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Updated incidence of neurological deficits following insular glioma resection: A systematic review and meta-analysis

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ABSTRACT

The resection of insular gliomas remains a neurosurgical challenge due to the close proximity of functionally-important cortical, white matter tracts, and vasculature structures. More recently, the feasibility of resection has gained traction, however, there is a lack of consolidated neurological deficit metrics. Thus, the aim of this study was to determine the incidences of neurological deficits following insular glioma resection to better guide selection algorithms and resource allocations. Searches of seven electronic databases from inception to August 2018 were conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Data were extracted and pooled using meta-analysis of proportions. Meta-regression was used to identify potential sources of heterogeneity. Nineteen observational studies reported the neurological outcomes of 890 insular glioma patients. The pooled incidences of new temporary and permanent motor deficits were 11% (95% CI, 6–17%) and 4% (95% CI, 2–7%) respectively, and new temporary and permanent language deficits were 11% (95% CI, 6–17%) and 2% (95% CI, 0–4%) respectively. Single-surgeon series reported significantly lower incidences of both permanent motor (2% vs 7%; $P < 0.001$) and language (1% vs 3%; $P = 0.03$) deficits. The incidences of motor and language neurological deficits following insular glioma resection have been quantified, and will assist in determining the suitability and appropriateness of pursuing surgical resection for insular glioma. We note that permanent neurological deficits are lowest when reported by series describing outcomes of a single surgeon, indicating most optimal outcomes may be best achieved after intense training and/or greater experience.

1. Introduction

The insular cortex is a surgically challenging area to access due to the overlying frontal, temporal and parietal opercula. Gliomas in the insular region are not uncommon, accounting for 25% of all low-grade intracranial glioma (LGG) and 10% of all high-grade intracranial glioma (HGG) [1–3]. Beyond the issue of access, a significant challenge facing surgeons in resection derives from the glioma proximity to eloquent and functionally-important structures in this area, as well as the delicate surrounding microvasculature [4,5]. These eloquent areas that are characteristic of this region control multiple motor and language domains, and, more specifically, house the blood supply to the descending motor pathway and perisylvian language network.

Nevertheless, the resection of glioma located in the insular region has emerged as a feasible management strategy [3]. Despite advances made in microsurgical and mapping techniques, given the potential damage to these essential neural networks, surgical resection still remains controversial in many clinical circles due to the risks of postoperative neurological deficits. Although individual studies have reported their neurological outcomes following this specialized type of surgery, there remains individual inconsistences in reported deficit incidences following resection. In fact, a generalized summary of neurological deficit incidences across the literature remains lacking. Furthermore, whether or not the transient vs permanent nature of neurological deficits is significantly different has yet to be firmly established. Thus, the aim of this study was to evaluate the current literature and establish the pooled trends of neurological deficits following resection of glioma in the insular region in order to better guide selection algorithms and resource allocations for surgeons and patients alike.

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2. Methods

2.1. Search strategy

The present review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and recommendations [6]. Electronic searches were performed using Ovid Embase, PubMed, SCOPUS, Cochrane databases from their dates of inception to August 2018. The literature was searched by using the following string of terms to detect all possible studies for inclusion: (insular) AND (intrinsic tumor OR glioma OR low-grade OR high-grade). All retrieved articles and their reference lists were reviewed independently by two investigators (V.M.L. and A.G.) for systematic assessment against inclusion and exclusion criteria.

2.2. Selection criteria

The inclusion criteria used to screen all identified articles were 1) confirmed glioma histopathology involving the insular region managed by surgical resection, 2) both temporary (short-term) and permanent (long-term) evaluation of 3) new language or motor neurological deficit outcomes, 3) involving adult patients (> 18 years old) only. Insular region involvement did not preclude involvement of adjacent brain regions, e.g. frontal, parietal, and temporal regions. New deficits included worsening of deficits present before surgery. The exclusion criteria applied to all identified articles were 1) cohorts where insular region was not confirmed, 2) anatomical/cadaveric/molecular studies, and 3) case reports or series (< 5 patients), reviews, abstracts, conference presentations, editorials and expert opinions. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, or when studies reported multiple time courses of the same treated cohort, only the most complete reports were included for quantitative assessment at each time interval. All efforts were made to ensure that no patient outcomes were not repeated. All publications were limited to those in the English language.

2.3. Data extraction

Our primary outcomes of interest were the incidences of neurological deficit following surgery, both motor and language that were transient and permanent. Transient and permanent deficits were defined as either 1) deficits apparent < 3 and ≥3 months post-operation respectively or 2) by study definition. Secondary outcomes analyzed included extent of resection (EOR), incidences of gross total resection (GTR; ≥90% EOR), quality of life, return to work, neuro-cognitive outcomes, and survival where reported. To test for confounding by various study design, demographic and surgical parameters, the following variables were also collected: study publication year, study size, study duration, cohort mean age, proportion of males, number of primary surgeries, tumor laterality, awake surgery, tumor histology, pure insular location (Yasargil Class 3 A), pre-operative tumor volume, seizure history at initial presentation, and trans-sylvian approach. Two investigators (V.M.L. and A.G.) independently reviewed each included article to extract data from article text, tables and figures. Any discrepancies resolved by discussion to reach consensus.

2.4. Meta-analysis

The outcomes of the included studies were pooled together for meta-analysis of proportions to provide overall summary statistics. Results are presented as forest plots. We employed a random-effect (RE) model only to take into account the possible clinical diversity and methodological variation between studies, as it assumes unequal variance between studies and distributes statistical weighting more conservatively [7]. The I^2 statistic was used to estimate the percentage of total variation across studies owing to heterogeneity rather than chance, with values > 50% considered as substantial heterogeneity [8]. Univariate meta-regression was performed to analyze potential effect modification by study design, demographic and clinical covariates for all outcomes reported. All P values were 2-sided with significance set at $P < 0.05$ to indicate significant deviation from the null. Statistical analyses were conducted with STATA 14.1 (StataCorp, College Station, Texas).

2.5. Quality assessment

The quality of evidence for each study was evaluated using a modified Newcastle-Ottawa Scale (NOS) [9] for assessment of non-comparative studies [10]. Overall methodologic quality was then summarized based on the quality trends observed. This serves as a surrogate indication for risk of inherent bias in the incorporated data of each study [11].

3. Results

3.1. Search strategy

A total of 565 articles were identified for evaluation **(**Fig. 1). After the removal of 306 duplicate articles, the title and abstract of the remaining 242 articles were evaluated against the selection criteria. Full-text analysis was performed for 47 articles, in which 19 cohort studies [3,12–29] were assessed to satisfy all criteria for inclusion into this systematic review. Data was primarily collected in a retrospective nature, with three [3,20,28] studies conducted in a prospective nature. Publication year ranged from 1996 to 2018, with average recruitment period of 7 years (Table 1).

3.2. Demographics and clinical course

The 19 studies pooled a cohort of 890 glioma cases involving the insular region managed with surgical resection (Table 1). Overall, mean age of the patients was 41.9 years, with 55% being male. At presentation, 77% of cases were primary diagnoses, and 52% of cases were located in the dominant hemisphere. Awake craniotomy was employed in 34%. Overall, histopathology of glioma was 56% LGG, and 44% HGG.

Where reported, patients presented with active seizure history 65% (479/742; n = 16 studies). Glioma were purely insular in 25% (90/358; n = 10 studies) of patients, with mean pre-operative tumor volume of 69 cm [3] (n = 6 studies). An average volumetric EOR of 87% (n = 8 studies) was achieved where reported, with incidence of GTR being 57% (452/796; n = 17 studies). Survivorship was reported by 9 studies, in which the survival rate at the end of a mean 28 months follow-up was 72% (323/451) across all grades – further delineation could not be calculated due to insufficient data.

3.3. Motor neurological deficits

The pooled incidences of new temporary and permanent motor deficits were 11% (95% CI, 6–17%; I^2 = 84.5%; $P < 0.001$) and 4% (95% CI, 2–7%; I^2 = 42.5%; $\mathbf{P < 0.001}$) across all studies respectively (Fig. 2). The difference in incidences between temporary and permanent deficits was statistically significant ($\mathbf{P = 0.025}$).

3.4. Language neurological deficits

The pooled incidences of new temporary and permanent language deficits were 11% (95% CI, 6–17%; I^2 = 83.5%; $\mathbf{P < 0.001}$) and 2% (95% CI, 0–4%; I^2 = 51.4%; $\mathbf{P < 0.001}$) across all studies respectively (Fig. 3). The difference in incidences between temporary and permanent deficits was statistically significant ($\mathbf{P < 0.001}$).

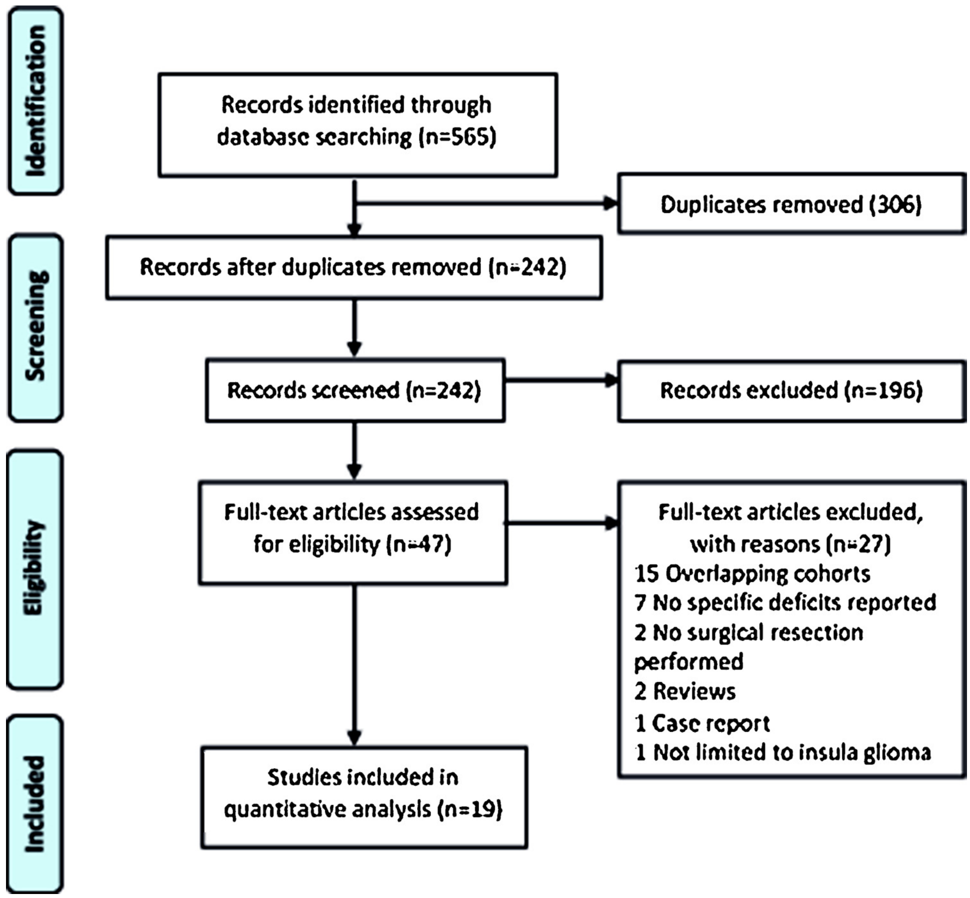

Fig. 1. Results of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) search strategy.

3.5. Single-surgeon series

Six studies [3,14,15,19,24,25] reported outcomes of single-surgeon series only. Sub-group analysis of all types of deficits revealed that compared to the remaining studies, single-surgeon series reported significantly lower incidences of permanent motor deficits, 2% (95% CI, 1–4%) vs 7% (95% CI, 4–10%; **P < 0.001**), and language deficits 1% (95% CI, 0–2%) vs 3% (95% CI, 0–6%; **P = 0.035**), (**Supplementary 1.** Figs. 1 and 2). There was no statistically significant difference in either temporary motor (P = 0.13) or language (P = 0.54) deficits.

3.6. Meta-regression for confounding parameters

Univariate meta-regression was performed to investigate potential modifying effect on neurological deficit incidences by study publication year, study size, study duration, cohort mean age, pre-operative tumor volume, as well as proportions of males, primary tumor, tumor laterality, awake craniotomy, tumor grade, pure insular location, seizure history at initial presentation, and trans-sylvian approach (**Supplementary 2.** Table 1). Effect by EOR and proportion of GTR was also evaluated. No parameter was found to exert a significant confounding effect on any reported outcome.

3.7. Quality assessment

Against the modified NOS criteria, the median score was 5 (range, 4–5) out of a maximum of 5 evaluating case series for selection, ascertainment, causality, and reporting, indicating the quality of the included studies to be good (**Supplementary 3**). The primary reason for studies not reporting a score of 5 was the lack of specification for deficit nature.

4. Discussion

The resection of insular glioma remains a great neurosurgical challenge. Due to its eloquent location and proximity to several critical cortical and subcortical structures, the risk of postoperative neurological deficit must be carefully titrated against the potential benefit of resection. In our study, we pooled the currently available literature to ascertain that motor and language deficits after surgery each occur transiently in approximately 1 of every 10 resections, and that the rate of permanent deficits of either type is significantly less, but nonetheless, not necessarily negligible. These deficits are less in series where surgeries were all performed by one surgeon as implied by the sub-group analysis. Better understanding of the acceptable risk of neurological deficits following insular glioma resection will enhance decision making algorithms in determining and evaluating the option of surgery at a patient-level.

Of the largest individual studies published in recent years, Eseonu et al. [15] reported rates of neurological deficits comparable or superior to that of the meta-analysis. Hervey-Jumper et al. [19] reported mostly comparable or superior incidences as well, however they did note a greater rate of transient language deficit following surgery. It is unclear if this is a simple consequence of a more thorough language evaluation, for exact evaluation approaches by most other studies were poorly/not reported. Nonetheless, this discrepancy highlights the inherent greater heterogeneity in assessment for language, with evaluation of language more vulnerable to subjective interpretation compared to motor evaluation. Specialist and extensive language evaluations can more often detect more subtle deficits which would propagate a higher sensitivity [30].

Multiple studies [15,25,31,32] have implicated greater EOR with improved survival metrics in these patients. Based on our meta-

Table 1
Study design and demographic characteristics of included studies. R, retrospective; P, prospective; CS, cohort study; LGG, low-grade glioma; HGG, high-grade glioma.

Study	Location*	Study period	Design	Cohort size (n)	Mean age (yrs)	Males (n, %)	Primary diagnosis (n, %)	Dominant hemisphere (n, %)	Awake surgery (n, %)	LGG (n, %)	HGG (n, %)	Median/ minimum follow-up (months)
Baran et al. 2018 [12]	Turkey	2010-2016	R CS	22	46.18	11, 50%	22, 100%	10, 45%	11, 50%	18, 81%	4, 18%	33.4
Sughrue et al. 2017 [13]	Australia	1995-2009	R CS	72	42	48, 67%	19, 26%	23, 32%	0	23, 32%	49, 68%	≥3
Panigrahi et al. 2017 [14]	India	2011-2015	R CS	61	44	21, 34%	9, 15%	31, 51%	0	40, 66%	21, 34%	≥3
Eseonu et al. 2017 [15]	US (Hopkins)	2006-2016	R CS	74	54	42, 57%	74, 100%	43, 58%	29, 39%	25, 34%	49, 66%	52.8
Chen et al. 2017 [16]	China (Beijing)	2010-2014	R CS	73	53.5	46, 63%	73, 100%	30, 41%	0	0	73, 100%	21
Zhuang et al. 2016 [17]	China (Shanghai)	2011-2013	R CS	30	45	19, 63%	29, 97%	30, 100%	20, 67%	21, 70%	9, 30%	25
Shah et al. 2016 [18]	India	2013-2014	R CS	5	39.6	4, 80%	5, 100%	1, 20%	0	2, 40%	3, 60%	15
Hervey-Jumper et al. 2016 [19]	US (UCSF)	2007-2014	R CS	129	41	74, 57%	80, 62%	68, 53%	58, 45%	70, 54%	59, 46%	42
Alimohamadi et al. 2016 [20]	Iran	2015-2016	P CS	10	43.6	4, 40%	10, 100%	10, 100%	10, 100%	7, 70%	3, 30%	11
Ius et al. 2015 [21]	Italy (Udine)	2000-2013	R CS	53	38	30, 57%	53, 100%	36, 68%	41, 77%	53, 100%	0	> 6
Wang et al. 2012 [22]	China (Wuxi)	2008-2010	R CS	12	40.5	5, 42%	12, 100%	7, 58%	0	10, 83%	2, 17%	NR
Majchrzak et al. 2011 [23]	Poland	2006-2009	R CS	30	43.5	18, 60%	30, 100%	18, 60%	0	17, 57%	13, 43%	> 6
Wu et al. 2011 [24]	US (MD Anderson)	1993-2008	R CS	33	38	21, 64%	33, 100%	23, 70%	33, 100%	18, 55%	15, 45%	≥3
Sanai et al. 2010 [25]	US (UCSF)	1997-2007	R CS	104	39.8	42, 40%	74, 71%	58, 56%	65, 63%	62, 60%	42, 40	50.4
Duffau et al. 2009 [3]	France	1997-2007	P CS	51	36	30, 59%	51, 100%	14, 27%	16, 31%	51, 100%	0	48
Moshel et al. 2008 [26]	US (NYU)	1995-2007	R CS	38	38	23, 61%	32, 84%	17, 45%	0	29, 76%	9, 24%	> 3
Ozyurt et al. 2003 [29]	Turkey	1996-2001	R CS	40	27	16, 40%	39, 98%	15, 38%	0	25, 63%	15, 37%	24
Vanaclocha et al. 1997 [27]	Spain	1989-1996	R CS	23	43.6	15, 65%	18, 78%	16, 70%	18, 78%	16, 70%	7, 30%	34.8
Zentner et al. 1996 [28]	Germany (Bonn)	1993-1995	P CS	30	42	18, 60%	26, 87%	15, 50%	0	15, 50%	15, 50%	8.5
			Sum (n, % total)	890 (100%)	41.9*	487 (55%)	689 (77%)	465 (52%)	301 (34%)	502 (56%)	388 (44%)	.

* City/institution listed in parentheses when country reported more than once.

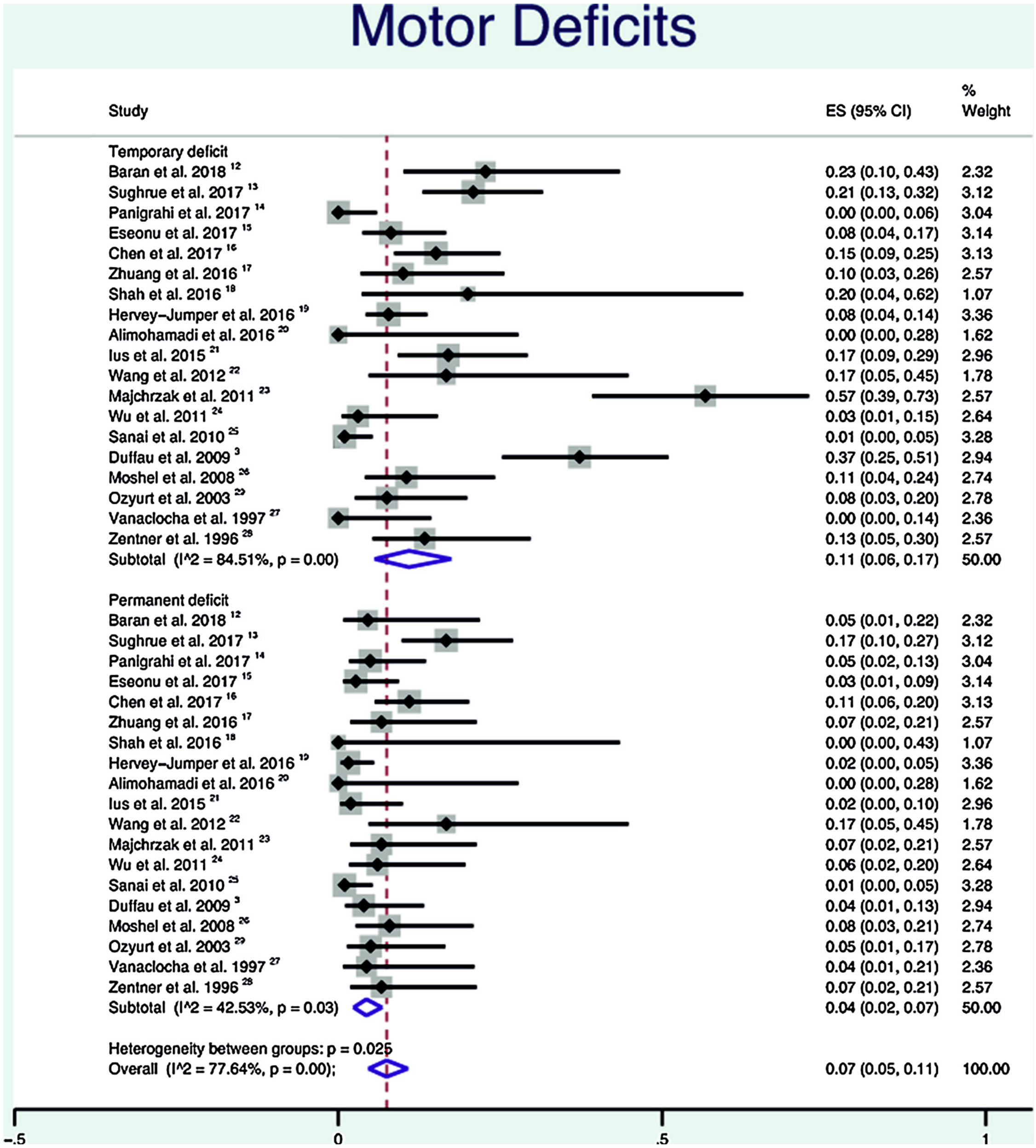

Fig. 2. Forest plot of the incidences of neurological motor deficits that were temporary and permanent in nature following surgical resection of insular glioma. The effect size (ES) of incidence, its 95% confidence interval (CI), and the relative weightings are represented by the middle of the square, the horizontal line, and the relative size of the square respectively.

regression results, neither percentage EOR or incidence of GTR significantly affected trends in any of the deficit outcomes. This finding may implicate that by virtue of an insular location surrounded by primary motor and language regions, the risk of neurological deficit is more inherent to the nature of surgical intervention to this area rather than the EOR achieved. In a similar vein, glioma grade (HGG vs LGG) remains a significant factor in prognosticating survival but our meta-regression did not identify proportion of HGG vs LGG as a modifying variable for any deficit outcome [33]. Thus, it would appear glioma grade is another independent clinical factor that exerts minimal effect on postoperative neurological deficits following insular glioma resection.

An intuitive indication for deficit risk could be surgical approach chosen, despite a negative finding by our meta-regression which was admittedly underpowered [27,34,35]. Although successful in providing direct access to the tumor, the more traditional trans-sylvian approach renders the surgical field vulnerable to vascular insult, with the addition of opercular region retraction increasing the risk of neurological damage further [36,37]. A trans-opercular approach may prove a worthwhile alternative, with components of the literature highlighting this approach can provide superior exposure and surgical freedom compared to the trans-sylvian approach [25,38]. Anecdotally, the few reported incidences of permanent motor and language deficits following the trans-opercular approach include: Baran et al. [12] 4.5% each, and Duffau et al. [3] 4% and 0% respectively. These single study outcomes are arguably comparable to that of the overall pooled findings of our meta-analysis, and thus until greater reporting is achieved, whether or not approach choice affects incidence neurological deficits remains unclear.

Pooling of the current literature indicates new permanent motor and language deficits following insular glioma resection occur in 4% and 2% of cases respectively, with this reduced to 2% and 1% based on

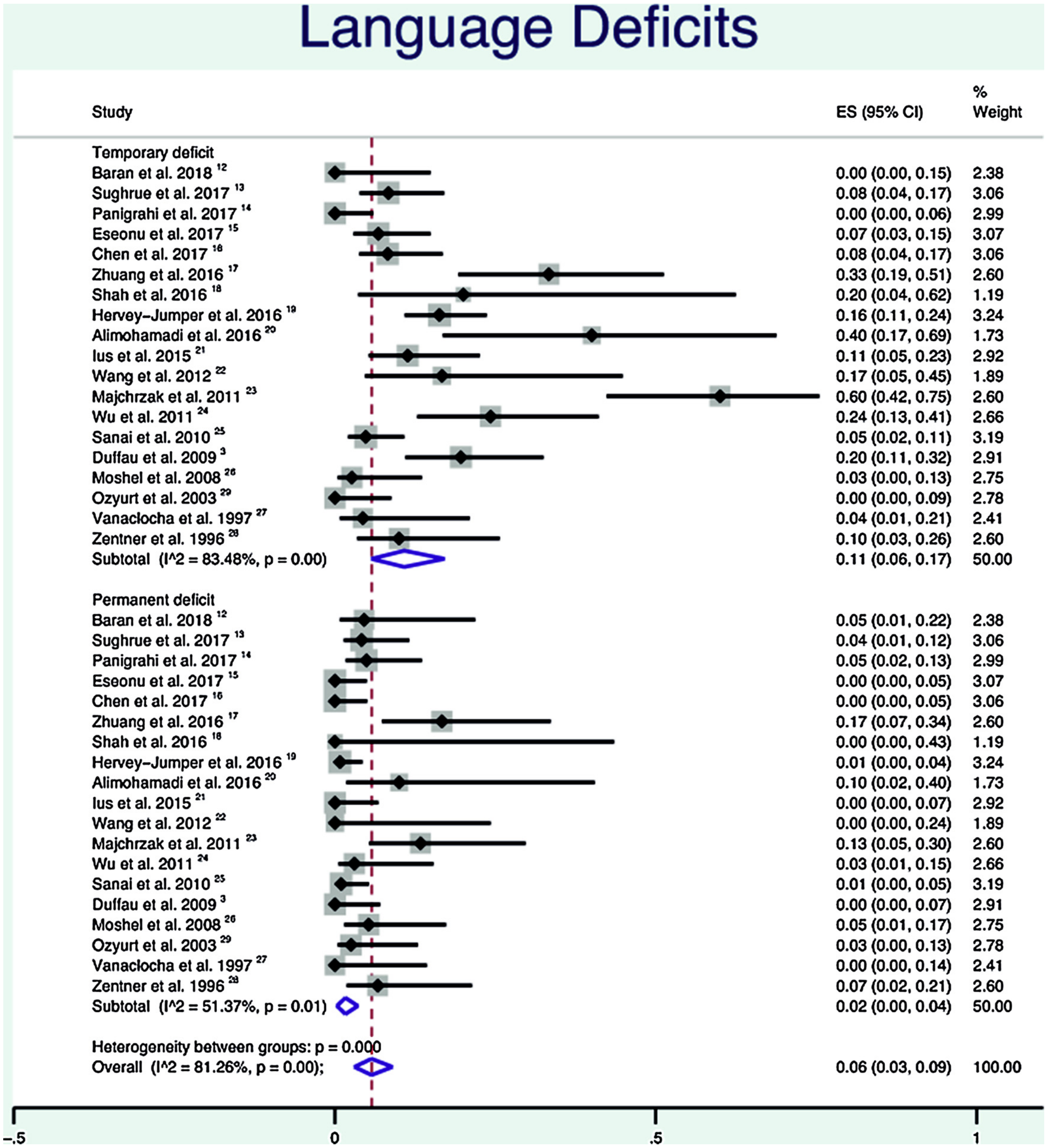

Fig. 3. Forest plot of the incidences of neurological language deficits that were temporary and permanent in nature following surgical resection of insular glioma. The effect size (ES) of incidence, its 95% confidence interval (CI), and the relative weightings are represented by the middle of the square, the horizontal line, and the relative size of the square respectively.

single-surgeon series only. Thus, despite concerns of large neurological morbidity following this type of surgery, in high-volume centers with well-trained and experienced surgeons, these risks appear minimizable in well-selected surgeons and patients. Indeed, these rates are comparable, if not superior, to resection of glioma located in eloquent areas generally [39].

4.1. Strengths and limitations

In this systematic review and meta-analysis, with strict adherence to the PRISMA guidelines, we successfully pooled new temporary and permanent motor and language deficits from controlled studies only – in the sense that all temporary and permanent deficits corresponded with each other from the same cohort. This improves the validity of the observation that permanent deficits are significantly less common than temporary deficits. Despite the overall quality impression of the included studies ranging from fair to good, we must acknowledge that the majority of them were retrospective in nature represents a low level of evidence involving patient outcomes, and that superior study designs in the future are required to confirm the pooled trends of this study [40].

The primary design limitation of a study like this is the inherent clinical heterogeneity that exists both within and between studies in terms of insular glioma surgery, which ultimately acts as an intangible selection bias. This reflects the variations possible in medical history, clinical presentation, prognostic demographics, tumor characteristics, and composition of the surgical and non-surgical management. Although complete control for all variable remains a theoretical exercise at best, we utilized a RE-model in pooling in accounting for this heterogeneity in an attempt to reduce some of the statistical interference. Furthermore, by restricting study inclusion to those reporting insular locations specifically (and excluding gliomas located in general 'eloquent' regions), we hope to have augmented the validity of our results available achievable by meta-analysis, and advocate for large, prospective studies to ratify the pooled trends of our study.

Furthermore, our meta-regression was not able to identify significant modification of the reported trends based on a number of potential confounding factors, which strengthens our confidence in the reported incidences to be truly reflective of the current literature. By appreciating the inherent biases involved in studies such as those included, it argues the utilization of larger, multi-institutional collaborations with longer follow-up is the optimal avenue to pursue for the future dissemination of insular glioma resection outcomes to better validate our understanding of the neurological deficit risks involved.

5. Conclusion

Resection of insular glioma carries a risk for neurological deficits involving both motor and language regions of the brain. This review of the literature demonstrated that overall, new temporary motor and language deficits each occur in 11% of patients postoperatively, with permanent deficits significantly less likely in 4% and 2% respectively. These risks appear to be lower with surgeons who have large experiences operating in this niche. With these measures in mind, clinicians will be able to better determine and evaluate the neurological risks involved in this highly specialized surgery.

Disclosure

There are no funding sources or conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2018.12.013.

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