Journal of Stroke and Cerebrovascular Diseases 31 (2022) 106609

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstrokecerebrovasdis

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], Simon Jung, MD[a]

[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
[i] Department of Medical Oncology, Inselspital, Bern University Hospital, and University of Bern, Switzerland

ARTICLE INFO

Article history:
Received 18 April 2022
Revised 8 June 2022
Accepted 16 June 2022

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

ABSTRACT

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 µ/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.

* Corresponding author.
E-mail address: morin.beyeler@insel.ch (M. Beyeler).
# equal contribution

https://doi.org/10.1016/j.jstrokecerebrovasdis.2022.106609

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

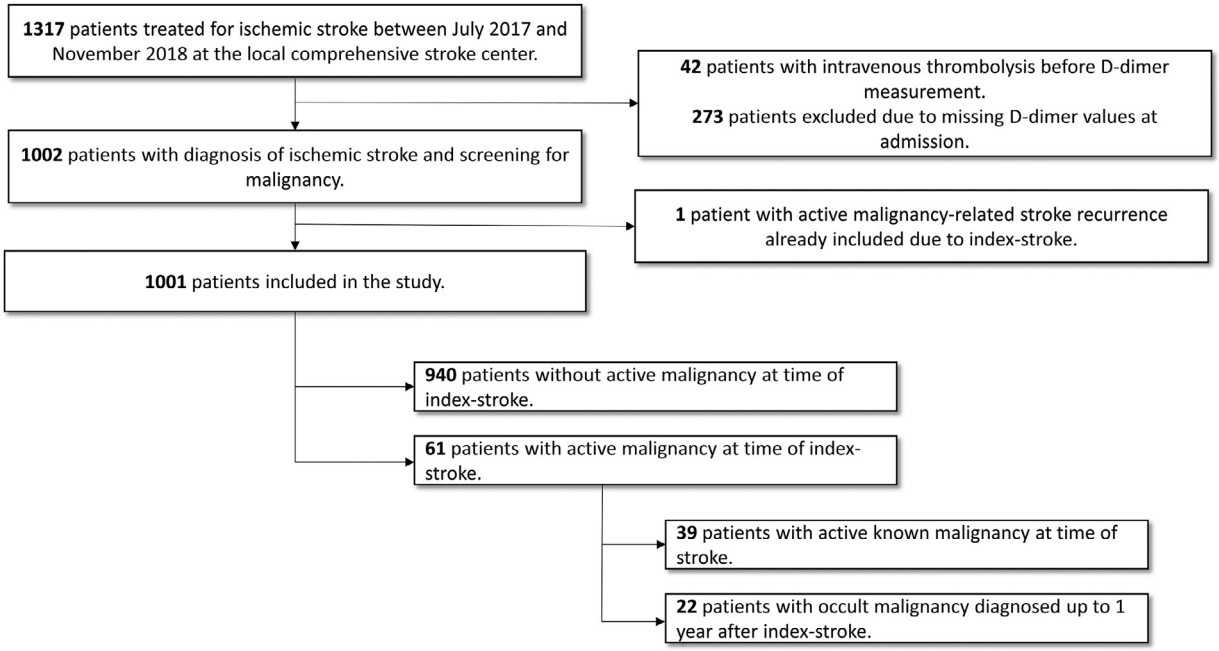

Fig. 1. Study flowchart. This figure shows the process of inclusion and exclusion of patients in the study.

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 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 $\geq$ 77 years, ESUS after initial stroke work-up, multi-territory infarcts, D-dimer level $\geq$ 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 $\geq$ 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

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

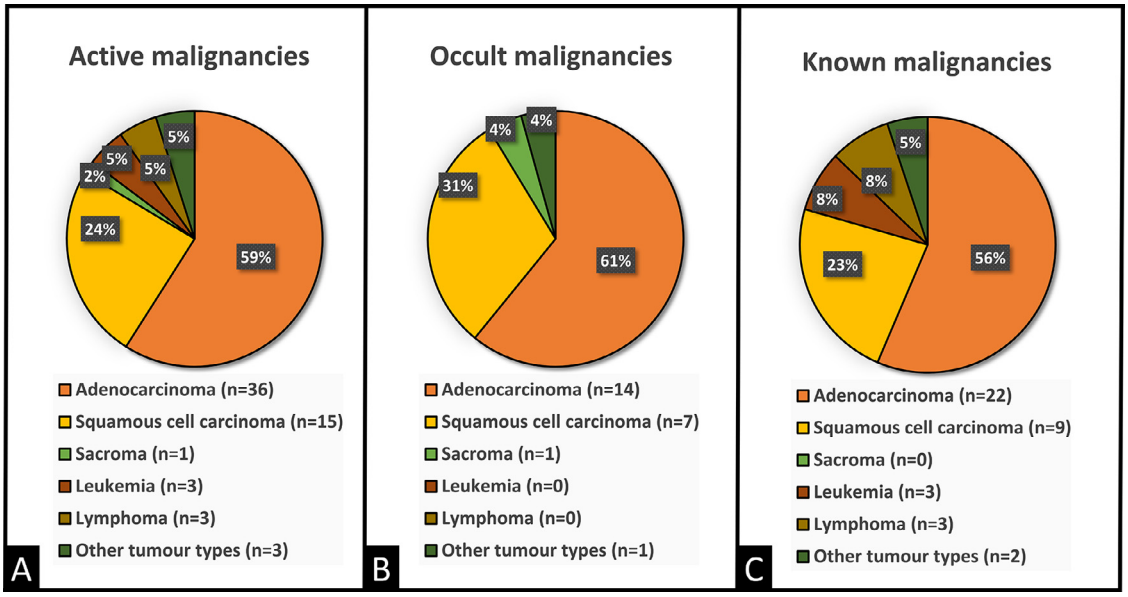

Fig. 2. Distribution of histological types according to the malignancy subgroups. Patients with active malignancy (Fig. 2A), were divided into patients with occult malignancy (Fig. 2B) and patients with active known malignancy (Fig. 2C). No significant difference was observed between occult malignancies 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).

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 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.

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.

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

Funding statement

There was no specific funding for this study.

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.

References

1. Zöller B, Ji J, Sundquist J, Sundquist K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden. *Eur J Cancer*. 2012;48(12):1875–1883. doi:10.1016/j.ejca.2012.01.005.
2. Navi BB, Iadecola C. Ischemic stroke in cancer patients: a review of an underappreciated pathology. *Ann Neurol*. 2018;83(5):873–883. doi:10.1002/ana.25227.
3. Kneihsl M, Enzinger C, Wünsch G, et al. Poor short-term outcome in patients with ischaemic stroke and active cancer. *J Neurol*. 2016;263(1):150–156. doi:10.1007/s00415-015-7954-6.
4. Jung JKK, Roh J. Clinical manifestation of cancer related stroke : retrospective case – control study. Published online 2013:295-301. doi:10.1007/s11060-012-1011-4
5. Nam KW, Kim CK, Kim TJ, et al. D-dimer as a predictor of early neurologic deterioration in cryptogenic stroke with active cancer. *Eur J Neurol*. 2017;24(1):205–211. doi:10.1111/ene.13184.
6. Aarnio K, Joensuu H, Haapaniemi E. Cancer in Young Adults With Ischemic Stroke. Published online 2015:1601-1606. doi:10.1161/STROKEAHA.115.008694
7. Cutting S, Wettengel M, Conners JJ, Ouyang B, Busl K. Three-month outcomes are poor in stroke patients with cancer despite acute stroke treatment. *J Stroke Cerebrovasc Dis*. 2017;26(4):809–815. doi:10.1016/j.jstrokecerebrovasdis.2016.10.021.
8. Lau K, Wong Y, Teo K, et al. Stroke Patients with a Past History of Cancer Are at Increased Risk of Recurrent Stroke and Cardiovascular Mortality. 2014;9(2). doi:10.1371/journal.pone.0088283
9. Dardiotis E, Aloizou AM, Markoula S, et al. Cancer-associated stroke: pathophysiology, detection and management (Review). *Int J Oncol*. 2019;54(3):779–796. doi:10.3892/ijo.2019.4669.
10. Navi BB, Kasner SE, Elkind MSV, Cushman M, Bang OY, Deangelis LM. Cancer and embolic stroke of undetermined source. *Stroke*. 2021(March):1121–1130. doi:10.1161/STROKEAHA.120.032002.
11. Bang OY, Chung JW, Lee MJ, Seo WK, Kim GM, Ahn MJ. Cancer-related stroke: an emerging subtype of ischemic stroke with unique pathomechanisms. *J Stroke*. 2020;22(1):1–10. doi:10.5853/jos.2019.02278.
12. Rioux B, Touma L, Nehme A, Gore G, Keezer MR, Gioia LC. Frequency and predictors of occult cancer in ischemic stroke : a systematic review and meta-analysis. *Int J Stroke*. 2020;0(0):1–8. doi:10.1177/1747493020971104.
13. Cocho D, Gendre J, Boltes A, et al. Predictors of occult cancer in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2015;24(6):1324–1328. doi:10.1016/j.jstrokecerebrovasdis.2015.02.006.
14. Selvik HA, Thomassen L, Bjerkreim AT, Næss H. Cancer-associated stroke: the bergen NORSTROKE study. *Cerebrovasc Dis Extra*. 2015;5(3):107–113. doi:10.1159/000440730.
15. Uemura J, Kimura K, Sibazaki K, Inoue T, Iguchi Y, Yamashita S. Acute stroke patients have occult malignancy more often than expected. *Eur Neurol*. 2010 Published online. doi:10.1159/000316764.
16. Kassubek R, Bullinger L, Kassubek J, et al. Identifying ischemic stroke associated with cancer : a multiple model derived from a case – control analysis. *J Neurol*. 2017;264(4):781–791. doi:10.1007/s00415-017-8432-0.
17. Kim SJ, Park JH, Lee MJ, Park YG, Ahn MJ, Bang OY. Clues to occult cancer in patients with ischemic stroke. *PLoS One*. 2012;7(9):1–8. doi:10.1371/journal.pone.0044959.
18. Sun B, Li Z, Liu L. Clinical and Neuroimaging Features of Acute Ischemic Stroke in Cancer Patients. Published online 2016:292-299. doi:10.1159/000447126
19. Babak B. Navi et al. Cancer and Embolic Stroke of Undetermined Source. 2021;(March):1121-1130. doi:10.1161/STROKEAHA.120.032002
20. Quintas S, Rogado J, Gullón P, et al. Predictors of unknown cancer in patients with ischemic stroke. *J Neurooncol*. 2018;137(3):551–557. doi:10.1007/s11060-017-2741-0.
21. Jiang J, Shang X, Zhao J, et al. Score for predicting active cancer in patients with ischemic stroke: a retrospective study. *Biomed Res Int*. 2021:2021. doi:10.1155/2021/5585206.
22. Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, Kvistad CE. When to screen ischaemic stroke patients for cancer. *Cerebrovasc Dis*. 2018;45(1-2):42–47. doi:10.1159/000484668.
23. Review C, Communication S, Principles G. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent*. 2014;81(3):14–18. doi:10.1093/acprof:oso/9780199241323.003.0025.
24. Frere C, Crichi B, Lejeune M, Spano J, Janus N. Are Patients with Active Cancer and Those with History of Cancer Carrying the Same Risks of Recurrent VTE and Bleeding While on Anticoagulants ? (Table 1):1-9.
25. Khorana A A, Noble S. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism : guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018:1891–1894 Published online. doi:10.1111/jth.14219.
26. Erichsen R, Sværke C, Sørensen HT, Sandler RS, Baron JA. Risk of colorectal cancer in patients with acute myocardial infarction and stroke: A nation-

wide cohort study. *Cancer Epidemiol Biomarkers Prev*. 2013;22(11):1994–1999. doi:10.1158/1055-9965.EPI-13-0444.
27. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2019;37(5):423–438. doi:10.1200/JCO.18.01160.
28. Glassman D, Hignett S, Rehman S, Linforth R, Salhab M. Adjuvant endocrine therapy for hormone-positive breast cancer, focusing on ovarian suppression and extended treatment: An update. *Anticancer Res*. 2017;37(10):5329–5341. doi:10.21873/anticanres.11959.
29. Samarasinghe Venura, Madan Vishal. Nonmelanoma skin cancer. *J Cutan Aesthet Surg*.. 2012(5):3–10 Jan-Mar.
30. Harold P BH, et al. Classification of subtype of acute ischemic stroke. *Stroke*. 1993;24(1).
31. Swaminathan B, Lavados P, Wang Y, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med*.. 2018:2191–2201 Published online. doi:10.1056/NEJMoa1802686.
32. Karli AG, Cz A, Karli MA. The Activity of Malignancy May Determine Stroke Pattern in Cancer Patients. 2015;24(4):778-783. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.11.003
33. Lee E, Nah H, Kwon J, Kang D, Kwon SU, Kim JS. Ischemic stroke in patients with cancer : Is it different from usual strokes ? 2014;9(June):406-412. https://doi.org/10.1111/ijs.12124
34. Xie X, Chen L, Zeng J. Clinical features and biological markers of lung cancer-associated stroke. Published online 2016. doi:10.1177/0300060516666398
35. Tomoyuki Kono, Toshiho Ohtsuki, Naohisa Hosomi IT, Shiro Aoki, Yoshimasa Sueda, Kayoko Ishihara TN, Matsumoto TY and M. Cancer-associated ischemic stroke is associated with elevated D -dimer and fibrin degradation product levels in acute ischemic. Published online 2012:468-474. doi:10.1111/j.1447-0594.2011.00796.x
36. Guo YJ, Chang MH, Chen PL, Lee YS, Chang YC, Liao YC. Predictive value of plasma d-dimer levels for cancer-related stroke: a 3-year retrospective study. *J Stroke Cerebrovasc Dis*. 2014;23(4):e249–e254. doi:10.1016/j.jstrokecerebrovasdis.2013.10.022.
37. Bang OY, Chung J, Lee J, Seo W, Kim G, Ahn M. Cancer-related stroke : an emerging subtype of ischemic stroke with unique pathomechanisms. 2020;22(1):1-10.
38. Rosenberg J, Do D, Cucchiara B, Mess SR. D-dimer and Body CT to Identify Occult Malignancy in Acute Ischemic Stroke. 2020;29(12):1-6. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105366