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# USE OF BIOMARKERS IN ISCHEMIC STROKES: THE PARTICULAR CASE OF CANCER-RELATED STROKES

PhD thesis submitted by

**Morin Beyeler MD**

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*Thesis Advisor*
Prof. Dr. med. Simon Jung
Department of Neurology
Faculty of Medicine, University of Bern

*Co-Thesis Advisor*
Prof. Dr. med. Martin Berger
Department of Medical Oncology
Faculty of Medicine, University of Bern

*Co-referee*
Prof. Dr. med. Thomas Pabst
Department of Medical Oncology
Faculty of Medicine, University of Bern

*International Fellowship Supervisor*
Prof. Babak Navi, MD
Department of Neurology,
Weill Cornell Medicine, New York City, USA

Accepted jointly by the Faculty of Medicine and Faculty of Human Sciences with the Latin honors “Insigni cum laude”.

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Prof. Dr. Virginia Richter, Rector University of Bern
Prof Dr. Claudio L.A. Bassetti, Dean Faculty of Medicine
Prof. Dr. Elmar Michael Anhalt, Dean Faculty of Human Sciences

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# Abstract

**Background:** Around 5–10% of all patients with acute ischemic stroke (AIS) have underlying active cancer at the time of their stroke and constitute the group of "cancer-related strokes". Cancer patients are known to have a higher risk of first and recurrent AIS, more severe stroke, and increased mortality after AIS. Although cancer-related strokes are thought to be caused by paraneoplastic coagulopathy, the complex relationship between cancer and AIS remains difficult to understand due to the multitude of cancer types and differing stages of cancer progression at the time of AIS.
Consequently, it is essential to improve our knowledge of cancer-related strokes and the management of the affected patients. The general aim of this PhD thesis was to elucidate the description of the incidence, characteristics and outcomes of cancer-related strokes.

**Methods:** The analyses that make up this PhD thesis are grouped into three subchapters corresponding to its three specific aims:
The first was to better understand the characteristics of known biomarkers for cancer-related strokes and to identify new and, if possible, specific biomarkers of cancer-related strokes. Such biomarkers are essential for assessing the severity of paraneoplastic coagulation, identifying patients at risk of underlying undetected cancer at the time of AIS (occult cancer) and assessing the prognosis of AIS patients with underlying active cancer.
The second aim was the investigation of AIS due to occult cancer. By proposing a clinical score to predict the presence of underlying occult cancer and investigating the outcomes for AIS patients with occult cancer, we sought to support the future implementation of a cancer-screening procedure in high-risk AIS patients.
The third aim was to investigate factors influencing the outcomes of cancer-related strokes. In addition to assessing the influence of biomarkers associated with cancer-related strokes on long-term outcomes after AIS, we investigated which type of antithrombotic drug was associated with the best outcomes in patients with cancer-related stroke.

To meet the aims of this PhD thesis, we created the Bernese Malignancy-in-Stroke (BMS) Database, which included cancer-specific data from all consecutive AIS patients treated between 2015 and 2020 at the Inselspital, University Hospital of Bern, Switzerland (N=5012). In parallel, we created the Bernese Transient Ischemic Attack (TIA) Database, which included data on all consecutive TIA patients treated at the Inselspital between 2015 and 2020 (N=1436). We used TIA patients without persisting brain damage as a comparison group in some of the studies presented in this thesis.

**Results:** In this PhD thesis, we demonstrated that common cancer-associated biomarkers in AIS patients were also present in TIA patients with cancer. Compared to TIA patients without cancer, those with cancer were more likely to have a history of smoking (adjusted odds ratio [aOR] 2.77, 95% confidence interval [CI] 1.34–5.7), elevated D-dimer (aOR 1.77, 95% CI 1.26–2.49), elevated lactate dehydrogenase (aOR 1.003, 95% CI 1.00–1.005), lower hemoglobin (aOR 1.02, 95% CI 1.00–1.04), and lower leukocyte count (aOR 1.20, 95% CI 1.04–1.38).
In AIS patients (independently of the presence of cancer), we demonstrated a time-dependent fluctuation in D-dimer levels. An early increase in D-dimer levels occurred within the first 6 hours after symptom onset (standardized beta coefficient [β] 0.728, 95% CI 0.324–1.121). Following this initial increase, the levels decreased (β −13.022, 95% CI −20.401 to −5.643) and a second increase was seen after 35 hours from symptom onset (β 11.750, 95% CI 4.71–18.791). No time-dependent fluctuation in D-dimer levels was observed in the control group of patients with TIA.
In our study on the identification of new biomarkers for cancer-related strokes, we demonstrated an association between active cancer and the susceptibility vessel sign (SVS), a non-invasive, in situ representation of an occlusive thrombus, reflecting its microscopic composition. The absence of the SVS was associated with the presence of cancer in AIS patients (aOR 3.14, 95% CI 1.45–6.80). In another study, we demonstrated an association between the absence of a right-to-left cardiac shunt (encompassing patent foramen ovale and atrial septal defect) and active cancer (aOR 2.29, 95% CI 1.14–

4.58). We were unable to demonstrate any association between increased left atrial volume index (≥35 mL/m$^2$ on echocardiography), representing atrial cardiopathy, and the presence of cancer in patients with AIS (aOR 0.91, 95% CI 0.60–1.37).
Based on our studies on occult cancers, we proposed the OCCULT-5 Score, which comprises five variables: age ≥ 77 years, embolic stroke of undetermined source, multi-territorial brain infarcts, D-dimer levels ≥ 820 µg/L, and female sex. A score of ≥ 3 predicted an underlying occult cancer in AIS patients, with a sensitivity of 64% and a specificity of 73%. Outcomes in patients with new cancer diagnosed immediately after the index AIS (during hospitalization) were no better than those with a cancer diagnosis obtained after discharge and within one year after the index AIS. In particular, there was no difference in long-term mortality between patient groups (adjusted hazard ratio [aHR] 1.16, 95% CI 0.53–2.52).
Regarding factors influencing outcomes, in AIS patients treated with mechanical thrombectomy, we demonstrated an association between the absence of the SVS and long-term mortality (aHR 2.11, 95% CI 1.35–3.29) and poor functional outcome in the long term (aOR 2.90, 95% CI 1.29–6.55). Interaction analyses did not reveal any substantial influence of the presence of active cancer on these associations (p for interaction=0.79 and 0.71, respectively).
Finally, there was no difference in outcomes between the two types of antithrombotic drug used for secondary prevention in AIS patients with active cancer. Anticoagulant and antiplatelet therapy were associated with similar risks of 1-year mortality (aHR 0.76, 95% CI 0.36–1.63) and long-term recurrent AIS (aHR 0.49, 95% CI 0.08–2.83).

**Discussion:** The projects comprising this PhD thesis covered many aspects of the "cancer-related stroke" field. The absence of the SVS, reflecting the predominance of platelets and fibrin in the microscopic composition of the occluding thrombus, was associated with cancer-related strokes (and also independently associated with platelet- and fibrin-rich thrombi). Since the presence of the SVS, by contrast, was mainly associated with erythrocyte-rich thrombi and cardioembolic AIS, the assessment of SVS status (giving us a direct insight into the thrombus composition in situ) is helpful to assess the most likely underlying stroke etiology. An association between active cancer and arterial causes of AIS is presumed due to the negative association with right-to-left cardiac shunts (as a surrogate marker for paradoxical embolism). Furthermore, our studies showed a trend towards non-cardioembolic causes of AIS in patients with active cancer due to the association with absence of the SVS and the lack of association with atrial cardiopathy. As only 1.4% of AIS patients are diagnosed with a new cancer in the year following an AIS (and up to 6.2% following cryptogenic strokes), it is important to identify patients at risk of occult cancer to speed up the time to cancer diagnosis and potentially positively influence patient outcomes. To our knowledge, our OCCULT-5 Score is the only model that provides a clinical score that can be easily used at the bedside to evaluate the probability of underlying occult cancer in AIS patients. Despite the large size of our BMS, only 59 patients with occult cancer were included in the study, which failed to demonstrate a difference in outcomes between patients diagnosed with a new cancer during hospitalization versus after discharge. This underscores the need for multicenter studies that include larger numbers of AIS patients with active cancer, and particularly occult cancers, to address unanswered research questions.
Finally, regarding secondary prevention, there are no conclusive guideline-based recommendations for the optimal antithrombotic strategy for patients with cancer-related strokes. Although our study (not published yet) on whether anticoagulants or antiplatelet drugs offered better secondary prevention has the advantage of including only patients with active cancer, it failed to demonstrate an advantage for either medication emphasizing the need for randomized clinical trials on this subject in the future.

**Outlook:** The establishment of a multicenter registry of cancer-related strokes with detailed information on individual cancers will enable investigators to perform studies analyzing the different types of cancer on a case-by-case basis, and potentially to propose individualized treatments. In addition, prospective studies are needed, both to assess the risk of occult cancer in AIS patients and to evaluate new biomarkers for cancer-related strokes.

# Chapter 1: Introduction

Approximately 40% of the population worldwide will face cancer in their lifetime, while 25% will suffer an acute ischemic stroke (AIS).[1] According to the International Society on Thrombosis and Haemostasis, active cancer is defined as any diagnosis, treatment, or known recurrence or metastasis of any malignant cancer within the past 6 months.[2] Around 5–10% of all AIS patients have underlying active cancer at the time of stroke and constitute the group of "cancer-related strokes".[1,3]

Cancer-related strokes are thought to be caused by paraneoplastic coagulopathy, which is induced by the expression of various procoagulant factors through cancer cells and an immune-mediated response.[4,5] The complex relationship between cancer and AIS remains difficult to understand due to the multitude of existing cancer types and the differing stages of cancer progression in individual patients.[4] Consequently, it is essential to improve our knowledge of cancer-related strokes and the management of affected patients, as they are known to have a higher risk of first and recurrent AIS, increased stroke severity and increased mortality after AIS.[4]

For this purpose, research should focus on investigating the pathophysiological mechanisms of arterial paraneoplastic coagulopathy, and also on identifying specific risk factors and biomarkers for cancer-related strokes.[6] Furthermore, as AIS can be the first manifestation of a cancer, a special effort must be made to diagnose underlying, previously undetected cancer (so-called occult cancer) at the time of AIS.[7]

Finally, as the antithrombotic treatment of choice for cancer-related strokes is not yet clear and cancer-related strokes are rarely included in stroke guidelines, it is important to tailor secondary prevention strategies for patients who experience cancer-related strokes.[8]

# Aims of PhD thesis

The general aim of this PhD thesis was to elucidate the description of the incidence, characteristics and outcomes of cancer-related strokes.

To meet the aim of the PhD thesis, we created the Bernese Malignancy-in-Stroke (BMS) database. This retrospective database is the extension of the local part of the Swiss Stroke Registry, which includes all consecutive AIS patients treated between 2015 and 2020 at the Inselspital, University Hospital of Bern, Switzerland.
In parallel, together with Philipp Bücke MD from the Department of Neurology, Inselspital, we created the Bernese Transient Ischemic Attack (TIA) database, which retrospectively included all consecutive TIA patients treated at the Inselspital between 2015 and 2020. We used TIA patients without persisting brain damage as a comparison group in some of the studies presented in this thesis.
We collected both cancer-specific and project-specific variables for the 5012 AIS patients and the 1436 TIA patients included in the two databases with the assistance of a group of medical students (Jayan Göcmen, Fabienne Steinauer, Erich Rea, Pasquale Castigliego, Selina Venzin, Marc Fluri, Carlo Felder and Victor Ziegler).

**Biomarkers in cancer-related strokes**

The first specific aim of this PhD thesis was to better understand the characteristics of known biomarkers for cancer-related strokes and to identify new and, if possible, specific biomarkers of cancer-related strokes.

D-dimer is a fibrin degradation product and a non-specific marker of blood clot formation.[9] An elevated D-dimer level is the most common pathological laboratory finding in cancer-related strokes and reflects the paraneoplastic coagulopathy.[10–16] As D-dimers are not specific for cancer-related strokes, we attempted to identify new biomarkers and assessed their specificity/sensitivity for this pathology. We assessed whether the addition of newly identified biomarkers to already known biomarkers increased the probability of predicting the presence of cancer-related strokes (AIS + active cancer).[1–3]

We also aimed to identify factors that influence D-dimer levels, as they may affect clinical decision-making regarding screening for occult cancer or reflect the efficacy of the antithrombotic therapy used in cancer-related strokes.[17,18]

**The special case of strokes due to occult cancer**

Occult cancer is generally defined as any new cancer diagnosed within the year following the AIS.[7] It is found in 1.4% of all AIS patients and in up to 6.27% of patients with embolic stroke of undetermined source.[7] Only 50% of the occult cancers are diagnosed during acute hospitalization.[19] The other 50% are diagnosed some time after discharge.

The second specific aim of the PhD thesis was the investigation of AIS due to occult cancer and this was addressed in two studies:
- The development of a clinical score to predict occult cancer in AIS patients.
- The assessment of long-term outcomes of AIS due to occult cancer.

We hypothesized that late diagnosis of cancer after AIS would be associated with poorer outcome due to delayed potential treatment of the cancer. Demonstrating such a difference would support the need for studies evaluating the efficacy of cancer screening in AIS patients at high risk. To identify such patients during acute hospitalization, we developed the OCCULT-5 score, a simple score that can be used in clinical practice.[19]

**Outcomes in cancer-related strokes**

The third aim of the PhD thesis was to identify factors influencing outcomes of cancer-related strokes.

As mentioned in the introduction, outcomes of cancer-related strokes are poorer than those of other AIS.[4] We first investigated the influence of biomarkers associated with cancer-related strokes on long-term outcomes after AIS.[20]
Secondly, there is currently no clear evidence nor any recommendations on the optimal antithrombotic strategy (anticoagulation versus antiplatelet drug) for treating cancer-related strokes.[8] For this reason, we investigated which antithrombotic drug was associated with the better outcomes in patients with cancer-related strokes who were included in our BMS database.

# Chapter 2: Results

# Chapter 2.1: Biomarkers in cancer-related strokes

## Confirmation of known cancer-related biomarkers in patients with transient ischemic attacks

Title of the manuscript:

Transient ischemic attacks in patients with active and occult cancer

Contributions of the PhD candidate:

- Conceptualization
- Data curation
- Formal analysis
- Visualization
- Writing – original draft

Results summary:

This retrospective monocentric study used information from our Bernese TIA database. We included TIA patients treated at our stroke center between 2015 and 2019. We aimed to compare the two sets of patients to find out whether the cancer-associated biomarkers already identified in AIS patients were also present in the TIA patients.

After identifying TIA patients with underlying active cancer, we compared the presence/level of cancer-associated biomarkers between TIA patients with and without active cancer. We demonstrated that TIA patients with cancer were more likely to have a history of smoking (adjusted odds ratio [aOR] 2.77, 95% confidence interval [CI] 1.34–5.7), elevated D-dimer (aOR 1.77, 95% CI 1.26–2.49), elevated lactate dehydrogenase (aOR 1.003, 95% CI 1.00–1.005), lower hemoglobin (aOR 1.02, 95% CI 1.00–1.04), and lower leukocyte count (aOR 1.20, 95% CI 1.04–1.38). This study demonstrated that the cancer-associated biomarkers already known in AIS patients were also present in TIA patients.

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EDITED BY
Giovanni Merlino,
Udine University Hospital, Italy

REVIEWED BY
Shihong Zhang,
West China Hospital, Sichuan University, China
Kenichi Todo,
Osaka University, Japan

*CORRESPONDENCE
Morin Beyeler
✉ morin.beyeler@insel.ch
Philipp Bücke
✉ philipp.buecke@insel.ch

†These authors have contributed equally to this work

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# Transient ischemic attacks in patients with active and occult cancer

Morin Beyeler[1,2]*, Pasquale Castigliego[1], Joel Baumann[1], Victor Ziegler[1], Moritz Kielkopf[1], Madlaine Mueller[1], Stefan A. Bauer-Gambelli[1], Adnan Mujanovic[3], Thomas Raphael Meinel[1], Thomas Horvath[1], Urs Fischer[1,4], Johannes Kaesmacher[3], Mirjam R. Heldner[1], David Seiffge[1], Marcel Arnold[1], Thomas Pabst[5], Martin D. Berger[5], Babak B. Navi[6,7], Simon Jung[1†] and Philipp Bücke[1*†]

[1]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [2]Graduate School for Health Sciences, University of Bern, Bern, Switzerland, [3]Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [4]Neurology Department, University Hospital of Basel, University of Basel, Basel, Switzerland, [5]Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland, [6]Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, NY, United States, [7]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

**Background and aim:** Paraneoplastic coagulopathy can present as stroke and is associated with specific biomarker changes. Identifying paraneoplastic coagulopathy can help guide secondary prevention in stroke patients, and early cancer detection might improve outcomes. However, unlike ischemic stroke, it remains unclear whether paraneoplastic coagulopathy is associated with transient ischemic attacks (TIA). This study assessed the presence of cancer-related biomarkers in TIA patients and evaluated long-term mortality rates in patients with and without active cancer.

**Methods:** Active cancer was retrospectively identified in consecutive TIA patients treated at a comprehensive stroke center between 2015 and 2019. An association between the presence of cancer and cancer-related biomarkers was assessed using multivariable logistic regression. Long-term mortality after TIA was analyzed using multivariable Cox regression.

**Results:** Among 1436 TIA patients, 72 had active cancer (5%), of which 17 were occult (1.2%). Cancer-related TIA was associated with male gender (adjusted odds ratio [aOR] 2.29, 95% CI 1.12–4.68), history of smoking (aOR 2.77, 95% CI 1.34–5.7), elevated D-dimer (aOR 1.77, 95% CI 1.26–2.49), lactate dehydrogenase (aOR 1.003, 95% CI 1.00–1.005), lower leukocyte count (aOR 1.20, 95% CI 1.04–1.38), and lower hemoglobin (aOR 1.02, 95% CI 1.00–1.04). Long-term mortality was associated with both active cancer (adjusted hazard ratios [aHR] 2.47, 95% CI 1.58–3.88) and occult cancer (aHR 3.08, 95% CI 1.30–7.32).

**Conclusion:** Cancer-related TIA is not uncommon. Biomarkers known to be associated with cancer-related stroke also seem to be present in TIA patients. Early identification would enable targeted treatment strategies and could improve outcomes in this patient population.

KEYWORDS

**transient ischemic attack, malignancy, biomarkers, cerebro-vascular disorders, D-dimer**

# Introduction

Interest in cancer-related ischemic stroke has grown in recent years (1, 2). Pathophysiologically, it is predominantly attributed to paraneoplastic coagulopathy, which is defined as the expression of pro-coagulant factors generated by active cancer (2). The following pathways have been implicated: tissue factor, inflammatory cytokines, fibrinolysis inhibitors, extracellular vesicles, and extracellular neutrophil traps (2). In addition to intravascular coagulopathy, other factors such as paradox embolism, non-bacterial endocarditis as well as an increase in the presence of traditional stroke risk factors also seem to contribute (1). Recent studies suggested several blood and imaging biomarkers to be associated with underlying cancer in stroke patients: elevated levels of D-dimer, fibrinogen, C-reactive protein (CRP), and lactate dehydrogenase (LDH); low hemoglobin levels; and multi-territory ischemic infarction on brain imaging (3–5). The optimal stroke secondary prevention in cancer-related stroke is controversial. Some observational studies suggest that patients with cancer-related stroke may benefit from early anticoagulation (direct oral anticoagulants or low molecular weight heparin), but major guidelines advocate for randomized trials of anticoagulant vs. antiplatelet therapy (1, 6–8). However, it remains unclear whether the abovementioned paraneoplastic mechanisms and biomarkers are also associated with the occurrence of transient ischemic attack (TIA). Clinically speaking, there is little rationale to distinguish between TIA and ischemic stroke patients in terms of etiology, diagnostic evaluation, and secondary prevention (6). However, the identification of an underlying paraneoplastic coagulopathy in TIA could help guide secondary prevention in this population. TIA-like ischemic stroke may be the first manifestation of an unknown cancer, termed "occult cancer." (3, 9). As underlying (known or occult) cancer is known to be associated with an increased rate of stroke recurrence, stroke severity, morbidity, and mortality, earlier detection of occult cancer would allow for more rapid cancer treatment, which could improve patient outcomes (9). In this study, we aimed to assess the presence of cancer-related biomarkers in TIA patients with underlying cancer and to evaluate the long-term mortality as compared to TIA patients without active cancer.

# Methods

## Study cohort

Consecutive patients evaluated for TIA at our stroke center between 1 January 2015 and 31 December 2019 were retrospectively assessed for eligibility. All patients with a reliable diagnosis of TIA (as defined below) were included in this analysis. Patients with recurrent TIA after the index event were considered only once (index event). The present study adheres to the STROBE checklist for cohort studies, which was used to report the present study (see Supplementary material).

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

## Standard protocol approvals, registrations, and patient consents

The local ethics committee approved the study in accordance with Swiss law (Project ID: 2022-01560; Kantonale Ethikkommission Bern). According to the ethics committee's decision, no written consent was required from the patients for inclusion in this retrospective study. Study data are available upon reasonable request to the corresponding authors and after clearance by the local ethics committee.

## Definition of transient ischemic attack

In order to reliably identify patients with TIA, we classified patients according to the definition used in the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT) as well as the National Institute of Neurological Disorders and Stroke (NINDS) criteria (10, 11). The final diagnosis of TIA was considered reliable when (1) neurological deficits were reversible within 24 h (time-based definition), (2) no signs of ischemia were present on acute brain imaging (in case of MRI: DWI [diffusion-weighted imaging] or perfusion deficit that might explain the focal neurological deficit leading to hospitalization; in case of CT: hypodensity in non-contrast CT or perfusion deficit; tissue-based definition), (3) clinical signs were consistent with a secure diagnosis of TIA (excluding isolated dizziness, double vision; sensory disturbances only affecting parts of a limb or the face).

## Definition of active cancer and occult cancer

Active cancer comprised the following two subgroups: known active cancer at the time of TIA or cancer diagnosed within 1 year after TIA and not known at the time of the initial TIA assessment (unknown cancer, named "occult cancer"). Known cancer was considered active when being newly diagnosed, recurrent, or treated within 6 months before the index TIA, or in case of metastatic spread (according to information obtained from our clinic information system) (12, 13). The limit of 12 months after TIA for the identification of occult cancer at the time of TIA was based on previous evidence (3, 14, 15). Occult cancer cases were either retrospectively identified in our clinic information system or documented in follow-up consultations. Focal non-melanoma skin cancers, such as basal cell carcinoma and squamous cell carcinoma, were not considered active cancers due to their tendency to remain local (16).

## Data collection

Five neurologists (MB, PC, JB, VZ, and PB) extracted the data analyzed in this study from the local emergency department information system (for out-patient treatment) and from the local stroke registry for hospitalized TIA patients (Swiss Stroke

Registry). Baseline data included age at admission, gender, pre-stroke functional independence (defined as a modified Rankin scale [mRS] ≤2), cerebrovascular risk factors (such as hypertension, diabetes mellitus type II, hyperlipidemia, and history of smoking), National Institutes of Health Stroke Scale (NIHSS) on admission, presence of previous brain infarcts at baseline (covert brain infarction or old symptomatic brain infarction), baseline imaging modality (see Supplementary material—Imaging Analysis), and the following laboratory values at admission: albumin in g/L, CRP in mg/L, LDH in U/L, total cholesterol in mmol/L, low-density lipoprotein (LDL) cholesterol in mmol/L, triglycerides in mmol/L, D-dimer in μg/L, hemoglobin in g/L, leukocytes in g/L, and platelet count in g/L. The assigned TIA etiology at discharge was categorized according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and extracted from the clinical information system (17). TIA etiology was dichotomized as undetermined etiology and common etiologies according to the TOAST classification. The $ABCD_2$ score was used to determine the risk of recurrent stroke after TIA (with a score of 6 or 7 points indicating a high-risk constellation). The occurrence of new cerebrovascular events (TIA or stroke) after discharge was evaluated through available follow-up reports. Deceased patients (long-term mortality rate) were identified through the Swiss Population Registry, which records the vital status of Swiss residents monthly. For surviving patients, the follow-up time was defined as the time from the index TIA to the last update of the Swiss Population Registry. For deceased patients, the follow-up time was defined as the time from the index TIA to the date of death.

## Statistical analysis

The characteristics of patients with and without active cancer are reported using median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. Differences between both groups were assessed with Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. Univariable and multivariable logistic regression models were used to evaluate for potential associations between TIA, active cancer, and the selected co-variables (male gender, age at admission, smoking history, CRP, D-dimer, LDH, platelet count, hemoglobin, leukocyte count, previous brain infarction on baseline imaging, and undetermined cause of TIA). Adjusted odds ratios (aORs) were reported with their corresponding 95% confidence intervals (95% CI). Long-term mortality rates for patients with and without cancer were reported via Kaplan–Meier curves using the log-rank test. Adjusted hazard ratios (aHRs) and their 95% CI were assessed with multivariable Cox regression analysis. Logarithmic transformation was applied to skewed distributed continuous variables. Continuous scales were inversed if lower laboratory values were associated with active cancer. In a secondary analysis comparing patients with occult malignancies vs. those without cancer, patients with previously known malignancies were excluded to avoid influencing the analysis of factors associated with malignancies (mainly blood parameter levels and the presence of multi-territory infarcts). No imputation was applied to compensate for missing data. Statistical analyses were performed with Stata 16 (StataCorp LLC).

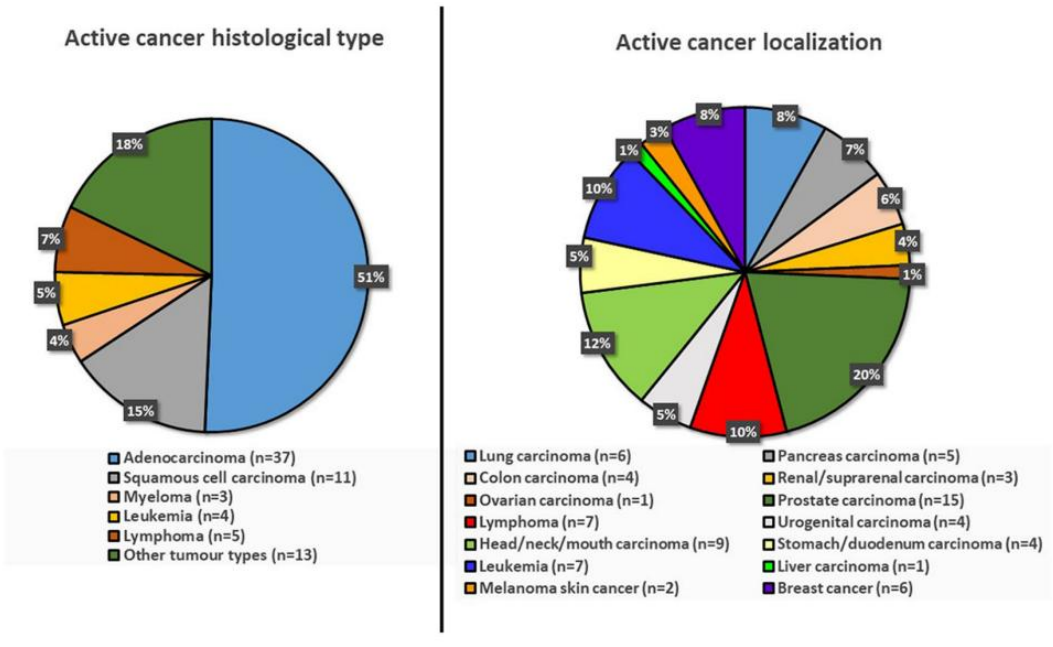


FIGURE 1
Histological types and locations of active cancer.

# Results

## Study population

Between January 2015 and December 2019, 6,815 patients with a differential diagnosis of TIA were seen at our emergency department. Of those, 1,436 had a reliable diagnosis of TIA and were consequently included in this study (Figure 1—study flowchart). Active cancer was present in 72 patients (5%). Out of those, 55 patients (3.8%) presented with known active cancer and 17 patients (1.2%) suffered from occult cancer. The localization and histological type of active cancer patients are summarized in Figure 1. In patients with active known cancer at the time of TIA, the median time between cancer diagnosis and TIA was 408 days (IQR 143–1,476).

## Baseline characteristics

The baseline differences between patients with and without active cancer are summarized in Table 1. Patients with active cancer compared to patients without cancer were more often male (68% vs. 53%, $P = 0.011$), older (75.4 years vs. 71 years, $P = 0.003$), and more likely to smoke (38% vs. 20%, $P = 0.001$). TIA patients with active cancer presented with higher plasma levels of D-dimer, CRP, high-sensitive Troponin T, and INR at admission. They also had lower total cholesterol, LDL cholesterol, and hemoglobin. Groups did not differ regarding previous ischemic stroke lesions (as detected on cerebral imaging).

## Characteristics of cancer-related TIA

In multivariable logistic regression analyses (summarized in Figure 2A), cancer-related TIA (active cancer overall) was associated with male sex (aOR 2.29, 95% CI 1.12–4.68) and a history of smoking (aOR 2.77, 95% CI 1.34–5.7). The presence of active cancer was also associated with higher D-dimer (aOR 1.77, 95% CI 1.26–2.49), LDH (aOR 1.003, 95% CI 1.00–1.005), lower leukocyte count (aOR 1.20, 95% CI 1.04–1.38), and lower hemoglobin (aOR 1.02, 95% CI 1.00–1.04).

In 15 of the 17 occult cancer patients (88%), diagnosis was made after discharge. The median time delay to diagnosis was 180 days (IQR 116–226). In multivariable logistic regression analyses after excluding patients with known active cancer (summarized in Figure 2B), occult cancer at the time of TIA was only associated with a history of smoking (aOR 4.32, 95% CI 1.20–15.58).

## Long-term outcomes in cancer-related TIA

Long-term follow-up data as obtained from the Swiss Population Registry were available for 1,021 (74.9%) patients without cancer as compared to 57 of all active cancer patients (79.1%) and 12 (100%) in the subgroup of occult cancer patients. The median long-term follow-up time for patients with active cancer was 807 days (IQR 410–1,577) and for patients without active cancer 1,732 days (IQR 1,247–2,261).

Patients with active cancer had a higher mortality rate during long-term follow-up (Figure 3A, log-rank test, $P < 0.001$) as compared to patients without cancer. In multivariable Cox regression analyses (Figure 4A), long-term mortality was strongly associated with active cancer (aHR 2.47, 95% CI 1.58–3.88) and previous brain infarcts (aHR 1.95, 95% CI 1.44–2.63). A weaker association with long-term mortality was also found for higher D-dimer and CRP and lower hemoglobin (Figure 4A).

In the subgroup of patients with occult cancer, the long-term mortality rate remained significantly higher than in patients without cancer (Figure 3B, log-rank test, $P < 0.001$). The median long-term follow-up time for patients with occult cancer was 1,163 days (IQR 640–1,861) and for patients without occult cancer 1,732 days (IQR 1,247–2,261). In multivariable Cox regression analyses (Figure 4B), long-term mortality was strongly associated with occult cancer (aHR 3.08, 95% CI 1.30–7.32), previous brain infarcts (aHR 2.22, 95% CI 1.62–3.06), and undetermined TIA etiology (aHR 1.56, 95% CI 1.09–2.22). Weaker significant associations were found with age at admission, elevated D-dimer, higher CRP, and lower hemoglobin.

# Discussion

The main findings of this study are TIA patients with active cancer present with characteristics and biomarkers similar to cancer-related stroke and experience higher mortality rates as compared to controls. As for occult cancer, the majority of cases were diagnosed after discharge and not during hospitalization.

Elevated D-dimer, a fibrin degradation product suggesting blood clot predilection or formation, is the most frequent biomarker associated with cancer in stroke patients (18, 19). Rosenberg et al. (20) retrospectively demonstrated that stroke patients with elevated D-dimer levels (median 2,520 µg/L, IQR 1,250–4,080) had a higher risk of being diagnosed with cancer when undergoing a whole-body CT in the post-stroke phase. In our study, an elevated D-dimer at admission was strongly associated with active cancer. This observation suggests a similar paraneoplastic coagulopathy phenomenon in cancer-related TIA compared to patients with cancer-related stroke. In our cohort, CRP levels were higher in the cancer group. However, there was no association with cancer-related TIA in the multiple logistic regression analyses. Karlinska et al. documented a median CRP level of 21 mg/L (IQR 4–76) in stroke patients with cancer, which is considerably higher than the median CRP level of 3.5 mg/L (IQR 1.5–9) found in our study. A potential explanation might be that the paraneoplastic inflammatory process is less active in patients with TIA (and therefore not yet leading to a subsequent permanent ischemia) (21) Cancer-related TIA was associated with decreased leukocyte count. Since there is currently no evidence of leukopenia or leukocytosis in cancer-related stroke, one possible explanation is the effect of cancer treatments (especially radiotherapy) known to cause lymphopenia (19, 22, 23). Reduced hemoglobin and elevated LDH, both correlating with cancer-related stroke, were weakly associated with cancer-related TIA (19, 24). A similar association was found

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TABLE 1 Comparison of baseline characteristics between patients with active cancer vs. no cancer.

| | All patients ($N = 1,436$) | No cancer ($N = 1,364$) | Active cancer ($N = 72$) | *P*-value |
|---|---|---|---|---|
| **Baseline** | | | | |
| Age at admission (median, IQR) | 71 (59–80.4) | 71 (59–82.0) | 75.4 (70–82.4) | 0.003 |
| Gender (male) No./total No. (%) | 767/1,436 (53.4%) | 718/1,364 (52.6%) | 49/72 (68.0%) | 0.011 |
| Prior independence (mRS ≤2) No./total no. (%) | 855/954 (89.6%) | 821/912 (90%) | 34/42 (81%) | 0.069 |
| **Risk factors No/total No. (%)** | | | | |
| Diabetes | 204/1,399 (14.6%) | 190/1,330 (19.0%) | 14/69 (20.3%) | 0.16 |
| Hypertension | 787/1,399 (56.3%) | 745/1,330 (56.0%) | 42/69 (60.9%) | 0.46 |
| Atrial fibrillation | 158/1,398 (11.3%) | 147/1,326 (11.1%) | 11/72 (15.9%) | 0.24 |
| Dyslipidemia | 687/1,398 (49.1%) | 652/1,329 (49.1%) | 35/69 (50.7%) | 0.81 |
| Smoking | 292/1,396 (20.9%) | 266/1,061 (25%) | 26/69 (37.7%) | 0.02 |
| History of stroke | 198/1,402 (14.1%) | 158/1,330 (11.9%) | 16/70 (17.1%) | 0.05 |
| History of TIA | 170/1,400 (12.1%) | 18/83 (21.7%) | 9/43 (21.0%) | 0.19 |
| Previous brain infarctions | 308/1,422 (21.6%) | 293/1,351 (21.7%) | 15/71 (21.1%) | 1.00 |
| Venous thromboembolism | 12/1,436 (0.8%) | 8/1,364 (0.6%) | 4/72 (5.6%) | 0.002 |
| **TIA characteristics** | | | | |
| NIHSS on admission (median, IQR) | 0 (0–1) | 0 (0–1) | 0 (0–2) | 0.18 |
| MRI as baseline imaging No./total No. (%) | 1,117/1,332 (83.9%) | 1,061/1,267 (83.7%) | 56/65 (86.2%) | 0.73 |
| $ABCD_2$ score (median, IQR) | 4 (3–5) | 4 (3–5) | 4 (3–5) | 0.88 |
| $ABCD_2$ score ≥6 (high risk) | 195/1,436 (13.6%) | 183/1,364 (13.4%) | 12/72 (16.7%) | 0.62 |
| **TIA etiology (TOAST) No./total No. (%):** | | | | |
| Cardioembolic | 125/1,394 (9%) | 118/1,325 (8.9%) | 7/69 (10.1%) | 0.35 |
| Small-vessel occlusion | 21/1,394 (1.5%) | 20/1,325 (1.5%) | 1/69 (1.4%) | |
| Competing etiologies | 47/1,394 (3.4%) | 43/1,325 (3.2%) | 4/69 (5.8%) | |
| Large-artery atherosclerosis | 97/1,394 (7%) | 89/1,325 (6.7%) | 8/69 (11.6%) | |
| TIA of other determined etiology | 22/1,394 (1.6%) | 21/1,325 (1.6%) | 1/69 (1.4%) | |
| TIA of undetermined etiology | 1,082/1,394 (77.6%) | 1,034/1,325 (78%) | 48/69 (69.6%) | |
| **Baseline laboratory findings** | | | | |
| Albumin in g/L (median, IQR) | 34 (31–37) | 34 (31–37) | 33.5 (29.5–37.5) | 0.60 |
| C-reactive protein in mg/L (median, IQR) | 2 (1–5) | 2 (1–4) | 3.5 (1.5–9) | <0.001 |
| LDH in U/L (median, IQR) | 385 (337–440) | 384.5 (337.5–437) | 433 (336.5–508.5) | 0.01 |
| Troponin T-high-sensitive in ng/L (median, IQR) | 8.36 (4.85–16.19) | 8.1 (4.82–16) | 11.9 (5.76–22.1) | 0.006 |
| Total cholesterol in mmol/L (median, IQR) | 4.82 (3.96–5.65) | 4.84 (4.01–5.67) | 4.42 (3.36–4.95) | <0.001 |
| LDL cholesterol in mmol/L (median, IQR) | 2.60 (1.92–3.30) | 2.62 (1.92–3.33) | 2.37 (1.88–2.91) | 0.025 |
| Leukocyte count in G/L (median, IQR) | 7.46 (6.2–9.1) | 7.5 (6.2–9.13) | 7.15 (5.78–8.40) | 0.15 |
| Hemoglobin in g/L (median, IQR) | 138 (128–147) | 138 (128–147) | 127 (113–145) | <0.001 |
| Platelet count in G/L (median, IQR) | 228 (194–270) | 228 (194–270) | 209.5 (174–279.5) | 0.19 |
| Fibrinogen in g/L (median, IQR) | 2.9 (2.46–3.45) | 2.9 (2.46–3.43) | 3 (2.48–3.6) | 0.42 |
| INR (median, IQR) | 1 (0.96–1.05) | 1 (0.96–1.05) | 1.02 (0.97–1.11) | 0.007 |
| D-dimer in µg/L (median, IQR) | 444 (247–819) | 434 (244–782) | 864.5 (364–2577.5) | <0.001 |
| HbA1c in % (median, IQR) | 5.6 (5.4–6) | 5.6 (5.4–6) | 5.6 (5.3–6) | 0.62 |

*(Continued)*

TABLE 1 (Continued)

| | All patients ($N = 1,436$) | No cancer ($N = 1,364$) | Active cancer ($N = 72$) | *P*-value |
|---|---|---|---|---|
| **Outcome** | | | | |
| Long-term follow-up time in days (median, IQR) | 1,699 (1,212–2,251) | 1,732 (1,247–2,261) | 807 (410–1,577) | <0.001 |
| Recurrent stroke | 74/1,250 (5.9%) | 69/1,184 (5.8%) | 5/66 (7.6%) | 0.59 |
| Recurrent TIA | 88/1,248 (7%) | 82/1,182 (6.9%) | 6/66 (9.1%) | 0.46 |
| Long-term deaths No./total No. (%) | 292/1,096 (26.6%) | 252/1,039 (24.3%) | 40/57 (70.2%) | <0.001 |

IQR indicates interquartile range; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.
The denominator differs according to the overall availability of the data (on the respective risk factor or laboratory finding).

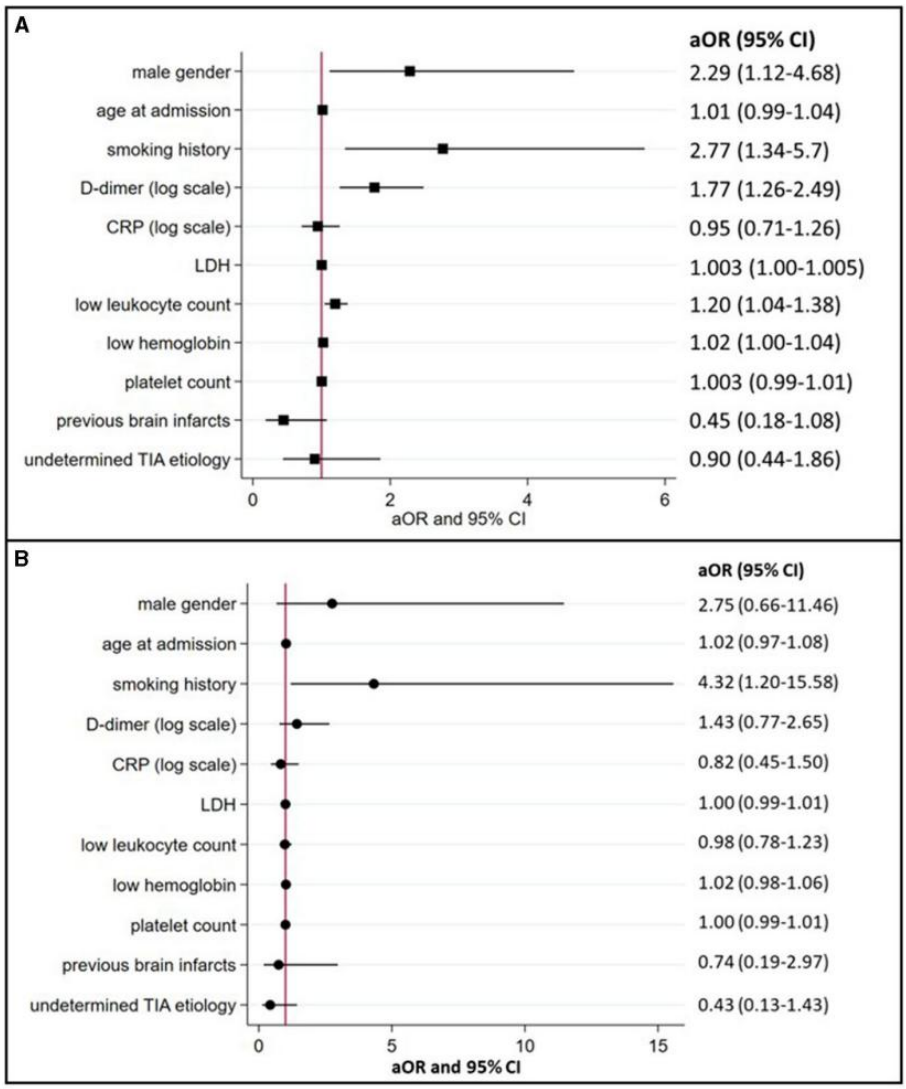


FIGURE 2
Associations between TIA patients with active or occult cancer and preselected demographics, risk factors, and biomarkers (multivariate logistic regression model). **(A)** (active cancer) and **(B)** (occult cancer) summarize the association between cancer in TIA patients and preselected demographics, risk factors, and blood biomarkers with corresponding aOR and 95% confidence intervals. aOR, indicates adjusted odds ratios; CI, confidence intervals; CRP, C-reactive protein; LDH, lactate dehydrogenase; and TIA, transient ischemic attack.

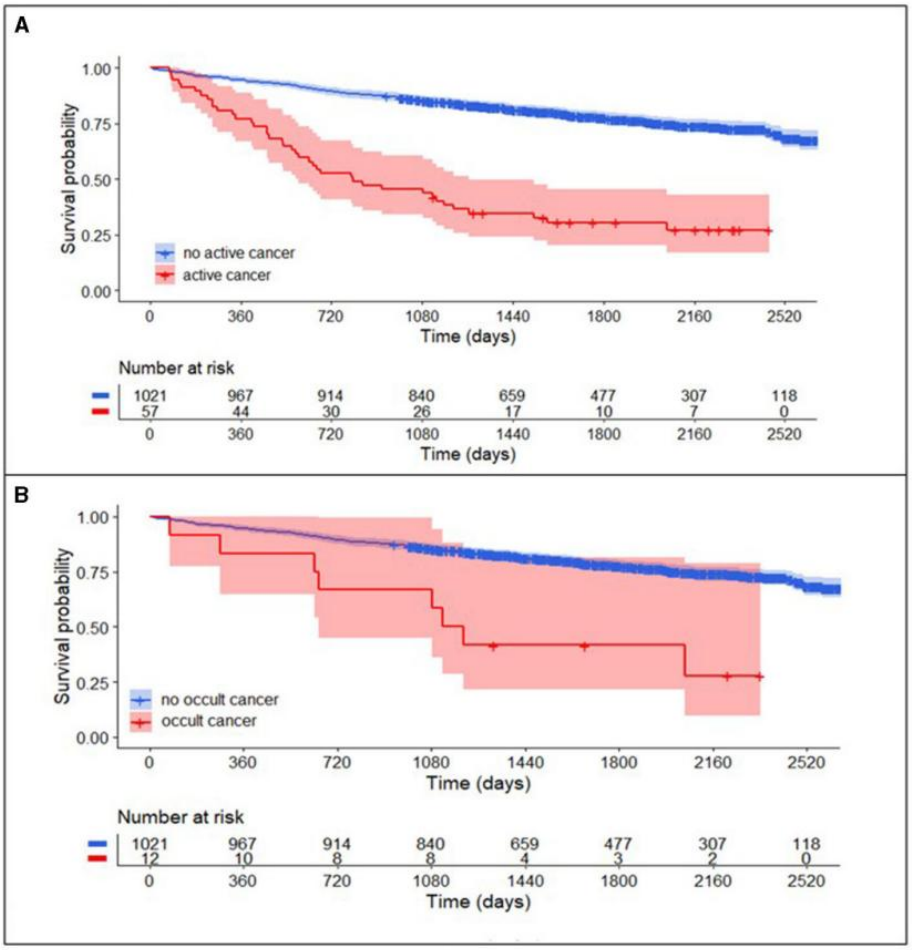


FIGURE 3
Long-term survival curve in TIA-patients with and without cancer. **(A)** Patients with active cancer (combined known active cancer and occult cancer; red) compared to patients without active cancer (blue) had higher mortality rates in the long-term follow-up after TIA (log-rank test, $P < 0.001$). After the exclusion of patients with known active cancer **(B)**, mortality rates in patients with occult cancer (red) compared to patients without active cancer (blue) in the long-term follow-up remained higher (log-rank test, $P < 0.001$).

for an elevated hs-Troponin T in our cohort. While being non-specific due to a number of potential causes, higher hs-Troponin T levels could be detected recently in ischemic stroke patients with concomitant active cancer (25).

Although not reaching statistical significance, there was an inverse correlation between cancer-related TIA and previous brain infarction on MRI. This finding was observed in active cancer patients. Currently, there is no persuasive explanation. It may be assumed that during the initial stroke work-up, a potential (paraneoplastic) coagulation disorder might have been detected and consecutively treated (e.g., anticoagulation). There was no difference between groups when looking at the $ABCD_2$ score which predicts recurrent cerebrovascular events after TIA (even for high-risk patients with an $ABCD_2$ score of six or higher, Table 1). One explanation might be that cancer and/or paraneoplastic coagulation disorder are not part of the score. Overall, active cancer is known to be an independent risk factor for recurrent events (9).

Cancer-related stroke is known to be associated with multiterritory infarcts (26). Finelli et al. described the "three-territory sign" as DWI restriction in all three vascular territories (bilateral anterior and posterior circulation) (26). The "three-territory sign" is highly suggestive of cancer-related stroke in the absence of an identifiable cause (e.g., atrial fibrillation) (27). To identify a potential radiological biomarker in cancer-related TIA, we assessed the presence of previous brain infarcts at baseline (covert brain infarction or old symptomatic brain infarction). No association between previous brain infarcts and either active cancer or occult cancer patients was found. In summary, features of paraneoplastic coagulopathy appear to be present in TIA patients with active cancer. Similar to ischemic stroke, the identification of a paraneoplastic coagulopathy seems to be of importance and has to be taken into consideration (especially in cases of an unknown etiology). These similar clinical characteristics could help guide secondary prevention management in these patients, including possible trials of anticoagulation.

Regarding the determination of predictors for a new cancer diagnosis within 1 year after TIA, this study did not identify potential predictors of occult malignancy except smoking habits. D-dimer levels were the same in TIA patients with occult

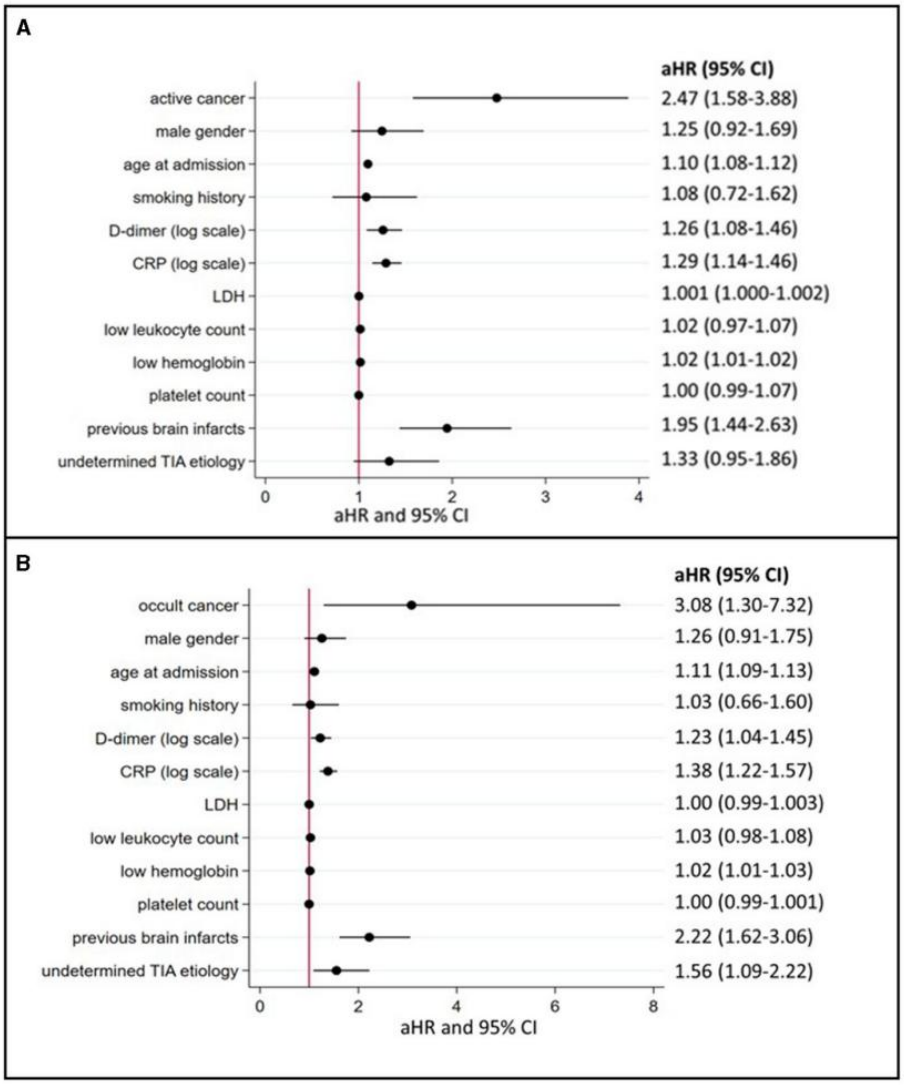


FIGURE 4
Predictors of long-term mortality in TIA patients with active or occult cancer (multivariate logistic regression model). **(A)** depicts the aHR from the multivariate Cox regression analyses regarding long-term mortality depending on the presence of active cancer and other cancer-related factors (for occult cancer, see **(B)**. aHR indicates adjusted hazard ratios; CI, confidence intervals; CRP, C-reactive protein; LDH, lactate dehydrogenase and TIA, transient ischemic attack.

cancer compared to patients without cancer. Further studies are needed to evaluate whether available predictive scores for occult cancer-related stroke can be used in TIA patients. Despite the low sensitivity of the above-mentioned biomarkers in occult malignancy, mortality rates in TIA patients with occult and active malignancy did not differ in our cohort (and were higher compared to patients without cancer). The abovementioned biomarkers might therefore not be suitable candidates for initial screening and assessment. However, especially in cases of unknown TIA etiology (and a history of smoking), our results support a thorough diagnostic work-up including the search for occult cancer and subsequent paraneoplastic coagulopathies. TIA, as the first manifestation of occult cancer, could accelerate the cancer diagnosis and thus potentially improve the prognosis of these patients.

## Limitations

Our study has several limitations. First, due to the retrospective study design, all attributed biases apply. The true incidence of occult cancer and recurrent TIA/stroke might be underestimated due to diagnoses made at other centers during follow-up. Second, because of the single-center design, the findings may not be generalizable. Third, the stage of the disease (cancer) at the time of TIA onset was not documented. This limits conclusions regarding the effect of advanced disease on paraneoplastic activity. Fourth, due to the small number of TIA attributable to occult cancer, effects or associations might be imprecise. In addition, indirect detection of a potential pro-thrombotic state (e.g., microembolic signaling in transcranial color Doppler) was not available. Moreover, it has to be mentioned that the complete etiological assessment of many

patients was completed in an outpatient setting. This could lead to a misinterpretation of some of the baseline information (e.g., TOAST criteria) as the final etiology might not go along with the one that was initially suspected.

## Conclusion

Our study indicates that cancer-related TIA is not uncommon and blood biomarkers known to be associated with cancer-related stroke are also present in TIA patients with active cancer. Similarly, patients with cancer-related TIA experience higher mortality rates. These biomarkers are smoking history, elevated D-dimer, elevated LDH, and low hemoglobin. Identification and analysis of these biomarkers might help to facilitate diagnosis and treatment which might be of clinical relevance. Future studies should validate these findings in prospective multicenter cohorts and investigate the optimal treatments for cancer-related TIA.

## Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding authors.

## Ethics statement

The study involving humans was approved by the Kantonale Ethikkommission Bern (Project ID: 2022-01560). The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

MB: Conceptualization, Data curation, Formal analysis, Investigation, Writing—original draft. PC: Data curation, Writing—review and editing. JB: Data curation, Writing—review and editing. VZ: Data curation, Writing—review and editing. MK: Writing—review and editing. MM: Writing—review and editing. SB-G: Writing—review and editing. AM: Writing—review and editing. TM: Writing—review and editing. TH: Conceptualization, Writing—review and editing. UF: Writing—review and editing. JK: Writing—review and editing. MH: Writing—review and editing. DS: Writing—review and editing. MA: Writing—review and editing. TP: Writing—review and editing. MDB: Writing—review and editing. BN: Writing—review and editing. SJ: Conceptualization, Resources, Supervision, Writing—review and editing. PB: Conceptualization, Data curation, Project administration, Supervision, Writing—original draft, Writing—review and editing.

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## Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1268131/full#supplementary-material

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# Factors impacting D-dimer levels in patients with acute ischemic cerebrovascular events

Title of the manuscript: Factors impacting D-dimer levels in patients with acute ischemic cerebrovascular events

Contributions of the PhD candidate:

- Conceptualization
- Data curation
- Formal analysis
- Visualization
- Writing – original draft
- Writing – review and editing
- Supervision

Results summary:

As elevated D-dimer level is a key biomarker of coagulation disorders, and of paraneoplastic coagulation in particular, it is important to know what factors influence D-dimer levels in the acute phase of AIS. For this purpose, this retrospective study investigated the fluctuation of D-dimer levels according to the time between symptom onset and blood draw in AIS patients and TIA patients (a control group without persisting brain damage). All patients were treated at our comprehensive stroke center between 2015 and 2020 and included in our BMS database or Bernese TIA database, respectively. AIS patients showed an early increase in D-dimer levels within the first 6 hours after symptom onset (standardized beta coefficient [β] 0.728, 95% CI 0.324–1.121). Following this, there was a decrease in D-dimer levels (β −13.022, 95% CI −20.401 to −5.643) and a second increase after 35 hours from symptom onset (β 11.750, 95% CI 4.71–18.791). No time-dependent fluctuation in D-dimer levels was observed in the control group of patients with TIA.

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# Factors impacting D-dimer levels in patients with acute ischemic cerebrovascular events

Recep-Ali Hacialioglu, MD [a,1], Moritz Kielkopf, MD [a,1], Mattia Branca, PhD [b], Leander Clenin, MD [a], Anna Boronylo, MD [a], Norbert Silimon, MD [a], Martina B. Göldlin, MD, PhD [a], Adrian Scutelnic, MD [a], Johannes Kaesmacher, MD, PhD [c], Adnan Mujanovic, MD [c], Thomas R. Meinel, MD, PhD [a], David J. Seiffge, MD [a], Mirjam R. Heldner, MD [a], Ava L. Liberman, MD [d], Babak B. Navi, MD, MS [d], Urs Fischer, MD, MS [a], Marcel Arnold, MD [a], Simon Jung, MD [a], Philipp Bücke, MD [a,1], Morin Beyeler, MD [a,d,e,1,*]

[a] Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[b] CTU Bern, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[c] Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[d] Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, NY, USA
[e] Graduate School for Health Sciences, University of Bern, Switzerland

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Symptom onset

ABSTRACT

*Background and objectives:* A better understanding of the factors influencing D-dimer levels in code stroke patients is needed to guide further investigations of concomitant thrombotic conditions. This study aimed to investigate the impact of time from symptom onset and other factors on D-dimer levels in patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA).

*Methods:* Data on consecutive AIS and TIA patients treated at our tertiary-care stroke center between January 2015 and December 2020 were retrospectively assessed. Patients with available D-dimer levels were evaluated for eligibility. Multivariable non-linear regression analyses were performed.

*Results:* In total, 2467 AIS patients and 708 TIA patients were included. The median D-dimer levels differed between the AIS and TIA groups (746 µg/L [interquartile range 381–1468] versus 442 µg/L [interquartile range 244–800], $p<0.001$). In AIS patients, an early increase in D-dimer levels was demonstrated within the first 6 h (standardized beta coefficient [β] 0.728; 95% confidence interval [CI] 0.324–1.121). This was followed by an immediate decrease (β −13.022; 95% CI −20.401 to −5.643) and then by a second, late increase after 35 h (β 11.750; 95% CI 4.71–18.791). No time-dependent fluctuation in D-dimer levels was observed in TIA patients.

*Conclusion:* The time from symptom onset may affect D-dimer levels in patients with AIS but not those with TIA. Further studies confirming these findings and validating time-specific variations are needed to enable D-dimer levels to be used efficiently as an acute stroke and thrombotic risk biomarker.

## Introduction

D-dimer is a cleavage product of cross-linked fibrin, usually obtained from blood plasma.[1] Increased D-dimer levels are the result of thrombus degradation and therefore indirectly suggest prior thrombus formation.[1] D-dimer measurement is routinely used to rule out venous thromboembolism (VTE), such as deep venous thrombosis and pulmonary embolism.[2] In the context of acute ischemic stroke (AIS), physiological D-dimer levels have been shown to effectively rule out VTE.[3] However, elevated D-dimer levels are also often seen in AIS patients without VTE

*Abbreviations:* ABCD2 score, age, blood pressure, clinical features, duration, diabetes - Score; AIS, Acute ischemic stroke; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; IVT, intravenous thrombolysis; IQR, Interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

* Corresponding author at: Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Freiburgstrasse 18, Bern CH-3010, Switzerland.
*E-mail address:* morin.beyeler@insel.ch (M. Beyeler).

[1] These authors contributed equally to this work.

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and can result from the AIS itself. This makes further management of AIS patients with elevated D-dimer levels challenging (i.e., potential search for VTE and underlying cancer).[3,4]

Our study aimed to investigate the influence of time from symptom onset to blood sample collection and other factors on D-dimer levels in patients with AIS. We hypothesized a time-dependent increase in D-dimer levels during the first hours and days after onset of AIS symptoms due to the degradation of occlusive thrombus in the hyperacute phase of AIS (<6 h after symptom onset) and the occurrence of cerebral thromboinflammation in the acute phase of AIS (between 6 and 48 h after symptom onset).[5,6] A group of patients with transient ischemic attack (TIA) formed a comparison group. We did not expect an increase in D-dimer levels in the TIA group over time because TIA is usually not associated with irreversible brain injury and, therefore, we assumed an absence of cerebral thromboinflammation.[7]

## Material and methods

### *Study cohort*

Consecutive patients diagnosed with AIS between January 1, 2015 and December 31, 2020 and consecutive patients diagnosed with TIA between January 1, 2015 and December 31, 2019 at our institution were assessed for eligibility. Patients with AIS were identified from the Swiss Stroke Registry, which includes prospective data recorded by qualified research personnel. Patients with TIA were retrospectively identified via a review of institutional electronic health records. The detailed definitions used to characterize patients with AIS and TIA are provided in the Supplementary Methods.

### *Standard protocol approvals, registrations, and patient consents*

The ethics committee approved the study in accordance with Swiss law (reference ID: 2021-01031 and ID: 2022-01560, Kantonale Ethikkommission Bern). The study adheres to the STROBE checklist for cohort studies. As stated by decision of the ethics committee, a written consent from patients was not required for performance of this retrospective study.

### *Data availability statement*

Data are available from the corresponding author upon reasonable request and after clearance by our institutional ethics committee.

### *Inclusion and exclusion criteria*

Patients were excluded in case of 1) missing D-dimer measurement during the index event or a D-dimer measurement made more than 7 days after the time of symptom onset, 2) unknown symptom-onset time (missing data and wake-up symptoms), 3) in-hospital event with D-dimer measurement prior to documented symptom onset, 4) outliers with D-dimer values exceeding 30,000 µg/L, 5) administration of intravenous thrombolysis (IVT) before D-dimer measurement, 6) mechanical thrombectomy prior to D-dimer measurement, 7) documented active cancer at the time of the index event, and 8) VTE diagnosed within 30 days before and up to 7 days after the index event.

Active cancer was defined according to the criteria from the Haemostasis and Malignancy Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[8]

### *Data collection*

D-dimer levels were obtained as part of a standardized blood sample panel, which is routinely measured in every patient with suspected AIS or TIA at our institution. The D-dimer value was measured using Innovance®.[9] For patients with multiple measurements, only the first D-dimer value was recorded.

The following data were extracted from the Swiss Stroke Registry or acquired through the review of electronic health records: 1) Epidemiological data including patients' age, sex, pre-stroke dependency defined as a modified Rankin Scale [mRS] ≥3, baseline imaging modality, use of anticoagulation and antiplatelet drugs before the event, and vascular risk factors including previous AIS, previous TIA, arterial hypertension, diabetes mellitus, hyperlipidemia, history of smoking, and atrial fibrillation; 2) event characteristics, such as time between symptom onset and D-dimer measurement at admission or during hospitalization for the index event, and AIS and TIA etiology at discharge according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. For AIS, the site of vessel occlusion was determined on admission imaging and categorized as: no vessel occlusion, intracranial carotid artery, M1 segment of middle cerebral artery (MCA), M2 segment of MCA, other occlusion in the anterior circulation, or occlusion in the posterior circulation. In patients with AIS, initial stroke severity was stratified according to the National Institutes of Health Stroke Scale (NIHSS), as follows: very minor (score 0), minor (score 1–4), moderate (score 5–14), severe (score 15–-24) and very severe (score >25). TIA patients were categorized according to the risk of subsequent AIS based on the ABCD2 score: low risk (score 0–3), medium risk (score 4–5), and high risk (score 6–7).[10] Besides plasma D-dimer, the following baseline blood parameters were recorded: C-reactive protein (CRP) in mg/L, glucose in mmol/L, fibrinogen in g/L and creatinine in µmol/L. The estimated glomerular filtration rate (eGFR) in mL/min/1.73 $m^2$ was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI 2021) formula.

### *Statistical analysis*

Baseline characteristics were reported using median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. Baseline differences were assessed for AIS and TIA patients combined. Differences between groups were assessed using Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. Scatter plots were displayed to visualize the distribution of continuous D-dimer levels over time from symptom onset in the AIS and TIA groups separately. Pearson's correlation coefficient (r) and its corresponding p-values were used to assess the linearity of the correlations between D-dimer levels and time from symptom onset to D-dimer measurement. In the case of non-linearity of the correlations (r between -0.1 and +0.1),[11] non-linear models with restricted cubic splines were created using the Stata command mkspline2.[12] The restricted cubic spline was chosen as a non-linear model (instead of fractional polynomials, for example) because it behaved better in relation to the data and its interpretation was more intuitive. Multivariable non-linear regression analyses using standardized variables were performed and the resulting standardized coefficients of regression (β), their corresponding 95% confidence intervals (CI) and p-values were reported. Multivariable non-linear regression analyses using standardized variables were performed and the resulting standardized coefficients of regression (β), their corresponding 95% confidence intervals (CI) and *p*-values were reported. Multivariable analyses were adjusted for the following covariables: age, sex, pre-stroke dependency, vascular risk factors (arterial hypertension, history of smoking and hyperlipidemia), prior anticoagulant use, prior antiplatelet use, eGFR, etiology according to TOAST, stroke severity (NIHSS grades), site of vessel occlusion for AIS, and the risk for subsequent AIS in TIA patients (ABCD2 scores). Variables were selected based on previous literature and pathophysiological considerations.[4,13]

Sensitivity analysis compared the association between D-dimer levels and time from symptom onset in AIS patients with at least one symptomatic intracranial arterial occlusion versus AIS patients without symptomatic intracranial occlusion. Associations were deemed significant if their *p*-value was <0.05. No imputation was applied to

compensate for missing data. All statistical analyses were performed using Stata v16.

## Results

### *Study population*

Of 6371 patients assessed for eligibility (AIS n=5012 and TIA n=1359), 3175 (AIS n=2467 and TIA n=708) were included in this study (Fig. 1: Study Flowchart).

### *Baseline characteristics*

The baseline differences between patients with AIS and TIA are summarized in eTable I. The time between symptom onset and D-dimer measurement was longer in AIS patients than in TIA patients (191 min [IQR 103–585] versus 161 min [IQR 106–286], $p<0.001$). The median D-dimer level differed between the AIS and TIA groups (746 µg/L [IQR 381–1468] versus 442 µg/L [IQR 244–800], $p<0.001$).

### *D-dimer levels in AIS patients*

No linear correlation was found between D-dimer levels and time from symptom onset for AIS patients in this study (r= −0.06, $P$=0.003, Fig. 2). Based on visual review of the distribution of D-dimer levels in AIS patients (Fig. 2A) and pathophysiological considerations mentioned in the introduction, we set time-specific knots at 6 h and 35 h after symptom onset to create a non-linear model.[5,6] In the resulting multivariable non-linear regression analysis (Table 1), an early increase in D-dimer levels was observed in AIS patients within the first 6 h after symptom onset (β 0.773; 95% CI 0.370–1.176). Between 6 h and 35 h after symptom onset, a decrease of the D-dimer levels was demonstrated (β −13.022; 95% CI −20.401 to −5.643). A second, late increase of D-dimer levels starting from 35 h after symptom onset was also observed (β 12.334; 95% CI 5.294 – 19.374). An adjusted model of D-dimer levels over the time between symptom onset and D-dimer measurement is displayed in Fig. 2B. Lower D-dimer levels were associated with prior anticoagulation; other factors affecting D-dimer levels during AIS work-up are reported in Table 1.

### *Influence of intracranial occlusion in AIS patients*

On baseline brain imaging, 1286 of the 2467 AIS patients (52%) were found to have an intracranial occlusion. The median D-dimer level differed between patients with and without intracranial occlusion (median 918 µg/L [IQR 474–1881] versus median 545 µg/L [IQR 326–1086], $p<0.001$). Patients with and without intracranial occlusion showed comparable time dynamics in the D-dimer values to those of the AIS group overall (eTable II and eFig. I).

### *D-dimer levels in TIA patients*

The distribution of D-dimer levels over the time between symptom onset and D-dimer measurement in TIA patients is displayed in Fig. 3A. No linear correlation was found between D-dimer levels and time from symptom onset for TIA patients (r= −0.05, $p$=0.193). Using the same time-specific knots as for AIS patients (at 6 h and 35 h after symptom onset) for the non-linear regression analysis (Table 1 and Fig. 3B), no significant association between the time from symptom onset and increased D-dimer levels was observed within the first 6 h after symptom onset (β −0.019; 95% CI −0.837 to 0.800), between 6 and 35 h after symptom onset (β 0.380; 95% CI −21.413 to 22.173) or from 35 h after symptom onset (β 0.041; 95% CI −22.111 to 22.192).

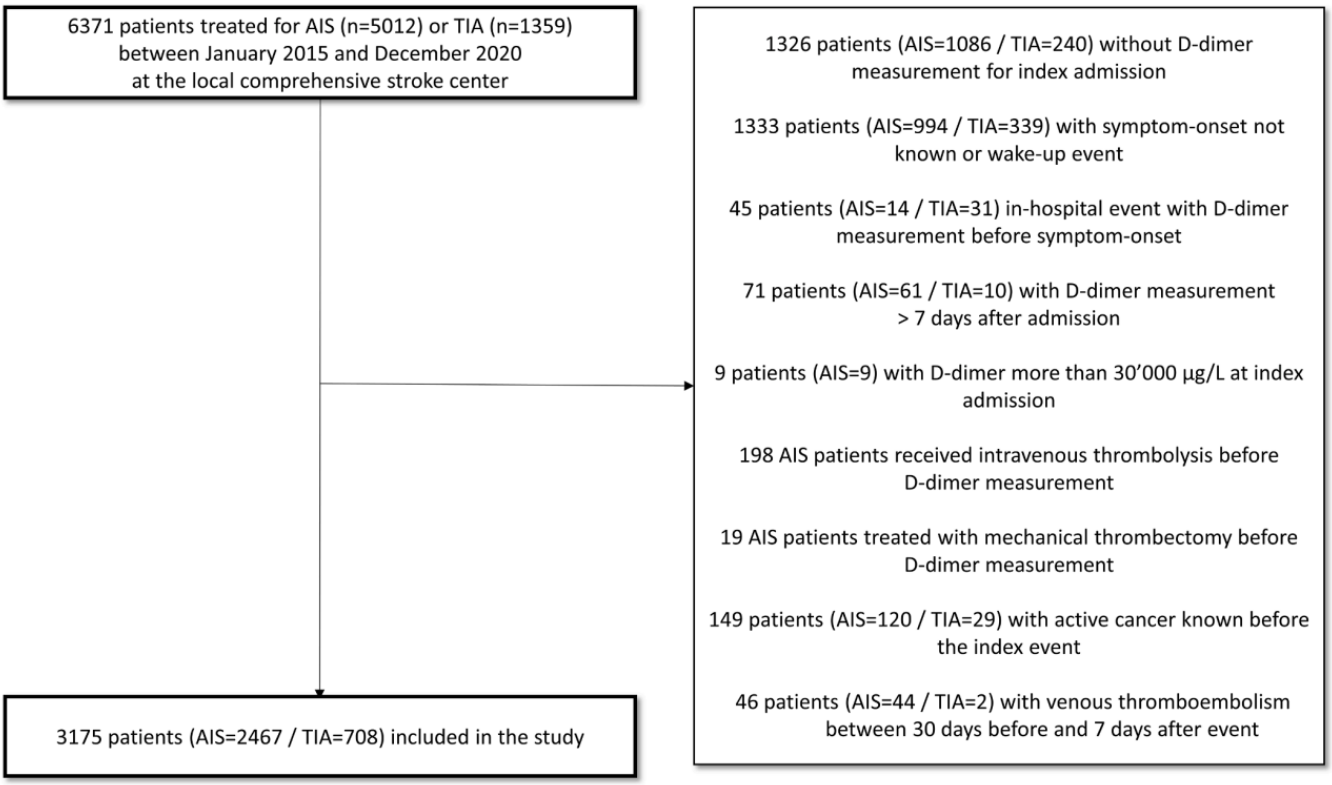


**Fig. 1.** Study Flowchart.
Inclusion and exclusion of study participants.
Abbreviations: AIS=acute ischemic stroke, TIA=transient ischemic attack.

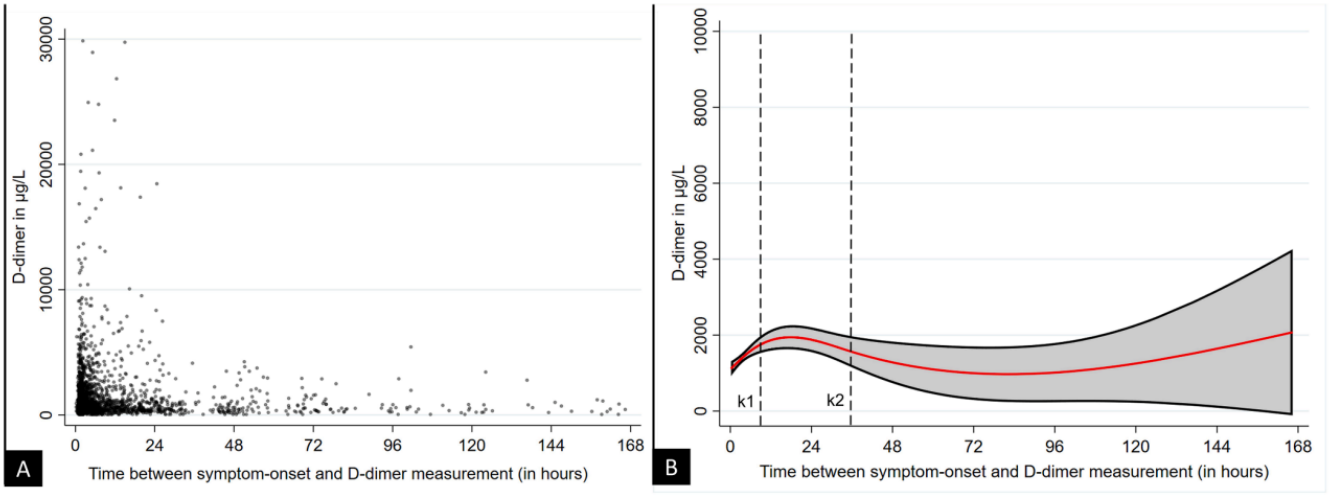


**Fig. 2.** Distribution (A) and Adjusted Model (B) of D-Dimer Levels Over Time from Symptom Onset to Blood Collection in Patients with AIS.
In Fig. 2A, gray dots represent individual D-dimer levels over time from symptom onset to blood collection for the index AIS (n = 2467). Fig. 2B displays the adjusted model with the restricted cubic spline regression line (red line) and its 95% CI (gray shading). The two knots at 6 h (k1) and 35 h (k2) after symptom onset are represented by the vertical black dashed lines. Abbreviations: AIS=acute ischemic stroke, CI=confidence interval.

**Table 1**
Predictors of Elevated D-Dimer Levels in Patients with Acute Ischemic Stroke (AIS) and Transient Ischemic Attack (TIA) Assessed in the Multiple Non-Linear Regression.

| **Multivariable non-linear regression model** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Predictive variables** | **Patients with AIS** | | | **Predictive variables** | **Patients with TIA** | | |
| | **β** | **95% CI** | ***p* value** | | **β** | **95% CI** | ***p* value** |
| Symptom onset to D-dimer < 6h | 0.773 | 0.370 – 1.176 | <0.001* | Symptom onset to D-dimer < 6h | −0.019 | −0.837 – 0.800 | 0.964 |
| Symptom onset to D-dimer ≥ 6h and < 35h | −13.022 | −20.401 – −5.643 | 0.001* | Symptom onset to D-dimer ≥ 6h and < 35h | 0.380 | −21.416 – 22.173 | 0.973 |
| Symptom onset to D-dimer ≥ 35h | 12.334 | 5.294 – 19.374 | 0.001* | Symptom onset to D-dimer ≥ 35h | 0.041 | −22.111 – 22.192 | 0.997 |
| Age at admission | 0.135 | 0.068 – 0.203 | <0.001* | Age at admission | 0.143 | −0.064 – 0.150 | 0.427 |
| Sex (male) | −0.034 | −0.085 – 0.017 | 0.193 | Sex (male) | −0.008 | −0.088 – 0.073 | 0.848 |
| Pre-stroke dependency (mRS ≥3) | 0.314 | 0.157 – 0.471 | <0.001* | Pre-stroke dependency (mRS ≥3) | 0.091 | 0.024 – 0.157 | 0.008 |
| Anticoagulation prior to event | −0.096 | −0.154 – −0.038 | 0.001* | Anticoagulation prior to event | 0.055 | −0.030 – 0.141 | 0.203 |
| Antiplatelet drugs prior to event | 0.024 | −0.031 – 0.078 | 0.392 | Antiplatelet drugs prior to event | 0.029 | −0.059 – 0.117 | 0.511 |
| Hypertension | −0.042 | −0.099 – 0.015 | 0.148 | Hypertension | −0.011 | −0.101 – 0.080 | 0.816 |
| Hyperlipidemia | −0.011 | −0.062 – 0.040 | 0.664 | Hyperlipidemia | 0.027 | −0.062 – 0.116 | 0.545 |
| History of smoking | 0.060 | 0.008 – 0.113 | 0.024* | History of smoking | −0.015 | −0.097 –0.069 | 0.726 |
| Lower eGFR | 0.131 | 0.071 – 0.192 | <0.001 | Lower eGFR | 0.065 | −0.040 – 0.169 | 0.222 |
| Stroke etiology | −0.032 | −0.086 – 0.022 | 0.251 | Stroke etiology | −0.014 | −0.101 – 0.073 | 0.750 |
| Stroke severity | 0.125 | 0.071 – 0.179 | <0.001* | Risk of AIS | 0.001 | −0.212 – 0.128 | 0.625 |
| Site of vessel occlusion | 0.010 | −0.041 – 0.062 | 0.694 | Site of vessel occlusion | | | |

AIS, acute ischemic stroke; TIA, transient ischemic attack; β, standardized regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
* Independent predictor of elevated D-dimer level identified by multiple regression analyses

## Discussion

The main findings of this study are: 1) An initial increase in D-dimer levels in AIS patients occurs during the first 6 h after symptom onset and a second increase after 35 h, with a decrease in between, 2), no time-dependent pattern of D-dimer levels was observed in TIA patients, 3) prior use of anticoagulants was associated with lower D-dimer levels.

Alongside its key role in exclusion of VTE, D-dimer is increasingly used in the evaluation of AIS.[14,15] Measuring D-dimer levels at hospital presentation for AIS or TIA could provide clues to patients' underlying cerebrovascular etiology as well as their risk of early neurological deterioration and recurrent stroke.[4,16] For instance, a very high D-dimer level in a patient with cryptogenic stroke could prompt an investigation for occult cancer or acute venous thromboembolism with corresponding paradoxical embolization.[3,17]

Further, a persistently elevated D-dimer value despite antiplatelet therapy in patient with cancer-related stroke could trigger the consideration of empiric anticoagulant therapy.

Among patients with AIS, elevated D-dimer levels have been most consistently associated with cardioembolic and large-artery atherosclerotic etiologies or comorbid cancer with associated hypercoagulability.[17,18] In addition, like previous reports,[19–22] our study found that intracranial occlusion, higher stroke severity, and increased age were associated with higher D-dimer levels. Until now, there were few data on the effect of time from symptom onset to blood collection and D-dimer levels in patients with AIS.[14] Retrospective studies had hypothesized an

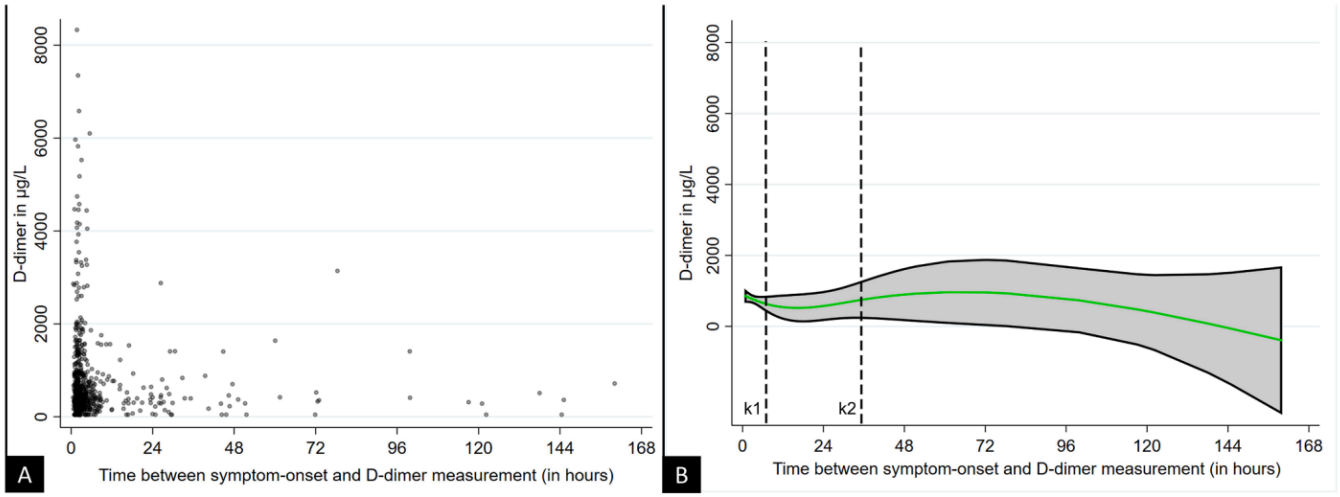


**Fig. 3.** Distribution (A) and Adjusted Model (B) of D-Dimer Levels Over Time from Symptom Onset to Blood Collection in Patients with TIA.
In Fig. 3A, gray dots represent individual D-dimer levels over time between symptom onset and blood collection for the index TIA (n = 708). Fig. 3B displays the adjusted model with the restricted cubic spline regression line (red line) and its 95% CI (gray shading). The two knots at 6 h (k1) and 35 h (k2) after symptom onset are represented by the vertical black dashed lines. Abbreviations: AIS=acute ischemic stroke, β=standardized regression coefficient, CI=confidence interval, TIA=transient ischemic attack.

initial rise in D-dimer levels within the first 24 h after symptom onset, followed by a gradual decline.[4,14,23] This is clinically relevant, as the timing of D-dimer measurements could lead to misinterpretation by treating physicians.

Pathophysiological mechanisms in the hyperacute phase of AIS (<6 h after symptom onset) determined by thrombus formation and subsequent resolution might explain the early rise in D-dimer levels.[5] Our finding of higher D-dimer levels in patients with intracranial vessel occlusions supports this hypothesis. The slight decrease in D-dimer levels between 6 and 35 h after symptom onset may be attributable to its rapid turnover resulting from a short half-life of 6 to 8 h.[24] A similar dynamic of decreasing D-dimer levels in the first hours after a thrombotic event has been reported in patients with VTE.[25] The second, later increase of D-dimer levels after 35 h may reflect the cerebral thromboinflammation process occurring in the late acute phase of AIS (6-48 h after symptom onset).[5,6] Although our study showed variations in D-dimer levels over time, further etiological investigations may be indicated if there is a clinical suspicion for venous thromboembolism with a D-dimer level ≥500 µg/L.[3] Furthermore, among patients with embolic stroke of undetermined source and concomitant cancer, emerging data indicate that D-dimer levels exceeding 2500 µg/L confer an increased risk for reS-current cerebrovascular events and other adverse outcomes.[26] For these reasons, and considering that the test is fairly inexpensive, it would be reasonable for hospital programs to integrate blood D-dimer measurements into their standard initial laboratory evaluations for patients presenting with AIS or TIA.

Overall, patients with TIA presented with lower D-dimer levels than patients with AIS.[27] This could be due to the lack of a persistent vessel occlusion and associated thrombus in TIA.[22] Furthermore, the fluctuation of D-dimer levels seen over time in AIS patients was not observed in TIA patients. A possible explanation could by the occurrence of initially smaller thrombi, their faster resolution and the absence of irreversible brain damage (resulting in cerebral thromboinflammation) in TIA patients. D-dimer may be a useful biomarker in patients with TIA, as it has been previously associated with confirmation of the underlying TIA diagnosis as well as the risk of subsequent AIS.[28,29] In AIS patients, anticoagulation was associated with consistently lower D-dimer levels (Table 1). This finding is in line with the current evidence from studies on VTE.[30,31] Studies in patients with cancer-related AIS have also demonstrated a reduction in D-dimer levels over time with anticoagulation.[32]

*Limitations*

This study has limitations. Firstly, all biases associated with a retrospective and single-center design apply. For instance, selection bias is possible, particularly because, at our institution, patients with AIS and TIA initially evaluated by internal medicine physicians do not receive systematic D-dimer assessments. This could have led to the non-differential exclusion of some patients with ischemic cerebrovascular events. Information bias is also possible as some relevant data were missing from the electronic medical records. Secondly, the D-dimer levels were routinely measured only at presentation or during the index hospitalization at our institution. The absence of follow-up D-dimer measurements in our cohort made it impossible to assess the dynamics of D-dimer levels over time at an individual level. Thirdly, information on infarct volume, previously associated with higher D-dimer levels on admission, is not available in our database.[19] Site of vessel occlusion and NIHSS score reflecting stroke severity were used as covariates to compensate for this. Fourthly, D-dimer levels can be influenced by external factors, including infection, systemic inflammation, atrial fibrillation, pregnancy, and trauma.[4,33–35] These factors need to be considered by clinicians when interpreting D-dimer levels in patients with AIS or TIA.

## Conclusion

Our study demonstrated that time from symptom onset to blood collection impacted D-dimer levels in patients with AIS but not those with TIA. We also found lower D-dimer levels in patients with AIS taking anticoagulants. A prospective study with sequential D-dimer measurements during the acute and subacute periods of ischemic cerebrovascular events (days 0-14) are needed to confirm these findings.

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## Ethical approval

The ethics committee approved the study in accordance with Swiss law (reference ID: 2021-01031 and ID: 2022-01560, Kantonale Ethikkommission Bern). The study adheres to the STROBE checklist for cohort studies. As stated by decision of the ethics committee, a written consent from patients was not required for the inclusion in this retrospective study.

## Informed consent

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

## Guarantor

Morin Beyeler & Philipp Bücke

## CRediT authorship contribution statement

**Recep-Ali Hacialioglu:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Moritz Kielkopf:** Writing – original draft, Investigation, Data curation, Conceptualization. **Mattia Branca:** Supervision, Formal analysis, Data curation. **Leander Clenin:** Validation. **Anna Boronylo:** Writing – review & editing. **Norbert Silimon:** Writing – review & editing. **Martina B. Göldlin:** Writing – review & editing. **Adrian Scutelnic:** Writing – review & editing. **Johannes Kaesmacher:** Writing – review & editing, Conceptualization. **Adnan Mujanovic:** Writing – review & editing. **Thomas R. Meinel:** Writing – review & editing. **David J. Seiffge:** Writing – review & editing. **Mirjam R. Heldner:** Writing – review & editing. **Ava L. Liberman:** Writing – review & editing. **Babak B. Navi:** Writing – review & editing. **Urs Fischer:** Writing – review & editing. **Marcel Arnold:** Writing – review & editing. **Simon Jung:** Writing – review & editing, Supervision, Conceptualization. **Philipp Bücke:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Morin Beyeler:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

Dr. Arnold reports personal fees from Bayer, Bristol-Myers Squibb, Medtronic, Amgen, Daiichi Sankyo, Nestlé Health Sciences, Boehringer Ingelheim, and Covidien during the conduct of the study.

Dr. Jung reports grants from the Swiss National Science Foundation and the Swiss Heart Foundation.

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None of the other authors report any conflicts of interest.

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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.2024.107834.

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# Absence of the susceptibility vessel sign in cancer-related strokes

Title of the manuscript: Absence of susceptibility vessel sign in patients with malignancy-related acute ischemic stroke treated with mechanical thrombectomy

Contributions of the PhD candidate:

- Conceptualization
- Data curation
- Formal analysis
- Visualization
- Writing – original draft

Results summary:

The susceptibility vessel sign (SVS) in magnetic resonance imaging (MRI) can be used for non-invasive, in situ characterization of thrombi. The presence of the SVS has been associated with a high proportion of erythrocytes and low proportion of platelets and fibrin in retrieved thrombi. Given that cancer-related strokes had previously been associated with platelet and fibrin-rich thrombi, we investigated whether the absence of the SVS was directly associated with the presence of cancer-related strokes. We used our retrospective, monocentric BEYOND SWIFT database, which included AIS patients treated with mechanical thrombectomy between 2010 and 2018.

Of 577 patients with AIS who had assessable SVS status, 40 (7%) had documented active cancer and 72 (13%) showed no SVS. We demonstrated that the absence of the SVS was associated with active cancer (aOR 4.85, 95% CI 1.94–12.11) or occult cancer (aOR 11.42, 95% CI 2.36–55.20). The performance of predictive models for cancer-related strokes incorporating and excluding SVS status was compared using areas under the receiver operating characteristics curve (auROC). The auROC of predictive models, including demographics and common cancer biomarkers, was higher when SVS status was included but not significantly so (0.85 vs 0.81, p = 0.07).

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# Absence of Susceptibility Vessel Sign in Patients With Malignancy-Related Acute Ischemic Stroke Treated With Mechanical Thrombectomy

*Morin Beyeler[1,2*†], Nebiyat F. Belachew[3,4†], Moritz Kielkopf[1], Enrique B. Aleman[4], Alejandro Xavier León Betancourt[1], Kotryna Genceviciute[1], Christoph Kurmann[3], Lorenz Grunder[3], Barbara Birner[1], Thomas R. Meinel[1], Adrian Scutelnic[1], Philipp Bücke[1], David J. Seiffge[1], Tomas Dobrocky[3], Eike I. Piechowiak[3], Sara Pilgram-Pastor[3], Heinrich P. Mattle[1], Pasquale Mordasini[3], Marcel Arnold[1], Urs Fischer[1,5], Thomas Pabst[6], Jan Gralla[3], Martin D. Berger[6], Simon Jung[1†] and Johannes Kaesmacher[3*†]*

[1] Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [2] Graduate School for Health Sciences, University of Bern, Bern, Switzerland, [3] Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [4] Department of Neuroradiology, Faculty of Medicine, Medical Center – University of Freiburg, University of Freiburg, Freiburg, Germany, [5] Department of Neurology, University Hospital of Basel, University of Basel, Basel, Switzerland, [6] Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

**Background and Purpose:** Clots rich in platelets and fibrin retrieved from patients with acute ischemic stroke (AIS) have been shown to be independently associated with the absence of the susceptibility vessel sign (SVS) on MRI and active malignancy. This study analyzed the association of SVS and the presence of active malignancy in patients with AIS who underwent mechanical thrombectomy (MT).

**Methods:** This single-center, retrospective, and cross-sectional study included consecutive patients with AIS with admission MRI treated with MT between January 2010 and December 2018. SVS status was evaluated on susceptibility-weighted imaging. Adjusted odds ratios (aORs) were calculated to determine the association between absent SVS and the presence of active or occult malignancy. The performance of predictive models incorporating and excluding SVS status was compared using areas under the receiver operating characteristics curve (auROC).

**Results:** Of 577 patients with AIS with assessable SVS status, 40 (6.9%) had a documented active malignancy and 72 (12.5%) showed no SVS. The absence of SVS was associated with active malignancy (aOR 4.85, 95% CI 1.94–12.11) or occult malignancy (aOR 11.42, 95% CI 2.36–55.20). The auROC of predictive models, including demographics and common malignancy biomarkers, was higher but not significant (0.85 vs. 0.81, $p = 0.07$) when SVS status was included.

**Conclusion:** Absence of SVS on admission MRI of patients with AIS undergoing MT is associated with malignancy, regardless of whether known or occult. Therefore, the SVS might be helpful in detecting paraneoplastic coagulation disorders and occult malignancy in patients with AIS.

**Keywords: susceptibility vessel sign, malignancy-related stroke, biomarkers, paraneoplastic coagulation disorders, ischemic stroke, mechanical thrombectomy, thrombus composition/occult malignancy**

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*Wen-Jun Tu,*
*Chinese Academy of Medical Sciences and Peking Union Medical College, China*

***Reviewed by:***
*Yang-Ha Hwang,*
*Kyungpook National University, South Korea*
*Neil Haranhalli,*
*Montefiore Medical Center, United States*

***Correspondence:**
*Morin Beyeler*
*morin.beyeler@insel.ch*
*Johannes Kaesmacher*
*johannes.kaesmacher@insel.ch*

*†These authors have contributed equally to this work*

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## INTRODUCTION

Patients with malignancy-related strokes are more likely to suffer more severe or fatal or recurrent strokes compared to other patients with stroke (1–3). Identifying patients with malignancy in the acute stroke setting would allow targeted treatment and secondary prevention and might improve outcome (4, 5). Thus, easily accessible biomarkers associated with malignancy are needed. Clots in patients with stroke with active malignancy retrieved *via* mechanical thrombectomy (MT) have been shown to contain more fibrin and platelets than clots from other patients (4, 6). A noninvasive, *in situ* characterization of clots may be achieved through appropriate imaging. Whereas computed tomography (CT) merely provides information on the density of the clot, magnetic resonance imaging (MRI) may allow more sophisticated characterization of their composition. The susceptibility vessel sign (SVS) identified on T2* gradient recalled echo imaging (T2* GRE) and susceptibility-weighted imaging (SWI) in brain MRI may serve this purpose (7, 8). The underlying stroke etiology influences the clot composition and, consequently, the SVS status on cerebral imaging (9). Thrombi from cardioembolic stroke and large artery atherosclerosis stroke (LAA) have a high proportion of erythrocytes in their histopathological composition (10, 11). Interestingly, a study also described a high proportion of platelets in thrombi from patients with LAA (12). Currently, only cardioembolic stroke has been associated with the presence of SVS (13, 14). In opposition, clots due to hypercoagulation states (a.o. disseminated intravascular coagulation by underlying malignancy) tend to be composed of more fibrin and platelet and seem to be more associated with absence of SVS (11, 15). Based on the current data, we hypothesized that the absence of SVS, which may indicate platelet and fibrin-rich thrombi, may also be associated with active malignancy. The aim of this study was to test this hypothesis and analyze models that include the SVS to predict the likelihood of active malignancy in patients with AIS.

## METHODS

### Study Cohort

This retrospective study evaluated all consecutive patients with stroke treated with MT at our comprehensive stroke center between January 1, 2010, and December 31, 2018. Inclusion criteria were as follows: (1) Ischemic stroke with at least one intracranial symptomatic occlusion on angiography, (2) MRI and SWI performed at admission, (3) SVS status assessable, and (4) MT performed. Patients who received intravenous thrombolytics before blood for laboratory analyses was drawn were excluded from some subanalyses. The local ethics committee approved the study in accordance with Swiss law (reference ID: 2019-00547, Kantonale Ethikkomission Bern). Study approval was restricted to patients treated with MT.

**Abbreviations:** AIS, acute ischemic stroke; CRP, C-reactive protein; DWI, diffusion-weighted imaging; ESUS, embolic stroke of undetermined source; INR, international normalized ratio; LAA, large artery atherosclerosis stroke; LR, likelihood ratio; MT, mechanical thrombectomy; NPV, negative predictive value; PPV, positive predictive value; SVS, susceptibility vessel sign; SWI, susceptibility-weighted imaging.

### Definition of Active Malignancy

Active malignancy was defined according to the Haemostasis and Malignancy Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (16, 17). Malignancy diagnosed within 1 year after the index stroke was defined as occult malignancy. However, occult malignancy was also considered active at the time of stroke and thus represented a subset of the active malignancy group (18–20). Patients with focal nonmelanoma skin cancer were excluded due to the nonsystemic nature of the disease and its low risk of metastatic spread (21). Patients receiving secondary prophylactic hormone therapy after breast cancer were considered in complete remission and without active malignancy (22, 23).

### Imaging Analysis

Imaging was performed on a 1.5 T or 3 T MR imaging scanner (1.5 T: Magnetom Avanto or Magnetom Aera; 3T: Magnetom Verio; Siemens). Magnetom Avanto 1.5 T SWI and 1.5 T Magnetom Aera SWI were performed with the following parameters: TR, 49 ms; TE, 40 ms; flip angle, 15.0°; section thickness, 1.6, 1.8, or 2.0 mm; and intersection gap, 0 mm. Magnetom Verio 3T SWI was performed with the following parameters: TR, 27 ms; TE, 20 ms; flip angle, 15.0°; section thickness, 2.0 mm; and intersection gap, 0 mm. The detailed method used to determine the presence of SVS in the cohort analyzed in this article was described by N. Belachew et al. in a previous publication (24). To summarize, SVS status was assessed retrospectively by two independent neuroradiologists (N.F.B. and E.B.A.). Both raters were blinded to clinical information and outcome, and were not involved in any patient treatment. Regardless of its diameter, SVS was determined to be present if a distinct signal loss corresponding to an occluded and symptomatic intracranial artery could be identified (**Figures 1A,B**), for which there was no alternative explanation (i.e., neighboring vein, petechial hemorrhage, or microcalcification in the neighboring parenchyma). If no such signal loss could be identified even though a symptomatic vessel occlusion was seen on angiography, SVS was determined to be absent (**Figures 1C,D**). Interrater reliability regarding SVS evaluation for the study cohort analyzed in this article has been assessed and published in a previous study showing very good correlation (Cohen's $\kappa = 0.873$, $p < 0.001$) (24).

### Data Collection

Demographics and baseline stroke characteristics were extracted from the local stroke registry. They included gender, age at admission, prestroke independence (defined as a modified Rankin Scale $\leq$ 2), blood pressure at admission, prior anticoagulation/antiplatelet therapy, prior statin therapy, cardiovascular risk factors (such as hypertension, diabetes, hyperlipidemia, smoking), National Institutes of Health Stroke Scale on admission, time between symptom-onset/last-seen-well and admission, intravenous thrombolytics before MT, and site of occlusion. Two neurology fellows (M.B. and M.K.), both blinded

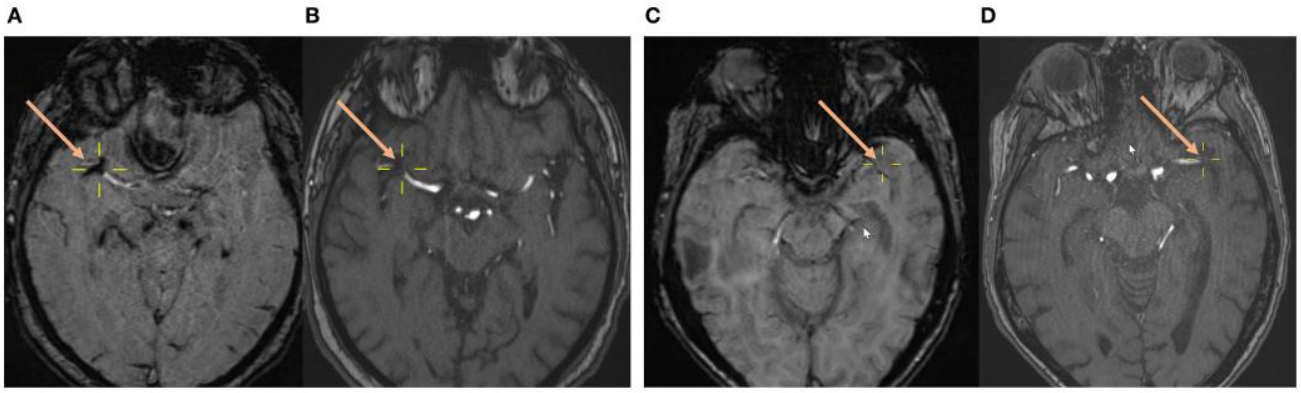


**FIGURE 1 |** Assessment of the susceptibility vessel sign status on baseline brain MRI. **(A,B)** A 74-year-old male patient with AIS and visible SVS as a circumscribed signal loss on the SWI **(A)** with complete occlusion of the right MCA (M1 segment) on arterial TOF **(B)**. **(C,D)** A 77-year-old female patient with AIS and absent SVS on the SWI **(C)** despite complete occlusion of the left MCA (M1 segment) on arterial TOF **(D)**. *Yellow crosshairs* and *salmon arrows* center, respectively, point to the proximal part of the vessel occlusion on SWI and TOF. AIS, acute ischemic stroke; MCA, middle cerebral artery; SVS, susceptibility vessel sign; SWI, susceptibility-weighted imaging; TOF, time-of-flight angiography.

to the SVS status, retrospectively identified active malignancy (known or occult at the time of stroke) from histological and clinical reports present in the clinical information system. After patients' identification, malignancy localization, histological type, metastatic state, and time metrics related to the malignancy diagnosis and treatment were extracted. The presence of multiterritory infarcts and the assigned stroke etiology at discharge, defined by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, was also extracted from neuroradiological reports and discharge letters (25). According to the TOAST classification, strokes associated with patent foramen ovale were classified as cardioembolic stroke. A subdivision between intracranial atherosclerosis and artery-to-artery embolism was made for LAA. Embolic stroke of undetermined source (ESUS) was assumed when nonlacunar ischemic stroke occurred in patients in which another underlying stroke etiology in line with the definition of the "NAVIGATE ESUS" trial could not be determined (26). The following laboratory values at admission were extracted from the hospital's clinical information system: D-dimer, fibrinogen, hemoglobin (Hb), C-reactive protein (CRP), leukocytes, thrombocytes, international normalized ratio (INR), thrombin time, and activated partial thromboplastin clotting time.

## Statistical Analysis

Baseline characteristics were compared using Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. Descriptive statistics were reported as number and percentage for categorical variables, and median and interquartile range (25–75%) for continuous variables. A logistic transformation was applied if the distribution of continuous values was skewed. The association between the SVS status and active malignancy was assessed using simple and multivariable logistic regression models. Results are displayed as odds ratios (ORs) and adjusted odds ratios (aORs). The association of SVS status with occult malignancies was assessed in a sensitivity analysis. All models were adjusted for demographic characteristics (such as gender and age at admission) and malignancy biomarkers known to be associated with malignancy-related stroke such as ESUS, multiterritory infarcts, D-dimer, leukocytes, CRP, INR, and Hb. The predictive value of SVS status was evaluated by assessing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR–). The performance of predictive models, including and excluding SVS status, was assessed by calculating areas under the receiver operating characteristics curve (auROC). The auROCs were cross-validated using bootstrapping, whereas they were compared using the DeLong test. All statistical analyses were performed using the Stata 16 and R software (version 3.6.0, R Core Team). The current STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies was used to report this study.

# RESULTS

## Study Population

Between January 2010 and December 2018, 1,317 patients with AIS were treated with MT at our stroke center. As already described by Belachew et al. and shown in **Supplementary Figure I** (study flowchart), 577 patients had SWI with assessable SVS status available at admission and met the inclusion criteria (24). Evidence of active malignancy at the time of stroke was found in 40 patients (6.93%), of which a subset of 9 patients (1.56%) had occult malignancy. Active malignancy characteristics are summarized in **Supplementary Figure II**. A total of eight patients (1.39%) were excluded from subgroup analysis of blood markers as they had received intravenous thrombolytics before blood was drawn for further analysis.

## Baseline Characteristics

The characteristics of patients with and without active malignancy are summarized in **Supplementary Table I**. SVS was absent in 12.5% of all patients ($n = 72/577$). Of the patients

with active malignancy, SVS was absent in 37.5% ($n = 15/40$), while only 4.3% (57/537, $p < 0.001$) of patients without active malignancy lacked the SVS. Patients with active malignancy were more likely to be functionally dependent before the index stroke, had lower diastolic blood pressure (<90 mmHg), and more often showed anterior and more distal middle cerebral artery occlusions. Intravenous thrombolysis before MT was less often administered to patients with stroke with active malignancy compared to patients without malignancy. ESUS and multiterritory infarcts were more frequent in the group with active malignancy. Active malignancy was associated with elevated D-dimer, low Hb, elevated CRP, elevated leukocytes, and higher INR.

## Association of Active Malignancy With Absence of SVS and Other Biomarkers

Simple logistic regression demonstrated absent SVS to be associated with active malignancy, multiterritory infarcts, elevated D-dimer, ESUS, elevated CRP, elevated leukocytes, and low Hb. All simple regression analyses are summarized in **Supplementary Figure III**. Multivariable regression analyses showed significant associations of active malignancy and absent SVS, multiterritory infarcts, elevated D-dimer, elevated leukocytes, and low Hb. Results of multivariable regression analyses, including ORs and 95% confidence intervals, are summarized in **Figure 2**.

## Diagnostic Value of SVS Status in Identifying Active Malignancy

Absence of SVS alone predicted active malignancy as follows: sensitivity 20.83%, specificity 95.05%, PPV 37.5%, NPV 89.38%, LR+ 4.21, and LR– 0.83. Predictive models incorporating age at admission, gender, and variables associated with active malignancy in the multivariate logistic regression as well as SVS status were tested. The auROC of the model, including SVS status, was 0.85 (95% CI 0.78–0.92, **Figure 3A**). The internal cross-validation using bootstrapping demonstrated no variation of auROC and 95% CI. If SVS status was excluded, the auROC of the model was 0.81 (95% CI 0.72–0.90, **Figure 3B**) while the internal cross-validation showed an auROC of 0.82 (95% CI 0.68–0.90). The DeLong test did not find a significant difference between the two models ($p = 0.07$).

Subgroup analyses using the same covariates as in the multivariate logistic regression showed that the absence of SVS remained associated with occult malignancy alone (aOR 11.42, 95% CI 2.36–55.20, $p = 0.002$) when patients with active malignancy diagnosed before the stroke were excluded. Absence of SVS predicted occult malignancy as follows: sensitivity 8.06%, specificity 99.17%, PPV 55.50%, NPV 89.38%, LR+ 9.76, and LR– 0.93.

## Subgroup Analyses According to the Underlying Stroke Etiology

According to the assigned stroke etiology, the point estimate of the association between absence of SVS and the presence of active malignancy differed slightly (**Supplementary Figure IV**). However, there was no significant heterogeneity of the association between absence of SVS and active malignancy ($p = 0.24$). After excluding patients with LAA ($n = 74$, two without SVS), the aOR for the association decreased from 4.89 (95% CI 1.94–12.11, **Figure 2**) to aOR 3.9 (95% CI 1.42–10.50). Excluding only cases where intracranial stenosis was the stroke etiology ($n = 11$, one without SVS) the aOR decreased to 4.77 (95% CI 1.91–11.89).

# DISCUSSION

The main findings of this study are as follows: (1) absence of SVS is associated with both active and occult malignancy in patients with ischemic stroke treated with MT; (2) absence of SVS in admission MRI as imaging biomarker may increase the performance of predictive models for active malignancy in patients with AIS; and (3) the association between the absence of SVS and active malignancy seems not to be influenced by the assigned etiology at discharge. Approximately 8% of patients with acute stroke have a concomitant active malignancy (known or occult) at the time of stroke (4, 27). Identifying the malignancy as the potential cause of the stroke in these patients is essential to guide secondary prevention, which includes therapeutic anticoagulation with low-molecular-weight heparin (4, 5). Strokes with concomitant malignancy are associated with nonspecific biomarkers such as elevated D-dimer, elevated CRP, elevated fibrinogen, elevated lactate dehydrogenase, low Hb, undetermined stroke etiology (especially ESUS), and multiterritorial infarcts in brain imaging (3, 4, 18, 28). These biomarkers may help to detect a malignancy-related coagulation disorder. However, proving the causality between active malignancy and an ischemic stroke event remains difficult. Considering the potential clinical ramifications, the search for further biomarkers that may improve the likelihood of detecting malignancy-related coagulopathy and occult malignancy at the time of stroke is warranted. Finelli et al. were the first to describe multiterritory infarcts seen on diffusion-weighted imaging as an independent imaging biomarker for malignancy-related stroke (29). Guo et al. demonstrated a specificity of 0.65 and a sensitivity of 0.92 for the prediction of occult malignancy in patients with stroke with undetermined stroke etiology if two or more vascular territories are affected (30). The results of our study add to the current evidence regarding the advantage of brain MRI in patients with malignancy-related stroke.

Susceptibility-weighted sequences such as T2* GRE and SWI are central to the MRI-based acute stroke workup (31, 32). SWI sequences provide reliable information on a potential hemorrhagic transformation but may also outline the occluded vessel depending on clot composition (9, 13, 15, 33, 34). Among others, Zhang et al. reported SVS to be present in 90% of cardioembolic strokes ($n = 35/39$), 53.5% of large-artery atherosclerosis strokes ($n = 23/43$), and 75.9% of strokes with undetermined etiology ($n = 22/29$), indicating that SVS status may differ depending on stroke etiology (13, 33, 34). However, a recent meta-analysis confirmed only the association between SVS and cardioembolic stroke (14). Histopathological

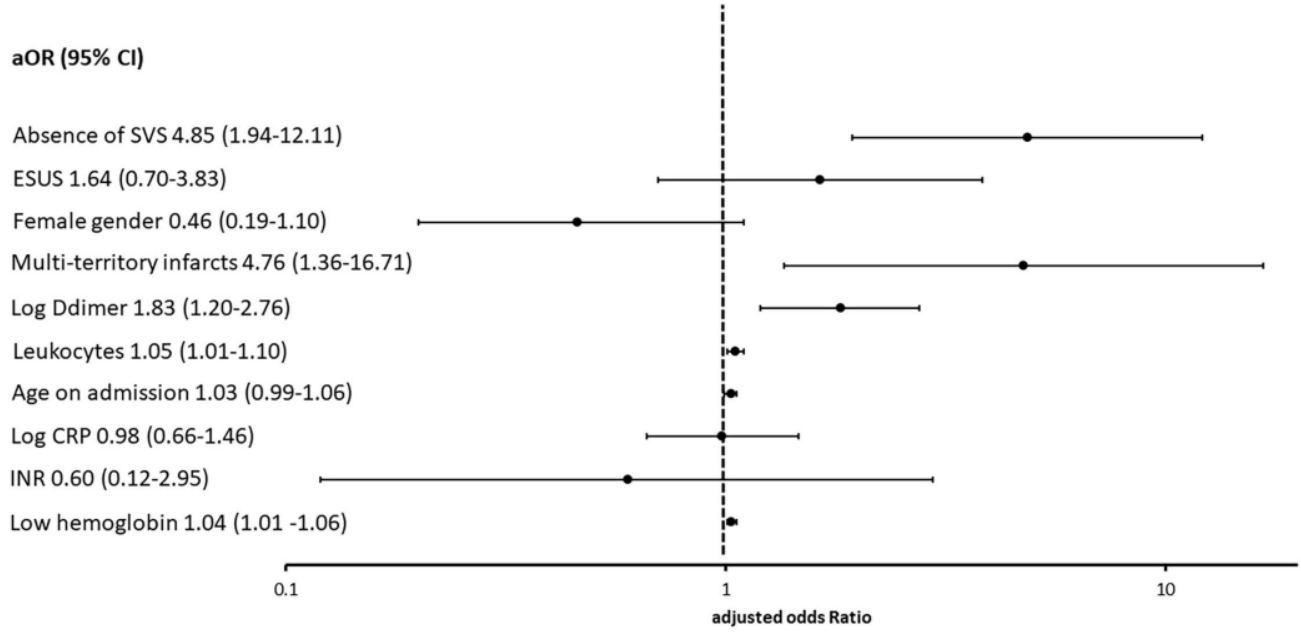


**FIGURE 2 |** Association between active malignancy, neuroimaging, and blood biomarkers in the multivariable logistic regression. According to the primary goal of this study and previous evidence, adjusted odds ratios (aOR) and their 95% confidence intervals (95% CI) for the association between active malignancy and preselected biomarkers are summarized in this figure. Absence of SVS showed the strongest association with the presence of active malignancy, followed by multiterritory infarcts. CRP, C-reactive protein; ESUS, embolic stroke of undetermined source; INR, international normalized ratio; SVS, susceptibility vessel sign.

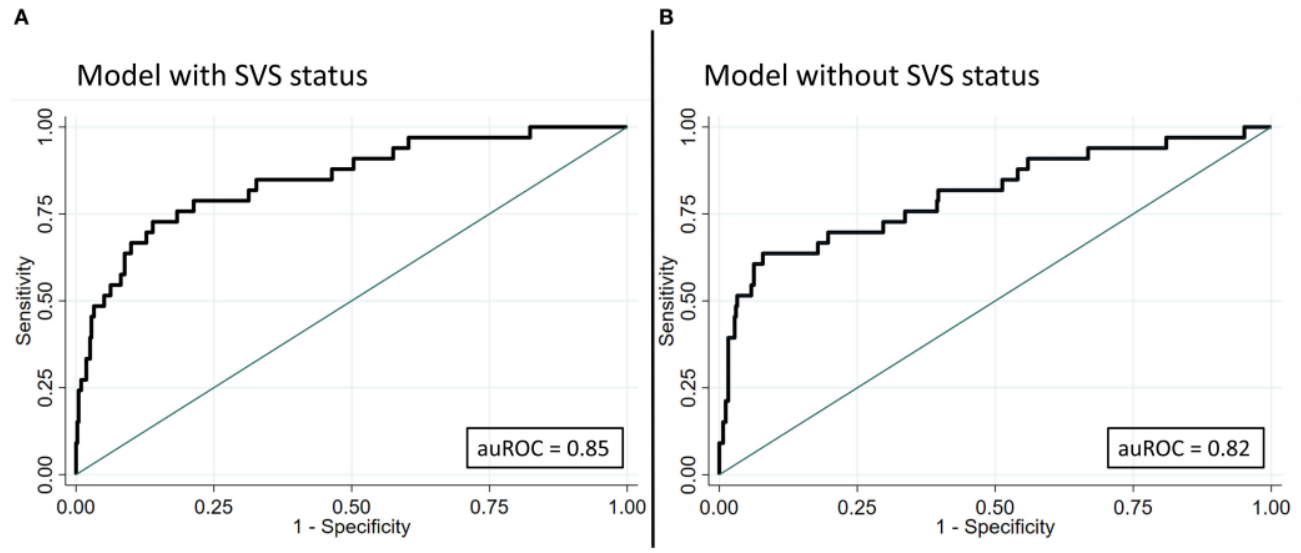


**FIGURE 3 |** Comparison of predictive models for active malignancy with and without SVS status. The covariables used for the predictive models were age at admission and gender and variables associated with active malignancy in the multivariable logistic regression (ESUS, multiterritory infarcts, D-dimer, Hb, leukocytes). The auROC of the model with SVS status was 0.85 (95% CI 0.78–0.92, **A**). The internal cross-validation demonstrated no variation of the auROC and 95% CI. In the absence of the SVS status, the auROC of the model was 0.81 (95% CI 0.72–0.90, **B**), the internal cross-validation showed an auROC of 0.82 (95% CI 0.68–0.90). The DeLong test did not show a significant difference between the two models ($p = 0.074$). auROC, area under the receiver operating characteristics curve; CRP, C-reactive protein; ESUS, embolic stroke of undetermined source; Hb, hemoglobin; SVS, susceptibility vessel sign.

analyses after MT have shown that thrombi with a cardioembolic genesis predominantly contain erythrocytes (35). Platelet and fibrin-rich thrombi have been shown to be independently associated with malignancy-related stroke, hypercoagulation, and the absence of SVS (4, 6, 11, 15, 36). Our study adds to this knowledge. It demonstrates that absent SVS is associated with active malignancy in AIS treated with MT, irrespective of whether known or unknown at time of stroke. Although the association between the absence of SVS and the presence of malignancy differed slightly by the assigned stroke etiology (**Supplementary Figure IV**), the lack of interaction did not allow any conclusions regarding the role of the assigned etiology on the relation between the absence of SVS and the presence of active malignancy. The exclusion of LAA did not increase the association between the absence of SVS and malignancy in our study population, thus suggesting no association between absent SVS and LAA (13). Predictive models for diagnostic workup are generally developed to help in decision-making for further investigations in complex clinical situations (37, 38). However, this study did not aim to conceptualize a new predictive model for active malignancy but rather to validate the SVS status as an additional biomarker. Although the difference in the auROCs only tended to be greater with SVS included, a more sophisticated SVS evaluation (i.e., quantitative susceptibility mapping) may increase predictive performance (39, 40). As MRI may not always be available or practicable in the acute stroke setting, density, which has also been shown to correlate with erythrocyte content, may be used in patients imaged with CT (33). Furthermore, the macroscopic characteristics of clots retrieved with MT ("white" indicating fibrin-rich thrombi vs. "red-black" indicating erythrocyte-rich thrombi) may provide additional hints about their composition (36, 41). In the same context, Bourcier et al. recently demonstrated an association between "red-black" clots and the presence of SVS, strengthening the evidence that SVS status is a reliable biomarker for their composition (15).

## LIMITATIONS

This study has several limitations. First, this was a monocentric and retrospective study, which may limit generalizability of results. Second, in accordance with the terms of the ethical approval, we included only patients who underwent MT. Further studies are needed to confirm our findings in a more general stroke population. Third, although the percentage of malignancies is consistent with studies in the literature, the small number of active or occult malignancies may reduce the statistical power of the results obtained. Additionally, the small number of malignancies precluded accurate subgroups analyses regarding assigned stroke etiology. Because the underlying etiology may influence the thrombus composition, further studies with more patients are needed. Fourth, the high rate of SVS reported in this study may result from a selection bias due to a specific subpopulation of patients with stroke eligible for thrombectomy and the inhomogeneous use of 1.5 and 3 T MRI. Fifth, concomitant microscopic analysis of the retrieved thrombi would have provided a more robust validation of the study hypothesis, assuming that the absence of SVS is a surrogate marker of platelet and fibrin-rich thrombi in case of malignancy-related stroke. Sixth, the comparison of predictive models is limited by the lack of an external validation group and by power considerations comparing auROC of different models according to the number of active malignancies. Finally, levels of lactate dehydrogenase, a well-known marker for the presence of active malignancy, were not available (3).

## CONCLUSION

Absent SVS on baseline MRI is associated with active malignancy in patients with AIS undergoing MT, regardless of whether the malignancy is known or unknown at the time of stroke. Using SVS as surrogate marker for clot composition may increase the chances of detecting occult malignancy in patients with AIS, which could be helpful both for the treatment of the malignancy and secondary stroke prevention and thus may lead to better outcomes.

## DATA AVAILABILITY STATEMENT

Data are available upon reasonable request, access requests should be directed to the authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kantonale Ethikkomission Bern. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

MB contributed to conception and design, data acquisition, analysis and interpretation of data, and writing of the publication. NB contributed to conception and design, data acquisition and writing of the publication. MK and EA contributed to data acquisition and critical revision of the manuscript for important intellectual content. KG and BB contributed to conception and design, and critical revision of the manuscript for important intellectual content. SJ and JK contributed to conception and design, critical revision of the publication for important intellectual content, and supervision. AL, CK, LG, TM, AS, PB, DS, TD, EP, SP-P, HM, PM, MA, UF, TP, JG, and MDB contributed to interpretation of data and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material and the STROBE checklist for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.930635/full#supplementary-material

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## Assessment of other thrombus imaging characteristics

Title of the manuscript: Absence of susceptibility vessel sign and hyperdense vessel sign in patients with cancer-related stroke

Contributions of the PhD candidate:

- Conceptualization
- Data curation
- Formal analysis
- Visualization
- Writing – original draft

Results summary: As the first study presented above was restricted to AIS patients treated with mechanical thrombectomy, in this study we generalized our results by investigating the association between the absence of SVS and the presence of active cancer in all AIS patients using our BMS database. We also assessed whether there was a correlation between the presence of active cancer in AIS patients and the absence of the hyperdense vessel sign (HVS), the counterpart of the SVS in computed tomography imaging. Of the 2256 patients whose thrombus imaging characteristics at baseline were available, 161 had active cancer (7%), of which 36 were occult at the time of index stroke (2% of the total). We were able to confirm the association between the absence of SVS and the presence of underlying cancer in all AIS patients (aOR 3.14, 95% CI 1.45–6.80). However, there was no association between HVS and the presence of cancer (aOR 1.07, 95% CI 0.54–2.11).

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EDITED BY
Shinichiro Uchiyama,
Sanno Medical Center,
Japan

REVIEWED BY
Kwon-Duk Seo,
National Health Insurance Service Ilsan Hospital,
Republic of Korea
Moritz Schmidbauer,
Ludwig Maximilian University of Munich,
Germany

*CORRESPONDENCE
Morin Beyeler
morin.beyeler@insel.ch
Johannes Kaesmacher
johannes.kaesmacher@insel.ch

†These authors have contributed equally to this work

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# Absence of susceptibility vessel sign and hyperdense vessel sign in patients with cancer-related stroke

Morin Beyeler[1,2*†], Lorenz Grunder[3†], Jayan Göcmen[1], Fabienne Steinauer[1], Nebiyat F. Belachew[4], Moritz Kielkopf[1], Leander Clénin[1], Madlaine Mueller[1], Norbert Silimon[1], Christoph Kurmann[3], Thomas Meinel[1], Philipp Bücke[1], David Seiffge[1], Tomas Dobrocky[3], Eike I. Piechowiak[3], Sara Pilgram-Pastor[3], Heinrich P. Mattle[1], Babak B. Navi[5], Marcel Arnold[1], Urs Fischer[1,6], Thomas Pabst[7], Jan Gralla[3], Martin D. Berger[7], Simon Jung[1†] and Johannes Kaesmacher[3*†]

[1]Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland, [2]Graduate School for Health Sciences, University of Bern, Bern, Switzerland, [3]Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland, [4]Department of Neuroradiology, University Hospital, Freiburg, Germany, [5]Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, NY, United States, [6]Neurology Department, University Hospital of Basel, University of Basel, Basel, Switzerland, [7]Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

**Background and aim:** Identification of paraneoplastic hypercoagulability in stroke patients helps to guide investigations and prevent stroke recurrence. A previous study demonstrated an association between the absence of the susceptibility vessel sign (SVS) on brain MRI and active cancer in patients treated with mechanical thrombectomy. The present study aimed to confirm this finding and assess an association between the absence of the hyperdense vessel sign (HVS) on head CT and active cancer in all stroke patients.

**Methods:** SVS and HVS status on baseline imaging were retrospectively assessed in all consecutive stroke patients treated at a comprehensive stroke center between 2015 and 2020. Active cancer, known at the time of stroke or diagnosed within 1year after stroke (occult cancer), was identified. Adjusted odds ratios (aOR) and their 95% confidence interval (CI) for the association between the thrombus imaging characteristics and cancer were calculated using multivariable logistic regression.

**Results:** Of the 2,256 patients with thrombus imaging characteristics available at baseline, 161 had an active cancer (7.1%), of which 36 were occult at the time of index stroke (1.6% of the total). The absence of SVS was associated with active cancer (aOR 3.14, 95% CI 1.45–6.80). No significance was reached for the subgroup of occult cancer (aOR 3.20, 95% CI 0.73–13.94). No association was found between the absence of HVS and active cancer (aOR 1.07, 95% CI 0.54–2.11).

**Conclusion:** The absence of SVS but not HVS could help to identify paraneoplastic hypercoagulability in stroke patients with active cancer and guide patient care.

KEYWORDS

cancer-related stroke, thrombus imaging characteristics, susceptibility vessel sign, hyperdense vessel sign, malignancy-related stroke

# Introduction

Cancer-related strokes are generally more severe than other stroke types and associated with an increased risk of stroke recurrence and poor outcomes (1, 2). Therefore, it is essential to identify them and initiate timely and adequate secondary prevention (3). Furthermore, earlier detection of occult cancer (defined as unknown cancer with ischemic stroke as first manifestation) in stroke patients would allow more rapid treatment of cancer, which could improve patient outcomes (4–7). Cancer-related strokes are often caused by paraneoplastic hypercoagulability and associated with abnormal coagulation and blood parameters [such as elevated D-dimer and C-reactive protein (CRP), lower hemoglobin (Hb)] as well as multiterritorial infarcts (8–10). In addition, fibrin and platelet-rich thrombi retrieved during mechanical thrombectomy are associated with cancer in stroke patients (11, 12). The composition of intracranial thrombi can be assessed non-invasively and *in situ* with thrombus imaging characterization as a surrogate marker (13). Our previous study demonstrated an association between the absence of the susceptibility vessel sign (SVS) in susceptibility-weighted imaging (SWI) on brain magnetic resonance imaging (MRI) and active cancer in patients treated with mechanical thrombectomy (14). The reason for the absence of SVS with active cancer may be due to a predominance of fibrin and platelets and a relative paucity of erythrocytes in these patients thrombus composition (11, 12, 15). The present study aimed to validate the association between the absence of SVS and active cancer in all stroke patients. Furthermore, we aimed to evaluate an association between active cancer and the absence of the hyperdense vessel sign (HVS) in native computed tomography (CT) as the absence of HVS has also been shown to be associated with fibrin and platelet-rich thrombi (16, 17).

# Methods

## Study population

This retrospective cohort study comprised consecutive patients diagnosed with acute ischemic stroke from January 1, 2015 to December 31, 2020 who were entered into our prospective institutional stroke registry. Study inclusion criteria were: (1) an acute ischemic stroke with the presence of at least one symptomatic intracranial arterial occlusion, (2) available acute imaging for review from an internal or external (before referral) baseline MRI brain scan with SWI sequences or CT head scan with standard sequences, and (3) sufficient quality of an acute baseline brain imaging sequences to assess for SVS and/or HVS (study flowchart – Supplementary Figure S1). Patients who underwent intravenous thrombolysis (IVT) before available baseline imaging were excluded. Additionally, when IVT was administered after baseline imaging but before blood examination, these patients were excluded from a secondary analysis involving blood biomarkers. The ethics committee approved the study's conduct in accordance with Swiss law (reference ID: 2021-01031, Kantonale Ethikkomission Bern). According to the ethics committee's decision, no informed consent was required for the inclusion of patients in the study.

## Definition of active cancer and occult cancer

Active cancer was identified according to the definition from the Haemostasis and Malignancy Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (18, 19). Newly diagnosed cancer within one year after the index stroke was defined as "occult cancer" at the time of stroke and considered an active cancer for the purposes of this study (4, 20, 21). As defined previously, patients with focal non-melanoma skin cancer and those treated with prophylactic hormone therapy for prior breast cancer were classified as not having active cancer (14, 22, 23).

## Imaging analysis

Acute imaging was performed on a 1.5 T or 3 T MR imaging scanner (Magnetom Avanto, Magnetom Aera, Magnetom Verio and Magnetom Vida; Siemens, Erlangen, Germany). 1.5 T SWI was performed with the following parameters: Repetition time (TR), 49 ms; echo time (TE), 40 ms; flip angle, 15.0°; section thickness, 1.6, 1.8, or 2.0 mm; and intersection gap, 0 mm. 3 T SWI was performed with the following parameters: TR, 27 ms; TE, 20 ms; flip angle, 15.0°; section thickness, 2.0 mm; and intersection gap, 0 mm. Standard native CT was performed on a 128-row CT scanner (Siemens SOMATOM Edge, Siemens Erlangen, Germany) by use of CarekV (Quality reference of 120 kV), modulated milliampere-seconds (mAs) with CareDose4D (Quality reference of 290 mAs), with 1.0 mm section thickness. CT angiography consisted of 0.6 mm slice thickness bolus-triggered acquisition, 1 mm slice thickness late venous acquisition with a 75-s delay after bolus administration. The side and site of intracranial arterial occlusion as well as the SVS and HVS status were assessed by a stroke neurologist and a neuroradiologist (M.B. and L.G.). Both raters were blinded to baseline characteristics and clinical outcomes. The SVS status was assessed according to the method described previously by Belachew et al. (24) SVS was considered to be present if signal loss corresponded to the symptomatic intracranial occlusion and no alternative reason existed (Figures 1A,B). HVS status was determined intrinsically on native CT at the location directly corresponding to the occlusion site on CT angiography. HVS was considered present in the case of local hyperdensity by co-locating the occluded artery with its contralateral homologue and the surrounding brain tissue (Figures 1C,D) (25).

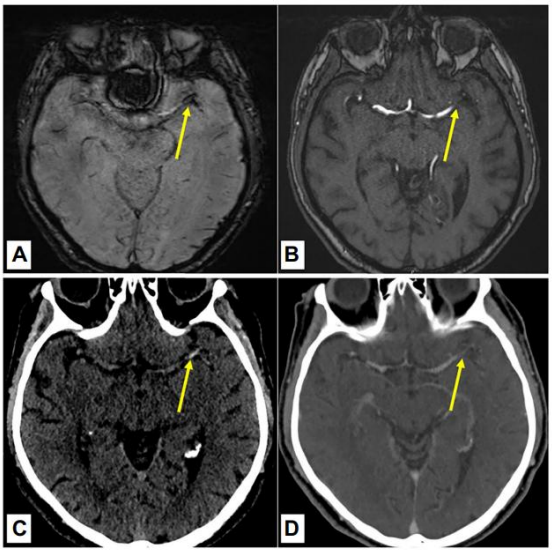


FIGURE 1
Assessment of the susceptibility vessel sign and hyperdense vessel sign status on baseline brain imaging. **(A,B)** 70-year-old male patient with an acute ischemic stroke due to the occlusion of the left MCA (M1 segment) diagnosed on baseline brain MRI with present SVS (arrowhead) as local hypointensity on the SWI **(A)** with confirmation of occlusion on the arterial TOF **(B)**. **(C,D)** Externally performed CT imaging of the same patient before referring for thrombectomy. Presence of HVS (arrowhead) as local hyperdensity in native CT **(C)** with confirmation of occlusion in the CT angiography **(D)**. Yellow arrows point to the proximal part of the vessel occlusion. HVS indicates hyperdense vessel sign; MCA, middle cerebral artery; SVS, susceptibility vessel sign; SWI, susceptibility weighted imaging and TOF, time of flight angiography.

Interrater reliability between investigators, as determined by Cohen's Kappa coefficient, was sustainable (0.770 for SVS and 0.610 for HVS). As HVS is more frequent in proximal than distal occlusions and the imaging characterization of thrombi is more accurate in proximal occlusion, we distinguished between proximal and distal occlusions for subgroup analysis (26). Visible vessel occlusions at baseline were assessed on CT angiography, time-of-flight MR angiography or contrast-enhanced MR angiography. Proximal occlusions were defined as intracranial occlusion of the internal carotid artery, M1 and M2 segments of the middle cerebral artery, A1 segment of the anterior cerebral artery, P1 segment of the posterior cerebral artery, vertebral artery and any segment of the basilar artery. Other occlusions were categorized as distal.

## Data collection

Demographics and baseline stroke characteristics were extracted from the local stroke registry. This included gender, age, prestroke independence (modified Rankin Scale ≤2), admission blood pressure, prior treatment with anticoagulants, antiplatelet drugs and lipid-lowering drugs, cardiovascular risk factors, National Institutes of Health Stroke Scale (NIHSS) score on admission, time from last-known-well to admission and imaging (LKW-imaging), IVT, acute baseline imaging modality from the referral center or at admission at the enrolling center and laboratory values at admission: glucose in mmol/L, low-density lipoprotein (LDL) cholesterol in mmol/L, total cholesterol in mmol/L, albumin in g/L, lactate dehydrogenase (LDH) in U/L, D-dimer in µg/L, Hb in g/L, CRP in mg/L, leukocytes in G/L, thrombocytes in G/L, fibrinogen in g/L and international normalized ratio (INR). Two neurology fellows (J.G. and F.S.), blinded to the thrombus imaging characterization, retrospectively identified patients with active cancer (known or occult cancer) at the time of stroke by reviewing discharge, follow-up reports or histological findings available in medical records. In the case of active cancer, we extracted data on type, histology and time of diagnosis. Stroke etiology at discharge was determined using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (27). Patent foramen ovale related strokes were classified as cardioembolic strokes according to recommended updated criteria (28). A subgroup of patients with undetermined etiology and non-lacunar ischemic stroke pattern on imaging were classified as embolic stroke of undetermined source (ESUS), according to published criteria (29, 30). The presence of multiterritory infarcts (i.e., involving 2 or more brain vascular territories) was identified through evaluation of baseline neuroradiological reports and imaging (10).

## Statistical analysis

Baseline differences between patients with and without active cancer were assessed for categorical variables with the Fisher's exact test and reported as absolute numbers and proportions. Continuous variables were assessed with the Mann–Whitney *U*-test and reported as median with interquartile range (IQR). Same analyses were performed regarding the absence or presence of SVS and HVS, respectively. Univariable and multivariable logistic regression were used to assess the association between thrombus imaging characterization (SVS and HVS, separately) and active cancer. Odds ratios (ORs) and adjusted odds ratios (aORs) were reported with their corresponding 95% confidence intervals (95% CI). All models were adjusted for baseline characteristics (gender, age at admission, prior treatment with anticoagulants and antiplatelet drugs), proximal occlusion, LKW-imaging, ESUS and cancer-related biomarkers such as multiterritory infarcts, CRP, D-dimer, fibrinogen, Hb and leukocytes. Skewed distributions of continuous variables were logarithmically transformed. The predictive values of SVS and HVS were assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−). When both imaging modalities (native CT + MRI with SWI) were available and had been acquired before initiating IVT, intermodal change in the thrombus imaging characterization was assessed. Sensitivity analyses were performed for (1) proximal versus distal occlusions, (2) time delays between last-known-well and imaging (LKW-imaging as a continuous value), (3) presence of ESUS at discharge and (4) occult cancer. Areas under the receiver operating characteristics curve (auROC) were calculated for predictive models including and excluding the SVS and the HVS status. After cross-validation using bootstrapping, the auROCs were compared using the Delong test. No imputation was applied to account for missing data. Statistical analyses were performed with Stata 16 (StataCorp LLC).

# Results

## Study population

Between 2015 and 2020, 5,012 patients with acute ischemic stroke were included in our local stroke registry. At baseline, 2509 of these patients had a symptomatic intracranial occlusion (study flowchart – Supplementary Figure S1). Thrombus imaging status in acute care setting was assessable in 2256 patients (1,175 with SVS status, 980 with HVS status and 101 with SVS and HVS status available) who were consequently included in the study. The distribution of occlusion sites is summarized in Supplementary Figure S2. Active cancer at the time of stroke was present in 161 included patients (7.1%) and occult cancer in 36 patients (1.6%). The characteristics of active cancers and occult cancers are summarized in Supplementary Figure S3. IVT treatment before the time of blood examination led to the exclusion of 298 patients (13.2%) from analyses involving blood biomarkers.

## Baseline characteristics

The characteristics of patients with and without active cancer are compared in Supplementary Table S1. Patients with active cancer showed multiterritorial infarcts more frequently, and usually presented with higher D-dimer, CRP, LDH, and INR and lower albumin, Hb, LDL cholesterol, total cholesterol and thrombocytes. SVS was absent in 27% of patients with active cancer ($n = 28/89$) and in 15% of those without active cancer ($n = 176/1187$) ($p = 0.004$). The absence of HVS did not differ between patients with active cancer ($n = 30/77$, 39%) and those without active cancer ($n = 319/1004$, 32%, $p = 0.21$). HVS was detected in 74% of patients with proximal occlusions ($n = 680/913$) and 31% of patients with distal occlusions ($n = 51/167$). In patients with cancer and distal occlusion only, 76% ($n = 19/25$) demonstrated present SVS and 10% ($n = 1/10$) present HVS. The Supplementary Table S2 summarized the characteristics differences between patients with and without SVS and patients with and without HVS, respectively. Besides the age at admission, time from last-known-well to admission, the proposition of ESUS, and levels of albumin and INR, there was no difference between SVS and HVS groups. Of patients who had both imaging modalities (native CT + MRI with SWI) available, and in whom IVT had not been administered in between ($n = 77$), 82% of those with no SVS ($n = 14/17$) also had no HVS. In contrast, only 47% of patients with no HVS ($n = 14/30$) also had no SVS (Supplementary Table S3).

## The absence of the susceptibility vessel sign and cancer-related stroke

In univariable analysis, the absence of SVS was associated with active cancer (OR 2.12, 95% CI 1.29–3.48). Figure 2 summarizes the results of the multivariable regression analyses. An association with active cancer was found for the absence of SVS (aOR 3.14, 95% CI 1.45–6.80), higher leukocyte counts in G/L (aOR 1.10, 95% CI 1.03–1.18), lower fibrinogen in g/L (aOR 1.55, 95% CI 1.02–2.36) and hemoglobin in g/L (aOR 1.03, 95% CI 1.01–1.05). The association between the absence of SVS and active cancer was not influenced by proximal occlusion ($p$ for interaction = 0.08), the LKW-imaging time ($p$ for interaction = 0.14) and ESUS ($p$ for interaction = 0.95). Too few cases with active cancer were available to perform subgroup analyses of the different common stroke etiologies at discharge. Regarding the prediction of active cancer, the absence of SVS taken alone had a sensitivity of 27% (95% CI 18–37%), specificity of 85% (83–87%), PPV of 12% (8–17%), NPV of 94% (92–95%), LR+ of 1.82 (1.26–2.63) and LR− of 0.86 (0.75–0.98). The absence of SVS was not associated with occult cancer neither in univariable (OR 1.91, 95% CI 0.69–5.34) nor multivariable analysis (aOR 3.20, 95% CI 0.73–13.94). Subgroup analyses were not performed due to insufficient sample size.

## The absence of the hyperdense vessel sign and cancer-related stroke

In univariable and multivariable logistic regression analyses, no association between active cancer and absence of HVS was found (OR 1.37, 95% CI 0.85–2.21 and aOR 1.07, 95% CI 0.54–2.11, respectively). The results of the multivariable analyses are summarized in Supplementary Figure S4. No interaction was found with proximal occlusion ($p = 0.99$) or LKW-imaging time ($p = 0.63$). Despite positive interaction for ESUS ($p = 0.04$), the association between active cancer and the absence of HVS in the subgroup of patients with ESUS remained non-significant (aOR 2.03, 95% CI 0.40–10.17).

## Predictive value of SVS and HVS in the diagnosis of cancer-related stroke

The variables included in logistic regression analyses were reused to assess predictive models including or excluding SVS status and HVS status separately.

The auROCs of the models including and excluding SVS were 0.726 (95% CI 0.632–0.820) and 0.717 (95% CI 0.619–0.815), respectively (Figure 3A). According to the DeLong test, both models showed no significant difference ($p = 0.73$). The auROCs of the models including and excluding HVS were 0.766 (95% CI 0.672–0.860) and 0.744 (95% CI 0.650–0.838), respectively (Figure 3B). The DeLong test did not show a significant difference between both models ($p = 0.41$).

# Discussion

This study's main findings are as follow: (1) The association between the absence of SVS at baseline and active cancer was confirmed in a large cohort of stroke patients, (2) absence of HVS showed no association with active or occult cancer, (3) the association between the absence of SVS and occult cancer did not reach statistical significance.

The confirmation of the association between the absence of SVS and active cancer in the overall stroke population will help to identify paraneoplastic hypercoagulability in the presence of underlying cancer. The optimal secondary prevention in cancer-related patients is still debated. Some studies support the use of anticoagulation over antiplatelet drugs (3). The TEACH Trial (pilot randomized trial) indicated the non-practicality of therapy with low molecular weight heparin in the long term (31). The use of oral anticoagulants seems more appropriate but major guidelines currently advocate for

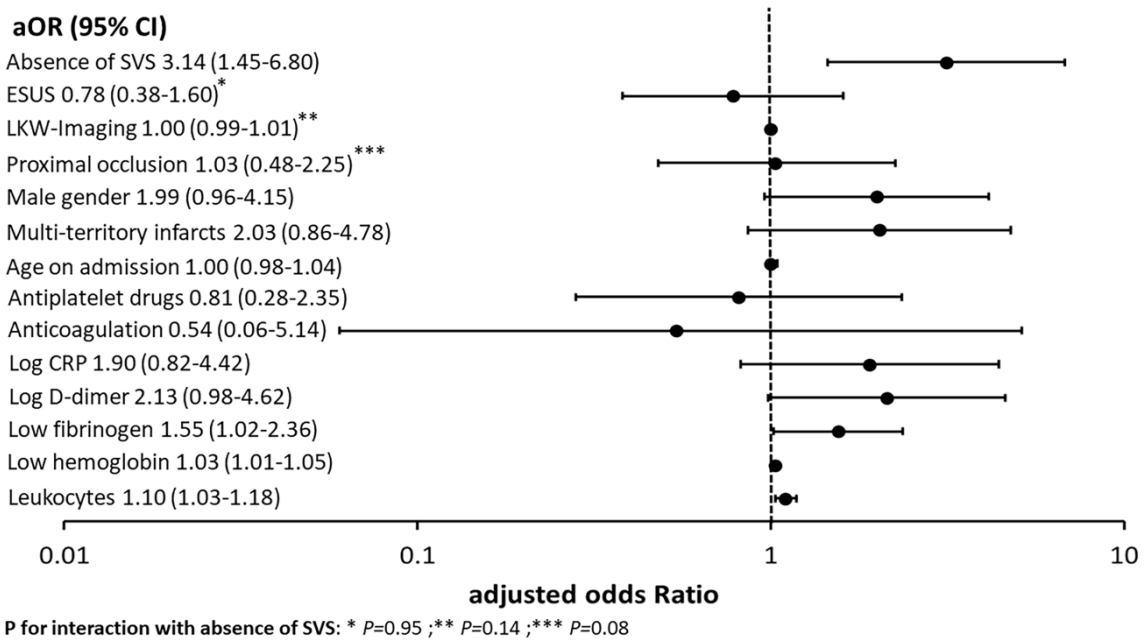


FIGURE 2
Association between active cancer, the absence of SVS, cancer-related imaging findings and blood biomarkers, and demographics in the multivariate logistic regression. This figure summarizes the association between active cancer, the absence of SVS and other preselected cancer-related biomarkers with corresponding adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). The absence of SVS showed the strongest association with active cancer in this study cohort. CRP indicates C-reactive protein; ESUS, embolic stroke of undetermined source; LKW-imaging, time between last-known-well to imaging and SVS, susceptibility vessel sign.

randomized trials (32, 33). According to previous evidence, the absence of SVS demonstrated the strongest association with active cancer in multivariable analysis (Figure 2) (14). Even if the auROC of the model with SVS tended to be greater, no statistical difference was found (Figure 3A). For this reason physicians must assess the absence of SVS in the clinical context by evaluating symptoms, other markers of cancer-related stroke and the presence of alternative causes of stroke before making a treatment decision (13). Like the presence of SVS, the presence of HVS is thought to indicate red blood cell-rich thrombi (16, 17, 34, 35). It is then commonly assumed that the absence of HVS corresponds to fibrin and platelet-rich thrombi (16). However, studies directly comparing HVS and SVS as surrogate marker for the microscopic composition of thrombi are scarce (16).

In our study, we could not demonstrate an association between the absence of HVS and active cancer. The predictive model including HVS performed slightly better than the model excluding HVS but was not statistically different (Figure 3B). One possible explanation for our results could be due to different sensitivities of SVS and HVS regarding the identification of intracranial occlusion. In line with the current evidence, SVS was more prevalent (84%) than HVS (68%) in the case of intracranial occlusion in our study (Supplementary Table S2) (36, 37). It is possible that HVS was absent because of lower sensitivity in intracranial occlusion detection rather than the presence of fibrin- and platelet-rich thrombus. In the literature, a positive HVS has been reported in 47% for proximal occlusions and 37% for distal occlusions (38). In our population, HVS was detected in 74% of patients with proximal occlusions (including basilar artery and vertebral artery) and in 31% of patients with distal occlusions. This discrepancy is most likely explained by the difference in slice thickness (1 mm in our population compared to a mean slice thickness of 1.65 to 4.5 mm), with the sensitivity of HVS increasing as the slice thickness decreases (38). There is no literature on the relevance of slice thickness of SWI regarding proximal or distal vessel occlusions. However, similar detection rates were observed in our population (73% in patients with active cancer and 85% in patients without active cancer) with SWI slice thickness of 1.6, 1.8 or 2.0 mm compared to studies with SWI slice thickness of 3 mm (79%) (39). The fact that the absence of SVS correlated more with the HVS status than the absence of HVS with the SVS status in the cases where intermodal comparison was available ($n = 77$) supports this hypothesis (Supplementary Table S2).

As HVS is considered time-dependent with loss of density over time and is more frequently seen in proximal occlusion, we performed a subgroup analysis (25, 26, 40). Nevertheless, no correlation of HVS-appearance with LKW-imaging time and proximal occlusion was found in our study cohort. The generalization of our previous findings in the context of occult cancer is inconclusive. It is estimated that occult cancer is present in 2–4% of the overall stroke population and this percentage can be as high as 10% in the subgroup of patients with undetermined stroke etiology (4–7, 41). The limited number of occult cancers in our study (1.6%), potentially due to the retrospective design, may be a possible explanation for our findings. Even if an interaction with ESUS was significant, the association between SVS and occult cancer remained statistically insignificant in the subgroup analysis. In patients with occult cancer, compared to patients with active known cancer, the impact of paraneoplastic hypercoagulability may be smaller as markers of coagulation (D-dimer) and inflammation (CRP and Hb) tend to be less altered at admission in the first group (20). This may influence the thrombus composition and consequently change the thrombus imaging characterization.

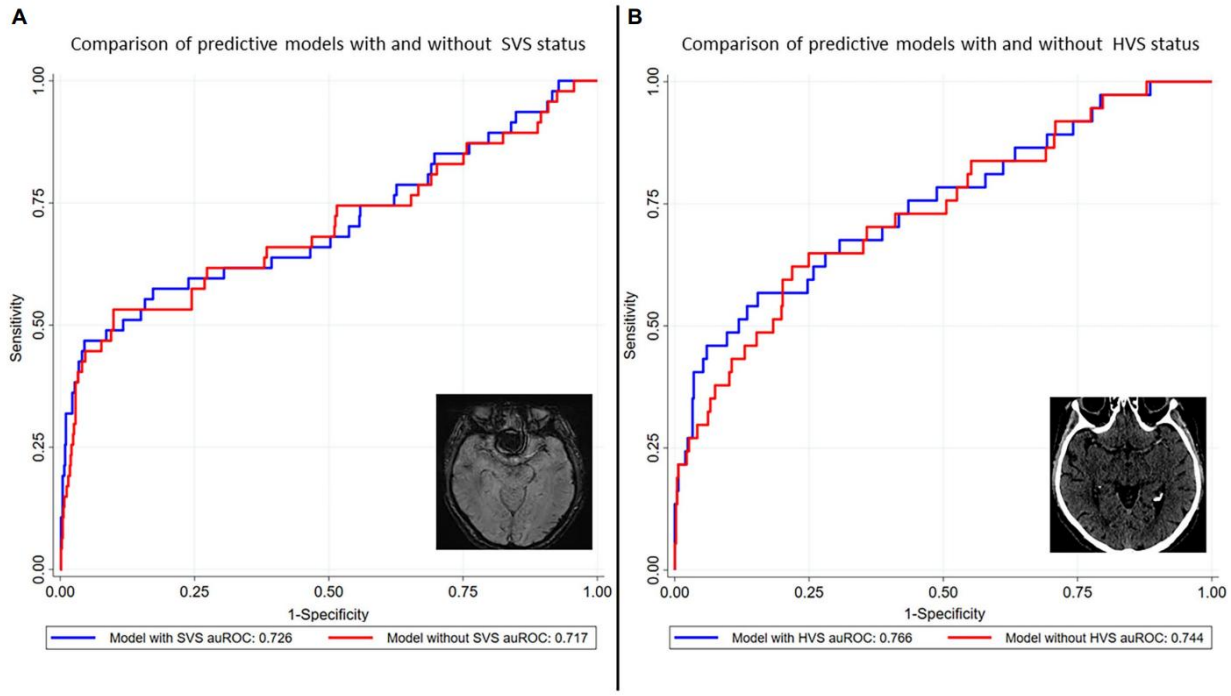


FIGURE 3
Predictive models for cancer-related stroke with and without SVS and HVS status. Models including and excluding SVS and HVS status, respectively, were developed using the covariates from logistic regression analyses (male gender, age at admission, prior treatment with anticoagulants and antiplatelet drugs, proximal occlusion, LKW-imaging, ESUS, multiterritory infarcts, CRP, D-dimer, fibrinogen, Hb and leukocytes). The auROCs of the models including and excluding SVS were 0.726 (95% CI 0.632–0.820) and 0.717 (95% CI 0.619–0.815), respectively **(A)**. According to the DeLong test, both models showed no significant difference ($p$=0.73). The auROCs of the models including and excluding HVS were 0.766 (95% CI 0.672–0.860) and 0.744 (95% CI 0.650–0.838), respectively **(B)**. The DeLong test did not show a significant difference between both models ($p$=0.41). auROC indicates area under the receiver operating characteristics curve; CRP, C-reactive protein; ESUS, embolic stroke of undetermined source; Hb, hemoglobin; HVS, hyperdense vessel sign; LKW-imaging, time between last-known-well to imaging; SVS, susceptibility vessel sign.

## Limitations

Firstly, our study was retrospective and included a largely homogeneous Swiss population, limiting the generalizability of the results and potentially underestimating the real incidence of occult cancer due to diagnoses made at other centers. Secondly, the local center followed an MRI-based acute stroke concept, which may have led to a selection bias regarding the association between the absence of HVS and active cancer. Further studies are needed, including patients with acute ischemic stroke principally diagnosed by CT and with available HVS status. Furthermore acute MRI is not routinely performed in all stroke centers. This could limit the generalization of our findings. Third, the lack of direct histological correlation to thrombus imaging characteristics limits the validation of the study hypothesis. Fourth, the variable use of 1.5 T and 3 T MRI could have influenced the determination of SVS status and, thus, the association between the absence of SVS and cancer (active or occult).

## Conclusion

This study confirmed the association between the absence of SVS and active cancer in all stroke patients. The LKW-imaging time, the site of occlusion and the absence of a common stroke etiology at discharge do not seem to play a role in this association. This study could not demonstrate an association between the absence of HVS and active cancer.

## Author's note

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## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Kantonale Ethikkomission Bern. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

MB contributed to conception and design, data acquisition, analysis and interpretation of data, and writing of the publication. LG contributed to conception and design, data acquisition, critical revision of the manuscript for important intellectual content. JG, FS, LC and CK contributed to data acquisition and critical revision of the manuscript for important intellectual content. NB contributed to conception and design and critical revision of the manuscript for important intellectual content. SJ contributed to conception and design, critical revision of the publication for important intellectual content, and supervision. JK contributed to conception and design, analysis and interpretation of data, critical revision of the publication for important intellectual content, and supervision. All other authors contributed to interpretation of data and critical revision of the manuscript for important intellectual content.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1148152/full#supplementary-material

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# The role of paradoxical embolism in stroke patients with cancer

Title of the manuscript: Prevalence of right-to-left shunt in stroke patients with cancer

Contributions of the PhD candidate:

- Conceptualization
- Data curation
- Formal analysis
- Visualization
- Writing – original draft
- Writing – review and editing
- Supervision

Results summary:

A right-to-left cardiac shunt (resulting from a patent foramen ovale or atrial septal defect) can result in the occurrence of a paradoxical embolism with venous thromboembolism leading to arterial occlusion (in our case, in the form of AIS). As venous thromboembolism occurs frequently in patients with cancer, we investigated whether the presence of a right-to-left cardiac shunt was associated with the presence of cancer in patients with AIS. To this end, we used information from our BMS database and investigated the presence of a right-to-left shunt in all our AIS patients.

Of the 2236 AIS patients included, 103 (5%) had active cancer, of whom 24 (23%) were diagnosed with right-to-left shunt. A right-to-left shunt was present in 774 of the 2133 AIS patients without active cancer (36%). After adjustment and weighting, the absence of right-to-left shunt was associated with active cancer (aOR 2.29, 95% CI 1.14–4.58). Right-to-left shunt was diagnosed less frequently in AIS patients with cancer than in cancer-free patients, suggesting that arterial sources may play a larger role in cancer-related strokes than paradoxical venous embolization.

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# Prevalence of right-to-left shunt in stroke patients with cancer

**Fabienne Steinauer[1*], Philipp Bücke[1*], Eric Buffle[2,3], Mattia Branca[4], Jayan Göcmen[1], Babak B Navi[5], Ava L Liberman[5], Anna Boronylo[1], Leander Clenin[1], Martina Goeldlin[1], Julian Lippert[1], Bastian Volbers[1], Thomas R Meinel[1], David Seiffge[1], Adnan Mujanovic[6], Johannes Kaesmacher[6], Urs Fischer[1,7], Marcel Arnold[1], Thomas Pabst[8], Martin D Berger[8], Simon Jung[1*] and Morin Beyeler[1,5,9*]**

## Abstract

**Background and Objectives:** Cancer is associated with an increased risk of acute ischemic stroke (AIS) and venous thromboembolism. The role of a cardiac right-to-left shunt (RLS) as a surrogate parameter for paradoxical embolism in cancer-related strokes is uncertain. We sought to investigate the relationship between the presence of an RLS and cancer in AIS patients.

**Methods:** We included consecutive AIS patients hospitalized at our tertiary stroke center between January 2015 and December 2020 with available RLS status as detected on transesophageal echocardiography (TEE). Active cancers were retrospectively identified and the association with RLS was assessed with multivariable logistic regression and inverse probability of treatment weighting to minimize the ascertainment bias of having a TEE obtained.

**Results:** Of the 2236 AIS patients included, 103 (4.6%) had active cancer, of whom 24 (23%) were diagnosed with RLS. An RLS was present in 774 out of the 2133 AIS patients without active cancer (36%). After adjustment and weighting, the absence of RLS was associated with active cancer (adjusted odds ratio (aOR) 2.29; 95% confidence interval (CI), 1.14–4.58). When analysis was restricted to patients younger than 60 years of age or those with a high-risk RLS (Risk of Paradoxical Embolism Score $\geq 6$), there was no association between RLS and cancer (aOR, 3.07; 95% CI, 0.79–11.88 and aOR, 0.56; 95% CI, 0.10–3.10, respectively).

[1]Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[2]Department of Cardiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[3]ARTORG Center, University of Bern, Bern, Switzerland
[4]CTU Bern, Department of Clinical Research, University of Bern, Bern, Switzerland
[5]Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, NY, USA
[6]Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[7]Neurology Department, University Hospital of Basel, University of Basel, Basel, Switzerland
[8]Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[9]Graduate School for Health Sciences, University of Bern, Bern, Switzerland

*equal contribution

**Corresponding author:**
Morin Beyeler, Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Freiburgstrasse 18, CH-3010 Bern, Switzerland.
Email: morin.beyeler@insel.ch

**Conclusion:** RLS was diagnosed less frequently in AIS patients with cancer than in cancer-free patients, suggesting that arterial sources may play a larger role in cancer-related strokes than paradoxical venous embolization. Future studies are needed to validate these findings and evaluate potential therapeutic implications, such as the general indication, or lack thereof, for patent foramen ovale (PFO) closure in this patient population.

**Keywords**
Acute ischemic stroke, right-to-left shunt, patent foramen ovale, cancer, venous thromboembolism

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## Introduction

Cancer-related stroke is a growing area of research.[1,2] While patients with cancer face an increased risk for acute ischemic stroke (AIS) through mechanisms similar to those in stroke patients without cancer, cancer-associated mechanisms also apply.[1,2] Cancer-mediated hypercoagulability is thought to be an important driver of cancer-related stroke. Hypercoagulable stroke mechanisms can be arterial (cerebral intravascular coagulation, nonbacterial thrombotic endocarditis) or venous (paradoxical embolization of a venous thromboembolism (VTE) via a cardiac right-to-left shunt (RLS)).[2,3] In most cases, RLS is attributable to a patent foramen ovale (PFO), a fetal connection between the right and the left cardiac atrium.[4] In approximately 25% of the general population, the foramen does not fully close in utero and persists throughout life.[4] A PFO is observed in up to 40% of patients with cryptogenic stroke classified as embolic stroke of undetermined source (ESUS).[5,6] A less frequent cause of an RLS is an atrial septal defect (ASD), a more serious congenital defect which can be seen in people with or without PFO.[7] Transesophageal echocardiography (TEE) and transcranial Doppler are considered to be the gold standards in RLS detection.[8] Up to 20% of patients with cancer develop a VTE during the course of their disease.[9] However, the role of RLS as a surrogate parameter for paradoxical embolism in patients with cancer, although often assumed, remains poorly investigated and, therefore, uncertain.[1,10–13] Earlier studies have been limited by their sample size, patient selection, or the diagnostic modality used for RLS detection.[12,13] This study investigated the association between the presence of RLS on TEE and the presence of cancer in AIS patients to explore the role of RLS in cancer-related stroke.

## Methods

### Study cohort

AIS patients hospitalized at our tertiary stroke center between 1 January 2015 and 31 December 2020 were evaluated for eligibility in this retrospective analysis of prospectively collected data from our institutional stroke registry (Figure 1). Patients were included if they met the following criteria: (1) imaging-proven ischemic stroke as detected on brain MRI (or CT if MRI was contraindicated) and (2) availability of TEE findings (either known from previous TEE studies or obtained from an examination during the index hospitalization) with documented RLS status. The study population was divided into two groups: patients with active cancer and patients without active cancer.

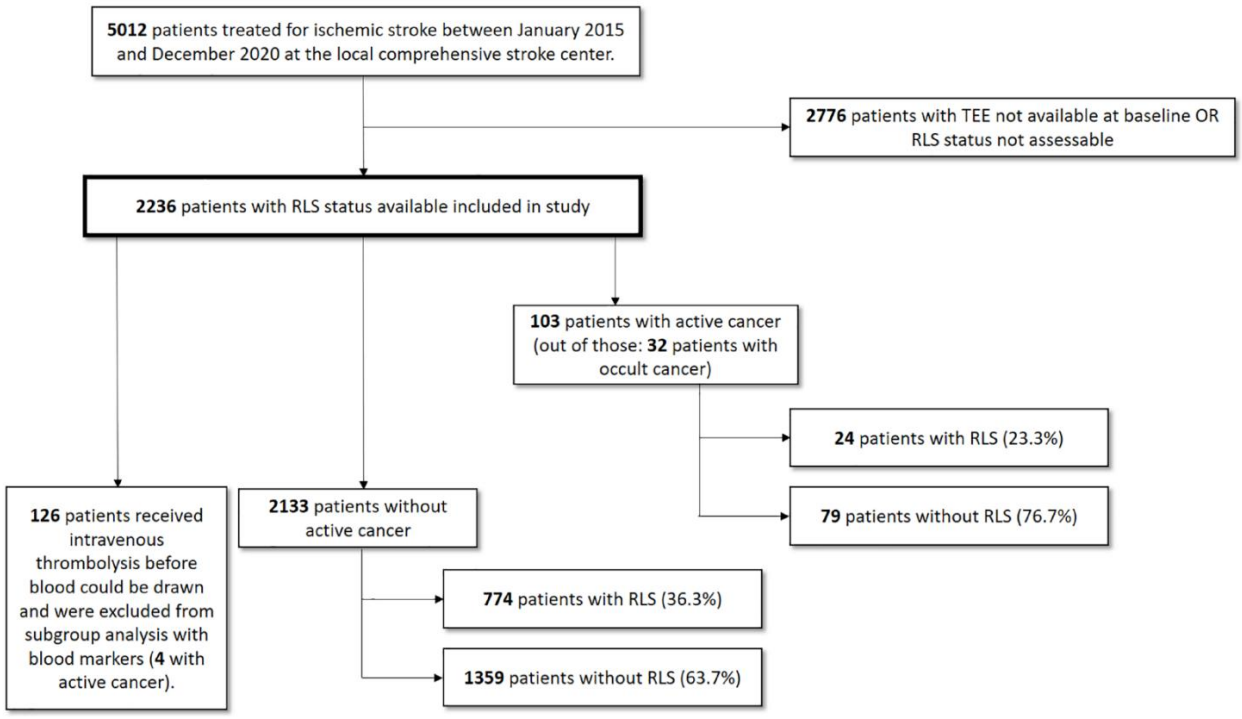
### Definition of active cancer and occult cancer

Known cancer was considered active if it fulfilled the criteria from the Hemostasis and Malignancy Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis.[14] Patients with cancer newly diagnosed within 1 year after the index hospitalization were classified as having "occult cancer." Occult cancers were also considered active at the time of the index event in line with previous studies.[15,16] In accordance with previous research practice, patients with focal non-melanoma skin cancer and prior breast cancer with prophylactic hormone therapy at the time of index event were not considered to have active cancer.[17]

### Indication for TEE

In our tertiary center, a TEE is usually performed in patients with suspected endocarditis, AIS of undetermined etiology (according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification), multiple or recurrent cerebrovascular events, or a high likelihood that the AIS source is an RLS if present as defined by a Risk of Paradoxical Embolism (RoPE) Score $\geq 6$ points.[18] RLS detection is part of every TEE examination. A TEE was not considered in patients with a known AIS etiology (e.g. cardioembolism or large artery atherosclerosis with $\geq 50\%$ luminal stenosis). In severely affected patients with refractory or terminal cancer, a TEE was performed only in case of approval by either the patient or relatives. Our institutional decision tree for TEE indications during the study time frame is provided in the Supplementary material (Supplementary Figure 1). In our center, other methods for RLS detection, such as transcranial Doppler, were not performed for that indication.

**Figure 1.** Study flowchart showing included versus excluded patients.




RLS indicates right-to-left shunt; TEE, transesophageal electrocardiograph.

### *Standard protocol approvals, registrations, and patient consents*

The study was approved by the local ethics committee (Project ID: 2022-01560; Kantonale Ethikkommission Bern). According to the ethics committee's decision, no informed consent from individual patients was required for inclusion in the study. Study data can be made available on reasonable request to the corresponding authors, and after clearance by the local ethics committee. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in the reporting of this study.

### *Data collection*

From our institutional stroke registry, we extracted the following variables: demographic and baseline patient characteristics, such as sex, age, pre-stroke functional independence (defined as a modified Rankin Scale (mRS) $\leqslant 2$), cardiovascular risk factors (including history of diabetes mellitus type II, hypertension, hyperlipidemia, smoking, stroke, and coronary artery disease), prior medications (antiplatelet or anticoagulant therapy), National Institutes of Health Stroke Scale (NIHSS) at admission, time from last known well to admission, and the site of the vessel occlusion. The presence of multi-territory infarction (involving at least two brain vascular territories) was determined from baseline neuroradiological reports and imaging. Stroke etiology was classified according to the TOAST and ESUS criteria, except that, for the purposes of this study, RLS-associated stroke was recorded as ESUS and not as cardioembolic stroke.[19,20]

A neurologist (F.S.) blinded to patients' cancer status abstracted the RLS status from the TEE reports and data on VTE from our institution's electronic health record. RLS was defined as any PFO or an ASD resulting in blood flow through the interatrial septum, regardless of the shunted volume, demonstrated spontaneously or with the help of the Valsalva maneuver or the use of agitated saline contrast bubble or both. In the case of an ASD, the shunt can be predominantly left to right due to higher left atrial pressure. However, the right atrial pressure can transiently exceed the left atrial pressure, resulting in RLS that might cause paradoxical embolism.[21] VTE was considered present if deep venous thrombosis or pulmonary embolism had been documented within 1 year before or after the index AIS. Documented VTEs were either symptomatic or asymptomatic and diagnosed as part of the AIS evaluation. Two neurologists (J.G. and M.B.) assessed the presence of known active and occult cancer and associated

characteristics (histological type, localization, and cancer stage at the time of AIS[22,23]) from our institution's electronic health record. We also collected data on leukocyte count, hemoglobin, platelet count, international normalized ratio (INR), fibrinogen, D-dimer, and C-reactive protein (CRP).

### *Outcome variables and statistical analysis*

Baseline characteristics were reported with median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. Differences between included and excluded patients were assessed with Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The same analyses were performed in included patients with and without active cancer.

Our first set of analyses used multivariable logistic regression models to determine potential associations between active cancer, RLS, and the following covariates (male sex, age at admission, prior antiplatelet drugs, prior anticoagulant drugs, VTE, CRP, D-dimer, hemoglobin, multi-territory infarction on baseline imaging, and ESUS). These covariates were selected based on previously published studies and pathophysiological considerations.[2,16,24] Interaction analyses were performed to identify conditions that could have influenced the association between active cancer and RLS (i.e. VTE status × absence of RLS interaction term with active cancer as dependent variable). Logarithmic transformation was applied to continuous variables with a skewed distribution. Patients who received intravenous thrombolysis before blood could be drawn for laboratory analysis (i.e. outside the hospital) were excluded from analyses that included blood biomarkers.

Our second set of analyses calculated propensity scores and used the inverse probability of treatment weighting (IPTW) method to minimize the confounding effects of TEE indication.[25] IPTW was applied with the use of stabilized weights to adjust for the covariates listed above to minimize the imbalance between the groups in the propensity scores.[26] Adjusted odds ratios (aORs) were reported with their corresponding 95% confidence intervals (95% CI).

We performed subgroup analyses based on age ($<80$ and $<60$ years of age), the presence of occult cancer only (occult cancer versus cancer-free patients after exclusion of patients with known active cancer), and among patients whose stroke would be more likely to be caused by PFO, if present (RoPE Score $\geq 6$) versus all others.

Cross-tabulations using the chi-square test were set up to assess, in patients with active cancer, the association between RLS and VTE. Distribution of cancer stage in cancer patients with and without diagnosis of RLS was assessed using median, IQR, and the Wilcoxon rank-sum test. Further analyses of the predictive value of RLS status and performance of predictive models are reported in the supplementary material (Supplementary Method and Results I).

No imputation was applied to compensate for missing data. An alpha error of less than 0.05 was considered statistically significant. Analyses were performed with Stata 16 (StataCorp LLC).

## Results

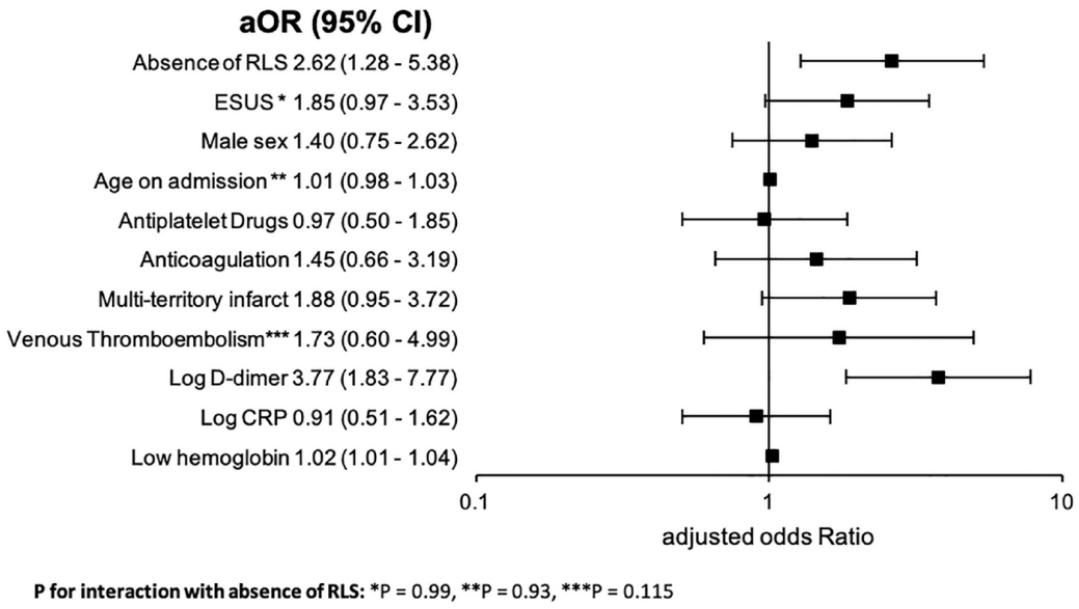
Of the 5012 patients with AIS treated at our tertiary stroke center from January 2015 through December 2020, 2236 patients (44.6%) with available TEE and assessable RLS status were included in this study (Figure 1). Active cancer was identified in 103 of these patients (4.6%), of whom 32 (1.4% of the total study population) had occult cancer. The detailed distribution of histological type and location of cancer is shown in Supplementary Figure 2. A comparison between included and excluded patients is provided in Supplementary Table 1. Compared to excluded patients, included patients were on average younger (median age (IQR) 68 (58–76) versus 78 (68–85) years) and had a lower prevalence of active cancer (7.3% versus 4.6%).

The baseline characteristics of included patients with and without active cancer are shown in Supplementary Table 2. Compared to patients without active cancer, patients with active cancer were significantly more often treated with anticoagulation before AIS, had higher NIHSS scores at admission, lower RoPE scores (median (IQR): 4 (3–5) in patients with active cancer versus 5 (4–6) in cancer-free patients), and higher frequency of VTE diagnoses (14.6% versus 2.5%). When subcategorized, deep venous thrombosis (7.8% versus 1.9%) and pulmonary embolism (6.8% versus 0.6%) were both more common in the active cancer group.

### *Association of active cancer with RLS status*

An RLS was detected in 35.7% of study patients (n = 798/2236). This comprised 23.3% (n = 24/103) of patients with active cancer and 36.3% (n = 774/2133) of patients without cancer (p = 0.008). Among patients with active cancer (n = 103), there was no association of comorbid VTE with the diagnosis of RLS (chi-square test: p = 0.323, Supplementary Table 3). Specifically, an RLS was diagnosed in 2 of the 15 patients with VTE (13%; 95% CI, 3%–41%) versus 22 of 88 patients without VTE (25%; 95% CI, 17%–35%). Information about cancer stage at the time of AIS was available in 93 patients. There was no difference in the cancer stage distribution in cancer patients with versus without the diagnosis of RLS (median (IQR) 3 (2–4) versus 3 (2–4), p = 0.82). In the first set of adjusted analyses using multivariable logistic regression, active cancer was associated with the absence of RLS (aOR, 2.62; 95% CI, 1.28–5.38) (Figure 2). The presence of VTE did not influence the association between active cancer and the

**Figure 2.** Multivariable logistic regression assessing the association between active cancer and co-variables reported as adjusted odds ratios (aOR) and their 95% CI. The absence of RLS and D-dimer levels was associated with active cancer.




aOR indicates adjusted odds ratio; CRP, C-reactive protein; ESUS, embolic stroke of undetermined source; RLS, right-to-left shunt; 95% CI, 95% confidence interval.

absence of RLS (p for interaction = 0.115, Figure 2). The association between active cancer and absence of RLS remained significant in patients younger than 80 years of age (n = 1913; aOR, 3.50; 95% CI, 1.52–8.07; Supplementary Figure 3) and patients in the occult cancer group (aOR, 5.40; 95% CI, 1.18–24.74; Supplementary Figure 4). However, among patients younger than 60 years of age (n = 646), the absence of RLS was no longer significantly associated with active cancer (aOR, 1.41; 95% CI, 0.17–11.53; Supplementary Figure 5). Similarly, when restricted to included patients with a RoPE Score ⩾ 6 (n = 218/1415), no association existed between active cancer and the absence of an RLS (aOR, 0.41; 95% CI, 0.10–1.58, p = 0.193).

In the second set of adjusted analyses using IPTW, the stabilized weights appeared normally distributed around one, with a few weights above two, which could have substantially impacted the results (Supplementary Figure 6). Using IPTW did not change the association between active cancer and the absence of RLS for the overall cohort (aOR, 2.29; 95% CI, 1.14–4.58), for patients younger than 80 years of age (aOR, 3.03; 95% CI, 1.39–6.62), and for patients with occult cancer at the time of AIS (aOR, 5.28; 95% CI, 1.12–24.88). The association between active cancer and RLS remained nonsignificant among patients younger than 60 years of age (aOR, 3.07; 95% CI, 0.79–11.88) and those with a RoPE score of ⩾ 6 (aOR, 0.56; 95% CI, 0.10–3.10).

## Discussion

Of the 2236 patients with AIS who underwent TEE at a tertiary care stroke center, we found that an RLS was less prevalent in patients with cancer than in patients without cancer. This inverse association was also present among patients aged below 80 years and among those assumed to have occult cancer at the time of AIS. Conversely, when restricted to patient subgroups considered to be at high risk for paradoxical embolization, namely those younger than 60 years with a high RoPE score, or a known VTE, there was no significant association between the presence or absence of an RLS and active cancer.

An RLS, predominantly from a PFO, is observed in approximately 25% of the general population and may be present in up to 40% of ESUS patients.[4–6] Based on the results of multiple randomized trials, the American Heart Association/American Stroke Association 2021 guideline update states that PFO closure for secondary stroke prevention might be beneficial in selected patients younger than 60 years with a RoPE score ⩾ 6.[27] Meanwhile, the role of PFO in cancer-associated AIS remains controversial. As VTE risk is increased approximately fivefold in patients with cancer, it is reasonable to assume that the presence of RLS may increase the risk of paradoxical embolization and subsequent AIS in some patients.[2,3,24] However, epidemiological data to support this supposition are scarce. To our

knowledge, only one study by Iguchi et al (n = 184 total AIS patients; n = 11 with AIS and cancer) has investigated the association between RLS and active cancer in AIS patients.[12] In this analysis, an RLS was more frequent in patients with active cancer than in patients without cancer (55% versus 15%, p = 0.001), suggesting that paradoxical embolism may be an important cause of stroke in patients with cancer. However, this study was limited by its small sample size, enrichment of patients with advanced stage cancers, and reliance on transthoracic echocardiography (TTE), instead of TEE, to detect RLS.[8,12]

In our study, which had a sample size more than 10-fold larger than that studied by Iguchi et al, an RLS was less prevalent in AIS patients with cancer than in those without cancer. We did not find a difference in cancer stage distribution in patients with versus without a diagnosis of RLS.

Furthermore, even among patients with known VTE, there was no positive association between the presence of an RLS and active cancer status. These data suggest that arterial stroke mechanisms through both distal embolism and in situ thrombosis predominate in cancer-related AIS. At the same time, paradoxical embolization from venous thrombi through an RLS seems less frequent.

To confirm this hypothesis, an analysis of thrombus composition in cancer-related stroke patients in the presence and absence of RLS should be carried out in future studies. Arterial thrombi are believed to generally contain higher fibrin and platelet fractions than venous thrombi, which tend to be more red blood cell (RBC)-rich.[28,29] Härtl et al. recently demonstrated in cryptogenic stroke patients with large vessel occlusion treated with mechanical thrombectomy that the RBC proportion was higher in patients with a PFO than in those without.[11] Their findings histologically support the concept of PFO having a causative role in cryptogenic ischemic stroke through paradoxical embolism of venous thrombi. Meanwhile, retrieved thrombi from cancer-related strokes have previously been shown to be fibrin- and platelet-rich.[30–32] However, the presence of a PFO was not taken into account in these studies. Therefore, it remains uncertain from such histopathological studies whether the presence of PFO in cancer-related stroke impacted the composition of retrieved thrombi from large vessel occlusion and contributed to stroke development.[33]

The findings from our study do not support the potential clinical benefit of PFO closure in patients with cancer and AIS, as discussed by Potugari et al. in their case report.[13] Given the inverse association we found between active cancer and the presence of RLS, one could argue that the focus of secondary stroke prevention in patients with active cancer and AIS, and concomitant PFOs should be antithrombotic therapy and not PFO closure.[14,34,35] Due to its medium sensitivity, low specificity and low positive predictive value (PPV) value, the absence of RLS alone is not sufficient for the prediction of underlying cancer in AIS patients (see Supplementary Method and Results I). As the difference between multivariable predictive models including and excluding RLS status was not significant, it is not suitable to characterize the absence of RLS as a candidate biomarker for cancer-related strokes (see Supplementary Method and Results I).

## Limitations

This study has several limitations. First, due to its retrospective cohort design, ascertainment bias of having a TEE obtained, is possible. Patients with cancer who harbored an RLS may have been less likely to undergo TEE because they were viewed as sicker or less likely to undergo subsequent PFO closure if an RLS was detected. This concern is somewhat mitigated by our institution's systematic decision tree for determining who should undergo TEE and our use of IPTW analyses to statistically account for potential differences in indication. Second, a systematic screening for VTE in AIS patients was not performed at our institution. The number of VTEs in this study may be underestimated, as only symptomatic VTEs or asymptomatic VTEs discovered during routine evaluation for the index AIS have been reported. Third, the frequency of patients with occult cancer is likely underestimated as we were unable to capture cancer diagnoses made at other centers after AIS. Moreover, the last clinical follow-up date at our center is unavailable in the database. It made it impossible to determine the proportion of included patients with a completed follow-up time (of at least 1 year) regarding the identification of occult cancer at the time of AIS. Fourth, due to the small number of patients considered to have occult cancer, the association analyses for this subgroup were imprecise. Fifth, our study was conducted at a tertiary care referral center in Europe where the patient population was predominantly White and therefore, our findings may not be generalizable to other settings.

## Conclusion

This study raises doubts concerning the assumed role of paradoxical embolism as a frequent cause of ischemic stroke in cancer patients because of the demonstrated negative correlation between RLS and cancer. Future research to determine alternative causes of stroke, such as arterial thromboembolism, in this patient population is warranted and could inform clinical practice and the potential utility or lack thereof for PFO closure.

### Author contributions

F.S. contributed to data acquisition, interpretation of data, and writing of the publication. P.B. contributed to the conception and design, interpretation of data, writing of the publication, and supervision. E.B. contributed to the conception and design, interpretation of data, and critical revision of the article for important

intellectual content. Ma.B. contributed to analysis and interpretation of data and critical revision of the article for important intellectual content. J.C. contributed to data acquisition and critical revision of the article for important intellectual content. S.J. contributed to the conception and design, critical revision of the publication for important intellectual content, and provided supervision. Mo.B. contributed to the conception and design, analysis and interpretation of data, critical revision of the publication for important intellectual content, and provided supervision. All other authors contributed to the critical revision of the article for important intellectual content.

## Declaration of conflicting interests

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## ORCID iDs

Philipp Bücke https://orcid.org/0000-0001-5204-2016
Mattia Branca https://orcid.org/0000-0002-8063-7882
Babak B Navi https://orcid.org/0000-0001-8424-6128
Martina Goeldlin https://orcid.org/0000-0001-5800-116X
Bastian Volbers https://orcid.org/0000-0003-0453-1530
David Seiffge https://orcid.org/0000-0003-3890-3849
Adnan Mujanovic https://orcid.org/0000-0002-6839-7134
Morin Beyeler https://orcid.org/0000-0001-5911-7957

## Supplemental material

Supplemental material for this article is available online.

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# Cancer and atrial cardiopathy

Title of the manuscript: Cancer and left atrial enlargement in patients with ischemic stroke

Contributions of the PhD candidate:

- Conceptualization
- Data collection
- Data curation
- Formal analysis
- Visualization
- Writing – original draft

This is the first study I carried out during my international research fellowship at the Weill Cornell Medical College in New York City, USA, under the supervision of Professor Babak Navi between September 2023 and September 2024.

Results summary:

Given that the association between cancer and atrial fibrillation in AIS patients is well documented, we aimed to assess whether cancer was also associated with atrial cardiopathy defined as a functional or structural disorder of the left atrium.

For this study, atrial cardiopathy was defined as a left atrial volume index ≥35 $mL/m^2$ on echocardiography. Using data from the Cornell Acute Stroke Academic Registry (CAESAR), we included 1104 AIS patients, of whom 10% had active cancer and 47% had atrial cardiopathy. There was no association between active cancer and atrial cardiopathy among the AIS cohort overall (aOR 0.91, 95% CI 0.60–1.37) nor in patients with embolic stroke of undetermined source, a subgroup of AIS patients more likely to have underlying cancer (aOR 0.64, 95% CI 0.30–1.36).

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# Cancer and left atrial enlargement in patients with ischemic stroke

Morin Beyeler, MD [a,b,c,1], Anokhi Pawar, BS [a,1], Eric Buffle, MD [d,e], Cenai Zhang, MS [a], Vanessa Liao, BS [a], Ava L. Liberman, MD [a], Thomas Pabst, MD [f], Martin D. Berger, MD [f], Simon Jung, MD [c], Hooman Kamel, MD [a], Babak B. Navi, MD MS [a,g,*]

[a] Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, USA
[b] Graduate School for Health Sciences, University of Bern, Switzerland
[c] Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland
[d] Department of Cardiology, Inselspital, Bern University Hospital and University of Bern, Switzerland
[e] ARTORG Center, University of Bern, Switzerland
[f] Department of Medical Oncology, Inselspital, Bern University Hospital and University of Bern, Switzerland
[g] Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, USA

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ABSTRACT

*Background:* Cancer is associated with an increased risk of atrial fibrillation. Whether cancer is also associated with atrial cardiopathy, another atrial pathology associated with heightened ischemic stroke risk, is uncertain.
*Methods:* We conducted a retrospective cross-sectional study among consecutive patients hospitalized with acute ischemic stroke at a quaternary care center in New York, United States from 2011 through 2016. The study exposure was active cancer. The study outcome was atrial cardiopathy, defined as a left atrial volume index ≥35 mL/m$^2$ on echocardiography. We used multivariable logistic regression, adjusting for baseline characteristics, to evaluate the relationship between cancer (active or historical) and atrial cardiopathy. We performed a subgroup analysis among patients with embolic stroke of undetermined source (ESUS).
*Results:* The final cohort included 1104 patients with acute ischemic stroke, of whom 10 % had active cancer and 47 % had atrial cardiopathy. Patients with atrial cardiopathy, compared to those without, were older (median age, 77 versus 68 years), and more frequently had hypertension, coronary disease, and atrial fibrillation. Active cancer was present in 9.6 % of patients with atrial cardiopathy ($n$ = 50/520) and 10.4 % of patients without ($n$ = 61/584). There was no association between active cancer and atrial cardiopathy among the overall ischemic stroke cohort (adjusted odds ratio [OR], 0.91; 95 % confidence interval [CI], 0.60-1.37) nor in patients with ESUS (aOR, 0.64; 95 % CI, 0.30-1.36). When the cancer exposure was broadened to include any history of cancer ($n$ = 236, 21.4 %), there still was no significant association with atrial cardiopathy (aOR, 0.93; 95 % CI, 0.68-1.25).
*Conclusions:* When defining atrial cardiopathy by left atrial volume, we did not find an association between cancer and atrial cardiopathy in patients with ischemic stroke, including among those with ESUS. Future studies, evaluating other atrial cardiopathy biomarkers and settings, are needed to further investigate any potential link between cancer and atrial cardiopathy.

## Introduction

Cancer-related stroke is an increasingly recognized subgroup of acute ischemic stroke (AIS).[1,2] However, in many cases, the mechanism causing AIS in patients with cancer is uncertain. Emerging data suggest that patients with cancer face an elevated risk of incident atrial fibrillation (AF).[3,4] This elevated risk may be attributable to frequent triggers for AF in patients with cancer, such as cancer-induced inflammation, surgery, sepsis, and the cardiotoxicity of anticancer treatments.[3,4] In addition, among patients with AF, concomitant cancer increases the risk for AIS.[5,6] However, beyond left ventricular dysfunction caused by certain cancer medications, there are currently no

* Corresponding author at: 420 East 70th Street, New York, NY 10021.
*E-mail address:* ban9003@med.cornell.edu (B.B. Navi).
[1] Equal contribution.

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convincing data to support an association between cancer and other cardioembolic sources of stroke.[7]

Atrial cardiopathy is defined as a functional or structural disorder of the left atrium and is associated with an increased risk for future AF.[7–9] Furthermore, even in the absence of AF, atrial cardiopathy is associated with an increased risk for embolic stroke of undetermined source (ESUS).[10,11] Around 50 % of cancer-related strokes are classified as ESUS according to standard criteria, and atrial cardiopathy, which is found in approximately 45 % of patients with ESUS, could be an important cause of AIS in this population.[12,13] However, there are scarce data on whether atrial cardiopathy, in the absence of AF, is associated with cancer-related stroke.[7,14] Therefore, we aimed to investigate the relationship between cancer and atrial cardiopathy among a well-characterized cohort of patients with AIS.

## Materials and methods

### *Design and setting*

We conducted a retrospective cross-sectional study of AIS patients enrolled in the Cornell AcutE Stroke Academic Registry (CAESAR). CAESAR is a prospective registry of consecutive patients hospitalized with acute stroke at an urban academic hospital and comprehensive stroke and cancer center serving New York, United States. CAESAR combines data prospectively collected by trained analysts for the American Heart Association's Get With The Guidelines (GWTG)–Stroke registry with additional clinical, laboratory, and radiographic data collected by automated electronic capture and manual abstraction. All AIS cases in CAESAR are reviewed by a panel of neurovascular physicians who adjudicate the mechanism per the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and the consensus definition of ESUS.[15,16] The Weill Cornell Medicine Institutional Review Board approved this study and granted a waiver of informed consent because of minimal risk to patients. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the reporting of this study.

### *Population*

For this analysis, we included all CAESAR patients registered between January 1, 2011 through December 31, 2016, who were aged 18 years or older and had echocardiography (transthoracic or transesophageal) performed within 21 days of admission for index AIS with available measurement of left atrial volume index (LAVI).

### *Exposures*

The primary study exposure was active cancer. Active cancer was defined according to the International Society on Thrombosis and Haemostasis criteria as a diagnosis, treatment, or known recurrence or metastasis of any malignant cancer within the past 6 months.[17] As cancers generally take years to develop, patients diagnosed with cancer in the 6 months after the index AIS were also included in the active cancer group. The secondary study exposure was defined as any history of cancer including patients with either active or inactive cancer.

### *Echocardiographic investigations*

At our hospital, a transthoracic echocardiogram (TTE) with or without agitated saline injection and/or contrast administration, as clinically warranted, is generally performed in patients with AIS during their index hospitalization or soon thereafter on an outpatient basis. A transesophageal echocardiogram (TEE) is performed less frequently on a case-by-case basis according to the treating physicians' discretion. Echocardiographic measurements are imported into the CAESAR registry from the institution's echocardiographic image management system (Xcelera, Philips Healthcare) through a Microsoft SQL server. The detailed list of echocardiographic variables imported into CAESAR has been published previously.[18]

### *Primary outcome*

The primary study outcome was atrial cardiopathy, defined as LAVI $\geq$35 mL/m$^2$, similar to prior studies.[19,20] We considered the LAVI values closest to the index AIS for patients with more than one echocardiogram within 21 days after index AIS. A board-certified cardiologist with specific echocardiography training manually verified LAVI outlier measurements $<$10 or $>$125 mL/m$^2$.

### *Covariates*

From the CAESAR registry, we extracted the following demographic and clinical characteristic data: sex, age at admission, race, presence of traditional cardiovascular risk factors (history of hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, congestive heart failure, cigarette smoking, and prior stroke), history of cancer, the National Institutes of Health stroke scale (NIHSS) at admission, history of AF (combining AF known prior to index AIS and AF newly diagnosed during the index hospitalization), and relevant laboratory data, which included leukocyte count, hemoglobin, platelet count, plasma D-dimer, C-reactive protein, and estimated glomerular filtration rate. Only laboratory values measured between 5 days before and 5 days after admission were assessed. For patients with multiple laboratory values, we used the value closest to the time of hospital admission. We also collected data on cancer type and histology.

### *Statistical analysis*

Baseline characteristics were reported via frequency and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. Differences between included and excluded patients and between included patients with and without atrial cardiopathy were assessed with Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Univariable and multivariable logistic regression models were used to evaluate the association between active cancer and atrial cardiopathy. Odds ratios (ORs) were reported with their corresponding 95 % confidence intervals (95 % CI). Multivariable regression analysis included the following clinically relevant covariates previously associated with atrial cardiopathy: age at admission, sex, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, and prior stroke.[20,21] Continuous variables with skewed distributions were logarithmically transformed.

In sensitivity analyses, we used different LAVI cutoffs to assess the association between different left atrial enlargement grades and the presence of active cancer. Mild left atrial enlargement was defined as LAVI $\geq$29 mL/m$^2$ and severe left atrial enlargement as LAVI $\geq$40 mL/m$^2$.[22]

We performed the following subgroup analyses: 1) among patients with ESUS at the time of hospital discharge, 2) after excluding patients with history of AF, and 3) including patients with any history of cancer, including both active and inactive cancers. Statistical analyses were performed by M.B. using Stata 16 (StataCorp LLC). No imputation was performed to compensate for missing data. Statistical significance was defined as $p < 0.05$.

### *Role of the funding source*

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

### *Patient characteristics*

Among the 2113 patients included in CAESAR between 2011 through 2016, 1104 patients (52 %) had available echocardiographic investigations and LAVI measurements and were included in this study (Fig. 1). The differences between included and excluded patients are summarized in Supplemental Table 1. Compared to excluded patients, included patients were on average younger (median age [IQR], 73 [61–82] years versus 74 [62–84] years, $p = 0.03$), had more frequent history of hypertension (71 % versus 66 %, $p = 0.04$), and more often had ESUS at discharge (30 % versus 25 %, $p = 0.01$).

Among the 1104 study patients, active cancer (known or diagnosed within 6 months after the index AIS) was identified in 111 patients (10 %), and a history of cancer (including patients with inactive cancer) was identified in 236 patients (21 %).

Of the 1104 study patients, 520 (47 %) had atrial cardiopathy according to the predefined cut-off of LAVI $\geq$35 mL/m$^2$. The differences between patients with and without atrial cardiopathy are summarized in Table 1. Patients with atrial cardiopathy were on average older (median age [IQR], 77 [67–84] years versus 68 [56–78] years, $p < 0.001$); more frequently had hypertension (76 % versus 66 %, $p < 0.001$), coronary artery disease (24 % versus 16 %, $p < 0.001$) and AF (44 % versus 10 %, $p < 0.001$); had higher initial NIHSS scores (5 versus 3, $p < 0.001$); and had more cardioembolism and less ESUS as their stroke mechanism. Patients with atrial cardiopathy also had lower hemoglobin and platelet counts and higher CRP levels than patients without atrial cardiopathy.

### *Active cancer and atrial cardiopathy*

Active cancer was present in 9.6 % of patients with atrial cardiopathy ($n = 50/520$) and 10.4 % of patients without ($n = 61/584$). The detailed distribution of cancer typed and histologies for all patients and those with atrial cardiopathy specifically is reported in Supplemental Figure 1. The cancer types most frequently identified in patients with atrial cardiopathy were leukemia/other hematopoietic malignancies ($n = 10/50$, 20 %), lung cancer ($n = 9/50$, 18 %) and colorectal cancer ($n = 5/50$, 10 %). The most common histology identified in patients with atrial cardiopathy was adenocarcinoma ($n = 19/50$, 38 %) followed by leukemia/other hematopoietic malignancies ($n = 10/50$, 20 %). There was no association between active cancer and atrial cardiopathy in univariable (OR, 0.91; 95 % CI, 0.62-1.35) or multivariable analyses (adjusted OR, 0.91; 95 % CI, 0.60-1.37; Fig. 2).

### *Active cancer and different grades of left atrial enlargement*

There was no association between active cancer and mild left atrial enlargement (defined as LAVI $\geq$29 mL/m$^2$) in univariable (OR, 1.01; 95 % CI, 0.67-1.53) or multivariable analyses (adjusted OR, 1.04; 95 % CI, 0.68-1.59; Supplemental Figure 2A). There was also no association between active cancer and severe left atrial enlargement (defined as LAVI $\geq$40 mL/m$^2$) in univariable (OR, 0.71; 95 % CI, 0.46-1.10) or multivariable analyses (adjusted OR, 0.71; 95 % CI, 0.45-1.12; Supplemental Figure 2B).

### *Any history of cancer and atrial cardiopathy*

A total of 125 patients with inactive cancer were grouped with the 111 patients with active cancer to assess whether history of cancer ($n = 236/1104$) was associated with atrial cardiopathy (LAVI $\geq$35 mL/m$^2$). In this analysis, there also was no significant association in both univariable (OR, 1.13; 95 % CI, 0.85-1.51) and multivariable models (adjusted OR, 0.93; 95 % CI, 0.68-1.25; Fig. 3).

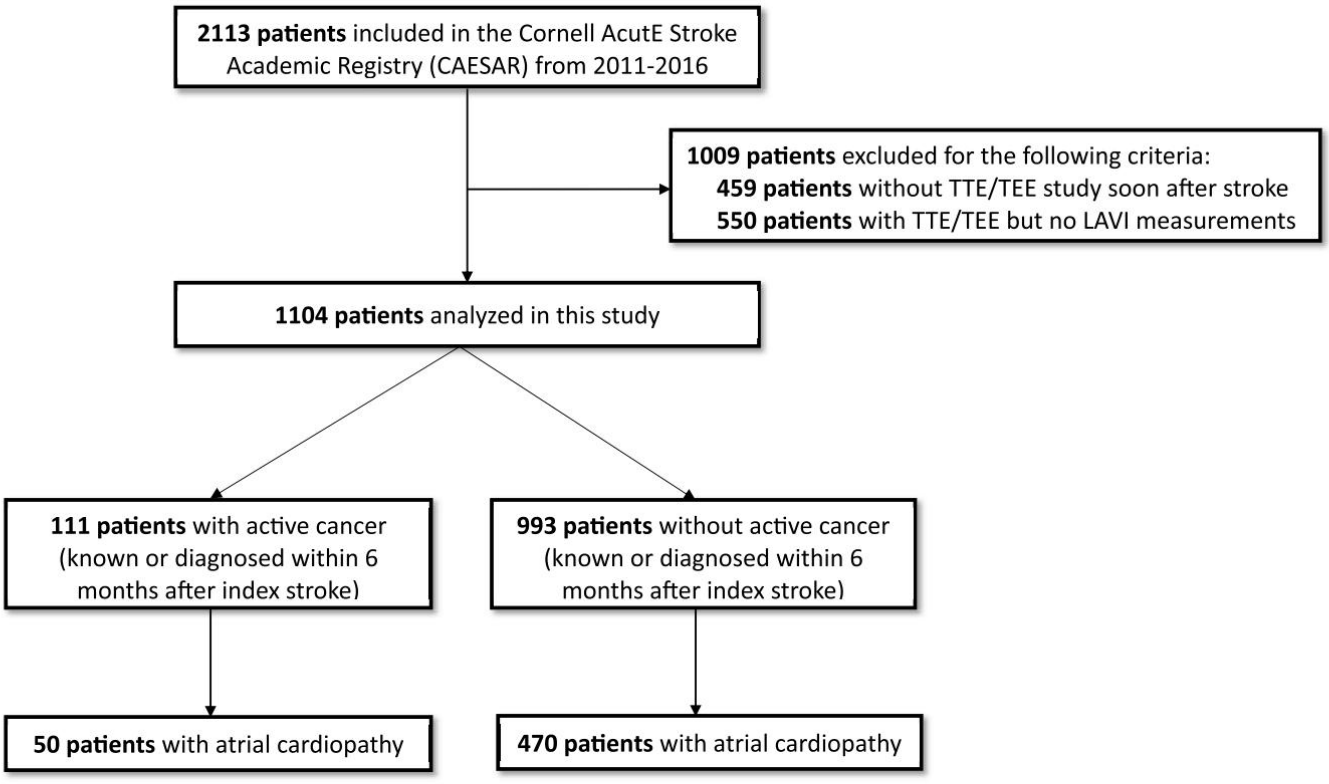


**Fig. 1.** Study flow diagram.
***Legend:*** Flow diagram describing how the final study cohort was reached and reasons for exclusion.

**Table 1**
Cohort Characteristics among Patients with and without Atrial Cardiopathy

| Characteristic* | All patients (*N* = 1104) | Absence of atrial cardiopathy (*N* = 584) | Presence of atrial cardiopathy (*N* = 520) | P-value† |
|---|---|---|---|---|
| **Demographics** | | | | |
| Sex, woman | 536 (49) | 268 (46) | 268 (52) | 0.06 |
| Age at admission | 73 (61-82) | 68 (56-78) | 77 (67-84) | <0.001 |
| Race | | | | 0.64 |
| White | 464 (42) | 242 (42) | 222 (43) | |
| Black | 112 (10) | 61 (10) | 51 (10) | |
| Other | 199 (18) | 111 (19) | 88 (17) | |
| Not recorded/ declined | 326 (30) | 167 (29) | 159 (31) | |
| **Medical history** | | | | |
| Heart failure | 59 (5) | 15 (3) | 44 (9) | <0.001 |
| Coronary disease | 221 (20) | 95 (16) | 126 (24) | 0.001 |
| Diabetes mellitus | 291 (26) | 161 (28) | 130 (25) | 0.34 |
| Hypertension | 780 (71) | 385 (66) | 395 (76) | <0.001 |
| Dyslipidemia | 544 (49) | 280 (48) | 264 (51) | 0.37 |
| Prior stroke | 212 (19) | 108 (19) | 104 (20) | 0.54 |
| Active smoking | 88 (8) | 58 (10) | 30 (6) | 0.01 |
| Atrial fibrillation | 290 (26) | 60 (10) | 230 (44) | <0.001 |
| **Stroke severity** | | | | |
| Initial NIHSS | 4 (1-12) | 3 (1-8) | 5 (2-15) | <0.001 |
| **Stroke mechanism** | | | | |
| Large-artery atherosclerosis | 156 (14) | 110 (19) | 46 (9) | <0.001 |
| Cardioembolic | 360 (32) | 105 (18) | 255 (49) | |
| Small-vessel disease | 106 (10) | 84 (15) | 22 (4) | |
| Other determined etiology | 44 (4) | 31 (5) | 13 (3) | |
| ESUS | 330 (30) | 205 (35) | 125 (24) | |
| Incomplete work-up | 41 (4) | 19 (3) | 22 (4) | |
| Multiple causes | 67 (6) | 30 (5) | 37 (7) | |
| **Cancer prevalence** | | | | |
| Active cancer | 111 (10) | 61 (10) | 50 (10) | 0.69 |
| Any history of cancer | 236 (21) | 119 (20) | 117 (23) | 0.42 |
| **Baseline laboratory values** | | | | |
| Leukocyte count, $10^3$/uL | 8.1 (6.5-10.6) | 8.1 (6.7-10.5) | 8.1 (6.3-10.6) | 0.68 |
| Hemoglobin, g/dL | 13.4 (11.9-14.7) | 13.75 (12.5-14.9) | 12.95 (11.5-14.2) | <0.001 |
| Platelet count, $10^3$/uL | 208 (168-258) | 218 (177-266) | 199 (160-246) | <0.001 |
| D-Dimer, µg/L | 494 (278-1133) | 464 (268-1064) | 584 (306-1320) | 0.25 |
| CRP, mg/L | 1.5 (0.7-5.3) | 1.2 (0.7-3.7) | 1.8 (0.7-7.9) | 0.048 |
| EGFR | 53 (42-57) | 53 (44-57) | 52 (40-57) | 0.15 |

Abbreviations: EGFR, estimated glomerular filtration rate; ESUS, embolic stroke of undetermined source; IQR, interquartile range; NIHSS, NIH Stroke Scale; CRP, C-reactive protein.

* Data reported as no. (%) for categorical variables and median (IQR) for continuous variables.

† Patients with and without atrial cardiopathy were compared with Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables

### *Subgroup analysis*

When only the 330 patients with ESUS (30 % of the primary AIS cohort) were analyzed, there was still no association between the presence of active cancer and atrial cardiopathy (LAVI ≥35 mL/m$^2$) in both univariable (OR, 0.68; 95 % CI, 0.34-1.35) and multivariable models (adjusted OR, 0.64; 95 % CI, 0.30-1.36; Fig. 4A). Similarly, after excluding 290 patients with history of AF from the study population, no association existed between the presence of active cancer and atrial cardiopathy in univariable (OR, 1.10; 95 % CI, 0.71-1.70) and multivariable analyses (adjusted OR, 1.09; 95 % CI, 0.69-1.72; Fig. 4B).

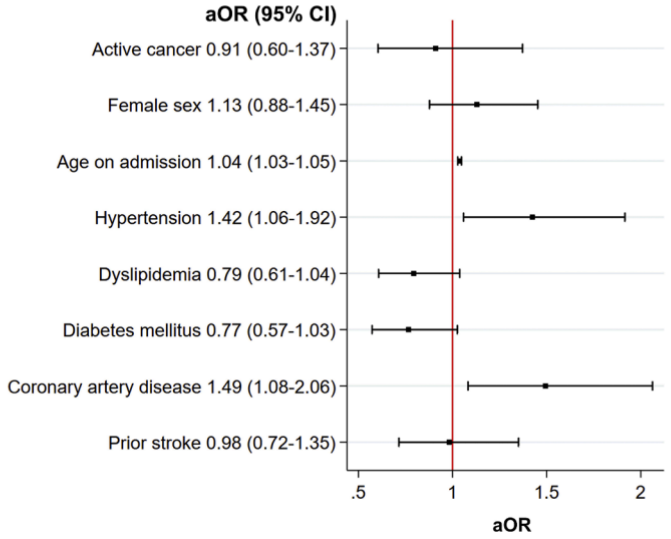


**Fig. 2.** Forest plot of multivariable logistic regression model evaluating the association between active cancer and atrial cardiopathy.
Legend: Multivariable logistic regression model assessing the association between active cancer and atrial cardiopathy while adjusting for potential confounders. Data reported as adjusted odds ratios (aOR) and their 95 % confidence intervals (CI).

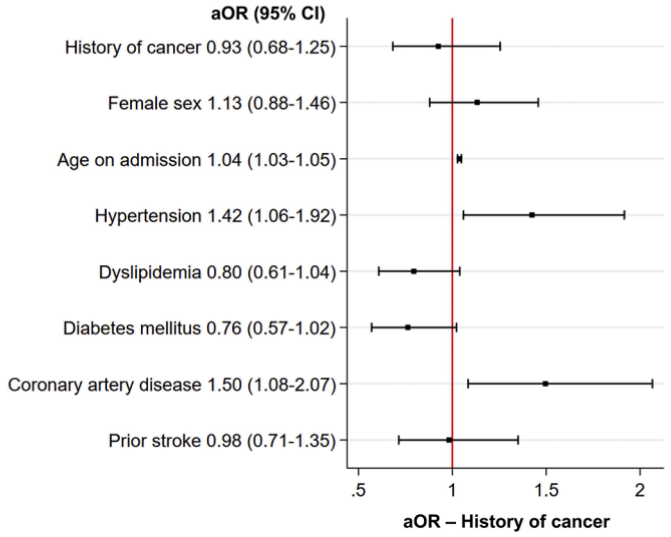


**Fig. 3.** Forest plot of multivariable logistic regression model evaluating the association between any history of cancer and atrial cardiopathy.
Legend: Multivariable logistic regression model assessing the association between history of cancer (active or inactive) and atrial cardiopathy while adjusting for potential confounders. Data reported as adjusted odds ratios (aOR) and their 95 % confidence intervals (CI).

## Discussion

Among a relatively large, well-characterized cohort of patients with AIS at an urban, quaternary-care, stroke and cancer center, we found no association between active or inactive cancer and atrial cardiopathy. This lack of association persisted in secondary analyses excluding patients with prevalent AF, using more or less stringent LAVI cutoffs to define atrial cardiopathy, and among patients whose stroke mechanism was categorized as ESUS.

According to the current literature, there is no standard definition of

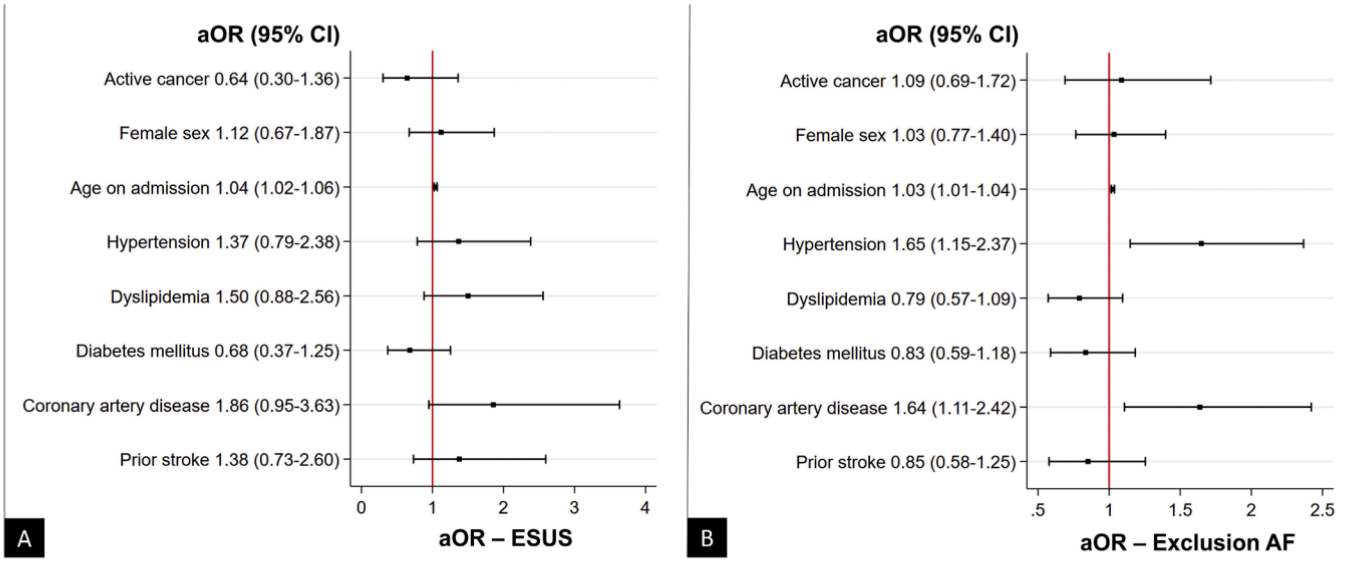


**Figure 4.** Forest plot of multivariable logistic regression model evaluating the association between active cancer and atrial cardiopathy among patient subgroups. Legend: Multivariable logistic regression models assessing the association between active cancer and atrial cardiopathy while adjusting for potential confounders among (A) patients with embolic stroke of undetermined source (ESUS) and (B) patients without atrial fibrillation (AF). Data reported as adjusted odds ratios (aOR) and their 95 % confidence intervals (CI).

atrial cardiopathy, nor universally accepted recommendations for its diagnosis.[8] LAVI assessment to identify atrial cardiopathy and subsequent risk of AIS is widely available and established.[23,24] Due to data availability at our center, we evaluated atrial cardiopathy as defined by a LAVI $\geq$35 mL/m$^2$ on echocardiography. A recent review by Kreimer et al provides an overview of the other methods and measurements currently used to evaluate atrial cardiopathy.[8] Alongside echocardiography, cardiac magnetic resonance imaging and cardiac computed tomography can be used to assess the size and structure of the left atrium.[9,25,26] However, echocardiography, especially TTE, remains the preferred screening and follow-up modality because of its extensive availability, rapid image acquisition, high temporal resolution, and relatively low cost.[8]

Atrial cardiopathy can also be clinically evaluated with an electrocardiogram (ECG), which can demonstrate conduction disturbances and electrical remodeling.[8] Atrial cardiopathies are generally associated with pathological changes in P-waves (representing atrial depolarization) and in fibrillatory "F" waves (found in place of P-waves in the case of AF).[8] Additionally, numerous blood biomarkers have been associated with atrial cardiopathy.[8] Besides specific markers of inflammation and fibrosis, N-terminal pro-B-type natriuretic peptide has been associated with atrial cardiopathy.[8]

No study has conclusively demonstrated a direct association between atrial cardiopathy and cancer.[7] In a case-control study of 92 patients with cancer and 40 matched controls with similar cardiovascular risk profiles, left atrial reservoir and conduit functions, assessed with volumetric and strain analysis, were more impaired in the cancer group.[27] Some markers of atrial cardiopathy, such as dilatation, maximal volume, and longitudinal strain, have been associated with an increased risk of cardiotoxicity from cancer treatments.[7,27,28] Ren et al demonstrated a higher long-term mortality rate (median follow-up 23 months) in cancer patients with atrial cardiopathy (68 %) than in those without (46 %).[14] However, they did not find an association between atrial cardiopathy and AIS in cancer patients. The authors note the small number of AIS events ($n$ = 12/306) and the large number of patients lost to follow-up as limitations. Our study also showed no association between cancer and atrial cardiopathy assessed with echocardiography in AIS patients. Further, the use of different definitions of left atrial enlargement, the exclusion of AF as a potential cofounder, and the combination of inactive cancer with active cancer did not change this absence of association.

The fact that both cancer and atrial cardiopathy are associated with increased thromboembolic risk in ESUS patients raises the possibility of a mechanistic link between these entities.[7,29] Overall, approximately 50 % of cancer-related strokes are ultimately classified as ESUS, and atrial cardiopathy is found in approximately 45 % of ESUS patients.[1,13] However, our study showed no association between cancer and atrial cardiopathy in ESUS patients only, arguing against a potential association between the two in an AIS population.[7]

Our study has several limitations. First, it was a single center retrospective study; therefore, our results could have been affected by referral and selection biases and have uncertain generalizability beyond our center. Second, only 52 % of the patients registered in CAESAR during the study period had available LAVI measurements to evaluate for the presence of atrial cardiopathy. It is possible that measured or unmeasured differences between patients with or without available LAVI data could have biased the relationship between atrial cardiopathy and cancer. Additionally, we only assessed CAESAR patients from 2011-2016 as those were the years when we had available echocardiography data. Third, we used LAVI to define atrial cardiopathy, but not other markers of atrial cardiopathy, including P-wave abnormalities on ECG, serum natriuretic peptides, and imaging abnormalities such as changes in atrial strain or fibrosis.[7–9] If these other markers were used to define atrial cardiopathy, it is possible that an association with cancer could have been identified. Finally, as our study only involved patients with AIS, a Simpson's paradox regarding our results cannot be ruled out.[30,31] The lack of association between cancer and atrial cardiopathy may not generalize to the general population, and further studies on this topic are warranted.

By evaluating LAVI using echocardiography, our study showed no association between atrial cardiopathy and cancer in patients with AIS, including those with ESUS. Further studies evaluating other modalities for the diagnosis of atrial cardiopathy are needed to confirm our findings.

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## CRediT authorship contribution statement

**Morin Beyeler:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Anokhi Pawar:** Project administration, Writing – review & editing. **Eric Buffle:** Conceptualization, Writing – review & editing. **Cenai Zhang:** Conceptualization, Formal analysis, Writing – review & editing. **Vanessa Liao:** Project administration, Writing – review & editing. **Ava L. Liberman:** Writing – review & editing. **Thomas Pabst:** Writing – review & editing. **Martin D. Berger:** Supervision, Writing – review & editing. **Simon Jung:** Supervision, Writing – review & editing. **Hooman Kamel:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Babak B. Navi:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing.

## Declaration of competing interest

Dr. Beyeler has received research support from the University of Bern, Switzerland. Dr. Navi has received personal fees for serving on an adjudication committee for MindRhythm Inc. Dr. Kamel reports serving as a PI for the ARCADIA trial (NIH/NINDS U01NS095869), which received in-kind study drug from the BMS-Pfizer Alliance for Eliquis® and ancillary study support from Roche Diagnostics; other funding from NIH (R01HL144541, R01NS123576, U01NS106513); serving as Deputy Editor for JAMA Neurology; serving on clinical trial steering/executive committees for Medtronic, Janssen, and Javelin Medical; serving on endpoint adjudication committees for AstraZeneca, Novo Nordisk, and Boehringer Ingelheim; and household ownership interests in TETMedical, Spectrum Plastics Group, and Burke Porter Group. The other authors declare no competing interests.

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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.2024.108045.

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# Chapter 2.2: The special case of occult cancer

# Prediction of occult cancer in stroke patients

Title of the manuscript: Development of a score for prediction of occult malignancy in stroke patients (OCCULT-5 Score)

Contributions of the PhD candidate:

- Conceptualization
- Data collection
- Data curation
- Formal analysis
- Visualization
- Writing – original draft

Results summary:

This study focused on so-called "occult cancer", defined as a new cancer diagnosed within the first year after AIS. As mentioned above, the cumulative incidence of occult cancers has been estimated to reach 2% in the overall AIS population. The aim of this study was to develop a clinical score for predicting the presence of occult cancer in AIS patients and thus identify high-risk patients requiring cancer screening. Based on our BMS database we evaluated AIS patients treated at our center between July 2017 and November 2018 for eligibility. Patients with active cancer at presentation, or with cancer diagnosed within 1 year thereafter and patients free of cancer were included and cancer-associated biomarkers were assessed. Of 1001 stroke patients, 61 (6%) presented with active cancer. Thirty-nine cancers (64%) were known and 22 (36%) were occult.

Five variables were included in the final OCCULT-5 score: age ≥ 77 years, embolic stroke of undetermined source, multi-territorial infarcts, D-dimer levels ≥ 820 µ/gL, and female sex. A score of ≥ 3 predicted an underlying occult cancer with a sensitivity of 64%, specificity of 73%, positive likelihood ratio of 2.35 and a negative likelihood ratio of 0.50.

# Development of a Score for Prediction of Occult Malignancy in Stroke Patients (Occult-5 Score)

Morin Beyeler, MD,[a,b,#] Barbara Birner, MD,[a,#] Mattia Branca, PhD,[c] Thomas Meinel, MD,[a] Jan Vynckier, MD,[a,d] Eric Buffle, MD,[e,f] Adrian Scutelnic, MD,[a] Mirjam R. Heldner, MD,[a] Philipp Bücke, MD,[a] David Seiffge, MD,[a] Pascale Mordasini, MD,[g] Tomas Dobrocky, MD,[g] Eike I. Piechowiak, MD,[g] Johannes Kaesmacher, MD,[g] Jan Gralla, MD,[g] Heinrich P. Mattle, MD,[a] Marcel Arnold, MD,[a] Urs Fischer, MD,[a,h] Thomas Pabst, MD,[i] Martin D. Berger, MD,[i] and Simon Jung, MD[a]

*Background and purpose:* Malignancy associated acute ischemic stroke (AIS) requires specific diagnostic work-up, treatment and prevention to improve outcome. This study aimed to develop a biomarker-based score for prediction of occult malignancy in AIS patients. *Methods:* Single-center cross-sectional study including consecutive AIS patients treated between July 2017 and November 2018. Patients with active malignancy at presentation, or diagnosed within 1 year thereafter and patients free of malignancy, were included and malignancy associated biomarkers were assessed. LASSO analyses of logistic regression were performed to determine biomarkers predictive of active malignancy. Predictors were derived from a predictive model for active malignancy. A comparison between known and unknown (=occult) malignancies when the index stroke occurred was used to eliminate variables not associated with occult malignancy. A predictive score (OCCULT-5 score) for occult malignancy was developed based on the remaining variables. *Results:* From 1001 AIS patients, 61 (6%) presented an active malignancy. Thirty-nine (64%) were known and 22 (36%) occult. Five variables were included in the final OCCULT-5 score: age $\geq$ 77 years, embolic stroke of undetermined source, multi-territorial infarcts, D-dimer levels $\geq$ 820 $\mu$/gL, and female sex. A score of $\geq$ 3 predicted an underlying occult malignancy with a sensitivity of 64%, specificity of 73%, positive likelihood ratio of 2.35 and a negative likelihood ratio of 0.50. *Conclusions:* The OCCULT-5 score might be useful to identify patients with occult malignancy. It may thus contribute to a more effective and timely treatment and thus lead to a positive impact on overall outcome.

*Abbreviations:* CRP, C-Reactive Protein; ESUS, Embolic Stroke of Undetermined Source; Hb, Hemoglobin; LASSO, Least Absolute Shrinkage and Selection Operator; LDH, Lactate Dehydrogenase; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-Terminal-pro B-type Natriuretic Peptide

From the [a]Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Switzerland; [b]Graduate School for Health Sciences, University of Bern, Switzerland; [c]CTU Bern, University of Bern, Bern, Switzerland; [d]Department of Neurology, Onze Lieve Vrouwziekenhuis Hospital, Aalst, Belgium; [e]ARTORG Center, University of Bern, Bern, Switzerland; [f]Department of Cardiology, Inselspital, Bern University Hospital, and University of Bern, Switzerland; [g]Department of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Switzerland; [h]Neurology Department, University Hospital of Basel, University of Basel, Basel, Switzerland; and [i]Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Switzerland.

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Corresponding author. E-mail: morin.beyeler@insel.ch.

[#]equal contribution

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**Key Words:** Biomarkers—Ischemic stroke—Malignancy-related stroke—Occult malignancy—Predictive score


## Introduction

### *Background/rationale*

Known or occult malignancy is a well-established risk factor for ischemic stroke, increased stroke severity, stroke recurrence, and high mortality.[1–8] Paraneoplastic coagulation disorder is thought to be the most frequent cause of malignancy-related strokes.[9] The reasons leading to a hypercoagulable state are complex and mediated by the expression of procoagulant factors (tissue factor, extracellular vesicles, inflammatory cytokines and inhibitors of fibrinolysis released by cancer cells and extracellular neutrophil traps).[10] Thrombi leading to stroke can be venous (deep vein thrombosis with paradoxical embolism), arterial (intravascular coagulopathy) or cardiac (nonbacterial thrombotic endocarditis).[11] Other common causes of stroke in patients with underlying malignancy are shared risk factors between stroke and malignancy such as smoking, obesity or inflammation, side effects of chemotherapy and direct occlusion by the tumor itself.[11] The prevalence of active malignancy in stroke patients is estimated to reach 10%.[10] According to a recent meta-analysis, the cumulative incidence of occult malignancy in the first year after stroke seems to be 1.4%.[12] The true rate of occult malignancy and consequently the global burden of malignancy-related stroke may be even higher than currently estimated by the retrospective studies available. In this context, better characterization of malignancy and of the underlying paraneoplastic coagulation disorders in stroke is crucial for the guidance of secondary prevention and faster diagnosis of occult malignancy after ischemic stroke. In the last decade, potential predictive and prognostic biomarkers such as D-dimer, fibrinogen, C-Reactive Protein (CRP), hemoglobin (Hb), multi-territory infarcts and embolic stroke of undetermined source (ESUS) have been identified in stroke patients with malignancy.[5,13–20] Because occult malignancy is rare, predictive models to identify patients that would benefit from malignancy screening are needed and currently not available.[16,21,22] The early diagnosis and thus more effective and timely treatment of occult malignancy may improve the outcomes of affected stroke patients. This study aimed to develop a score based on biomarkers to predict occult malignancy in stroke patients.

## Methods

### *Study cohort*

This single-center, retrospective, and cross-sectional study assessed all consecutive patients admitted for acute ischemic stroke at a comprehensive stroke center between July 2017 and November 2018 who were prospectively included in a single-center stroke-registry ($n$=1317). To ensure the availability of biomarkers, all patients with missing D-dimer values at admission and those in whom intravenous thrombolysis was started prior to D-dimer measurement were excluded. Patients with recurrent stroke due to an active malignancy after the index-event were not assessed a second time. This study conforms with the World Medical Association Declaration of Helsinki.[23] In accordance with Swiss law, the local ethics committee approved this study and waived the need for written patient consent (reference ID: 2021-01031).

### *Definition of active known malignancy and occult malignancy*

Active known malignancy was defined as a new or recurrent malignancy, diagnosed or treated within 6 months prior to the index stroke, or metastatic malignancy.[24,25] According to the current literature, malignancies diagnosed within 1 year after the index stroke were defined as occult malignancy. They represent a subgroup of active malignancies when the index stroke occurs.[2,13,26] Patients with breast cancer and receiving secondary prophylactic hormone therapy were considered cured and in complete remission without active malignancy.[27,28] Focal non-melanoma skin cancer were not considered as active malignancy due to the low risk of metastatic spread and their non-systemic nature.[29]

### *Data extraction and analysis*

Ischemic stroke was confirmed by cranial magnetic resonance imaging (MRI) or computed tomography. Two neurologists from the University Department of Neurology Bern (M.B. and B.B.) assessed all consecutive stroke patients treated between July 2017 and November 2018 at the local comprehensive stroke center for the diagnosis of active known malignancy at the time of the index stroke and occult malignancy up to 1 year after the index stroke. Histological proof of malignancy or oncological diagnosis based on clinical investigations were used to identify patients with malignancy from the local clinical information system. Baseline characteristics of patients were extracted from the local stroke registry. Demographic information and risk factors included sex, age at admission, prestroke disability, previous stroke, arterial hypertension, diabetes mellitus, hyperlipidemia, smoking status, atrial fibrillation and coronary heart disease. The stroke characteristics investigated were neurological

deficit at admission assessed with the National Institutes of Health Stroke Scale (NIHSS), stroke recurrence, time of symptom-onset, infarct distribution (single vs. multi-territory infarct and number of territories involved), and stroke etiology at discharge of the index hospitalization defined according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification.[30] Strokes associated with patent foramen ovale were classified as cardioembolic stroke. In line with the "NAVIGATE ESUS" randomized trial, ESUS was defined as nonlacunar ischemic stroke occurring in a patient in whom investigations did not show another underlying stroke etiology.[31] Laboratory values at admission were extracted from the local clinical information system: D-dimer, Hb, CRP, N-terminal-pro B-type natriuretic peptide (NT-proBNP), lactate dehydrogenase (LDH), low-density lipoprotein (LDL) cholesterol, total cholesterol, creatinine, and glucose.

### *Statistical analysis*

All statistical analyses were performed using Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) and R (v 3.6.0 or newer, R Core Team). Baseline characteristics are presented using frequency with percentage for categorical variables and median with interquartile range for continuous variables. The comparison between groups was performed using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Simple and multiple logistic regression were performed to determine the odds ratio (OR) or adjusted odds ratio (aOR) for the presence of an active malignancy (active known malignancies and occult malignancies together) and an occult malignancy alone. Because of the low rate of occult malignancy, its predictors were derived from a predictive model for active malignancy (see Supplementary Method and Results I). The ability of the predictive model for active malignancy and the predictive score for occult malignancy were determined by analyses of the area under the Receiver Operating Characteristics curve (auROC). After calculating the regression coefficient for each item selected for the score for occult malignancy, we attributed 1 point to the smallest regression coefficient, which served as the least common denominator for the assignment of point value for the other items. Bayesian decision theory was used to evaluate the posterior probability of the predictive score for occult malignancy. A two-sided $P$ value $< 0.05$ was considered statistically significant. Using the "pmsampsize" function in STATA 16 and assuming a prevalence of 0.10 for active malignancy, including 12 candidate predictor parameters (see Supplementary Method and Results I) and reusing a c-statistic of previous test of 0.83 this study needed to include at least 720 patients.[10,21]

## Results

### *Study population*

Overall, 1317 consecutive patients were treated for ischemic stroke between 07/2017 and 11/2018 at the local comprehensive stroke center. Of these, 273 patients with missing D-dimer values at admission and 42 patients who had received intravenous thrombolysis prior to D-dimer measurement were excluded. After identification of underlying active malignancy, one patient with active known malignancy was excluded because of stroke recurrence. For the final analysis, 1001 stroke patients were included (Fig. 1 Study Flowchart).

### *Baseline characteristics*

Comparison between included and excluded patients is summarized in the eTable I.

Of the patients included in the study, 61 (6%) had an active known malignancy at the time of stroke or received the diagnosis of malignancy up to 1 year after hospitalization. Differences between patients with or without active malignancy are summarized in Table 1 and reported in the supplementary material.

### *Difference between occult malignancy and active known malignancy*

There were 61 patients with active malignancy at time of stroke (6%), 22 with occult (36%) and 39 with known malignancy (64%). Comparison of baseline characteristics between both groups is given in eTable IIa. As demonstrated in eTable IIb, the localization of underlying malignancy was different in both groups ($P$=0.011). Metastatic state of malignancy (68% versus 68%, $P$=1.00) and histological type of malignancy ($P$=0.47) were similar in both groups. The Fig. 2 summarizes the distribution of histological types according to the malignancy subgroups.

Compared to patients with active known malignancy, those with occult malignancy had lower CRP in mg/L (median 3 versus 15, IQR 3-14 versus 4-37, $P$=0.009) and higher Hb in g/L (median 130 versus 118, IQR 120-143 versus 105-136, $P$=0.017). Women showed a higher occult malignancy incidence than men (59% versus 41%, $P$=0.028).

### *Development of a predictive score for occult malignancy (OCCULT-5)*

Our model for active malignancy (known and occult) identified the following predictors: Male sex, ESUS, multi-territory infarcts, age, NIHSS on admission, D-dimer, Hb, LDH, and CRP (See Supplementary Method and Results I). We eliminated variables found only in patients with active known malignancy (low CRP and high Hb), with not enough observations (LDH), and results not supported by published evidence (NIHSS). We changed the

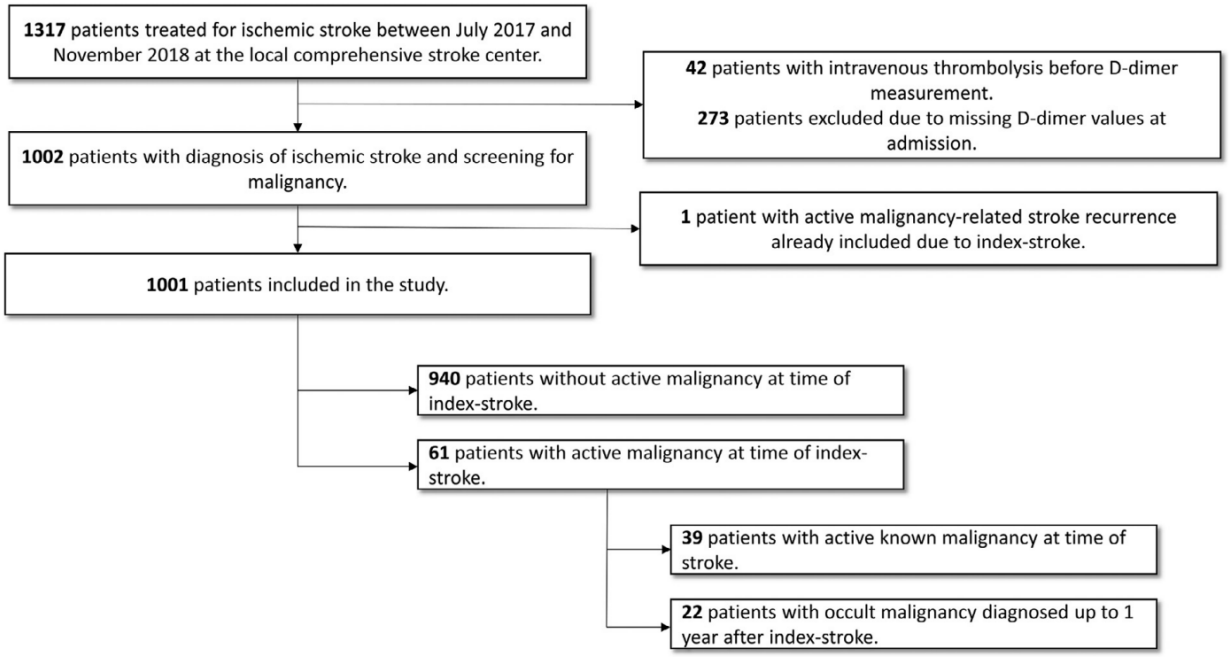


**Fig. 1.** *Study flowchart. This figure shows the process of inclusion and exclusion of patients in the study.*

predictor "sex" from male to female because of the higher proportion of women with occult malignancy. The OCCULT-5 score, based on 5 malignancy-related variables, includes age at admission ≥ 77 years, ESUS after initial stroke work-up, multi-territory infarcts, D-dimer level ≥ 820 µ/gL, and female sex (Table 2). The score performance was assessed on 997 patients, including 22 with occult malignancy. The auROC of the proposed score was 0.7 (95% CI 0.57−0.82). The OCCULT-5 score ranges from 0 to 5. Individual regression coefficients and points are reported in Table 2. A meaningful cut-off for clinical use was set at ≥ 3 points based on a sensitivity of 64%, a specificity of 73%, a positive likelihood ratio of 2.35, and a negative likelihood ratio of 0.49. The performance of all individual cut-offs including also the positive and negative predictive values and the posterior probability is shown in Table 3.

### *Further characteristics of occult malignancy*

The first investigations, which detected or suspected an occult malignancy are summarized in eTable III. Regarding radiological investigation, 73% of occult malignancies (*n*=16) were detected with computed tomography from the chest or abdomen and 64% (*n*=14) by combined computed tomography of chest, abdomen and pelvis. In patients with occult malignancy at time of stroke, the median time between index stroke and diagnosis was 3.5 days (IQR 1−74). In 50% (*n*=11) occult malignancy was detected during the index hospitalization. In the other patients (*n*=11) median time between discharge and diagnosis of occult malignancy was 71 days (IQR 20 − 175).

## Discussion

The main findings of this study are: (1); Patients with occult malignancy present characteristics that are different from those with known malignancy: More female sex, lower CRP and higher Hb values. (2); The proposed predictive score for occult malignancy (OCCULT-5 score) has for ≥ 3 points a sensitivity of 64%, a specificity of 73%, positive likelihood ratio of 2.35, and negative likelihood ratio of 0.5.

According to a recent literature review from Dardiotis et al., active malignancy in stroke patients are associated with several biomarkers.[9] In addition to the most often reported biomarkers, which were also used in this study (elevated D-dimer, CRP, and LDH; low hemoglobin; multi-territory infarcts; and ESUS), elevated fibrinogen and higher erythrocyte sedimentation rate were also frequently associated with malignancy-related stroke.[13,14,32–35]

Factors, that had been found to be associated with occult malignancy at time of stroke, were older age, history of smoking, undetermined stroke etiology, multi-territory infarcts, low hemoglobin levels, higher CRP, higher D-dimers and higher fibrinogen.[13,15,16,20,26,36] In our study, the etiological distribution of occult malignancies does not differ from active known malignancy (Fig. 2). However, analyses involving more patients with occult malignancies are needed to validate this observation in the future. A predictive score for the presence of occult malignancy at the time of stroke would be helpful to decide whether to screen for malignancy. Previous studies focused on the prediction of active malignancy (known and occult malignancy together), but a predictive score

**Table 1.** *Comparison of baseline characteristics in patients with and without active malignancy.*

| | All patients (*N*=1001) | No malignancy (*N*=940) | Active malignancy (*N*=61) | *p*-value |
|---|---|---|---|---|
| Baseline | | | | |
| Sex, Female No. / total No. (%) | 414 (41.4%) | 390/940 (31.5%) | 24/61 (39.3%) | 0.79 |
| Age at admission (median, IQR) | 73.8 (63−82.4) | 73.5 (62.5−82.3) | 76.8 (71.1−83.4) | 0.025 |
| Prestroke disability (mRS, median, IQR) | 0 (0−1) | 0 (0−1) | 1 (0−1.5) | 0.028 |
| Risk factors | | | | |
| Previous stroke No. / total No. (%) | 92 (15.5%) | 76/488 (15.6%) | 3/30 (10%) | 0.60 |
| Hypertension No. / total No. (%) | 398 (67%) | 315/487 (64.7%) | 25/30 (82.8%) | 0.046 |
| Diabetes No. / total No. (%) | 103 (17.3%) | 84/487 (17.2%) | 5/30 (16.7%) | 1.00 |
| Hyperlipidemia No. / total No. (%) | 349 (58.7%) | 287/487 (58.9%) | 18/30 (60%) | 1.00 |
| Smoking No. / total No. (%) | 118 (20%) | 97/485 (20.0%) | 6/29 (21.4%) | 1.00 |
| Atrial Fibrillation No. / total No. (%) | 189 (31.1%) | 147/499 (29.5%) | 11/31 (35.5%) | 0.54 |
| Coronary heart disease No. / total No. (%) | 82 (13.8%) | 62/487 (12.7%) | 5/30 (16.7%) | 0.57 |
| Stroke characteristics | | | | |
| NIHSS on admission, (median, IQR) | 4 (1−9) | 4 (1−9) | 5 (2−9) | 0.10 |
| **Stroke Etiology (TOAST)** No. / total No. (%): | | | | |
| Cardioembolic | 257 (25.7%) | 242/938 (25.8%) | 15/61 (24.6%) | 0.58 |
| Small−vessel occlusion | 47 (4.7) | 45/938 (4.8%) | 2/61 (3.3%) | |
| Large−artery atherosclerosis | 142 (14.2%) | 137/938 (14.6%) | 5/61 (8.2%) | |
| Stroke of other determined etiology and multiple etiology | 32 (3.2%) | 30/938 (3.2%) | 2/61 (3.3%) | |
| Stroke of undetermined etiology | 521 (52.1%) | 484/938 (51.6%) | 37/61 (60.7%) | |
| Stroke of undetermined etiology vs. other etiologies No. / total No. (%): | 521 (52.1%) | 484/938 (51.6%) | 37/61 (60.7%) | 0.17 |
| Embolic stroke of undetermined source (ESUS) No. / total No. (%): | 388 (38.8%) | 356/938 (37.9%) | 32/61 (52.5%) | 0.024 |
| Stroke recurrence No. / total No. (%): | 33 (5.6%) | 25/488 (5.1%) | 4/31 (12.9%) | 0.086 |
| Stroke in multiple territories, No. / total No. (%): | 149 (14.9%) | 127/938 (13.5%) | 22/61 (36.1%) | <0.001 |
| Number of territories involved **No. / total No. (%):** | | | | |
| 0 | 43 (4.3%) | 43/938 (4.6%) | 0/61 (0.0%) | <0.001 |
| 1 | 807 (80.8%) | 768/938 (81.9%) | 39/61 (63.9%) | |
| 2 | 106 (10.6%) | 98/938 (10.4%) | 8/61 (13.1%) | |
| 3 | 23 (2.3%) | 21/938 (2.2%) | 2/61 (3.3%) | |
| 4 | 20 (2%) | 8/938 (0.9%) | 12/61 (19.7%) | |
| Baseline laboratory findings | | | | |
| Glucose in mmol/L (median, IQR) | 6.3 (5.6−7.6) | 6.3 (5.6−7.6) | 6.3 (5.8−7.4) | 0.82 |
| Cholesterol total in mmol/L (median, IQR) | 4.8 (4.01−5.59) | 4.81 (4.02−5.63) | 4.62 (3.73−5.31) | 0.10 |
| Cholesterol LDL in mmol/L (median, IQR) | 2.67 (1.98−3.45) | 2.69 (1.98−3.47) | 2.57 (1.78−3.09) | 0.10 |
| Creatinine in µmol/L (median, IQR) | 79 (65−95) | 79 (65−94) | 82 (63−105) | 0.46 |
| D−dimer in µg/L (median, IQR) | 726 (380−1644) | 701 (367.5−1524.5) | 1689 (652−6852) | <0.001 |
| Hb in g/L (median, IQR) | 137 (126−147) | 139 (128−148) | 123 (112−136) | <0.001 |
| CRP in mg/L (median, IQR) | 3 (3−7) | 3 (3−6) | 9 (3−24) | <0.001 |
| NT−proBNP in pg/mL (median, IQR) | 264 (97−888) | 249.5 (93−865) | 508.5 (251.5−1546) | <0.001 |
| LDH in U/L (median, IQR) | 400.5 (348−474) | 397 (348−466) | 472.5 (373−652.5) | <0.001 |

CRP, C-reactive protein; IQR, interquartile range; Hb, Hemoglobin; LDH, Lactate dehydrogenase; LDL, Low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal-pro B-type natriuretic peptide; TOAST, Trial of ORG 10172 in Acute Stroke Treatment

for occult malignancy would be more useful. Based on a study in 82 patients with active malignancy out of 1646 ischemic stroke patients, Selvik et al. proposed a multivariable predictive clinical score (total 3 points) based on D-dimer level, Hb-level and smoking status.[22] In patients younger than 75 years fulfilling all criteria, the auROC was 0.73 (95% CI 0.65−0.81). For patients older than 75 years the auROC was less with 0.66 (95% CI 0.59−0.73). Most recently, Jiang et al. proposed a score derived from 53 patients with active malignancy (6.63%) of 799 ischemic stroke patients.[21] The 3-points score consists of absence of hyperlipidemia, elevated D-dimer and elevated fibrinogen level. The score showed a good performance (auROC 0.83) and good posterior probability. However, despite a specificity of 99% for a score of 3/3, the corresponding sensitivity of 19% is insufficient to prompt further investigation to search for occult malignancy.

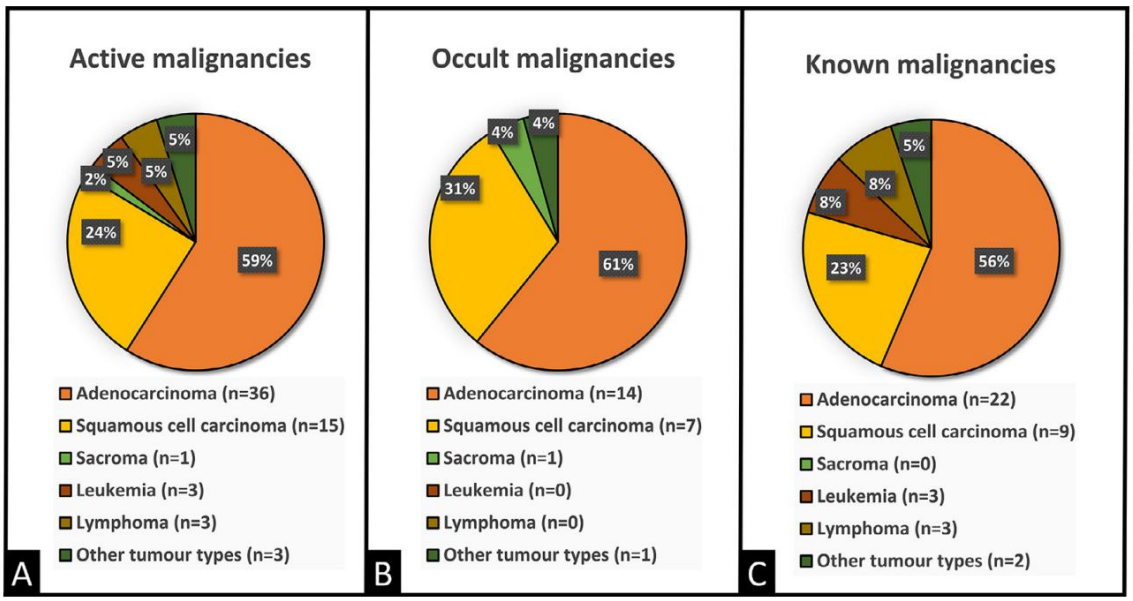


**Fig. 2.** *Distribution of histological types according to the malignancy subgroups. Patients with active malignancy (Fig. 2A), were divided into patients with occult malignancy (Fig. 2B) and patients with active known malignancy (Fig. 2C). No significant difference was observed between occult malignancies and active known malignancies (Fisher's exact test: P=0.47). However, hematologic malignancies were absent in the subgroup with occult malignancies.*

**Table 2.** *OCCULT-5 score for prediction of occult malignancy in ischemic stroke patients.*

| OCCULT-5 | Criteria | Regression coefficients | Points |
|---|---|---|---|
| Age | ≥ 77 years old | 0.662 | 1 |
| ESUS | Yes | 0.507 | 1 |
| Multi-territory infarcts | Yes | 0.634 | 1 |
| D-dimer | ≥ 820 µ/gL | 0.633 | 1 |
| Female sex | Yes | 0.475 | 1 |
| Total | | | 5 points |

Components of the OCCULT-5 score were selected based on the LASSO selection for prediction of active malignancy (known and occult malignancies). Selected variables were eliminated for the final score if not found in patients with occult malignancy, clinically not meaningful due to the small sample size (NIHSS), and because of too many missing values (LDH).

**Table 3.** *Performance and posterior probabilities of the OCCULT-5 score for prediction of occult malignancy in patients with ischemic stroke.*

| Score | No. of patients (*N*=997) | Sensitivity | Specificity | LR + | LR - | PPV | NPV | Posterior probability |
|---|---|---|---|---|---|---|---|---|
| ≥0 | 997 | 100% | 0% | 1.00 | NA | 100% | 0% | 2.20% |
| ≥1 | 854 | 86.36% | 14.36% | 1.00 | 0.95 | 2.22% | 97.9% | 2.22% |
| ≥2 | 573 | 86.36% | 43.18% | 1.52 | 0.32 | 3.32% | 99.29% | 3.31% |
| ≥3 | 278 | 63.64% | 72.92% | 2.35 | 0.50 | 5.04% | 98.89% | 5.02% |
| ≥4 | 93 | 27.27% | 91.08% | 3.05 | 0.80 | 6.45% | 98.23% | 6.43% |
| 5 | 13 | 4.55% | 98.77% | 3.69 | 0.97 | 7.69% | 97.86% | 7.68% |

LR+, positive likelihood ratio; LR -, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value

According to the current evidence and in line with the observations from our study combined chest, abdomen, and pelvis computed tomography should be considered when malignancy-related biomarkers are present.[37,38] Nevertheless no official guidelines on how and when to screen for occult malignancy are published yet.

Because of the low rate of occult malignancy, the predictive score for occult malignancy was derived from selected variables of the model for active malignancy (see Supplementary Method and Results I). Only variables associated with occult malignancy when compared to active known malignancy were included in the final OCCULT-5 score. Because of the low rate of occult malignancy (2.2% in this study and 1.4% according to the meta-analysis by Rioux et al.)[12] and low sensitivity in high scores, the predictive values and posterior probability of the OCCULT-5 score remain low. In addition, the OCCULT-5 score needs to be externally validated, first in

a retrospective and then in a prospective cohort. When the score can be externally validated and turns out to be reliable, it might accelerate detection of malignancy in stroke patients and improve their outcome.

## Limitations

This study has several limitations; first, this was a monocentric study and retrospective analysis. This may lead to an underestimation of the real rate of occult malignancy.[12] Second, the number of patients with active malignancy, and especially with occult malignancy, was low. This led to a low posterior probability for detection of occult malignancy and it could limit the applicability of the OCCULT-5 score. Third, malignancy-related biomarkers were available in most but not all patients. This was particularly the case of fibrinogen. Fourth, differences between included and excluded patients (especially regarding the age at admission) might have led to selection bias.

## Conclusion

We developed the OCCULT-5 score to predict occult malignancy in ischemic stroke patients with an optimal balance of sensitivity and specificity. If the OCCULT-5 score will be validated in an external cohort it might help to guide the search for malignancy in specific stroke patients, help to detect malignancy faster and improve the outcome of stroke patients with occult malignancy. Therefore the OCCULT-5 score might be helpful to manage such stroke patients and improve their outcome.

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## Contributorship statement

Morin Beyeler contributed to conception and design, data acquisition, analysis and interpretation of data, and writing of the publication.

Barbara Briner contributed to conception and design, data acquisition, critical revision of the manuscript for important intellectual content.

Mattia Branca contributed to data interpretation and critical revision of the manuscript for important intellectual content.

Thomas Meinel contributed to data interpretation and critical revision of the manuscript for important intellectual content.

Eric Buffle contributed to data interpretation and critical revision of the manuscript for important intellectual content.

Jan Vynckier contributed to data interpretation and critical revision of the manuscript for important intellectual content.

Simon Jung contributed to conception and design, critical revision of the publication for important intellectual content, and supervision.

All other authors contributed to critical revision of the manuscript for important intellectual content.

## Data sharing

Data are available upon reasonable request

## Competing Interests Statement

Dr. Branca is employed by CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest, see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html Dr. Meinel reports research support from the Bangerter Rhyner Foundation, Swiss National Foundation, and the Swiss Heart Foundation not related to this work. Dr. Heldner reports research support from the Bangerter Foundation, scientific advisory board honoraria from Amgen, and personal fees from Bayer. Dr. Mordasini reports receipt of research support from Siemens, Cerenovus, iSchmaview, Medtronic, Stryker, the Swiss Heart Foundation and the Swiss National Foundation, receipt of consultant fees payed to the institution from Medtronic, Cerenovus, Phenox and Microvention during the conduct of the study, unrelated to the submitted work. Dr. Kaesmacher reports grants from the Swiss Academy of Medical Sciences/Bangerter Foundation, Swiss Stroke Society, and Clinical Trials Unit Bern during the conduct of the study. Dr. Mattle reports personal consulting fees outside of this study from Servier, Bayer, Medtronic, Stryker and Cerenovus. Dr. Arnold reports personal fees from Bayer, Bristol-Myers Squibb, Medtronic, Amgen, Daiichi Sankyo, Nestlé Health Sciences, Boehringer Ingelheim, and Covidien during the conduct of the study. Dr. Fischer reports grants during the conduct of the study from Medtronic, Stryker, and CSL Behring, unrelated to the submitted work. Dr. Jung reports grants from the Swiss National Science Foundation and the Swiss Heart Foundation.

## Conflicts of Interest

None of the other authors report any.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106609.

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## Mortality of stroke patients with new diagnosis of cancer

Title of the manuscript: Mortality in acute ischemic stroke patients with new cancer diagnosed during the index hospitalization versus after discharge

Contributions of the PhD candidate:

- Conceptualization
- Data collection
- Data curation
- Formal analysis
- Visualization
- Writing – review and editing
- Supervision

Results summary:

In this study, we investigated the difference in mortality between patients with a new cancer (occult cancer) diagnosed during hospitalization versus after discharge in the year following the AIS. Using data from our BMS database, we included all AIS patients treated from 2015 to 2020 for whom long-term follow-up was available. Of 3894 AIS patients with available long-term follow-up data, 59 (2%) were diagnosed with a new cancer within one year after the index AIS. 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 days), 70% of patients (n=19) whose cancer was diagnosed during hospitalization had died, compared to 63% of patients (n=20) 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 [aHR] 1.16, 95% CI 0.53–2.52; p=0.71).

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

Jayan Göcmen, MS [a], Fabienne Steinauer, MS [a], Moritz Kielkopf, MD [a], Mattia Branca, PhD [b], Christoph C. Kurmann, MD [c,d,e], Adnan Mujanovic, MD [c], Leander Clénin, MD [a], Norbert Silimon, MD [a], Anna Boronylo, MD [a], Adrian Scutelnic, MD [a], Thomas Meinel, MD [a], Johannes Kaesmacher, MD [c], Philipp Bücke, MD [a], David Seiffge, MD [a], Gianluca Costamagna, MD [f,g], Patrik Michel, MD [g], Urs Fischer, MD [a], Marcel Arnold, MD [a], Babak B. Navi, MD, MS [h], Thomas Pabst, MD [i], Martin D. Berger, MD [i], Simon Jung, MD [a,1], Morin Beyeler, MD [a,d,h,1,*]

[a] Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Switzerland
[b] CTU Bern, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[c] Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Switzerland
[d] Graduate School for Health Sciences, University of Bern, Switzerland
[e] Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, and University of Bern, Switzerland
[f] Stroke Unit, Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy
[g] Stroke Center, Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[h] Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, New York, USA
[i] Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Switzerland

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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.

* Corresponding author at: Department of Neurology, Inselspital, University of Bern, Freiburgstrasse 18, CH-3010, Switzerland.
*E-mail address:* morin.beyeler@insel.ch (M. Beyeler).

[1] Equal contribution.

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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 $\leq 2$), 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.

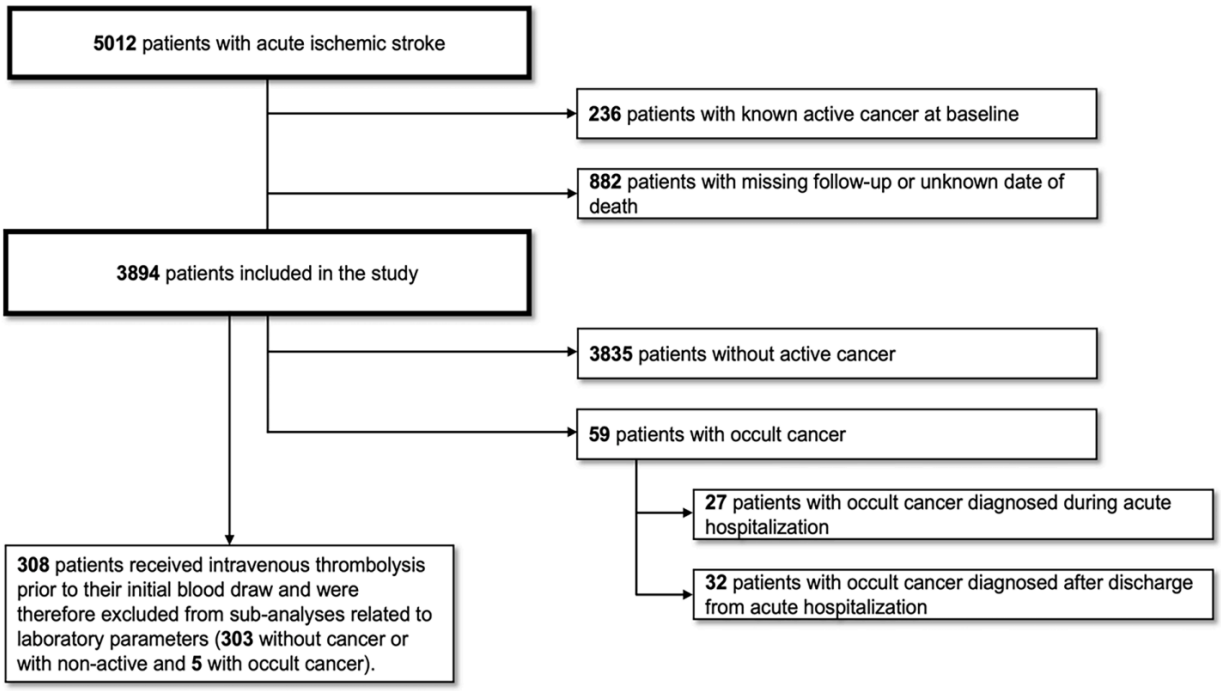


**Fig. 1.** Study flowchart.
Flow diagram describing how the final cohort was reached and relevant exclusions.

**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

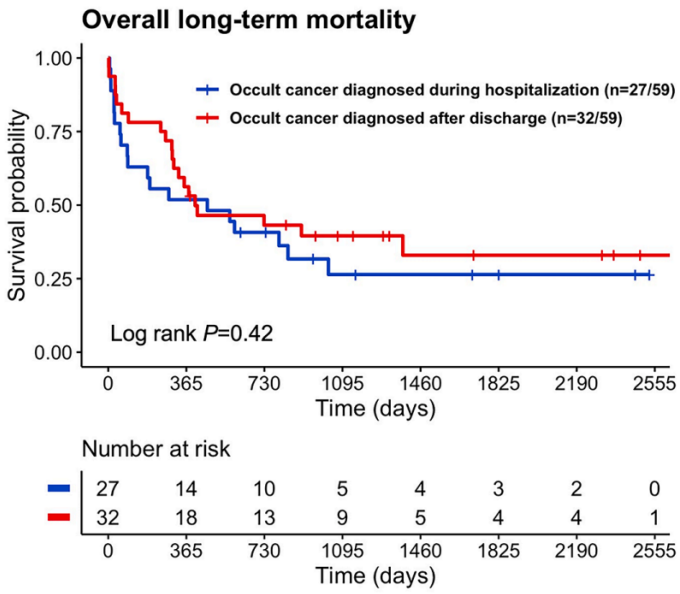


**Fig. 2.** Long-term survival curves for AIS patients with occult cancer diagnosed during hospitalization and after discharge.
No difference in overall long-term mortality was found between occult cancer diagnosed during hospitalization (blue) and after discharge (red) when compared using the log-rank 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

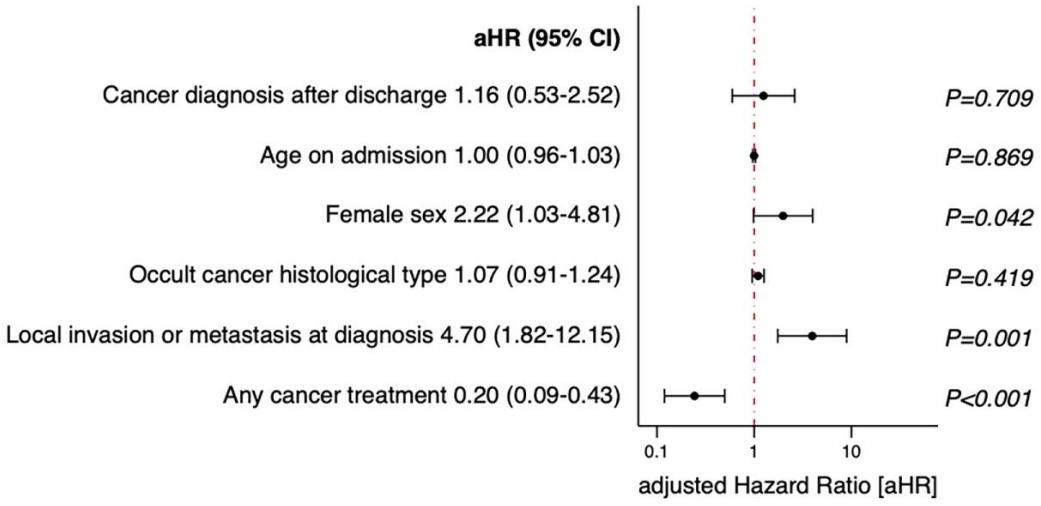


**Fig. 3.** Multivariable Cox analysis evaluating the association between the timing of occult cancer diagnosis (during hospitalization versus after discharge) and long-term mortality.
The primary adjusted analysis model evaluating a restricted number of covariates due to the small number of patients 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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# Chapter 2.3: Outcomes in cancer-related strokes

## The impact of susceptibility vessel sign on long-term outcome

Title of the manuscript: Susceptibility vessel sign, a predictor of long-term outcome in patients with stroke treated with mechanical thrombectomy

Contributions of the PhD candidate:

- Conceptualization
- Data collection
- Data curation
- Formal analysis
- Visualization
- Writing – original draft

Results summary:

After describing an association between the absence of the SVS and the presence of cancer, we studied the impact of SVS status on long-term outcomes in AIS patients. Our assumption was that the absence of the SVS would reflect an underlying pathology that could have a negative effect on outcomes.

For this purpose, we used information from our retrospective, monocentric BEYOND SWIFT database, which included AIS patients treated with mechanical thrombectomy between 2010 and 2018.

After exclusion of patients without available long-term follow-up, we assessed the predictors of long-term mortality and poor functional outcome (modified Rankin Scale [mRS] ≥3) up to 8 years after AIS.

Of the 558 patients included, SVS was absent in 13% (n=71) and present in 87% (n=487) on baseline imaging. Patients without SVS were more likely to have active cancer (p=0.003) and diabetes mellitus (p<0.001) at the time of AIS.

After adjustment for active cancer and diabetes mellitus, among others, the absence of SVS was associated with long-term mortality (aHR 2.11, 95% CI 1.35–3.29) and poor functional outcome in the long term (aOR 2.90, 95% CI 1.29–6.55). Interaction analyses did not demonstrate any substantial influence of the presence of active cancer on these associations (p for interaction=0.79 and 0.71, respectively).

Original research

# Susceptibility vessel sign, a predictor of long-term outcome in patients with stroke treated with mechanical thrombectomy

Morin Beyeler ,[1,2] Erich Rea,[1] Loris Weber,[1] Nebiyat Filate Belachew ,[3,4] Enrique Barvulsky Aleman,[4] Moritz Kielkopf,[1] Christoph C Kurmann ,[3] Lorenz Grunder,[3] Eike Immo I Piechowiak ,[3] Thomas R Meinel ,[1] Mirjam R Heldner,[1] David Seiffge ,[1] Sara Pilgram-Pastor,[3] Tomas Dobrocky ,[3] Thomas Pabst,[5] Martin D Berger,[5] Simon Jung,[1] Marcel Arnold,[1] Jan Gralla,[3] Urs Fischer,[1,6] Johannes Kaesmacher ,[3] Adnan Mujanovic [3]

## ABSTRACT

**Background** The absence of the susceptibility vessel sign (SVS) in patients treated with mechanical thrombectomy (MT) is associated with poor radiological and clinical outcomes after 3 months. Underlying conditions, such as cancer, are assumed to influence SVS status and could potentially impact the long-term outcome. We aimed to assess SVS status as an independent predictor of long-term outcomes in MT-treated patients.

**Methods** SVS status was retrospectively determined in consecutive MT-treated patients at a comprehensive stroke center between 2010 and 2018. Predictors of long-term mortality and poor functional outcome (modified Rankin Scale (mRS) ≥3) up to 8 years were identified using multivariable Cox and logistic regression, respectively.

**Results** Of the 558 patients included, SVS was absent in 13% (n=71) and present in 87% (n=487) on baseline imaging. Patients without SVS were more likely to have active cancer (P=0.003) and diabetes mellitus (P<0.001) at the time of stroke. The median long-term follow-up time was 1058 days (IQR 533–1671 days). After adjustment for active cancer and diabetes mellitus, among others, the absence of SVS was associated with long-term mortality (adjusted HR (aHR) 2.11, 95% CI 1.35 to 3.29) and poor functional outcome in the long term (adjusted OR (aOR) 2.90, 95% CI 1.29 to 6.55).

**Conclusion** MT-treated patients without SVS have higher long-term mortality rates and poorer long-term functional outcome. It appears that this association cannot be explained by comorbidities alone, and further studies are warranted.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The absence of the susceptibility vessel sign (SVS) on admission susceptibility-weighted imaging is associated with lower successful reperfusion rates after mechanical thrombectomy (MT) and overall poorer outcomes at 3 months. Furthermore, the absence of the SVS is associated with underlying conditions, such as cancer and diabetes mellitus, which are known to impact overall long-term outcomes. Whether SVS alone is associated with long-term outcomes in patients with stroke undergoing MT remains unknown.

### WHAT THIS STUDY ADDS

⇒ The absence of SVS is independently associated with poorer outcomes and higher mortality rates during long-term follow-up after MT, even after adjustment for underlying conditions and interventional parameters that are known to be associated with the absence of SVS and poor outcomes.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A thorough understanding of potential factors affecting long-term outcomes and SVS status is essential for stroke physicians. Special consideration should be given to factors which are already known to be associated with the absence of SVS in the acute phase. Future studies should elucidate the association between SVS and other underlying conditions in patients with stroke.

## INTRODUCTION

Despite technical advances in stroke management, half the patients undergoing mechanical thrombectomy (MT) do not have a good functional outcome.[1] Several parameters obtainable by non-invasive admission imaging are known to impact patient outcome (eg, occlusion site, number of occluded vessels and infarct volumes).[1] The susceptibility vessel sign (SVS) can be assessed by susceptibility-weighted imaging (SWI) on admission and indicates a high proportion of deoxyhemoglobin which causes inhomogeneity in the magnetic field.[2–4] Pathohistologically, this could reflect a larger proportion of erythrocytes in the thrombus composition.[3] These erythrocyte-rich thrombi tend to induce signal loss on SWI (ie, indicating the

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For numbered affiliations see end of article.

**Correspondence to**
Dr Adnan Mujanovic; adnan.mujanovic@insel.ch and Dr Morin Beyeler; morin.beyeler@insel.ch

JK and AM contributed equally.

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presence of the SVS), while fibrin- and platelet-rich thrombi do not show this loss of signal (ie, appearing as absence of SVS).[2] Prior studies have also shown that MRI-based SVS correlates with the CT-based hyperdense vessel sign (HVS) regarding the thrombus composition.[4 5] However, a direct transposition of the SVS evidence is not applicable and independent evidence for the HVS itself is required. Recent studies in patients with stroke undergoing MT reported that the absence of the SVS is associated with functional deterioration and an overall poorer outcome at 3 months.[6 7] The absence of SVS is assumed to be associated with underlying clinical conditions, such as cancer, which are known to impact overall long-term outcome.[8] Moreover, hypercoagulopathy, which is often observed in cancer patients, is associated with a higher percentage of fibrin- and platelet-rich thrombi.[9] Observational studies have also associated the absence of SVS with stroke of undetermined etiology; however, recent meta-analyses have not investigated stroke etiology in patients without SVS.[10–12] Therefore, the association between SVS and potential outcome drivers remains unclear,[8–12] and the extent to which the absence of SVS could be associated with patients' long-term outcome is presently unknown.[6 13 14] We hypothesized that SVS status could serve as an independent predictor of long-term outcome in MT-treated patients.

## METHODS

### Study cohort

All consecutive stroke patients treated with MT between January 1, 2010 and December 31, 2018 from our institution's prospective registry were retrospectively assessed for eligibility. Inclusion criteria were: (1) acute ischemic stroke treated with MT; (2) SWI performed as baseline imaging with SVS status available; (3) long-term outcome and follow-up time available. Only patients undergoing MT with the stent-retrievers were considered for the present study. Patients with intravenous thrombolysis (IVT) administered before SWI acquisition were excluded. Furthermore, patients receiving IVT before blood examination were excluded from analyses involving blood biomarkers. To avoid potential survivorship bias, all eligible patients were included in the main analyses even if they had died before the 3-month follow-up.[15] The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist was used for the present study.

### Data collection

Baseline and 90-day follow-up data were extracted from the stroke registry. These included sex, age at admission, prestroke independence (defined as a modified Rankin Scale (mRS) score ≤2), prestroke anticoagulation/antiplatelet therapy, cerebrovascular risk factors (such as hypertension, diabetes mellitus, dyslipidemia, smoking, previous stroke, coronary artery disease), National Institutes of Health Stroke Scale (NIHSS) score on admission, time between last known well and admission, time between last known well and groin puncture, IVT before MT, and site of occlusion. Sites of occlusion were defined as internal carotid artery, M1 segment of the middle cerebral artery (MCA), M2 segment of the MCA, other anterior occlusions, and posterior occlusions. The presence of active cancer (known or occult at the time of stroke) was determined retrospectively by two neurologists (MB and MK). The definition of active cancer and detailed characteristics of cancers found in the study cohort were previously published by Beyeler *et al*.[8] The assigned stroke etiology at discharge was defined by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification and extracted from the clinical information system.[16] The following laboratory values at admission were extracted: D-dimer in µg/L, hemoglobin in g/L, C-reactive protein (CRP) in mg/L, leukocytes in g/L, thrombocytes in g/L, fibrinogen in g/L, and international normalized ratio (INR).

### Imaging analysis

Imaging was performed on a 1.5T or 3T MRI scanner. The SWI sequences were performed as part of our institution's stroke protocol.[7] Technical details on MRI scanners and our institution's stroke protocol are shown in online supplemental eTable I. To summarize, the presence or absence of SVS was determined retrospectively by two independent neuroradiologists blinded to clinical data and patient outcome (NFB and EBA). The presence of SVS was determined as a distinct signal loss which directly corresponded to the site of angiographically-confirmed occlusion and for which there was no alternative explanation (ie, neighboring vein, petechial hemorrhage or microcalcification in the neighboring parenchyma). The absence of SVS was defined as the absence of signal loss despite a clearly visible occlusion on the first angiographic imaging run (figure 1A–B). Inter-rater reliability regarding SVS evaluation (dichotomized: present or absent) was very good (Cohen $\kappa=0.873$, $P<0.001$).[7] Alberta Stroke Program Early CT Score (ASPECTS) was assessed on diffusion-weighted imaging (DWI) by neuroradiologists with 5 years of experience. The final reperfusion grade was core lab adjudicated using the expanded Treatment in Cerebral Ischemia (eTICI) score.[17 18] A score of eTICI2b50 or higher was considered as successful reperfusion.

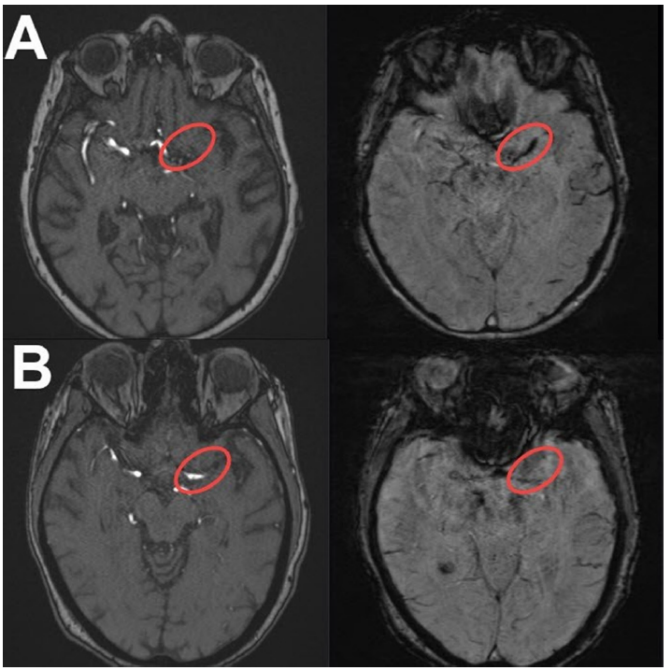


**Figure 1** Susceptibility vessel sign assessment. Admission MRI. (A) TOF shows an occlusion in the M1-MCA segment on the left side (left panel) with a visible SVS sign on SWI (right panel). (B) Similar to the previous case, TOF again shows an occlusion in the M1-MCA segment on the left side (left panel); however, the SVS sign on SWI is absent (right panel). MCA, middle cerebral artery; SWI, susceptibility-weighted imaging; TOF, time-of-flight angiography.

### Long-term follow-up

Patients who had survived or died in the long term were identified using the Swiss Population Registry (SPR), which records the vital status of Swiss residents monthly. Two neurologists (MB and LW) contacted the surviving patients, their next of kin or healthcare providers between September 2019 and June 2020 to assess long-term functional outcome based on the mRS. Details of the informed consent process and data collection are published elsewhere.[19] Long-term poor functional outcome was defined as mRS 3–6. For the survival analysis, follow-up time was defined as the time from the index ischemic stroke to the last update of the SPR or date of death, which is also reported in the SPR. For the functional outcome analysis, follow-up time was defined as the time from index ischemic stroke to the telephone interview or date of death extracted from the SPR.

### Statistical analysis

Differences in baseline characteristics between patients with and without SVS were reported for continuous variables using median and interquartile range (IQR) and for categorical variables using frequency (percentage). Fisher's exact test and the Mann–Whitney U test were used to assess the differences between the two groups for categorical and continuous variables, respectively. For survival analyses, Kaplan–Meier curves with a log-rank test stratified by SVS status were plotted to display mortality rates during the long-term follow-up. Adjusted hazard ratios (aHRs) and their 95% confidence intervals (CI) were assessed with multivariate Cox regression analysis. For outcomes analysis, odds ratios or adjusted odds ratios (aOR) and their 95% CI were calculated from univariate and multivariate logistic regression, respectively. Multivariate regression analysis included the following clinically relevant covariates: age at admission, sex, diabetes mellitus, active cancer, prestroke independence, time from last known well to admission, NIHSS score on admission, occlusion site, ASPECTS at admission, IVT, successful reperfusion (binary variable)/eTICI grade (ordinal variable with a stepwise increase), stroke etiology according to TOAST and CRP. Interaction modeling was used to identify conditions that could impact the association between SVS and long-term follow-up based on previously reported findings (ie, SVS status*active cancer interaction term with long-term follow-up defined as the dependent variable).[8] For outcomes analyses (assessing the long-term mRS), subgroups with equal numbers of patients according to follow-up times were defined to limit the heterogeneity of the long-term follow-up due to the cross-sectional conduct of the telephone interview. Mixed-effects models with predefined follow-up times used as random effects were then applied. Due to the long recruitment period, sensitivity analyses were independently performed for the different follow-up groups. No imputation method was used for missing data. Statistical analyses were performed with Stata 16 (StataCorp) and R (version 3.6.0, R Core Team).

## RESULTS

### Study population

Of the 1317 patients undergoing MT, 577 had assessable SVS status. Of these, 19 had missing long-term follow-up data, resulting in 558 patients being finally included in the study (see online supplemental eFigure I). SVS was present in 87% of all patients (n=487/558) and absent in 13% (n=71/558) on baseline imaging.

### Baseline characteristics

The baseline characteristics of patients with and without SVS are summarized in table 1. SVS was more often absent in female than in male patients (63.4% vs 36.6%). Compared with patients with SVS, those without SVS were less independent at the time of the stroke (mRS≤2: 82.9% vs 93.0%, P=0.009), more likely to have active cancer (21.1% vs 5.1%, P<0.001), diabetes mellitus (26.8% vs 12.7%, P=0.003), had a lower NIHSS score at admission (9 vs 12, P=0.049), a higher likelihood of stroke of undetermined etiology (56.3% vs 39.6%, P=0.010), and a higher level of CRP (4.5 vs 3 mg/L, P=0.030). For imaging characteristics, there was no difference between the two groups with respect to the MRI field strength or time between last known well and admission imaging. Patients without SVS had a poorer prognosis at 3 months and also during the long-term follow-up (table 1).

### Association between absence of SVS and long-term mortality

The median long-term follow-up time was 1058 days (IQR 533–1671 days). In patients in whom the SVS was absent it was 587 days (IQR 44–1334 days) and, for patients in whom SVS was present, it was 1132 days (IQR 590–1710 days). The mortality rate in patients without SVS was higher during the long-term follow-up (figure 2, log-rank test P<0.001). In multivariable Cox regression analyses (figure 3), long-term mortality was associated with absence of SVS (aHR 2.11, 95% CI 1.35 to 3.29), active cancer (aHR 3.08, 95% CI 1.93 to 4.91), diabetes mellitus (aHR 1.78, 95% CI 1.19 to 2.64), lower ASPECTS (aHR 1.14, 95% CI 1.05 to 1.23), older age at admission (aHR 1.07, 95% CI 1.05 to 1.09) and elevated CRP (aHR 1.004, 95% CI 1.001 to 1.007). Higher levels of reperfusion were correlated with lower rates of long-term mortality, whether dichotomized for successful reperfusion (aHR 0.46, 95% CI 0.30 to 0.69, figure 3) or according to increasing eTICI grade (aHR 0.82, 95% CI 0.74 to 0.91, online supplemental eFigure II). Interaction analyses found no influence of active cancer, diabetes mellitus or successful reperfusion/eTICI grade on the association between the absence of SVS and long-term mortality.

### Association between absence of SVS and long-term functional outcome

For the analysis of functional outcome, follow-up groups were created, as summarized in online supplemental eFigure III. From the 476 patients with long-term outcome (mRS) available, 184 were included in the group with a follow-up time of 1.2 to 3 years (follow-up group 1), 150 in the group with a follow-up time of 3 to 5 years (follow-up group 2) and 142 in the group with a follow-up time of 5 to 9.5 years (follow-up group 3). Poor functional outcome (mRS 3–6) in the long term was associated with absence of SVS (aOR 2.90, 95% CI 1.29 to 6.55, online supplemental eFigure IV), active cancer (aOR 3.97, 95% CI 1.53 to 10.28), diabetes mellitus (aOR 2.85, 95% CI 1.39 to 5.85), low ASPECTS (aOR 1.23, 95% CI 1.07 to 1.40) and older age at admission (aOR 1.07, 95% CI 1.04 to 1.09). Higher levels of reperfusion were correlated with lower rate of poor functional outcome, whether dichotomized for successful reperfusion (aOR 0.32, 95% CI 0.16 to 0.67, online supplemental eFigure IV) or according to increasing eTICI score (aOR 0.75, 95% CI 0.63 to 0.88, online supplemental eFigure V). Again, interaction analyses found no influence of active cancer, diabetes mellitus or successful reperfusion/eTICI grade on the association between the absence of SVS and long-term poor functional outcome. In univariate sensitivity analyses of follow-up groups, the absence of

**Table 1** Comparison of baseline characteristics, short-term and long-term outcomes between patients with and without susceptibility vessel sign

| | All (n=558) | SVS present (n=487) | SVS absent (n=71) | P value |
|---|---|---|---|---|
| Baseline | | | | |
| Age at admission median (IQR) | 72.75 (61–80.7) | 72.66 (60–80.86) | 74.2 (62.44–80) | 0.71 |
| Sex (female), n/N (%) | 286/558 (51.3%) | 241/487 (49.5%) | 45/71 (63.4%) | 0.031 |
| Independence before stroke (mRS ≤2), n/N (%) | 551/557 (91.7%) | 453/487 (93.0%) | 58/70 (82.9%) | 0.009 |
| Anticoagulation (vitamin K-antagonist and NOAC) prior to stroke, n/N (%) | 65/557 (11.7%) | 56/486 (11.5%) | 9/71 (12.7%) | 0.84 |
| Antiplatelet drugs prior to stroke, n./N (%) | 178/557 (32%) | 152/486 (31.3%) | 26/71 (36.6%) | 0.41 |
| Risk factors, n/N (%) | | | | |
| Diabetes | 81/558 (14.5%) | 62/487 (12.7%) | 19/71 (26.8%) | 0.003 |
| Hypertension | 366/558 (65.6%) | 318/487 (65.3%) | 48/71 (67.6%) | 0.79 |
| Dyslipidemia | 323/556 (58%) | 279/485 (57.5%) | 44/71 (62.0%) | 0.52 |
| Smoking | 140/557 (25.1%) | 123/486 (25.3%) | 17/71 (23.9%) | 0.88 |
| Previous stroke | 62/558 (11.1%) | 51/487 (10.5%) | 11/71 (15.5%) | 0.22 |
| Active cancer | 40/558 (7.1%) | 25/487 (5.1%) | 15/71 (21.1%) | <0.001 |
| Stroke characteristics | | | | |
| Time from last known well to admission in min, median (IQR) | 126 (71–286) | 126 (73–277) | 146 (70–322) | 0.83 |
| NIHSS on admission, median (IQR) | 12 (7–17) | 12 (7–18) | 9 (5–16) | 0.049 |
| 3 Tesla MRI, n/N (%) | 184/555 (33%) | 157/484 (32%) | 27/71 (38%) | 0.35 |
| Time from last known well to imaging in min, median (IQR) | 161 (101–320) | 161 (101–305) | 170 (103–377) | 0.51 |
| ASPECTS score, median (IQR) | 8 (6–9) | 8 (6–9) | 8 (7–9) | 0.003 |
| IVT prior to MT, n/N (%) | 217/558 (38.9%) | 192/487 (39.4%) | 25/71 (35.2%) | 0.52 |
| Time from last known well to groin puncture in min, median (IQR) | 234 (164–397) | 233 (166–391) | 268 (157–431) | 0.60 |
| Number of maneuvers, median (IQR) | 1 (1–2) | 1 (1–2) | 1 (1–3) | 0.76 |
| Successful reperfusion, n/N (%) | 474/552 (85.9%) | 418/481 (86.9%) | 56/71 (78.9%) | 0.098 |
| eTICI categories, n/N (%) | | | | |
| eTICI 0 | 24/552 (4.35%) | 18/481 (3.7%) | 6/71 (8.5%) | 0.51 |
| eTICI 1 | 12/552 (2.17%) | 11/481 (2.3%) | 1/71 (1.4%) | |
| eTICI 2a | 42/552 (7.61%) | 34/481 (7.1%) | 8/71 (11.3%) | |
| eTICI 2b50 | 64/552 (11.59%) | 56/481 (11.6%) | 8/71 (11.3%) | |
| eTICI 2b67 | 132/552 (23.91%) | 117/481 (24.3%) | 15/71 (21.1%) | |
| eTICI 2c | 131/552 (23.73%) | 116/481 (24.1%) | 15/71 (21.1%) | |
| eTICI 3 | 147/552 (26.63%) | 129/481 (26.8%) | 18/71 (25.4%) | |
| Site of occlusion, n/N (%) | | | | |
| ICA | 94/558 (16.9%) | 88/487 (18.1%) | 6/71 (8.5%) | 0.010 |
| M1 | 292/558 (52.3%) | 258/487 (53.0%) | 34/71 (47.9%) | |
| M2 | 119/558 (21.3%) | 100/487 (20.5%) | 19/71 (26.8%) | |
| Posterior occlusion | 44/558 (7.9%) | 36/487 (7.4%) | 8/71 (11.3%) | |
| Other anterior occlusion | 9/558 (1.6%) | 5/487 (1.0%) | 4/71 (5.6%) | |
| Stroke etiology (TOAST), n/N (%) | | | | |
| Cardioembolic | 222/558 (39.8%) | 196/487 (40%) | 26/71 (37%) | 0.016 |
| More than one cause | 1/558 (0.1%) | 1 (0.2%) | 0/71 (0%) | |
| Large artery atherosclerosis | 73/558 (13.1%) | 71 (15%) | 2/71 (3%) | |
| Stroke of other determined etiology | 28/558 (5%) | 25 (5%) | 3/71 (4%) | |
| Stroke of undetermined etiology | 234/558 (41.9%) | 194 (40%) | 40/71 (56%) | |
| Stroke of undetermined etiology vs other etiologies, n/N (%) | 233/558 (41.8%) | 194/487 (40%) | 40/71 (56.3%) | 0.010 |
| Baseline laboratory findings | | | | |
| D-dimer, µg/L, median (IQR) | 888 (497–1758) | 869 (495.5–1743) | 1020 (543–2731) | 0.17 |
| Hb, g/L, median (IQR) | 135 (124–146) | 136 (124–147) | 130.5 (119–144) | 0.11 |
| CRP, mg/L, median (IQR) | 3 (3–8) | 3 (3–8) | 4.5 (3–12.5) | 0.030 |
| Leukocytes, g/L, median (IQR) | 8.3 (6.6–10.3) | 8.21 (6.6–10.3) | 8.8 (7.2–10.3) | 0.21 |
| Thrombocytes, g/L, median (IQR) | 221 (180.5–268) | 220 (182–268) | 225 (177–278) | 0.92 |

Continued

**Table 1** Continued

| | All (n=558) | SVS present (n=487) | SVS absent (n=71) | P value |
|---|---|---|---|---|
| Fibrinogen, g/L, median (IQR) | 3.08 (2.56–3.7) | 3.085 (2.59–3.67) | 3.01 (2.385–4.055) | 0.98 |
| INR, median (IQR) | 1.01 (1–1.07) | 1 (1–1.07) | 1.03 (1–1.08) | 0.11 |
| Stroke outcomes | | | | |
| Death before 3 months, n/N (%) | 102/558 (18.3%) | 79/487 (16.2%) | 23/71 (32.4%) | 0.003 |
| mRS at 3 months, median (IQR) | 2 (1–4) | 2 (1–4) | 3.5 (1–6) | 0.004 |
| Poor functional outcome at 3 months (mRS 3–6), n/N (%) | 239/539 (44.3%) | 197/469 (42.0%) | 42/70 (60.0%) | 0.006 |
| Long-term follow-up time, days, median (IQR) | 1058 (533–1671) | 1132 (590–1710) | 587 (44–1334) | <0.001 |
| Long-term deaths, n/N (%) | 189/558 (33.9%) | 151/487 (31.0%) | 38/71 (53.5%) | <0.001 |
| Long-term mRS, median (IQR) | 3 (1–6) | 2 (1–6) | 6 (2–6) | <0.001 |
| Long-term poor functional outcome (mRS 3–6), n/N (%) | 248/476 (52%) | 203/411 (49.4%) | 45/65 (69.2%) | 0.003 |

ASPECTS, Alberta Stroke Program Early CT Scores; CAD, coronary artery disease; CRP, C-reactive protein; eTICI, expanded treatment in cerebral infarction; Hb, hemoglobin; ICA, internal carotid artery; INR, international normalized ratio; IQR, interquartile range; IVT, intravenous thrombolysis; M1 and M2, first and second segment of the middle cerebral artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; SVS, susceptibility vessel sign; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

SVS was associated with poor functional outcomes in follow-up group 1 (OR 2.62, 95% CI 1.16 to 5.89) and follow-up group 3 (OR 5.06, 95% CI 1.10 to 23.21) but not in follow-up group 2 (OR 1.88, 95% CI 0.67 to 5.31). In the multivariate sensitivity analyses of the follow-up groups, the absence of SVS was not associated with poor functional outcomes in any of the follow-up groups (online supplemental eFigure VI).

## DISCUSSION

This study's main finding is that the absence of SVS remained associated with poorer outcomes and higher mortality during the long-term follow-up even after adjustment for underlying conditions and interventional outcome parameters known to be associated with the absence of SVS and poor outcome (such as active cancer and diabetes mellitus).

### Long-term outcome and survival rates

Reports on the association between the SVS and functional outcome are conflicting. A single-center retrospective registry study reported that poor outcome was more common in patients with SVS (present vs absent: 57.1% vs 33.3%, P=0.02).[14] However, multivariable analysis identified only age and reperfusion as independent predictors of clinical outcome. Conversely, Bourcier *et al* reported higher rates of poor outcome among patients without SVS (present vs absent: 35% vs 74%, P=0.004) and this association was also perceptible after correcting for other cofactors known to be associated with functional outcome (aOR 8.7; 95% CI 1.1 to 69.4).[6] A post hoc analysis of the Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER) trial reported no difference in functional outcome at 3 months between patients with and without SVS (risk ratio (RR) 1.27, 95% CI 0.9 to 1.6; P=0.08); however, this trial was not powered to detect such an association.[13] A recent meta-analysis reported that patients with SVS were more likely to have a poor functional outcome at 3 months (RR 1.5,

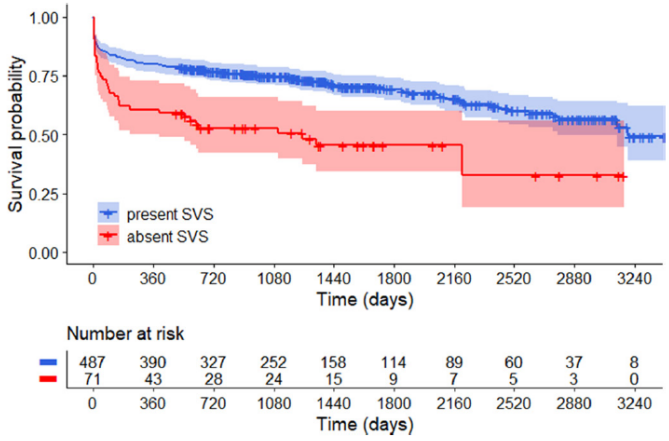


**Figure 2** Long-term survival curve for patients with and without susceptibility vessel sign (SVS). Compared with patients in whom SVS was present (blue), patients in whom SVS was absent (red) had higher mortality rates during the long-term follow-up after ischemic stroke treated with mechanical thrombectomy (log-rank test, P<0.001).

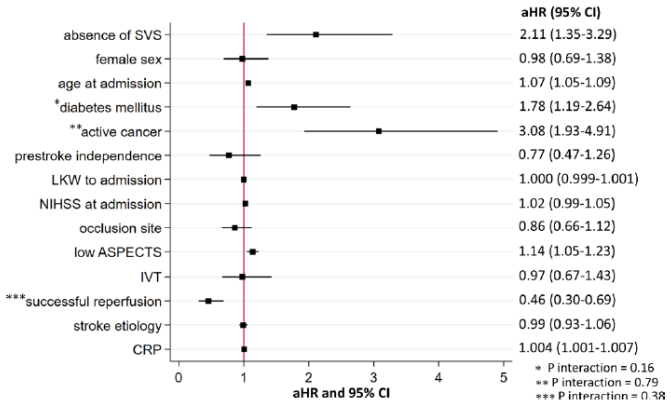


**Figure 3** Association between long-term mortality and demographic characteristics, relevant risk factors, and stroke parameters. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) from the multivariate Cox regression analyses comparing long-term mortality and demographics, relevant risk factors and stroke parameters. Long-term mortality was associated with absence of SVS, diabetes mellitus, active cancer, low ASPECTS, older age at admission and increased CRP. Interaction analyses (*, **, ***) did not identify any substantial influence of diabetes mellitus, active cancer or successful reperfusion on the relationship between absence of SVS and long-term mortality. P interaction indicates P value for corresponding interaction terms. ASPECTS, Alberta Stroke Program Early CT Score; CRP, C-reactive protein; IVT, intravenous thrombolysis; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale; SVS, susceptibility vessel sign.

95% CI 1.3 to 1.7), although wide heterogeneity among the studies was noted ($I^2$=87.8%, P<0.001).[12]

Here we report similar results to those of Bourcier *et al*—namely, a poor 3-month outcome was more often observed in patients in whom SVS was absent. Moreover, this association was present even when looking at the adjusted long-term clinical outcome and survival rates. We assume that the non-significant results in the sensitivity analyses of follow-up groups are attributable to the small number of patients in each group, leading to imprecise estimates (online supplemental eFigure VI).[20] The association between SVS and long-term patient outcome could potentially be explained by thrombus composition: white thrombi are more common in patients without SVS and red thrombi in patients with SVS.[2] More specifically, red thrombi are easier to manipulate during the intervention and often yield higher reperfusion rates after the endovascular procedure.[21 22] Patients with SVS would therefore be more likely to have a favorable outcome, as they would tend to have higher reperfusion rates after MT. Another potential explanation for differences in long-term outcome between patients with and without SVS might reflect underlying conditions, which would affect the thrombus composition and also the long-term survival rates. An association between cancer, diabetes mellitus and the SVS has been previously described in the same cohort.[7 8] Fibrin-rich thrombi are strongly correlated with cancer-related stroke,[9] and changes of the inner lining of blood vessels caused by diabetes mellitus increase the chances of adhesion of thrombi that are rich in fibrin and have a low erythrocyte count.[23 24] Both conditions would therefore increase the chance of SVS being absent in this subgroup of stroke patients. However, we saw no significant interaction effect between these cofactors (successful reperfusion, active cancer and diabetes mellitus) and SVS status on long-term outcome rates. This further underlines present uncertainties between SVS and other factors that may affect the outcome.[8–12]

A potentially relevant finding of this study is that the CRP level was higher in patients with absent SVS and was also associated with a higher mortality event rate after adjustment for SVS (figure 3). Therefore, a potential underlying acute or chronic inflammation could be related to the formation of fibrin- and platelet-rich thrombi, the absence of SVS and, finally, a poorer long-term outcome.[25 26] Further prospective studies could include other potential causes of acute and chronic inflammation to elucidate the association between possible inflammatory factors impacting the outcome and the absence of SVS. More aggressive treatment of such underlying conditions could then improve long-term outcome rates.

SVS positivity is subject to time-dependent variations in deoxyhemoglobin; however, detection of SVS in our study seemed to be independent of MRI field strength and time from last known well to imaging.[3] Our results could be partly explained by our stringent inclusion criteria as we focused on patients presenting with large vessel occlusion in the early time window (see Methods). The acquisition of SWI sequences in institutions with available MRI for acute stroke diagnosis is of clinical relevance given the prognostic value of SVS (better reperfusion rate after thrombectomy and higher mid- and long-term survival) as well as its diagnostic value (detection of hemorrhage, concomitant microbleeds and recognition of underlying treatable conditions more quickly).[7 8 27] Despite the known time-consuming cost of acquiring SWI sequences, Fischer *et al* showed that conducting brain MRI at admission (compared with brain CT) showed no difference in door-to-puncture time in MT-treated patients, even those with early presentation and severe stroke.[28] Additionally, the development and implementation of faster SWI acquisition methods (highly accelerated wave–controlled aliasing in parallel imaging (CAIPI) SWI) should enable a reduction of SWI sequence acquisition times (currently ~5 min) by a factor of 3–5 in the future, making the SWI acquisition even more valuable.[29] Furthermore, as most sites use CT rather than MRI for acute stroke work-up, our findings must be confirmed in a CT-diagnosed stroke population to generalize the prognostic value of thrombus imaging characterization in the long-term outcome. Even if the correlation between SVS and HVS was described previously, the analyses performed in our study should be performed for HVS independently.[4 5]

### Limitations

Our study has several limitations. First, it is a single-center retrospective study with all the commonly attributed biases. Second, even if no difference in the identification of SVS was found between 1.5T and 3T MRI in this study, this limitation may have influenced the sensitivity for detecting SVS and consequently the predictive value of the absence of SVS for poorer long-term outcomes. Third, due to the retrospective design, not all underlying conditions, potentially leading to the absence of SVS and poor long-term outcomes, were systematically documented and assessable. Furthermore, the lack of direct histological examination of the thrombus composition limits the broader interpretation of the study results. Fourth, although patients were treated with second-generation devices, the long recruitment period with not well-established MT procedures at the beginning of recruitment, could have introduced biased reperfusion success assessment due to interventionalist experience and in-hospital workflows. Fifth, in the sensitivity analyses of the follow-up groups, the number of patients per subgroup was insufficient and caution is advised when interpreting these results.

## CONCLUSION

The absence of SVS is independently associated with poor long-term outcome and higher mortality rates in patients with stroke after MT. It appears that this association cannot be explained by already associated comorbidities alone, and further studies are warranted.

**Author affiliations**
[1]Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[2]Graduate School for Health Sciences, University of Bern, Bern, Switzerland
[3]Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[4]Department of Neuroradiology, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[5]Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland
[6]Neurology Department, University Hospital of Basel, University of Basel, Basel, Switzerland

**X** Morin Beyeler @Morin_Beyeler, Christoph C Kurmann @chris_kurmann, Urs Fischer @FishingNeurons and Adnan Mujanovic @adnan_mujanovic

**Contributors** MB: conception and design, data acquisition, analysis and interpretation of data, and writing of the manuscript. ER: data acquisition and critical revision of the manuscript for important intellectual content. LW: data acquisition and critical revision of the manuscript for important intellectual content. CCK: data acquisition and critical revision of the manuscript for important intellectual content. EIIP: data acquisition and critical revision of the manuscript for important intellectual content. UF: conception and design, critical revision of the manuscript for important intellectual content. JK: conception and design, analysis and interpretation of data, writing of the manuscript, critical revision of the manuscript for important intellectual content, and supervision. AM: conception and design, interpretation of data, critical

revision of the manuscript for important intellectual content, supervision and action as the guarantor of the study. All other authors contributed to critical revision of the manuscript for important intellectual content.

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**ORCID iDs**
Morin Beyeler http://orcid.org/0000-0001-5911-7957
Nebiyat Filate Belachew http://orcid.org/0000-0001-5285-5922
Christoph C Kurmann http://orcid.org/0000-0001-5770-5675
Eike Immo I Piechowiak http://orcid.org/0000-0001-5609-0998
Thomas R Meinel http://orcid.org/0000-0002-0647-9273
David Seiffge http://orcid.org/0000-0003-3890-3849
Tomas Dobrocky http://orcid.org/0000-0002-6167-3343
Johannes Kaesmacher http://orcid.org/0000-0002-9177-2289
Adnan Mujanovic http://orcid.org/0000-0002-6839-7134

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## Secondary prevention after cancer-related strokes

Title of the manuscript: Anticoagulant versus antiplatelet treatment for secondary stroke prevention in patients with active cancer

Contributions of the PhD candidate:

- Conceptualization
- Data collection
- Data curation
- Formal analysis
- Visualization
- Writing – review and editing
- Supervision

Results summary:

Although 5–10% of AIS patients have active underlying cancer, the optimal antithrombotic strategy for cancer-related strokes remains unknown. This study compared clinical outcomes among patients with cancer-related strokes treated with anticoagulation versus an antiplatelet drug for secondary prevention. We used our BMS database to identify all patients with active cancer treated between 2015 and 2020 at our stroke center. After exclusion of patients with cardioembolic stroke with indication for anticoagulation, we included 135 patients with active cancer, of whom 58 (43%) were treated with anticoagulant and 77 (57%) with an antiplatelet drug. Anticoagulants and antiplatelet drugs were associated with similar risks of 1-year mortality (aHR 0.76, 95% CI 0.36–1.63) and long-term recurrent AIS (aHR 0.49, 95% CI 0.08–2.83). After excluding 22 patients with documented venous thromboembolism treated with anticoagulant therapy at the time of hospital discharge following the index AIS, the risk of 1-year mortality remained similar between patients treated with an anticoagulant and those treated with an antiplatelet drug (aHR 0.65, 95% CI 0.28–1.47).

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# Anticoagulant versus Antiplatelet Treatment for Secondary Stroke Prevention in Patients with Active Cancer

Moritz Kielkopf MD[a], Jayan Göcmen MD[a], Selina B. Venzin MS[a], Fabienne Steinauer MS[a], Mattia Branca PhD[b], Anna Boronylo MD[a], Martina B. Göldlin MD PhD[a], Johannes Kaesmacher MD PhD[c], Adnan Mujanovic MD[c], Gianluca Costamagna MD[d,e], Thomas R. Meinel MD PhD[a], David J. Seiffge MD[a], Philipp Bücke MD[a], Mirjam R. Heldner MD[a], Ava L. Liberman MD[f], Hooman Kamel MD[f], Urs Fischer MD[a], Marcel Arnold MD[a], Thomas Pabst MD[g], Martin D. Berger MD[g], Simon Jung MD[a], Adrian Scutelnic MD[a], Babak B. Navi MD*[f], Morin Beyeler MD*[a,f,h]

* Equal contribution

a) Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

b) CTU Bern, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

c) Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

d) Stroke Center, Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

e) Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Italy

f) Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, New York, USA

g) Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Switzerland

h) Graduate School for Health Sciences, University of Bern, Switzerland

# Abstract

## Background

Approximately 5-10% of patients with acute ischemic stroke (AIS) have known active cancer. These patients are at high risk for both recurrent AIS and major bleeding. The optimal antithrombotic strategy for cancer-related stroke is uncertain. This study compared clinical outcomes among patients with cancer-related stroke treated with anticoagulant versus antiplatelet therapy for secondary prevention.

## Methods

We identified consecutive patients with AIS and active cancer hospitalized at our comprehensive stroke center at Bern, Switzerland from 2015 through 2020. Patients with cardioembolic mechanisms were excluded. We used adjusted Cox regression and inverse probability of treatment weighting (IPTW) analyses to evaluate the associations between type of antithrombotic therapy at discharge (anticoagulant versus antiplatelet therapy) and the main outcomes of 1-year mortality and long-term recurrent AIS.

## Results

Among 5012 AIS patients, 306 had active cancer. After applying study eligibility criteria, we analyzed 135 patients (median age 72 years; 44% women), of whom 58 (43%) were treated with anticoagulant and 77 (57%) with antiplatelet therapy. The median follow-up time was 495 days (IQR, 57–1029). Anticoagulant versus antiplatelet therapy was associated with similar risks of 1-year mortality (adjusted hazard ratio [aHR], 0.76; 95% confidence interval [CI], 0.36-1.63) and long-term recurrent AIS (aHR 0.49; 95% CI 0.08-2.83). The IPTW analyses for 1-year mortality confirmed the results of the main analyses (HR 0.82; 95% CI 0.39-1.72, P=0.61).

## Conclusions

Similar outcomes were observed with anticoagulant versus antiplatelet therapy in patients with cancer-related stroke, highlighting the need for future randomized trials to determine the preferred antithrombotic strategy.

## Introduction

Active cancer is a comorbid condition in 5-10% of patients with acute ischemic stroke (AIS).[1] This stroke subgroup, known as ''cancer-related stroke'' is presumed to result of paraneoplastic coagulopathy.[1,2] This prothrombotic process is multifactorial and involves platelet, coagulation, and endothelium activation.[3] Patients with cancer-related stroke face an increased risk of more severe strokes, AIS recurrence, and mortality compared to other AIS patients.[4]

There are no clear guideline-based recommendations for the preferred antithrombotic strategy in cancer-related stroke. According to the American Heart Association guidelines, further research should be conducted to evaluate the benefit of anticoagulation in persons with stroke attributable to cancer-related hypercoagulability as robust data is lacking.[5] Secondary analyses of the NAVIGATE ESUS and ARCADIA randomized controlled trials have demonstrated neutral results in recurrent stroke risk between the anticoagulant and antiplatelet treatment groups.[6,7] However, because both studies included patients with both active and inactive cancer, with the exact proportions of each uncertain, these data should be interpreted with caution.

Given the lack of dedicated, adequately powered clinical trials assessing the most appropriate secondary prevention strategy for cancer-related stroke, more retrospective data are needed. We investigated long-term outcomes of patients with active cancer and AIS stratified by the employed antithrombotic treatment strategy (anticoagulant versus antiplatelet therapy) at discharge in a large institutional registry.

## Patients and Methods

### Design

We conducted a retrospective cohort study of consecutive patients treated for AIS at a comprehensive stroke center in Bern, Switzerland between January 1, 2015 and December 31, 2020. These patients were prospectively enrolled in the Swiss Stroke Registry, which was accessed for data analysis.

The study was approved by the local ethics committee in accordance with Swiss regulations (Project ID: 2022-01560; Kantonale Ethikkommission Bern), and the requirement for written consent was waived. This analysis adhered to the STROBE checklist guidelines for cohort studies. Access to the study data can be requested from the corresponding author and is subject to clearance by the local ethics committee.

### Population

The study population consisted of patients with AIS and known active cancer at the time of AIS or new

cancer diagnosed during the hospitalization for the index AIS. Active cancer was defined according to the criteria recommended by the International Society on Thrombosis and Haemostasis.[8] This comprised a new or recurrent cancer that was diagnosed or treated within six months prior to the index AIS, or known metastatic cancer. According to the definition, hematological malignancies that were not in complete remission for more than 5 years were also considered active. Patients diagnosed with a new cancer during the index hospitalization were considered to have occult cancer at the time of AIS, and were included in the known active cancer group for analyses.[9,10] Patients diagnosed with cancer after discharge for the index AIS were excluded, as this sequence of events may have influenced antithrombotic management decisions and clinical outcomes.

We excluded patients with focal non-melanoma skin cancer because of their low risk of dissemination as well as patients with breast cancer in complete remission who were receiving maintenance hormonal therapy.[8,11,12] Other exclusion criteria were (i) death during the index hospitalization or missing follow-up data regarding vital status, (ii) no antithrombotic therapy prescription at discharge, and (iii) a cardioembolic stroke mechanism at discharge necessitating anticoagulation (e.g., atrial fibrillation, mechanical valve).

**Measurements**

Demographic and clinical characteristic data were collected from the Swiss Stroke Registry and electronic health records (EHR). These included age at admission, sex, pre-stroke functional status (independency defined as a pre-stroke modified Rankin Scale [mRS] score ≤2), baseline imaging modality, and history of cardiovascular risk factors (prior stroke, hypertension, diabetes mellitus, hyperlipidemia, smoking history, and atrial fibrillation). The presence of multi-territory brain infarcts (involving at least two different cerebrovascular territories) was determined using data from baseline neuroradiological imaging. Data on the primary cancer type, stage[13], and presence of metastasis at the time of AIS was collected from EHRs. Laboratory measurements included D-dimer, C-reactive protein (CRP), hemoglobin, platelet count, fibrinogen, and lactate dehydrogenase (LDH). For patients with multiple measurements, the baseline value was recorded. Two neurologists determined the AIS mechanism at discharge, classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria and the embolic stroke of undetermined source (ESUS) classification.[14,15] The diagnosis of venous thromboembolism (VTE), including deep vein thrombosis and/or pulmonary embolism, in the year before and after the index AIS was recorded.

The study exposure was the type of antithrombotic therapy (anticoagulant or antiplatelet therapy) prescribed at hospital discharge from the index AIS. The anticoagulant group consisted of patients

treated with therapeutic doses of any oral or parenteral anticoagulant. These included vitamin K antagonists, low-molecular-weight heparins (LMWH) such as enoxaparin or tinzaparin, and direct oral anticoagulants (DOACs) such as edoxaban, rivaroxaban, dabigatran, or apixaban. Patients treated with recommended dosing regimens adjusted for age, weight, or renal function were classified as receiving therapeutic anticoagulation. The antiplatelet group included standard-dose aspirin, clopidogrel, or both. Patients treated with both therapeutic-dose anticoagulant and antiplatelet therapy were included in the anticoagulant group.

The primary outcome of the study was mortality at 1 year after the index AIS. Patients' vital status was determined from the Swiss Population Registry, which records the vital status of Swiss residents on a monthly basis. Secondary outcomes were (i) all-cause long-term mortality, (ii) recurrent AIS during the entire follow-up period, and (iii) symptomatic intracranial hemorrhage (sICH) during the entire follow-up period. For long-term mortality, follow-up time was defined as the time from the index AIS to the date of death for deceased patients or to the last update of the Swiss Population Registry for surviving patients. For incident cerebrovascular events (recurrent AIS or sICH), follow-up time was defined as the time from index AIS to the date of event or to the last documented follow-up in the EHR if no event was reported. Symptomatic ICH was determined based on the ECASS III definition.[16]

**Analysis**

Baseline characteristics were reported as median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. Differences between groups were assessed using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Kaplan-Meier curves were used to estimate the cumulative rates of time-to-event endpoints. The log-rank test and multivariable Cox regression were used to compare the outcomes between antithrombotic treatment groups. All multivariable models were adjusted for patient age, sex, initial D-dimer level, documented metastases at the time of the index AIS, and the presence of multi-territory brain infarcts. These covariates were selected because they either significantly differed between study groups or they were previously associated with adverse clinical outcomes in patients with cancer-related stroke. Adjusted hazard ratios (aHRs) were reported with their associated 95% confidence interval (CI). Patients who received intravenous thrombolysis before D-dimer assessment were excluded from the multivariable analyses because intravenous thrombolysis can influence levels of coagulation parameters such as D-dimer and fibrinogen.[17] Subgroup analyses were performed in patients whose index AIS mechanism was cryptogenic and who met embolic stroke of undetermined source (ESUS) criteria. In sensitivity analyses, we excluded patients with a history of venous thromboembolism (VTE) treated with anticoagulant therapy at discharge for the index AIS.

Because antithrombotic prescription patterns likely varied according to physicians' perceptions of how prothrombotic and high-risk individual patients were, we performed a second set of analyses calculating propensity scores and using the Inverse Probability of Treatment Weighting (IPTW) method with stabilized weights to minimize potential confounding.[18] For IPTW, we reported hazard ratios (HRs) with their associated 95% CI.

Continuous variables with skewed distributions were logarithmically transformed. Missing data were not imputed. Statistical significance was defined as a p-value of <0.05. All analyses were performed using Stata 16 (StataCorp LLC) and R (version 3.6.0, R Core Team).

## Results

### Patient Characteristics

Of 5,012 patients with AIS assessed for eligibility, 306 had active cancer at the time of the index hospitalization (Figure 1 – Study flowchart). Among these patients, we excluded 35 who died during the hospitalization, 30 whose cancer was diagnosed after hospital discharge, 33 without available follow-up, 63 with a cardioembolic indication for anticoagulation, and 10 who were not prescribed an antithrombotic medication at discharge. The baseline characteristics of included and excluded AIS patients with active cancer are shown in eTable I. The final study population comprised 135 patients, including 58 (43%) in the anticoagulant group and 77 (57%) in the antiplatelet group (Table 1). As shown in Table 2, median follow-up time for long-term mortality was 495 days (IQR 57-1,029) for the overall cohort, 133 days (IQR 43–506) for the anticoagulant group, and 797 days (IQR 218-1,483) for the antiplatelet group.

Patients treated with anticoagulant therapy, compared to patients treated with antiplatelet therapy, were younger (69 years [IQR 62-75] versus 75 years [IQR 65-82], P=0.01), had more multi-territory brain infarcts (47% versus 17%, P<0.001), and more often had an ESUS mechanism (82% versus 50%, P<0.001). Data on the primary cancer site in the overall study population and stratified by the individual treatment groups are provided in eFigure I. The distribution of primary cancer sites differed between groups with higher rates of lung and pancreatic cancers in the anticoagulant group (P<0.001). Additionally, patients in the anticoagulant group had more frequent metastases at the time of AIS (72% versus 41%, P<0.001). There were 23 patients with documented VTEs, of whom 22 were prescribed anticoagulant therapy at hospital discharge.

Four patients in the antiplatelet group received intravenous thrombolysis before D-dimer sampling and were excluded from analyses including laboratory parameters. Compared to patients in the antiplatelet

group, patients in the anticoagulant group had higher D-dimer levels in µg/L (median [IQR]: 8,536 [2,080-13,726] versus 1,010 [495-2,090], P<0.001) and higher CRP levels in mg/L (median [IQR]:18 [5-50] versus 4 [2-24], P=0.01).

**Primary outcome**

As depicted in Figure 2, the estimated cumulative 1-year mortality rate was higher in the anticoagulant group (66%, 95% CI 53%-77%) than in the antiplatelet group (33%, 95% CI 23%-44%) (log-rank test P<0.001). In multivariable Cox regression analysis, anticoagulant use was associated with a similar 1-year mortality rate as antiplatelet use (aHR 0.76; 95% CI 0.36-1.63; P=0.47) (Figure 3). Factors independently associated with 1-year mortality after AIS were initial D-dimer levels (aHR 4.59; 95% CI 2.24-9.38; P<0.001) and multi-territory brain infarction (aHR 2.13; 95% CI 1.19-3.82; P=0.01).

**Secondary outcomes**

Patients treated with anticoagulant therapy had higher long-term mortality compared to patients treated with antiplatelet therapy (88%, 95% CI 77%-94% versus 52%, 95% CI 41%-63%, log-rank test P<0.001). However, after adjustment for potential confounders, there was no difference in long-term mortality between the groups (aHR 1.29; 95% CI 0.67-2.47; P=0.44) (eFigure II).

The median total follow-up time for cerebrovascular events was 165 days (IQR 80–707) for the overall cohort, 107 days (IQR 40-232) for the anticoagulant group, and 178 days (IQR 99-940) for the antiplatelet group. After one year and also during the entire follow-up period, 9% (n=5/58) of patients treated with anticoagulant therapy had a recurrent AIS compared to 8% (n=6/77) of patients treated with antiplatelet therapy (aHR 0.49; 95% CI 0.08-2.83; P=0.83, eFigure III). There were no cases of sICH in either group during long-term follow-up.

**Subgroup analyses**

Of the 135 index AIS, 86 (64%) were classified as ESUS. In the ESUS subgroup (eTable II), patients treated with anticoagulant therapy were on average younger and more often had metastatic disease compared to those treated with antiplatelet therapy. After multivariable adjustment, anticoagulant therapy, compared to antiplatelet therapy, was associated with similar mortality at one year after AIS (aHR 0.51; 95% CI 0.21-1.22; P=0.11, eFigure IV). Similar to the overall cohort, D-dimer levels were associated with 1-year mortality after ESUS.

After excluding 22 patients with documented VTE treated with anticoagulant therapy at the time of index AIS hospital discharge, the risk of 1-year mortality remained similar between patients treated with

anticoagulant therapy and those treated with antiplatelet therapy (aHR 0.65; 95% CI 0.28-1.47; P=0.30, eFigure V).
After excluding the same 22 patients with documented VTE treated with anticoagulant therapy at index AIS hospital discharge from the ESUS cohort, 1-year mortality remained similar between antithrombotic treatment groups (aHR 0.38; 95% CI 0.14-1.05; P=0.06, eFigure VI).

**Inverse probabilty of treatment weighting analyses**
In the second round of analyses employing IPTW, the stabilized weights exhibited a near-normal distribution centered around one, albeit with a few weights surpassing two, which could have a significant impact on study outcomes (eFigure VII).

The IPTW analysis for 1-year mortality (eFigure VIII) corroborated the main analyses for the primary AIS cohort (HR 0.82; 95% CI 0.39-1.72, P=0.61) and the ESUS subgroup (HR 0.51; 95% CI 0.20-1.29; P=0.15). These results were unchanged after excluding patients with documented VTE from the primary cohort (HR 0.73; 95% CI 0.32-1.66; P=0.46) and the ESUS subgroup (HR 0.46; 95% CI 0.16-1.34; P= 0.30).

## Discussion

Among 135 patients with active cancer and non-cardioembolic AIS at a comprehensive stroke center in Switzerland, long-term clinical outcomes did not differ between patients treated with anticoagulant therapy at discharge and those treated with antiplatelet therapy. Study groups differed substantially, as treatment with anticoagulation was associated with more advanced and historically aggressive cancer types with predilections for hypercoagulability. However, even when accounting for these differences, rates of long-term mortality and recurrent AIS were comparable between treatment groups. These neutral findings persisted when analyses were limited to patients with ESUS and when excluding patients with VTE.

In the absence of specific guidelines and robust prospective data on secondary prevention in patients with AIS and active cancer, neurologists often rely on theoretical considerations and institutional practice patterns to guide treatment decisions.[5] As prothrombotic processes play a central role in many cancer-related strokes, some neurologists favor empiric anticoagulant therapy in these patients.[19] In patients with cancer-mediated hypercoagulability, it is purported that high thrombin levels promote the conversion of fibrinogen to fibrin and platelet activation, and this may be more effectively targeted by anticoagulant therapy than by antiplatelet therapy.[20] D-dimer, a degradation product of cross-linked fibrin, is widely used as a surrogate marker of hypercoagulability in patients with cancer-related stroke.[21]

The OASIS-Cancer study demonstrated a reduction in 1-year mortality among patients whose D-dimer levels were effectively lowered with anticoagulant therapy.[22] However, this study lacked an antiplatelet arm, and provided little information on cancer treatments administered, which, by targeting the underlying cancer driving hypercoagulability, may influence clinical outcomes more than the type of antithrombotic therapy selected.[22] In contrast, patients with active cancer and AIS also face an increased risk of major bleeding, approaching 20% at 1-year in prospective studies[23], and anticoagulant therapy is known to increase the risk of bleeding compared with antiplatelet therapy.[24]

Given our neutral findings and the existing data[20], the potential efficacy of antiplatelet therapy in cancer-related stroke warrants further investigation. Thrombi retrieved from patients with active cancer and AIS have been shown to be platelet-rich and erythrocyte-poor.[25] This histopathological specificity could have an influence on the efficacy of different secondary preventions.[26] Few studies have compared clinical outcomes in cancer-related stroke by antithrombotic treatment strategy. In a retrospective analysis of 172 patients with active cancer and AIS at a comprehensive cancer center in New York, the rates of recurrent thromboembolism or death did not differ between patients treated with antiplatelet versus anticoagulant therapy[27]. A subgroup analysis of the NAVIGATE ESUS trial evaluating 543 ESUS patients with any history of cancer reported no difference in the risk of recurrent AIS or mortality between patients treated with rivaroxaban versus aspirin.[7] However, only 9% of patients in this post-hoc analysis had their cancer diagnosed in the year prior to the index AIS, so many of the included cancers were likely inactive during follow-up. A recently-published post hoc analysis investigated 137 patients with history of cancer in the ARCADIA trial, which compared apixaban to aspirin in patients with cryptogenic stroke and biomarker evidence for atrial cardiopathy.[6] This study showed no significant difference in the risk of major ischemic and hemorrhagic events between antithrombotic treatment groups. However, once again, cancer status at the time of stroke was unknown, making it difficult to draw conclusions about optimal secondary stroke prevention for patients with active cancer based on these data.

The results of the current analysis support the existence of clinical equipoise between anticoagulant and antiplatelet therapy for the treatment of cancer-related stroke, and further support the guidelines' calls for randomized trials to determine the optimal strategy. An important consideration when deciding on the antithrombotic management of this patient group is the presumed stroke mechanism. As many ESUS in cancer patients are attributed to hypercoagulability, this subgroup may be the most likely to preferentially benefit from anticoagulant therapy.

Our study has several limitations. Firstly, confounding by indication bias is possible because patients treated with anticoagulant therapy were more likely to have elevated D-dimer levels, multi-territory

brain infarcts, and metastatic disease at the time of AIS, biomarkers associated with cancer-associated hypercoagulability and worse outcomes after cancer-related stroke.[23] In such scenarios, IPTW is the recommend method for addressing casual inference, but residual confounding remains a concern.[18,28] Secondly, our study was conducted at a single comprehensive stroke center in Switzerland, which limits external generalizability. Thirdly, because of the retrospective study design, we relied on EHRs to determine clinical data, which may have led to measurement error in patients' clinical characteristics as well as missed clinical outcomes during follow-up. In particular, rates of recurrent AIS and sICH may have been underestimated because incident diagnoses made in the outpatient setting or at other medical centers may have been missed. Fourthly, our study exposure was the type of antithrombotic therapy administered at hospital discharge, a single timepoint, and antithrombotic prescription patterns may have changed during follow-up due to clinical events and patient and physician preferences. Fifthly, our database lacked data on the specific cause of death.

## Conclusion

In our study, there were no differences in mortality or recurrent AIS in patients with active cancer and AIS treated with anticoagulant therapy versus those treated with antiplatelet therapy. These data combined with those from existing studies as well as the lack of clear recommendations by major guidelines highlight the need for dedicated fully-powered clinical trials to determine the optimal antithrombotic strategy for the secondary prevention of cancer-related stroke.

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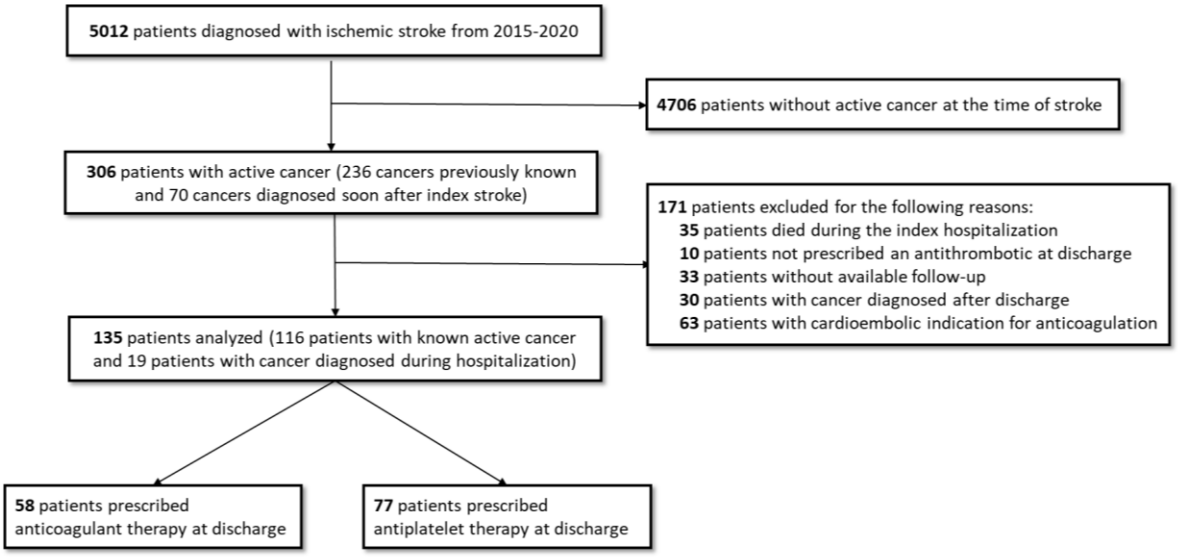


**Figure 1** – Study flowchart with inclusion and exclusion of patients.

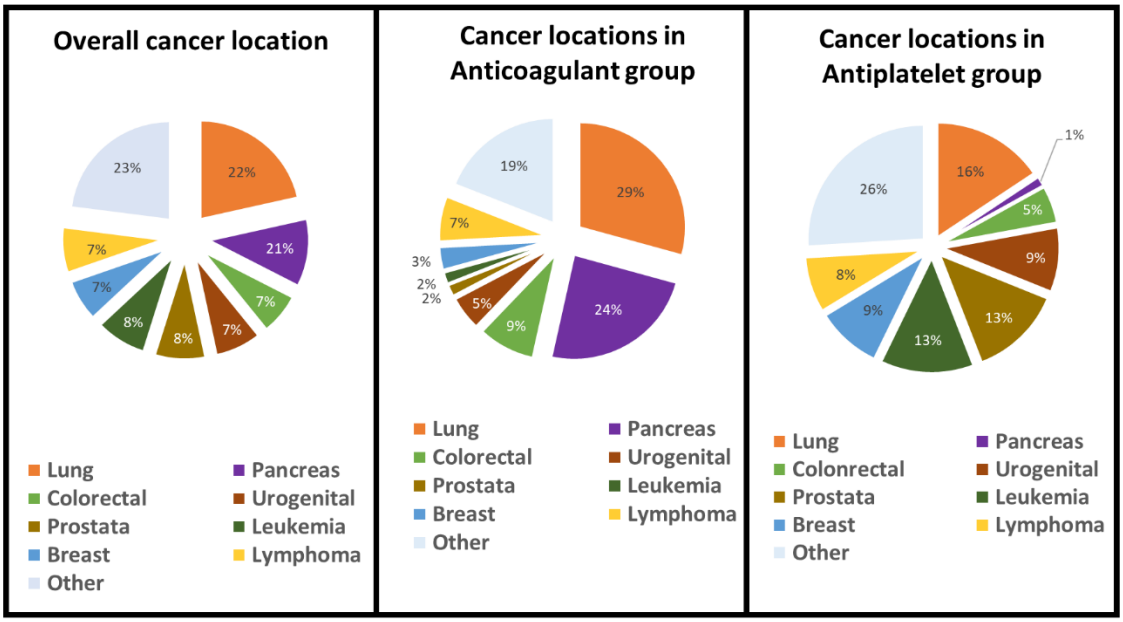


**Figure 2** – Long-term survival curves for patients with cancer treated with antiplatelet therapy or anticoagulant therapy for secondary stroke prevention.

Compared to patients treated with antiplatelet therapy (in blue), patients treated with anticoagulant therapy (in red) had higher mortality rates at one year (log-rank test, P<0.001) and during long-term follow-up (log-rank test, P<0.001) after their index ischemic stroke.

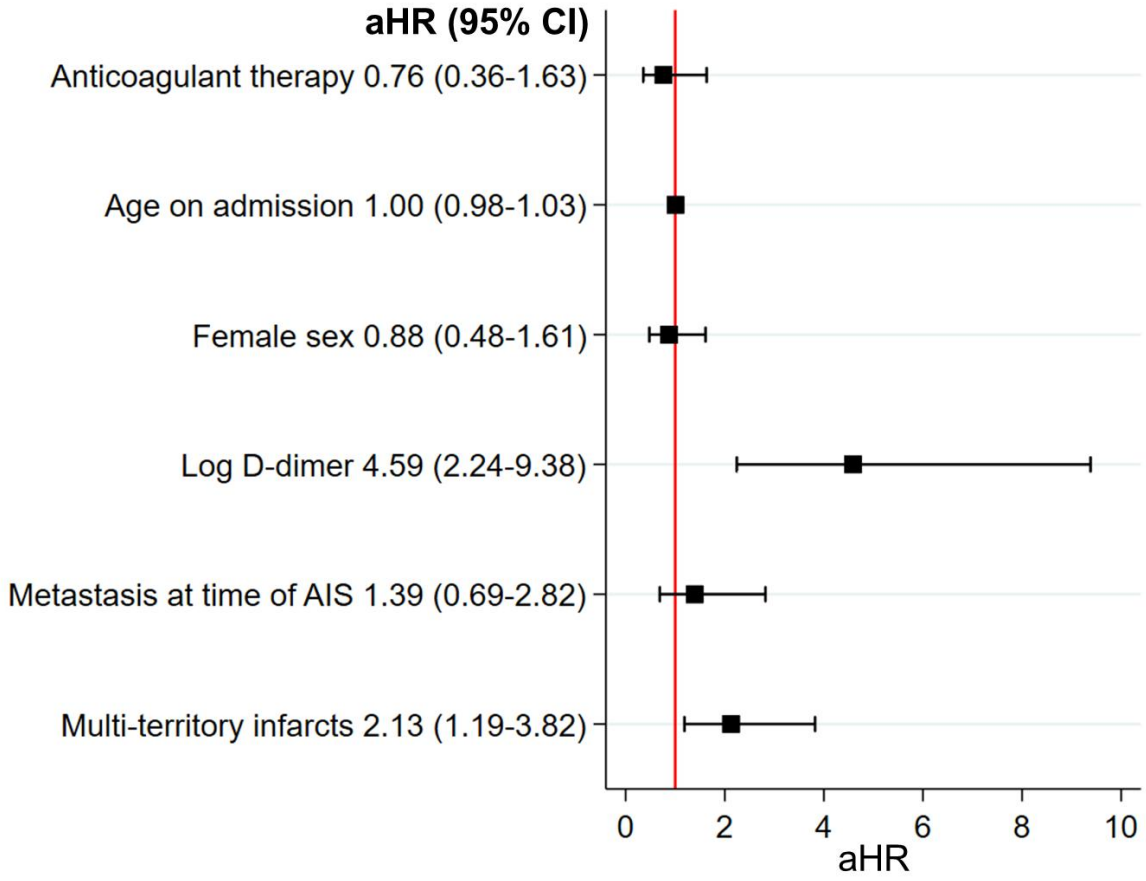


**Figure 3** – Multivariable model studying the association between antithrombotic treatment strategies at hospital discharge for AIS and 1-year mortality.

There was no association between anticoagulant therapy, as compared to antiplatelet therapy, and 1-year mortality in the main analysis. Higher D-dimer levels and multi-territory brain infarcts were both strongly associated with 1-year mortality in these patients. D-dimer was abnormally distributed so it was log transformed. Abbreviations: aHR, adjusted hazard ratio; AIS, acute ischemic stroke.

**Table 1:** Baseline characteristic data in patients with active cancer and ischemic stroke stratified by antiplatelet versus anticoagulant therapy.

| | All patients (N= 135) | Antiplatelet therapy (N=77) | Anticoagulant therapy (N=58) | p-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Sex, female No./total No. (%) | 60/135 (44) | 31/77 (40) | 29/58 (50) | 0.30 |
| Age at admission median (IQR) | 72 (64-80) | 75 (65-82) | 69 (62-75) | 0.01 |
| **Medical history No. / total No. (%)** | | | | |
| Previous ischemic stroke | 20/96 (21) | 8/53 (15) | 12/43 (28) | 0.14 |
| Hypertension | 65/96 (68) | 38/53 (72) | 27/43 (63) | 0.39 |
| Diabetes Mellitus | 21/95 (22) | 10/52 (19) | 11/43 (26) | 0.47 |
| Hyperlipidemia | 66/95 (70) | 38/52 (73) | 28/43 (65) | 0.50 |
| Smoking history | 28/90 (31) | 15/49 (31) | 13/41 (32) | 1.00 |
| **Venous thromboembolic events No. / total No. (%)** | | | | |
| Any venous thromboembolism | 23/135 (17) | 1/77 (1) | 22/58 (38) | <0.001 |
| Deep venous thrombosis | 14/135 (10) | 1/77 (1) | 13/58 (22) | <0.001 |
| Pulmonary embolism | 16/135 (12) | 0/77 (0.0) | 16/58 (28) | <0.001 |
| **Stroke characteristics** | | | | |
| Independence before stroke (mRS ≤ 2) No./total No. (%) | 54/135 (44) | 30/33 (91) | 24/27 (89) | 1.00 |
| Initial NIHSS, median (IQR) | 5 (2-9) | 4 (2-8) | 6 (3-10) | 0.31 |
| MRI during admission No./total No. (%) | 59/80 (73) | 36/48 (75) | 23/32 (72) | 0.8 |
| Multi-territory infarct No./total No. (%) | 40/135 (30) | 13/77 (17) | 27/58 (47) | <0.001 |
| **Stroke etiology No. / total No. (%)** | | | | |
| Large-artery atherosclerosis | 24/135 (18) | 19/77 (25) | 5/58 (9) | 0.011 |
| Cardioembolic | 0/135 (0) | 0/77 (0) | 0/58 (0) | |
| Small-vessel occlusion | 3/135 (2) | 3/77 (4) | 0/58 (0) | |
| More than one or other determined etiology | 7/135 (5) | 2/77 (2) | 5/58 (9) | |
| Undetermined etiology | 101/135 (75) | 53/77 (69) | 48/58 (82) | |
| ESUS | 86/135 (64) | 38/77 (50) | 48/58 (82) | <0.001 |
| **Cancer characteristics at time of AIS** | | | | |
| Cancer stage median (IQR) | 4 (2-4) | 3 (2-4) | 4 (3-4) | <0.001 |
| Distant metastases No./total No. (%) | 65/135 (48) | 27/77 (41) | 38/58 (72) | <0.001 |
| **Baseline laboratory findings median (IQR)** | | | | |
| D-dimer in µg/L | 752 (382-1559) | 1010 (495-2090) | 8536 (2080-13726) | <0.001 |
| CRP in mg/L | 3 (1-8) | 4 (2-24) | 18 (5-50) | 0.005 |
| Fibrinogen in g/L | 3.1 (2.6-3.7) | 3.3 (2.6-3.9) | 2.7 (2.0-3.5) | 0.003 |
| LDH in U/l | 396 (339-480) | 387 (344-499) | 650 (446-833) | <0.001 |
| Platelet count in G/L | 225 (186-271) | 229 (191-267) | 181 (144-250) | 0.013 |
| Hemoglobin in g/dL | 13.8 (12.6-14.9) | 13 (10.5-14.2) | 11.8 (10.8-13.4) | 0.25 |

Abbreviations: CRP, C-reactive protein; ESUS indicates embolic stroke of undetermined source; IQR, interquartile range; LDH, Lactate dehydrogenase; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; VTE, venous thromboembolism.

**Table 2**: Clinical outcomes in patients with active cancer and AIS stratified by antiplatelet versus anticoagulant therapy

| | All patients (N=135) | Antiplatelet therapy (N=77) | Anticoagulant therapy (N=58) | p-value |
|---|---|---|---|---|
| **90-day follow-up No. / total No. (%)** | | | | |
| Good functional outcomes (mRS ≤2) | 39/78 (50) | 29/44 (66) | 10/34 (29) | 0.003 |
| Mortality rate | 19/78 (24) | 5/44 (11) | 14/34 (41) | 0.003 |
| Recurrent AIS | 3/66 (5) | 3/43 (7) | 0/23 (0) | 0.55 |
| Occurrence of ICH | 0/66 (0) | 0/43 (0) | 0/23 (0) | |
| **Long-term follow-up** | | | | |
| Follow-up time for long-term mortality in days median (IQR) | 495 (57-1029) | 797 (218-1483) | 133 (43-506) | <0.001 |
| Mortality rate at one year No./total No. (%) | 63/135 (47) | 25/77 (33) | 38/58 (66) | <0.001 |

# Chapter 3: Discussion

The projects comprising this PhD thesis covered many aspects of the "cancer-related stroke" research field. Firstly, we investigated conventional research topics, such as the validation of known cancer-associated biomarkers in patients with TIA, and the analysis of the most effective secondary prevention for cancer-related strokes (anticoagulants versus antiplatelet drugs).[22]

Secondly, we investigated some of the possible causes of cancer-related strokes to provide a better understanding of the underlying mechanisms.[23,24]

Finally, more innovative studies aiming to extend research on cancer-related strokes into new areas were conducted, such as the investigation of thrombus imaging characteristics and occult cancers.[19,25–27]

One of the key factors that made all the studies presented in this PhD thesis possible was the creation of the Bernese Malignancy-in-Stroke (BMS) database (N=5012), one of the largest databases in the field of cancer-related strokes. However, despite the large size of this database, the number of patients with active cancer included remains relatively low, and multicenter studies will be needed to answer open questions about cancer-related strokes in the future.

## 3.1 Biomarkers in cancer-related strokes

The susceptibility vessel sign (SVS), a hypointense signal in MRI susceptibility-weighted-imaging, is associated with thrombi that are rich in erythrocytes in their microscopic composition.[28] Both SVS and erythrocyte-rich thrombi have been predominantly associated with cardioembolic causes of stroke.[28–30] Thrombi from patients with cancer-related strokes are richer in platelets and fibrin, and, as demonstrated in this PhD thesis, are associated with the absence of the SVS.[26,27,31] The relationship between the microscopic composition of a thrombus and the suspected AIS etiology is fundamental to gaining a better understanding of the mechanisms of thrombus formation specific to the different causes of AIS. An association between active cancer and arterial causes of AIS is assumed due to the negative association with right-to-left shunts (a surrogate marker for paradoxical embolism).[23] Furthermore, our studies showed a trend towards non-cardioembolic causes of AIS in patients with active cancer, due to the association with the absence of the SVS and the lack of association with atrial cardiopathy.[20,24] A better understanding of the underlying mechanisms of cancer-related strokes is important to enable specific treatments to be developed in the future.

The biomarkers evaluated in this PhD thesis depend on the investigations performed and, in the case of the SVS, on the presence of a visible occlusion. Consequently, our results are not generalizable to all AIS patients.

It is important to consider general biomarkers when assessing the risk of paraneoplastic coagulation in patients with AIS and active cancer. Commonly available laboratory parameters can help evaluate the

potential for clotting or bleeding complications related to the underlying cancer. As well as elevated D-dimers, other hematological biomarkers were also associated with cancer-related strokes.[3] In cancer-related strokes, hypercoagulability is usually reflected by low fibrinogen and high or low platelet count; systemic inflammation by elevated CRP and elevated leukocytes; and finally chronic anemia by low hemoglobin.[6,32]

## 3.2 The special case of occult cancer

Occult cancer in patients with AIS remains underinvestigated.[7] This is illustrated by the lack of clinical trials evaluating the effectiveness of cancer screening in AIS patients, and the absence of recommendations for cancer screening in most stroke guidelines.

In recent years, several models to predict occult cancer in AIS patients have been proposed.[19,33,34] To our knowledge, our OCCULT-5 score is the only model to provide a clinical score that can be easily used at the bedside to evaluate the probability of underlying occult cancer in AIS patients. However, our score still requires external validation before it can be used in clinical routine or in clinical trials assessing the effectiveness of cancer-screening in AIS patients, for example.[19]

A recent meta-analysis estimated the rate of cancer diagnosis in the first year after AIS at 1.4%.[7] This percentage was higher for cryptogenic strokes (6.2%) and when cancer-screening has been performed (3.9%). However, the percentages reported in this meta-analysis may be underestimated due to the retrospective design of the studies included.

Aside from the incidence of cancer diagnosed in the year following AIS, there is little evidence regarding outcomes for AIS patients with occult cancer, the influence of the time to cancer diagnosis and to start of cancer treatment. Our study comparing mortality rates between AIS patients with a new diagnosis of cancer during acute hospitalization with those of patients diagnosed after discharge failed to demonstrate a difference in mortality between the two groups.[7] However, the number of patients with occult cancer included in the study was low (n=59, 1.5% of the 3894 AIS patients with long-term follow-up available for the study period). This highlights the need for multicenter studies that include larger numbers of AIS patients with active cancer, and particularly occult cancers, to address unanswered research questions.

## 3.3 Outcomes in cancer-related strokes

As mentioned in the introduction, the morality rate is higher and outcomes worse in patients with cancer-related strokes compared to other AIS patients.[35,36] It is well established that patients with more advanced

cancers (particularly metastatic cancer) and higher D-dimer levels at the time of AIS have a poorer prognosis.[32,37]

For this reason, it is important to identify further biomarkers associated with outcomes to refine prognostic evaluation and possibly to guide secondary stroke prevention.

In this PhD thesis, we demonstrated an association between the absence of the SVS and higher mortality in the long-term in AIS patients treated with mechanical thrombectomy.[20] Unfortunately, an interaction analysis failed to identify a substantial influence of the presence of active cancer on the relationship between the absence of the SVS and long-term mortality.[20] Further studies are now needed to identify other outcome predictors in patients with cancer-related strokes.

Regarding secondary prevention, there are no conclusive guideline-based recommendations for the optimal antithrombotic strategy for patients with cancer-related stroke.[38] Secondary analyses of the NAVIGATE ESUS and ARCADIA randomized controlled trials have shown neutral outcomes in terms of recurrent stroke risk in patients treated with anticoagulants or antiplatelet drugs.[8,39] However, a limitation of both studies is that they included not only patients with active cancer but also patients with inactive cancer. Although our study (not published yet) on the best secondary prevention has the advantage of including only patients with active cancer, it did not demonstrate an advantage of either medication, even after statistical analysis designed to limit possible bias.

# Chapter 4: Outlook

Research on cancer-related strokes can benefit from the advances made in the current era of precision medicine. Cancer-related strokes affect a heterogeneous group of patients with multiple cancer genotypes and phenotypes. The establishment of a multicenter registry on cancer-related strokes that includes data on a large number of AIS patients with cancer and detailed information on individual cancers will enable investigators to perform studies analyzing the different types of cancer on a case-by-case basis. This may lead to individualized treatments in the future.

In addition, it is important to continue exploring the molecular mechanisms involved in the initiation of paraneoplastic coagulation, as done by Bang et al. in the OASIS Cancer Study and Navi et al. in the MOST-Cancer Study.[3,40] This is also the aim of our planed pilot study “CIRculating tumor DNA in patients with active CAncer and ischemic STroke: The CIRCAST-Study”.

Finally, our ongoing INVISIBLE-1 study, aims to prospectively determine the incidence and characteristics of occult cancer in high-risk patients in the year following index AIS. The results of this study will support and inform the implementation of the first clinical trial for cancer screening in high-risk AIS patients.

To conclude, the field of cancer-related-stroke research is relatively new, and there are many open questions to be addressed in the coming years to improve the diagnosis and outcomes for AIS patients with cancer.

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