Clinical study

Low-dose statins improve prognosis of patients with ischaemic stroke undergoing intra-arterial thrombectomy: A prospective cohort study

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ABSTRACT

Background: High-dose statins are recommended as preventive drugs in guidelines for patients with ischaemic stroke undergoing thrombectomy. Not only in clinical practice but also based on large-scale studies, low-dose statins have been widely used and demonstrated to be efficient in Asian populations. However, it remains unknown whether a low-dose statin is related to the prognosis of patients with thrombectomy. Can low-dose statins reduce the risk of bleeding at the same time?

Methods: We prospectively collected data from patients with acute ischaemic stroke undergoing intra-arterial thrombectomy. Efficacy outcomes were National Institutes of Health Stroke Scale (NIHSS) score improvement at 7 days after admission and a favourable functional outcome (FFO) at 90 days. Safety outcomes were rates of in-hospital haemorrhage events and death within 2 years.

Results: We included 256 patients in this study. Compared with the control group, the low-dose statin group had a higher NIHSS improvement rate at 7 days, a higher FFO rate at 90 days and a lower death rate within 2 years. The low-dose statin group had a lower percentage of gastrointestinal haemorrhage. Statin use was significantly related to an improved NIHSS score (p = 0.028, OR = 1.773) at 7 days and FFO (p < 0.001, OR = 2.962) at 90 days and to lower death rates (P = 0.025, or = 0.554) within 2 years.

Conclusion: In Asian acute ischaemic stroke patients with intra-arterial thrombectomy, low-dose statin use was significantly related to NIHSS improvement at 7 days, FFO at 90 days and decreased death rates within 2 years.

1. Introduction

Intravenous thrombolysis and intra-arterial thrombectomy is the recommended reperfusion therapy for patients with acute ischaemic stroke [1–2]. Statins are recommended as preventive drugs in guidelines for patients with ischaemic stroke [1]. According to guidelines, these patients should start high-intensity statins for secondary prevention immediately after onset [1].

The recommended high-intensity statins of current guidelines is based on a series of studies in Caucasians. In clinical practice in China, low-dose statins are commonly used in patients with ischaemic stroke due to different basic low-density lipoprotein levels and metabolic differences [3]. A previous study showed that pretreatment with statins is related to improved recanalization in acute ischaemic stroke patients after intra-arterial thrombectomy [4], though statin use does not correlate with the functional outcome or prognosis of patients. But the results were a subgroup analysis and the study included a lesser patient. In our previous studies, low-dose statins were associated with good functional outcomes in patients with recurrent stroke or thrombolysis treatment, but patients with thrombectomy were not included [5,6]. Overall, in patients with ischaemic stroke undergoing intra-arterial thrombectomy, it is unknown whether low-dose statin is related to prognosis.

In particular, it is controversial whether thrombectomy can increase the risk of cerebral haemorrhage of patients with ischaemic stroke [4,7–8]. Moreover, it is also controversial whether the use of high-intensity statins are associated with cerebral haemorrhage of patients with ischaemic stroke treated with thrombolysis [2,9]. Therefore, it needs to be investigated whether reducing the dose of statins results in a better prognosis and reduces the risk of bleeding at the same time in patients receiving thrombectomy.

To address this, we evaluated whether low-dose statins are related to...
an improved condition in the hospital and to improved functional outcomes 90 days after onset for acute ischaemic stroke patients who undergo intra-arterial thrombectomy. We also explored whether low-dose statins affect haemorrhage events in the hospital and death within 2 years.

2. Methods

2.1. Participants

The study was a prospective cohort study in which consecutive acute ischaemic stroke patients with intra-arterial thrombectomy were enrolled in the Department of Neurology, West China Hospital of Sichuan University. Diagnosis of stroke met the WHO (World Health Organization) stroke diagnostic criteria. Before intra-arterial thrombectomy treatment, all patients had a CTA + CTP examination. The thrombectomy devices included Rebar 18 microcatheter, and Synchro 14 micro guidewire. The intracranial rescue stenting with or without balloon angioplasty used Solitaire® (Medtronic, Dublin, Ireland) or Wingspan® (Stryker, Kalamazoo, MI, USA). We recruited patients from November 2018 to November 2020 and followed them through February 2021.

Patients who started low-dose statins within 24 h after intra-arterial thrombectomy were included in the low-dose statin group; patients who did not use statins during hospital were included in the control group. Except for using statins, low dose statin group and control group patients all had the same standard care by the guidelines. Low-dose statins were defined as atorvastatin 20 mg, simvastatin 10 mg and rosuvastatin 10 mg daily after onset [6].

We estimated the number of participants based on a previous study [9], 240 patients need to be included to achieve effective statistical efficacy considering a 20% loss of follow-up.

The inclusion criteria for acute ischaemic stroke patients were as follows. (1) Patients who were 18 years old or older and received intra-arterial thrombectomy within 24 h after onset; before intra-arterial thrombectomy treatment, the patients could receive intravenous thrombolysis treatment according to their condition. (2) Patients who did not receive any dose of statins or other lipid-lowering agent before onset. (3) Patients in the statin group started with low-dose statins within 24 h after thrombectomy. (4) Diagnosis was confirmed by neuroimaging evidence (CTA + CTP). (5) All patients had regular secondary therapy such as statins after discharge.

The exclusion criteria were as follows: (1) a modified Rankin scale (mRS) score ≥ 2 before onset; (2) placement of a stent or other endovascular treatment; (3) treatment with other doses of statins after discharge. (4) Patients who did not receive any dose of statins during hospital were included in the control group. Except for using statins, low-dose statin group and control group patients all had the same standard care by the guidelines. Low-dose statins were defined as atorvastatin 20 mg, simvastatin 10 mg and rosuvastatin 10 mg daily after onset [6].

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The exclusion criteria were as follows: (1) a modified Rankin scale (mRS) score ≥ 2 before onset; (2) placement of a stent or other endovascular treatment; (3) treatment with other doses of statins after the onset of the disease; (4) stroke associated with trauma or surgery; and (5) intracerebral haemorrhage, subarachnoid haemorrhage, or coagulopathy.

2.2. Definitions of risk factors

The definition of vascular risk factors was by AHAASA (American Heart Association/American Stroke Association) 2018 guidelines for ischaemic stroke [1], including hypertension, AF (atrial fibrillation) and other ages, sex, heart disease, diabetes, smoking, hypercholesterolemia, and smoking, among others. Stroke type was classified in accordance with the diagnostic standard of TOAST [10]. Cardioembolic stroke was proven by a definitive history or electrocardiography and cardiac colour ultrasound. ICH (intracerebral haemorrhage) was proven by CT in the hospital regardless of whether the condition of the patient changed. Gastrointestinal haemorrhage events included haematemesis and haematochezia. Seven-day LDL-C (low-density lipoprotein cholesterol) standard was defined as LDL-C less than or equal to 1.8 mmol/L. At 7 days after admission or a decrease in LDL-C by more than 50% at 7 days after admission [1]. Bridging therapy refers to thrombolytic therapy before endovascular thrombectomy. An Mrs (modified Rankin scale) score of 0–2 was defined as a favourable functional outcome (FFO). A difference in the National Institutes of Health Stroke Scale (NIHSS) scores between admission and at 7 days after admission greater than 4 was defined as NIHSS improvement.

2.3. Data collection and outcomes

Baseline data were collected from electronic medical records, and structured questionnaires were completed by the patients or their relatives. The data collected included demographic characteristics, condition at admission, medical disease and drug histories, and laboratory data at admission. In-hospital drug use and thrombectomy data (bridging treatment, location of vascular blockage, blood flow rating after thrombus removal) were also collected.

Efficacy outcome was NIHSS score improvement at 7 days and FFO (mRS≤−2) at 90 days; safety outcomes were intracerebral haemorrhage and gastrointestinal haemorrhage events in the hospital and death events within 2 years after onset. We performed subgroup analysis by evaluating different risk factors and thrombectomy factors. We collected NIHSS scores and haemorrhage events in the hospital through face-to-face interviews and electronic clinical records. Embolectomy data were evaluated and determined by professional neurointerventional physicians according to interventional operation data and digital subtraction angiography (DSA) images. We collected mRS scores and death events via telephone (two different phone numbers were used to contact the patients or their relatives), WeChat (an instant messaging application) or e-mail. All outcome events were evaluated by two neurologists, and any dispute was resolved by another senior neurologist. The group of patients was blinded to the evaluators.

2.4. Statistical analysis

To describe baseline characteristics, different types of variables are expressed as means and standard deviations (SDs), medians and frequencies, or numbers and percentages. Nonparametric tests and chi-square tests were conducted to compare differences between groups and outcomes.

We included risk factors according to the definition of guidelines and clinical significance [1]. Univariate and multivariate logistic analyses were applied to analyse the correlation between different risk factors and outcome events. First, univariate logistic analysis was employed to analyse the correlation between a single risk factor and the main outcome indicators. After univariate analysis, factors meeting the following requirements were included in the multivariate logistic analysis: (1) the P-value in the univariate logistic analysis was <0.1; (2) the index had clinical significance. Through logistic analysis, we calculated the likelihood ratio (ORS) and its 95% confidence interval (P-value). Multivariate logistic analysis was performed by using the forward step method. We analysed differences in outcome events according to whether the patients’ LDL-C level reached the guideline standard 7 days after admission.

In subgroup analysis, stroke type was subdivided as non-cardioembolic or cardioembolic. The type of therapy was subdivided into bridge therapy (thrombolysis before thrombectomy therapy) or thrombectomy therapy alone. The location of the thrombus was subdivided into the anterior (internal carotid, arterial cerebri anterior or middle cerebral artery) or posterior (posterior cerebral artery, vertebral basilar artery) circulation. The condition of recanalization was subdivided into complete (TICI (thrombolysis in cerebral infarction) 3, TICI 2b) and incomplete (TICI 0, TICI 1, TICI 2a). Effects of subgroup risk factors on outcomes were analysed using univariable logistic regression methods. Statistical significance was considered at P < 0.05. SPSS 23.0 was used to process the data.
3. Results

3.1. Patients

For 37 patients refused to participate in the study, we screened 300 patients this study finally included 256 patients (183 in the low-dose statin group and 73 in the control group) (Supplementary Fig. 1). The mean age was 66.62 ± 13.397 years, and 119 (46.5%) were female. The median (interquartile range) NIHSS score at admission was 15 (12–20).

In a comparison of the baseline data for two groups, the low-dose statin groups had a higher INR (international normalized ratio) value than the control group at admission; the LDL value was lower at 7 days after admission, and the proportion of patients with LDL reaching the standard at 7 days after admission was higher. There was no significant difference in baseline medicine and other baseline data between the two groups (Table 1).

In a comparison of the condition of thrombectomy therapy for two groups, the low-dose statin groups and control groups had a similar NIHSS score after thrombectomy and time from admin to thrombectomy. The two groups had not a significant difference in percentage of anterior circulation thrombus, bridge therapy, Intraarterial thrombolysis and complete recanalization (Table 1).

3.2. Efficacy outcomes

We found that the statin group had a greater NIHSS score improvement rate (P < 0.001) at 7 days and a higher FFO rate (P < 0.001) at 90 days than the control group (Table 1).

In univariate logistic regression analysis, the use of low-dose statins after onset (P < 0.001, or $= 2.246$) was associated with an improvement in the NIHSS score at 7 days after admission. The use of low-dose statins after onset (P < 0.001, or $= 3.585$) positively correlated with favourable functional outcomes 90 days after onset. The use of antiplatelet drugs and anticoagulants was associated with different outcomes (Supplementary Table 1).

In multivariable logistic regression analysis, we included all factors that had a significant association with the outcome of univariate logistic regression. We found that the use of low-dose statins after onset (P = 0.028, or $= 1.773$) still positively correlated with NIHSS score improvement at 7 days after admission after adjustment for risk factors. The use of low-dose statins after onset (P < 0.001, or $= 2.962$) also still positively correlated with favourable functional outcomes, as did the association of the use of antiplatelet drugs and anticoagulants with different outcomes (Table 2).

3.3. Safety outcomes

Compared with the control group, there was no significant difference in the incidence of a cerebral haemorrhage in the statin group (P = 0.261). The low-dose statin group had a lower rate of gastrointestinal haemorrhage than the control group (P = 0.016). The statin group had a lower death event rate (P < 0.001) within 2 years than the control group (Table 1).

In univariate logistic regression analysis, the use of low-dose statins after onset (P = 0.037, or $= 0.597$) negatively correlated with cerebral haemorrhage during hospitalization, and the use of low-dose statins after onset (P = 0.013, or $= 0.339$) negatively correlated with gastrointestinal bleeding during hospitalization. The use of antiplatelet drugs and anticoagulants was associated with different outcomes. the use of low-dose statins after onset (P < 0.001, or $= 0.343$) negatively correlated with death within 2 years. Furthermore, higher NIHSS scores 7 days after admission were associated with death events (Supplementary Table 2).

In multivariable logistic regression analysis, we included all factors that had a significant association with the outcome of univariate logistic regression. We found that after adjustment for risk factors, the use of anticoagulants during hospitalization still negatively correlated with cerebral haemorrhage, that other factors were no longer related to cerebral haemorrhage, and that no factors were related to gastrointestinal haemorrhage. the use of low-dose statins after onset (P = 0.025, or $= 0.554$) is still negatively correlated with death within 2 years, with higher NIHSS scores 7 days after admission still being associated with death events (Table 3).

3.4. Low-density lipoprotein subgroup analysis

We then performed a subgroup analysis of outcome events according to whether low-density lipoprotein (LDL-C) reached the recommended

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**Fig. 1.** Subgroup analysis of statins effect by type of stroke.
However, the incidence of gastrointestinal bleeding did not differ significantly (Table 4).

### Standard at 7 days after admission and showed that the proportion of NIHSS score improvement at 7 days and good functional outcome at 90 days in the standard subgroup was higher than that in the nonstandard group. The incidence of cerebral haemorrhage and death within 2 years in the standard subgroup was lower than that in the nonstandard subgroup. However, the incidence of gastrointestinal bleeding did not differ significantly (Table 4).

### Table 1

| Variables | Statins group (n = 183) | Control group (n = 73) | P* |
|-----------|-------------------------|------------------------|----|
| Age, years | 67.12 (13.653) | 67.43 (13.102) | 0.902 |
| Gender, female | 83(45.4) | 34(46.6) | 0.346 |
| Admission NIHSS score | 15(11.9) | 16(12.2) | 0.221 |
| NIHSS score after thrombectomy | 3(8-28) | 9(4-30) | 0.106 |
| Length of stay, days, mean (SD) | 9.34 (2.21) | 11.23 (1.92) | 0.117 |
| Anterior circulation thrombus, % | 153(83.6) | 63(86.3) | 0.597 |
| Bridge therapy, % | 50(27.3) | 21(28.8) | 0.698 |
| Intracerebral thrombolysis | 22(12.0) | 9(12.3) | 0.871 |
| Time from admission to thrombectomy, minute | 98.23 (20.133) | 101.01 (22.631) | 0.328 |
| Number of thrombectomies | 11(1-3) | 1(1-4) | 0.113 |
| Tic 2b-3 after thrombectomy, % | 156(85.2) | 61(83.6) | 0.196 |
| Anticoagulation drugs included warfarin, low molecular weight heparin, rivaroxaban and dabigatran. |

### Table 2

#### Multivariate logistic regression analysis results in efficacy outcome.

| Risk factor | NIHSS improvement at 7 days | FFO at 90 days |
|-------------|-----------------------------|---------------|
| OR(95%CI) P* | OR(95%CI) P* |
| Using low-dose statins | 1.773 (0.646-2.952) <0.001 | 2.962 (1.624-5.400) <0.001 |
| Using anticoagulation | 3.755 (1.899-7.422) 0.019 | 2.570 (1.166-5.665) 0.016 |
| Using low-dose statins | 3.602 (1.442-8.025) 0.024 | 2.728 (1.139-6.353) 0.028 |
| NIHSS at admission | – | 0.882 (0.811-0.960) 0.004 |
| INR | – | 0.608 (0.005-0.876) 0.399 |
| Glucose | 0.894 (3.086-0.992) 0.035 | – |

P* was calculated by multivariable logistic regression analysis. FFO favourable functional outcome; NIHSS National Institutes of Health Stroke Scale; TICI thrombolysis in cerebral infarction. In multivariable logistic regression analysis, we included all factors that had a significant association with outcome in univariate logistic regression (supplementary table 1).

### Table 3

#### Multivariate logistic regression analysis results in safety outcome.

| Risk factor | ICH | Death events within 2 years |
|-------------|-----|-----------------------------|
| OR(95%CI) P* | OR(95%CI) P* |
| Using low-dose statins | – | – | 0.554 (0.339-0.930) 0.025 |
| NIHSS at admission | – | – | 1.141 (1.119-1.173) <0.001 |
| Using anticoagulation | 0.330 (0.122-0.887) 0.001 | – |

P* was calculated by multivariable logistic regression analysis. NIHSS National Institutes of Health Stroke Scale; ICH intracerebral haemorrhage. In multivariable logistic regression analysis, we included all factors that had a significant association with outcome in univariate logistic regression (supplementary table 1).

### Table 4

#### Outcome events analysed by the LDL subgroup.

| Outcome | LDL-C standard group N = 88 | LDL-C non-standard group N = 134 | P* |
|---------|------------------------------|---------------------------------|----|
| NIHSS improvement, % | 74(73.3) | 93(62.4) | 0.074 |
| FFO at 90 days, % | 53(60.2) | 63(47.0) | 0.054 |
| ICH, % | 14(13.9) | 36(24.2) | 0.053 |
| Gastrointestinal haemorrhage, % | 9(8.9) | 13(8.7) | 0.959 |
| Death within 2 years, % | 20(22.5) | 39(29.1) | 0.272 |

P* was calculated by the Chi-square test. FFO favourable functional outcome; ICH intracerebral haemorrhage; LDL-C, low-density lipoprotein; NIHSS National Institutes of Health Stroke Scale.

### 3.5. Subgroup analysis

In subgroup analysis, the relationship between low-dose statin use and the outcome was significant in noncardioembolic patients, but the relationship between statins and gastrointestinal haemorrhage events was not significant. Nonetheless, the relationship between low-dose statin use and FOO was significant in patients with cardioembolism (Fig. 1), and the relationship between statins and outcome was significant in patients with anterior circulation thrombus but not in those with gastrointestinal haemorrhage. In addition, the relationship between...
scores at 7 days after admission; a higher proportion of patients also had gastrointestinal haemorrhage during hospitalization, and a lower proportion of patients had a cerebral haemorrhage and favourable functional outcomes at 90 days after onset. In the statin group, a lower proportion of patients had improved NIHSS in the complete recanalization subgroup. Overall, the location of the thrombus and bridging therapy had no significant effect on the correlation between low-dose statin use and outcome events. For lesser patients or events in the bridge therapy subgroup, posterior circulation thrombus and incomplete or nonrecanalization subgroup, these subgroup analysis results were inconclusive.

Though the cardiogenic stroke patients usually predominate over large-artery atherosclerosis in candidates for thrombectomy [11]. But the large-artery atherosclerosis patients had a higher proportion in the hospital [5,6]. Difference distract could partly explain the condition. So, the two types of patients’ thrombectomy had a similar in the study. The control group patients had a more severe condition than the statins group though the difference had not significant. And the control group of patients had more side-effect of statins. These could partly explain the control patients had not taken statins. In the meanwhile, these could partly explain the control patients had higher mortality.

Statin use was related to an improved short-term NIHSS score in this study, and the effect was significant in most subgroups. These results are consistent with studies involving ischaemic stroke patients with thrombolysis [7,12] and with other studies of ischaemic stroke populations [13]. The LDL value in the statin group after admission was opposite to that before admission, lower than that in the control group, and the proportion of patients with an LDL level reaching the guideline standard was also higher than that in the control group. According to the analysis of whether the LDL level reached the guideline standard, it was found that 7 days after admission, more patients in statins group met the standard. And these patients whose LDL level reached the guideline standard had a better prognosis than other patients, but the difference was not statistically significant.

Statin use was also related to a long-term FFO. The statin group had a higher FFO rate than the control group, and the effect was also significant in most subgroups. These results are consistent with those of other studies reporting that statins affect FFOs at 3 months in all acute ischaemic stroke patients [14].

The statin group had lower rates of ICH or gastrointestinal haemorrhage than the other groups. In univariate logistic regression analysis, the use of statins, antiplatelet drugs and anticoagulants was inversely related to the rate of ICH; the use of statins and antiplatelet drugs was inversely related to the rate of gastrointestinal haemorrhage. However, the effect was not significant in most subgroups, especially for gastrointestinal haemorrhage. This result suggests weak statistical power for this relationship. Nevertheless, statins might decrease the rate of gastrointestinal haemorrhage, as one study showed that statins can decrease the gastrointestinal haemorrhage rate in myocardial infarction patients [15]. Regardless, additional studies are needed to conclude the fewer gastrointestinal haemorrhage events in our study. The statin group had a lower death rate within 2 years than the control group; indeed, statin use was significantly related to decreased death rates within 2 years, and the effect was significant in most subgroups. Statins have a similar effect on mortality in ischaemic stroke patients after stenting [16]. Overall, the results suggest that statins do not increase the

4. Discussion

This study found that compared with the control group, a higher proportion of patients in the low-dose statin group had improved NIHSS scores at 7 days after admission; a higher proportion of patients also had favourable functional outcomes at 90 days after onset. The use of low-dose statins was associated with NIHSS score improvement at 7 days after admission and good functional outcome at 90 days after onset but not with cerebral haemorrhage and gastrointestinal haemorrhage during hospitalization. Moreover, low-dose statin use was associated with fewer deaths within 2 years of onset. Subgroup analysis showed that the correlation between statins and outcome events was statistically significant in the non-cardiogenic stroke subgroup but not in the cardiogenic stroke subgroup; the correlation between statins and outcome events was statistically significant in the complete recanalization subgroup but not in the incomplete recanalization subgroup. Overall, the location of the thrombus and bridging therapy had no significant effect on the correlation between low-dose statin use and outcome events. For lesser patients or events in the bridge therapy subgroup, posterior circulation thrombus and incomplete or nonrecanalization subgroup, these subgroup analysis results were inconclusive.

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![Fig. 2. Subgroup analysis statins effect by the position of thrombus.](image-url)
risk of haemorrhage events in patients with intra-arterial thrombectomy.

Our study had several limitations. First, this was an observational cohort study, and only correlation results were obtained. Second, we did not compare the specific doses of statins in our study because high-intensity statins are rarely used in Asian clinical practice; thus, it is difficult to obtain relevant data. Accordingly, the correlation between high-intensity statins and the prognosis of patients with thrombectomy needs further investigation. Third, the study included patients with thrombectomy and bridging. We conducted subgroup analysis according to different treatment methods, and bridging treatment did not change the correlation between statins and outcomes and prognosis, which is also similar to the results of the latest study [17]. Finally, the cardioembolic stroke patients were a lower proportion in our cohort than in other cohorts. Therefore further study including a higher proportion of cardioembolic stroke patients was needed.

In conclusion, the use of low-dose statin was associated with NIHSS score improvement at 7 days after admission and favourable functional outcomes at 90 days in patients with acute ischaemic stroke undergoing intra-arterial thrombectomy. The use of low-dose statins was not associated with cerebral haemorrhage or gastrointestinal haemorrhage during hospitalization. Low-dose statins were associated with fewer deaths within 2 years after onset. The beneficial effect of statins was more significant in patients with noncardiogenic stroke and those with complete recanalization after thrombectomy.
5. Declarations

Ethics approval and consent to participate: The study was performed by the Declaration of Helsinki and the ethical standards of the institutional and national research committees. The study was approved by the Ethics Committee of West China Hospital, Sichuan University, under approval number 2019 (319). All patients had given informed consent to participate.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: Chaohua Cui, Shuju Dong, Qian Liu, Jiajia Bao, Lijie Gao, Yanbo Li and Li He declares that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2022.07.001.

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