



CLINICAL INVESTIGATIVE STUDY

Chronic cerebral infarctions and white matter lesions link to long-term survival after a first ischemic event: A cohort study

Marina Schilter¹ | Alessandra Epstein¹ | Jan Vynckier¹ | Adnan Mujanovic² |
Nebiyat Filate Belachew² | Morin Beyeler¹ | Bernhard Siepen¹ | Martina Goeldlin¹ |
Adrian Scutelnic¹ | David Julian Seiffge¹ | Simon Jung¹ | Jan Gralla² |
Tomas Dobrocky² | Marcel Arnold¹ | Johannes Kaesmacher² | Urs Fischer³ |
Thomas Raphael Meinel¹

¹Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

²Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

³Department of Neurology, Basel University Hospital, University of Basel, Bern, Switzerland

Correspondence

Thomas Meinel, Department of Neurology,
University of Bern, Freiburgstrasse 8,
CH-3010 Bern, Switzerland.
Email: thomas.meinel@insel.ch

Funding information

Bangerter Rhyner Foundation; Swiss National
Foundation; Bangerter-Rhyner-Foundation;
Swiss Stroke Society; Mittelbauvereinigung
der Universität Bern; Swiss Academy of
Medical Sciences (SAMS), Grant/Award
Number: YTCR 03/19; University of Bern
(Strategische Forschungsförderung)

Abstract

Background and Purpose: To investigate the association of different phenotypes, count, and locations of chronic covert brain infarctions (CBI) with long-term mortality in patients with first-ever manifest acute ischemic stroke (AIS) or transient ischemic attack (TIA). Additionally, to analyze their potential interaction with white matter hyperintensities (WMH) and predictive value in addition to established mortality scores.

Methods: Single-center cohort study including consecutive patients with first-ever AIS or TIA with available MRI imaging from January 2015 to December 2017. Blinded raters adjudicated CBI phenotypes and WMH (age-related white matter changes score) according to established definitions. We compared Cox regression models including prespecified established predictors of mortality using Harrell's C and likelihood ratio tests.

Results: A total of 2236 patients (median [interquartile range] age: 71 [59-80] years, 43% female, National Institutes of Health Stroke Scale: 2 [1-6], median follow-up: 1436 days, 21% death during follow-up) were included. Increasing WMH (per point adjusted Hazard Ratio [aHR] = 1.29 [1.14-1.45]), but not CBI (aHR = 1.21 [0.99-1.49]), were independently associated with mortality. Neither CBI phenotype, count, nor location was associated with mortality and there was no multiplicative interaction between CBI and WMH ($p > .1$). As compared to patients without CBI or WMH, patients with moderate or severe WMH and additional CBI had the highest hazards of death (aHR = 1.62 [1.23-2.13]). The Cox regression model including CBI and WMH had a small but significant increment in Harrell's C when compared to the model including 14 clinical variables (0.831 vs. 0.827, $p < .001$).

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Journal of Neuroimaging* published by Wiley Periodicals LLC on behalf of American Society of Neuroimaging.



Discussion: WMH represent a strong surrogate biomarker of long-term mortality in first-ever manifest AIS or TIA patients. CBI phenotypes, count, and location seem less relevant. Incorporation of CBI and WMH slightly improves predictive capacity of established risk scores.

KEYWORDS

acute ischemic stroke, covert brain infarction, mortality, TIA, white matter hyperintensities

INTRODUCTION

White matter hyperintensities (WMH) and covert brain infarctions (CBI) have been shown to be associated with increased risk for subsequent death both in patients without¹⁻³ and with⁴⁻¹² manifest acute ischemic stroke (AIS).

However, little is known about potential differences regarding phenotypes, count, or locations of CBI. Those phenotypes include markers of small-vessel disease such as WMH and lacunes,¹³ but also non-small-vessel disease phenotypes including cortical lesions.^{14,15} Additionally, there is a close association of CBI and WMH,¹⁴ but potential interactions between these neuroimaging biomarkers regarding mortality have not been addressed.

Therefore, this study aimed to investigate the association of different phenotypes, count, and locations of CBI and WMH as well as the interaction of both biomarkers with long-term mortality in patients with AIS or transient ischemic attack (TIA). Furthermore, we wanted to test the hypothesis that the addition of CBI and WMH to established stroke mortality predictors enhances their predictive performance.

METHODS

Study cohort

This retrospective observational study uses data from a prospective registry collected at a single comprehensive stroke center. We included consecutive, first-ever manifest AIS patients between January 1, 2015 and December 31, 2017 who had MRI either on admission or during the first week of hospitalization for the index event. We excluded patients with CT imaging only, patients actively vetoing the use of their health data for research, and patients with diagnoses potentially causing brain lesions that could mimic CBI (see Figure 1 for full exclusion criteria). We chose to exclude CT patients, since phenotypes of CBI¹⁶ cannot be reliably assessed by CT, whereas MRI can.^{17,18}

Standard protocol approvals, registrations, and patient consents

Bern ethics committee approved this study (reference ID 2020-01696).

Imaging

Type of MRI, used protocols, and interrater reliability have previously been described.¹⁴ Importantly, MRI used different field strengths (1.5 and 3 Tesla). Phenotypes of CBI and WMH were rated as reported earlier by two experienced vascular neurologists with more than 5 years of experience blinded to the outcome.¹⁴ Briefly, CBI phenotypes included lacunes (of presumed vascular origin), but also non-small-vessel disease phenotypes such as combined gray and white matter lesions, isolated gray matter lesions, and large subcortical (non-cavitary) infarcts. WMH were rated according to the age-related white matter changes (ARWMC) scale.¹⁹ The main rationale behind this classification is to differentiate between lesions that correspond to ischemic injury due to small-vessel disease and ischemic injury likely to be caused by embolism from proximal sources (see Vynckier et al.¹⁴ for details and examples).

Locations of CBIs were mapped in the following anatomical locations: basal ganglia (deep nuclei, including thalamus), subcortical supratentorial (white matter only), cortical supratentorial, cerebellar, and brainstem. Also, the total count of CBI was adjudicated (none, one, two, three, or more than three). Agreement for assessment of phenotypes and location was analyzed using Cohen's kappa statistics to report interrater agreement.

Data collection

Baseline data were extracted from the local stroke registry including laboratory values on admission. The primary outcome of this study was all-cause mortality. The information on the vital status was extracted from the Swiss Population Registry in January 2021. The follow-up time was defined as the interval between the index stroke and the date of extraction of the vital status. Patients lost to follow-up (1.3%) were excluded.

Statistical analysis

Baseline differences were assessed between patients with and without fatal outcome during follow-up. Descriptive statistics using the Fisher's exact test and the Wilcoxon rank-sum were reported as number and percentage for categorical variables and median and interquartile

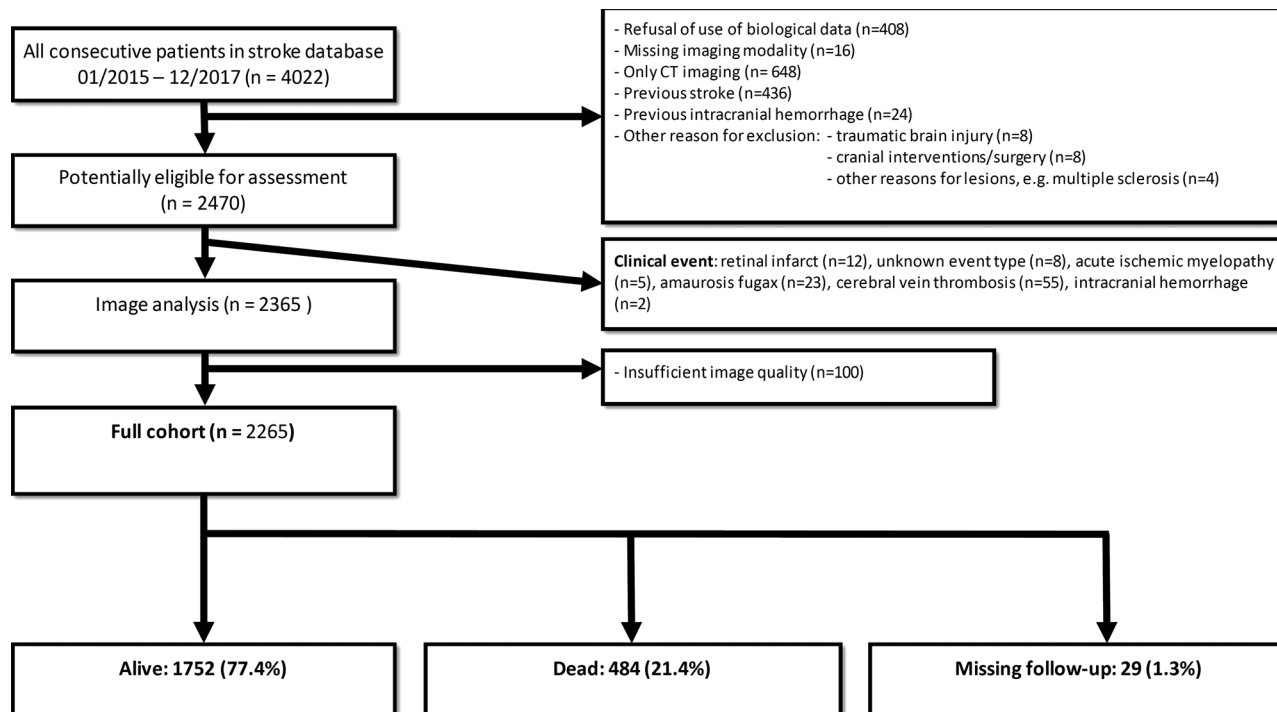


FIGURE 1 Study flow chart: Excluded patients had more severe stroke and more cardiovascular risk factors. *n*, number

range for continuous variables. Kaplan-Meier estimates with log-rank test were used to calculate differences in the mortality hazard rate over the follow-up timeframe and differences according to neuroimaging strata. We calculated unadjusted hazard ratios (HR) and adjusted hazard ratios (aHR) for association between CBI and WMH and death from cox regression (right-censored data) with adjustment for available baseline confounders (no time dependency) reported earlier in established death prediction algorithms including the I-Score,²⁰ Get with the Guidelines,²¹ preadmission comorbidities, level of consciousness, age, and neurological deficit scores.²²

Those included age on admission, sex, National Institutes of Health Stroke Scale on admission, TIA (as compared to AIS), prestroke independency (modified Rankin scale 0-2), atrial fibrillation, hypertension, coronary heart disease, diabetes, hyperlipidemia, smoking, peripheral artery disease, active cancer, creatinine, and magnetic field strength (1.5 vs. 3.0 Tesla). To evaluate the influence of CBI on the association between WMH and death, an interaction term was used (ie, WMH×CBI). Predictive capacity is presented as Harrel's C (95% confidence interval). Likelihood ratio test was used to compare improvement in predictive capacity of the models with and without including imaging biomarkers. Quantitative variables were kept as such without grouping. All statistical analyses were performed with Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) including the table 1_mc and somersd²³ packages. We performed full case analysis without imputation and a significance level of .05 was used without adjustment for multiple testing. Due to limited data on CBI phenotypes, no study size calculation was possible. Sensitivity analysis was done for TIA patients only and patients with a detectable vessel occlusion on brain imaging.

Data availability

Investigators may request access to anonymized individual patient data and redacted documents including do-files. Prior to use of the data, proposals need to be approved by Bern ethics committee and a signed data sharing agreement will then be approved.

RESULTS

A total of 3374 out of 4022 (84%) patients had MRI available during the study timeframe. Of those, 2265 patients with first clinically evident AIS fulfilled the in- and exclusion criteria (see Figure 1 for flow chart). Patients not included in the study were older, had more severe stroke, more often atrial fibrillation, and more cardiovascular risk factors. Only 29 patients (1.3%) were lost to follow-up, since foreign patients were not captured in the national mortality registry. There were no differences in baseline variables between patients with and without available mortality information. Median age was 71 (59-80) years, 43% were female, median National Institutes of Health Stroke Scale was 2 (1-6). Median follow-up duration was 4 years (48 months) with a total follow-up time of 8179 patient-years. A total of 484 deaths (21%) occurred during follow-up.

The interrater agreement was substantial for assessment of phenotypes (82%, kappa = .70, $p < .001$) and location of CBI (agreement 89%, kappa = .74, $p < .001$).

Patients who died during follow-up were older, more often women, and had more cardiovascular risk factors and active cancer (Table 1 for full baseline differences).

**TABLE 1** Baseline characteristics according to death during follow-up

	Alive (N = 1752)	N available	Death (N = 484)	N available	p
Epidemiology					
Age (years) at admission, median (IQR)	67.7 (56.4-76.7)	1752	81.5 (73.8-85.9)	484	<.001
Female sex, N (%)	717 (40.9%)	1752	232 (48.0%)	484	.008
National Institutes of Health Stroke Scale on admission, median (IQR)	2 (0-5)	1597	6 (2-13)	431	<.001
TIA as compared to stroke, N (%)	377 (21.5%)	1752	54 (11.2%)	484	<.001
Follow-up time, months, median (IQR)	52 (43-60)	1752	10 (1-29)	484	<.001
Prestroke living at home, N (%)	1,571 (97.6%)	1609	382 (87.0%)	439	<.001
Admission systolic blood pressure, mmHg median (IQR)	160 (139-178)	1595	161 (140-180)	431	.35
Medical history of cardiovascular risk factors					
Atrial fibrillation/flutter, N (%)	243 (15.1%)	1610	159 (35.8%)	444	<.001
Hypertension, N (%)	1005 (62.4%)	1610	356 (80.5%)	442	<.001
Coronary heart disease, N (%)	213 (13.2%)	1610	107 (24.2%)	443	<.001
Diabetes mellitus, N (%)	233 (14.5%)	1610	117 (26.5%)	442	<.001
Hyperlipidemia, N (%)	882 (54.8%)	1610	242 (54.8%)	442	.99
Smoking, N (%)	402 (25.2%)	1597	80 (18.9%)	424	.007
Peripheral artery disease, N (%)	55 (3.4%)	1610	35 (7.9%)	443	<.001
Active cancer, N (%)	27 (1.7%)	1607	50 (11.3%)	442	<.001
Etiology of the event					
Cardiac embolism, N (%)	266 (19.8%)	1344	137 (36.1%)	408	<.001
Large artery atherosclerosis, N (%)	181 (13.5%)		51 (13.5%)		
Small vessel disease, N (%)	152 (11.3%)		46 (12.1%)		
Other determined etiology, N (%)	48 (3.6%)		28 (7.4%)		
Cervical artery dissection, N (%)	89 (6.6%)		3 (0.8%)		
Persistent foramen ovale, N (%)	56 (4.2%)		1 (0.3%)		
Unknown, N (%)	552 (41.1%)		113 (29.8%)		
Laboratory values					
Glucose, mmol/L median (IQR)	6.3 (5.6-7.4)	932	6.8 (5.88-8.4)	325	<.001
Creatinine, μ mol/L median (IQR)	78 (65-90)	1599	88 (71-111)	440	<.001
Imaging Biomarkers					
White matter hyperintensity score, median (IQR)	1 (0-2)	1751	2 (1-2)	487	<.001
Any CBI, N (%)	581 (33.2%)	1752	237 (49.0%)	484	<.001

Abbreviations: CBI, chronic covert brain infarction; IQR, interquartile range; N, number; TIA, transient ischemic attack; WMH, white matter hyperintensities.

Patients with WMH were more likely to die during follow-up ($p < .001$). Of those without WMH (ARWMC 0), only 9% died during follow-up and rates increased with increasing WMH: ARWMC 1, 20%; ARWMC 2, 29%; ARWMC 3, 49%. This resulted in an unadjusted HR for death for one point increase in ARWMC rating scale of 1.81 (1.66-1.99; Figure 2B).

Similarly, patients with any CBI were more likely to die during follow-up (29% vs. 17%, $p < .001$; Figure 2A). This resulted in an unadjusted HR for death for any CBI of 1.79 (1.49-2.14). When combining those biomarkers, patients without CBI and only minimal WMH (ARWMC 0 or 1) were least likely to die (13%), followed by patients

with any CBI but no or minimal WMH (ARWMC 0 or 1; 22%) and moderate or severe WMH (ARWMC 2 or 3; 33%). Mortality was highest for patients with moderate or severe WMH (ARWMC 2 or 3) and additional CBI (37%, $p < .001$; Figure 3).

After adjustment for confounders, WMH remained associated with increased risk of death during follow-up (aHR = 1.29 [1.14-1.45]) with highest rates observed in ARWMC 3 as compared to the reference ARWMC 0 (aHR = 2.29 [1.53-3.43]). For the presence of any CBI, this association did not reach statistical significance (aHR = 1.21 [0.99-1.49]). There was no multiplicative interaction between CBI and WMH ($p > .1$) when incorporating the interaction term in the model.

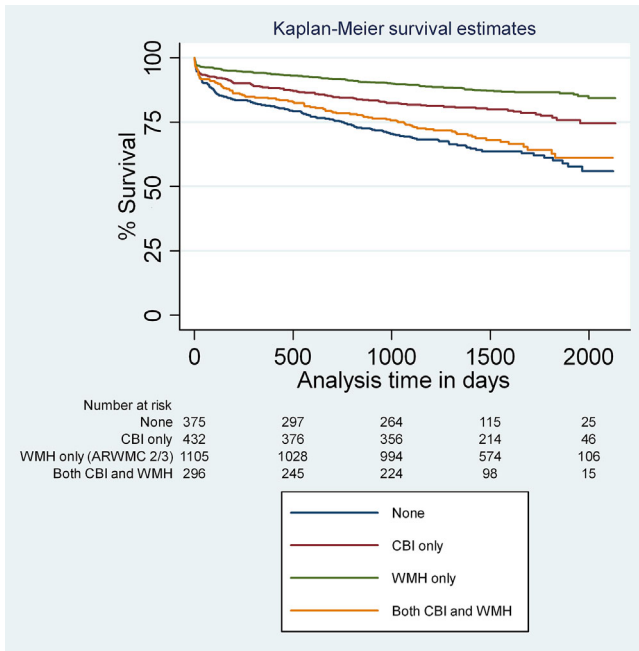


FIGURE 2 Unadjusted Kaplan-Meier survival estimates according to presence of any CBI and ARWMC. (A) Survival estimates according to presence of any CBI. (B) Survival estimates according to severity of WMH (ARWMC). Analysis time in days after index stroke. CBI, chronic covert brain infarction; WMH, white matter hyperintensities; ARWMC, age-related white matter changes score

Unadjusted HR for death were highest for severe WMH without additional CBI, or when multiple CBI phenotypes were present (see Table 2). After adjustment, neither phenotype nor location was associ-

ated with death during follow-up. There was no clear dose dependency according to CBI count and the association only reached significance for patients with three CBIs in the adjusted analysis (Table 2).

Adding CBI and WMH into the prognostic models modestly improved its predictive performance (Harrel's C = 0.831 [0.813-0.849]) as compared to models without the imaging biomarkers (Harrel's C = 0.827 [0.810-0.845]; *p*-value for likelihood ratio test <.001).

When only analyzing TIA patients, the association of WMH with increased rates of death was even more pronounced in the unadjusted analysis with increasing unadjusted rates as compared to the reference ARWMC 0: ARWMC 1 (HR = 4.0 [0.94-17.5]), ARWMC 2 (HR = 12 [2.8-52]), and ARWMC 3 (HR = 17 [3.9-77]). However, the association was not significant after adjustment: ARWMC 1 (aHR = 1.06 [0.23-5.02]), ARWMC 2 (aHR = 1.3 [0.27-7.13]), and ARWMC 3 (aHR = 1.76 [0.35-9.35]). Presence of any CBI was also associated with increased hazards of death in TIA patients in unadjusted (HR = 3.21 [1.83-5.62]) but not adjusted analysis (aHR = 1.6 [0.85-3.07]). Point estimates for the association of the imaging biomarkers with increased rates of death were similar when the analysis was restricted to patients with (aHR for CBI = 1.18 [0.91-1.54], aHR per point ARWMC = 1.34 [1.14-1.57]) and without (aHR for CBI = 1.21 [0.87-1.70], aHR per point ARWMC = 1.22 [1.00-1.49]) detectable vessel occlusion.

DISCUSSION

This study exploring the association of CBI and WMH with long-term mortality after AIS or TIA has the following main findings:

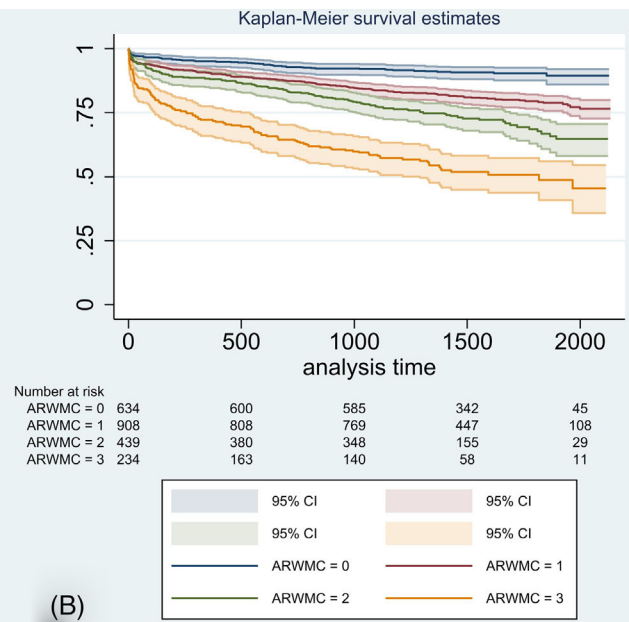
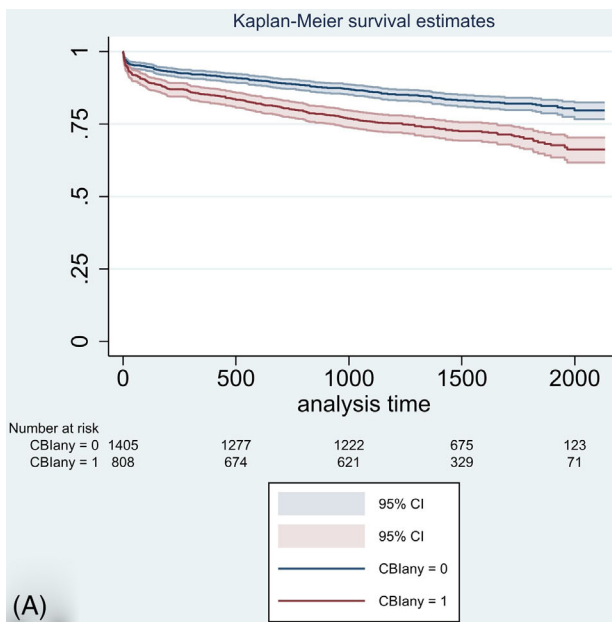


FIGURE 3 Unadjusted Kaplan-Meier survival estimates according to presence of CBI and/or moderate to severe WMH. None: No chronic CBI as well as no or only minimal WMH (ARWMC 0 or 1); CBI only: presence of any chronic CBI and no or minimal WMH (ARWMC 0 or 1); WMH only: moderate or severe WMH (ARWMC 2 or 3) without additional CBI; Both CBI and WMH: moderate or severe WMH (ARWMC 2 or 3) with additional CBI. Analysis time in days after index stroke. WMH, white matter hyperintensities; CBIany, presence of any phenotype of chronic covert brain infarction; ARWMC, age-related white matter changes score; CI, confidence interval

**TABLE 2** Unadjusted and adjusted hazard rates for all-cause death according to imaging biomarkers

	N (% of all patients)	Unadjusted HR	Adjusted HR
Any CBI		1.79, 1.49-2.14	1.21, 0.99-1.49
Phenotypes of CBI			
Lacunar	268 (12%)	2.33, 1.76-3.08	1.19, 0.84-1.69
Large noncavitatory subcortical	38 (2%)	1.82, 0.90-3.72	1.07, 0.49-2.35
Isolated cortical	75 (3%)	1.70, 1.01-2.84	0.96, 0.54-1.71
Combined gray and white matter	134 (6%)	2.24, 1.54-3.25	0.93, 0.60-1.45
Multiple CBI phenotypes	307 (14%)	2.80, 2.14-3.58	1.17, 0.83-1.64
Pure severe WMH (ARWMC ≥ 2)	303 (14%)	2.84, 2.19-3.67	^a
Location of CBI			
Subcortical, any	286 (13%)	1.60, 1.25-1.97	1.15, 0.84-1.56
Cortical, any	282 (13%)	1.49, 1.18-1.87	0.90, 0.69-1.22
Cerebellar, any	367 (16%)	1.35, 1.09-1.67	1.10, 0.84-1.49
Brainstem, any	26 (1%)	0.66, 0.25-1.77	0.68, 0.22-2.04
Basal Ganglia, any	110 (5%)	1.40, 0.99-2.00	1.17, 0.76-1.76
Number of CBIs			
One	442 (20%)	1.74, 1.39-2.18	1.20, 0.93-1.55
Two	209 (9%)	1.67, 1.24-2.26	1.16, 0.80-1.63
Three	84 (4%)	2.69, 1.88-3.85	1.92, 1.28-2.90
More than three	83 (4%)	1.45, 0.91-2.31	1.00, 0.58-1.68
WMH			
ARWMC 0 (reference)	636 (29%)		
ARWMC 1	910 (41%)	2.18, 1.63-2.93	1.27, 0.89-1.79
ARWMC 2	448 (20%)	3.33, 2.44-4.53	1.30, 0.89-1.90
ARWMC 3	236 (11%)	6.74, 4.92-9.24	2.29, 1.53-3.43
ARWMC per point increase		1.81, 1.66-1.99	1.29, 1.14-1.45
Combination of CBI and WMH			
None (reference)	1111 (50%)		
CBI only	436 (20%)	1.73, 1.33-2.24	1.24, 0.93-1.65
WMH only (ARWMC 2/3)	303 (14%)	2.84, 2.19-3.68	1.29, 0.96-1.74
Both CBI and WMH (ARWMC 2/3)	381 (17%)	3.30, 2.61-4.17	1.62, 1.23-2.13

Abbreviations: ARWMC, age-related white matter changes severity scale; CBI, chronic covert brain infarction; HR, hazard ratio; N, number; WMH, white matter hyperintensities.

^aCould not be calculated due to low number in the model. Percentage of 2236 patients overall.

1. In unadjusted analysis, both WMH and CBI were associated with long-term mortality and patients with severe WMH have a 5-year life expectancy of about 50%.
2. After adjustment, only WMH remained significantly associated with mortality, hence WMH seems more useful for determining prognosis regarding long-term mortality than CBI including its phenotypes, total count, and different locations.
3. No multiplicative interaction of both biomarkers was found.
4. Adding CBI and WMH into established mortality prediction scores modestly improved predictive performance.

The appeal of both biomarkers is that brain imaging is anyway performed and those brain frailty markers can easily be assessed without

the need for advanced postprocessing. Although WMH can be reliably assessed on both routine MRI and CT, reliable CBI phenotyping warrants MRI.¹⁵

There are conflicting findings regarding CBI and mortality with some studies showing no significant association such as IST-3 (odds ratio = 1.05 [0.87-1.26]),¹⁰ the Helsinki Young Stroke Registry,¹² and a Dutch single-center cohort.²⁴ However, the Prevention Regimen for Effectively Avoiding Second Strokes Imaging Substudy found an increased unadjusted mortality risk in patients with CBI as compared to patients without CBI over a median follow-up of 2.5 years (6.8% vs. 3.2%; $p = .02$).²⁵

Although in patients without manifest cerebrovascular disease, CBI may reflect a high-risk cerebrovascular condition, not fully explained



by other independent risk factors,²⁶ this does not seem to apply to patients who already suffered an AIS or TIA. In our adjusted models, neither CBI nor any phenotype or location remained significantly associated with death, although the point estimates indicate higher risk and the study might have been underpowered to reach significance for this association. Nevertheless, CBI, its phenotypes, and locations seem to be less useful in determining prognosis regarding long-term mortality than WMH.

Our results confirm that WMH are a strong surrogate biomarker for long-term death in patients with stroke.⁴⁻¹² The association follows a dose-response pattern, with severe WMH associated with an overall 5-year survival of about 50%.^{6,7} It is likely that small vessel disease contributes to excess mortality by its manifestations of gait problems, falls, psychiatric manifestations, dementia, and frailty. Knowledge of this association may aid prognostication, and serve as a surrogate if detailed clinical information cannot be obtained. However, the limitations of this observational dataset should be kept in mind as it is possible that clinicians were already influenced by those brain frailty neuroimaging markers when withdrawing treatment or pursuing less active treatment in such patients.

The increase in short-term risk of death after index stroke might be due to faster infarct growth and larger infarct volumes in stroke patients with severe WMH.^{27,28} Additionally, severe WMH are a well-known risk factor for symptomatic intracerebral hemorrhage after intravenous thrombolysis.²⁹ Additionally, patients with WMH are at higher risk for delirium, which represents a risk factor for early mortality.^{30,31}

However, the Kaplan-Meier curves also show a long-term increased risk of death according to WMH severity. Ryu et al. found that the association of WMH volume with mortality was attributable to mainly nonvascular causes.¹¹ However, given the high-risk vascular profile of patients with severe WMH, also vascular events are likely to contribute to all-cause mortality in the long term.^{14,32} Fittingly, brain-related death and recurrent AIS were found to represent the dominant causes of death in patients with WMH.⁷ Additionally, WMH have also been shown to impair cognitive reserve as well as other brain networks resulting in dementia with its associated complications.^{33,34} This potentially results in delayed rehabilitation failure and mid- and long-term adverse outcomes.

Our study expands those findings to patients with TIA, in whom the overall prognosis was better, but still a dose-response association of WMH with mortality could be found, more prominent in the midterm and long term and less in the early phase after the index event.

Our data confirm several other independent predictors of poor post stroke survival including age, stroke severity, and several cardiovascular risk factors, but also other factors currently not consistently used in the risk prognostication tools considered in this study, such as active cancer and renal function.

Although other studies have found no incremental discrimination improvement of cerebral small-vessel disease markers for functional outcome,³⁵ our study showed that incorporation of those markers modestly improves established mortality risk scores. A review regarding this topic concluded that neuroimaging markers including CBI were

poor prognostic markers for several outcomes including long-term functional outcome.³⁶ However, our data and other high-quality studies indicate that subcortical WMH seem to be a powerful surrogate parameter for multiple outcome parameters, especially death.^{5,7,8,10} Further studies and prospective validation are, however, necessary, before clinicians can correctly implement the information of brain frailty markers into individual treatment decisions.³⁷ In upcoming trials, patients should be specifically addressed according to WMH severity, and WMH should be considered as a relevant confounder and potential effect modifier of treatment approaches.

Our study has several strengths including (1) a large, prospectively collected sample. (2) Image reading was done harmonized according to recent definitions and with blinded assessors skilled in stroke imaging. (3) Data completeness was excellent (99% for death) and the median follow-up time was 4 years. (4) CBI phenotyping could be performed with the gold-standard MRI in 83% of patients during the study timeframe.

Obviously, our study has also several limitations: (1) The statistical analysis was retrospective and therefore prone to bias. (2) Field strength of the MRI was heterogeneous and due to a low rate of high-field MRI (3 or 7 Tesla), we could not analyze cortical microinfarcts and the pattern of WMH was not scored, which might also be important.³⁸ Nevertheless, all biomarkers assessed in this study are reliably detected on both 1.5 and 3 Tesla MRI. (3) Imaging acquisition parameters were somewhat heterogeneous throughout the study period, but this might also assure feasibility and generalizability in external centers. (4) Our study was limited to patients without a history of stroke, and we excluded patients with only CT imaging or poor image quality. Hence, the findings might not be applicable to those patients who are unable to undergo MRI due to more severe stroke, vomiting, agitation, pacemakers, or frailty. (5) Cause of death was unavailable for this analysis, so we can only speculate whether some of the deaths might be preventable by more aggressive secondary prevention. (6) Some potentially important confounders such as therapy withdrawal (eg, those with active cancer or with large infarcts) were not available; however, the excess mortality was not restricted to the first months after stroke. (7) Information on acute therapy, therapy at discharge, and recurrent events was unavailable, hence no inference on potential treatment options to reduce mortality is possible.

In conclusion, WMH are a more suitable surrogate marker than CBI for long-term mortality after stroke or TIA than CBI. Patients with severe WMH have a life expectancy of around 50% at 5 years after the index event. CBI including its phenotypes and different locations are less useful in determining prognosis regarding long-term mortality. Adding CBI and WMH into established mortality prediction scores modestly improved predictive performance. Prospective studies need to disentangle the contributing etiologic pathways and clarify whether novel treatment approaches might be able to reduce the high mortality.

ACKNOWLEDGEMENTS AND DISCLOSURES

Dr. Meinel reports research support from the Bangerter Rhyner Foundation, Swiss National Foundation, and the Swiss Heart Foundation. Dr. Goeldlin reports grants from Bangerter-Rhyner-Foundation,



Swiss Stroke Society, Mittelbauvereinigung der Universität Bern, and a congress grant from Pfizer (all outside the submitted work). The authors declare no conflict of interest.

Open access funding provided by Inselspital Universitatsspital Bern.

ORCID

Thomas Raphael Meinel  <https://orcid.org/0000-0002-0647-9273>

REFERENCES

- Debette S, Schilling S, Duperron MG, et al. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol.* 2019;76:81–94.
- Gutierrez J, Gil-Guevara A, Ramaswamy S, et al. Classification of covert brain infarct subtype and risk of death and vascular events. *Stroke.* 2020;51:90–8.
- Kent DM, Leung LY, Zhou Y, et al. Association of silent cerebrovascular disease identified using natural language processing and future ischemic stroke. *Neurology.* 2021;97:e1313–21.
- Baik M, Kim K, Yoo J, et al. Differential impact of white matter hyperintensities on long-term outcomes in ischemic stroke patients with large artery atherosclerosis. *PLoS ONE.* 2017;12:1–13.
- Georgakis MK, Duering M, Wardlaw JM, et al. WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis. *Neurology.* 2019;92:E1298–308.
- Hasan TF, Barrett KM, Brott TG, et al. Severity of white matter hyperintensities and effects on all-cause mortality in the Mayo Clinic Florida Familial Cerebrovascular Diseases Registry. *Mayo Clin Proc.* 2019;94:408–16.
- Oksala NKJ, Oksala A, Pohjasvaara T, et al. Age related white matter changes predict stroke death in long term follow-up. *J Neurol Neurosurg Psychiatry.* 2009;80:762–6.
- Appleton JP, Woodhouse LJ, Adami A, et al. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology.* 2020;94:E439–52.
- Song TJ, Kim J, Song D, et al. Total cerebral small-vessel disease score is associated with mortality during follow-up after acute ischemic stroke. *J Clin Neurol.* 2017;13:187–95.
- Wardlaw JM, Sandercock P, Cohen G, et al. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third international stroke trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet Neurol.* 2015;14:485–96.
- Ryu WS, Schellingerhout D, Hong KS, et al. White matter hyperintensity load on stroke recurrence and mortality at 1 year after ischemic stroke. *Neurology.* 2019;93:E578–89.
- Putala J, Haapaniemi E, Kurkinen M, et al. Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. *Neurology.* 2011;76:1742–9.
- Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12:822–38.
- Vynckier J, Kaesmacher J, Wardlaw JM, et al. Phenotypes of chronic covert brain infarction in patients with first-ever ischemic stroke: a cohort study. *Stroke.* 2022;53:558–68.
- Fanning JP, Wesley AJ, Wong AA, et al. Emerging spectra of silent brain infarction. *Stroke.* 2014;45:3461–71.
- Meinel TR, Kaesmacher J, Roten L, et al. Covert brain infarction. *Stroke.* 2020;51:2597–606.
- Hanning U, Sporns PB, Schmidt R, et al. Quantitative rapid assessment of leukoaraiosis in CT: comparison to gold standard MRI. *Clin Neuroradiol.* 2019;29:109–15.
- Chen L, Jones ALC, Mair G, et al. Rapid automated quantification of cerebral leukoaraiosis on CT images: a multicenter validation study. *Radiology.* 2018;288:573–81.
- Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke.* 2001;32:1318–22.
- Sapostnik G, Kapral MK, Liu Y, et al. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation.* 2011;123:739–49.
- Smith EE, Shobha N, Dai D, et al. Risk score for in-hospital ischemic stroke mortality derived and validated within the get with the guidelines-stroke program. *Circulation.* 2010;122:1496–504.
- O'Donnell MJ, Fang J, D'Uva C, et al. The PLAN score: a bedside prediction rule for death and severe disability following acute ischemic stroke. *Arch Intern Med.* 2012;172:1548–56.
- Newton RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *Stata J.* 2010;10:339–58.
- Boon A, Lodder J, Van RLH, et al. Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke relationship with index-stroke subtype, vascular risk factors, and mortality. *Stroke.* 1994;25:2384–90.
- Weber R, Weimar C, Wanke I, et al. Risk of recurrent stroke in patients with silent brain infarction in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) imaging substudy. *Stroke.* 2012;43:350–5.
- Vermeer SE, Longstreth WT, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol.* 2007;6:611–9.
- Henninger N, Khan MA, Zhang J, et al. Leukoaraiosis predicts cortical infarct volume after distal middle cerebral artery occlusion. *Stroke.* 2014;45:689–95.
- Ay H, Arsava EM, Rosand J, et al. Severity of leukoaraiosis and susceptibility to infarct growth in acute stroke. *Stroke.* 2008;39:1409–13.
- Kongbunkiat K, Wilson D, Kasemsap N, et al. Leukoaraiosis, intracerebral hemorrhage, and functional outcome after acute stroke thrombolysis. *Neurology.* 2017;88:638–45.
- Nitchingham A, Kumar V, Shenkin S, et al. A systematic review of neuroimaging in delirium: predictors, correlates and consequences. *Int J Geriatr Psychiatry.* 2018;33:1458–78.
- Oldenbeuving AW, De Kort PLM, Jansen BPW, et al. Delirium in the acute phase after stroke: incidence, risk factors, and outcome. *Neurology.* 2011;76:993–9.
- Staals J, Makin SDJ, Doubal FN, et al. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology.* 2014;83:1228–34.
- Valdés Hernández MdC, Booth T, Murray C, et al. Brain white matter damage in aging and cognitive ability in youth and older age. *Neurobiol Aging.* 2013;34:2740–7.
- Brickman AM, Siedlecki KL, Muraskin J, et al. White matter hyperintensities and cognition: testing the reserve hypothesis. *Neurobiol Aging.* 2011;32:1588–98.
- Coutureau J, Asselineau J, Perez P, et al. Cerebral small vessel disease MRI features do not improve the prediction of stroke outcome. *Neurology.* 2021;96:e527–37.
- Kim BJ, Lee SH. Prognostic impact of cerebral small vessel disease on stroke outcome. *J Stroke.* 2015;17:101–10.
- Yassi N, Flicker L, Campbell BCV. Brain frailty and small vessel disease for stroke outcome prediction: are we there yet? *Neurology.* 2020;94:191–2.
- Charidimou A, Boulouis G, Haley K, et al. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology.* 2016;86:505–11.

How to cite this article: Schilter M, Epstein A, Vynckier J, et al. Chronic cerebral infarctions and white matter lesions link to long-term survival after a first ischemic event: A cohort study. *J Neuroimaging.* 2022;32:1134–1141. <https://doi.org/10.1111/jon.13033>