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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Increased risk for cancer after stroke at a young age: etiological relevance or incidental finding?

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Abstract

Background Etiological factors, such as a malignant disease, in young stroke patients are often neglected. Therefore, in this study, we aimed to investigate the risk of developing cancer in young stroke survivors.

Methods The current case–control study sample included patients who received an initial ischemic stroke diagnosis documented in the Disease Analyzer database (IQVIA), which compiles data such as risk factors, drug prescriptions, and diagnoses obtained from general practitioners and specialists.

Results The stroke and non-stroke groups included 18,668 patients each; each group had 2836 (15.3%) participants ≤ 55 years. The cancer incidence in the stroke group over the age of 55 years was higher than in the younger subgroup (29.4% versus 17.3%). The proportions of cancer patients within 10 years of follow-up were higher in the stroke group versus the non-stroke group, as well as in the subgroup of patients aged ≤ 55 versus patients > 55 years (17.3% versus 9.5% and 29.4% versus 24.9%, respectively). The calculated hazard ratio for developing cancer within 10 years of follow-up was higher in the younger stroke population (≤ 55 years) than in the older population (hazard ratio: 1.47 (CI 1.18–1.83) versus 1.17 (CI 1.10–1.25).

Conclusion In our cohort, young individuals aged ≤ 55 years who suffered a stroke had twice as high risk for developing cancer within 10 years after the index event compared to the control group. Stroke might have implication regarding the subsequent development of cancer and vice versa.

Keywords Young stroke · Cancer · Stroke etiology

Introduction

While stroke is a pathology mostly found in older patients, younger individuals have been increasingly affected by the disease (Aigner et al. 2017; Putaala et al. 2012; Rolfs et al. 2013; Tanislav et al. 2014). The majority of stroke victims are > 75 years of age, but 10% of hospitalized stroke patients are aged ≤ 55 years (Aigner et al. 2017; Putaala et al. 2012; Rolfs et al. 2013; Tanislav et al. 2014). A number of recent studies focusing on young stroke sufferers reported important information about age and sex distribution, risk factors, etiological factors, and imaging findings, thus indicating that the established stroke risk factors are more common than previously assumed (Aigner et al. 2017; Putaala et al. 2012; Rolfs et al. 2013; Tanislav et al. 2014). However, while etiologies can mostly be explained by classical vascular risk factors in general stroke populations the etiology remains undetermined in about one-third of younger stroke patients (Rolfs et al. 2013.

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Many reports indicate cancer-induced thrombophilia as causing venous thromboses as well as arterial embolic events (Bergqvist 2002; Falanga 2005; Oren and Herrmann 2018). In this context, the direct and subsequent screening for cancer in unexplained vascular events may be useful and may potentially clarify the etiology and unveil a malignant disease at an early stage. The relationship between cancer and stroke has been well investigated, but most studies have focused on stroke after a cancer diagnosis (Aarnio et al. 2015; Dearborn et al. 2014; Selvik et al. 2015; Zoller et al. 2012). However, less data are available on the cancer incidence in stroke survivors (Chen et al. 2017; Cocho et al. 2015; Jacob and Kostev 2019; Quintas et al. 2018; Qureshi et al. 2015). In a recent publication, Jacob and colleagues reported an increased cancer incidence following stroke (Jacob and Kostev 2019). Considering the high proportion of unexplained strokes in young patients, a malignant disease in the context of an acute cerebrovascular event appears even more likely.

Therefore, we aimed to investigate the cancer risk in young stroke survivors after 10 years of follow-up in a large cohort in Germany.

Methods

Database

This study is based on data from the Disease Analyzer database (IQVIA), which compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists (Rathmann et al. 2018). Diagnoses ([international Classification of Diseases, 10th revision (ICD-10)], prescriptions (Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are monitored by IQVIA based on a number of criteria (e.g., completeness of documentation, linkage between diagnoses, and prescriptions).

In Germany, the sampling methods used for the selection of physicians' practices are appropriate for obtaining a representative database of general and specialized practices (Rathmann et al. 2018).

Study population and variables

The current study sample included patients who received an initial ischemic stroke diagnosis [International Classification of Diseases, 10th edition (ICD-10): I63, I64] and were followed up on in one of 1262 general practices in Germany between 2006 and 2015 (index date). The inclusion criteria were as follows: follow-up time of at least 12 months prior to and after the index date; no diagnosis of cancer (C00–C99), in situ neoplasms (D00–D09), or neoplasms of uncertain or unknown behavior (D37–D48) prior to the index date; and age $\geq$ 18 years at the index date. After applying similar inclusion criteria, patients without stroke were matched (1:1) to patients with stroke based on propensity scores using a greedy algorithm and derived from the logistic regression using age, gender, index year, and 16 co-morbidities diagnosed in the 12 months prior to the index date.

The 16 co-morbidities were certain infectious and parasitic diseases (A00–B99); benign neoplasms (D10–D36); diseases of the blood and blood-forming organs, and certain disorders involving the immune mechanism (D50–D89); endocrine, nutritional, and metabolic diseases (E00–E90); mental and behavioral disorders (F00–F99); diseases of the nervous system (G00–G99); diseases of the eye and adnexa (H00–H59); diseases of the ear and mastoid process (H60–H95); diseases of the circulatory system (I00–I99), excluding stroke (I63, I64); diseases of the respiratory system (J00–J99); diseases of the digestive system (K00–K93); diseases of the skin and subcutaneous tissue (L00–L99); diseases of the musculoskeletal system and connective tissue (M00–M99); diseases of the genitourinary system (N00–N99); congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99); and injury, poisoning, and certain other consequences of external causes (S00–T98). The index date for participants without stroke was a randomly selected visit date between 2006 and 2015. A total of 18,668 patients with and 18,668 patients without stroke were included (Fig. 1).

Study outcome

The main outcome of the study was the risk of cancer (C00–C97) as a function of stroke within 10 years of the index date. Analyses were performed separately for patients aged $\leq$ 55 and > 55 years.

Statistical analyses

Descriptive analyses were obtained for all demographic and clinical variables, and mean $\pm$ SD was calculated for age. The cumulative incidence of any cancer in the stroke and non-stroke groups was calculated for up to 10 years after the index date using Kaplan–Meier curves in patients $\leq$ 55 and > 55 years, respectively. Patients were censored at the time of first cancer diagnosis or loss to follow-up, whichever occurred first. As no information on death was available, dead patients were considered as lost to follow-up in this study. Multivariate Cox regression models were used to investigate the association between stroke and cancer, adjusting for stroke risk factors such as hypertension (ICD 10: I10), diabetes mellitus (ICD 10:

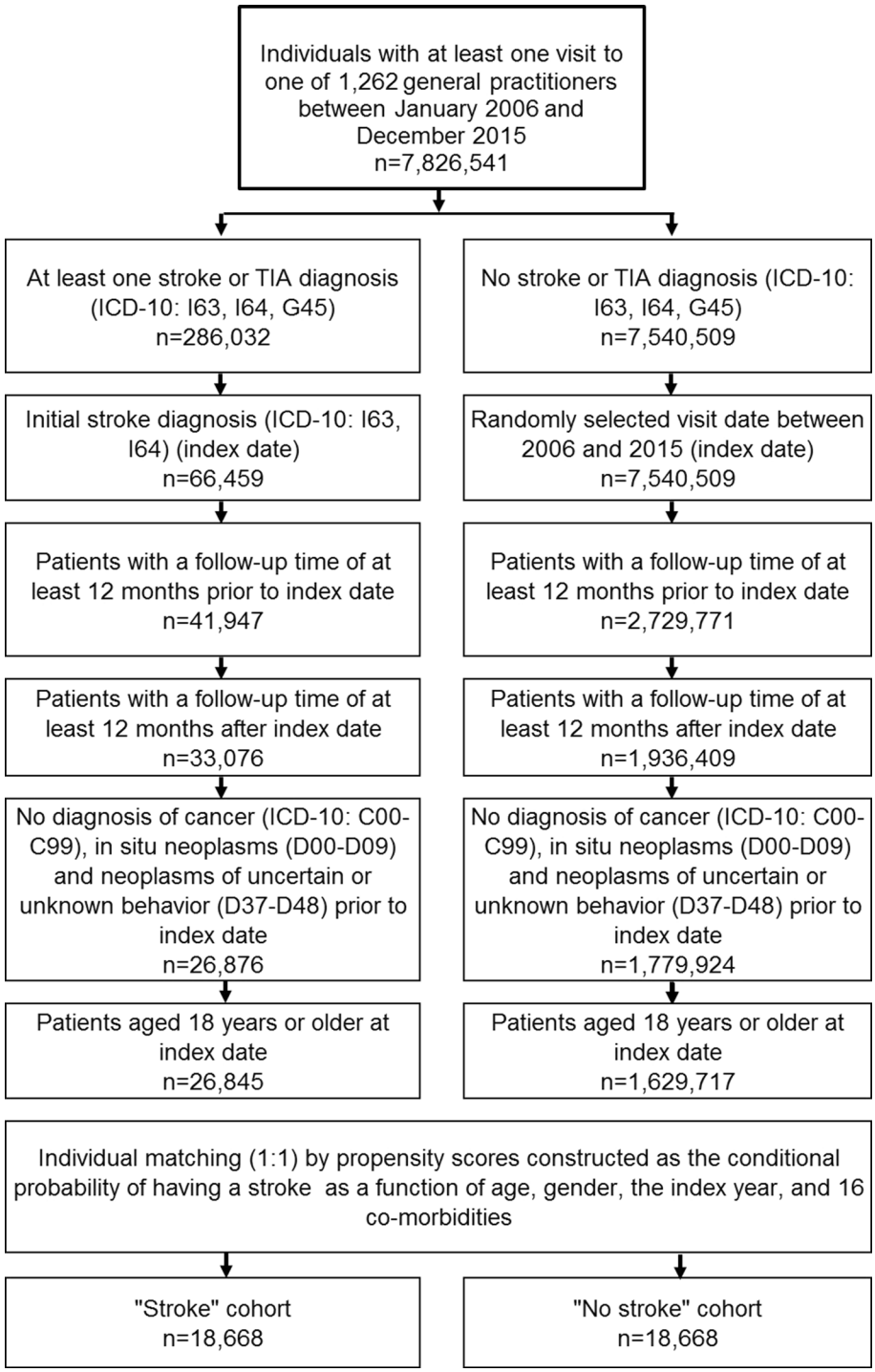

Fig. 1 Selection of study patients

E10-14), atrial fibrillation (ICD 10: I48.0, I48.1, I48.2, I48.9), obesity (ICD 10: E66), and hyperlipidemia (ICD 10: E78). A p value of < 0.05 was considered statistically significant. The analyses were carried out using SAS 9.4.

Results

After the selection procedure (Fig. 1), the stroke and non-stroke groups included each 18,668 patients; 2836 (15.3%)

participants in each group were aged ≤ 55 years (Table 1). Comparing stroke patients according to age (≤ 55 versus > 55 years), the younger subgroup had a higher proportion of males (59.0% versus 49.9%) and higher percentages of vascular risk factors (Table 2). The cancer incidence in the stroke group aged > 55 years was higher than in the younger subgroup (29.4% versus 17.3%), (Table 2).

We observed no differences regarding the age and sex distributions between stroke and non-stroke patients in each subgroups of patients ≤ 55 and > 55 years of age, respectively. Cancer proportions within 10 years of follow-up were higher in stroke patients versus non-stroke patients, as well as in the subgroup of patients aged ≤ 55 versus patients > 55 years (17.3% versus 9.5% and 29.4% versus 24.9%); the calculated hazard ratio for developing cancer within 10 years of follow-up was higher in the younger stroke population (≤ 55 years) than in the older population [hazard ratio: 1.47 (CI 1.18–1.83) versus 1.17 (CI 1.10–1.25)], (Fig. 2).

Discussion

In our cohort of young stroke sufferers aged ≤ 55 years ($n = 2836$), we found a twice as high risk for developing cancer within 10 years after the index event as compared to the corresponding matched group without stroke (17.3% versus 9.5%). In contrast, in the older populations (aged > 55 years), the difference between stroke patients and controls was not that pronounced (29.4% versus 24.9%). Despite a lack of direct evidence, our results may support the hypothesis that young stroke patients' subsequent cancer diagnoses may have implications regarding the pathophysiology of the initial cerebrovascular event. On the other hand a modified life style after stroke determining an increased exposure for developing cancer, might influenced to some extend our results (Qureshi et al. 2015). However, a positive screening for cancer in young stroke patients directly or in a subsequent phase may contribute to explaining the stroke mechanism while also facilitating an early diagnosis of a malignant disease.

Table 1 Baseline characteristics in stroke and non-stroke patients

	Overall cohort ($n = 37,336$)	Stroke patients ($n = 18,668$)	Non-stroke patients ($n = 18,668$)	p value
Sex				
Male	51.3	51.3	51.3	1.000
Female	48.7	48.7	48.7	
Age (mean, SD)	69.1 (12.6)	69.1 (12.6)	69.1 (12.6)	1.000
≤ 55 years	15.3	15.3	15.3	1.000
> 55 years	84.7	84.7	84.7	
Diagnoses in the 12 months prior to the index date				
Certain infectious and parasitic diseases (A00–B99)	9.6	9.6	9.6	1.000
Benign neoplasms (D10–D36)	0.6	0.6	0.6	1.000
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	22.2	22.2	22.2	1.000
Endocrine, nutritional and metabolic diseases (E00–E90)	55.2	55.2	55.2	1.000
Mental and behavioral disorders (F00–F99)	20.0	20.0	20.0	1.000
Diseases of the nervous system (G00–G99)	21.7	21.7	21.7	1.000
Diseases of the eye and adnexa (H00–H59)	5.5	5.5	5.5	1.000
Diseases of the ear and mastoid process (H60–H95)	2.8	2.8	2.8	1.000
Diseases of the circulatory system (I00–I99), excluding stroke (I63, I64)	72.3	72.3	72.3	1.000
Diseases of the respiratory system (J00–J99)	26.1	26.1	26.1	1.000
Diseases of the digestive system (K00–K93)	26.2	26.2	26.2	1.000
Diseases of the skin and subcutaneous tissue (L00–L99)	9.8	9.8	9.8	1.000
Diseases of the musculoskeletal system and connective tissue (M00–M99)	44.3	44.3	44.3	1.000
Diseases of the genitourinary system (N00-N99)	13.6	13.6	13.6	1.000
Congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99)	1.0	1.0	1.0	1.000
Injury, poisoning, and certain other consequences of external causes (S00–T98)	13.6	13.6	13.6	1.000

Table 2 Comparison of patients with a previous stroke, dichotomized by age

	Age ≤ 55 years ($n = 2863$)	Age > 55 years ($n = 15{,}805$)	p value
Sex			
Male	59.0	49.9	< 0.001
Female	41.0	50.1	
Cancers within 10 years of follow-up			
All cancers (C00–C97)	17.3	29.4	< 0.001
Lip, oral cavity, and pharynx (C00–C14)	0.4	0.5	0.565
Digestive organs (C15–C26)	1.6	5.1	< 0.001
Respiratory and intrathoracic organs (C30–C39)	1.1	2.7	0.015
Bone and articular cartilage (C40–C41)	0.0	0.2	0.523
Skin (C43–C44)	1.5	5.9	< 0.001
Mesothelial and soft tissue (C45–C49)	0.0	0.3	0.071
Breast (C50)	1.2	1.7	0.075
Female genital organs (C51–C58)	1.7	2.4	0.019
Male genital organs (C60–C63)	0.8	2.9	< 0.001
Urinary tract (C64–C68)	0.5	1.9	< 0.001
Eye, brain, and other parts of the central nervous system (C69–C72)	0.5	0.3	0.695
Thyroid and other endocrine glands (C73–C75)	0.1	0.1	< 0.597
Lymphoid, hematopoietic, and related tissue (C81–C96)	0.7	3.1	< 0.001
Risk factors (known at the index event)			
Hypertension	39.4	60.3	< 0.001
Diabetes mellitus	12.1	26.2	< 0.001
Atrial fibrillation	2.9	12.2	< 0.001
Hyperlipidemia	22.3	30.9	< 0.001
Obesity	10.9	11.2	0.649

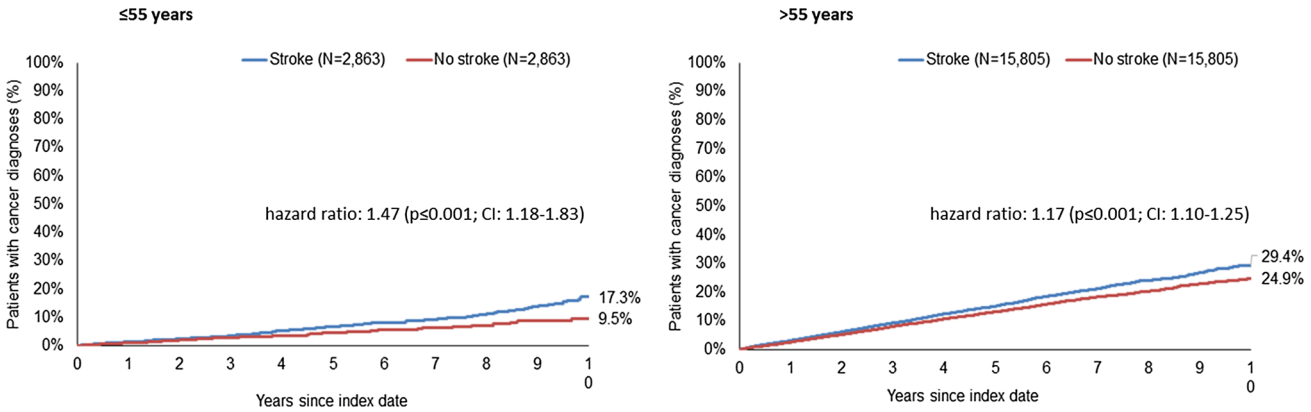

Fig. 2 Kaplan–Meier curves for time to diagnosis of any cancer in patients with or without stroke followed for up to 10 years dichotomized by age

Reviewing the literature, a thrombophilic condition in malignant disorders is considered a commonly occurring and acquired pathology (Falanga and Rickles 1999; Falanga 2005). This hypercoagulability state is mostly attributed to the capacity of tumor cells to interact with the hemostatic system; furthermore, an interfering paraneoplastic syndrome is assumed to activate the coagulation cascade (Bergqvist 2002; Falanga and Rickles 1999; Falanga 2005). The majority of cancer patients exhibit abnormalities of the hemostatic system, presenting with one or more deviant values in laboratory coagulation testing (Falanga 2005). Even a correlation between cancer progression and an increasing

hypercoagulability state could be proven (Edwards et al. 1987). Therefore, cancer patients are expected to be exposed to an increased risk for clot formation, causing venous and arterial thromboembolic clinical events (Falanga 2005). However, depending on the type of cancer, 5–20% of these patients may experience a manifest thrombosis in the course of their disease (Blom et al. 2005; Donati 1995; Falanga 2005; Mulder et al. 2019). When screening for cancer in patients with an unprovoked venous thrombosis, the results depend on the diagnostic approach and the follow-up time (Carrier et al. 2015; Piccioli et al. 2004; Prandoni et al. 2016). When applying an extensive screening work-up in patients with unprovoked thrombosis, a rate of around 13% occult cancers within a subsequent period of 2 years can be expected (Carrier et al. 2015; Piccioli et al. 2004; Prandoni et al. 2016).

Considering the hypercoagulability state in cancer patients, the low-pressure conditions within veins can be considered a predisposing factor for clot formation. In contrast, the high pressure in the arterial system may provide a certain protection against blood clotting. However, investigations indicate the substantial risk for arterial thromboembolism in patients with thrombophilic conditions such as cancer (Navi et al. 2015, 2017, 2019; Oren and Herrmann 2018). According to the current state of knowledge, a 10% risk for arterial thromboembolic events within 2 years of follow-up in cancer patients can be expected (Navi et al. 2015, 2017, 2019; Oren and Herrmann 2018). The type and staging of the cancer are also determinants for overall risk (Oren and Herrmann 2018). Early stages of cancer are associated with a lower risk of arterial embolic events (around 6% within 2 years), but a higher risk (around 10%) can be expected (around 10% within 2 years) in advanced stages (Oren and Herrmann 2018). Pancreatic and lung cancers seem to be more pathogenic than other types of cancers, as indicated by increased rates of stroke in these groups (Navi et al. 2015).

Recent publications have focused on the prevalence and incidence of cancer in stroke survivors. They showed an increased incidence in stroke patients compared to matched non-stroke patients (Jacob and Kostev 2019; Quintas et al. 2018; Qureshi et al. 2015). Screening for cancer in the acute stage of a stroke may unveil an occult malignant disease in some cases; Cocho and colleagues depicted malignancy in 2.1% of acute stroke patients (Cocho et al. 2015). Screening in the subsequent phase of stroke (within 18 month), a rate of 7.6% could be expected (Cocho et al. 2015). Extending the period of observation over 10 years, a quarter of stroke survivors may experience a malignant disease (Jacob and Kostev 2019). Moreover, these studies showed a substantial risk increase for developing cancer after stroke, underlying the mutual relationship (Jacob and Kostev 2019; Quintas et al. 2018; Qureshi et al. 2015). As previously speculated by other authors, cancer potentially precedes the stroke event, which is then facilitated by the hypercoagulability state of malignancy (Caine et al. 2002; Jacob and Kostev 2019). On the other hand, as the degree of disability after stroke represents the main modifying determinant in behavior, a change in life style after stroke might also explain to some extend our results (Qureshi et al. 2015). In this context, Quershi and co-workers found increased rates of cancer after stroke in 3247 patients with a nondisabling cerebral infarction (standardized incidence ratio = 1.2), indicating that the modification in life style after stroke is not the single factor determining a diagnosis of cancer subsequently (Qureshi et al. 2015).

However, all investigations focused on general stroke populations, including mostly elderly patients (Jacob and Kostev 2019; Quintas et al. 2018; Qureshi et al. 2015). As this factor is concerned, our results underline that age matters when interpreting cancer's potential involvement in stroke mechanisms. We detected a diagnosis of cancer in 17.3% of the participants in our cohort of young stroke patients aged ≤ 55 years within a follow-up period of 10 years. In contrast, in the control group of non-stroke patients, 9.5% of the individuals developed cancer during the observation period. The latter may represent the natural history of cancer in this age group without any history of stroke. In contrast, in the older age group (> 55 years), our analysis revealed a smaller gap in cancer rates between stroke and non-stroke patients. This finding is in line with the current state of knowledge; strokes in the elderly are mostly caused by vascular risk factors, while in a considerable proportion of young stroke victims, the etiology remains undetermined (Adams et al. 1993; Aigner et al. 2017; Rolfs et al. 2013). Our results might thus support the hypothesis that a malignant disease is potentially involved in the mechanism of stroke, especially among young individuals. Direct evidence needs to be established in further investigations proving a potential hypercoagulability state in young stroke patients diagnosed of cancer subsequently. However, in young stroke victims, screening for cancer can be considered in the immediate diagnostic work-up, as well as after the acute phase, especially in those with an unclear stroke etiology.

One of the strengths of our study is the high number of young stroke patients and the long follow-up period. With 2836 young stroke patients, our study analyzed the largest cohort with such an extended time of subsequent observation (10 years). Furthermore, to avoid bias regarding stroke mimics in TIA, we included only stroke in our analysis; up to 30% of the TIAs cases are stroke mimics rather than real cerebrovascular events (Kozera-Strzelinska et al. 2019; Liberman and Prabhakaran 2017).

However, the study also has several limitations. First, no data were available on the patients' smoking and alcohol status, although these variables can be associated with both stroke and cancer. Second, since the regression used for

propensity scores did not include the identification number of general practices, the distribution of these practices may differ between cases and controls. Third, no information about death was provided, and since both stroke and cancer have a significant impact on survival, this is an important limitation. Finally, it was not possible to identify patients with a stroke of undetermined etiology, which would have enabled us to verify to what extent the cancer may explain strokes in this subgroup.

Conclusion

Our study underlined that a cancer diagnosis after stroke is of particular relevance, especially in young patients, suggesting that the malignant disease may have some implications in the pathophysiology of the acute event.

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Compliance with ethical standards

Conflict of interest All authors report to have no conflicts of interest or competing interests related to the current manuscript.

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