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ORIGINAL RESEARCH

Observation of the Therapeutic Effect of Dual Antiplatelet Therapy with Aspirin and Clopidogrel on the Incidence, Characteristics, and Outcome in Acute Ischemic Stroke Patients with Cerebral Microbleeds at a Teaching Hospital, China

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Background: Cerebral microbleeds (CMBs) are an important risk factor for stroke recurrence and prognosis. However, there is no consensus on the safety of antiplatelet therapy in patients with ischemic stroke and CMBs.

Objective: This study aimed to observe the effects of dual antiplatelet therapy with aspirin and clopidogrel on bleeding conversion in patients with different degrees of CMBs.

Materials and Methods: An observational retrospective study was conducted on 160 patients with acute mild ischemic stroke admitted to the Stroke Center, Affiliated Hospital of Beihua University between March 2021 and December 2022. Patients were divided into the CMBs and non-CMB groups. The CMB group was then divided into the low, medium and high-risk groups. In two groups, all patients were administered dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg orally once a day for 21 days according to the Chinese Stroke Guidelines of 2018), and no other anticoagulant or antiplatelet drugs were administered during the treatment period. Head CT, National Institutes of Health Stroke Scale(NIHSS) and modified Rankin Scale (mRS) score were re-checked, and the number of bleeding conversions was calculated at 21 days.

Results: Five patients in the CMB group had intracranial hemorrhage (5/116, 4.3%), while no intracranial hemorrhage was observed in the non-CMB group. There were no differences in the conversion rate of cerebral hemorrhage, NIHSS score, or mRS score between two groups after dual antiplatelet therapy ($p>0.05$). The conversion rate of cerebral hemorrhage in the high-risk group was higher than that in the non-CMB group ($p<0.05$), but the NIHSS and mRS score showed no difference between the high-risk and non-CMB groups ($p>0.05$).

Conclusion: Dual antiplatelet therapy with aspirin and clopidogrel does not significantly increase the risk of bleeding transformation; however, it improves neurological recovery or long-term prognosis in patients with acute ischemic cerebral stroke complicated by low-risk and middle-risk CMBs.

Keywords: acute ischemic cerebral infarction, cerebral microbleeds, dual antiplatelet therapy

Introduction

Cerebral microbleeds (CMBs) result from hemosiderin deposition caused by subclinical terminal microvascular diseases. Focal low signals can be seen on gradient echo T_2-weighted MR images (GE-T2W-MR, abbreviated herein as GRE-T2) of the brain, and there is no edema around them.[1] CMBs are also classified as old (static) CMBs, resting CMBs, lacunar hemorrhage, type-II lacuna, chronic micro-intracerebral hemorrhage, or punctate intracerebral hemorrhage.[2,3] Generally,

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CMBs have no clinical symptoms; however, CMBs occur widely in the cortex, subcortical white matter, and basal ganglia, resulting in brain tissue damage in the corresponding parts, and may cause cognitive dysfunction.[4,5] CMBs are closely related to symptomatic cerebral hemorrhage, ischemic stroke, white matter lesions, lacunar cerebral infarction, and are independent risk factors for symptomatic stroke.[6–8]

Recently, more CMB lesions were found in patients with stroke, cognitive dysfunction, and cerebral amyloid angiopathy.[9–11] CMBs have become an important risk factor affecting stroke recurrence, prognosis, and bleeding transformation and leading to cognitive impairment.[12] The literature reports that the incidence of CMBs abroad is 3.1–8.0% in the normal population.[13] The incidence of CMBs was 53–78% among those with hypertension, 26.9% among diabetics, 26.3% in hyperlipidemia patients, 80.0% among those exhibiting hypertension with diabetes, and 61.1% among those exhibiting hypertension with hyperlipidemia.[14–16] According to a Chinese report, the highest incidence of primary cerebral hemorrhage is 66–80%.[17] In addition, magnetic sensitivity-weighted imaging (SWI) is applied in clinical practice. It can reveal microhemorrhages and small vessels by exploiting differential imaging of magnetic sensitivity between tissues and is more sensitive to the diagnosis of CMBs.[18–20] Moreover, SWI can reveal hyperacute bleeding, which is conducive to more informed clinical treatment.[21]

At present, there is no unified opinion on the safety of antiplatelet therapy for ischemic stroke patients with CMBs (either in China or abroad), especially regarding balancing the risk of cerebral hemorrhage after aspirin clopidogrel dual antiplatelet therapy with the early benefits of dual antiplatelet therapy for ischemic stroke.[22–24] In the past, there was no relevant literature on the stratified evaluation of patients with acute ischemic stroke complicated by CMBs.

To formulate standard operating procedures for the standardized diagnosis and treatment of stroke, build a continuous improvement model for the quality of Chinese stroke medicine, and enact clinical norms, health education, and training, a retrospective analysis of the clinical treatment of 160 patients with acute mild ischemic stroke was conducted. This study discussed the risk of bleeding transformation after dual antiplatelet therapy in patients with low-, medium-, and high-risk CMBs, accurately evaluated relevant risk factors of disease outcome, and provided prognostic guidance to provide a theoretical basis for the use of dual antiplatelet therapy and the application time thereof in such patients.

Materials and Methods

Study Design and Patient Selection

This was a retrospective, observational study. A total of 160 patients with acute mild ischemic stroke were admitted to the Stroke Center, Department of Neurology, Affiliated Hospital of Beihua University, from March 2021 to December 2022. The patients were older than 18 years, and the onset time was within 24 h. Neurological deficits were scored according to the National Institute of Health Stroke Scale (NIHSS), with an NIHSS score of ≤ 3 points used as the assessment criterion. Among them, 120 patients with CMBs were identified using susceptibility-weighted imaging (SWI) as the CMB group (116 patients were finally recruited into the group, except that four participants went missing), and 39 patients as the non-CMB group.

The inclusion criteria were as follows: ① Computed tomography (CT) of the head excluding bleeding, which was clinically diagnosed as acute ischemic stroke, and the NIHSS score was ≤ 3 points; ② Head CT, SWI, and NIHSS score performed upon admission. After 21 days, the CT and NIHSS score of the head were rechecked. After 21 days, 3 months, and 6 months of medication, magnetic resonance spectroscopy was performed to detect the recovery of neurological function of the patients, and modified Rankin Scale (mRS) score was evaluated; ③ The enrolled patients were more than 18 years old, and the basic information pertaining to each patient was complete; ④ Dual antiplatelet therapy was acceptable for patients without contraindications.

The exclusion criteria: ① Those who have) diagnosed of other serious systemic diseases in the past or after admission; ② Cerebral hemorrhage, brain space-occupying lesions, brain trauma, nervous system infectious diseases, and demyelinating diseases; ③ allergy to aspirin or clopidogrel; ④ coma and contraindication to brain magnetic resonance examination; ⑤ receiving anticoagulation treatment before admission and during treatment; ⑥ history of peptic ulcer and recent black stool, frequent (and recent) gingival bleeding, and slight ecchymosis or ecchymosis on the skin and mucous membrane, respectively; ⑦ Those who worry about the risk of bleeding voluntarily choosing monoclonal antibody therapy.

Grouping and Treatment Plan

According to the SWI examination results, the patients were divided into CMB and non-CMB groups (control group). According to the number and location of microbleeds, as well as the NIHSSscore, the observers in the CMB group were subdivided into three sub-groups: a low-risk group (39/116, 33. 6%), medium-risk group (39/116, 33. 6%), and high-risk group (38/116, 32. 8%), with 39 patients in the non-CMB group. Patients in each group received conventional treatment after admission. In the CMB and non-CMB groups, all patients were administered dual antiplatelet therapy as soon as possible (aspirin 100 mg and clopidogrel 75 mg orally once a day for 21 days according to the Chinese Stroke Guidelines of 2018, after which aspirin 100 mg once a day or clopidogrel 75 mg once a day was administered as monotherapy), and no other anticoagulant or antiplatelet drugs were administered during the treatment period. A CONSORT flow diagram is illustrated in Figure 1.

Data Collection and Efficacy Evaluation

General basic information of the enrolled patients was collected, including their name, sex, and age. In addition, information about whether they had hypertension or diabetes was collected. Clinical data included the number, diameter, and location of CMBs and number of cerebral hemorrhages. The NIHSS scores of patients with stroke were recorded upon admission and 21 days thereafter, and the mRS scores of patients were recorded after 21 days, 3 months, and 6 months of treatment. Evaluation criteria of imaging data were as follows: ① conversion criteria of cerebral hemorrhage: no acute intracranial hemorrhage was found in the first CT examination after the onset, but scattered and uniform high-density shadows appeared in the second CT examination, except basal calcification and cavernous hemangioma; ② SWI examination: the head magnetic resonance examination was performed using a Philips superconducting MRI scanner, and the magnetic field intensity was 3.0 T; ③ The diagnostic criteria of cerebral micro-hemorrhage were round or oval; 2 mm to 10 mm in diameter; the T_1 or T_2-weighted phase showed high signal loss; the T_2-weighted phase appeared black, showing a "blooming" effect; at least half of the lesions were surrounded by brain tissue; other causes such as history of

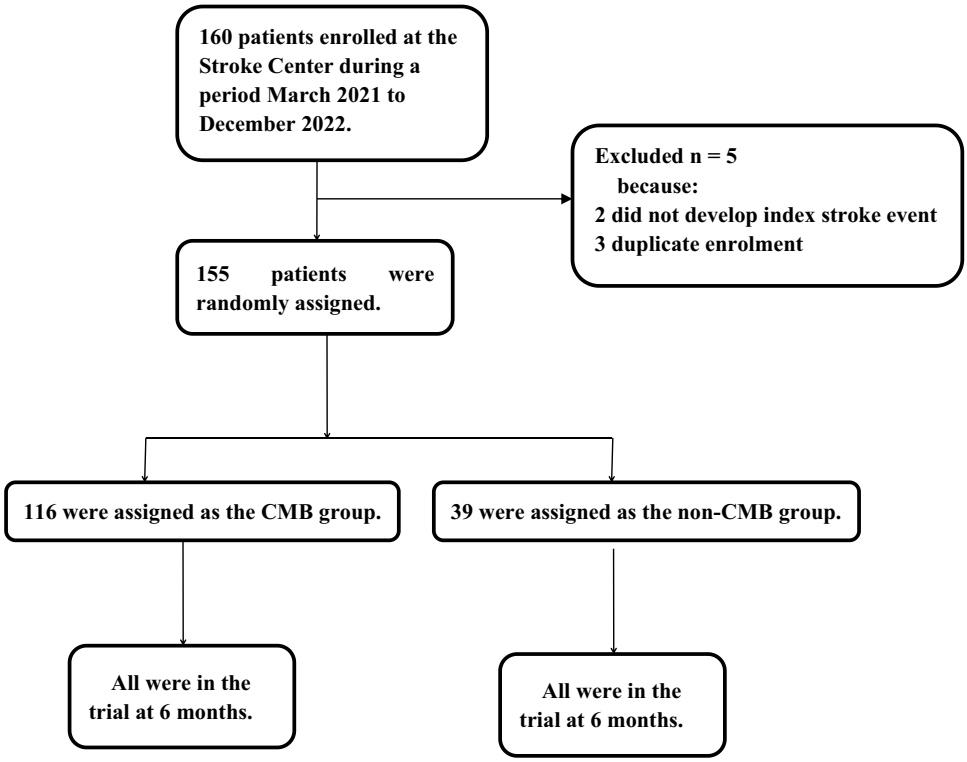

Figure 1 Flowchart of the search process.
Abbreviation: CMB, cerebral microbleed.

craniocerebral trauma were excluded. Grading of the degree of cerebral micro-hemorrhage: The Neuropathy Symptom Score (NSS) for imaging evaluation of CMB severity was used to determine the degree of cerebral micro-hemorrhage. The NSS score: ① The number of incidences of micro-bleeding (*N*) 1 or 2 was scored as 1 point, 3 to 9 was scored as 2 points, and more than 10 was scored as 3 points; ② the diameter (*D*) < 3 mm was scored as 1 point, 3 mm ≤ *D*< 7 mm was scored as 2 points, 7 mm ≤ *D*< 10 mm was scored as points; ③ the location (*L*) in the infratentorial brainstem/cerebellum was scored as 1 point, if in the deep brain area it was scored as 2 points, and if in the cortex it was scored as 3 points. For each item, only the highest score was calculated, and the total score was the sum of the three items, that is, the total score was $N + D + L$, with a total score between 3 and 9 points.Patients with NSSs of 3–4, 5–7, and 8–9 points were classified into the low-risk, medium-risk, and high-risk groups, respectively (Figure 2).

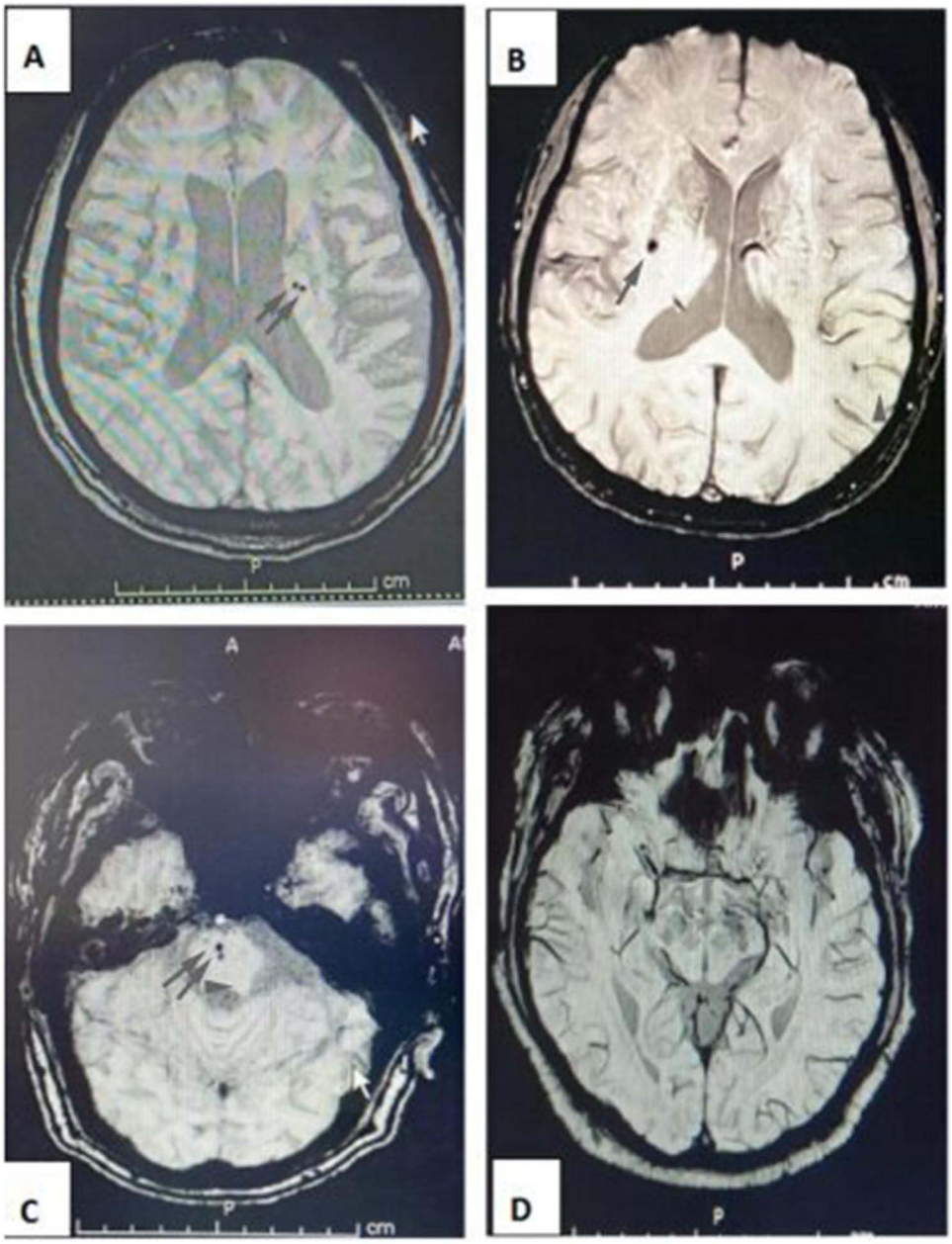

Figure 2 Distribution and characteristic of cerebral microbleed in three sub-groups of CMB group (a low-risk, medium-risk and high-risk group), and comparison with non-CMB group. (**A**) Distribution of CMB in the high-risk group. (**B**) Distribution of CMB in the medium-risk group. (**C**) Distribution of CMB in the low-risk group. (**D**) Distribution of cerebral bleed in non-CMB group.
Abbreviation: CMB, cerebral microbleed.

Statistical Analysis

Statistical software SPSS 25.0 was used for statistical analysis. Descriptions and analyses were conducted on sex; age; hypertension and diabetes; number, diameter, and location of cerebral micro-hemorrhages; number of cerebral hemorrhages; NIHSS score of stroke patients upon admission and 21 days thereafter; and the mRS score of patients 21 days, 3 months, and 6 months after treatment. The measured data were expressed as $x \pm s$, the inter-group comparison was based on the independent sample *t*-test, and the groups were compared using a single-factor analysis of variance (*F*-test). Categorical data are expressed as frequencies and percentages, and comparisons between groups were performed using the χ^2-test or Fisher' sexact test. $P< 0.05$.

Ethics Statement

This study was approved by the Institutional Review Board and Ethics Committee of the Affiliated Hospital, Beihua University (formal ethical approval number: Protocol Number 2021–23) and conducted according to the Declaration of Helsinki. All patients signed an informed consent form before being randomly assigned to treatment.

Results

General Data Analysis

This study included 155 patients who met our inclusion criteria. A total of 120 patients with with acute mild ischemic stroke formed the CMB group (116 patients were finally included therein, except that 4 patients went missing), as evidenced by magnetic sensitivity testing of the head. Observers were divided into low-, medium-, and high-risk groups according to their NSS score, 39 patients were finally included in the non-CMB group. Eligible patients were aged between 20 years and 85 years. There were no significant differences in the general condition and vascular risk factors between the CMB and non-CMB groups ($p>0.05$) (Table 1). There were no significant differences in the general situation and vascular risk factors among the low-, medium-, high-, and non-CMB groups ($p>0.05$) (Table 2).

Table 1 General Information and Vascular Risk Factors of Subjects Between CMBs Group and Non-CMBs Group

Group	N	Gender (Male) [n(*η*/%)]	Age (year) ($\bar{x}\pm$ s)	Hypertension [n(*η*/%)]	Diabetes [n(*η*/%)]
Non-CMBs	39	23 (59.0)	65.91±9.78	27 (69.2)	16 (41.0)
CMBs	116	67 (57.8)	63.86±10.51	78 (67.2)	52 (44.8)
X^2/t		0.018	1.076	0.053	0.171
P		0.894	0.284	0.818	0.679

Table 2 General Information and Vascular Risk Factors of Subjects in Low-Risk, Middle-Risk and High-Risk of CMBs Group and Non-CMBs Group

Group	n	Gender (Male) [n(*η*/%)]	Age (year) ($\bar{x}\pm$ s)	Hypertension [n(*η*/%)]	Diabetes [n(*η*/%)]
Non-CMBs	39	23 (59.0)	65.91±9.78	27 (69.2)	16 (41.0)
CMBs high-risk	38	20 (52.6)	64.61±9.65	26 (68.4)	15 (39.5)
CMBs middle- risk	39	23 (59.0)	63.72±9.96	24 (61.5)	20 (51.3)
CMBs low-risk	39	24 (61.5)	63.28±11.96	28 (71.8)	17 (43.6)
x^2/F		0.680	0.482	1.028	1.298
P		0.878	0.696	0.795	0.730

Evaluation of Intracranial Micro-Hemorrhage Transformation, Neurological Function Recovery, and Long-Term Prognosis

The subjects in both groups were administered dual antiplatelet therapy for 21 days and then underwent head CT examination; their NIHSS scores were recorded. Among them, five female patients had intracranial hemorrhage (5/116, 4.3%) in the CMB group, while no intracranial hemorrhage was observed (0/39, 0.0%) among the non-CMB group, with no significant difference ($p>0.05$). The NIHSS score was used to evaluate the recovery of neural function in the two groups of subjects upon admission and 21 days after dual-antibody treatment. The results showed that there was no significant difference between the two groups in terms of NIHSS score ($p>0.05$) (Table 3). The mRS was used to evaluate the prognosis of patients in the two groups at 21 days, 3 months, and 6 months after dual-antibody treatment. The results showed that there was no significant difference in the mRS scores between the two groups ($p>0.05$) (Table 4).

Evaluation of Hemorrhage Transformation, Neural Function, and Prognosis Among Sub-Groups

The subjects in the subgroups and the non-CMB group were treated with dual antiplatelet therapy, and head CT was performed 21 days later to assess the extent of bleeding transformation of the subjects in each group after treatment with dual antiplatelet therapy. Among them, five female patients had intracranial hemorrhage (5/38, 13.2%) in the high-risk group, they were elderly people aged 80–85, those in the medium-risk group had no intracranial hemorrhage (0/39, 0.0%), those in the low-risk group had no intracranial hemorrhage (0/39, 0.0%), and those in the non-CMB group also had no intracranial hemorrhage (0/39, 0.0%).There was no significant difference in the percentage of intracranial hemorrhage between the low-, medium-, and non-CMB groups ($p>0.05$); however, there was a significant difference in the percentage of intracranial hemorrhage between the high-risk and non-CMB groups ($p<0.05$). The NIHSS score was assessed 21 days later and showed that there was no significant difference in the recovery of neurological function among the subjects in each group after the application of dual antiplatelet therapy ($p>0.05$) (Table 5). Patients in each group were scored using the mRS 21, 3, and 6 months after treatment. The results of the prognosis after dual antiplatelet therapy showed no significant difference between the mRS scores of patients in the low-risk, medium-risk, and high-risk groups and the non-CMB group at the same time during treatment ($p>0.05$) (Table 6).

Table 3 NIHSS Scores of Subjects in Two Groups at Admission and 21 d After Dual Anti-Treatment ($\bar{x}\pm s$)

Group	n	Admission	21d after dual anti-treatment
Non-CMBs	39	2.10±0.58	1.48±0.51
CMBs	116	2.07±0.63	1.60±0.49
T		0.273	1.374
P		0.785	0.171

Table 4 mRS Scores of Subjects in Two Groups at 21 d, 3 Months and 6 Months After Dual Anti-Treatment [n(η/%)]

Group	n	21d after dual anti-treatment		3 months after dual anti-treatment		6 months after dual anti-treatment	
		Good	Bad	Good	Bad	Good	Bad
Non-CMBs	39	38 (97.4)	1 (2.6)	38 (97.4)	1 (2.6)	38 (97.4)	1 (2.6)
CMBs	116	109 (94.0)	7 (6.0)	111 (95.7)	5 (4.3)	112 (96.6)	4 (3.4)
χ^2		0.184		0.000		0.064	
P		0.668		0.992		0.800	

Notes: $\chi^{2:}$ Adjusted χ^2 value.

Table 5 NIHSS Scores of Subjects in Each Group at 21d After Dual Anti-Treatment ($\bar{x}\pm s$)

Group	n	NIHSS score
Non-CMBs	39	1.48±0.51
CMBs high-risk	38	1.67±0.54
CMBs middle-risk	39	1.61±0.46
CMBs low-risk	39	1.52±0.49
F		1.271
P		0.287

Table 6 mRS Scores of Subjects in Each Group at 21 d, 3 Months and 6 Months After Dual Anti-Treatment [n(η/%)]

Group	n	21d after dual anti-treatment				3 months after dual anti-treatment				6 months after dual anti-treatment			
		Good	Bad	χ^2	*P*	Good	Bad	χ^2	*P*	Good	Bad	χ^2	*P*
Non-CMBs	39	38 (97.4)	1 (2.6)			38 (97.4)	1 (2.6)			38 (97.4)	1 (2.6)		
CMBs high-risk	38	36 (94.7)	2 (5.3)	0.001	0.982	36 (94.7)	2 (5.3)	0.001	0.982	36 (94.7)	2 (5.3)	0.001	0.982
CMBs middle-risk	39	37 (94.9)	2 (5.1)	0.000	1.000	37 (94.9)	2 (5.1)	0.000	1.000	38 (97.4)	1 (2.6)	0.000	1.000
CMBs low-risk	39	38 (97.4)	1 (2.6)	0.000	1.000	38 (97.4)	1 (2.6)	0.000	1.000	38 (97.4)	1 (2.6)	0.000	1.000

Notes: χ^2: Adjusted χ^2 value.

Follow-Up: Adverse Reactions and Their Occurrence

On day 13 of treatment, three patients stopped using dual antiplatelet therapy due to upper gastrointestinal symptoms, and two patients switched to aspirin (0.1 g oral antiplatelet aggregation) on days 16 and 21, respectively, due to personal preference. None of the patients experienced cerebral hemorrhage after discharge.

Discussion

An observational study was performed to compare the risk-benefit ratio of dual antiplatelet therapy with aspirin in combination with clopidogrel between the CMB and non-CMB groups. Only 4.3% (5/116) of patients had recurrent intracranial hemorrhage in the high-risk subgroup among the CMB group. Guidelines for ischemic stroke recommend antiplatelet aggregation as the basic drug for treatment and secondary prevention.[25] Intracranial hemorrhage is the most important complication associated with such treatments. The selection of the optimal therapy for the prevention of secondary stroke is key.[26] Aspirin remains the only drug recommended for its antiplatelet aggregation effect, as confirmed by clinical studies; it exerts a positive influence in reducing ischemic events in high-risk groups.[27] Aspirin can inhibit platelet aggregation by inhibiting the cyclooxygenase pathway, which can improve cardiovascular and cerebral circulation, in addition to improving the elasticity of blood vessels. In addition, it was deemed safe and less damaging to the human gastrointestinal tract, so it is more readily accepted by patients; however, because platelet aggregation can be activated via multiple pathways, aspirin can only inhibit the cyclooxygenase pathway, it has little effect on the adenosine diphosphate P2Y12 receptor pathway.[23] Clopidogrel, on the other hand, permanently binds to adenosine diphosphate receptors on the surface of platelets, thereby blocking adenosine diphosphate receptors and inhibiting platelet aggregation.[20] Published trial data suggests an aspirin combination with clopidogrel is safe and effective with synergistic function in comparison to single antiplatelet therapy for secondary prevention.[28] It is noteworthy that both aspirin and clopidogrel for the recommended maintenance dose and loading dose were distinct in Chinese guidelines and in several other countries.[29] Our findings revealed that dual antiplatelet therapy was safe for use among ischemic stroke patients with CMBs. These results are consistent with those of previous studies.[30–32] Chai et al found that the combination of clopidogrel and aspirin can significantly improve the therapeutic effect, reduce the

incidence of adverse reactions, and improve the quality of life and neurological function in patients with acute cerebral infarction complicated with cerebral micro-hemorrhage.[33] A study proposed that CMBs occurring in the cortex and subcortical white matter area, basal nucleus, and thalamus are closely related to primary intracerebral hemorrhage (pICH), and that the intensity of the connection between them in the cortex and subcortical white matter areas is higher than that in the basal nucleus and thalamus.[1,34] Roob et al found that most CMBs in the basal nuclei and thalamus were found in patients with pICH in the basal nuclei or thalamus regions, and most CMBs in the cortex and subcortical regions were found in patients with lobar hemorrhage. The locus of CMB may be where pICH will occur in the future.[35]

CMB is an early warning signal for amyloid angiopathy and hypertensive cerebrovascular disease.[36] CMB can predict recurrent ICH, ICH after anticoagulation, or ICH during antiplatelet therapy to prevent ischemic stroke and other complications. Therefore, MRI examination for CMB has important clinical value in the primary and secondary prevention and treatment of ischemic stroke and coronary heart disease during thrombolytic therapy. It is a thrombolytic contraindication for patients with a history of ICH, confirmed by CT, to be ready for thrombolytic and anticoagulant therapy.[37] A literature reported that the incidence of CMB was high after SWI in patients with acute ischemic stroke on admission, and there was a potential association between the use of antiplatelet drugs and CMBs.[38,39] The early discovery of factors that may lead to the transformation of bleeding after thrombolytic therapy will help screen thrombolytic cases, thus minimizing the occurrence of complications and reducing medical disputes.[40–42]

In this study, factors associated with an increased risk of ischemic events included elderly people aged 80 or more older, women suffering from lacunar infarct more frequently with obesity, diabetes and hypertension. Severe or life-threatening bleeding occurred in 4.3% (5/116) in the high-risk subgroup among the CMB group during follow-up the dual therapy period. The five female patients were elderly more than 80 with the similar demographics and risk factors. Our findings were in accordance with the previously reporters.[43,44]

Limitations of the Study

This study has certain shortcomings related to the short follow-up time and the small sample size. As a single-center cross-sectional study, the results of this study may be biased, and some patients were unable to cooperate with long-term SWI examinations for personal reasons; therefore, there remains a lack of long-term imaging data. Therefore, our research team will increase the sample size, extend the observation time, and explore the relationship between the number, location, and diameter of CMBs and antithrombotic therapy through a detailed study of subgroups in the future. To clarify whether patients with ischemic stroke complicated by CMB in the high-risk group will be subjected to bleeding transformation after dual antibody treatment, and whether the SWI sequence can be used as a routine screening sequence for patients who received antiplatelet treatment, especially those requiring long-term antiplatelet treatment, to identify disease risk factors and guide the prognosis of patients.

Conclusion

The results showed that the use of dual antiplatelet therapy in patients with ischemic stroke complicated by CMBs did not increase the risk of intracranial microbleed transformation and affected the recovery of neural function and long-term prognosis. The findings prove that the use of dual antiplatelet therapy in patients with ischemic stroke complicated by CMBs can increase the risk of bleeding transformation in high-risk groups by further classifying the severity of low-, medium-, and high-risk patients. The risk of bleeding transformation in the low- and medium-risk groups was not high, and the effects on neurological function recovery and prognosis in the three subgroups were insignificant. Therefore, dual antiplatelet therapy may be safe and seems to be a pharmacotherapeutic regimen that could be recommended for patients with ischemic stroke complicated by CMBs. Before stopping antiplatelet therapy, the risk-benefit ratio should be evaluated. Besides, a better knowledge of age and gender-related differences in the ischemic events' risk factors may be useful for the stratification of CMB patients in dual antiplatelet therapy in the subgroup of very old patients, especially in women (aged 80 years or older).

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

The study was approved by the Ethics Committee of our hospital (formal ethical approval number: Protocol Number 2021-23) and all patients signed an informed consent form.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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