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Mortality in acute ischemic stroke patients with new cancer diagnosed during the index hospitalization versus after discharge☆

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ABSTRACT

Background: Early diagnosis of previously unknown cancer (i.e., occult cancer) after an acute ischemic stroke (AIS) could result in faster initiation of cancer therapy and potentially improve clinical outcomes. Our study aimed to compare mortality rates between AIS patients with occult cancer diagnosed during the index stroke hospitalization versus those diagnosed after hospital discharge.

Methods: Among consecutive AIS patients treated at our stroke center from 2015 through 2020, we identified new cancer diagnoses made within the year after the AIS. We used multivariable Cox regression analyses to evaluate the association between the timing of occult cancer diagnosis (during the AIS hospitalization versus after discharge) and long-term survival.

Results: Of 3894 AIS patients with available long-term follow-up data, 59 (1.5 %) were diagnosed with a new cancer within one year after index stroke. Of these, 27 (46 %) were diagnosed during the index hospitalization and 32 (54 %) were diagnosed after discharge. During a median follow-up of 406 days (interquartile range, 89–1073), 70 % ($n = 19$) of patients whose cancer was diagnosed during hospitalization had died, compared to 63 % ($n = 20$) of patients whose cancer was diagnosed after discharge ($p = 0.58$). In our main multivariable model, there was no difference in long-term mortality between patient groups (adjusted hazard ratio, 1.16; 95 % confidence interval, 0.53–2.52; $p = 0.71$).

Conclusions: In this analysis, timing of a new cancer diagnosis after AIS did not seem to influence patients' long-term survival. Given the fairly small number of included patients with previously occult cancer, larger multi-center studies are needed to confirm our results.

☆ Mortality in Stroke Patients with Occult Cancer.

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Nonstandard abbreviations and acronyms

AIS	acute ischemic stroke
CRP	C-reactive protein
ESUS	embolic stroke of undetermined source
HDL	high-density lipoprotein
INR	international normalized ratio
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
NIHSS	National Institutes of Health Stroke Scale
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Introduction

Active cancer is a possible cause of acute ischemic stroke (AIS).[1] Approximately 5-10 % of all hospitalized AIS patients have active cancer, and this stroke subgroup is often referred to as "cancer-related stroke".[2,3] Cancer-related stroke tends to be more severe than AIS without cancer and is more likely to recur.[4] In some patients cancer and stroke may be causally linked through cancer-mediated hypercoagulability and complications of cancer treatments, while in other patients the association may be an epi-phenomenon due to shared risk factors.[1,5] Pathophysiological mechanisms implicated in cancer-mediated hypercoagulability include circulating cancer-derived microparticles, promotion of neutrophil extracellular trap formation, activation of platelets and the coagulation cascade, and endothelial dysfunction.[6–9]

AIS can serve as the presenting manifestation of undiagnosed cancer, herein referred to as "occult cancer".[10] According to a large, matched cohort study, in the year before cancer diagnosis, the risk of ischemic stroke is increased approximately 60 %.[11] The estimated 1-year cumulative incidence of occult cancer following AIS is around 1.4 %, with higher incidence rates (6.2 %) reported among patients with an undetermined stroke mechanism.[12] Half the time, these occult cancers remain undetected during the AIS hospitalization.[13] Rapid diagnosis of occult cancer in AIS patients could enable earlier initiation of cancer therapy which could translate into improved clinical outcomes.[14] However, at present, it is unknown whether an earlier diagnosis of occult cancer in a patient with AIS influences subsequent clinical outcomes, particularly survival. The present study aimed to compare mortality rates between AIS patients diagnosed with an incident cancer during the index AIS hospitalization versus those diagnosed after discharge.

Methods

Study cohort

Among consecutive patients admitted to our tertiary stroke center with AIS between January 1, 2015 and December 31, 2020 ($n = 5012$), we retrospectively identified patients with occult cancer at the time of hospital presentation. Occult cancer was defined as cancer newly diagnosed during the index AIS hospitalization or within 1 year after admission.[12,13] As cancers generally take years to develop, cancers diagnosed within 1 year of AIS were considered to be active at the time of the AIS. For this analysis, patients with previously known active cancer at the time of stroke and those with missing long-term follow-up data were excluded. Active cancer was defined according to the International Society of Thrombosis and Haemostasis criteria as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer not in complete remission.[15] Focal non-melanoma skin cancers were not considered active as they rarely spread or produce systemic effects.[16] Additionally, patients who received intravenous thrombolysis before their initial blood draw were excluded from analyses including laboratory parameters such as D-dimer and fibrinogen because the fibrinolytic effect of these drugs can influence coagulation parameters.[5,17,18]

We adhered to the STROBE guideline for cohort studies. This study was approved by the local ethics committee in accordance with Swiss law (Project ID: 2022-01560; Kantonale Ethikkommission Bern). As determined by the ethics committee, the requirement for informed consent was waived for this retrospective analysis. Study data are available upon reasonable request to the corresponding author and after approval by the ethics committee.

Measurements

Baseline and 90-day follow-up data were collected from the local stroke registry. Extracted data included age at admission, sex, pre-stroke functional independence (defined as a modified Rankin Scale [mRS] score ≤ 2), cerebrovascular risk factors (such as hypertension, diabetes mellitus, smoking, atrial fibrillation, presence of patent foramen ovale), stroke severity on admission determined by the National Institutes of Health stroke scale (NIHSS), baseline brain imaging (CT or MRI), presence of multi-territory infarctions on brain imaging, and acute stroke treatment with intravenous thrombolysis or endovascular thrombectomy. Stroke etiology at discharge was determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[19] Patients with undetermined stroke etiology after a completed standard workup were classified as embolic stroke of undetermined source (ESUS) per published criteria.[20]

The following hematological data at admission were collected: Leukocyte count, hemoglobin, platelet count, international normalized ratio (INR), fibrinogen, D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), and total and low-density lipoprotein (LDL) cholesterol.

The presence of known and occult active cancer was retrospectively determined by two neurologists (J.G. and M.B.) using all available electronic health record data. Collected cancer-related data included: date of cancer diagnosis, histological type (categorical variable as listed in **eFigure I**), primary site (categorical variable as listed in **eFigure II**), presence of local invasion or metastasis at the time of cancer diagnosis, presence of splenomegaly or gastrointestinal tract obstruction during the index AIS hospitalization, cancer treatment, and the date of first treatment. The date of cancer diagnosis was defined as the earliest available pathological report of a primary tumor or metastasis. In the absence of pathological confirmation, we identified suspected cancer based on radiological, cytological, and laboratory (tumor markers) findings, with cancer being documented as the most likely diagnosis according to the treating physician. Local invasion or metastasis at diagnosis was determined based on radiological reports or documented TNM classification if available. Local invasion was defined as the infiltration of adjacent organs (T3/T4) or the presence of affected locoregional lymph nodes (N+). In patients with hematological cancers, we did not determine local invasion or metastasis at the time of diagnosis, with the exception of solid lymphomas, where local invasion was determined through radiological findings.

Deceased patients were identified through the Swiss Population Registry, a nationwide dataset assessing the vital status of Swiss residents each month. The long-term follow-up time was defined as the time from the index AIS to the last update of the Swiss Population Registry for surviving patients and to the date of death for deceased patients.

Statistical analysis

Baseline characteristics were compared between patients with occult cancer and patients without active cancer to identify markers associated with occult cancer. Additionally, patients with occult cancer diagnosed during the index AIS hospitalization were compared to those diagnosed

after discharge. Continuous variables were reported using median and interquartile range (IQR) and categorical variables using frequency and percentages. Differences between groups were assessed with Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables.

Kaplan-Meier survival statistics and the log-rank test were used to compare long-term mortality rates between patients with occult cancer diagnosed during hospitalization versus after discharge. Multivariable Cox regression models investigated the association between the timing of occult cancer diagnosis (dichotomized as during hospitalization versus after discharge) and long-term mortality while adjusting for potential confounders. To minimize the risk of overfitting because of the fairly small number of deaths among patients with occult cancer, two different models were used for our adjusted analyses. The first (main) model was based on the "one-in-ten rule" proposed by Harrell et al, which recommends adding one covariate for every ten outcome events.[21,22] Consequently, this parsimonious model included standard demographics (age, sex) and a limited number of influential covariates that the authors believed would be most likely to affect patient survival: cancer histology, presence of local invasion or metastasis at the time of cancer diagnosis, and any administered cancer treatment. The second (exploratory) model was more comprehensive and included additional covariates (initial NIHSS, presence of multi-territory infarction, leukocyte count, hemoglobin, and D-dimer) that have been previously linked to survival in patients with cancer-related AIS.[6–9] The proportional hazard assumption was tested using Schoenfeld residuals. Variables with skewed distributions were logarithmically transformed. Statistical analyses were performed with STATA 17 (StataCorp LLC) and R (version 4.2.1). A p-value <0.05 defined statistical significance.

Results

Study population

Among 5012 AIS patients treated at our local comprehensive stroke center, we excluded patients with known active cancer at stroke onset (n = 236) and those with missing long-term follow-up data (n = 882) (Fig. 1). The main analytical cohort included 3894 patients (median age, 75 [IQR, 63–83] years, 42 % female). Occult cancer was identified in 1.5 % (n = 59/3894) of these patients. There were 308 patients (including 5 with occult cancer) who received intravenous thrombolysis before their initial blood test and were excluded from analyses including laboratory parameters.

Baseline characteristics

Compared to patients without active cancer, patients with occult cancer were more likely to have a history of smoking, ESUS, multi-territory infarctions, and absence of patent foramen ovale (**eTable I**). Patients with occult cancer presented with higher leukocyte counts; higher levels of INR, D-dimer, LDH, and CRP; and lower levels of total and LDL cholesterol. The diagnostic modalities used to identify patients' occult cancers are described in **eTable II**. Comparing patients with occult cancer diagnosed during AIS hospitalization versus after discharge, there were no differences in baseline clinical characteristics and laboratory parameters (Table 1). Initial NIHSS score did not differ between patients with occult cancer and those without active cancer, nor between patients with occult cancer diagnosed during the index hospitalization versus after discharge.

Cancer characteristics

In 46 % (n = 27) of patients with occult cancer, cancer was diagnosed during the index AIS hospitalization. The remaining 54 % (n = 32) of cancer diagnoses occurred after discharge. The median time between AIS and cancer diagnosis was 1 (IQR, 0-6) day in patients diagnosed during the hospitalization and 49 (IQR, 15-139) days in patients diagnosed after discharge. The most frequent cancer histologies were adenocarcinoma (n = 32, 54 %), lymphoma (n = 7, 12 %), and squamous cell carcinoma (n = 4, 7 %) (**eFigure I**). There was no difference between the two groups in the distribution of cancer histologies (p = 0.07). The most frequent primary sites were lung (n = 8, 30 %) and pancreas (n = 4, 15 %) for cancers diagnosed during the index hospitalization and lung (n = 7, 22 %) and colon (n = 4, 12 %) for cancers diagnosed after discharge.

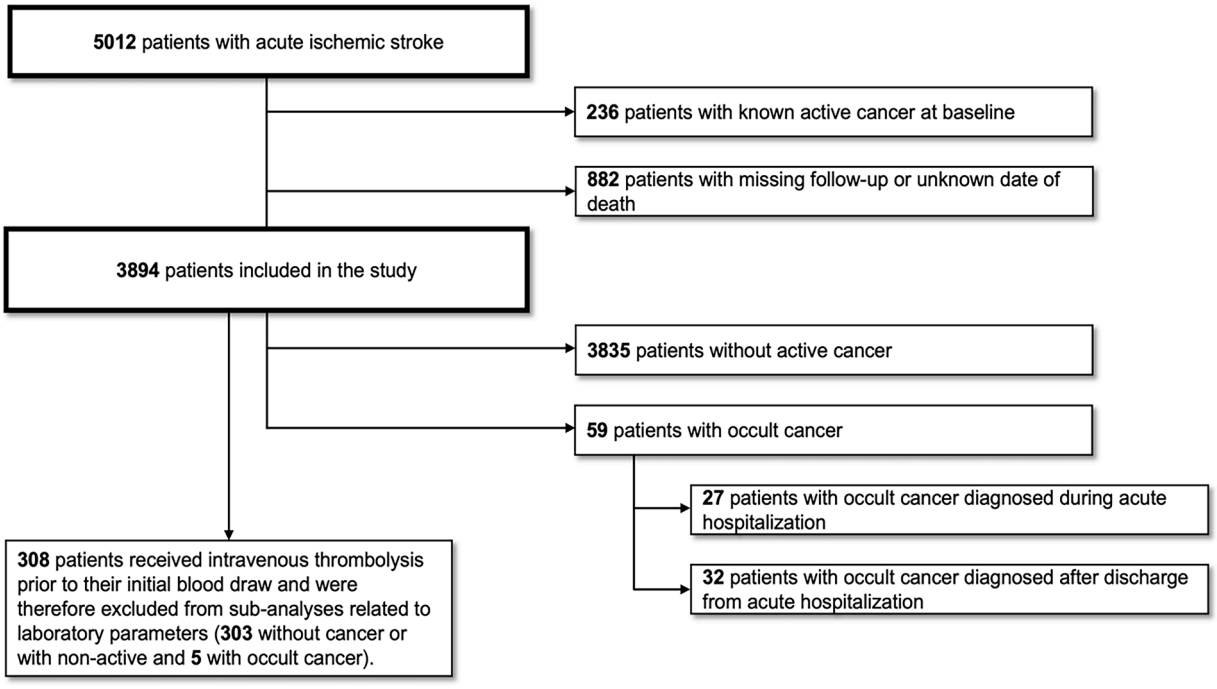

Fig. 1. Study flowchart.
Flow diagram describing how the final cohort was reached and relevant exclusions.

Table 1
Comparison of baseline characteristics and laboratory parameters between stroke patients with occult cancer diagnosed during hospitalization and after discharge.

	Occult cancer diagnosed during hospitalization, $n = 27/59$	Occult cancer diagnosed after discharge, $n = 32/59$	p-value
Baseline clinical characteristics			
Sex, female No./total No. (%)	13/27 (48)	14/32 (44)	0.8
Age at admission, median (IQR)	74 (67–83)	77 (71–81)	0.62
Prestroke mRS 0–2 No./ total No. (%)	16/16 (100)	15/17 (88)	0.48
Previous stroke No./total No. (%)	5/21 (24)	6/26 (23)	1
Hypertension No./total No. (%)	15/21 (71)	21/26 (81)	0.5
Diabetes No./total No. (%)	2/21 (10)	6/26 (23)	0.27
Hyperlipidemia No./total No. (%)	16/21 (76)	19/26 (73)	1
Smoking No./total No. (%)	7/20 (35)	11/25 (44)	0.76
Splenomegaly No./total No. (%)	1/27 (4)	0/32 (0)	0.46
Gastrointestinal tract obstruction No./total No. (%)	2/27 (7)	0/32 (0)	0.21
Patent foramen ovale No./ total No. (%)	2/14 (14)	1/16 (6)	0.39
NIHSS on admission, median (IQR)	6 (2–14)	3 (1–10)	0.18
First brain imaging type on admission No./total No. (%)			
Computed tomography	5/15 (33)	9/19 (47)	0.5
Magnetic resonance imaging	10/15 (67)	10/19 (53)	0.5
Multi-territory infarctions, No./total No. (%)	7/27 (26)	11/32 (34)	0.58
Stroke etiology (TOAST) No./total No. (%)			
Cardioembolism	3/27 (11)	10/32 (31)	0.21
Large-artery atherosclerosis	4/27 (15)	4/32 (13)	
Dissection	1/27 (4)	0/32 (0)	
Undetermined etiology	19/27 (70)	18/32 (56)	
Embolic stroke of undetermined source No./total No.	17/27 (63)	16/32 (50)	0.43
Intravenous thrombolysis No./total No.	3/21 (14)	7/27 (26)	0.48
Endovascular thrombectomy No./total No.	11/22 (52)	9/26 (35)	0.25
Study-specific parameters			
Follow-up time in days, median (IQR)	463 (55–960)	394.5 (257–1216)	0.35
Time from stroke to cancer diagnosis, median days (IQR)	1 (0–6)	49 (15–139)	**<0.001**
Adenocarcinoma, No./total No. (%)	11/27 (41)	21/32 (66)	0.07
Time from cancer diagnosis to start of cancer treatment, median days (IQR)	15 (3–48)	29 (7–57)	0.39
Local invasion or metastasis at diagnosis No./total No. (%)	15/23 (65)	20/32 (63)	1
Any cancer treatment No./ total No. (%)	10/27 (37)	22/32 (69)	**0.02**
Long-term mortality No./ total No. (%)	18/27 (70)	20/32 (63)	0.58
Laboratory values, median (IQR)			
Leukocyte count [G/L]	9.8 (7.1–11.8)	9.2 (7.6–12.1)	0.97
Hemoglobin [g/L]	128 (120–146)	136 (123–144)	0.43
Platelet count [G/L]	218 (161–261)	219 (170–262)	0.98
INR	1.09 (1.00–1.31)	1.05 (0.98–1.10)	0.16
Fibrinogen [g/L]	2.6 (2.0–3.6)	3.1 (2.7–3.8)	0.21
D-dimer [μg/L]	1842 (645–5312)	1335 (436–3117)	0.43
Lactate dehydrogenase [U/ L]	460 (344–694)	424 (372–546)	0.7
Total cholesterol [mmol/L]	4.2 (3.5–4.8)	3.7 (3.2–4.8)	0.44
LDL-cholesterol [mmol/L]	2.14 (1.48–2.81)	2.09 (1.24–2.75)	0.5
C-reactive protein [mg/L]	7 (3–26)	3 (1–12)	0.14

Abbreviations: INR, international normalized ratio; IQR, interquartile range; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Overall, there was no difference between the two groups in the distribution of primary cancer sites ($p = 0.11$, **eFigure II**). For all patients with occult cancer, local invasion or metastasis at the time of cancer diagnosis was present in 56 % ($n = 15$) of patients diagnosed during the index hospitalization and in 63 % ($n = 20$) of patients diagnosed after discharge ($p = 1.00$). However, lung cancers in particular were less often metastatic when diagnosed during the index hospitalization ($n = 1/8$, 13 %) versus after discharge ($n = 6/7$, 86 %). Rates of administered cancer treatments were higher in patients diagnosed after discharge compared to those diagnosed during hospitalization ($p = 0.02$).

Mortality analyses

In patients with occult cancer, the median follow-up time was 406 (IQR, 89–1073) days, and there was no difference between patients diagnosed during hospitalization versus after discharge ($p = 0.35$). Long-term mortality rates were 70 % ($n = 18$) for patients with occult cancer diagnosed during the AIS hospitalization versus 63 % ($n = 20$) for those diagnosed after discharge. In Kaplan-Meier analysis, cumulative

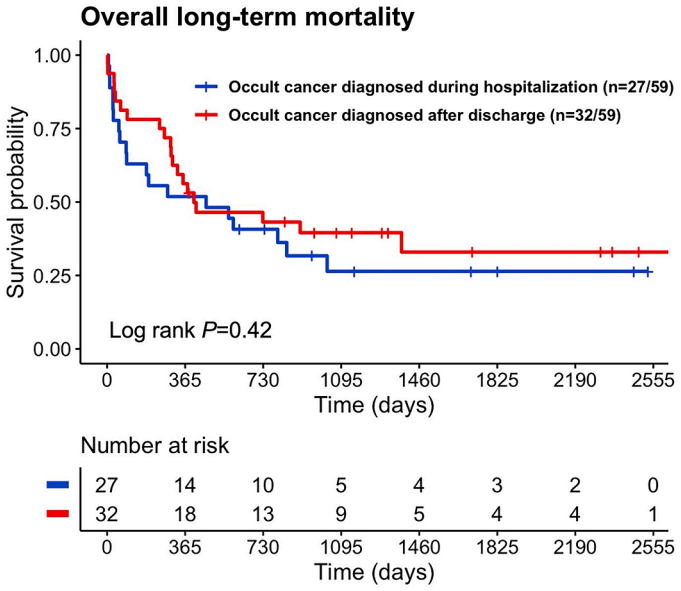

Fig. 2. Long-term survival curves for AIS patients with occult cancer diagnosed during hospitalization and after discharge.
No difference in overall long-term mortality was found between occult cancer diagnosed during hospitalization (blue) and after discharge (red) when compared using the log-rank test ($p = 0.42$). Abbreviations: AIS = acute ischemic stroke.

death rates did not differ between groups (log-rank $p = 0.42$, Fig. 2).

In the multivariable Cox regression models, the proportional hazards assumption was met for each exposure variable and for the global tests. In the first (main) model, female sex and the presence of local invasion or metastasis at the time of cancer diagnosis were associated with long-term mortality, but the timing of occult cancer diagnosis was not (adjusted hazard ratio, 1.16; 95 % confidence interval, 0.53-2.52; $p = 0.71$; Fig. 3). In the second (exploratory) model, an occult cancer diagnosis after discharge, as compared to a diagnosis made during the index hospitalization, was independently associated with long-term mortality (adjusted hazard ratio, 3.25; 95 % confidence interval, 1.20-8.81; $p = 0.02$; **eFigure III**). Other factors independently associated with long-term mortality were the presence of local invasion or metastasis at the time of cancer diagnosis, cancer histology, and NIHSS.

Discussion

In a large cohort study of patients hospitalized with AIS at a comprehensive stroke center in Switzerland, there was no clear difference in survival among the subgroup with occult cancer who were diagnosed during the acute hospitalization versus after discharge. However, in an exploratory Cox regression analysis, which accounted for a larger number of influential factors, an earlier cancer diagnosis was associated with prolonged survival, although confidence intervals were broad and therefore type 1 error is possible, so these results should be interpreted with caution. The second major finding from this study is that there were no significant differences in the primary site or histology of cancer based on the timing of an occult cancer diagnosis.

Among patients with AIS, comorbid cancer is associated with worse outcomes, including a substantially increased risk of death.[23,24] Cancer-mediated hypercoagulability is purported to be a leading cause of AIS in patients with both known and occult cancer.[23] The risk of AIS with cancer is not uniform and is highest with lung and pancreatic primary sites and advanced cancer stages.[25] It is reasonable to assume that a faster diagnosis of cancer would translate into less tumor dissemination and perhaps a better response to treatment. Studies implementing cancer screening during AIS hospitalization have reported higher rates of occult cancer detection than studies without cancer screening.[12] Nevertheless, the role of routine cancer screening in patients with AIS remains controversial, and in our primary analysis we did not find a survival benefit when occult cancers were diagnosed during the index AIS hospitalization as opposed to later.[12] As international guidelines do not provide concrete recommendations regarding cancer screening among patients with AIS, published risk stratification scores could facilitate clinical practice.[5,13,14] Broad-based imaging techniques, such as a body CT or ^{18}F-fluorodeoxyglucose positron emission tomography, are commonly used in clinical practice for cancer investigations and could serve as an additional screening tool in AIS patients considered high-risk to harbor cancer after the initial diagnostic evaluation.[26,27]

The most frequent cancer primary sites identified in our study were lung, pancreas, and colorectal cancers, consistent with previous reports.[28,29] Additionally, primary cancer sites were similarly distributed between patients diagnosed during the index hospitalization and those diagnosed after discharge. However, lung cancer, which accounted for a quarter of all cases, may exhibit a different pattern, as most cases detected after hospital discharge had spread beyond the lungs whereas those diagnosed during the index hospitalization were mostly locally invasive or confined to the lungs. This discrepancy could have resulted from the incidental detection of apical pulmonary lesions seen on vessel imaging studies of the head and neck, as previously reported.[30]

Limitations

This study has several limitations. Firstly, the retrospective and monocentric design may have led to missed occult cancer diagnoses, as well as some missing data on cancer stage and treatments, which could have introduced bias and led to type 2 error for our multivariable analyses. Follow-up studies with less missing data for these influential variables are needed to validate our results. Secondly, the sample size of 59 patients with AIS and occult cancer was fairly small, which limited statistical power, leading to imprecise risk estimates with wide confidence intervals. This includes the potential overfitting of our secondary adjusted analyses. However, our database on cancer-related stroke is one of the largest available, and to our knowledge this is the first dedicated study assessing the impact of the timing of occult cancer diagnoses after AIS on patient survival. Thirdly, not all occult cancer diagnoses had pathological confirmation and we included suspected cancer diagnoses based on radiological, cytological, and laboratory findings. This could have led to an overestimation of the number of occult cancer cases. However, we prioritized a more inclusive approach, which we felt was justified based on the retrospective nature of our study. Finally, the full extent of cancer investigations during and after the index hospitalization was not evaluated, preventing us from

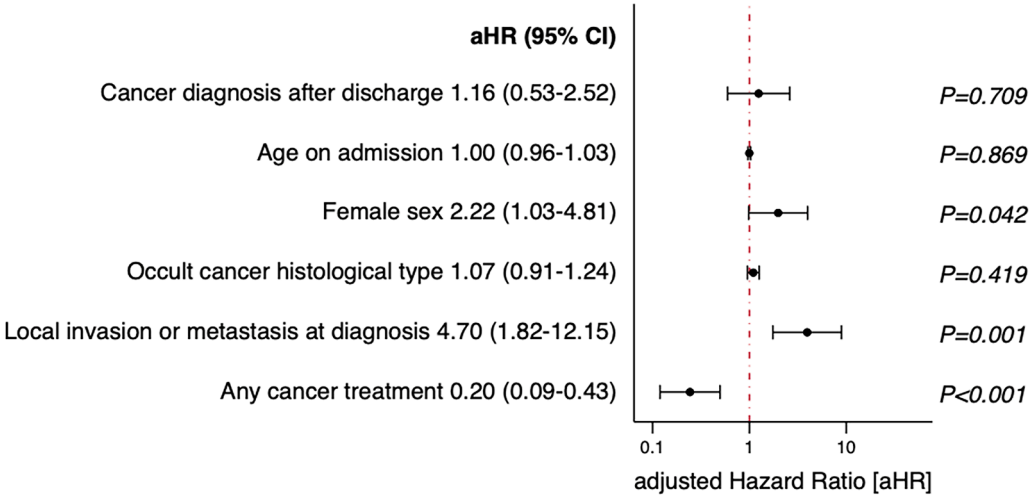

Fig. 3. Multivariable Cox analysis evaluating the association between the timing of occult cancer diagnosis (during hospitalization versus after discharge) and long-term mortality.
The primary adjusted analysis model evaluating a restricted number of covariates due to the small number of patients and outcomes in the study. Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; NIHSS = National Institutes of Health Stroke Scale.

assessing the diagnostic utility of individual tests and their impact on survival.

Conclusion

Our study showed no apparent difference in long-term mortality between AIS patients diagnosed with new cancer during acute hospitalization versus after discharge. However, some of our results suggest the possibility of a difference between groups, and therefore further studies including more patients with occult cancer are needed. Additionally, to optimize secondary stroke prevention and cancer management, clinicians should maintain a low threshold to screen for cancer in patients with AIS who are most likely to harbor an occult malignancy, specifically those with cryptogenic mechanisms, multi-territory brain infarctions, and unexplained extreme elevations in D-dimer and other coagulation parameters.[5,26]

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Ethical approval

The ethics committee approved the study's conduct in accordance with Swiss law (reference ID: 2021-01031, Kantonale Ethikkomission Bern).

Informed consent

According to the ethics committee's decision, no informed consent was required for the inclusion of patients in the study.

Guarantor

Simon Jung and Morin Beyeler.

CRediT authorship contribution statement

Jayan Göcmen: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fabienne Steinauer:** Writing – review & editing, Investigation, Data curation. **Moritz Kielkopf:** Writing – review & editing, Validation. **Mattia Branca:** Writing – review & editing, Validation, Formal analysis. **Christoph C. Kurmann:** Writing – review & editing, Validation. **Adnan Mujanovic:** Writing – review & editing, Validation. **Leander Clénin:** Writing – review & editing, Validation. **Norbert Silimon:** Writing – review & editing, Validation. **Anna Boronylo:** Writing – review & editing, Validation. **Adrian Scutelnic:** Writing – review & editing, Validation. **Thomas Meinel:** Writing – review & editing, Validation. **Johannes Kaesmacher:** Writing – review & editing, Validation. **Philipp Bücke:** Writing – review & editing, Validation. **David Seiffge:** Writing – review & editing, Validation. **Gianluca Costamagna:** Writing – review & editing, Validation. **Patrik Michel:** Writing – review & editing, Validation. **Urs Fischer:** Writing – review & editing, Validation. **Marcel Arnold:** Writing – review & editing, Validation. **Babak B. Navi:** Writing – review & editing, Validation. **Thomas Pabst:** Writing – review & editing, Validation. **Martin D. Berger:** Writing – review & editing, Validation. **Simon Jung:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Morin Beyeler:** Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Morin Beyeler reports research support from the "Kurt und Senta Hermann-Stiftung", the Department of Neurology, Inselspital, Bern University Hospital and the University of Bern, Switzerland.

None of the other authors report any conflicts of interest in relation with this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.107899.

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