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ORIGINAL RESEARCH

Outcomes of Eyes Lost to Follow-Up in Patients with Central Retinal Vein Occlusion Who are Receiving Anti-Vascular Endothelial Growth Factor Treatment

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Background: To evaluate the anatomic and functional outcomes in eyes of patients with macular edema (ME) caused by central retinal vein occlusion (CRVO) who were lost to follow-up (LTFU) for more than 6 months following treatment with anti-vascular endothelial growth factor (VEGF) therapy and to determine the predictive factors of visual prognosis in these patients.

Methods: This study was conducted as a retrospective, case series investigation. Patients whose eyes were receiving intravitreal anti-VEGF treatment for CRVO-ME, with the next follow-up visit occurring more than 6 months following treatment were identified. Baseline disease characteristics (at the last visit before being LTFU), cause and duration of treatment interruption, and the resulting disease progression, complications, and outcomes were assessed. Baseline characteristics predictive of visual outcome were also analyzed.

Results: This study included a total of 17 eyes of 17 patients. The mean duration of being LTFU was 7.8 ± 2.1 months. On the return visit after being LTFU, 7 of 17 eyes (41.2%) developed neovascular complications. Despite treatment, 12 eyes (70.1%) lost ≥3 best-corrected visual acuity (BCVA) lines, with 2 eyes (11.8%) developing a final BCVA of hand motion or more severe. At the final visit, the mean logarithm of minimal angle of resolution (logMAR) BCVA deteriorated significantly compared to before being LTFU ($P < 0.001$). The increasing duration of being LTFU is associated with a deterioration of visual acuity prognosis.

Conclusion: In CRVO-ME patients who are receiving anti-VEGF therapy, unintentional treatment interruptions can cause visually disastrous consequences, including irreversible blindness. Patients who were LTFU for a long period should be strongly warned about their poor visual prognosis.

Keywords: central retinal vein occlusion, macular edema, anti-vascular endothelial growth factor, loss to follow-up

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Introduction

Central retinal vein occlusion (CRVO) is one of the most common causes of visual loss.[1,2] Loss of visual acuity following CRVO occurs commonly as a result of macular edema (ME), but can also occur following neovascular complications, such as vitreous hemorrhage and neovascular glaucoma.[3] Today, anti-vascular endothelial growth factor (anti-VEGF) is the standard of therapy for CRVO-ME.[4] The CRUISE trial was a large prospective randomized controlled trial that demonstrated

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intravitreal ranibizumab (IVR) therapy was effective for CRVO-ME.[5] Long-term data obtained from the extension trials demonstrated that the functional improvement was preserved in patients with CRVO-ME after 4 years who followed a PRN treatment protocol of ranibizumab injections.[6,7] These results also indicated that in a long-term follow-up, patients with CRVO still require ranibizumab injections to control ME.[6,7]

However, these clinical outcomes were obtained in the tightly controlled setting of randomized clinical trials. In real-life setting, 25.4% of patients with ME secondary to retinal vein occlusion (RVO) receiving anti-VEGF therapy were lost to follow-up (LTFU) for more than 12 months.[8] Recent published papers revealed that unintentional treatment interruptions in patients with diabetic retinopathy (DR), who are managed with anti-VEGF monotherapy, can result in irreversible blindness.[9] However, there is limited evidence on the outcomes of eyes LTFU that received anti-VEGF therapy for CRVO-ME. Therefore, this study aimed to demonstrate that patients with ME caused by non-ischemic CRVO treated with anti-VEGF therapy and were LTFU for more than 6 months may experience marked disease progression with potentially devastating and irreversible visual consequences.

Methods

This study was conducted as a retrospective case series review of patients who received anti-VEGF therapy for ME secondary to non-ischemic CRVO and whose history showed a period of LTFU for greater than 6 months. Patients were identified between June 1, 2018, and June 1, 2019, at the Department of Ophthalmology of the First Hospital of China Medical University (Shenyang, China). The Ethical Committee and the Institutional Review Board of China Medical university approved the study protocol, which was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before receiving treatment. Patients were excluded if ischemic CRVO was identified before treatment interruptions and by the presence of neovascularization on the disc or elsewhere, rubeosis iridis, ≥10 disc areas of nonperfusion based on fluorescein angiography (FA), or Hayreh's criteria.[10] Other exclusion criteria were diabetes mellitus, previous treatment with intravitreal injection of corticosteroids or laser photocoagulation, glaucoma or ocular hypertension, and retinal conditions other than CRVO. The baseline disease characteristic (at the last visit before being LTFU), the reason for and the duration of treatment interruptions, and the resulting disease progression, complications, and the eventual outcomes at the return visit after being LTFU and the final clinic visit were evaluated.

Statistical analysis was conducted using SPSS version 20.0 (SPSS, Inc., Chicago, IL). For statistical analysis, we converted the Snellen visual acuity into logarithm of the minimal angle of resolution (logMAR) equivalent. All data were expressed as the mean ± standard deviation (SD) and the median (range). Count fingers (CF), hand motion (HM), light perception (LP), and no light perception (NLP) visual acuities were assigned the following values based on a previously used scale: 2.00, 2.30, 2.60, and 2.90, respectively.[9] All data were tested for normality employing histogram graphical analysis and Shapiro–Wilk test. When data conformed to normality, a 2-tailed *t*-test was conducted to compare 2 groups; if data were not normally distributed, a Mann–Whitney *U*-test or Wilcoxon signed rank test was used. In the cases of categorical data, Fisher's exact test was applied. To evaluate the predictive factors associated with the final visual outcome, stepwise linear regression analysis was conducted, including the following factors: patients' age and sex, presence of hypertension, injection numbers before being LTFU, treatment length before being LTFU, BCVA and CRT before being LTFU, and LTFU duration. *P*-values < 0.05 were considered statistically significant.

Results

In total, we included 17 patients (17 eyes) treated with anti-VEGF therapy for ME secondary to non-ischemic CRVO who had a period of being LTFU for greater than 6 months. The baseline characteristics of study patients are presented in Table 1. For patients included in the study, the average age was 60.2 ± 7.2 years (range, 49–71 years). Before being LTFU, these patients had been treated on average for a period of 6.1 ± 3.3 months (range, 2–14 months), with a mean of 4.5 ± 1.5 injections (range, 2–8 injections). Nine eyes (52.9%) received ranibizumab; seven (41.2%), conbercept; and one (5.9%), aflibercept. The Snellen BCVA values seen at baseline ranged from 20/160 to 20/40, with a median reading of 20/80 (Table 2). Prior to becoming LTFU, the mean ± SD logMAR BCVA was 0.59 ± 0.18 (20/79 in Snellen equivalent). The baseline mean ± SD central retinal thickness (CRT) was 360.9 ± 87.6 μm, as measured by OCT.

The most common reasons for treatment interruptions included noncompliance (35%), financial issues (29%),

Table 1 Demographic and Baseline Clinical Features of Patients Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Treatment

Feature	Number
Age (yrs), mean±SD (range)	60.2 ± 7.2 (49–71)
Sex, n (%)	
Male	10 (58.8)
Female	7 (41.2)
Hypertension, n (%)	13 (76.5)
Anti-VEGF therapy, n (%)	
Ranibizumab	9 (52.9)
Conbercept	7 (41.2)
Aflibercept	1 (5.9)
Injections before being LTFU, mean±SD (range)	4.5 ± 1.5 (2–8)
Treatment length before being LTFU (months), mean±SD (range)	6.1 ± 3.3 (2–14)

Abbreviation: VEGF, vascular endothelial growth factor.

Table 2 Treatment Interruption and Resulting Complications in Patients Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Treatment

Feature	Number
BCVA before being LTFU (logMAR), mean ±SD	0.59 ± 0.18
CRT before being LTFU (μm), mean±SD	360.9 ± 87.6
Reason for being LTFU, n (%)	
Noncomliance	6 (35)
Financial issues	5 (29)
Intercurrent illness	4 (24)
Other	2 (12)
LTFU length (months), mean±SD (median)	7.8 ± 2.1 (7.0)
BCVA on return visit (logMAR), mean±SD	1.54 ± 0.61
CRT on return visit (μm), mean±SD	738.7 ± 143.6
Complication on return visit, n (%)	
ME worsening	13 (76.5)
Vitreous hemorrhage	4 (23.5)
NVD or NVE	3 (17.6)
Neovascular glaucoma	1 (5.9)
Follow-up length from return to final visit (months), mean±SD (range)	8.5 ± 2.5 (6–13)
BCVA at final visit (logMAR), mean±SD	1.26 ± 0.57
CRT at final visit (μm), mean±SD	469.9 ± 302.9

Note: CRT on return visit available for 13 eyes without vitreous hemorrhage.
Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; LogMAR, logarithm of minimal angle of resolution; SD, standard deviation; LTFU, lost to follow-up; ME, macular edema; NVD, neovascularization of the disc; NVE, neovascularization elsewhere.

and intercurrent illness (24%), and the mean duration of being LTFU was 7.8 ± 2.1 months (range, 6–14 months). On the return visit after being LTFU, the mean ± SD logMAR BCVA had worsened significantly to 1.54 ± 0.61 (Snellen equivalent of 20/693) ($P < 0.001$). Of the 17 eyes, 7 (41.2%) developed neovascular complications, including 4 eyes (23.5%) having vitreous hemorrhage, 3 eyes (17.6%) having neovascularization on the disc (NVD) or neovascularization elsewhere (NVE), and 1 eye (5.9%) having neovascular glaucoma (NVG). On the return visit after treatment interruptions, CRT was measured in 13 eyes without vitreous hemorrhage, and all eyes exhibited ME that was more pronounced than that at baseline. The mean ± SD CRT significantly increased to 738.7 ± 143.6 μm ($P < 0.001$).

Subsequently, these patients received anti-VEGF therapy or were switched to dexamethasone intravitreal implant for the treatment of ME, and laser photocoagulation was performed for eyes with NVD or NVE. Patients with vitreous hemorrhage underwent vitrectomy with photocoagulation and internal limiting membrane removal, and massive retinal hemorrhage and NVD and/or NVE were detected during surgery. The eye with NVG (also having NVD) was LTFU for 14 months and received anti-VEGF therapy, laser photocoagulation, and filtration surgery. Despite attempts to treat arising complications, 12 eyes (70.1%) lost ≥3 BCVA lines, with 2 eyes (11.8%) deteriorating to a final BCVA of HM or worse. At the final visit, the Snellen BCVA ranged from LP to 20/125, with a median of 20/200. The mean ± SD logMAR BCVA was 1.26 ± 0.57 (20/364 in Snellen equivalent) at the final visit (Table 2), which was a significant decrease from before being LTFU ($P < 0.001$), and no significant difference was observed when compared with the initial return visit after being LTFU ($P = 0.122$). The mean ± SD CRT was 469.9 ± 302.9 μm at the final visit, exhibiting no significant difference when compared with that before being LTFU ($P = 0.306$), whereas it significantly decreased compared with that on the return visit after being LTFU ($P < 0.001$).

Table 3 presents the clinical characteristics of the patients with and without neovascular complications. No significant difference in the number of injections,

Table 3 Comparison of Clinical Features in Patients without or with Neovascular Complications

Feature	Non Neovascualr Complications n=10	Neovascular Complications n=7	*P* value
Age (yrs), mean±SD (range)	58.8 ± 5.3 (53–67)	62.3 ± 9.3 (49–71)	0.364
Sex, n (%) Male Female	 7 (60) 3 (40)	 3 (57.1) 4 (42.9)	0.350
Hypertension, n (%)	7 (80)	6 (71.4)	0.603
Injections before being LTFU, mean±SD (range)	4.1 ± 1.4 (2–7)	5.0 ± 1.6 (3–8)	0.270
Treatment length before being LTFU (months), mean±SD (range)	5.2 ± 3.0 (2–12)	7.4 ± 3.6 (3–14)	0.161
BCVA before being LTFU (logMAR), mean±SD	0.56 ± 0.20	0.64 ± 0.15	0.364
CRT before being LTFU (μm), mean±SD	348.1 ± 103.6	379.3 ± 60.7	0.193
LTFU length (months), mean±SD (median)	6.7 ± 0.8 (6.3)	9.3 ± 2.4 (9)	0.007*
BCVA on return visit (logMAR), mean±SD	1.14 ± 0.33	2.11 ± 0.41	0.001*
Follow-up length from return to final visit (months), mean ±SD (range)	7.7 ± 2.1 (6–12)	9.6 ± 2.8 (6–13)	0.161
BCVA at final visit (logMAR), mean±SD	1.05 ± 0.35	1.56 ± 0.72	0.070
CRT at final visit (μm), mean±SD	530.6 ± 307.5	383.3 ± 296.5	0.550

Note: *Indicates statistically significant P value.
Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; LogMAR, logarithm of minimal angle of resolution; SD, standard deviation; LTFU, lost to follow-up.

treatment length, BCVA, and CRT were seen prior to becoming LTFU between the groups. The LTFU duration was longer in patients with neovascular complications (P = 0.007). On the return visit after being LTFU, the mean BCVA was worse in patients with neovascular complications (P = 0.001). However, the differences observed between either BCVA or CRT at the final visit between patients with and without neovascular complications were not significant. In the multivariate analysis, an increased duration of LTFU had an association with a worsened visual acuity prognosis (Table 4).

Discussion

Recent studies have revealed that anti-VEGF therapy with ranibizumab, aflibercept, or conbercept is efficacious for treating patients with CRVO-ME when given in the highly regulated setting of a clinical trial where compliance is closely maintained.[5–7,11–13] A 12-month study consisting of 392 eyes compared the efficacy of two doses of ranibizumab (0.3 and 0.5 mg) for CRVO, to that of sham treatment. A mean increase in BCVA of 13.9 letters was seen in both the 0.5 and 0.3 mg treatment groups.[5] Extension studies provided additional insight into the outcome of patients receiving anti-VEGF therapy for CRVO for a period of up to 4 year. In these extension studies, however, there was a significant loss to follow-up, and of the initial 392 eyes with CRVO, only 181 remained by the end of the study.[6] A recent study reported that 25.4% of RVO patients that developed secondary ME who received anti-VEGF therapy were LTFU for more than 12 months in clinical practice.[8] In another study, non-adherence was reported in 25% of patients with ME caused by branch RVO (BRVO) while receiving anti-VEGF therapy.[14] In patients with DR managed with anti-VEGF monotherapy, being LTFU for an extended period of time can caused serious irreversible consequences, including blindness.[9] In the retrospective case series, 77% of eyes lost ≥3 BCVA lines, and 46% of eyes had a final BCVA of HM or worse when patients were LTFU. However, to date, a thoroughly evaluation of the consequence of being LTFU on eyes that received anti-VEGF therapy for CRVO-ME remains limited in the literature. To the best of our knowledge, our case series, for the first time, reveals the potentially devastating visual consequences that may occur in a real-world

Table 4 Association Between Baseline Characteristics and Best-Corrected Visual Acuity at Final Visit After Treatment Discontinuation

Baseline Characteristics	*P* value	β	95% Confidence Intervals
Age (yrs)	0.940		
Sex, male: female	0.464		
Hypertension	0.594		
Number of injections before being LTFU	0.240		
Treatment length before being LTFU (months)	0.158		
BCVA before being LTFU (logMAR)	0.548		
CRT before being LTFU (μm)	0.169		
LTFU length (months)	<0.001	0.917	0.191–0.312

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; LogMAR, logarithm of minimal angle of resolution; LTFU, lost to follow-up.

setting when patients with CRVO-ME are treated with anti-VEGF therapy and have an unanticipated treatment interruption.

Prior research describing the natural progression of CRVO reported a 0% to 33% incidence of neovascularization post-CRVO over a 12- to 15-month period in patients with non-ischemic CRVO.[15] In the current study, neovascular complications developed in 41.2% of eyes after a mean of 7.8 months of anti-VEGF treatment interruptions, including 23.5% of eyes having vitreous hemorrhage, 17.6% having NVD or NVE, and 5.9% having NVG. Moreover, the period of being LTFU was longer in eyes with neovascular complications than in eyes without. The higher incidence of neovascular complications in eyes LTFU may be explained by the hypothesis that interfering with the VEGF pathway through anti-VEGF therapy may result in an increased expression of VEGF receptors within the retina.[16] The increase abundance of VEGF receptors may increase the sensitive of endothelial cells to VEGF, resulting in excessive ME or neovascular complications after long-term treatment interruptions. In line with this, a previous study described a CRVO case of rebound neovascularization following bevacizumab treatment. On treatment cessation because of being LTFU, the patient developed significantly more severe extensive neovascularization than was seen at initial presentation.[17] Similar results have also been observed in patients with DR. Wubben et al reported that in three eyes who were being treated with anti-VEGF therapy for nonproliferative DR (NPDR) with diabetic macular edema (DME) had a VA of >20/40 before treatment was interrupted. Following interruption, all eyes had VA of HM or worse at their final visit due to NVG in two eyes and a vitreous hemorrhage in one eye.[9] The results of the CRUISE trial demonstrated that six consecutive injections were insufficient to achieve long-term benefit in 85.4–90.9% of patients with CRVO-ME who required retreatment.[5] Moreover, over half of patients with CRVO (56%) exhibited a no complete resorption of ME despite maintaining uninterrupted treatment for up to year 4 and still had an uncertain future.[7] Altogether, these findings suggest that anti-VEGF therapy for patients with CRVO-ME is an approach that requires ongoing uninterrupted treatment in the majority of eyes. Otherwise, patients who experience long-term treatment interruption are at risk for progressive neovascular tissue growth and the development of severe adverse visual sequelae. In our recent study evaluating the impact of the COVID-19 pandemic on anti-VEGF treatment in ophthalmology patients, 59 eyes of 46 patients (including 10 eyes of 10 patients with CRVO-ME) were receiving 3+PRN anti-VEGF treatment prior to the outbreak of the COVID-19 pandemic and all of these patients experienced treatment interruptions due to COVID-19-associated reasons. Anatomic and functional outcomes suggest that patients with anti-VEGF treatment interruptions are at risk for severe adverse visual sequelae.[18]

In the CRUISE trial, 15.4% of patients in the group that received sham injections lost ≥15 letters (3 lines) from their baseline BCVA letter score at month 6, which is considered similar to the natural loss of visual acuity over a 6-month period.[5] A recent meta-analysis conducted for 24 studies determined that the pooled mean decrease was 10 letters in visual acuity from baseline to 6 months and 3 letters from baseline to ≥12 months for eyes with non-ischemic CRVO. For those with ischemic CRVO, the pooled mean decrease was 15 letters from baseline to 6 months and 35 letters from baseline to 12 months or beyond.[15] In our study cohort, despite treatment of the

complications after being LTFU, 70.1% of eyes lost ≥3 lines of BCVA, with 11.8% having a final BCVA of HM or worse after a mean of 8.5 months of follow-up. The mean ± SD logMAR BCVA was 1.26 ± 0.57 (20/364 in Snellen equivalent) at the final visit, which was significantly worse (decrease of 6.7 lines) than that before being LTFU (0.59 ± 0.18; 20/79 in Snellen equivalent). Furthermore, an increased LTFU was generally accompanied by a worse visual acuity prognosis at the last visit. Similarly, in patients with DR receiving anti-VEGF monotherapy, final visual acuity worsened with increasing length of treatment Interruption.[9] The results of the study evaluating the impact of the COVID-19 pandemic on anti-VEGF treatment in ophthalmology patients also demonstrated that longer treatment interruption was associated with worsened visual acuity.[18] Again, these findings emphasize the importance of normative, adequate course of anti-VEGF therapy in patients with CRVO-ME.

In 1995, the Central Vein Occlusion Study (CVOS) evaluated the efficacy of prophylactic pan-retinal scatter laser photocoagulation in eyes with CRVO in comparison with frequent observations alone.[19] In this study, no significant reduction in the development of neovascularization was observed between the two groups. Considering these results, scatter laser photocoagulation has been indicated only in patients with active neovascularization till date. However, the role of scatter laser photocoagulation in patients with CRVO has not yet been completely investigated in the era of anti-VEGF therapy. In the RELATE trial, Campochiaro et al compared BCVA, CRT, and the number of IVR injections among patients with CRVO between two groups (IVR with scatter photocoagulation of peripheral retina vs ranibizumab monotherapy) without specification of the perfusion status.[20] In scatter photocoagulation group, all peripheral retina outside the macula was treated by scatter photocoagulation in CRVO eyes. They found that BCVA, CRT, and the number of injections were unable to determine any statistical differences between the groups. Contrarily, a study evaluating the effect of a combination of ranibizumab and laser photocoagulation on peripheral retinal areas of nonperfusion in patients with non-ischemic CRVO reported that selective laser photocoagulation of peripheral areas of nonperfusion appears to lead to additional visual improvement in patients with CRVO-ME treated with ranibizumab.[21] Similarly, another study demonstrated that photocoagulation of nonperfused areas of the retina in patients with ME caused by ischemic CRVO might amplify the positive therapeutic effects of bevacizumab treatment on BCVA and CRT and could result in to a dramatic decrease in the frequency of bevacizumab treatment.[22] However, it is not known whether scatter photocoagulation of peripheral retina or photocoagulation of peripheral areas of nonperfusion could decrease neovascular complications in patients with CRVO-ME who are treated with anti-VEGF therapy. Nevertheless, as unintentional treatment interruptions in patients with CRVO-ME receiving anti-VEGF therapy can result in irreversible blindness, as observed in our chart, prophylactic scatter photocoagulation should be considered in CRVO patients with ischemia or non-ischemic CRVO patients who show areas of nonperfusion, where a close follow-up is not possible.[4] A recent study compared the effectiveness of panretinal laser photocoagulation targeting far-periphery (dense photocoagulation of far-periphery over 360°) versus conventional panretinal laser photocoagulation (standard photocoagulation of the mid-periphery) in patients with ischemic CRVO in terms of the degree of macular edema and showed that selective laser treatment of the far-periphery results in significant reduction of ME associated with severe retinal ischemia.[23] Additional studies are needed to investigate the beneficial effect of the combination of selective scatter photocoagulation and anti-VEGF therapy in patients with CRVO-ME.

In our study, there were several limitations, in addition to being retrospective in nature and having a limited sample size. Given the retrospective nature of our case series, our study lacks a standardized control group for comparison. Another potentially troubling finding is that after being LTFU for more than 6 months, many patients never returned. This is problematic as we were unable to evaluate those eyes to determine their outcome. Future studies with a better ability to reach LTFU CRVO-ME patients who do not return are required to determine the true consequence of being LTFU.

Conclusions

In conclusion, many patients with CRVO-ME are subject to substantial interruptions in follow-up due to reasons such as noncompliance, financial hardship, illness, and other issues. In patients with CRVO-ME receiving anti-VEGF therapy, such unintentional treatment interruptions can result in visually disastrous consequences, including irreversible blindness, as observed in this retrospective case series. Furthermore, increasing the duration of being LTFU is associated with the development of neovascular complications and a worse visual acuity prognosis. These

concerning findings of patients with CRVO-ME receiving anti-VEGF therapy who are being LTFU should serve as a serious caveat to physicians who are treating such patients.

Abbreviations

anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; BRVO, branch RVO; CF, count fingers; CRT, central retinal thickness; CRVO, central retinal vein occlusion; CVOS, Central Vein Occlusion Study; DR, diabetic retinopathy; FA, fluorescein angiography; HM, hand motion; IVR, intravitreal ranibizumab; logMAR, logarithm of the minimal angle of resolution; LP, light perception; LTFU, lost to follow-up; ME, macular edema; NLP, no light perception; NPDR, nonproliferative diabetic retinopathy; NVD, neovascularization on the disc; NVE, neovascularization elsewhere; NVG, neovascular glaucoma; RVO, retinal vein occlusion; SD, standard deviation.

Ethics Approval and Consent to Participate

The Ethical Committee and the Institutional Review Board of China Medical university First Hospital approved the study protocol, which was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interests.

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