

Metformin use is associated with low risk of case fatality and disability rates in first-ever stroke patients with type 2 diabetes

Wen-Jun Tu*, Zheng Liu*, Bao-Hua Chao, Feng Yan, Lin Ma, Lei Cao, Xun-Ming Ji and Long-De Wang 

Abstract

Background: To assess the effectiveness of metformin treatment on long-term outcomes in first-ever stroke patients with type 2 diabetes mellitus (T2DM) in China.

Methods: From August to September 2019, all patients with first-ever stroke and T2DM from 232 hospitals in China Mainland were included. The enrolled patients were divided into two groups: the metformin treatment (MT) and the no-metformin treatment (No-MT) groups. All discharged patients would receive a telephone follow-up at 12-month after admission.

Results: In total, 7587 first-ever stroke patients with T2DM [age: median (IQR) = 66 (57–73) years; 57.35% male] were recruited. Out of those 7587 included patients, 3593 (47.36%) received MT. The in-hospital case fatality rate was lower in the MT group than the No-MT group [MT group *versus* No-MT group: 1.09% *versus* 2.30%; absolute difference = -1.75% (95% CI = -2.15 to -1.17%); OR = 0.63 (95% CI = 0.47 to 0.84)]. The 12-month case fatality rate was lower in the MT group than the No-MT group [4.72% *versus* 8.05%; absolute difference = -4.05% (95% CI = -5.58 to -2.41); OR = 0.69 (95% CI = 0.50 to 0.88)]. The 12-month disability rate was also lower in the MT group than the No-MT group [14.74% *versus* 19.41%; absolute difference = -5.70% (95% CI = -7.25 to -3.22); OR = 0.83 (95% CI = 0.70 to 0.95)]. Furthermore, the recurrence rate did not differ significantly between the MT and No-MT groups ($p=0.29$).

Conclusion: The study reveals that metformin use in stroke patients with T2DM results in a less severe stroke and lower fatality and disability rates.

Keywords: metformin, prognosis, stroke, type 2 diabetes

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Background

China accounts for the most significant number of people with type 2 diabetes mellitus (T2DM), and the weighted prevalence of T2DM in Chinese adults using the World Health Organization (WHO) criteria was 11.2%.¹ T2DM is a stroke risk factor, and it may be responsible for more than 8% of first ischemic stroke.² Stroke is associated with the highest disability-adjusted life-year loss in China, and the burden is expected to continue to rise.³ Therefore, the prevention and treatment of stroke and diabetes are of great significance

to the work of chronic non-communicable diseases in China.

To date, several anti-diabetic agents (metformin, pioglitazone, and semaglutide) have been shown to affect stroke prevention positively.² Metformin, a well-established AMPK activator, is the most promising first-line anti-diabetic drug.⁴ In the United States, metformin was the eighth most commonly prescribed drug consistently from 2008 (51.6 million) to 2012 (61.6 million).⁵ In addition, metformin has also been shown to be

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effective in various other conditions, including cancer,⁶ weight reduction,⁷ fragile X syndrome,⁸ cardiovascular diseases,⁹ anti-aging,¹⁰ and stroke.²

Previous animal experiments have shown that pre-treatment with metformin offers neuroprotection against mitochondrial brain dysfunction, apoptosis, and microglial activation in an adenosine 5'-monophosphate-activated protein kinase (AMPK)-independent manner following cardiac ischemia/reperfusion injury.^{11,12} Furthermore, another study demonstrated that metformin has age- and sex-dependent effects on neural precursor cells that correlate with functional recovery, which has important implications for neural repair in the neonatal stroke model.¹³ Furthermore, Cheng *et al.*¹⁴ showed that metformin therapy could reduce stroke incidence in patients with diabetes. At the same time, another study found that administration of metformin in DM patients before stroke onset was associated with reduced neurological severity and improved acute-phase therapy outcomes.¹⁵ Furthermore, metformin could reduce the incidence and severity of stroke in patients with T2DM,¹⁶ and AMPK (which is a target for metformin) is a significant potential target for stroke treatment and prevention.¹⁷

In China and other parts of the world, pre-stroke metformin treatment (MT) on long-term prognosis in stroke patients with T2DM is unproved. Therefore, a prospective nationwide hospital-based cohort study was conducted to assess the effectiveness of MT on long-term outcomes in first-ever stroke patients with T2DM in China.

Patients and methods

This was a prospective nationwide hospital-based cohort study. From August to September 2019, 232 hospitals from 30 provinces (not including Tibet) in China Mainland were included.¹⁸ During the investigation, all patients with first-ever stroke [ischemic stroke (ICD63), intracerebral hemorrhage (ICD61), and subarachnoid hemorrhage (ICD60)] and T2DM were included. Patients were eligible for inclusion if admitted to the hospitals with a stroke defined according to the WHO criteria and with symptom onset within 14 days. CT and MRI were used to verify the diagnosis at admission. T2DM included the number of patients with self-reported diabetes and the number of patients with newly diagnosed

diabetes at admission according to the WHO criteria (among the participants without self-reported diabetes: fasting plasma glucose ≥ 7.0 mmol/l or oral glucose tolerance test: 2-h plasma glucose ≥ 11.1 mmol/l).¹⁹ This study's data collection and reporting system was the Bigdata Observatory Platform for Stroke of China (BOSC; <https://www.chinasdc.cn/>).

Hospitals with a sample size of less than 50 and a follow-up rate of less than 80% will be excluded. Also, patients with (1) lack of informed consent, (2) lost to follow-up, and (3) lack of crucial clinical information [such as MT information (yes or no) and functional scores during follow-up] would be excluded. The Ethics Committee of Brain Hospital of Hunan Provincial (No. Z2019007), Changsha, China, approved the study protocol according to the Declaration of Helsinki. Written informed consent was obtained from patients before enrollment. Patients or the public were not involved in our research design, conduct, reporting, or dissemination plans.

At admission, hospital characteristics [including hospital level (tertiary and secondary), teaching hospital (yes or no), province, and stroke unit (yes or no)] and patient baseline characteristics [including age, sex, race/ethnicity, hypertension, duration of diabetes, hyperlipidemia, atrial fibrillation, transient ischemic attack (TIA), and family history of stroke] were recorded. Stroke severity at admission was assessed by our cerebrocardiac health advisors (CHAs), according to the National Institutes of Health Stroke Scale (NIHSS). All CHAs need to be uniformly trained and certified before taking up their jobs. Acute treatment (thrombolysis and endovascular treatment) for ischemic stroke was recorded, and door-to-needle time (DNT) was calculated (≤ 45 , 45–60, 60–90, and > 90 min). Medical insurance (yes or no), length of stay, and medical expenses were also obtained. MT before and during hospitalization was recorded (yes or no). Finally, the outcome of hospitalization (death, discharge against medical advice, medical discharge, and transfer) was obtained.

Follow-up and outcomes

All discharged patients would receive a telephone follow-up at 12-month after admission. CHAs were blinded to the clinical information and used

a standardized questionnaire to interview patients or caregivers. The primary endpoint was a good functional outcome, defined as a modified Rankin Scale (mRS) score (ranging from 0 to 6) of 0–2 points. Disability events were defined as an mRS score of 3–5 points. The secondary endpoint was death within the follow-up. Furthermore, stroke recurrence events were also recorded, defined as suddenly deteriorated neurological function evaluated as a decreased NIHSS score of 4 or more or a new focal neurological deficit of vascular origin that lasted for more than 24 h.

Calculation and justification of the sample size

In this study, the in-hospital case fatality was decreased by 1.21% from 2.30% (No-MT group) to 1.09% (MT group), and the death rate in the follow-up was reduced 3.33% from 8.05% (No-MT group) to 4.72% (MT group). Therefore, a total of 3566 patients (1783 patients per group) would be required to detect a 1.21% improvement in in-hospital case fatality, with 80% power (two-sided $p=0.05$) and an intra-cluster correlation coefficient (ICC) of 0.02.²⁰ Finally, we recruited a sample of about 3500 cases in each group (from 3554 to 3994), suggesting that the sample size of this study could meet the research requirements.

Statistical analysis

The data were shown as n (%) for categorical variables and as median (IQR) for continuous variables. Chi-square test and Mann–Whitney's U test were used for comparison between groups.

The enrolled patients were divided into two groups according to MT or not: MT group (defined as MT before and during hospitalization) and No-MT group. Multivariable regression models were used to compare the outcomes between the MT and No-MT groups, and the absolute differences with 95% CIs were presented. All multivariable models were adjusted for patient characteristics and hospital characteristics including province, hospital level, teaching hospital, stroke unit, age, sex, race, hypertension, hyperlipidemia, atrial fibrillation, TIA, family history of stroke, duration of diabetes, NIHSS at admission, acute treatment (thrombolysis and endovascular), and length of stay. The results were presented as odds ratio (OR) and 95% confidence intervals (CIs).

All p -values less than 0.05 were the threshold for statistical significance. All statistical analyses were conducted with SAS version 9.4 and Stata version 14.1.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

As shown in Figure 1, 232 hospitals from 30 provinces participated in this study. Of which, 28 hospitals had been excluded, and 194 hospitals were finally included. In total, 7587 first-ever stroke patients with T2DM [age: median (IQR) = 66 (57–73) years; 57.35% male] were recruited. Among these patients, 3911 (51.55%) were from tertiary hospitals, 878 (11.57%) from teaching hospitals, and 4215 (55.56%) from stroke unit hospitals. A total of 5947 (78.38%) patients had a history of hypertension, 1834 (24.17%) had hyperlipidemia, 421 (5.55%) were diagnosed with atrial fibrillation, 446 (5.88%) had a family history of stroke, and 128 (1.69%) had TIA. The median duration of diabetes was 12 (IQR = 8–19) years.

At admission, the median NIHSS score was 3 (IQR = 1–5) points. The rate of intravenous thrombolysis in acute ischemic stroke was 7.66% (515/6719), and more than three-quarters (76.9%) of patients have a DNT time of less than 1 h. The median length of hospital stay was 10 (IQR = 8–14) days, and the medical expense was ¥ 12,452 (IQR = 8032–19,989). More information is listed in Table 1.

Demographic and clinical information between MT and No-MT groups

In total, 3593 (47.36%) out of 7587 included patients received MT. Patients receiving MT were more likely coming from tertiary (58.89% *versus* 45.22%) and stroke unit (62.48% *versus* 49.32%) hospitals. These patients were more likely young [65 (IQR = 57–72) *versus* 66 (57–74) years], female (43.92% *versus* 41.51%), and Han nationality (98.50% *versus* 96.90%). As shown in Table 1, these patients were less likely to have atrial fibrillation (4.65% *versus* 6.36%).

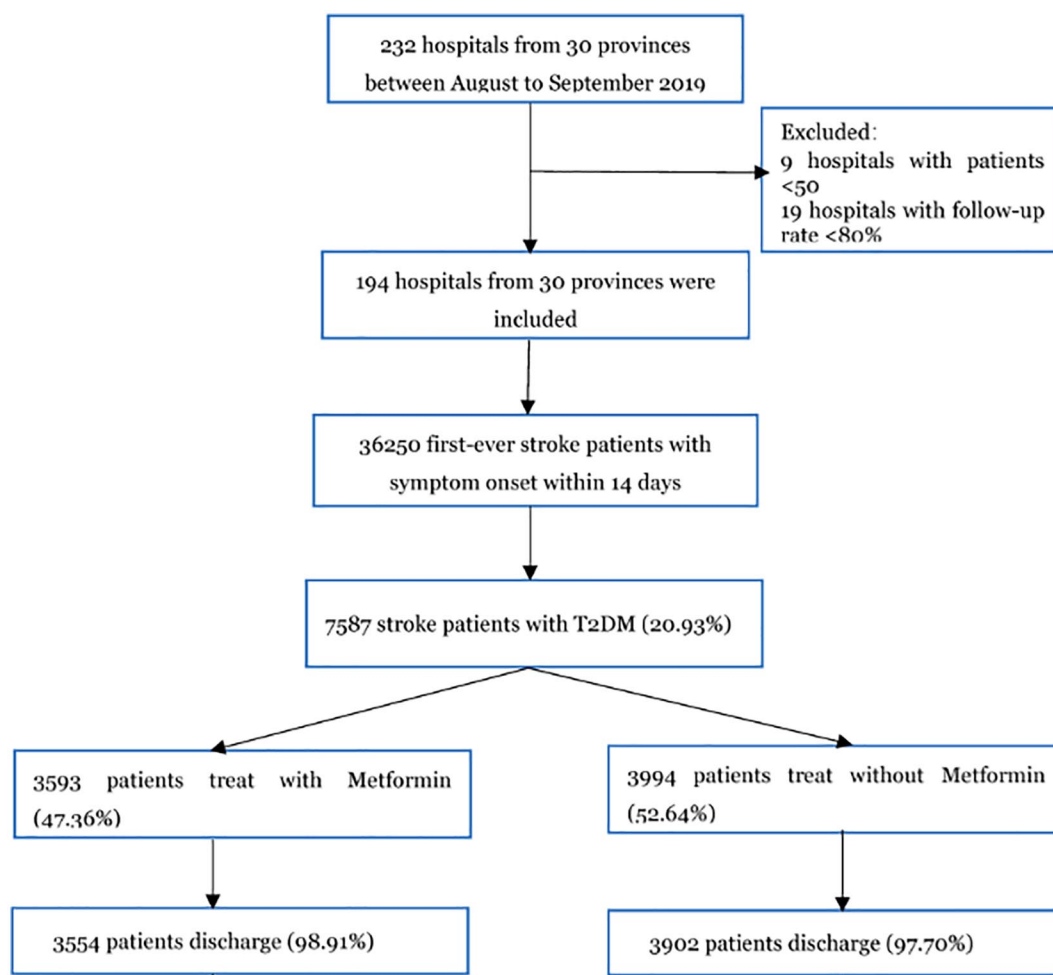


Figure 1. Study profile/flow sheet of the study.

Besides, these patients had a shorter duration of diabetes [10 (IQR = 6–17) *versus* 14 (11–22) days] and less severe illness at admission [NIHSS score: 3 (1–5) *versus* 3 (1–6)]. Furthermore, these patients were less likely to receive thrombolytic therapy (6.88% *versus* 8.40%), while shorter DNT had been obtained in these patients (DNT \leq 60 min: 82.14% *versus* 72.85%). Finally, patients receiving MT were more likely to have medical insurance (94.60% *versus* 92.49%) and paid fewer medical expenses during hospitalization [¥ 11,612 (IQR = 7557–1837) *versus* 13,263 (8513–21,587)]. The length of stay did not differ significantly between these two groups ($p=0.75$). More information is listed in Table 1.

In-hospital and follow-up results

Table 1 shows the in-hospital case fatality and discharge against medical advice rates. At discharge,

the case fatality rate and fatality/discharge against medical advice rate were 1.73% (95% CI = 1.43 to 2.02) and 5.92% (5.38 to 6.45), respectively. The in-hospital case fatality rate was lower in the MT group than the No-MT group [MT group *versus* No-MT group: 1.09% *versus* 2.30%; absolute difference = -1.75% (95% CI = -2.15 to -1.17); OR = 0.63 (95% CI = 0.47 to 0.84)]. The in-hospital case fatality/discharge against medical advice rate was also lower in the MT group than the No-MT group [MT group *versus* No-MT group: 4.40% *versus* 7.29%; absolute difference = -3.56% (95% CI = -4.88 to -2.15); OR = 0.79 (95% CI = 0.60 to 0.91)].

Table 2 shows the long-term case fatality, recurrence, and disability outcomes at 12 months after admission. The 12-month case fatality, recurrence and disability rates were 6.46% (95% CI = 5.88 to 7.04), 7.17% (6.54 to 7.80), and

Table 1. Demographic characteristics and clinical information of the included patients.^a

| | All | Metformin treatment | | p ^b |
|--|------------------------|------------------------|------------------------|----------------|
| | | Yes | No | |
| No. of patients, n | 7587 | 3593 | 3994 | – |
| Hospital level: tertiary, n (%) | 3911 (51.55) | 2105 (58.89) | 1806 (45.22) | < 0.001 |
| Teaching hospitals, n (%) | 878 (11.57) | 442 (12.30) | 436 (10.92) | 0.060 |
| Stroke unit, n (%) | 4215 (55.56) | 2245 (62.48) | 1970 (49.32) | < 0.001 |
| Sex: male, n (%) | 4351 (57.35) | 2015 (56.08) | 2336 (58.49) | 0.034 |
| Ages (years), median (IQR) | 66 (57–73) | 65 (57–72) | 66 (57–74) | < 0.001 |
| Ethnic: Han, n (%) | 7409 (97.65) | 3539 (98.50) | 3870 (96.90) | < 0.001 |
| Basic illness, n (%) | | | | |
| Hypertension | 5947 (78.38) | 2789 (77.62) | 3158 (79.07) | 0.127 |
| Hyperlipidemia | 1834 (24.17) | 867 (24.13) | 967 (24.21) | 0.934 |
| Atrial fibrillation | 421 (5.55) | 167 (4.65) | 254 (6.36) | 0.001 |
| TIA | 128 (1.69) | 59 (1.64) | 69 (1.73) | 0.773 |
| Family history of stroke | 446 (5.88) | 211 (5.87) | 235 (5.88) | 0.983 |
| Duration of diabetes (years), median (IQR) | 12 (8–19) | 10 (6–17) | 14 (11–22) | 0.008 |
| NIHSS score at admission | 3 (1–5) | 3 (1–5) | 3 (1–6) | < 0.001 |
| Acute treatment for ischemic stroke, n | 6719 | 3255 | 3464 | – |
| Thrombolysis | 515 (7.66) | 224 (6.88) | 291 (8.40) | < 0.001 |
| DNT, min | – | | – | < 0.001 |
| <45 | 248 (48.16) | 115 (51.34) | 133 (45.70) | – |
| 45–60 | 148 (28.74) | 69 (30.80) | 79 (27.15) | – |
| 60–90 | 55 (10.68) | 21 (9.38) | 34 (11.68) | – |
| >90 | 64 (12.43) | 19 (8.48) | 45 (15.46) | – |
| Endovascular treatment | 263 (3.91) | 99 (3.04) | 164 (4.73) | < 0.001 |
| No medical insurance, n (%) | 494 (6.51) | 194 (5.40) | 300 (7.51) | < 0.001 |
| Length of stay (days), median (IQR) | 10 (8–14) | 10 (8–14) | 10 (8–14) | 0.746 |
| Medical expense (CNY), median (IQR) | 12,452 (8032–19,989) | 11,612 (7557–1837) | 13,263 (8513–21,587) | < 0.001 |
| Discharge, n [% (95% CI)] | | | | < 0.001 |
| Death | 131 [1.73 (1.43–2.02)] | 39 [1.09 (0.75–1.42)] | 92 [2.30 (1.84–2.77)] | – |
| Discharge against medical advice | 318 (4.19) | 119 (3.31) | 199 (4.98) | – |
| Discharge according to medical advice | 7138 (94.08) | 3435 (95.60) | 3703 (92.71) | – |
| Death/discharge against medical advice | 449 [5.92 (5.38–6.45)] | 158 [4.40 (3.73–5.07)] | 291 [7.29 (6.48–8.09)] | < 0.001 |

CNY, China Yuan; DNT, door-to-needle; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

^aContinuous variables are presented as median (IQR) and categorical variables as frequency (%).

^bChi-square test and Mann–Whitney's U-test were applied for comparing groups.

Table 2. The 12-month follow-up information of the included patients.^a

| | All | Metformin treatment | | <i>p</i> ^b |
|-------------------------------------|----------------------------|---------------------------|---------------------------|-----------------------|
| | | Yes | No | |
| No. of patients at discharge, n | 7456 | 3554 | 3902 | – |
| Follow-up, n [%] | | | | 0.322 |
| Lost the follow-up | 550 (7.38) | 251 (7.06) | 299 (7.66) | – |
| Finished the follow-up | 6906 (92.62) | 3303 (92.94) | 3603 (92.34) | – |
| Follow-up outcome, n [% (95% CI)] | | | | |
| Case fatality | 446 [6.46 (5.88–7.04)] | 156 [4.72 (4.00–5.45)] | 290 [8.05 (7.16–8.94)] | < 0.001 |
| Survivors | 6460 (93.54) | 3147 (95.28) | 3313 (91.95) | < 0.001 |
| Recurrence of stroke | 463 [7.17 (6.54–7.80)] | 244 [7.75 (6.82–8.69)] | 219 [6.61 (5.76–7.46)] | 0.075 |
| mRS score of those stroke survivors | | | | < 0.001 |
| 0 | 2566 (39.7) | 1313 (41.7) | 1253 (37.8) | |
| 1 | 1821 (28.2) | 906 (28.8) | 915 (27.6) | |
| 2 | 966 (15.0) | 464 (14.7) | 502 (15.2) | |
| 3 | 668 (10.3) | 295 (9.4) | 373 (11.3) | |
| 4 | 306 (4.7) | 120 (3.8) | 186 (5.6) | |
| 5 | 133 (2.1) | 49 (1.6) | 84 (2.5) | |
| Case disability (mRS, 3–5) | 1107 [17.14 (16.22–18.06)] | 464 [14.74 (13.51–15.98)] | 643 [19.41 (18.06–20.76)] | < 0.001 |

CI, confidence interval; IQR, interquartile range; mRS, modified Rankin Scale.
^aContinuous variables are presented as median (IQR) and categorical variables as frequency [% (95% CI)].
^bChi-square test and Mann–Whitney's U-test were applied for comparing groups.

17.14% (16.22 to 18.06). The case fatality rate was lower in the MT group than the No-MT group [MT group *versus* No-MT group: 4.72% *versus* 8.05%; absolute difference = –4.05% (95% CI = –5.58 to –2.41); OR = 0.69 (95% CI = 0.50 to 0.88)] (Figure 2). Figure 3 shows the mRS score of those stroke survivors stratified according to MT. The disability rate was also lower in the MT group than the No-MT group [MT group *versus* No-MT group: 14.74% *versus* 19.41%; absolute difference = –5.70% (95% CI = –7.25 to –3.22); OR = 0.83 (95% CI = 0.70 to 0.95)]. Furthermore, the recurrence rate did not differ significantly between the MT and No-MT groups [MT group *versus* No-MT group: 7.75% *versus* 6.61%; absolute

difference = 0.68% (95% CI = –0.37 to 1.55); OR = 1.03 (95% CI = 0.82 to 1.23); *p* = 0.29].

Subgroup analysis

We also examined the relationship between the prognostic role of MT and stroke subtypes. In ischemic stroke patients, the 12-month case fatality rate was lower in the MT group than the No-MT group [MT group *versus* No-MT group: 3.69% *versus* 6.66%; absolute difference = –3.49% (95% CI = –5.05 to –2.29); OR = 0.65 (95% CI = 0.48 to 0.84)] (Figure 4). In hemorrhage stroke (cerebral hemorrhage and subarachnoid hemorrhage) patients, the 12-month case fatality did not differ significantly

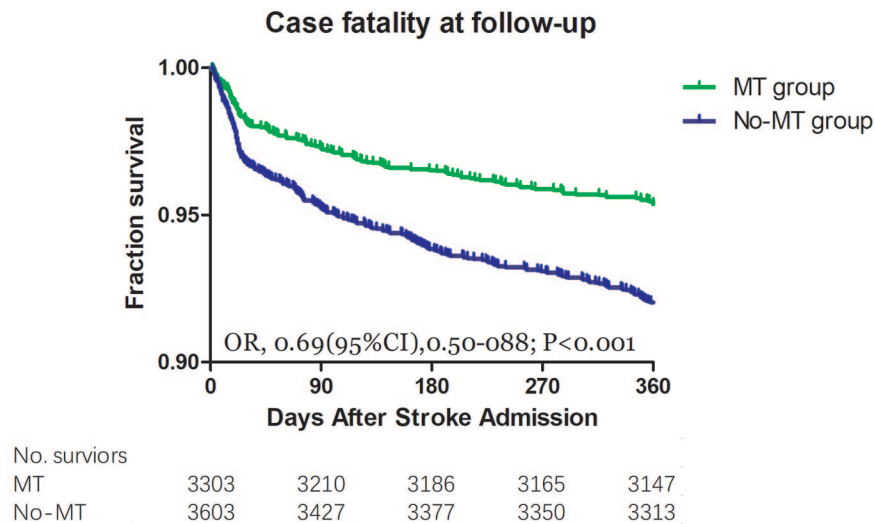


Figure 2. Case fatality at 12-month follow-up among the stroke patients with T2DM implementing MT treatment *versus* No-MT treatment. The log-rank test was used to compare the days after stroke admission to the case fatality. The numbers below the figure represent the number of surviving patients at different time points. MT, metformin; OR, odds ratio.

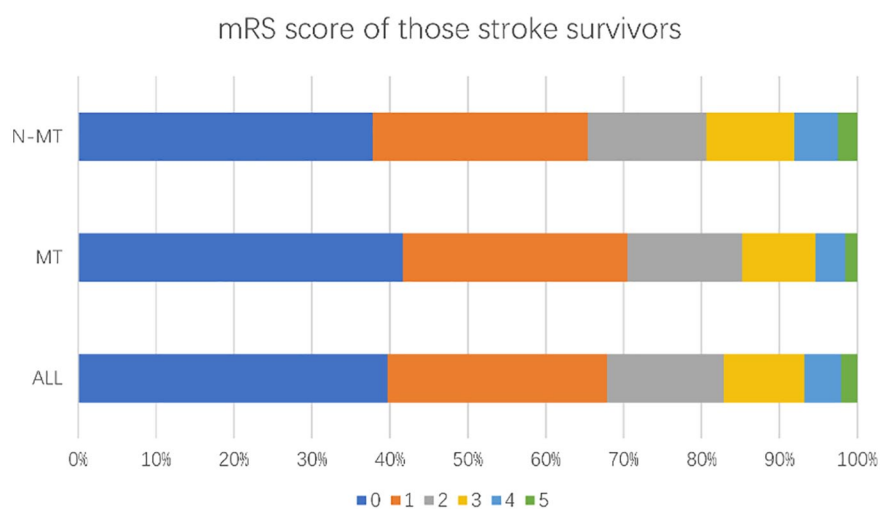


Figure 3. mRS score of those stroke survivors at 12-month follow-up stratified according to metformin treatment.

between the MT and No-MT groups [MT group *versus* No-MT group: 15.17% *versus* 18.81%; absolute difference = -4.05% (95% CI = -6.83 to -1.54); OR = 0.85 (95% CI = 0.68 to 1.26); $p=0.63$].

Discussion

This multicenter observational cohort study demonstrated that (1) stroke patients with T2DM receiving MT had less severe strokes on

admission and less case fatality rate at discharge compared to those not pretreated with metformin; (2) stroke patients with T2DM receiving MT had less long-term case fatality and disability rates compared to those not pretreated with metformin; (3) the long-term recurrence rate did not differ significantly between the MT and No-MT groups ($p=0.29$); (4) the association between stroke prognosis and metformin use was obtained in ischemic stroke rather than in hemorrhagic stroke.

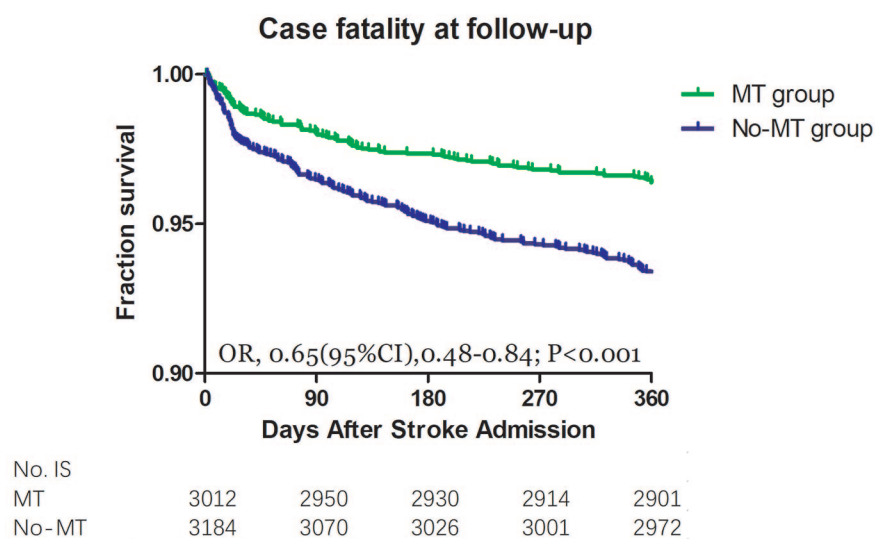


Figure 4. Case fatality at 12-month follow-up among the ischemic stroke patients with T2DM implementing MT treatment *versus* No-MT treatment. The log-rank test was used to compare the days after stroke admission to the case fatality. The numbers below the figure represent the number of surviving patients at different time points. MT, metformin; OR, odds ratio.

Consistent with our findings, Westphal *et al.*²¹ included 1919 patients with stroke and T2DM who underwent intravenous thrombolysis and found that patients receiving MT had less severe strokes on admission and a better functional outcome at 3 months, suggesting a protective effect of metformin resulting in less severe strokes as well as beneficial thrombolysis outcome. In a cohort of 12,156 patients with T2DM and high cardiovascular risk, Bergmark *et al.*²² reported that metformin use was associated with lower all-cause mortality rates, but not lower rates of the composite endpoint of cardiovascular death or ischemic stroke. Bromage *et al.*²³ showed that metformin use at the time of first acute myocardial infarction was associated with an increased risk of cardiovascular disease and death in patients with T2DM. A retrospective cohort study of 174,882 US veterans showed that monotherapy treatment with metformin, compared with a sulfonylurea, was associated with a lower risk of major adverse cardiovascular events (MACE) among patients with diabetes and reduced kidney function.²⁴

Furthermore, various evidence supports a reduced risk of adverse cardiovascular outcomes in T2DM.²⁵ One study reported that metformin use was associated with a lower risk of heart failure hospitalization in patients with new-onset

T2DM,²⁶ while another study found that metformin could lower the risk of death and cardiovascular events in individuals with T2DM and chronic kidney disease.²⁷ A cohort study showed that using metformin compared with sulfonylureas for the initial treatment of diabetes was associated with a reduced hazard of cardiovascular events or death.²⁸ A systematic meta-analysis found that metformin use could reduce all-cause mortality and aging diseases, suggesting that metformin could extend life and healthspans by acting as a neuroprotective agent.²⁹

In this study, we found that MT could not affect long-term stroke recurrence events. A meta-analysis of randomized trials did not confirm that metformin could reduce the risk of cardiovascular disease among patients with T2DM.³⁰ A nested case-control study, including 17,760 patients with T2DM and new-onset hemodialysis, showed that metformin use was associated with high stroke risk in hemodialysis patients with DM.¹⁶ Further research is needed to analyze these differences.

Metformin may improve stroke prognosis through the following pathways. (1) Metformin has antioxidant and anti-inflammatory properties by activating AMPK.³¹ Metformin mediated post-stroke recovery by enhancing angiogenesis, and these

effects are mediated by AMPK signaling.³² In addition, metformin might protect cells through modulating inflammatory and Nrf2 antioxidant pathways via induction of AMPK.³³ One study showed that metformin down-regulated ICAM-1 in an AMPK-dependent manner, which could effectively prevent ischemia-induced brain injury by alleviating neutrophil infiltration.³⁴ (2) AMPK-mediated microglia/macrophage polarization and angiogenesis may play essential roles in metformin-promoted, long-term functional recovery following stroke.⁴ Jin *et al.*³⁵ showed that post-stroke chronic MT improved functional recovery following MCAO via AMPK-dependent M2 polarization. (3) Metformin showed neuroprotection against ischemic brain injury after sudden cardiac arrest/cardiopulmonary resuscitation by augmenting AMPK-dependent autophagy activation.³⁶ (4) One study confirmed that metformin exerts neuroprotective effects by regulating ischemic stroke-induced oxidative stress injury via the lncRNA-H19/miR-148a-3p/Rock2 axis,³⁷ while another study suggested that metformin protected the hippocampus from ischemic damage through PI3 K/Akt1/JNK3/c-Jun signaling pathway in rats.³⁸ (5) One study suggested that metformin could directly inhibit glutamate-induced excitotoxicity in neurons.³⁹ Also, metformin attenuated stroke-induced nitric oxide signaling in diabetic rats.⁴⁰

This study had limitations. First, the causal relationship between metformin and stroke outcomes could not be confirmed by the observational study. Whether MT can improve the prognosis after stroke in patients with and without T2DM requires further research. A previous study showed that treatment with metformin in patients with TIA or minor ischemic stroke and impaired glucose tolerance was safe but led to minor side effects.⁴¹ In addition, MT before and during hospitalization was recorded. Most patients (97.5%) had been on metformin historically but not at the moment of hospitalization. Second, some patients who died may be caused by stroke recurrence. Unfortunately, we excluded dead patients during the analysis of recurrence events. This may reduce the correlation between metformin and stroke recurrence. Third, MT information was collected on admission. Some newly diagnosed diabetic patients might also be treated with metformin during the follow-up process, which had mixed effects on the results. In addition, some key variables were not included in the studies, including

metformin compliance, metformin dosage, and duration of MT. These factors may affect the association between metformin use and stroke prognosis. Further study should consider those uncertain factors. Fourth, it would be useful for the readers to understand this study if we could perform sensitivity analysis to see if our results were robust, such as defining MT group as continued use of metformin for at least 28 days or 3 months. However, in this study, we did not obtain the information about the duration of metformin prescribed. Further study should be carried out to perform sensitivity analysis to see if our results were robust. Finally, most of the patients included in this study were Chinese Han people (>98%). Whether patients from other nations and countries have similar conclusions remains to be studied. However, the Han nationality is the leading ethnic group in China (more than 90% of the total population), and we believe that our research sample can represent the entire Chinese population.

Conclusion

In conclusion, this study is the first to examine the outcome of metformin use and long-term prognosis in first-ever stroke patients with T2DM. It reveals that metformin use in stroke patients with T2DM results in a less severe stroke and lower fatality and disability rates. Our findings might support the clinical recommendations that metformin should be prescribed to stroke patients with T2DM. Randomized controlled studies are also required to determine whether metformin use may have a protective effect against the poor functional outcome in first-ever stroke patients with T2DM.

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Availability of data and materials

Please contact the author for data requests.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics statements

The Ethics Committee of Brain Hospital of Hunan Provincial (No. Z2019007), Changsha, China, approved the study protocol according to the Declaration of Helsinki. Written informed

consent was obtained from patients before enrollment.

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