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Impact of cerebral microbleeds on bleeding and outcome after stroke thrombolysis

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Abstract

Background Cerebral microbleeds may be responsible for bleeding and poor functional outcome following thrombolysis of acute ischemic stroke. We tried to assess the association between cerebral microbleeds, hemorrhagic complication and functional outcome following intravenous thrombolysis in Egyptian acute ischemic stroke patients. We evaluated 66 acute ischemic stroke patients treated with intravenous thrombolysis for cerebral microbleeds using T2* weighted Magnetic Resonance Imaging Gradient echo. Distribution, number, and predictors of microbleeds were assessed. The effect of microbleeds presence and burden on development of hemorrhage after thrombolysis and 90 days functional outcome was evaluated.

Results Out of 66 stroke patients treated with intravenous thrombolysis, 33 patients had microbleeds. Multivariate analysis shows that hypertension, diabetes mellitus, atrial fibrillation, smoking and leukoaraiosis were independently associated with microbleeds. Post-thrombolysis symptomatic intracerebral hemorrhage occurred in 12/66 (18.1%). Multivariate analysis shows that high burden microbleeds (≥ 10), leukoaraiosis, stroke severity, delayed thrombolysis were independently associated with intracerebral hemorrhage. Post-thrombolysis hemorrhage was statistically higher in microbleeds group (51.5%) than non-microbleeds group (9.1%) ($p < 0.001$). Parenchymal hemorrhage represents (58.8%) of hemorrhagic cases in microbleeds group in comparison to (33.3%) of non-microbleeds group ($p = 0.62$). Parenchymal hemorrhage represents (50%) of hemorrhagic cases with microbleeds < 10, while it represents (100%) of hemorrhagic cases with microbleeds ≥ 10. Favorable modified Rankin Scale (0–2) was more prevalent in non-microbleeds group (72.7%) than microbleeds group (45.5%) at 90 days ($p = 0.024$). Favorable outcome at discharge and at 90 days was statistically more prevalent in patients with microbleeds < 10 ($p = 0.004$).

Conclusion High burden cerebral microbleeds should be considered a risk for parenchymal hemorrhage following intravenous thrombolysis. The presence and burden of microbleeds may affect prognosis 90 days after thrombolytic therapy.

Keywords Intravenous thrombolysis, Stroke, Cerebral microbleeds, Intracerebral hemorrhage, Post-thrombolysis hemorrhage

Background

Intracerebral hemorrhage (ICH) is considered the most feared and unpredictable complication of intravenous thrombolysis (IVT) in acute ischemic stroke (AIS) patients [1]. Various predictors of this hemorrhagic complication were studied to select eligible candidate for IVT. Advanced age, initial stroke severity, hypertension, diabetes mellitus (DM) and signs of early ischemia on imaging were among these predictors [2, 3]. Cerebral microbleeds

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(CMBs) visualized on T2*gradient echo or susceptibility weighted magnetic resonance imaging (MRI) represent markers of fragile microangiopathic cerebral vasculature (mainly hypertensive arteriopathy and cerebral amyloid angiopathy) which lead to intracerebral hemorrhage (ICH) [4, 5] especially if present in large numbers [6–8]. CMBs are present in nearly 15%-38% of AIS patients on pretreatment imaging [8, 9]. It has been noticed in different studies the association between CMBs and poor functional outcome following IVT [3, 7, 8, 10]. Despite a well-documented prognostic importance of CMBs in thrombolyzed AIS patients, still there is uncertainty regarding selection of candidate for IVT from patients with baseline CMBs [11]. That was reflected in the recommendation of American heart association/American stroke association guidelines which stated that IVT in the presence of CMBs may be associated with risk of ICH and there's uncertainty of treatment benefit in patients with high burden CMBs [9]. In this study, we aimed to investigate an Egyptian sample of AIS patients to see if the presence and burden of CMBs is related to the occurrence and severity of post-IVT hemorrhagic complication. Also, to explore if the presence and burden of CMBs may affect the functional outcome 90 days after IVT.

Methods

Based on review of past literature of Seet et al. [12], who found that approximately 2% to 10% of the patients with ischemic stroke receiving IVT will develop symptomatic ICH depending on the definition and cohort characteristics. The sample size was calculated using statistics and sample size pro program version 6. The least sample size is 31 subjects. The power of study was 80% and confidence level was 95%.

We included AIS patients from single stroke center in Egypt who were eligible for IVT using recombinant tissue plasminogen activator (alteplase, standard dose 0.9 mg/kg). Patients were chosen either within 4.5 h after symptom onset or by the presence of diffusion–FLAIR mismatch on MRI in patients without identified time of symptom onset [9, 13]. Patients without identified time of symptom onset, who received IVT depending on diffusion–FLAIR mismatch, were classified according to onset to needle time into either before 6 or after 6 h of last time seen normal. Patients were included in the period between February 2022 and March 2023. Patients with unstable vitals or contraindications to MRI or low image quality due to motion artifacts were excluded. No patients received mechanical thrombectomy. No antithrombotic agents were given within 24 h after IVT. Written consents were obtained from patients. Ethical approval from our institution was taken (Registration No. 3/2022NEUR16).

Clinical data were obtained including age, sex, stroke risk factors including hypertension, DM, smoking and atrial fibrillation (AF). Time interval from stroke onset to IVT was recorded. Patients were evaluated for stroke severity before IVT infusion, by physicians qualified to assess the National Institutes of Health Stroke Scale (NIHSS). Clinical outcome and mortality were evaluated 90 days after IVT using the modified Rankin Scale (mRS). Favorable clinical outcome was defined as (mRS 0–2).

A non-contrast enhanced CT brain (NCCT) was performed for all patients initially before IVT to exclude contraindication of thrombolytic therapy and repeated 24 h post-thrombolysis and upon any worsening of the neurological status during hospital admission to assess for hemorrhagic complications. Symptomatic ICH (sICH) was defined as an ICH associated with increase in NIHSS of ≥ 4 points or death (European Cooperative Acute Stroke Study–III criteria) [3, 14]. Hemorrhagic complications were classified according to European Cooperative Acute Stroke Study criteria into four categories: hemorrhagic infarction (HI-1), (HI-2), parenchymal hematoma (PH-1), and (PH-2) [14].

Due to logistic difficulty, all the included patients underwent brain MRI with T2*-weighted images to detect CMBs one day after IVT without baseline T2*-weighted images prior to IVT. All exams were performed on a 1.5T MRI scanner (Exclart Vantage, Toshiba (now Cannon), Japan). The routine MRI protocol in our institution included axial T1, T2, DWI and FLAIR, sagittal T1 and coronal T2WI. Additional T2*-weighted imaging was added (repetition time 520 ms; echo time 20 ms; field of view 24 × 24 cm, slice thickness 5 mm).

All scans were examined for the location of the ischemic insult as well as the CMBs. CMBs were detected on T2*-weighted Gradient echo (GRE) MRI and were defined as small (up to 10 mm in diameter), oval or rounded hypointense lesions associated with blooming effect [15]. CMBs mimics were excluded such as signal loss caused by globus pallidus calcifications, normal vessels seen in cross-section, or a thrombus in a cerebral artery, iron deposits from other causes and hemorrhagic metastases (e.g., melanoma) [3, 16]. CMBs were rated by radiologist (S.A). In cases of doubtful CMBs, a second rater (K.A) was consulted. All raters have experience in detecting CMBs. The first rater (S.A) was blinded to clinical information. We scanned for the presence, number, and anatomical location of CMBs on MRI. CMBs were classified as intralesional (in the infarcted area) or extralesional (outside infarct tissue). The CMBs location (lobar, deep, or mixed) was identified [15]. Strictly lobar location of CMBs was assumed to be related to cerebral amyloid angiopathy (CAA) [8, 17], while strictly deep or mixed CMBs were assumed to be related to hypertensive

arteriopathy [8, 16]. In case of presence of CMBs, cases were classified as low burden (< 10 CMBs) or high burden (≥ 10 CMBs). Also, presence of leukoaraiosis was assessed in MRI.

Data were calculated using SPSS, version 21 (Armonk, New York, USA) and formulated as the mean ± SD. Group differences were analyzed by Student's *t*-test, and Chi square (χ^2)-test for normally distributed, and non-continuous variables, respectively. *p* values less than or equal to 0.05 were considered statistically significant.

Results

The studied population was (66 AIS patients) who received IVT. After analysis of MRI-images, they were divided into 2 groups (33 patients with CMBs) and (33 patients without CMBs). Mean age of (CMBs group) was (65 ± 10.23), 23 (69.7%) were male. Comparison of stroke risk factors (hypertension, DM, smoking and AF) between both groups shows statistically significant increase in hypertension ($p = 0.005$) and AF ($p = 0.002$) in (CMBs group) than (non-CMBs group). Also, Initial stroke severity (measured by admission NIHSS) was statistically higher in (CMBs group) in comparison to (non-CMBs group) ($p = 0.002$). Stroke in the carotid territory and leukoaraiosis were higher in (CMBs group) and that was of statistical significance ($p = 0.012$), ($p = 0.0001$), respectively (Table 1).

From different risk factors associated with CMBs, multivariate logistic regression analysis shows that hypertension, DM, AF, smoking and leukoaraiosis were independent factors associated with CMBs (Table 2).

As regards anatomical location of CMBs, 4/33 (12.1%) were lobar (cortical and cortico-subcortical), 10/33 (30.3%) were deep (Basal ganglia) and mixed in 19/33 (57.6%). CMBs were strictly extralesional (not in the

Table 2 Multivariate logistic regression analysis of risk factors of CMBs

	Odds ratio	95% CI	*p* value
Age	0.843	0.695–1.023	0.084
Gender			
Male	1.398	0.125–15.676	0.786
Risk factors			
Smoking	13.494	0.207–28.617	**0.022**
Hypertension	22.816	1.999–51.596	**0.030**
Diabetes mellitus	1.266	0.029–3.424	**0.029**
Atrial fibrillation	97.816	40.168–153.475	**0.005**
Admission NIHSS	1.204	0.931–1.556	0.157
IVT after 6 h	0.191	0.010–3.774	0.277
Vascular territory			
Carotid	2.805	0.863–11.531	0.074
Vertebrobasilar	0.360	0.101–1.465	0.079
Leukoaraiosis	49.199	24.003–62.776	**0.005**

CI: confidence interval; CMBs: cerebral microbleeds; NIHSS: National Institutes of Health Stroke Scale; IVT: intra-venous thrombolysis; DM: diabetes mellitus; AF: atrial fibrillation

P-value: significant (< 0.05)

Table 1 Comparison of characteristics between patients with and without CMBs

Variable		Patients with CMBs (*n* = 33)		Patient without CMBs (*n* = 33)		*p* value
		n	%	*n*	%	
Age	Mean ± SD	65.67 ± 10.23		65.12 ± 6.20		0.794
	Range	47–85		55–75		
Gender	Male	23	69.7%	26	78.8%	0.398
	Female	10	30.3%	7	21.2%	
Risk factors	Hypertension	31	93.9%	22	66.7%	**0.005**
	Diabetes mellitus	22	66.7%	23	69.7%	0.792
	Atrial fibrillation	8	24.2%	1	3%	**0.012**
	Smoking	6	18.2%	2	6.1%	0.131
Admission NIHSS	Mean ± SD	15.42 ± 5.14		11.42 ± 4.81		**0.002**
	Range	4–28		3–21		
Timing of IVT	Before 6 h	9	27.3%	3	9.1%	0.056
	After 6 h	24	72.7%	30	90.9%	
Vascular territory	Carotid	32	97%	25	75.8%	**0.012**
	Vertebrobasilar	1	3%	8	42.2%	
Leukoaraiosis		29	87.9%	9	27.3%	**< 0.0001**

SD: standard deviation; CMBs: cerebral microbleeds; IVT: intravenous thrombolysis; NIHSS: National Institutes of Health Stroke Scale

p-value: significant (< 0.05)

infarct zone) in 19/33 (57.6%) and were combined intralesional and extralesional in 14/33 (42.4%). The total number of CMBs was (< 10 CMBs) in 29/33 (87.9%) patients and (≥ 10 CMBs) in 4/33 (12.1%) patients. Post-thrombolysis ICH occurred in 20/66 (30.3%) patients, 12/66 (18.1%) were symptomatic ICH. Mean age was (69.65 ± 10.17), 10/20 (50%) were male. Upon studying risk factors associated with post-thrombolysis ICH, multivariate logistic regression analysis shows that high burden CMBs (≥ 10), leukoaraiosis, admission NIHSS, delayed IVT (after 6 h) and stroke risk factors (Hypertension, DM, Smoking and AF) were independent factors associated with ICH (Table 3).

Post-IVT ICH was statistically higher in (CMBs group) 17/33 (51.5%) than (non-CMB group) 3/33 (9.1%) ($p < 0.001$). From post-IVT ICH cases in (CMB group), 14/17 (82%) had CMBs < 10 while 3/17 (17%) had CMBs ≥ 10. ICH was symptomatic in 10/17 (58.8%) of (CMBs group) and in 2/3 (66.7%) of (non-CMB group) ($p = 0.7$) (Table 4).

According to ECASS grading of post-IV thrombolysis ICH, parenchymal hemorrhage (PH) occurs in 10/17 (58.8%) of (CMB-group) in comparison to 1/3 (33.3%) of (non-CMB group) ($p = 0.62$) (Table 4). PH1and PH2 represents 7/14 (50%) of ICH patients with (CMBs < 10), while it represents 3/3 (100%) of ICH patients with (CMB ≥ 10) (Table 5).

Regarding functional outcome and prognosis, it was found that favorable mRS (0–2) was more prevalent in (non-CMBs group) than (CMBs group) at hospital discharge 8/33 (24.2%) and at 90 days 24/33 (72.7%), but it was only statistically significant regarding 90 days ($p = 0.024$). Also, mortality within 90 days was more prevalent in (CMBs group) 9/33 (27.3%) than (non-CMB group) 5/33 (15%), but it was not statistically significant ($p = 0.22$) Table 6.

Favorable outcome mRS (0–2) at discharge and at 90 days was statistically higher in patients with (CMBs < 10) ($p = 0.004$) (Table 7).

Table 3 Multivariate logistic regression analysis of risk factors of ICH

	Odds ratio	95% CI	*p* value
Age	1.056	0.946–1.179	0.334
Gender			
Male	0.170	0.019–1.490	0.110
Risk factors			
Smoking	1.971	0.490–4.699	**0.037**
Hypertension	1.040	0.270–3.167	**0.026**
Diabetes mellitus	6.123	0.940–19.289	**0.013**
Atrial fibrillation	39.19	2.464–92.793	**0.001**
Admission NIHSS	1.429	0.989–1.948	**0.016**
IVT after 6 h	2.273	0.184–28.035	**0.025**
Vascular territory			
Carotid	1.156	0.037–3.043	0.320
Vertebrobasilar	0.865	0.028–6.986	0.113
High burden CMBs (≥ 10)	3.033	0.622–14.785	**0.017**
Leukoaraiosis	42.631	1.658–96.229	**0.024**

CI: confidence interval; CMBs: cerebral microbleeds; NIHSS: National Institutes of Health Stroke Scale; IVT: intra-venous thrombolysis

p-value: significant (< 0.05)

Table 4 Post-IV thrombolysis hemorrhagic complication in 66 AIS patients

	Patients with CMBs (*n* = 33)		Patient without CMBs (*n* = 33)		*p* value
	n	%	*n*	%	
ICH (*n* = 20)	17	51.5%	3	9.1%	< **0.0001**
Symptomatic ICH (No = 12)	10	58.8%	2	66.7%	0.798
ECASS classification					
HI	7	21.2	2	66.6%	0.447
PH	10	58.8%	1	33.3%	

ICH: intracerebral hemorrhage; AIS: acute ischemic stroke; HI: hemorrhagic infarction; PH: parenchymal hemorrhage'; ECASS: European Cooperative Acute Stroke Study; CMBs: cerebral microbleeds

p-value: significant (< 0.05)

Discussion

Many studies reported increased risk of post-thrombolysis ICH in the vicinity of CMBs especially in high burden CMBs [6, 18–20]. Moreover, others introduce CMBs as prognostic factor for poor functional outcome post-thrombolysis [21, 22]. In this Egyptian experience, we tried to answer 4 questions regarding the association between CMBs and post-thrombolysis ICH and future outcome in AIS patients. First: are CMBs considered risk for IVT-related ICH? Second: does high burden CMBs (≥ 10) increase risk of IVT-related ICH? Third: does presence and burden of CMBs affect severity of

Table 5 Relation between grading of ICH and number of CMBs

	< 10 CMBS (*n* = 14)		≥ 10 CMBS (*n* = 3)		*p*-value
	n	%	*n*	%	
ECASS					
HI	7	50.0	0	0	**0.334**
PH	7	50.0	3	100	

HI: hemorrhagic infarction; PH: parenchymal hemorrhage; ECASS: European Cooperative Acute Stroke Study; CMBs: cerebral microbleeds

p-value: significant (< 0.05)

Table 6 Functional outcome of 66 AIS patients

	Patients with CMBS (*n* = 33)		Patient without CMBS (*n* = 33)		*p*-value
	n	%	*n*	%	
mRS at discharge					
Mean ± SD	4.12 ± 1.39		3.33 ± 1.31		**0.021**
Range	1–6		1–6		
mRS at 90 days					
Mean ± SD	3.27 ± 2.04		2.03 ± 1.98		**0.014**
Range	0–6		0–6		
Favorable mRS at discharge (0–2)	6	18.2%	8	24.2%	0.547
Favorable mRS at 90 days (0–2)	15	45.5%	24	72.7%	**0.024**
Mortality within 3 months	9	27.3%	5	15.2%	0.228

CMBs: cerebral microbleeds; mRS: modified Rankin scale

p-value: significant (< 0.05)

Table 7 Functional outcome in relation to CMBs burden

	< 10 CMBS (*n* = 29)		≥ 10 CMBS (*n* = 4)		*P*-value*
	n	%	*n*	%	
Favorable mRS at discharge (*n* = 6)	6	20.6	0	0.0	**0.004**
Favorable mRS at 90 days (*n* = 15)	14	48.2	1	25.0	**0.014**
Mortality within 3 months (*n* = 8)	6	20.6	1	25.0	**0.027**

CMBs: cerebral microbleeds; mRS: modified Rankin scale

P-value: significant (0.05)

IVT-related ICH? Fourth: does the presence and burden of CMBs affect prognosis and functional outcome after IVT? New CMBs after IVT represent a small percentage (around 4%) [15, 23, 24]. Because of difficulty performing pretreatment MRI in our center, only post-IVT MRI was done and this is one of our limitations. We suppose that most of CMBs detected in our cohort were old ones that were present before IVT. Supporting that idea is the study of Braemswig et al. who found that new CMBs were mainly lobar in location [15] (a pattern associated with CAA) and strictly lobar CMBs in our study represent 12%, while majority of CMBs were deep (30.3%) or mixed (57.6%) (a pattern attributed to hypertensive arteriopathy). So, we can suppose that new CMBs in our study represent around 10% of the whole cohort. New CMBs are thought to be the result of underlying CAA, a hypothesis supported by histopathological studies [25]. That was supported by the finding that patients with old strictly lobar CMBs were more likely to develop new CMBs, while patients with deep or mixed CMBs were not [15]. In our study the significant association between hypertension and CMBs suggests that most CMBs are related to hypertensive arteriopathy and not CAA. So, the majority of CMBs are supposed to be old ones. But to verify that CAA is the cause of new CMBs, we had to search for another imaging marker of CAA like cortical superficial siderosis in post-IVT MRI. Braemswig et al. found that high burden CMBs on pretreatment MRI were associated with new CMBs after IVT [15]. Another supporting evidence that around 10% of our CMBs group is due to new ones is that only 12% of our cohort has high burden CMBs which is interestingly the same percentage as the strictly lobar CMBs 12%. About 20% of AIS patients develop new CMBs in the first few days indicating an active, widespread microangiopathy, which could cause ICH with the administration of IVT [26].

In our study, post-IVT related ICH was statistically higher in CMBs group than non-CMBs group. That was like the results of different metanalyses [7, 8, 10, 27–29] and another recent study in which the authors stated that despite the association between CMBs and hemorrhagic complications, that association was equally present in patients receiving IVT and patients receiving placebo [11]. CMBs may increase the risk of IVT-related ICH either as a direct source of bleeding or, more likely, as a general marker of bleeding-prone vasculopathy [28]. It seems that vasculopathy (including CAA and hypertensive arteriopathy), causing the blood vessel walls to become diseased and fragile, may interact with factors that aggravate bleeding risk after IVT, such as upregulation of matrix metalloproteinases, breakdown of blood–brain barrier, hypertension, and hyperglycemia [30, 31] lowering the threshold for IVT-related ICH [32]. To the opposite of that is the result of systematic review and meta-analysis of 800 AIS patients showing that CMBs on a pretreatment MRI scan is not associated with a statistically significant risk of symptomatic ICH after thrombolysis [19]. Despite that, there was a tendency towards

higher ICH risk in patients with CMBs [19]. Another study concluded that the presence of cerebral microbleeds does not increase the risk of brain hemorrhage following IVT between 3 and 6 h after stroke onset [33]. Leukoaraiosis, in our study was an independent predictor for CMBs and also IVT-related ICH in multivariate analysis, a finding similar to a previous study reporting that the rate of IVT-related ICH is increased in the presence of moderate-to-severe leukoaraiosis, indicating that cerebral small vessel is a risk factor for ICH [34]. However, leukoaraiosis devoid of pathological specificity, in contrast to CMBs, which appear to specifically represent small areas of bleeding from vessels affected by bleeding-prone vasculopathy (hypertensive arteriopathy or CAA) [35]. Regarding functional outcome, we found that favorable mRS was more common in (non-CMBs group) at 90 days. Andreas Charidimou et al. stated in their comprehensive metanalysis that CMBs are associated with symptomatic ICH risk and poor functional outcome after IVT [10]. Similar to our results is the result of Choi et al. who stated that CMBs, and especially high burden (≥5) and lobar distribution, are independent predictors of unfavorable outcomes at 90 days and may increase the hemorrhagic risk in AIS patients with recanalization [22]. They suggested that CMBs cause more unfavorable outcome in patients with recanalization of large vessel occlusion than in patients without recanalization. They demonstrated that CMBs have a statistically significant major impact on outcomes in patients treated with MT than those treated with IVT alone and this may be due to the high recanalization rate with MT than IVT alone [22].

Tipirneni et al. in their meta-analysis underscores a significant relation between CMBs and poor outcomes encompassing sICH, hemorrhagic transformation, poor functional outcome at 90 days, and increased mortality in AIS patients undergoing reperfusion therapy (including intravenous thrombolysis, mechanical thrombectomy, and bridging therapy [36]. One of our limitations is the exclusion of patients receiving MT. Also, our results are consistent with previous studies suggesting a significant association between high burden CMBs (≥3) and 90 days functional outcomes [8, 21]. To the opposite of that is the result of Schlemm et al. who demonstrated similar beneficial outcome at 90 days in patients with and without CMBs who received IVT and hence they recommended that presence of CMBs on MRI should not prevent doctors from treating stroke patients with IVT [11]. Others have reported that even a high burden of CMBs add no significant impact on 90 days functional outcomes [3, 37, 38]. We can think of poor prognosis related to CMBs as a consequence of not only IVT-related ICH, but also because of the global brain dysfunction secondary to the fragile vascular wall, endothelial activation, damage and blood brain barrier breakdown due to the underlying bleeding-prone small vessel angiopathy [5, 7, 22]. According to that concept, preexisting CMBs are more accused than new ones by worsening the functional outcome of AIS patients treated with thrombolytic therapy. Regarding the burden of CMBs, we suggest a potential increased risk of hemorrhagic complications with high burden CMBs (≥10) and increase in poor functional outcome at 90 days. Our results are consistent with previous studies suggesting an association between burden of CMBs and hemorrhagic complications and functional outcome [3, 5, 7, 8, 11, 22, 27, 29]. Particularly, high burden CMBs were associated with a threefold and sevenfold rise in risk of symptomatic ICH in comparison with AIS with low burden CMBs (1–10 CMBs) in the individual patient data and the pairwise meta-analyses, respectively [7]. To the opposite of that is the result of Kim et al. who stated that multiple microbleeds are not an independent risk factor for IVT-related ICH [18]. The increased rate of ICH in those with a higher burden of CMBs might reflect the more extensive vasculopathy (1). Parenchymal hemorrhage was more prevalent in (CMB-group). Moreover, PH represents all cases of high burden CMBs (CMB≥10), a result which can suggest that CMBs may not only increase the risk of post-IVT ICH, but also may potentiate the severity of ICH. A meta-analysis done to study the impact of CMBs on ICH and poor functional outcome of AIS patients treated with IVT concluded that CMBs presence increased the risks of 3-month parenchymal hemorrhage, poor functional outcome after IVT [39]. The limitation of this study may be related to small sample size (33 AIS patients treated with IVT showing CMBs). Furthermore, results may be subjected to selection bias since not all AIS treated with IVT in our center undergo T2*-GRE MRI. Also, we did not relate ICH to the anatomical location of CMBs. Another limitation is that we did not study the effect of prior use of antithrombotic or recurrence of stroke on the risk of development of CMBs and IVT-related ICH. Ghaly et al. 2022 in their study of CMBs in 65 AIS patients, considered antiplatelets medications significant risk factor for the development of CMBs [40]. Also, Elkhatib et al. considered anticoagulant treatment as independent risk factors associated with CMB in AF ischemic stroke patients [41]. To our knowledge, this is the first Egyptian study evaluating the association between CMBs and hemorrhagic complications following IVT and the later functional outcome. We can conclude from these results that CMBs, especially high burden ones (≥10) should be considered a risk for parenchymal ICH following IVT. The presence and burden of CMBs may affect prognosis 90 days after IVT.

Conclusion

We can conclude from these results that CMBs, especially high burden ones (≥ 10) should be considered a risk for parenchymal ICH following IVT. The presence and burden of CMBs may affect prognosis 90 days after IVT. We recommend that Patients with a higher risk for symptomatic ICH (high burden CMBs, severe leukoaraiosis, higher blood pressure) might benefit from close follow-up, more restricted blood pressure control and not the absolute withholding of IVT. The challenge remains in recognizing CMBs burden in Egyptian stroke centers where NCCT is the only available imaging technique for management of AIS.

Abbreviations

ICH	Intracerebral hemorrhage
IVT	Intravenous thrombolysis
AIS	Acute ischemic stroke
DM	Diabetes mellitus
CMBs	Cerebral microbleeds
MRI	Magnetic resonance imaging
ICH	Intracerebral hemorrhage
AF	Atrial fibrillation
NIHSS	National Institutes of Health Stroke Scale
mRS	modified Rankin Scale
NCCT	Non-contrast enhanced CT
CAA	Cerebral amyloid angiopathy
HI	Hemorrhagic infarction
GRE	Gradient echo
PH	Parenchymal hemorrhage

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Author contributions
All the authors contributed to study concept and design, the data analysis and interpretation, wrote the manuscript, and provided the clinical data. All authors have read and approved the final manuscript.

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Availability of data and materials
The data sets generated and/or analyzed during the current study are not publicly available due to the current Menoufia University regulations and Egyptian legislation, but they are available by a reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical approval from Faculty of medicine, Menoufia university ethical committee was taken (Registration No. 3/2022NEUR16). Written consents were obtained from patients prior to the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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References

1. Lin X, Cao Y, Yan J, Zhang Z, Ye Z, Huang X, et al. Risk factors for early intracerebral hemorrhage after intravenous thrombolysis with alteplase. J Atheroscler Thromb. 2020;27(11):1176–82.
2. Mullen MT, Pisapia JM, Tilwa S, Messé SR, Stein SC. Systematic review of outcome after ischemic stroke due to anterior circulation occlusion treated with intravenous, intra-arterial, or combined intravenous+ intra-arterial thrombolysis. Stroke. 2012;43(9):2350–5.
3. Dannenberg S, Scheitz JF, Rozanski M, Erdur H, Brunecker P, Werring DJ, et al. Number of cerebral microbleeds and risk of intracerebral hemorrhage after intravenous thrombolysis. Stroke. 2014;45(10):2900–5.
4. Linn J. Imaging of cerebral microbleeds. Clin Neuroradiol. 2015;25(Suppl 2):167–75.
5. Shoamanesh A, Yan S, Charidimou A. New cerebral microbleeds and mechanism of post-thrombolysis remote intracerebral hemorrhage: "red meets white" revisited. Front Neurol. 2015;6:203.
6. Fiehler J, Albers GW, Boulanger J-M, Derex L, Gass A, Hjort N, et al. Bleeding Risk Analysis in Stroke Imaging Before ThromboLysis (BRASIL) pooled analysis of T2*-weighted magnetic resonance imaging data from 570 patients. Stroke. 2007;38(10):2738–44.
7. Tsivgoulis G, Zand R, Katsanos AH, Turc G, Nolte CH, Jung S, et al. Risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden: a meta-analysis. JAMA Neurol. 2016;73(6):675–83.
8. Charidimou A, Turc G, Oppenheim C, Yan S, Scheitz JF, Erdur H, et al. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis: individual patient data meta-analysis. Stroke. 2017;48(8):2084–90.
9. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–418.
10. Charidimou A, Shoamanesh A, Initiative IM-M. Clinical relevance of microbleeds in acute stroke thrombolysis: comprehensive meta-analysis. Neurology. 2016;87(15):1534–41.
11. Schlemm L, Braemswig TB, Boutitie F, Vynckier J, Jensen M, Galinovic I, et al. Cerebral microbleeds and treatment effect of intravenous thrombolysis in acute stroke: an analysis of the WAKE-UP randomized clinical trial. Neurology. 2022;98(3):e302–14.
12. Seet R, Rabinstein AA. Symptomatic intracranial hemorrhage following intravenous thrombolysis for acute ischemic stroke: a critical review of case definitions. Cerebrovasc Dis. 2012;34(2):106–14.
13. Ebinger M, Scheitz J, Kufner A, Endres M, Fiebach J, Nolte C. MRI-based intravenous thrombolysis in stroke patients with unknown time of symptom onset. Eur Neurol. 2012;19(2):348–50.
14. Trouillas P, von Kummer R. Classification and pathogenesis of cerebral hemorrhages after thrombolysis in ischemic stroke. Stroke. 2006;37(2):556–61.
15. Braemswig TB, Villringer K, Turc G, Erdur H, Fiebach JB, Audebert HJ, et al. Predictors of new remote cerebral microbleeds after IV thrombolysis for ischemic stroke. Neurology. 2019;92(7):e630–8.
16. Ii Y, Ishikawa H, Matsuyama H, Shindo A, Matsuura K, Yoshimaru K, et al. Hypertensive arteriopathy and cerebral amyloid angiopathy in patients with cognitive decline and mixed cerebral microbleeds. J Alzheimer's Dis. 2020;78:1765–74.
17. Yates PA, Sirisriro R, Villemagne VL, Farquharson S, Masters CL, Rowe CC, Group AR. Cerebral microhemorrhage and brain β-amyloid in aging and Alzheimer disease. Neurology. 2011;77(1):48–54.
18. Kim HS, Lee DH, Ryu CW, Lee JH, Choi CG, Kim SJ, Suh DC. Multiple cerebral microbleeds in hyperacute ischemic stroke: impact on prevalence and severity of early hemorrhagic transformation after thrombolytic treatment. AJR. 2006;186(5):1443–9.

19. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and the risk of intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: systematic review and meta-analysis. JNNP. 2013;84(3):277–80.
20. Lee S-J, Hwang Y-H, Hong JM, Choi JW, Park JH, Park B, et al. Influence of cerebral microbleeds on mechanical thrombectomy outcomes. Sci Rep. 2022;12(1):3637.
21. Yan S, Jin X, Zhang X, Zhang S, Liebeskind DS, Lou M. Extensive cerebral microbleeds predict parenchymal haemorrhage and poor outcome after intravenous thrombolysis. JNNP. 2015;86(11):1267–72.
22. Choi K-H, Kim J-H, Kang K-W, Kim J-T, Choi S-M, Lee S-H, et al. Impact of microbleeds on outcome following recanalization in patients with acute ischemic stroke. Stroke. 2019;50(1):127–34.
23. Kimura K, Aoki J, Shibazaki K, Saji N, Uemura J, Sakamoto Y. New appearance of extraischemic microbleeds on T2*-weighted magnetic resonance imaging 24 hours after tissue-type plasminogen activator administration. Stroke. 2013;44(10):2776–81.
24. Yan S, Chen Y, Zhang X, Liebeskind DS, Lou M. New microbleeds after thrombolysis: contiguous thin-slice 3T MRI. Medicine. 2014;93(20): e99.
25. Charidimou A, Nicoll JA, McCarron MO. Thrombolysis-related intracerebral hemorrhage and cerebral amyloid angiopathy: accumulating evidence. Front Neurol. 2015;6:99.
26. Miwa K, Koga M, Inoue M, Yoshimura S, Sasaki M, Yakushiji Y, et al. Cerebral microbleeds development after stroke thrombolysis: a secondary analysis of the THAWS randomized clinical trial. IJS. 2022;17(6):628–36.
27. Shoamanesh A, Kwok CS, Lim PA, Benavente OR. Postthrombolysis intracranial hemorrhage risk of cerebral microbleeds in acute stroke patients: a systematic review and meta-analysis. IJS. 2013;8(5):348–56.
28. Charidimou A, Shoamanesh A, Wilson D, Gang Q, Fox Z, Jäger HR, et al. Cerebral microbleeds and postthrombolysis intracerebral hemorrhage risk: updated meta-analysis. Neurology. 2015;85(11):927–34.
29. Zand R, Tsivgoulis G, Singh M, McCormack M, Goyal N, Ishfaq MF, et al. Cerebral microbleeds and risk of intracerebral hemorrhage post intravenous thrombolysis. J Stroke Cerebrovasc Dis. 2017;26(3):538–44.
30. Derex L, Nighoghossian N. Intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: an update. JNNP. 2008;79(10):1093–9.
31. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe implementation of treatments in stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke. 2012;43(6):1524–31.
32. Pantoni L, Fierini F, Poggesi A. Thrombolysis in acute stroke patients with cerebral small vessel disease. J Stroke Cerebrovasc Dis. 2014;37(1):5–13.
33. Capuana ML, Lorenzano S, Caselli MC, Paciaroni M, Toni D. Hemorrhagic risk after intravenous thrombolysis for ischemic stroke in patients with cerebral microbleeds and white matter disease. Neurol Sci. 2021;42(5):1969–76.
34. Frey BM, Shenas F, Boutitie F, Cheng B, Cho TH, Ebinger M, et al. Intravenous thrombolysis in patients with white matter hyperintensities in the WAKE-UP trial. Stroke. 2023;54(7):1718–25.
35. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and recurrent stroke risk. Stroke. 2013;44(4):995–1001.
36. Tipirneni S, Stanwell P, Weissert R, Bhaskar SMM. Prevalence and impact of cerebral microbleeds on clinical and safety outcomes in acute ischaemic stroke patients receiving reperfusion therapy: a systematic review and meta-analysis. Biomedicines. 2023;11(10):2865.
37. Gratz PP, El-Koussy M, Hsieh K, von Arx S, Mono M-L, Heldner MR, et al. Preexisting cerebral microbleeds on susceptibility-weighted magnetic resonance imaging and post-thrombolysis bleeding risk in 392 patients. Stroke. 2014;45(6):1684–8.
38. Turc G, Sallem A, Moulin S, Tisserand M, Machet A, Edjlali M, et al. Microbleed status and 3-month outcome after intravenous thrombolysis in 717 patients with acute ischemic stroke. Stroke. 2015;46(9):2458–63.
39. Wang S, Lv Y, Zheng X, Qiu J, Chen H-S. The impact of cerebral microbleeds on intracerebral hemorrhage and poor functional outcome of acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. J Neurol. 2017;264:1309–19.
40. Ghaly AM, Elzayat S, Ali AE, Elshamy MI. Evaluation of cerebral microbleeds in patients with acute ischemic stroke. AIMJ. 2022;3(11):60–5.
41. Elkhatib THM, Elsaid AF, Al-Molla RM, Khamis MEM, Fahmi RM. Prevalence and associated risk factors of cerebral microbleeds in Egyptian patients with acute ischemic stroke and atrial fibrillation. J Stroke Cerebrovasc Dis. 2020;29(5): 104703.

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