Perfusion imaging and recurrent cerebrovascular events in intracranial atherosclerotic disease or carotid occlusion

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Abstract
Background: Large vessel disease stroke subtype carries the highest risk of early recurrent stroke. In this study we aim to look at the association between impaired perfusion and early stroke recurrence in patients with intracranial atherosclerotic disease or total cervical carotid occlusion.

Methods: This is a retrospective study from a comprehensive stroke center where we included consecutive patients 18 years or older with intracranial atherosclerotic disease or total cervical carotid occlusion admitted with a diagnosis of ischemic stroke within 24 h from symptom onset with National Institute Health Stroke Scale < 15, between 1 December 2016 and 30 June 2017. Patients with (1) evidence of ≥ 50% stenosis of a large intracranial artery or total carotid artery occlusion, (2) symptoms referable to the territory of the affected artery, and (3) perfusion imaging data using the RAPID processing software were included. The primary predictor was unfavorable perfusion imaging defined as Tmax > 6 s mismatch volume (penumbra volume–infarct volume) of 15 ml or more. The outcome was recurrent cerebrovascular events at 90 days defined as worsening or new neurological symptoms in the absence of a nonvascular cause attributable to the decline, or new infarct or infarct extension in the territory of the affected artery. We used Cox proportional hazards models to determine the association between impaired perfusion and recurrent cerebrovascular events.

Results: Sixty-two patients met our inclusion criteria; mean age 66.4 ± 13.1 years, 64.5% male (40/62) and 50.0% (31/62) with intracranial atherosclerotic disease. When compared to patients with favorable perfusion pattern, patients with unfavorable perfusion pattern were more likely to have recurrent cerebrovascular events (55.6% (10/18) versus 9.1% (4/44), p < 0.001). This association persisted after adjusting for potential confounders (adjusted hazard ratio 10.44, 95% confidence interval 2.30–47.42, p = 0.002).

Conclusion: Perfusion mismatch predicts recurrent cerebrovascular events in patients with ischemic stroke due to intracranial atherosclerotic disease or total cervical carotid occlusion. Studies are needed to determine the utility of revascularization strategies in this patient population.

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Introduction

Large vessel disease (LVD) accounts for approximately 20% of ischemic strokes. A recent study observed a significantly increased risk of recurrent cerebrovascular events (RCVEs) in minor stroke patients with LVD subtype, particularly in the first few days. While urgent revascularization has been shown to reduce the risk of recurrence in patients with severe symptomatic extracranial carotid stenosis, revascularization strategies have shown a significant risk among patients with symptomatic LVD attributed to intracranial atherosclerotic disease (ICAD) or total cervical carotid occlusion (TCCO). The identification of a subgroup at high risk for RCVE among this subgroup can aid in risk stratification and potentially influence acute management to mitigate further morbidity and mortality in such patients.

While perfusion imaging has been recently used to aid with acute stroke treatment decisions in patients with emergent large vessel occlusion, there are limited data on the utility of perfusion imaging to predict the risk of early recurrence in patients with ischemic stroke due to ICAD/TCCO. In this study, we retrospectively reviewed consecutive patients who presented with acute ischemic stroke due to ICAD/TCCO who received magnetic resonance perfusion (MRP) imaging with the postprocessing software program RAPID (iSchemaView, Menlo Park, CA). We hypothesized that patients with ICAD/TCCO and a predefined unfavorable perfusion imaging pattern would have a higher rate of RCVEs compared to those patients with favorable perfusion imaging.

Methods

Study population

With local Institutional Review Board approval, we analyzed data from our prospective ischemic stroke inpatient database and included consecutive patients 18 years or older admitted to our comprehensive stroke center with a diagnosis of ischemic stroke within 24 h from symptom onset, between 1 December 2016 and 30 June 2017. In general, our institutional protocol requires that all patients presenting to the emergency department (ED) with a diagnosis of ischemic stroke are admitted for diagnostic evaluation and receive both an emergent noncontrast computerized tomography (CT) scan of the brain and CT angiography (CTA) of the head and neck. Further, in cases of ≥50% intracranial stenosis or TCCO on CTA with referable symptoms, patients undergo emergent MRP with postprocessing via RAPID software in our ED. We included patients with (1) intracranial atherosclerotic etiology causing ≥50% luminal narrowing on baseline CTA or TCCO, (2) symptoms referable to the territory of the affected artery, (3) perfusion imaging data using the RAPID processing, and (4) mild to moderate stroke (National Institute Health Stroke Scale (NIHSS) <15). Patients with renal disease defined as glomerular filtration ratio <30 ml/min per 1.73 m², claustrophobia, contraindication to magnetic resonance imaging (MRI) such as ferromagnetic material, or severe stroke did not undergo MRP. All patients in this study were managed with best medical treatment including antiplatelet agents (typically dual antiplatelet agents) and high-intensity lipid lowering agents. Blood pressure goals followed American Heart Association guidelines of systolic blood pressure <220 mmHg and diastolic blood pressure <120 mmHg during the first 24–48 h after admission and systolic blood pressure <180 mmHg and diastolic blood pressure <105 mmHg for the first 24 h in patients who received intravenous thrombolytic therapy. Patients with significant perfusion mismatch who had RCVE were considered for emergent reperfusion therapy on a case-by-case basis and were included in the analysis. Since this was an exploratory analysis and the sample size was not based on prespecified power calculations but we rather included all patients who met the study inclusion criteria.

Study variables

Demographic and clinical variables. We collected demographic data (age and sex), clinical risk factors (history of hypertension, history of diabetes, history of hyperlipidemia, history of coronary heart disease, history of prior stroke, smoking status, history of peripheral vascular disease), admission NIHSS score, and medications administered for secondary stroke prevention (e.g. antiplatelet agents, anticoagulants, statin).

Vascular imaging. CTA head and neck studies were reviewed by neuroradiologists and the degree of stenosis was measured based on the NASCET criteria for...
cervical lesions and by standardized method for intracranial lesions. Symptomatic ICAD was defined as large artery atherosclerosis ≥50% by CTA and TCCO was defined as cervical occlusion of the internal carotid artery on CTA. Patients were further classified depending on the degree of narrowing (50–69% versus ≥70%). Symptomatic carotid stenosis was defined as 50–99% stenosis of the cervical internal carotid artery with presence of acute infarct in the same territory was required to be considered “symptomatic.”

Perfusion imaging. The MRI protocol included the RAPID software analysis of diffusion-weighted imaging and perfusion imaging data, along with a fluid-attenuated inversion recovery and gradient echo sequence and was performed on a 1.5 T magnet in the ED. Tissue volumes in the territory of the symptomatic cervical or intracranial artery for both \( T_{\text{max}} > 4 \text{s} \) and \( T_{\text{max}} > 6 \text{s} \) were calculated from the RAPID processed images. The core infarct was obtained from diffusion-weighted imaging sequences. Unfavorable MRP pattern was defined as \( T_{\text{max}} > 6 \text{s} \) mismatch volume (penumbra–core infarct volume) ≥15 ml, a criterion used to select patients for mechanical thrombectomy in acute stroke studies (CT02586415). We secondarily investigated a broader definition of significant mismatch volume of \( T_{\text{max}} > 4 \text{s} \) in ≥15 ml similar to one prior study. Perfusion imaging was obtained within 24 h from stroke onset.

Additional diagnostic tests. All patients underwent a diagnostic evaluation to exclude a competing cardioembolic mechanism and this included a trans thoracic echocardiography, baseline electrocardiogram, and telemetry.

Outcomes. All patients were followed prospectively via a telephone call at day 7 and day 90 postdischarge from the stroke to identify any new or worsening symptoms by an investigator blinded to MRP results. Patients were also evaluated in the outpatient clinic 90 days from discharge. The outcome was RCVEs defined as worsening or new neurological symptoms in the absence of a medical or nonvascular cause of the decline, or new infarct or infarct extension in the territory of the stenotic artery. All recurrent events were confirmed by a follow-up brain MRI and adjudicated independently by two vascular neurologists (SY and SC). In cases of disagreement, a consensus was established between the two raters. Functional outcome was assessed using the modified Rankin Scale (mRS) obtained by a blinded investigator (MH) through a structured telephone questionnaire at 90 days. Good functional outcome was defined as mRS 0 or 1 at 90 days.

Statistical analysis

We compared clinical characteristics between those with and without RCVE using independent sample t-tests for continuous variables and Fisher’s exact test for categorical variables. Kaplan–Meier survival analysis was performed to determine the association between unfavorable MRP pattern and RCVE within 90 days. Cox-Hazard models were performed to estimate the hazards ratio (HR) and 95% confidence intervals (CI) for independent factors associated with RCVE. We included unfavorable MRP pattern as the predictor variable of interest and adjusted for other variables associated with the outcome on univariate tests and associated with receipt of MRP to reduce the effects of confounding and bias. Statistical analysis was performed using SPSS version 18.0 (IBM, Chicago, IL) and we considered \( p < 0.05 \) as statistically significant.

Results

We identified 135 patients with LVD stroke subtype during the study period; 78 patients had ICAD/TCCO. Perfusion imaging was obtained on 62 patients. Reasons for not obtaining MRP were as follows: renal disease defined as glomerular filtration ratio <30 ml/min per 1.73 m² (n = 3), claustrophobia (n = 3), contraindication to MRI such as ferromagnetic material (n = 1), severe stroke (NIHSS ≥15; n = 9).

The mean age in years was 66.4 ± 13.1, 64.5% (40/62) were male; 31 had ICAD and 31 had TCCO. Among patients with ICAD, 96.8% (30/31) had lesions causing ≥70% luminal narrowing. One patient had a tandem intracranial internal carotid artery and middle cerebral artery stenosis.

Baseline characteristics of patients with and without perfusion imaging obtained

The baseline characteristics of patients with and without MRP obtained are shown in Table 1. Patients who underwent MRP were less likely to have hyperlipidemia (72.5% (35/62) versus 31.3% (5/16), \( p = 0.003 \)) and as expected had a lower median NIHSS (3 (interquartile range 2–6) versus 17 (interquartile range 4–21), \( p < 0.001 \)). Other baseline characteristics and rates of RCVE were similar between the two groups (Table 1).

Predictors of RCVEs

Among the 62 patients who underwent MRP, 22.6% (14/62) patients had RCVE (13 ischemic stroke and one TIA). The RCVE occurred within 48 h from the initial event in 28.5% of patients (4/14) and within one week in 71.4% (10/14) of patients. Figure 1 shows the
Table 1. Baseline characteristics and outcomes of patients with and without perfusion imaging obtained.

<table>
<thead>
<tr>
<th></th>
<th>Perfusion imaging (n = 62)</th>
<th>No perfusion imaging (n = 16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>66.4 ± 13.1</td>
<td>65.8 ± 16.5</td>
<td>0.885</td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>64.5% (40)</td>
<td>75.0% (12)</td>
<td>0.557</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>82.3% (51)</td>
<td>68.8% (11)</td>
<td>0.298</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27.4% (17)</td>
<td>33.3% (4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>1.6% (1)</td>
<td>6.3% (1)</td>
<td>0.300</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td><strong>72.5% (45)</strong></td>
<td><strong>31.3% (5)</strong></td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>30.7% (19)</td>
<td>31.3% (5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>17.7% (11)</td>
<td>31.3% (5)</td>
<td>0.297</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>4.8% (3)</td>
<td>12.5% (2)</td>
<td>0.270</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>37.1% (23)</td>
<td>31.3% (5)</td>
<td>0.775</td>
</tr>
<tr>
<td>NIHSS (median, IQR)</td>
<td><strong>3 (2–6)</strong></td>
<td><strong>17 (4–21)</strong></td>
<td>&lt;<strong>0.001</strong></td>
</tr>
<tr>
<td>Dual antiplatelet agents (%)</td>
<td>74.2% (46)</td>
<td>50.0% (8)</td>
<td>0.071</td>
</tr>
<tr>
<td>Intracranial atherosclerotic disease (%)</td>
<td>50.0% (31)</td>
<td>62.5% (10)</td>
<td>0.413</td>
</tr>
<tr>
<td>Intravenous tissue plasminogen activator (%)</td>
<td>30.7% (19)</td>
<td>31.3% (5)</td>
<td>1.000</td>
</tr>
<tr>
<td>RCVE (%)</td>
<td>22.5% (14)</td>
<td>25.0% (4)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

IQR: interquartile range; RCVE: recurrent cerebrovascular event; SD: standard deviation; TIA: transient ischemic attack. Bold values are statistically significant.

Figure 1. Kaplan–Meier survival analysis showing an association between unfavorable imaging and RCVEs.
Kaplan–Meier survival analysis, showing an increased risk of RCVE in patients with unfavorable MRP pattern as compared to those with favorable MRP pattern.

When compared to patients with favorable MRP pattern, patients with unfavorable MRP pattern were more likely to have RCVE (55.6% (10/18) versus 9.1% (4/44), p < 0.001). In addition, the median mismatch volume in milliliters was significantly larger in patients with versus without RCVE (58 (interquartile range 0–133) versus 0 (0–7), p = 0.002). Furthermore, patients with RCVE were less likely to have received intravenous thrombolytic therapy (7.1% (1/14) versus 37.5% (18/48), p = 0.045). Other variables were not different between patients with and without RCVE (Table 2).

When we considered a $T_{\text{max}} > 4 \text{s}$ to define unfavorable MRP pattern, the proportions of RCVE in patients with favorable versus unfavorable MRP patterns were not significantly different (85.7% (12/14) versus 62.5% (30/48), p = 0.2).

The percentage of patients with good functional outcome was similar in patients with RCVE as compared to those without RCVE (42.9% (6/14) versus 60.4% (29/48), p = 0.4). Six patients with unfavorable MRP pattern (two with extracranial carotid occlusion, one with intracranial ICA stenosis, and three with

Table 2. Baseline characteristics of patients with and without recurrent cerebrovascular events

<table>
<thead>
<tr>
<th></th>
<th>Recurrent cerebrovascular events (RCVE) (n=14)</th>
<th>No RCVE (n=48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>65.3 ± 16.2</td>
<td>66.7 ± 12.2</td>
<td>0.752</td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>71.4% (10)</td>
<td>62.5% (30)</td>
<td>0.430</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>92.9% (13)</td>
<td>79.2% (38)</td>
<td>0.490</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>21.4% (3)</td>
<td>29.2% (14)</td>
<td>0.739</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>7.1% (1)</td>
<td>0% (0)</td>
<td>0.226</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>71.4% (10)</td>
<td>72.9% (35)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>35.7% (5)</td>
<td>29.2% (14)</td>
<td>0.744</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>14.3% (2)</td>
<td>18.8% (9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>7.1% (1)</td>
<td>6.3% (3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>14.3% (2)</td>
<td>43.8% (21)</td>
<td>0.061</td>
</tr>
<tr>
<td>NIHSS (mean, IQR)</td>
<td>3 (2–7)</td>
<td>3 (2–6)</td>
<td>0.712</td>
</tr>
<tr>
<td>Dual antiplatelet agents (%)</td>
<td>78.6% (11)</td>
<td>72.9% (35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Intracranial location (%)</td>
<td>5.7% (8)</td>
<td>47.9% (23)</td>
<td>0.762</td>
</tr>
<tr>
<td>Intravenous tissue plasminogen activator (%)</td>
<td>71.4% (10)</td>
<td>37.5% (18)</td>
<td>0.046</td>
</tr>
<tr>
<td>Stenosis 50–69% (%)</td>
<td>0% (0)</td>
<td>2.1% (1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Mismatch volume in milliliters (median, IQR)</td>
<td>58 (0–133)</td>
<td>0 (0–7)</td>
<td>0.017</td>
</tr>
<tr>
<td>Unfavorable imaging (mismatch &gt; 15 ml) (%)</td>
<td>71.4% (10)</td>
<td>16.7% (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mismatch volume ($T_{\text{max}} &gt; 4 \text{s}$ &gt; 15 ml (%)</td>
<td>85.7% (12)</td>
<td>62.5% (30)</td>
<td>0.192</td>
</tr>
<tr>
<td>Discharge mRS 0–1</td>
<td>28.5% (4)</td>
<td>39.6% (19)</td>
<td>0.546</td>
</tr>
<tr>
<td>90 day mRS 0–1</td>
<td>42.9% (6)</td>
<td>60.4% (29)</td>
<td>0.359</td>
</tr>
</tbody>
</table>

IQR: interquartile range; mRS: modified Rankin Scale; SD: standard deviation; TIA: transient ischemic attack. Bold values are statistically significant.
MCA stenosis) underwent emergent revascularization after neurological deterioration. Five out of six patients who had successful revascularization, none had recurrent events after the procedure, and four out of six had good functional outcome at 90 days (mRS 0–1).

**Multivariable analysis**

We performed multivariable analysis adjusting for variables associated with acquisition of MRP to account for potential selection bias and variables significant on univariate analyses. After adjusting for NIHSS score, history of hyperlipidemia, and intravenous thrombolytic therapy, the association between unfavorable MRP pattern and RCVE persisted (adjusted HR 10.44 95% CI 2.30–47.42).

**Sensitivity analysis**

We performed additional analyses to investigate the association between unfavorable MRP in each of ICAD and TCCO separately. Patients with ICAD who had RCVE were more likely than those without RCVE to have unfavorable MRP (50.0% (4/8) versus 13.0% (3/23), p = 0.05); the results were similar for TCCO (100.0% (6/6) versus 20.0% (5/25), p < 0.001).

**Discussion**

In this single-center, retrospective study of patients with symptomatic ICAD/TCCO undergoing perfusion imaging, patients with a predefined unfavorable perfusion imaging pattern were significantly more likely to have RCVE compared to patients with a favorable pattern, even after adjusting for potential confounders. Median mismatch volumes were also significantly larger in those who had RCVE. Furthermore, nearly 70% of RCVE occurred within the first week of presentation suggesting an opportunity to intervene early to reduce RCVE in patients with symptomatic ICAD/TCCO and an unfavorable imaging pattern. A recent study from a single center reported a recurrent stroke rate of 20.2%, which compares well with our rate of 25.6% for our entire cohort, including those who did and did not undergo perfusion imaging.9

In general, LVD causes ischemic stroke typically either by artery-to-artery embolism or perfusion failure.7,10 Atheromatous perforator occlusion can cause stroke in ICAD as well. While interventional options exist for symptomatic extracranial carotid disease, current guidelines recommend medical management for treatment of TCCO and ICAD.11

A large portion of patients who underwent perfusion imaging were prescribed dual antiplatelet agents (74.2%) and high intensity statin therapy (100%), reflecting an increased use of this management strategy in patients with LVD at our center. Despite this aggressive medical management strategy, our study and others12–14 show a relatively high risk of recurrent events, especially in patients with impaired distal blood flow. While aggressive medical therapy may be useful in stabilizing atherosclerotic plaques and reducing the risk of artery-to-artery embolization, it is unlikely that it will result in a significant increase in blood flow to tissue at risk and prevent RCVE. Impaired distal flow by noninvasive phase-contrast imaging has been shown to predict stroke risk in patients with symptomatic vertebrobasilar disease and may be useful to identify a subset of patients who may benefit from reperfusion therapy.15 Therefore, it is likely that patients with ICAD/TCCO and unfavorable perfusion may benefit from revascularization therapy beyond aggressive medical management alone.

The two prior randomized trials that assessed interventions for intracranial atherosclerotic stenosis, the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial and the Vitesse Intracranial Stent Study for Ischemic Therapy trial, did not select patients based on perfusion status.12,14 Recently, results from the Wingspan Stent System Post Market Surveillance registry of symptomatic intracranial atherosclerosis showed a relatively low risk of peri-procedural complications with stenting when compared to SAMMPRIS. The authors attribute this to waiting beyond seven days from the initial event to intervene as opposed to SAMMPRIS where the majority of patients were treated within seven days of acute event. Others have suggested a strategy of submaximal angioplasty alone without stent placement as a treatment option for ICAD.17,18 Since a large proportion of recurrent events occurred within one week from the initial event in our study, patients with unfavorable perfusion may be distinctive group where the additional risks of early stenting and/or angioplasty alone may be outweighed by the benefits of preventing RCVE. Future randomized clinical trials might consider safer interventions in a subset of patients with unfavorable perfusion.

Our study does have several limitations due to its retrospective nature and its relatively small sample size. Several patient characteristics differed between patients who underwent perfusion imaging at presentation that may have introduced selection bias. However, the risks of RCVE in those with and without perfusion imaging were not significantly different arguing against clinician selection of those at high risk of deterioration for perfusion imaging. We also did not analyze the infarct patterns related to the stenosis, which has been shown to differentiate between several mechanisms

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**International Journal of Stroke, 0(0)**
of stroke in patients with intracranial stenosis.\textsuperscript{19} Significant mismatch on perfusion imaging, however, is suggestive of a hemodynamic mechanism rather than an embolic mechanism. Another limitation of this study was the lack of follow-up perfusion imaging data on the majority of patients and the lack of ability to correlate between perfusion imaging obtained more than 24 h from stroke onset and the risk of ischemic event recurrence. Furthermore, since most CTAs obtained were single phase, we were unable to obtain with good accuracy the collateral score and determine an association between poor collaterals and recurrent events, as other studies have shown.\textsuperscript{20} Lastly, despite aiming for relatively high blood pressure targets immediately after presentation, we did not compile inpatient blood pressure data among patients to evaluate whether blood pressure fluctuations contributed to RCVE risk.

**Conclusion**

Using perfusion imaging criteria, we observed that a subset of acute ischemic stroke patients with ICAD/TCCO and an unfavorable perfusion pattern were more likely to have RCVE. Further studies are needed to validate our findings in multicenter cohorts and evaluate the potential benefit of revascularization therapy in these patients.

**Authors’ contributions**

DCS: Data collection and manuscript preparation. SMC: Outcome adjudication and data collection. RAM: Manuscript revision, study concept, and design. ADC: Data analysis. MH: Data collection. BM: Manuscript revision. MSS: Manuscript revision. TB: Manuscript revision. BT: Manuscript revision. SKR: Manuscript revision. SP: Manuscript revision. RSM: Manuscript revision. JZW: Manuscript revision. MSVE: Manuscript revision, study concept and design. PK: Manuscript revision, study concept and design. KLF: Manuscript revision, study concept and design. MVJ: Manuscript revision, study concept and design. SY: Data collection, study concept and design, outcome adjudication, manuscript preparation.

**Declaration of conflicting interests**

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

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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**References**


