Comparison of the outcomes following bevacizumab and/or temozolamide/radiosurgery treatment in patients with glioblastoma

AIKATERINI ARAVANTINOU-FATOROU[1], VASILIKI EPAMEINONDAS GEORGAKOPOULOU[2], NIKOLAOS MATHIOUDAKIS[3], PETROS PAPALEXIS[4,5], KYRIAKOS TARANTINOS[6], ILIAS TRAKAS[1], NIKOLAOS TRAKAS[7], DEMETRIOS A. SPANDIDOS[8] and GEORGE FOTAKOPOULOS[9]

[1]First Department of Internal Medicine, Departments of [2]Infectious Diseases and COVID-19 Unit, [3]Renal Transplantation, [4]Unit of Endocrinology, First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens 11527; [5]Department of Biomedical Sciences, University of West Attica, Athens 12243; [6]First Pulmonology Department and [7]Department of Biochemistry, Sismanogleio Hospital, Athens 15126; [8]Laboratory of Clinical Virology, School of Medicine, University of Crete, Heraklion 71003; [9]Department of Neurosurgery, General University Hospital of Larisa, Larisa 41221, Greece

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Abstract. Glioblastoma multiforme (GBM) is the most frequent and malignant primary central nervous system tumor in adults. The gold-standard management of GBM includes post-operative radiotherapy (RT) with concurrent and secondary temozolomide (TMZ) treatment. The present meta-analysis study examined the efficacy of the early administration of bevacizumab prior to standard RT plus TMZ in managing patients with GBM and unfavorable prognostic factors. Between 1983 and 2020, the present study looked for comparative articles involving standard RT plus TMZ and RT/TMZ combined with bevacizumab treatment in patients with GBM. The primary outcomes involved in this study include progression-free survival and overall survival. The present study suggested that bevacizumab administration plus standard RT/TMZ (BEV group) treatment was associated with increased survival of patients with GBM compared with those treated with standard RT/TMZ (CG/Control group) treatment only.

Contents

Correspondence to: Dr George Fotakopoulos, Department of Neurosurgery, General University Hospital of Larisa, Mezourlo 1, Larisa 41221, Greece
E-mail: gfotakop@yahoo.gr

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1. Introduction

Glioblastoma multiforme (GBM) is certainly the most frequent and malignant primary central nervous system (CNS) tumor appearing in adults, as <20% of these survive ~1 year after diagnosis (1).

The gold-standard management of GBM includes post-operative radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ) (2). However, numerous elderly patients with glioblastoma are considered too frail to tolerate the TMZ/RT combination (3). Furthermore, the absence of previous tumor resection surgery leads to greater neurological instability during treatment, indicating a clear need for alternative methods.

Bevacizumab is a VEGF-targeting antibody and is considered to be one of the most favorable candidate treatments to improve the outcome of elderly patients with glioblastoma. Nevertheless, in the first-line setting, only three trials favored the advantage of bevacizumab in frail and elderly patients (4-6).

The present meta-analysis study examined the efficacy of the early administration of bevacizumab prior to standard RT plus TMZ in managing patients with GBM and unfavorable prognostic factors.

2. Sources and data extraction

Literature search strategy. The present study searched comparative articles involving standard RT plus TMZ and RT/TMZ

accompanied by bevacizumab treatment in patients with GBM through electronic databases, including the Cochrane Library, Medline (1983-2020.8; https://www.cochranelibrary.com/), PubMed (1983-2020.8; https://pubmed.ncbi.nlm.nih.gov/), and EMBASE (1983-2020.8; https://www.elsevier.com/solutions/embase-biomedical-research) Preferred reporting items for systematic reviews and meta-analyses (PRISMA) were applied for establishing protocol and manuscript design (7). The present study used the keywords 'radiotherapy,' 'chemotherapy,' 'temozolomide,' 'bevacizumab,' and 'chemo-radiotherapy' in the MeSH list.

Inclusion and exclusion criteria. The literature was included in the present meta-analysis if the article met the following criteria, as determined by PICOS: i) Population: Limited to patients with GMB; ii) Intervention: For GBM, the standard RT/TMZ and bevacizumab plus standard RT/TMZ treatment were used. iii) Comparison: the outcomes were compared. Table I contains detailed data on these articles.

Outcome measures: It involved one of the primary outcomes, including progression-free survival (PFS) and overall survival (OS). To avoid publication bias, the final aim was to collect a homogenous pool of manuscripts, including articles that compared only two modalities: standard RT/TMZ or bevacizumab plus standard RT/TMZ.

Articles that were excluded from that article pool were those that were editorials, reviews, case reports, articles focusing on the pediatric population, unrelated outcomes, co-morbidities, experimental techniques, or one of the two treatment modalities and all those that demonstrated mixed or unclear results, being separated between standard RT plus TMZ (CG/Control group) or bevacizumab plus standard RT/TMZ (BEV group) treatment (Fig. 1).

Data extraction and definition of outcomes. In the present study, two of the reviewers (GF and VEG) independently extracted data from the included articles, following the guidelines of the epidemiology of meta-analysis. The following essential information was captured: The main authors, year of publication, total case number in the BEV and CG/Control groups, study type and outcome indicator. The extracted data were entered into a designed, standardized table according to the Cochrane Handbook. When there was disagreement, another authority author had the final say.

The primary outcomes involved in the present study included PFS and OS. PFS was defined as the time from inclusion to the first documented progression or mortality from any cause. OS was defined as the time from inclusion to mortality from any cause. The outcomes reported by the included articles were assessed at least six months after the treatment (standard RT plus TMZ or bevacizumab plus standard RT/TMZ). Additionally, to decrease the risk of bias in poor articles, a quality assessment tool (the Newcastle-Ottawa Scale) was used (Table II) (8).

Additionally, the patients were divided into two groups: Those receiving therapy with bevacizumab plus standard RT/TMZ (BEV group) and those receiving therapy with standard RT plus TMZ (CG/Control group).

Statistical analysis. All analyses were carried out using STATA, version 16 (StataCorp LLC). Heterogeneity across trials was identified using 12 statistics; considering 12 >50% as high heterogeneity, a meta-analysis was conducted using a random-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0; www.cochrane-handbook.org). Otherwise, the fixed-effect model was performed. The continuous outcomes were expressed as a weighted mean difference with 95% confidence intervals (CIs). For discontinuous variables, odds ratios (OR) with 95% CIs were applied for the assessment. $P<0.05$ was considered to indicate a statistically significant difference.

3. Data on the comparison of the outcome after bevacizumab administration at the temozolamide or/plus radiosurgery treatment in patients with glioblastoma

After the initial search, 55 articles were eligible for further analysis. Applying all exclusion and inclusion criteria, four articles were left in the final article pool (Fig. 1) (4,5,9,10).

The total number of patients included in those four articles was 2,592 (872 in the BEV group and 1,720 in the CG/Control group). The detailed results of these articles are presented in Table III.

OS. Information regarding the OS was available in all articles (4,5,9,10). There were 109 patients in the total group of patients (109/2,592): 56 in the BEV group and 53 in the CG/Control group. The pooled results demonstrated a statistically significant difference between the BEV and CG/Control groups [OR 0.67, CI 95% (0.28-1.07), and $P<0.05$] with no heterogeneity ($P=0.85$ and $I^2=-270.32\%$ (Fig. 2A and B).

PFS. The four articles (4,5,9,10) contained information about PFS. There were 66 patients in total (66/2,592): 39 in the BEV group and 27 in the CG/Control group, with no heterogeneity ($P=0.52$ and $I^2=-31.49\%$) (Fig. 3A and B).

4. Discussion

The present study suggested that bevacizumab administration plus standard RT/TMZ (BEV group) treatment was associated with increased survival of patients with GBM compared with those treated with standard RT/TMZ (CG/Control group) treatment alone. More precisely, OS and PFS were statistically significant parameters in patients with GBM, showing the superiority of bevacizumab administration over the standard RT/TMZ treatment. The findings of the present meta-analysis study suggested that this treatment may benefit the management of GBM.

According to reports with bevacizumab management in GBM patients, the benefit may be pronounced in elderly and poor patients (11-13). In addition, a predisposition to extended OS has been noted in patients with lower Karnofsky performance scores and those who did not obtain additional medication at the time of cancer development (14). However, these explanations lack statistical significance.

Additionally, according to patients' accounts, quality of life was preserved under bevacizumab treatment for at least up to tumor development and more patients received corticoids with bevacizumab (10). On the other hand, in some studies, there is an association between bevacizumab treatment and worse cognitive functioning, encouraging the assumption of

Table I. Design and baseline characteristics of included trials.

	Sample size		Mean age (years)		Number of males		OS		PFS		
Trial, year	BEV	CG/ Control	BEV	CG/ Control	BEV	CG/ Control	BEV	CG/ Control	BEV	CG/ Control	(Refs.)
Chinot *et al*, 2014	458	921	56	57	NR	NR	17	17	11	6	(4)
Gilbert *et al*, 2014	320	637	NR	NR	NR	NR	16	16	11	7	(5)
Balana *et al*, 2016	44	87	62.9	62	31	25	11	8	5	2	(9)
Wirsching *et al*, 2018	50	75	70	70	32	16	12	12	12	12	(10)

OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab plus standard RT/TMZ treatment; CG/Control, RT plus TMZ; NR, not recorded.

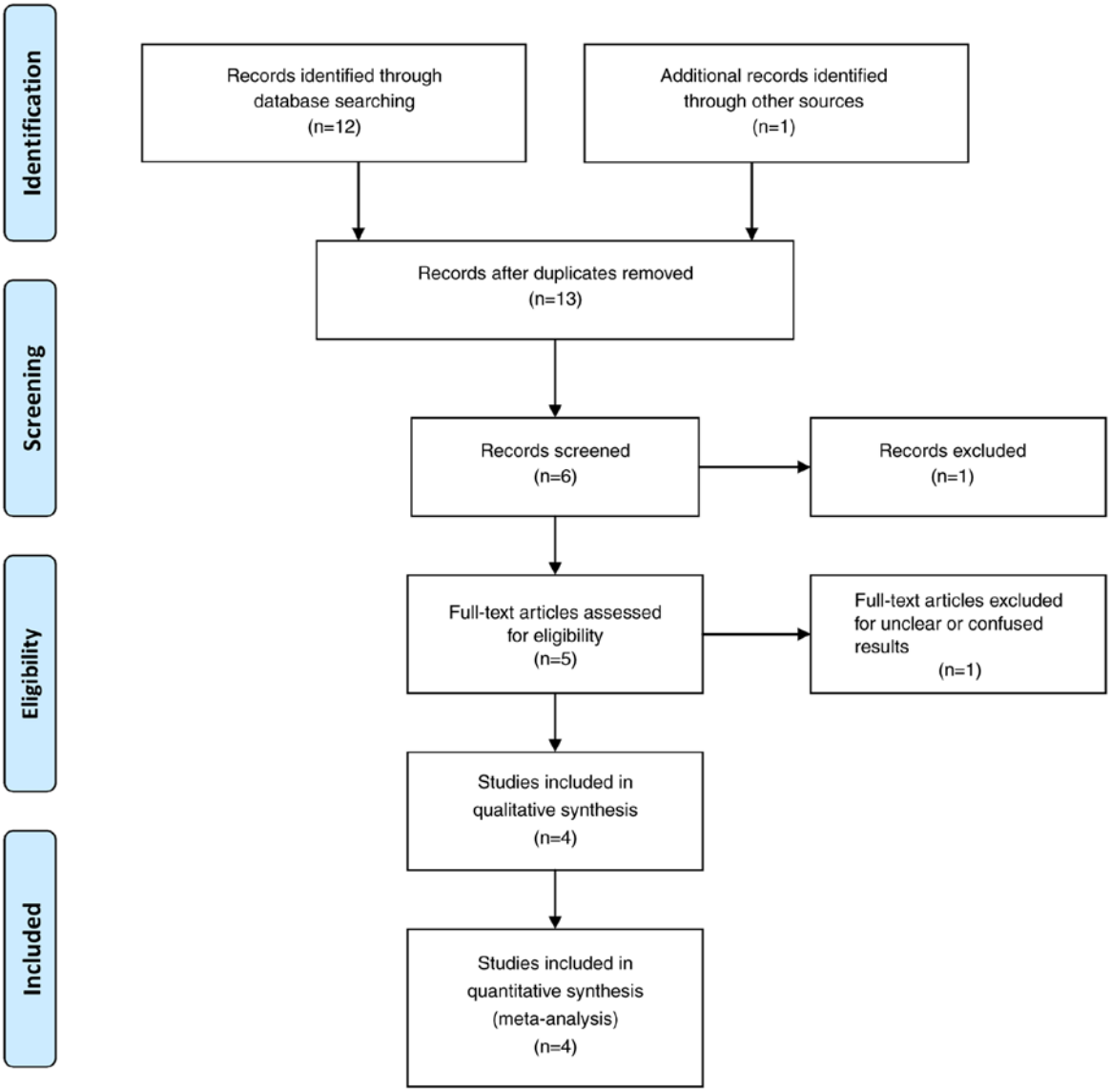

Figure 1. Flowchart of the study selection process.

presumed neurotoxicity (13,15,16). However, other causes possibly affecting cognitive function in individual patients are the instabilities in cognitive behavior at baseline, the extended cure, and unknown cancer evolution (13,15,16).

Table II. Newcastle-Ottawa Scale quality assessment of the final article pool.

Trial, year	Study design	Selection	Newcastle-Ottawa Scale			
			Comparability	Exposure	Total scores	(Refs.)
Chinot *et al*, 2014	prosp	3	3	3	9	(4)
Gilbert *et al*, 2014	prosp	3	3	3	6	(5)
Balana *et al*, 2016	prosp	3	3	3	9	(9)
Wirsching *et al*, 2018	prosp	3	2	2	7	(10)

prosp, prospective.

Table III. Meta-analysis results.

Outcomes	Trial, n=4	Groups		Overall effect			Heterogeneity	
		BEV	CG/Control	Effect estimate	CI 95%	P-value	I^2 (%)	P-value
OS	4	56	53	0.67	(0.28-1.07)	<0.05	-270.32	0.85
PFS	4	39	27	0.92	(0.41- 1.43)	<0.05	-31.49	0.52

RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab plus standard RT/TMZ treatment; CG/Control, RT plus TMZ; CI, confidence interval; I^2 shows the percentage of total variation across studies that is due to heterogeneity rather than chance; OS, overall survival; PFS, progression-free survival.

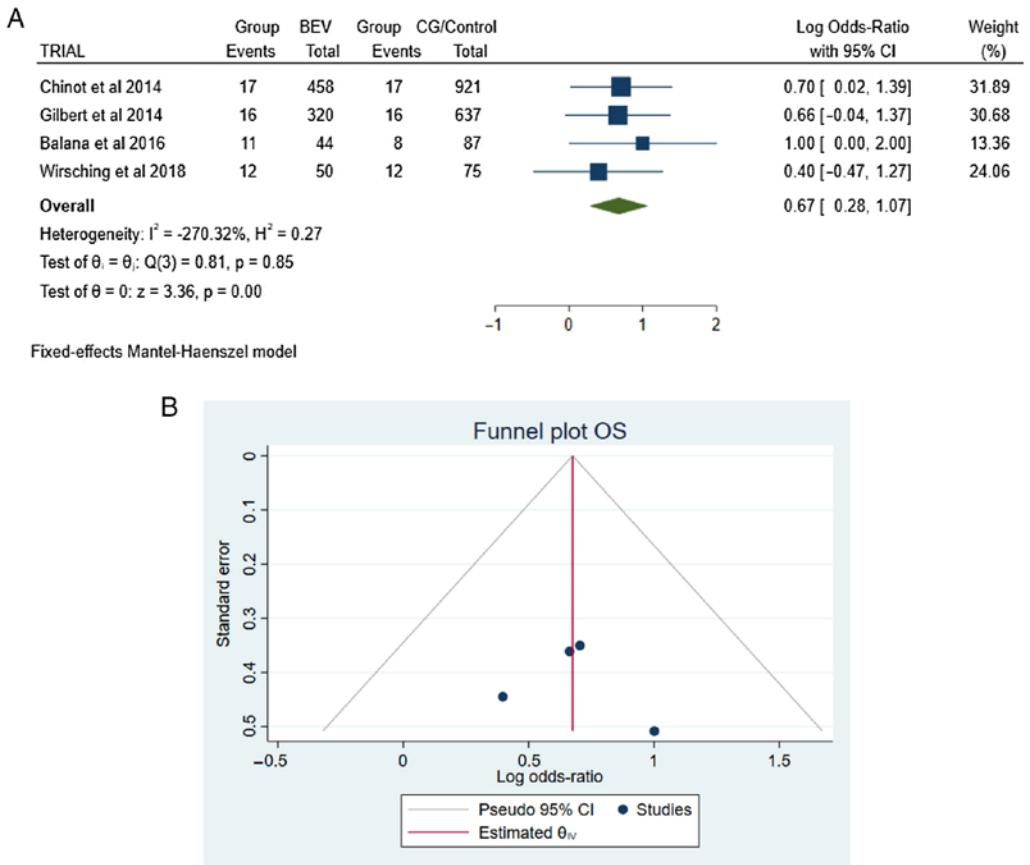

Figure 2. (A) Forest plot OS: Results demonstrated a statistically significant difference between the BEV and CG/Control groups [OR 0.67, CI 95% (0.28-1.07), and P<0.05. (B) Funnel plot, testing the sensitivity with funnel plot for OS there was no statistically significant superiority between groups, with no heterogeneity (P=0.85 and I^2=-270.32%. OS, overall survival; RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab plus standard RT/TMZ treatment; CG/Control, RT plus TMZ; OR, Odds Ratio; I^2 shows the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

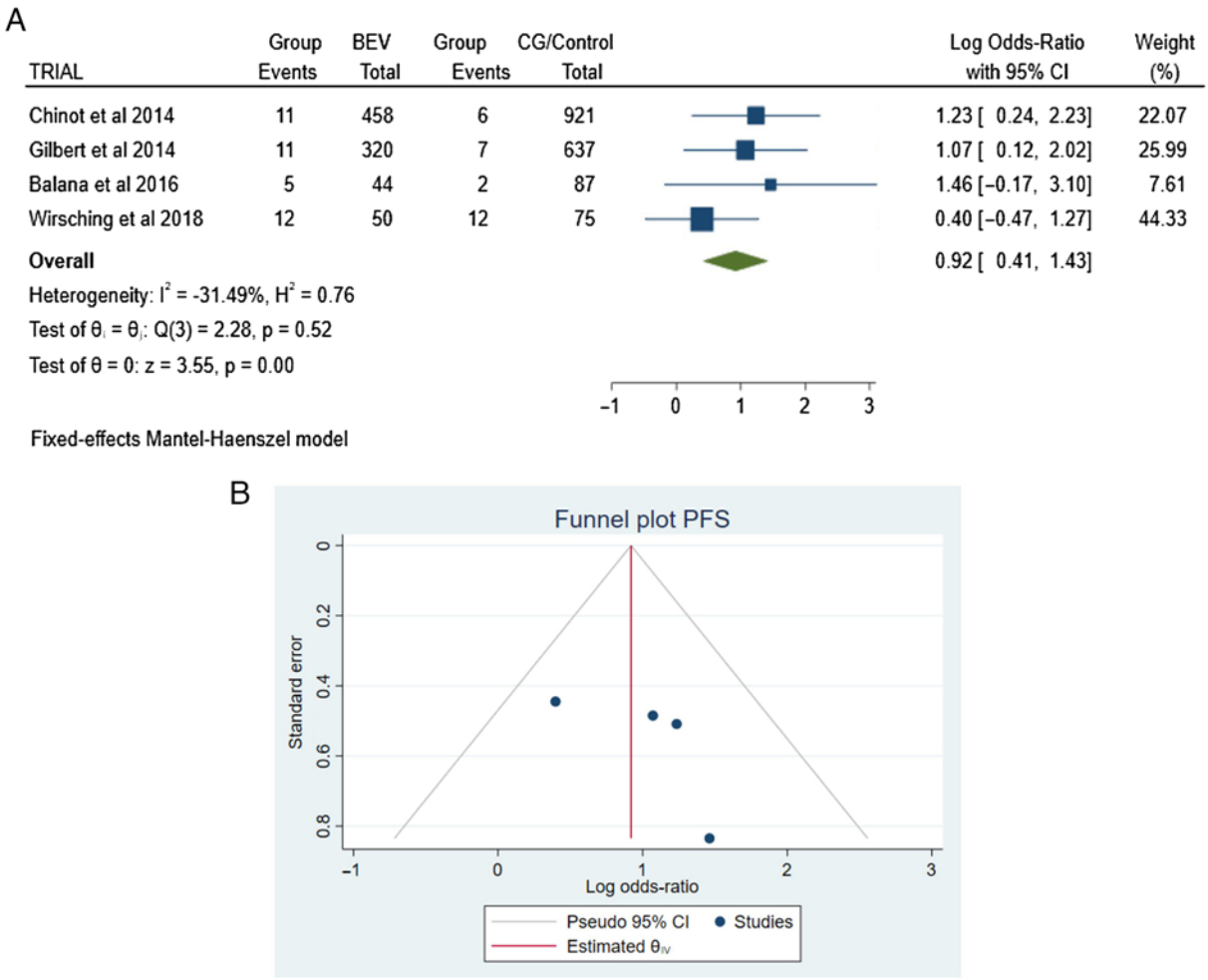

Figure 3. (A) Forest plot PFS. Results demonstrated a statistically significant difference between treatments [OR- 0.92, CI 95% (0.41- 1.43), and P<0.05]. (B) Funnel plot, testing the sensitivity with funnel plot for GCS of admission; there was no statistically significant superiority between groups, with no heterogeneity (P=0.52 and I^2=-31.49%). PFS, progression-free survival; OR, Odds Ratio; I^2 shows the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; GCS, Glasgow Coma Scale/Score.

Glioblastoma is commonly an unoperated tumor with residual mass (17-19), and those patients have an unfortunate outcome (2).

In the TEMAVIR trial (20) with unresected GBM patients and bevacizumab as first-line treatment, although PFS was longer in the TMZ plus BEV arm, the trial did not achieve its main endpoint of an increase from 50-66% in 6-month PFS.

Intriguingly, the objective response was associated with extended survival in all patients receiving bevacizumab, suggesting that reducing quantifiable illness can allow patients to attain longer OS (21). A randomized study also detected an association between the objective response and OS (22). Although objective response has never been measured as a good substitute for extended survival in GBM, there are increasing signs that it can have an affirmative effect on PFS or OS (23).

Although the present study provided evidence of benefit with bevacizumab in combination with RT/TMZ, the effect of bevacizumab may have been narrowed to a pseudo response, as has been observed with other antiangiogenics (24).

There are several limitations to the present study. First, even though all of the eligible reports that were included were prospective, some heterogeneity was found among included trials in the study protocols, patient characteristics, definitions of clinical endpoints Additionally, in order to eliminate the bias, the article pool was very small.

5. Conclusion

In conclusion, the current study added to the evidence that additional treatment with bevacizumab in combination with temozolomide may be more effective in terms of response and tumor reduction than standard RT/TMZ alone in patients with glioblastoma, with no negative impact on survival.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

GF and VEG conceived the current study. VEG, AAF, KT, IT, DAS, GF and NT analyzed the data and wrote and prepared the draft of the manuscript. VEG and GF provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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