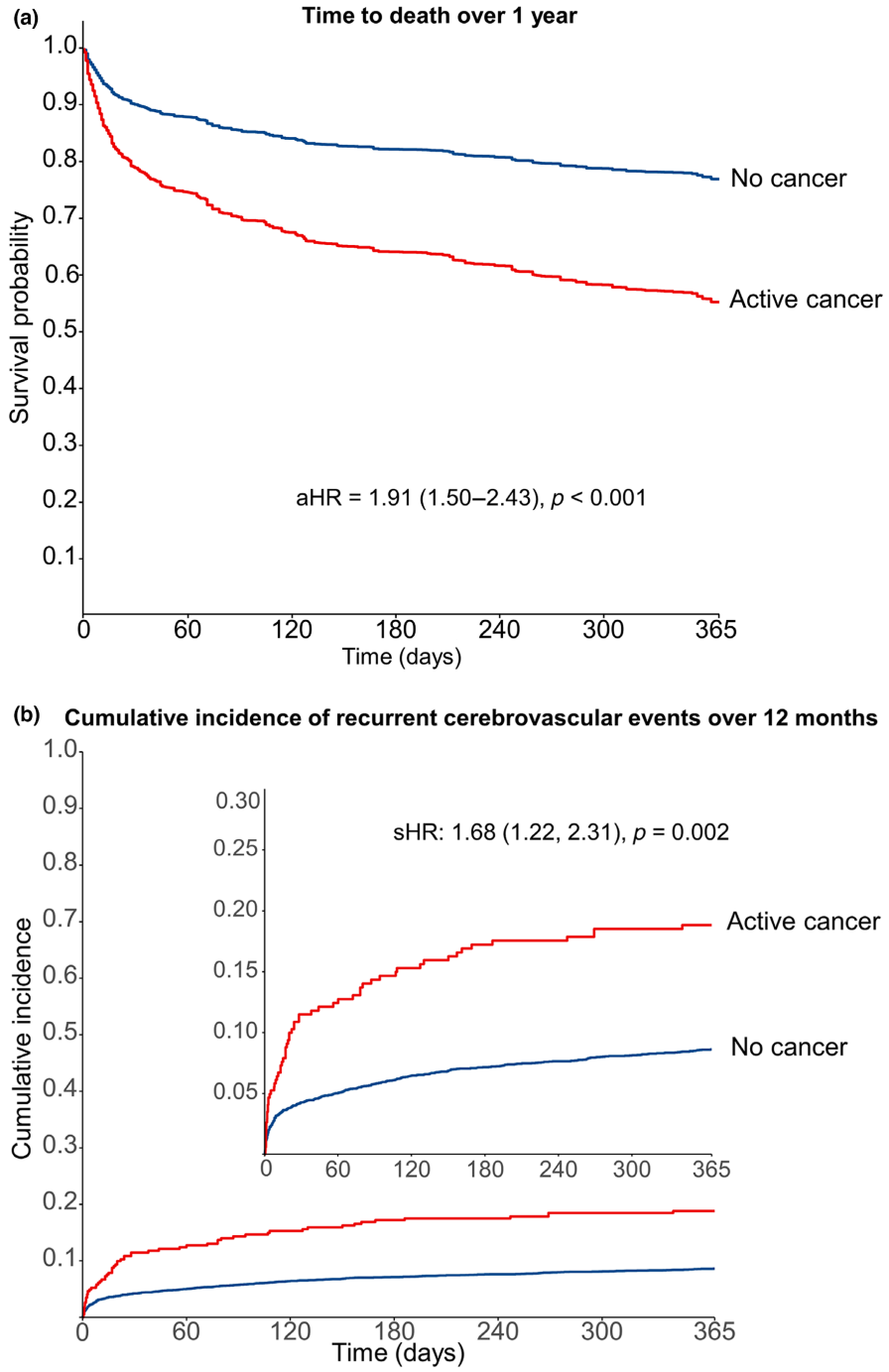

FIGURE 2 Mortality and cerebrovascular recurrence at 12 months in active cancer (AC) versus non-cancer (NC) patients. AC patients present a 91% higher death risk (adjusted HR 1.91, 95% CI 1.50–2.43, p value < 0.001) (a) and a 68% higher risk of cerebrovascular recurrence (sub-distribution HR 1.68, 95% CI 1.22–2.31, $p = 0.002$) over 12 months compared to NC patients (b).

study demonstrating a reduction in recurrent strokes without significantly increasing major bleeding in AC patients treated with antithrombotic medications [45].

The preferred antithrombotic therapy at discharge after AIS in AC patients is still unclear. In a subgroup analysis of the NAVIGATE ESUS randomized trial comparing aspirin to rivaroxaban in patients with ESUS, 543 (7.5%) had cancer (although only 9% of cancers were diagnosed in the previous year so presumably many of these cancers were inactive). Although the risk of recurrence between treatment groups was not different, cancer patients had higher rates of recurrent stroke, and aspirin may have performed better at secondary prevention and with less risk of major bleeding [46]. In addition, intracranial thrombi retrieved with EVT from cancer patients with ESUS are platelet-rich, further supporting a potential benefit of antiplatelets in this population [47]. Collectively, these findings reinforce the notion that current secondary prevention strategies in AIS patients with cancer provide suboptimal protection for recurrence, and that alternative antithrombotic strategies should be tested in targeted clinical trials. Given that cancer-related hypercoagulability may play a key role in AIS pathogenesis, particularly in patients with extensive disease [10,40], more aggressive antithrombotic therapies come first to mind to prevent recurrence. On the other hand, targeting the underlying cancer with specific and intensive cancer therapies could hold more promise to halt further thromboembolic events.

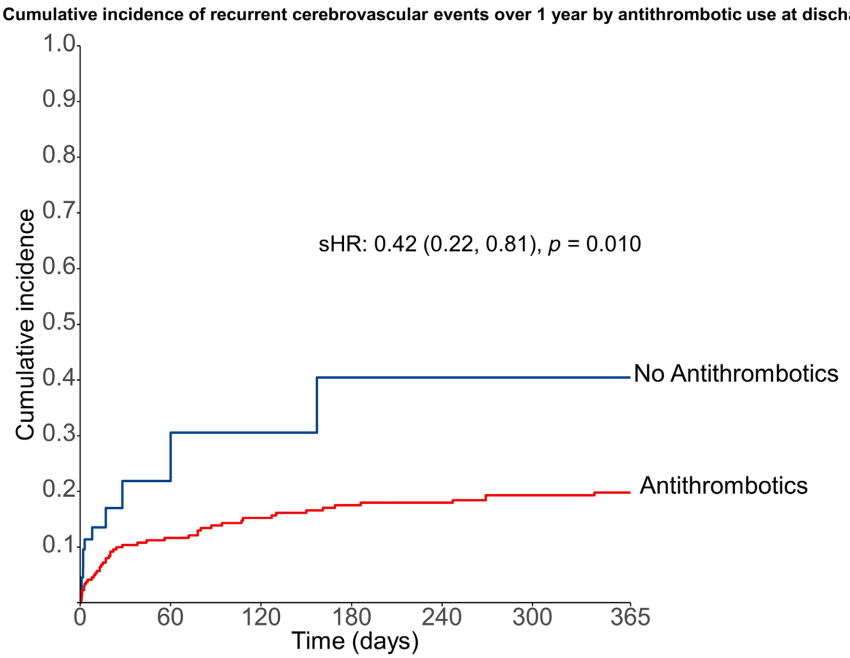

FIGURE 3 Cerebrovascular recurrence at 12 months in active cancer patients stratified by use of antithrombotic medications. Patients with active cancer taking antithrombotic medications at discharge present a 58% lower risk of cerebrovascular recurrence (sub-distribution HR 0.42, 95% CI 0.22–0.81, $p = 0.010$) over 12 months compared to untreated patients.

Our study has some limitations. First, this is a quality assurance project in a single institution and the results may not apply to other settings or patient groups, in particular to non-Caucasian younger populations. Secondly, our AIS cohort spanned a long period (>18 years) during which stroke and oncological care have evolved, potentially introducing temporal confounders regarding the association between cancer and stroke. Thirdly, our definition of rare cancer-related causes of stroke included presumed hypercoagulability, based on D-dimer levels or the presence of monomers that were only measured in a subset of patients, potentially leading to an underestimation of this stroke mechanism. Further, D-dimer and other fibrin split products are not specific to hypercoagulability and can be increased by other factors, including age, recent surgery or trauma, atrial fibrillation, concurrent venous thromboembolism [48]. Fourthly, there was no comparison between AC and IC patients, a distinct subset of patients who may exhibit varying risks, pathophysiology and outcomes [43]. Lastly, the precise cause of death was not recorded in ASTRAL, and therefore it is not known whether patients with cancer died of cancer-related causes.

CONCLUSION

In a large registry-based study of patients with AIS spanning nearly two decades, it was found that 5.5% had an active malignancy at admission or within 12 months of the index stroke. Even if more than one-third of AC patients regained functional independence after AIS, 12-month mortality and cerebrovascular recurrence risk were nearly two-fold higher in AC patients compared with the NC group after adjusting for confounders and PM. This risk seems to be associated with having a rare stroke cause including cancer-related mechanisms, raising questions on the timing to (re)start cytoreductive therapies for cancer and the most appropriate secondary prevention approaches. One planned (TEACH2, Trial of Apixaban versus Aspirin in Cancer Patients with Cryptogenic Ischaemic Stroke) and one ongoing clinical trial (ENCHASE, Edoxaban for the Treatment of Coagulopathy in Patients with Active Cancer and Acute Ischaemic Stroke) may help to determine the best antithrombotic strategy.

Prospective studies are needed to corroborate our findings. If confirmed, they may motivate further research on the pathophysiological mechanisms underlying AIS in patients with cancer, better inform clinicians about prognosis after AIS in this subgroup, and prompt further studies on the most suitable secondary prevention strategies after AIS.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Wilbers J, Sondag L, Mulder S, Siegerink B, van Dijk EJ, Group the DS-PSS. Cancer prevalence higher in stroke patients than in the general population: the Dutch string-of-pearls institute (PSI) stroke study. *Eur J Neurol*. 2020;27:85-91.
2. Kiyuna F, Sato N, Matsuo R, et al. Association of embolic sources with cause-specific functional outcomes among adults with cryptogenic stroke. *JAMA Netw Open*. 2018;1:e182953.
3. Kim SJ, Park JH, Lee M-J, Park YG, Ahn M-J, Bang OY. Clues to occult cancer in patients with ischemic stroke. *PLoS ONE*. 2012;7:e44959.
4. Navi BB, Reiner AS, Kamel H, et al. Arterial thromboembolic events preceding the diagnosis of cancer in older persons. *Blood*. 2019;133:781-789.
5. Zaorsky NG, Zhang Y, Tchelebi LT, Mackley HB, Chinchilli VM, Zacharia BE. Stroke among cancer patients. *Nat Commun*. 2019;10:5172.
6. Gon Y, Zha L, Sasaki T, et al. Stroke mortality in cancer survivors: a population-based study in Japan. *Thromb Res*. 2023;222:140-148.
7. Schwarzbach CJ, Fatar M, Eisele P, Ebert AD, Hennerici MG, Szabo K. DWI lesion patterns in cancer-related stroke—specifying the phenotype. *Cerebrovasc Dis Extra*. 2015;5:139-145.
8. Grazioli S, Paciaroni M, Agnelli G, et al. Cancer-associated ischemic stroke: a retrospective multicentre cohort study. *Thromb Res*. 2018;165:33-37.
9. Olaiya MT, Andrew NE, Dalli LL, et al. Does a history of cancer influence the effectiveness of statins on outcomes after stroke? *Stroke*. 2022;53:3202-3205.
10. Lee MJ, Chung J-W, Ahn M-J, et al. Hypercoagulability and mortality of patients with stroke and active cancer: the OASIS-CANCER study. *J Stroke*. 2016;19:77-87.
11. Dardiotis E, Aloizou A-M, Markoula S, et al. Cancer-associated stroke: pathophysiology, detection and management (review). *Int J Oncol*. 2019;54:779-796.
12. Tinker RJ, Smith CJ, Heal C, et al. Predictors of mortality and disability in stroke-associated pneumonia. *Acta Neurol Belg*. 2021;121:379-385.
13. Cutting S, Wettengel M, Conners JJ, Ouyang B, Busl K. Three-month outcomes are poor in stroke patients with cancer despite acute stroke treatment. *J Stroke Cerebrovasc Dis*. 2017;26:809-815.
14. Nam K-W, Kim CK, Kim TJ, et al. D-dimer as a predictor of early neurologic deterioration in cryptogenic stroke with active cancer. *Eur J Neurol*. 2017;24:205-211.
15. Nam K-W, Kim CK, Kim TJ, et al. Predictors of 30-day mortality and the risk of recurrent systemic thromboembolism in cancer patients suffering acute ischemic stroke. *PLoS ONE*. 2017;12:e0172793.
16. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology*. 2014;83:26-33.
17. Strambo D, Zachariadis A, Lambrou D, et al. A score to predict one-year risk of recurrence after acute ischemic stroke. *Int J Stroke*. 2021;16:602-612.
18. Federica L, Giovanni P, Valentina S, et al. Endovascular treatment in patients with acute ischemic stroke and comorbid cancer: analysis of the Italian Registry of Endovascular Treatment in Acute Stroke. *Stroke Vasc Interv Neurol*. 2022;3:e000423.
19. Caimano D, Letteri F, Capasso F, et al. Endovascular treatment in patients with acute ischemic stroke and cancer: systematic review and meta-analysis. *Eur Stroke J*. 2022;7:204-211.
20. Verschoof MA, Groot AE, de Bruijn SFTM, et al. Clinical outcome after endovascular treatment in patients with active cancer and ischemic stroke: a MR CLEAN registry substudy. *Neurology*. 2022;98:e993-e1001.
21. Yoo J, Kim YD, Park H, et al. Immediate and long-term outcomes of reperfusion therapy in patients with cancer. *Stroke*. 2021;52:2026-2034.
22. Kneihsl M, Enzinger C, Wünsch G, et al. Poor short-term outcome in patients with ischaemic stroke and active cancer. *J Neurol*. 2016;263:150-156.
23. Selvik HA, Thomassen L, Bjerkreim AT, Næss H. Cancer-associated stroke: the Bergen NORSTROKE study. *Cerebrovasc Dis Extra*. 2015;5:107-113.
24. Costamagna G, Hottinger AF, Milionis H, et al. Clinical and demographic characteristics, mechanisms, and clinical outcomes in patients with acute ischemic stroke with newly diagnosed vs. known active cancer. *Neurology*. 2023;100:e2477-e2489.
25. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol*. 2019;20:1493-1505.
26. Michel P, Odier C, Rutgers M, et al. The Acute STroke Registry and Analysis of Lausanne (ASTRAL). *Stroke*. 2010;41:2491-2498.
27. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16:1891-1894.
28. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study investigators. *Lancet*. 1998;352:1245-1251.
29. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35-41.
30. Strambo D, Sirimarco G, Nannoni S, et al. Embolic stroke of undetermined source and patent foramen ovale: risk of paradoxical embolism score validation and atrial fibrillation prediction. *Stroke*. 2021;52:1643-1652.
31. Vicino A, Sirimarco G, Eskandari A, et al. Rare stroke mechanisms in 4154 consecutive patients: causes, predictors, treatment, and outcomes. *Neurol Sci*. 2022;43:6359-6369.
32. Costamagna G, Navi BB, Beyeler M, Hottinger AF, Alberio L, Michel P. Ischemic stroke in cancer: mechanisms, biomarkers, and implications for treatment. *Semin Thromb Hemost*. 2023.
33. Marto JP, Strambo D, Livio F, Michel P. Drugs associated with ischemic stroke: a review for clinicians. *Stroke*. 2021;52:e646-e659.
34. Home—electronic medicines compendium (emc) [Internet]. [cited 2022 Oct 19]. Available from: https://www.medicines.org.uk/emc
35. Meyler's Side Effects of Drugs—16th Edition [Internet]. [cited 2022 May 11]. Available from: https://www.elsevier.com/books/meylers-side-effects-of-drugs/aronson/978-0-444-53717-1
36. Nezu T, Hosomi N, Naito H, et al. Clinical characteristics and tumor markers in ischemic stroke patients with active cancer. *Intern Emerg Med*. 2022;17:735-741.
37. Yoo J, Nam HS, Kim YD, Lee HS, Heo JH. Short-term outcome of ischemic stroke patients with systemic malignancy. *Stroke*. 2019;50:507-511.
38. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 update to the 2018 guidelines for the Early Management of Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344-e418.
39. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I-LXII.
40. Navi BB, Iadecola C. Ischemic stroke in cancer patients: a review of an underappreciated pathology. *Ann Neurol*. 2018;83:873-883.

41. Gon Y, Okazaki S, Terasaki Y, et al. Characteristics of cryptogenic stroke in cancer patients. *Ann Clin Transl Neurol*. 2016;3:280-287.
42. Navi BB, Singer S, Merkler AE, et al. Cryptogenic subtype predicts reduced survival among cancer patients with ischemic stroke. *Stroke*. 2014;45:2292-2297.
43. Shalabi F, Sacagiu T, Honig A, et al. Does malignancy status affect outcomes in patients with large vessel occlusion stroke and cancer who underwent endovascular thrombectomy? *J Am Heart Assoc*. 2023;12:e029635.
44. Lau K-K, Wong Y-K, Teo K-C, et al. Stroke patients with a past history of cancer are at increased risk of recurrent stroke and cardiovascular mortality. *PLoS ONE*. 2014;9:e88283.
45. Gon Y, Sakaguchi M, Yamagami H, et al. Predictors of survival in patients with ischemic stroke and active cancer: a prospective, multicenter, observational study. *J Am Heart Assoc*. 2023;12:e029618.
46. Martinez-Majander N, Ntaios G, Liu YY, et al. Rivaroxaban versus aspirin for secondary prevention of ischaemic stroke in patients with cancer: a subgroup analysis of the NAVIGATE ESUS randomized trial. *Eur J Neurol*. 2020;27:841-848.
47. Park H, Kim J, Ha J, et al. Histological features of intracranial thrombi in stroke patients with cancer. *Ann Neurol*. 2019;86:143-149.
48. Dai H, Zhou H, Sun Y, et al. D-dimer as a potential clinical marker for predicting metastasis and progression in cancer. *Biomed Rep*. 2018;9:453-457.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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