Systematic Review and Meta-Analysis

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Whether statin use improves the survival of patients with glioblastoma?

A meta-analysis

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Abstract

Background: Glioblastomas are malignant brain tumors associated with high mortality and poor prognosis. Evidence from preclinical studies suggests that statins have an antitumor role, but their effects on the survival of patients with glioblastoma remain controversial. This meta-analysis attempts to assess the association between statins and glioblastoma.

Methods: We searched 4 databases (PubMed, Web of Science, Embase, and Cochrane Library) for articles that evaluate the effect of statins on the survival of patients with glioblastoma. Two reviewers were asked to assess the quality of the studies and extract the data regarding progression-free survival (PFS) and overall survival (OS).

Result: A total of 5 studies met the inclusion criteria with 430 statin users and 2089 nonstatin users. All 5 studies were retrospectively analyzed. The pooled hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. There was no benefit of statins found pertaining to the survival of glioblastoma patients in both PFS (HR, 0.97; CI, 0.84–1.13) and OS (HR, 0.98; CI, 0.87–1.11). In a subgroup defined by the patterns of statin use, it was determined that usage before glioblastoma diagnosis favored the OS of patients (HR, 0.85). The result, however, failed to demonstrate a statistically significant difference.

Conclusion: Use of statins was not associated with prolonged survival of patients with glioblastoma. Further well-designed randomized controlled trials are needed to confirm.

Abbreviations: CI = confidence interval, GBM = glioblastoma, HR = hazard ratio, NOS = Newcastle–Ottawa Quality Assessment Scale, OS = overall survival, PFS = progression-free survival, RCT = randomized controlled trial.

Keywords: glioblastoma, meta-analysis, overall survival, progression-free survival, statins

1. Introduction

Glioblastoma (GBM) is the most malignant and common type of glioma with a high mortality,[1] and the median overall survival (OS) of GBM patients still remain poor, which is approximately 1.5 years after surgical resection followed by concomitant radiation therapy/chemotherapy and adjuvant chemotherapy.[2]

Statins are HMG-CoA reductase inhibitors that are widely used to lower cholesterol, and have been shown to inhibit proliferation or angiogenesis in various animal models of cancers, including glioma cells.[3] In human glioma cells, atorvastatin demonstrated a cytotoxic effect to glioma cells. Similar to temozolomide, it could reduce the migration and proliferation of tumor cells, with no toxicity to astrocytes.[4] In animal model, statins were suggested as a combination drug for treating GBM, considering its role on toxicity reduction from high doses of irinotecan.[5] In clinical, few studies report the effect of statins on the survival of patients with GBM, and whether patients can benefit from statin treatment remains controversial.

Therefore, we performed a survival analysis to discuss statin treatment for the outcome of adult patients with GBM.

2. Methods

This meta-analysis collected and analyzed data from previous published studies which have included ethical approvals; thus, ethical approval was not conducted in this study.

2.1. Search strategy

We searched for articles that evaluated the effect of statins on the survival of patients with GBM in PubMed, Web of Science, Embase, and Cochrane Library from January 1995 to September 2019. Databases were queried by using keywords as following:

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"Glioblastoma," "Malignant brain tumor," "GBM," "Statins," "Atorvastatin," "Simvastatin," "Lovastatin," "Rosuvastatin," and "Fluvastatin." The results were limited to human subjects, English language, and published data. We also checked the references manually for the potential relevant studies.

2.2. Study selection and data extraction

All studies were scanned independently by 2 reviewers with the following inclusion criteria:

1. Patient: glioblastoma in adults whose ages were >17 years.
2. Intervention: use of statins before or after diagnosis.
3. Comparison: if statins were used or not.
4. Outcome: progression-free survival (PFS) and OS.
5. Study set: randomized controlled trial (RCT), prospective observational study, and retrospective cohort study.

2.3. Data extraction and study quality assessment

Assessment of study qualities and extraction of data were conducted by 2 independent reviewers. Only observational studies were found in our study, and the qualities were assessed via the Newcastle–Ottawa Quality Assessment Scale (NOS). The data that were extracted from eligible articles included the first author, year of publication, sample size of statin use or not, and study design and major outcomes.

2.4. Data analyses

Statistical analyses were performed using Stata 12.0. Time-to-event variables were evaluated as hazard ratio (HR) with 95% confidence interval (CI). Heterogeneity between studies was investigated using the chi-square test and I^2 statistic. We used a fixed-effects model when $P > .10$ or $I^2 < 50\%$, but if that criteria was not met, we used a random-effects model. Publication bias was evaluated using Egger and Begg tests, and $P < .05$ was considered statistically significant.

2.5. Sensitivity analyses

In order to determine whether individual studies influenced the total result inappropriately, the results of analyses were recalculated by removing studied one by one.

3. Results

With exclusion of duplicates, total 196 articles were identified from electronic databases and reference lists. After a review of titles and abstracts, 32 articles were read. Then 5 articles that met the inclusion criteria were used in our analysis (Fig. 1). Although

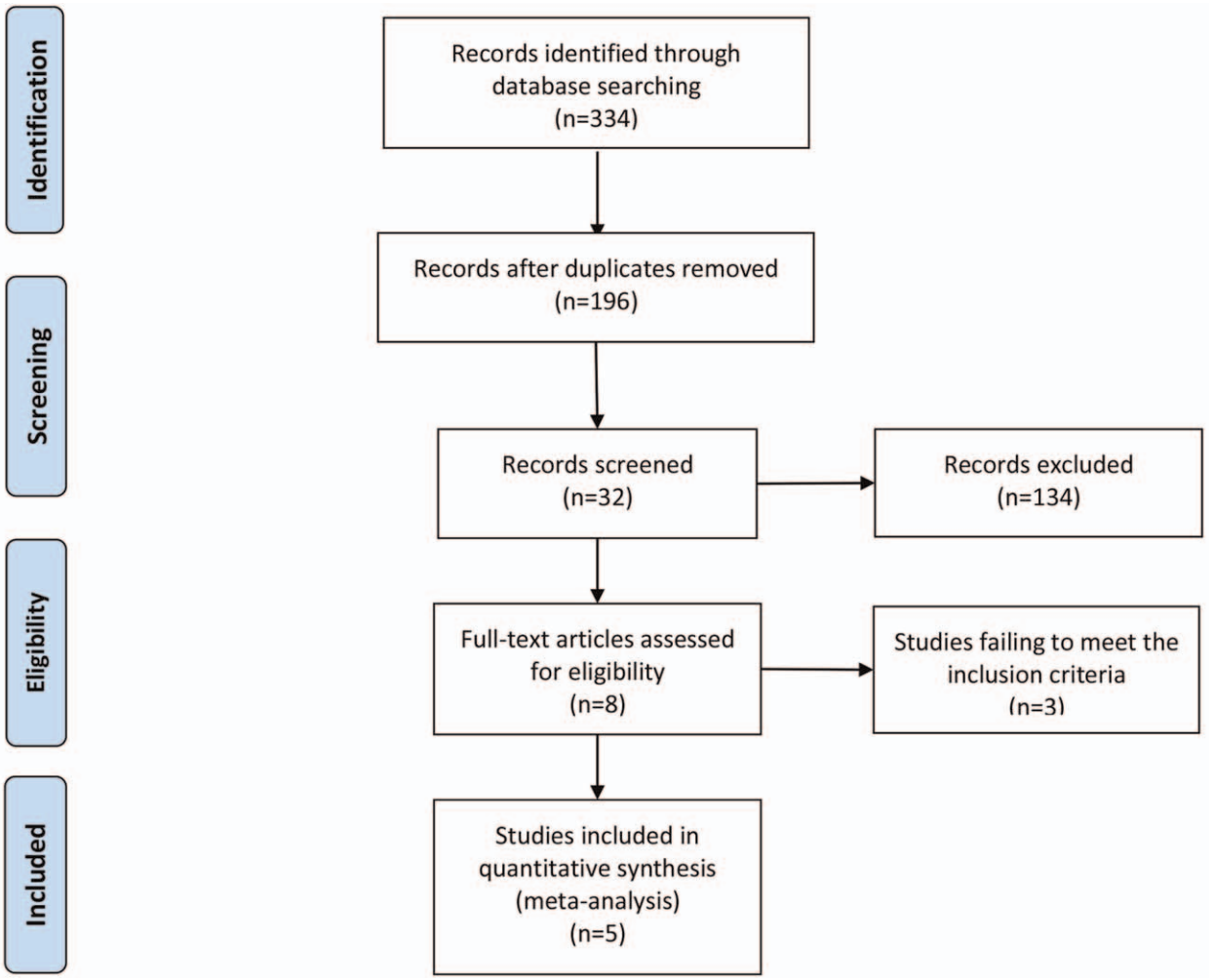

Figure 1. Flow diagram of the study selection process.

Table 1

Characteristics of studies used for meta-analysis.

Author and year	Country	SSU	SNSU	Study	Outcome
Happold, 2018	Multiple countries	93	717	Multiple centers	PFS and OS
Seliger, 2018	Germany	106	756	Multiple centers	PFS and OS
Bhavsar, 2016	United States	78	206	Single center	PFS and OS
Gaist, 2014	Denmark	113	226	Multiple centers	OS
Henker, C, 2019	Germany	40	184	Two centers	OS

OS = overall survival, PFS = progression-free survival, SNSU = sample of no-statins users, SSU = sample of statins users.

there were 2 ongoing clinical trials to evaluate the role of statins on the outcome of glioma combined with standard therapy (NCT02115074 and NCT02029573), no result can be referenced at the time this analysis was conducted. The details of the studies are listed in Table 1. According to the NOS, the quality of all 5 retrospective studies was >5 points.

There were a total of 2519 patients with GBM from 5 eligible articles, including 430 statin users and 2089 nonstatin users. One article collected and retrospectively analyzed the data from 2 large multicenter studies,[6] the randomized phase III clinical study CENTRIC[7] and the randomized phase II study CORE.[8] The HRs for PFS and OS were reported separately and together. In our study, they were analyzed as 2 data groups to reduce bias.

As shown in Figure 2, 3 articles reported the PFS, and no significant heterogeneity between the articles was found (P = .738), I^2 = 0.0%. Thus, a fixed-effects model was used. GBM patients using statins showed an HR of 0.97 with a 95% CI of 0.84 to 1.13, when comparing with patients who did not use statins. As shown in Figure 3, all 5 articles reported the OS associated with statin treatment. One article favored the use of statins,[9] but the others did not find positive results and suggested further works.[6,10–12] A moderate heterogeneity was found in 5 articles (P = .128), I^2 = 41.6%, and this meta-analysis could not identify the benefit of statins on total survival (HR, 0.98; CI, 0.87–1.11). To analyze the reason of heterogeneity, all 6 results of statins on the OS were each removed individually, and the meta-analysis was repeated with the remaining. As shown in Figure 4, all HRs were similar to the total HR varying from 0.94 to 1.07. The lower limit of the 95% CI varied from 0.82 to 0.92 and the upper limit varied from 1.07 to 1.23. Meanwhile, a subgroup was set according to the use of statins before or after diagnosis, and patients using statins before diagnosis showed an HR of 0.85 with a 95% CI of 0.70 to 1.02 versus patients without statin use, whereas patients using statins after diagnosis presented

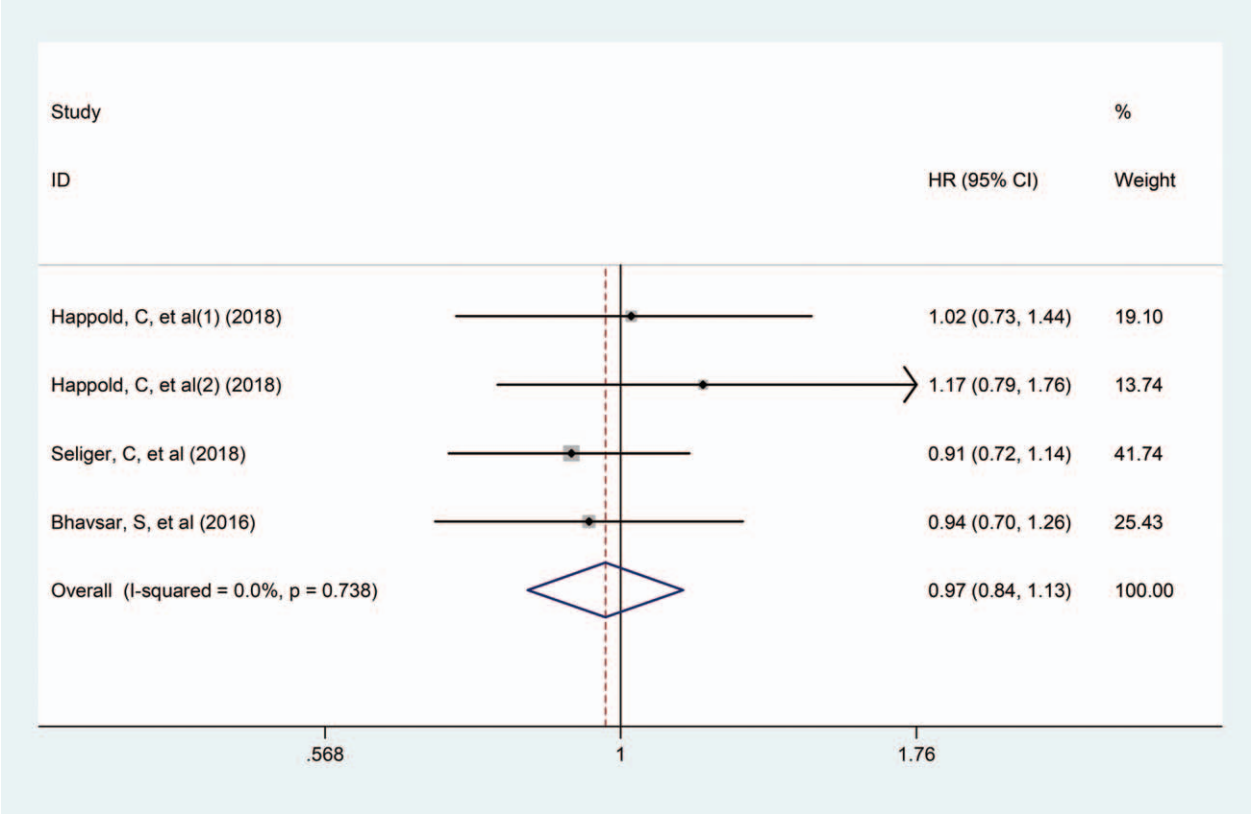

Figure 2. Forrest plot of HR on progression-free survival. Happold et al (1) refers data from the randomized phase III clinical study CENTRIC, and Happold et al (2) refers data from the randomized phase II study CORE. CI = confidence interval, HR = hazard ratio.

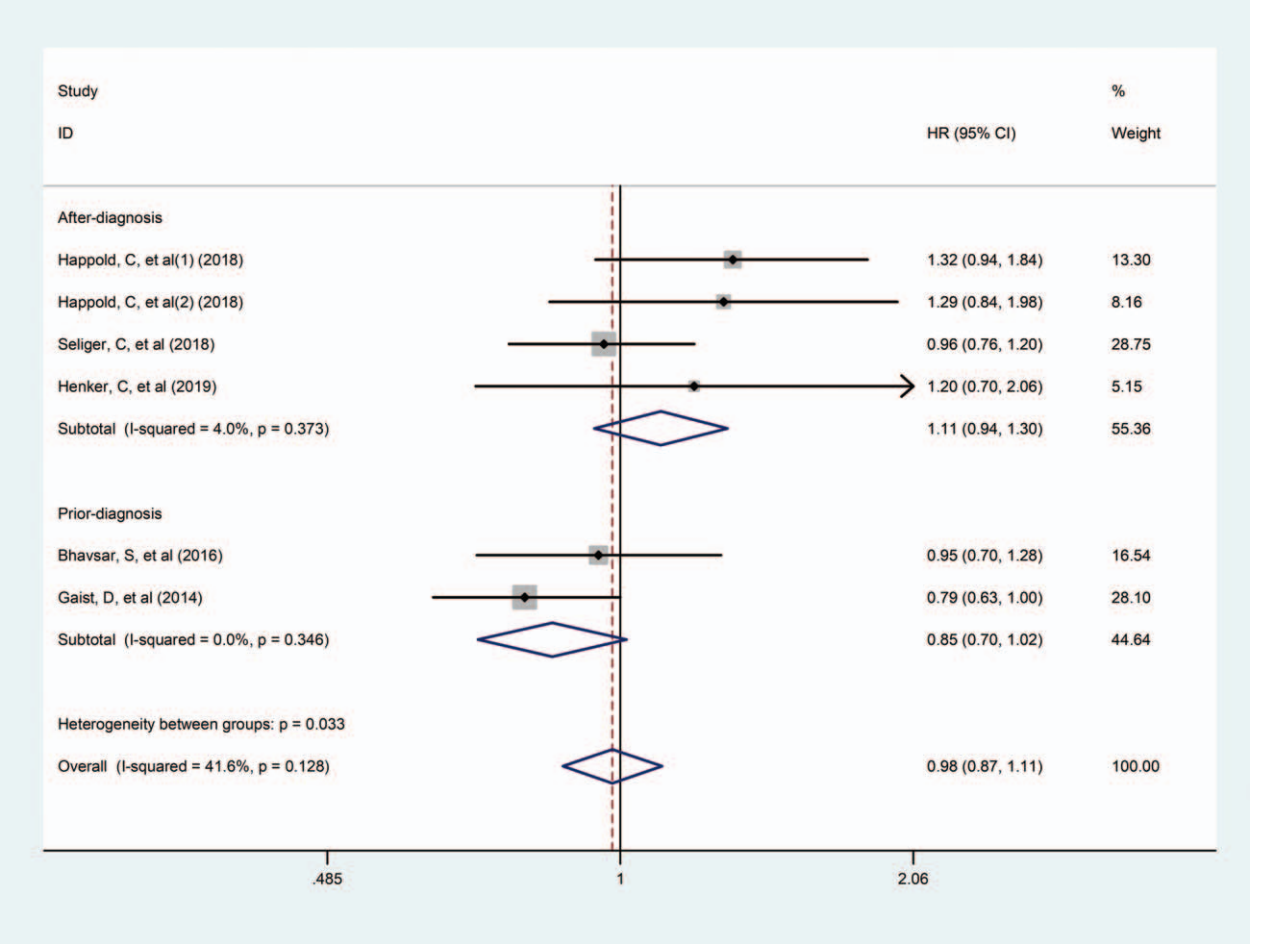

Figure 3. Forrest plot of HR on overall survival and subgroup analysis. Happold et al (1) refers data from the randomized phase III clinical study CENTRIC, and Happold et al (2) refers data from the randomized phase II study CORE. CI = confidence interval, HR = hazard ratio.

an HR of 1.11 with a 95% CI of 0.94 to 1.30 versus no statin use. There was no detection of publication bias (Egger, $P = .094$; Begg, $P = .452$).

4. Discussion

The objective of this meta-analysis was to evaluate the potential survival advantage of statins in patients with GBM. To the best of our knowledge, there has not been a meta-analysis conducted that explores this topic. Unfortunately, based on the pooled HRs of PFS, and OS from 2519 patients that either used or did not use statins, there was no benefit of statins pertaining to the outcome of GBM found in our analysis. When compared with the patients who did not use statins, the HR of statin use on the PFS was 0.97 with a 95% CI varying from 0.84 to 1.13, and the HR regarding the OS was 0.98 with a 95% CI varying from 0.87 to 1.11.

Continuous preclinical evidences suggest statins have potential as antitumor drugs because of their association with reduced tumor-related mortality for various cancers,[13] but the exact mechanism is still not well-characterized. In glioblastoma, statins may induce apoptosis in glioma cells via suppression of ERK1/2 and activation of AKT,[14] as well as downregulation of Bcl-2.[15] The invasion, migration, and proliferation of glioma cells could be inhibited by statins though Ras-/Rho-prenylation.[16] Similar results were also found in animal models of glioblastoma multiforme.[17] Although preclinical evidence supports the antitumor role of statins in glioblastoma, few clinical studies assess the association between statins and survival of patients with GBM. There were only 5 retrospective studies that reported the data, in terms of PFS or OS. Similar to some clinical trials investigating the role of statins on the survival of other malignancies,[18,19] statins failed to provide survival benefits to patient with GBM in our meta-analysis.

Considering that the patterns of statin use may interfere with the results of the analysis, we conducted a subgroup analysis based on the use of statins before or after diagnosis of GBM, and the trends depicted in Figure 3 show that the use of statins before diagnosis favors OS of GBM (HR, 0.85), but statin use after diagnosis might be harmful (HR 1.11). This may explain why statins do not improve the outcome of GBM in total analysis. In addition, there are some variables that must be considered, such as the presence of cardiovascular disease. Patients with cardiovascular disease or stroke frequently take statins as treatment, and these patients may suffer a worse outcome. The dosage and type of statins may also interfere with the results. One of the 5 included articles assess the association between dose of statins and survival of patients with GBM, and they found that high-intensity statin use reduced HR of death (HR 0.66, 95% CI:

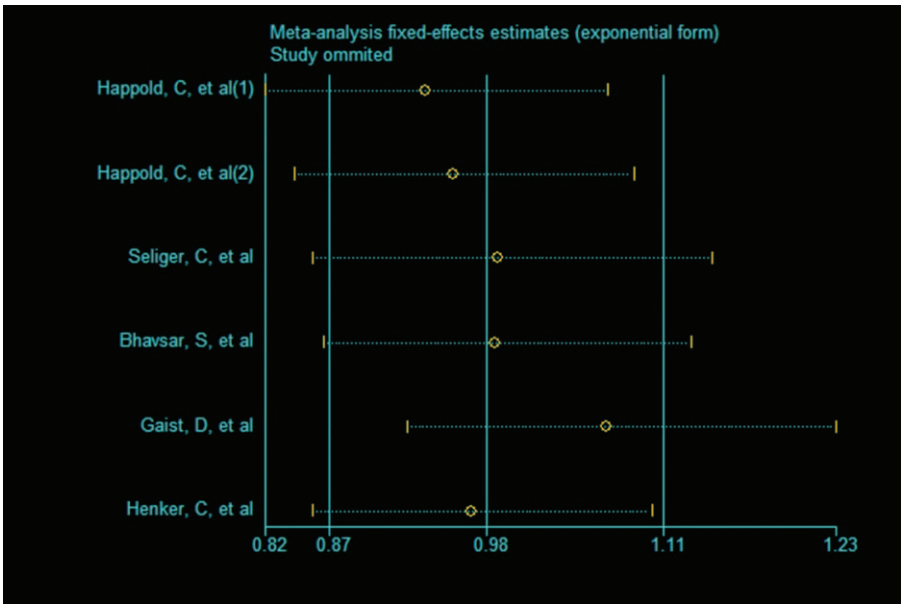

Figure 4. Sensitivity analyses of studies.

0.44–0.98),[9] but there was no correlation mentioned in the other studies. We must also take note of other drugs that are commonly used together, such as aspirin and steroid. Therefore, we anxiously await the results of 2 RCTs, a phase I trial evaluating the safety of fluvastatin and celecoxib (Celebrex) association in gliomas (NCT02115074), and a phase II Study assessing the efficacy and safety of atorvastatin in combination with radiotherapy and temozolomide in glioblastoma (NCT02029573). Other RCTs considering the above interferences also need to be designed.

Notably, there were some limitations in our study. First, all 5 articles were retrospectively designed, and no RCT was included, some heterogeneities might be generated when we incorporated these articles together. Secondly, only published and English articles were reviewed, which may contribute to bias. Thirdly, several heterogeneities should be acknowledged such as age, sex, cardiovascular disease, and so on. Each of these could influence the results. Lastly, we only analyzed PFS and OS, but other outcomes could be considered, such as the complications of glioma and the side effects of statins.

5. Conclusion

In summary, the results of our study indicate that statins do not improve the PFS and OS of patients with glioblastoma. And we do not recommend the use of statins as an adjunctive treatment for glioblastoma patients. Statin use before diagnosis of GBM might, however, prolong the OS of patients. Future trials, especially well-designed and multicenter randomized controlled clinical trials are warranted.

Author contributions

Conceived and designed the analysis: Xuchen Qi and Shuxu Yang.
Searched articles online and selected the eligible articles: Yonglin Xie, Qin Lu and Daoyang Zhou.
Collected and analyzed data: Yonglin Xie and Qin Lu.
Wrote the manuscript: Qin Lu and Yonglin Xie.
Edited the manuscript and given the Language help: Cameron Lenahan.
Given financial support: Xuchen Qi and Qin Lu.

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