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Cosmetic Outcomes of Supraorbital Keyhole Craniotomy Via Eyebrow Incision: A Systematic Review and Meta-Analysis

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Abstract	Background Supraorbital eyebrow craniotomy is a minimally invasive alternative to a frontotemporal craniotomy and is often used for tumor and vascular pathologies. The purpose of this study was to investigate how patient cosmetic outcomes are affected by technique variations of this approach.
	Methods PubMed, Embase, and Scopus databases were systematically searched, and results were reported according to PRISMA guidelines. For the meta-analysis portion, the DerSimonian–Laird random effects model was used, and the primary end points were patient satisfaction and percentage of permanent cosmetic complications.
	Results A total of 2,629 manuscripts were identified. Of those, 124 studies (8,241 surgical cases) met the inclusion criteria. Overall, $93.04 \pm 11.93\%$ of patients reported favorable cosmetic outcome following supraorbital craniotomy, and mean number of cases with permanent cosmetic complications was $6.62 \pm 12.53\%$. We found that vascular cases are associated with more favorable cosmetic outcomes than tumor cases ($p = 0.0001$). Addition of orbital osteotomy or use of a drain is associated with adverse cosmetic outcomes ($p = 0.001$ and $p = 0.0001$, respectively). The location of incision,
Keywords ► cosmesis ► eyebrow	size of craniotomy, utilization of an endoscope, method of cranial reconstruction, skin closure, use of antibiotics, and addition of pressure dressing did not significantly impact cosmetic outcomes ($p > 0.05$ for all).
 keyhole orbital osteotomy supraorbital technique 	Conclusions Supraorbital craniotomy is a minimally invasive technique associated with generally high favorable cosmetic outcomes. While certain techniques used in supraorbital keyhole approach do not pose significant cosmetic risks, utilization of an orbital osteotomy and the addition of a drain correlate with unfavorable cosmetic outcomes.

Introduction

The supraorbital keyhole craniotomy has gained traction as an effective and minimally invasive neurosurgical technique for the management of various lesions of the anterior and

received June 1, 2022 accepted July 8, 2022 article published online September 15, 2022 middle cranial fossae.^{1–4} As a less-invasive alternative to the traditional pterional craniotomy, the supraorbital keyhole craniotomy helps avoid the risks of soft tissue and temporalis muscle injury, facial nerve palsy, frontal sinus violation, odynophagia, and temporal hollowing.^{1,5} Prior studies

© 2022. Thieme. All rights reserved. Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany DOI https://doi.org/ 10.1055/s-0042-1755575. ISSN 2193-6331. have found that the supraorbital keyhole craniotomy has a similar safety and efficacy profile to the standard larger craniotomies.^{1,6} Compared with the pterional craniotomy, the minimization of number of burr holes, size of bone flap, and disruption of temporalis muscle intuitively decrease the risk for surgical site deformity and injury to nearby structures associated with the supraorbital keyhole approach. Several retrospective studies have compared cosmetic outcomes between pterional and supraorbital keyhole approaches, and results have either favored supraorbital keyhole craniotomy or been statistically insignificant.^{7–9} For example, Park and colleagues surveyed 21 patients who had previously undergone supraorbital and pterional craniotomies on separate occasions for treatment of anterior circulation aneurysms and compared patient-reported outcomes.⁹ The authors found increased overall patient satisfaction, decreased postoperative pain, and surgical site palpable irregularities in the supraorbital group. On multivariate analysis, cosmetic outcome was the most important factor in determining overall patient satisfaction.

In a recent meta-analysis, our group found that the supraorbital keyhole approach has high technical success rate with generally low complications and mortality in the treatment of both tumor and vascular pathologies, particularly in patients with anterior skull base extra-axial tumors and anterior circulation aneurysms.² The craniofacial nature of this approach has important implications for cosmetic outcomes and there are significant variations in the surgical technique used for the supraorbital keyhole approach.9,10 Therefore, the potential impact of these technical variations used in the supraorbital eyebrow approach on cosmetic outcomes is an important consideration that needs to be explored further. In this systematic review and meta-analysis, our aim was to investigate the relationship(s) between patient cosmetic outcomes and surgical technique variations used in the supraorbital eyebrow keyhole approach.

Materials and Methods

Literature Search

The authors performed comprehensive searches of PubMed, Embase/MEDLINE, and Scopus databases on August 11th, 2020. Keywords or MeSH terms included "supraorbital keyhole," "supraorbital eyebrow," "supraorbital craniotomy," "supraorbital approach," "keyhole eyebrow," "transciliary," and "superciliary" (**-Table 1**). The references of eligible studies were also reviewed for additional articles not identified by the initial electronic search. The results of the search were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹

Study Eligibility

Records were screened for eligible studies first by title and abstract and subsequently by full text by two independent reviewers (Z.M.R. and C.P.). Results were limited to studies with human subjects with intracranial pathologies that were operated on via a supraorbital eyebrow surgical approach. The authors included original prospective and retrospective studies with at least two patients, case series, operative videos, and technical notes. Single case reports, letters to the editors, cadaveric studies, commentaries, abstracts to meetings, systematic reviews, reviews, meta-analysis, studies with insufficient or not extractable data, editorials, animal studies, and non-English language articles were excluded from this systematic review.

Data Extraction and Risk of Bias Assessment

For the critical appraisal portion of this study, two reviewers (Z.M.R. and C.P.) independently reviewed and analyzed eligible articles. Differences between the two reviewers were resolved via discussion and reaching consensus. The risk of bias quality assessment was independently performed according to the National Institutes of Health Quality Assessment Tool for retrospective case series, cohort, and case-control studies. Studies that were qualified as "good" or "fair" had low risk of bias, whereas those appraised as "poor" had high risk of bias. An interval of at least three months was used for minimal adequate follow-up criteria. A standardized computerized spreadsheet was used to collect baseline characteristics and outcomes from the selected studies. The following data were collected from each study as available: total number of subjects, mean age, pathology, percentage of permanent cosmetic complications, percentage of patients with satisfactory cosmesis, location of incision, size of craniotomy, addition of orbital osteotomy, endoscope, use of cautery, type of cranial reconstruction, method of skin closure, use of perioperative antibiotics, use of pressure dressing and subgaleal drain.

Statistical Analysis

The main primary outcome, which was percentage of patients with permanent cosmetic complications, was assessed via meta-analysis. The DerSimonian–Laird random effects model

Table 1 Search syntax

PubMed Search Accessed on	EMBASE Search Accessed on	Scopus Search Accessed on
August 11, 2020 (817 Articles) ^a	August 11, 2020 (807 Articles) ^a	August 11, 2020 (1,005 Articles) ^a
(((((supraorbital craniotomy) OR (supraorbital keyhole)) OR (supraorbital eyebrow)) OR (supraorbital approach)) OR (keyhole eyebrow)) OR (transciliary)) OR (superciliary) Filters: English	"supraorbital craniotomy" OR (supraorbital AND keyhole) OR (supraorbital AND eyebrow) OR "supraorbital approach" OR (keyhole AND eyebrow) OR transciliary OR superciliary	(TITLE-ABS-KEY (supraorbital AND craniotomy) OR TITLE-ABS-KEY (supraorbital AND keyhole) OR TITLE-ABS-KEY (supraorbital AND eyebrow) OR TITLE-ABS-KEY (supraorbital AND approach) OR TITLE-ABS-KEY (keyhole AND eyebrow) OR TITLE-ABS-KEY (transciliary) OR TITLE-ABS-KEY (superciliary)) AND (LIMIT-TO (LANGUAGE, "English"))

^aSearch limited to articles available in English language.

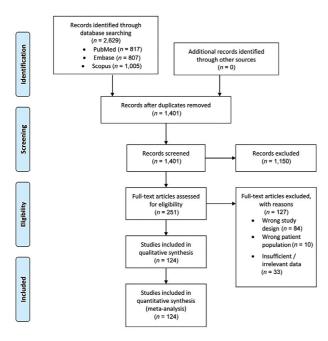


Fig. 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

was used for meta-analysis as high variability between the studies was expected.¹² The heterogeneity was then reported in forest plots as I^2 . For the primary end point of interest, 95% confidence intervals were also estimated. When applicable, the *t*-test was used to compare types of operative pathologies, locations of incision, size of craniotomies, use of orbital osteotomy, endoscopy, cautery, methods of cranial reconstruction, types of skin closure, use of antibiotics, use of subgaleal drain, and postoperative pressure dressing in terms of postoperative patient cosmetic outcomes. Statistical analysis was performed using Open-Meta [Analyst] software (http://www. cebm.brown.edu/openmeta/).

Results

Literature Search and Risk of Bias

The search strategy yielded 2,629 articles through database searching, including 817 from PubMed, 807 from Embase, and 1,005 from Scopus (**-Fig. 1**). Once duplicates were removed and records were screened by title and abstract, 251 studies were eligible for full-text review. This review yielded 124 studies that were eligible, all of which were included in the qualitative and quantitative synthesis as well as risk of bias appraisal.^{3,4,7-10,13-130} Sixty-six studies that were included in this meta-analysis were appraised as good, whereas 58 were appraised as fair according to the National Institutes of Health Quality Assessment Tool. Of the 124 studies, all were retrospective in design as either case series, cohort studies, or case-control studies. There were no prospective studies or clinical trials related to this topic (**-Table 2**).

Cosmetic Outcomes and Technique Variations

There was a total of 8,241 supraorbital eyebrow craniotomy cases amongst the 124 studies included in the systematic

review (**►Table 3**). The number and percentage of total studies reporting on pathologies, patient satisfaction, and cosmetic complications as well as the number and percentage of total studies reporting cosmetic outcomes related to technical variations are detailed in **►Table 3**. It is important to note that several outcomes do not sum to 100% as they were not reported by all analyzed studies.

Of the studies with reportable data, the mean age was 46.7 ± 15.5 years and 58% of patients were female. Pathologies included vascular lesions or clipped aneurysms (6,150 cases, 74.6% of total), tumors (2,045 cases, 24.8% of total), and other cases (46 cases, 0.6% of total). Mean number of cases with permanent cosmetic complications was $6.62 \pm 12.53\%$, and the majority (93.04 \pm 11.93%) of patients reported overall favorable cosmetic outcomes following supraorbital eyebrow keyhole craniotomy.

With respect to technique variations, the location of the incision varied with 32.3% of all 124 studies utilizing a transciliary incision (hidden within the eyebrow), 17.7% utilizing a superciliary incision (just above the eyebrow), and 1.6% using a crease in the forehead. Orbital osteotomy was performed in 8.1% of the cases reporting cosmetic outcomes. Twenty one percent of cases with cosmetic outcomes reported use of an endoscope and 11.3% of the studies used some form of cautery. With respect to cranial reconstruction, the majority of cases replaced bone with titanium plates and screws (24.2%); other craniotomy repair techniques included the use of cement or a bone filler (8.1%), dissolvable plates (5.6%), bone plating with sutures (4%), and use of mesh (0.8%). A subgaleal drain and postoperative pressure dressing were used in 4% and 2.4% of the studies, respectively. With respect to the method of skin closure, most closed the skin with absorbable subcuticular suture (11.3%), however the use of a nonabsorbable suture (5.6%) and Dermabond adhesive (2.4%) was also reported.

Meta-analysis of Cosmetic Outcomes

The aim of this study was to investigate how certain technique variations of the supraorbital keyhole approach influence patient cosmetic outcomes (**-Fig. 2**; **-Table 4**). The authors defined permanent cosmetic complications to include muscle atrophy or palsy, scarring, other skin or bony defects, and proptosis.

First, with respect to the type of pathology, we found that vascular cases $(0.1 \pm 0.008\%)$ had fewer cosmetic complications than tumor cases $(3.3 \pm 0.5\%)$ (p = 0.0001) (**-Fig. 3A,B**). The proportion of patients with permanent cosmetic complications did not differ between those with a transciliary and superciliary incision $(4.2 \pm 0.8\% \text{ vs. } 3.2 \pm 0.9\%; p = 0.436)$ (**-Fig. 3C,D**). There were too few studies with incision on the forehead crease to report any meaningful meta-analysis. The size of the craniotomy did not affect cosmetic outcomes either, with $4.3 \pm 1\%$ having cosmetic complications in the <2.5 cm group compared with $3.7 \pm 0.9\%$ in the >2.5 cm group (p = 0.656) (**-Fig. 3E,F**). Addition of an orbital osteotomy was found to negatively affect patient cosmetic outcomes, with $7.2 \pm 2.8\%$ having permanent cosmetic complications compared with $2.1 \pm 0.4\%$ of patients without an orbital osteotomy

	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
1	Adawi and AbdelbakyValidity of the supraorbital approach as a minimally invasive corridor for orbital lesions		2015	10	Retrospective case series	Fair
2	Al-Mefty et al	Optic nerve decompression in osteopetrosis	1988	6	Retrospective case series	Good
3	Alekseev et al	A supraorbital trans-eyebrow approach in surgery of chiasmatic-sellar and anterior cranial fossa tumors	2017	31	Retrospective case series	Good
4	Ansari et al	The supraorbital eyebrow craniotomy for intra- and extra-axial brain tumors: a single- center series and technique modification	2020	117	Retrospective case series	Good
5	Banu et al	Endoscope-assisted endonasal versus supraorbital keyhole resection of olfactory groove meningiomas: comparison and combination of 2 minimally invasive approaches	2016	7	Retrospective comparative study	Good
6	Bassiouni et al	Olfactory groove meningiomas: functional outcome in a series treated microsurgically	2007	3	Retrospective case series	Good
7	Benifla et al	Supraciliary keyhole craniotomy for anterior frontal lesions in children	2016	14	Retrospective case series	Fair
8	Bhatoe	e Transciliary supraorbital keyhole approach in the 2009 52 Retrospective management of aneurysms of anterior circulation: operative nuances			Good	
9	Bhattarai et al	Factors determining the side of approach for clipping ruptured anterior communicating artery aneurysm via supraorbital eyebrow keyhole approach	2020	85	Retrospective case series	Good
10	Bhattarai et al	Supraorbital eyebrow keyhole approach for microsurgical management of ruptured anterior communicating artery aneurysm	2020	85	Retrospective case series	Fair
11	Brydon et al	Supraorbital microcraniotomy for acute aneurysmal subarachnoid hemorrhage: results of first 50 cases	2008	50	Prospective case series	Fair
12	Burks et al	Management of intracranial meningiomas using keyhole techniques	2016	10	Retrospective case series	Fair
13	Cai et al	Trans-eyebrow supraorbital keyhole approach to tuberculum sellae meningiomas: a series of 30 cases with long-term visual outcomes and recurrence rates	2019	30	Retrospective case series	Good
14	Cai et al	Trans-eyebrow supraorbital keyhole approach in suprasellar and third ventricular craniophar- yngioma surgery: the experience of 27 cases and a literature review	2018	27	Retrospective case series	Good
15	Chalouhi et al	Surgical treatment of ruptured anterior circula- tion aneurysms: comparison of pterional and supraorbital keyhole approaches	2013	47	Retrospective cohort study	Fair
16	Chen et al	Supraorbital keyhole surgery for optic nerve decompression and dura repair	2004	11	Retrospective case series	Fair
17	Chen et al	Is eyebrow approach suitable for ruptured anterior circulation aneurysms on early stage: a prospective study at a single institute		88	Retrospective case series	Good
18	Chen and Tzaan	Microsurgical supraorbital keyhole approach to the anterior cranial base	2010	21	Retrospective case series	Fair
19	Choi et al	Intradural procedural time to assess technical difficulty of superciliary keyhole and pterional approaches for unruptured middle cerebral artery aneurysms	2016	124	Retrospective cohort study	Fair

Table 2 Stu	udies incl	uded in	the s	ystematic	review
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	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
20	Czirják and Szeifert	Surgical experience with frontolateral keyhole craniotomy through a superciliary skin incision	2001	155	Retrospective case series	Fair
21	Czirják and Szeifert	The role of the superciliary approach in the surgical management of intracranial neoplasms	2006	76	Retrospective case series	Good
22	Czirják et al	Bilateral supraorbital keyhole approach for multiple aneurysms via superciliary skin incisions	2002	36	Retrospective case series	Fair
23	Dare et al	Eyebrow incision for combined orbital osteot- omy and supraorbital minicraniotomy: applica- tion to aneurysms of the anterior circulation	2001	10	Retrospective case series	Good
24	de Oliveira et al	The supraorbital eyebrow approach for removal of craniopharyngioma in children: a case series	2017	8	Retrospective case series	Good
25	Delitala et al	Supraorbital endoscopic approach to colloid cysts	2011	7	Retrospective case series	Good
26	Ditzel Filho et al	Supraorbital eyebrow craniotomy for removal of intraaxial frontal brain tumors: a technical note	2014	10	Retrospective case series	Good
27	Dlouhy et al	The supraorbital eyebrow approach in children: clinical outcomes, cosmetic results, and complications	2015	54	Retrospective case series	Good
28	Dye et al	Frontal bur hole through an eyebrow incision for image-guided endoscopic evacuation of spontaneous intracerebral hemorrhage	2012	6	Retrospective case series	Good
29	Dzhindzhikhadze et al	Supraorbital keyhole craniotomy in surgery of anterior circle of Willis aneurysms	2016	27	Retrospective case series	Fair
30	El Shafei	Anterolateral mini fronto-orbito-zygomatic craniotomy via an eyebrow incision in pediatrics: technical notes and evaluation	2011	18	Retrospective c ase series	Good
31	Elkheshin and Soliman	Supraorbital keyhole microsurgical fenestration of symptomatic temporal arachnoid cysts in children: advantages and limitations	2017	25	Retrospective case series	Good
32	Eroglu et al	Supraorbital keyhole approach: lessons learned from 106 operative cases	2019	106	Retrospective case series	Fair
33	Fan et al	Individualized surgical strategies for Rathke cleft cyst based on cyst location	2013	17	Retrospective case series	Good
34	Fatemi et al	Endonasal versus supraorbital keyhole removal of craniopharyngiomas and tuberculum sellae meningiomas	2009	11	Retrospective cohort study	Fair
35	Fernandes et al	Supraorbital Minicraniotomy	1997	6	Retrospective case series	Fair
36	Fernandes et al	Supraorbital eyebrow approach to skull base lesions	2002	16	Retrospective case series	Fair
37	Feroze et al	Utility of calcium phosphate cement cranioplasty following supraorbital approach for tumor resection	2018	8	Retrospective case series	Good
38	Fischer et al	The keyhole concept in aneurysm surgery: results of the past 20 years	2011	793	Retrospective case series	Fair
39	Gandhoke et al	Supraorbital versus endoscopic endonasal approaches for olfactory groove meningiomas: a cost-minimization study	2017	5	Cost effectiveness study	Good
40	Gazzeri et al	Endoscopic supraorbital eyebrow approach for the surgical treatment of extraaxial and intraaxial tumors	2014	97	Retrospective case series	Good
41	Genesan et al	A comparative study between supraorbital keyhole and pterional approaches on anterior circulation aneurysms	2018	41	Retrospective cohort study	Fair

	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
42	Hassler and Schick	The supraorbital approach—a minimally invasive approach to the superior orbit		20	Retrospective case series	Good
43	He et al	Contralateral approach based on a preoperative 3-dimensional virtual osteotomy technique for anterior circulation aneurysms	2019	11	Retrospective case series	Good
44	He et al	Eyebrow incision for combination supraorbital minicraniotomy with orbital osteotomy: application to cranio-orbital lesions	2018	16	Retrospective case series	Good
45	He et al	Outcomes after pterional and supraorbital eyebrow approach for cranio-orbital lesions communicated via the supraorbital fissure—a retrospective comparison	2019	13	Retrospective cohort study	Fair
46	Hendrix et al	Olfactory Dysfunction in Patients undergoing supraorbital keyhole craniotomy for clipping of unruptured aneurysms	2020	14	Retrospective case series	Fair
47	Hopf et al	Surgical management of bilateral middle cerebral artery aneurysms via a unilateral supraorbital key-hole craniotomy	2009	15	Retrospective case series	Fair
48	Hwang et al	Reduction of supraorbital fractures via a short sub-brow incision	2018	2	Retrospective case series	Fair
49	lacoangeli et al	Piezosurgery as a further technical adjunct in minimally invasive supraorbital keyhole approach and lateral orbitotomy	2015	15	Retrospective case series	Fair
50	lacoangeli et al	Minimally invasive supraorbital key-hole approach for the treatment of anterior cranial fossa meningiomas	2016	23	Retrospective case series	Good
51	lacoangeli et al	Supraorbital subfrontal trans-laminar endo- scope-assisted approach for tumors of the posterior third ventricle	2017	7	Retrospective case series	Good
52	Igressa et al	Endoscope-assisted keyhole surgery via an eyebrow incision for removal of large meningi- omas of the anterior and middle cranial fossa	2015	40	Retrospective case series	Fair
53	Ivan and Lawton	Mini Supraorbital Approach to Inferior Frontal Lobe Cavernous Malformations: Case Series	2013	2	Retrospective case series	Fair
54	Jallo et al	A superciliary approach for anterior cranial fossa lesions in children	2005	27	Retrospective case series	Good
55	Jho	Orbital Roof Craniotomy Via an Eyebrow Inci- sion: A Simplified Anterior Skull Base Approach	1997	11	Retrospective case series	Good
56	Jian et al	Surgical biopsies in patients with central diabe- tes insipidus and thickened pituitary stalks	2014	13	Retrospective case series	Good
57	Joseph and Chacko	Suprabrow minicraniotomy for suprasellar tumors	2005	18	Retrospective case series	Fair
58	Kabil and Shahinian	Application of the Supraorbital Endoscopic Approach to Tumors of the Anterior Cranial Base	2005	24	Retrospective case series	Fair
59	Kabil and Shahinian	The endoscopic supraorbital approach to tumors of the middle cranial base	2006	2	Retrospective case series	Fair
60	Kabil and Shahinian	A Fully Endoscopic Supraorbital Suprafrontal Approach to Frontal and Frontoparietal Convexity/Parasagittal Meningiomas	2006	2	Retrospective case series	Fair
61	Kabil and Shahinian	Fully Endoscopic Supraorbital Resection of Congenital Middle Cranial Fossa Arachnoid Cysts: Report of 2 Cases	2007	2	Retrospective case series	Fair
62	Kang et al	Comparative Analysis of the Mini-pterional and Supraorbital Keyhole Craniotomies for Unrup- tured Aneurysms with Numeric Measurements of Their Geometric Configurations	2013	4	Retrospective cohort study	Fair

(Continued)

	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
63	Khanapure et al	Supraorbital Craniotomy for Large Anterior Skull20197RetrospectiveBase Meningiomas: A Technical Note20197case series		Fair		
64	Kim et al	Modified Supraorbital Keyhole Approach to Anterior Circulation Aneurysms	2016	20	Retrospective cohort study	Good
65	Ko et al	Eyebrow incision using tattoo for anterior fossa lesions: technical case reports	2001	7	Retrospective case series	Fair
66	Krishna et al	Trans-lamina terminalis approach to third ventricle using supraorbital craniotomy: technique description and literature review for outcome comparison with anterior, lateral and trans-sphenoidal corridors	2011	3	Retrospective case series	Fair
67	Lan et al	Microsurgical experience with keyhole operations on intracranial aneurysms	2006	91	Retrospective case series	Fair
68	Lan et al	Keyhole approach for clipping intracranial aneurysm: comparison of supraorbital and pterional keyhole approach	2017	195	Retrospective cohort study	Good
69	Lan et al	Microsurgical treatment of posterior cerebral circulation aneurysms via keyhole approaches	2015	15	Retrospective case series	Fair
70	Lin et al	Lin et al Anterior skull base tumor resection by 2018 62 Retro		Retrospective case series	Good	
71	Linsler et al	Endoscopic assisted supraorbital keyhole approach or endoscopic endonasal approach in cases of tuberculum sellae meningioma: which surgical route should be favored?	2017	16	Retrospective cohort study	Good
72	Marx et al	The value of endoscope assistance during trans- cranial surgery for tuberculum sellae meningiomas	2017	8	Retrospective case series	Good
73	McLaughlin et al	The supraorbital approach for recurrent or residual suprasellar tumors	2011	11	Retrospective case series	Good
74	McLaughlin et al	Side-cutting aspiration device for endoscopic and microscopic tumor removal	2012	3	Retrospective case series	Fair
75	Melamed et al	The supraorbital approach: an alternative to traditional exposure for the surgical manage- ment of anterior fossa and parasellar pathology	2005	25	Retrospective case series	Good
76	Menovsky et al	Endoscope-assisted supraorbital craniotomy for lesions of the interpeduncular fossa	1999	7	Retrospective case series	Fair
77	Mitchell et al	Supraorbital eyebrow minicraniotomy for anterior circulation aneurysms	2005	47	Retrospective case series	Good
78	Niknejad et al	Minimally invasive aneurysm clipping: the extent of the supraorbital approach	2019	142	Retrospective case series	Fair
79	Noggle et al	Supraciliary keyhole craniotomy for brain abscess debridement	2008	3	Retrospective case series	Good
80	Ottenhausen et al	Decision-making algorithm for minimally invasive approaches to anterior skull base meningiomas	2018	11	Retrospective cohort study	Fair
81	de Paiva-Neto et al	Supra-orbital keyhole removal of anterior fossa and parasellar meningiomas	2010	24	Retrospective case series	Good
82	Paladino et al	Eyebrow keyhole approach in vascular neurosurgery	1998	37	Retrospective case series	Fair
83	Paladino et al	The keyhole concept in aneurysm surgery - a com- parative study: keyhole versus standard craniotomy	2005	383	Retrospective cohort study	Fair
84	Park et al	Postoperative subdural hygroma and chronic subdural hematoma after unruptured aneurysm surgery: age, sex, and aneurysm location as independent risk factors	2016	290	Retrospective case series	Good

	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
85	Park et al	Minimally invasive and rapid surgical embolectomy (MIRSE) as rescue treatment following failed endo- vascular recanalization for acute ischemic stroke	2014	4	Retrospective case series	Good
86	Park et al	Preoperative percutaneous mapping of the frontal branch of the facial nerve to assess the risk of frontalis muscle palsy after a supraorbital keyhole approach	2013	52	Retrospective case series	Good
87	Park et al	Superciliary keyhole surgery for unruptured posterior communicating artery aneurysms with oculomotor nerve palsy: maximizing symptomatic resolution and minimizing surgical invasiveness	2011	13	Retrospective case series	Fair
88	Park et al	Risk factor analysis for poor outcomes in supraorbital keyhole aneurysm clipping for ruptured anterior circulation aneurysms	2018	188	Retrospective case series	Good
89	Park et al	Microsurgical experience with supraorbital keyhole operations on anterior circulation aneurysms	2009	50	Retrospective cohort study	Fair
90	Park et al	Height of aneurysm neck and estimated extent of brain retraction: powerful predictors of olfactory dysfunction after surgery for unrup- tured anterior communicating artery aneurysms	2016	78	Retrospective case control study	Good
91	Park et al	Pterional versus superciliary keyhole approach: direct comparison of approach-related com- plaints and satisfaction in the same patient	2018	21	Retrospective cohort study	Good
92	Park et al	Superciliary keyhole approach for small unrup- tured aneurysms in anterior cerebral circulation	2011	120	Retrospective cohort study	Good
93	Peng et al	The supraorbital keyhole approach to the suprasellar and supra-intrasellar rathke cleft cysts under pure endoscopic visualization	2016	13	Retrospective case series	Good
94	Pitskhelauri et al	The trans-eyebrow supraorbital approach for removal of anterior cranial fossa and suprasellar meningiomas	2017	7	Retrospective case series	Fair
95	Prat et al	Trans-eyebrow supraorbital approach in large suprasellar craniopharyngioma surgery in adults: analysis of optic nerve length and extent of tumor resection. Original article	2017	21	Retrospective case series	Good
96	Prat-Acin et al	Supraorbital trans-eyebrow craniotomy and fluorescence-guided resection of fronto-basal high grade gliomas	2013	6	Retrospective case series	Good
97	Ramos-Zuniga et al	Trans-supraorbital approach to supratentorial aneurysms	2002	20	Retrospective case series	Good
98	Raza et al	The supraorbital craniotomy for access to the skull base and intraaxial lesions: a technique in evolution	2010	24	Retrospective case series	Good
99	Reisch et al	Patients' cosmetic satisfaction, pain, and func- tional outcomes after supraorbital craniotomy through an eyebrow incision	2014	408	Retrospective case series	Fair
100	Reisch and Perneczky	Ten-year experience with the supraorbital sub frontal approach through an eyebrow skin incision	2005	450	Retrospective case series	Fair
101	Reisch et al	The minimally invasive supraorbital subfrontal key-hole approach for surgical treatment of temporomesial lesions of the dominant hemisphere	2009	15	Retrospective case series	Fair
102	Reisch et al	The supraorbital endoscopic approach for aneurysms	2014	793	Retrospective case series	Fair

(Continued)

	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
103	Russo et al	Endoscopic approaches to intraventricular lesions	2015	6	Retrospective case series	Fair
104	Sanchez-Vasquez et al	Transciliary subfrontal craniotomy for anterior skull base lesions	1999	41	Retrospective case series	Good
105	Schick et al	Treatment of orbital schwannomas and neurofibromas	2003	2	Retrospective case series	Fair
106	Schroeder et al	Endoscope-assisted microsurgical resection of skull base meningiomas	2011	11	Retrospective case series	Fair
107	Sharma et al	Endoscopic controlled clipping of anterior circulation aneurysms via keyhole approach: our initial experience	2015	7	Retrospective case series	Good
108	Shin and Park	Unruptured supraclinoid internal carotid artery aneurysm surgery: superciliary keyhole approach versus pterional approach	2012	70	Retrospective cohort study	Fair
109	Tang et al	Supraorbital keyhole approach for anterior circulation aneurysms	2013	76	Retrospective case series	Good
110	Tawk et al	Transciliary supraorbital approach (eyebrow approach) for resection of retrochiasmatic craniopharyngiomas: an alternative approach, case series, and literature review	2014	6	Retrospective case series	Good
111	Telera et al	Supraorbital keyhole approach for removal of midline anterior cranial fossa meningiomas: a series of 20 consecutive cases	2012	20	Retrospective case series	Good
112	Thaher et al	Supraorbital keyhole approach to the skull base: evaluation of complications related to CSF fistulas and opened frontal sinus	2015	350	Retrospective case series	Fair
113	Toyooka et al	Potential risks and limited indications of the supraorbital keyhole approach for clipping internal carotid artery aneurysms	2019	51	Retrospective case series	Good
114	Tra et al	Minipterional and supraorbital keyhole craniot- omies for ruptured anterior circulation aneur- ysms: experience at single center	2018	12	Retrospective cohort study	Fair
115	van Lindert et al	The supraorbital keyhole approach to supra- tentorial aneurysms: concept and technique	1998	139	Retrospective case series	Good
116	van Lindert	Microsurgical third ventriculocisternostomy as an alternative to ETV: report of two cases	2008	2	Retrospective case series	Fair
117	Warren and Grant	Transciliary orbitofrontozygomatic approach to lesions of the anterior cranial fossa	2009	105	Retrospective case series	Good
118	Wiedemayer et al	The supraorbital keyhole approach via an eyebrow incision for resection of tumors around the sella and the anterior skull base	2004	9	Retrospective case series	Good
119	Wongsirisuwan and Karnchanapandh	Comparative outcomes of keyhole supraorbital approach (KSA) and endonasal endoscopic transsphenoidal approach (EETA) in pituitary surgery	2014	92	Retrospective cohort study	Fair
120	Wu et al	Comparison of supraorbital and pterional keyhole approach for clipping middle cerebral artery aneurysm: a Chinese population-based study	2019	77	Retrospective cohort study	Good
121	Yu et al	Supraorbital keyhole versus pterional cranioto- mies for ruptured anterior communicating artery aneurysms: a propensity score-matched analysis	2018	70	Retrospective cohort study	Good
122	Zhang et al	The supraorbital keyhole approach with eyebrow incisions for treating lesions in the anterior fossa and sellar region	2004	54	Retrospective case series	Fair

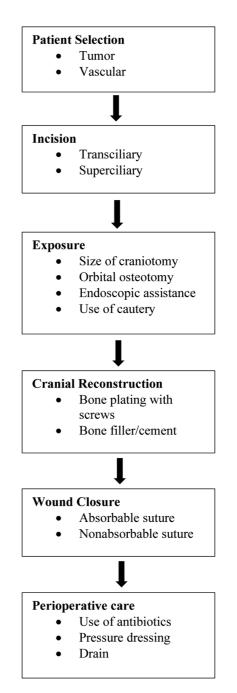
	First author	Title of the article	Year	Total cases (N)	Study design	Quality assessmenta
123	Zhang et al	Clinical application of the supraorbital key-hole approach to the treatment of unilateral-domi- nant bilateral frontal contusions	2017	26	Retrospective cohort study	Good
124	Zheng et al	Endoscope-assisted supraorbital keyhole ap- proach for the resection of benign tumors of the sellar region	2007	35	Retrospective case series	Good

Studies arranged alphabetically by the last name of the first author.

^aQuality assessment was performed according to the NIH Quality Assessment Tool. Studies appraised as good or fair had low risk of bias, whereas those appraised as poor had high risk of bias.

variations	
Total studies in meta-analysis	124
Total N of cases	8,241
Mean age (years)	46.7 ± 15.5
Vascular pathology N (%)	6,150 (74.6)
Tumor pathology N (%)	2.045 (24.8)
Other pathology N (%)	46 (0.6)
Studies reporting patient satisfaction <i>N</i> (%)	25 (20.16)
Mean % of patients with satisfactory cosmesis	93.04±11.93
Studies reporting cosmetic complications N (%)	67 (54.03)
Mean permanent cosmetic complications (%)	6.62 ± 12.53
Studies reporting the following variables with cosmetic outcomes <i>N</i> (%)	
Transciliary incision	40 (32.3)
Superciliary incision	22 (17.7)
Forehead wrinkle incision	2 (1.6)
Use of endoscope	26 (21)
Use of cautery	14 (11.3)
Orbital osteotomy	10 (8.1)
Titanium bone plating with screws	30 (24.2)
Dissolvable plates	7 (5.6)
Bone plating with sutures	5 (4)
Use of mesh	1 (0.8)
Use of cement or bone filler	10 (8.1)
Subgaleal drain	5 (4)
Postoperative pressure dressing	3 (2.4)
Absorbable skin suture	14 (11.3)
Nonabsorbable skin suture	7 (5.6)
Dermabond	3 (2.4)

 Table 3 Demographics, cosmetic outcomes, and technique variations



Note: Values are reported as means $\pm\, \text{standard}$ deviation where appropriate.

Fig. 2 Cosmetic variables.

Table 4	Meta-analysis of	cosmetic outcomes	depending on	operative technique

Variable	Results of meta-analysis for % of patients with permanent cosmetic problem(s) \pm SEM	No. of studies reporting outcome	[95% CI]	<i>p</i> -Value
Patient selection				
Tumor	0.033 ± 0.005	60	[0.022, 0.043]	0.0001
Vascular	0.001 ± 0.0008	55	[0.000, 0.003]	1
Incision				
Transciliary incision	0.042 ± 0.008	40	[0.027, 0.058]	0.436
Superciliary incision	0.032 ± 0.009	22	[0.014, 0.050]	1
Exposure				
Craniotomy <2.5 cm	0.043 ± 0.010	23	[0.023, 0.063]	0.656
Craniotomy >2.5 cm	0.037 ± 0.009	29	[0.019, 0.054]	1
Orbital osteotomy	0.072 ± 0.028	10	[0.018, 0.126]	0.001
No orbital osteotomy	0.021 ± 0.004	57	[0.014, 0.029]	1
Endoscope	0.030 ± 0.007	26	[0.016, 0.044]	0.115
No endoscope	0.018 ± 0.004	40	[0.010, 0.025]	1
Cautery	0.031±0.010	14	[0.011, 0.050]	0.307
No cautery	0.046 ± 0.007	53	[0.032, 0.060]	1
Cranial reconstruction				
Titanium plates and screws only	0.052 ± 0.009	30	[0.033, 0.070]	0.957
Cement / bone filler	0.053 ± 0.017	10	[0.021, 0.086]	1
Wound closure				
Absorable suture	0.034 ± 0.013	14	[0.010, 0.059]	0.206
Non-absorbable suture	0.068 ± 0.026	7	[0.018, 0.118]	1
Perioperative care				
Antibiotics	0.068 ± 0.032	6	[0.005, 0.130]	0.181
No antibiotics	0.039 ± 0.006	61	[0.027, 0.050]	1
Pressure dressing	0.039 ± 0.020	3	[-0.001, 0.079]	0.320
No pressure dressing	0.020 ± 0.004	64	[0.013, 0.027]	1
Drain	0.183 ± 0.095	5	[-0.004, 0.370]	0.0001
No drain	0.022 ± 0.004	63	[0.015, 0.029]	1

Abbreviations: CI, confidence interval; SEM, standard error of mean.

Note: *p*-Value(s) of <0.05 (in bold) were considered statistically significant; Values are reported as proportions/mean values ± standard error of mean where appropriate.

(p = 0.001) (**~ Fig. 3G,H**). Use of an endoscope and cautery did not significantly affect patient cosmetic outcomes (p = 0.115 and p = 0.307, respectively) (**~ Fig. 3I–L**).

With respect to closure, permanent cosmetic complications were reported in $5.2 \pm 0.9\%$ of the patients who received standard titanium plating with screws and $5.3 \pm 1.7\%$ of those who had additional cement or a bone filler to fill the gaps (p = 0.957) (**~Fig. 3M,N**). The type of suture used for skin closure also did not statistically affect cosmetic outcomes, with permanent cosmetic outcomes reported in $3.4 \pm 1.3\%$ of the absorbable suture group and $6.8 \pm 2.6\%$ in the nonabsorbable skin suture group (p = 0.206) (**~Fig. 30, P**). Perioperative antibiotics also did not correlate with cosmetic complications (p = 0.181) (**~Fig. 3Q,R**). Use of a postoperative pressure dressing also did not affect patient cosmetic outcomes (p = 0.320) (**\succ Fig. 3S,T**). However, the use of a subgaleal drain was found to be associated with worse cosmetic outcomes than in those without drain placement (18.3 ± 9.5% vs. 2.2 ± 0.4%; p = 0.0001) (**\succ Fig. 3U,V**).

Discussion

In this systematic review and meta-analysis, we report on cosmetic outcomes in patients undergoing the supraorbital eyebrow keyhole approach and how they are influenced by variations in surgical technique. To our knowledge, this is the first meta-analysis study focusing on cosmesis following a supraorbital keyhole craniotomy. We found that this approach is associated with overall high patient satisfaction and a low percentage of patients experience permanent

Studies	Estimate (95% C.I.)	Ev/Trt	
Adawi et al 2015	0.056 (0.000, 0.205)	0/8	
Alekseev et al 2017	0.387 (0.216, 0.559)		
Ansari et al 2020	0.068 (0.023, 0.114)	8/117	
Banu et al 2016			
	0.062 (0.000, 0.230)	0/7	
Bassiouni et al 2007	0.125 (0.000, 0.449)	0/3	
Benifla et al 2016	0.167 (0.000, 0.588)	0/2	
Burks et al 2016	0.045 (0.000, 0.169)	0/10	
Cai et al 1 2019	0.033 (0.000, 0.098)	1/30	
Cai et al 2 2018	0.018 (0.000, 0.067)	0/27	
Chen and Tzaan 2010	0.083 (0.000, 0.304)	0/5	
Czirjak and Szeifert 1 2001	0.009 (0.000, 0.035)	0/53	l ■ t
Czirjak and Szeifert 2 2006	0.039 (0.000, 0.083)	3/76	- -
de Oliveira et al 2017	0.056 (0.000, 0.205)	0/8	
Delitala et al 2011	0.062 (0.000, 0.230)	0/7	
Ditzel Filho et al 2014	0.045 (0.000, 0.169)	0/10	
Dlouhy et al 2015	0.038 (0.000, 0.089)	2/53	_ _
Elkheshin and Soliman 2017	0.019 (0.000, 0.072)	0/25	
Eroglu et al 2019	0.061 (0.003, 0.118)	4/66	
Fatemi et al 2009	0.100 (0.000, 0.363)	0/4	
Feroze et al 2018	0.056 (0.000, 0.205)	0/8	
Gandhoke et al 2017	0.083 (0.000, 0.304)	0/5	
Gazzeri et al 2014	0.062 (0.014, 0.110)	6/97	
Hassler and Schick 2009	0.028 (0.000, 0.104)	0/17	
He et al 2 2018	0.188 (0.000, 0.379)	3/16	
He et al 3 2019	0.036 (0.000, 0.133)	0/13	
lacoangeli et al 2 2016	0.043 (0.000, 0.127)	1/23	
lacoangeli et al 3 2017	0.062 (0.000, 0.230)	0/7	
Igressa et al 2015	0.012 (0.000, 0.046)	0/40	
Jallo et al 2005	0.019 (0.000, 0.069)	0/26	-
Jho 1997	0.042 (0.000, 0.155)	0/11	
Jian et al 2014	0.036 (0.000, 0.133)	0/13	-
Joseph and Chacko 2005	0.026 (0.000, 0.098)	0/18	
Kabil and Shahinian 2005	0.042 (0.000, 0.122)	1/24	
Khanapure et al 2019	0.062 (0.000, 0.230)	0/7	
Krishna et al 2011	0.333 (0.000, 0.867)	1/3	•
Lin et al 2018	0.016 (0.000, 0.047)	1/62	-
Linsler et al 2017	0.062 (0.000, 0.181)	1/16	
Marx et al 2017	0.056 (0.000, 0.205)	0/8	
McLaughlin et al 1 2011	0.042 (0.000, 0.155)	0/11	
McLaughlin et al 2 2012	0.125 (0.000, 0.449)	0/3	
Melamed et al 2005	0.028 (0.000, 0.104)	0/17	
Menovsky et al 1999	0.833 (0.412, 1.000)	2/2	
Ottenhausen et al 2018	0.042 (0.000, 0.155)	0/11	
de Paiva-Neto and de Tella 2010	0.020 (0.000, 0.075)	0/24	-
Peng et al 2016	0.036 (0.000, 0.133)	0/13	
Pitskhelauri et al 2017	0.062 (0.000, 0.230)	0/7	
Prat et al 2017	0.023 (0.000, 0.085)	0/21	
Prat-Acin et al 2013	0.167 (0.000, 0.465)	1/6	
Raza et al 2010	0.023 (0.000, 0.085)	0/21	
Reisch and Perneczky 2005	0.002 (0.000, 0.009)	0/206	
Reisch et al 2009	0.031 (0.000, 0.117)	0/15	
Russo et al 2015	0.071 (0.000, 0.262)	0/6	
Schick et al 2003	0.167 (0.000, 0.588)	0/2	
Schroeder et al 2011	0.042 (0.000, 0.155)	0/11	
Tawk et al 2014	0.071 (0.000, 0.262)	0/6	
Telera et al 2012	0.024 (0.000, 0.089)	0/20	
Warren and Grant 2009	0.018 (0.000, 0.067)	0/20	
Wiedemayer et al 2004	0.018 (0.000, 0.007) 0.111 (0.000, 0.316)	1/9	
	0.054 (0.008, 0.101)		
•		5/92	
Zheng et al 2007	0.029 (0.000, 0.084)	1/35	
Overall (140-05-00.9/ D. 0.040)	0.022 /0.022 0.012	E4/1E01	
Overall (I^2=25.38 % , P=0.042)	0.033 (0.022, 0.043)	54/1521	Y
-			
Α			0 0.2 0.4 0.6 0.8
			Proportion

Fig. 3 Forest plots of techniques used with respect to (A) tumor pathology, (B) vascular pathology, (C) transciliary incision, (D) superciliary incision, (E) craniotomy <2.5 cm in greatest width, (F) craniotomy >2.5 cm, (G) orbital osteotomy, (H) no orbital osteotomy, (I) endoscopic-assisted, (J) non-endoscopic assisted, (K) use of cautery, (L) no cautery, (M) titanium bone plating with screws only, (N) addition of cement/bone filler for gaps, (O) absorbable skin suture, (P) nonabsorbable skin suture, (Q) use of antibiotics, (R) no antibiotics, (S) postoperative pressure, (T) no postoperative pressure dressing, (U) use of subgaleal drain, (V) no subgaleal drain.

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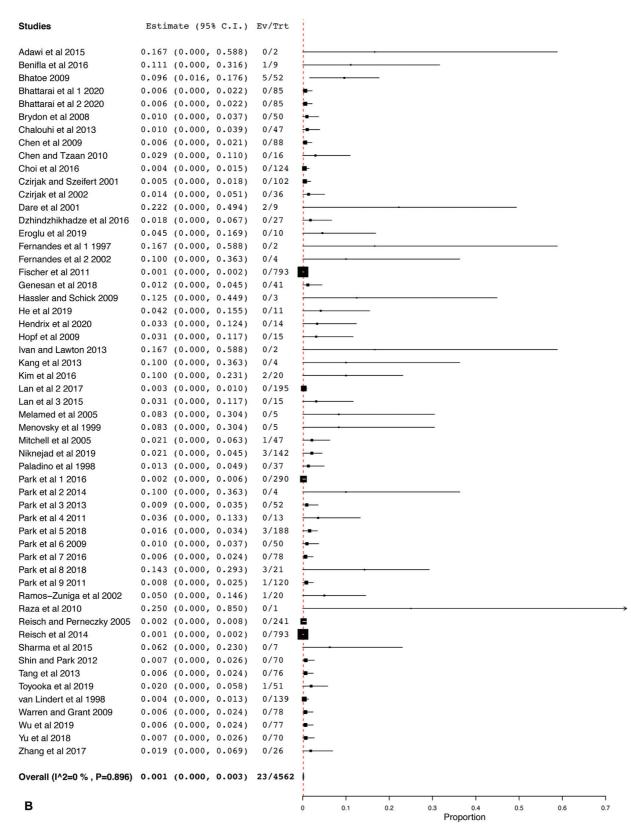


Fig. 3 (Continued)

01					Ĩ.			
Studies	Estimat	te (95%	C.I.)	Ev/Trt				
Adawi et al 2015	0.045 (0	0.000, 0	0.169)	0/10				
Alekseev et al 2017	0.419 (0			13/31	-	•		-
Ansari et al 2020	0.060 (0			7/117				
Bhatoe 2009	0.058 (0		,	3/52				
Cai et al 1 2019	0.033 (0			1/30				
Cai et al 2 2018	0.018 (0			0/27				
Chen et al 2009	0.006 (0			0/88				
Chen and Tzaan 2010	0.023 (0			0/21	-			
Dzhindzhikhadze et al 2016	0.018 (0			0/27				
Eroglu et al 2019 Fatemi et al 2009	0.009 (0			1/106 0/13				
Fernandes et al 1 1997	0.167 (0			1/6				
Fernandes et al 2 2002	0.062 (0			1/16				
Hassler and Schick 2009	0.550 (0			11/20	-	-		
He et al 2 2018	0.125 (0			2/16				
He et al 3 2019	0.385 (0			5/13				
lacoangeli et al 2016	0.043 (0			1/23				
Kabil and Shahinian 1 2005	0.020 (0			0/24				
Kabil and Shahinian 2 2006	0.167 (0	0.000, 0	0.588)	0/2				-0
Khanapure et al 2019	0.062 (0	0.000, 0	0.230)	0/7				
Kim et al 2016	0.024 (0	0.000, 0	0.089)	0/20				
Ko et al 2001	0.062 (0	0.000, 0	0.230)	0/7				
Krishna et al 2011	0.125 (0	0.000, 0	0.449)	0/3				
Linsler et al 2017	0.125 (0			2/16				
Menovsky et al 1999	0.143 (0			1/7				
Paladino et al 1998	0.013 (0			0/37	.			
Park et al 2018	0.016 (0			3/188	a			
Pitskhelauri et al 2017	0.062 (0			0/7				
Ramos-Zuniga et al 2002	0.050 (0			1/20				
Raza et al 2010	0.125 (0			3/24		-		
Reisch et al 1 2014	0.051 (0		,	21/408				
Reisch et al 2 2009	0.031 (0			0/15				
Reisch and Perneczky 2005	0.131 (0			59/450 0/41				
Sanchez–Vasquez et al 1999 Schroeder et al 2011	0.012 (0			0/41				
Shin and Park 2012	0.042 (0			1/70				
Telera et al 2012	0.014 (0			0/20				
Toyooka et al 2019	0.010 (0			0/51				
Warren and Grant 2009	0.019 (0			2/105				
Transfer and Grant 2000			,					
Wiedemaver et al 2004	0.222 (0	.000. 0	0.494)	2/9				
Wiedemayer et al 2004	0.222 (0	0.000, 0	0.494)	2/9			_	
Wiedemayer et al 2004 Overall (I^2=69.34 % , P< 0.001)					→			
						I I 0.3 0.4	0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001)					r	0.3 0.4 Proportion	0.5	T T 0.6 0.7
Overall (I^2=69.34 % , P< 0.001)					r		I 0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001)					r		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C	0.042 (0).027, (0.058)	141/2158	r		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001)	0.042 (0).027, (0.058)		r		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies	0.042 (0 Estimat).027, (0.058) C.I.)	141/2158 Ev/Trt	r		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016	0.042 (0 Estimat).027, (te (95% 0.000,	0.058) C.I.) 0.206)	141/2158 Ev/Trt 1/14	0 0.1 0.2		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016	0.042 (0 Estimat 0.071 (0 0.004 (0).027, (te (95% 0.000, 0.000,	C.I.) 0.206) 0.015)	141/2158 Ev/Trt 1/14 0/124	0 0.1 0.2		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Choi et al 2016 Czirjak and Szeifert 2001	0.042 (0 Estimat 0.071 (0 0.004 (0 0.019 (0).027, (te (95% 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041)	Ev/Trt 1/14 0/124 3/155	0 0.1 0.2		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001	0.042 (0 Estimat 0.071 (0 0.004 (0 0.019 (0 0.050 (0	<pre>).027, (te (95% 0.000, 0.000, 0.000, 0.000,</pre>	C.I.) 0.206) 0.015) 0.041) 0.185)	141/2158 Ev/Trt 1/14 0/124 3/155 0/9	0 0.1 0.2		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017	0.042 (0 Estimat 0.071 ((0.004 ((0.019 ((0.050 ((0.250 ()	<pre>D.027, 0 te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,</pre>	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550)	141/2158 Ev/Trt 1/14 0/124 3/155 0/9 2/8	0 0.1 0.2		0.5	0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017 Diouhy et al 2015	0.042 (0 Estimat 0.071 ((0.019 ((0.250 ((0.190 ((<pre>b.027, (te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,</pre>	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309)	141/2158 Ev/Trt 1/14 0/124 0/9 2/8 8/42	0 0.1 0.2		0.5	1 1 0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017 Dlouhy et al 2015 El Shafei 2011	0.042 (0 Estimat 0.071 ((0.004 ((0.050 ((0.250 ((0.250 ((0.190 ((0.611 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.002, 0.386,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.836)	Ev/Trt 1/14 0/124 0/9 2/8 8/42 11/18	0 0.1 0.2		0.5	0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2011 de Oliveira et al 2017 Diouhy et al 2015 El Shafei 2011 Gazzeri et al 2014	0.042 (0 Estimat 0.071 ((0.004 ((0.050 ((0.250 ((0.190 ((0.611 ((0.062 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.002, 0.386, 0.014,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.836) 0.110)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97	0 0.1 0.2		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013	0.042 (0 Estimat 0.071 ((0.004 ((0.019 ((0.190 ((0.190 ((0.161 ((0.167 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.386, 0.014,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.836) 0.110) 0.588)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2	0 0.1 0.2		0.5	0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Diouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005	0.042 (0 Estimat 0.071 (C 0.004 (C 0.019 (C 0.050 (C 0.190 (C 0.191 (C 0.062 (C 0.0167 (C 0.018 (C	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.386, 0.014, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.3550) 0.309) 0.836) 0.100) 0.588) 0.067)	141/2158 Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27	0 0.1 0.2		0.5	0.6 0.7
Overall (I^2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013	0.042 (0 Estimat 0.071 ((0.004 ((0.019 ((0.190 ((0.190 ((0.161 ((0.167 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.014, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.836) 0.110) 0.588) 0.588) 0.555)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2	0 0.1 0.2		0.5	0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997	0.042 (0 Estimat 0.071 (0 0.004 (0 0.019 (1 0.050 (0 0.190 (1 0.062 (0 0.018 (1 0.018 (1 0.018 (1	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.836) 0.110) 0.588) 0.067) 0.155) 0.098)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11	0 0.1 0.2		0.5	0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2001 de Oliveira et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005	0.042 (0 Estimat 0.071 (0 0.004 (0 0.050 (0 0.050 (0 0.050 (0 0.050 (0 0.019 (0 0.0611 (0 0.0612 (0 0.018 (0 0.018 (0 0.018 (0	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.309) 0.836) 0.110) 0.838) 0.110) 0.588) 0.067) 0.155) 0.098) 0.363)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4	0 0.1 0.2			0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2010 de Oliveira et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013	0.042 (0 Estimat 0.071 ((0.004 ((0.019 ((0.050 ((0.190 ((0.061 ((0.061 ((0.0167	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.309) 0.309) 0.110) 0.588) 0.110) 0.588) 0.067) 0.155) 0.098) 0.363) 0.309)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4				0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Diouhy et al 2017 Diouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005	0.042 (0 Estimat 0.071 ((0.004 ((0.019 ((0.050 ((0.190 ((0.018 ((0.026 ((0.018 ((0.026 ((0.018 ((0.026 ((0.100 ((0.010 ((0.010 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.309) 0.836) 0.110) 0.588) 0.110) 0.588) 0.1155) 0.097) 0.363) 0.363) 0.399) 0.449)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4 0/47 0/3				0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005 Noggle et al 2008	0.042 (0 Estimat 0.071 ((0.004 ((0.019 ((0.050 ((0.050 ((0.062 ((0.0167 ((0.0168 ((0.042 ((0.026 ((0.0167 ((0.0125 ((0.0125 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.014, 0.000, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.309) 0.309) 0.310) 0.110) 0.588) 0.067) 0.155) 0.098) 0.363) 0.363) 0.363) 0.335)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4 0/47 0/3				0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Diouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005 Noggle et al 2008 Park et al 3 2013	0.042 (0 Estimat 0.071 (C 0.004 (C 0.019 (C 0.050 (C 0.050 (C 0.050 (C 0.019 (C 0.018 (C 0.018 (C 0.042 (C 0.010 (C 0.010 (C 0.010 (C 0.010 (C 0.0125 (C 0.009 (C	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.1100) 0.588) 0.067) 0.155) 0.098) 0.363) 0.309) 0.349) 0.349) 0.349) 0.349) 0.35)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4 0/47 0/3 0/52 1/13				0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Diouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005 Noggle et al 2008 Park et al 3 2013 Park et al 4 2011	0.042 (0 Estimat 0.071 (0 0.004 (0 0.019 (0 0.019 (0 0.019 (0 0.012 (0 0.016 (0 0.016 (0 0.016 (0 0.016 (0 0.0125 (0 0.010 (0 0.012 (0 0.0	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.155) 0.309) 0.836) 0.110) 0.388) 0.367) 0.155) 0.098) 0.363) 0.098) 0.363) 0.098) 0.363) 0.035) 0.035) 0.222) 0.037)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4 0/47 0/3 0/52 1/13				0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Dlouhy et al 2017 Dlouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005 Nogle et al 2008 Park et al 3 2013 Park et al 4 2011 Park et al 6 2009	0.042 (0 Estimat 0.071 ((0.004 (0 0.019 ((0.050 ((0.190 ((0.016 ((0.042 ((0.016 ((0.012 ((0.010 ((0.010 ((0.010 ((0.010 ((0.010 ((0.010 ((0.010 ((0.010 ((te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.550) 0.309) 0.836) 0.110) 0.588) 0.055) 0.055) 0.055) 0.055) 0.055) 0.039) 0.363) 0.039) 0.363) 0.039) 0.363) 0.039) 0.363) 0.039) 0.358)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4 0/4 0/4 0/4 0/4 0/3 0/52 1/13 0/50				0.6 0.7
Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Czirjak and Szeifert 2001 Dare et al 2017 Diouhy et al 2017 El Shafei 2011 Gazzeri et al 2017 Diouhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005 Noggle et al 2008 Park et al 3 2013 Park et al 6 2009 Park et al 8 2018	0.042 (0) Estimat 0.071 ((0.004 ((0.019 ((0.050 ((0.190 ((0.019 ((0.016 ((0.026 ((0.0125 ((0.010 ((0.0125 ((0.0125 ((0.0126 ((0.0127 ((0.0127)	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,000,	C.I.) 0.206) 0.015) 0.041) 0.185) 0.309) 0.363) 0.110) 0.588) 0.363) 0.363) 0.363) 0.363) 0.363) 0.363) 0.363) 0.355) 0.355) 0.355) 0.358) 0.358)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/27 0/17 0/18 0/4 0/47 0/3 0/50 4/21				0.6 0.7
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Overall (I*2=69.34 % , P< 0.001) C Studies Benifla et al 2016 Choi et al 2016 Cirijak and Szeifert 2001 Dare et al 2017 Douhy et al 2017 Douhy et al 2015 El Shafei 2011 Gazzeri et al 2014 Ivan and Lawton 2013 Jallo et al 2005 Jho 1997 Joseph and Chacko 2005 Kang et al 2013 Mitchell et al 2005 Nogle et al 2008 Park et al 3 2013 Park et al 4 2011 Park et al 6 2009 Park et al 8 2018 Park et al 9 2011 Zhang et al 2004 Zheng et al 2007	0.042 (0) Estimat 0.071 ((0.004 (0) 0.050 (0) 0.190 (0) 0.190 (0) 0.0611 (0) 0.0621 (0) 0.042 (0) 0.042 (0) 0.042 (0) 0.016 (0) 0.025 (0) 0.010 (0) 0.019 (0) 0.019 (0) 0.019 (0) 0.009 (0) 0.009 (0) 0.009 (0)	te (95% 0.000, 0.000, 0.000, 0.000, 0.000, 0.072, 0.386, 0.014, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,000,	C.I.) 0.206) 0.015) 0.041) 0.155) 0.550) 0.309) 0.836) 0.110) 0.588) 0.067) 0.155) 0.098) 0.363) 0.035) 0.035) 0.222) 0.037) 0.222) 0.037) 0.2358) 0.222) 0.037) 0.358) 0.222)	Ev/Trt 1/14 0/124 3/155 0/9 2/8 8/42 11/18 6/97 0/2 0/27 0/11 0/18 0/4 0/47 0/3 0/52 1/13 0/50 4/21 7/102 0/54 0/35				0.6 0.7
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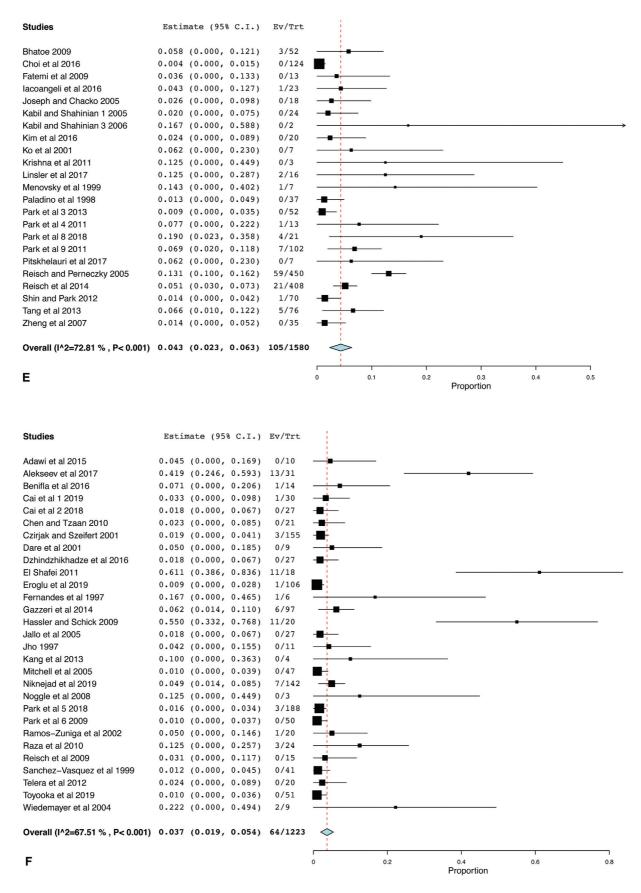
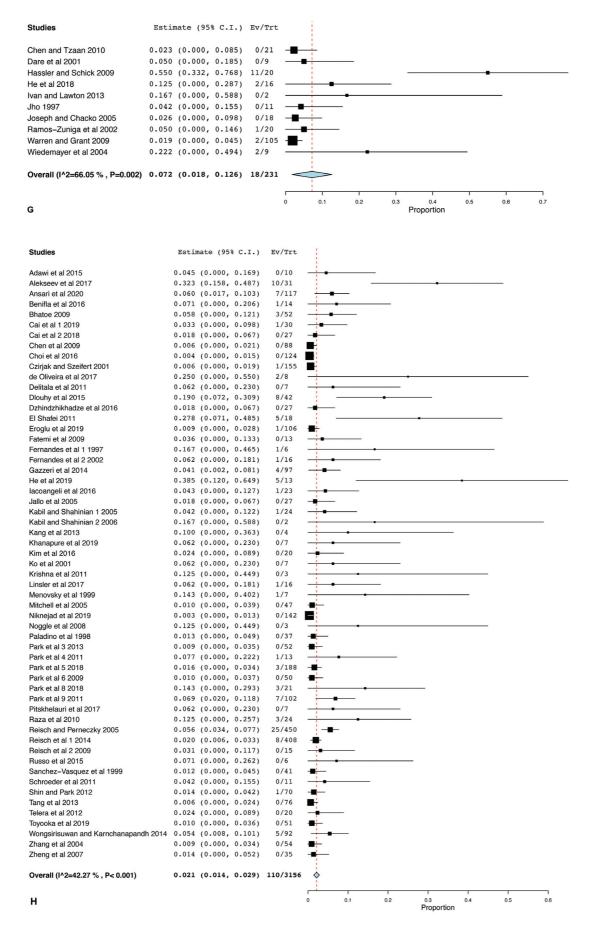
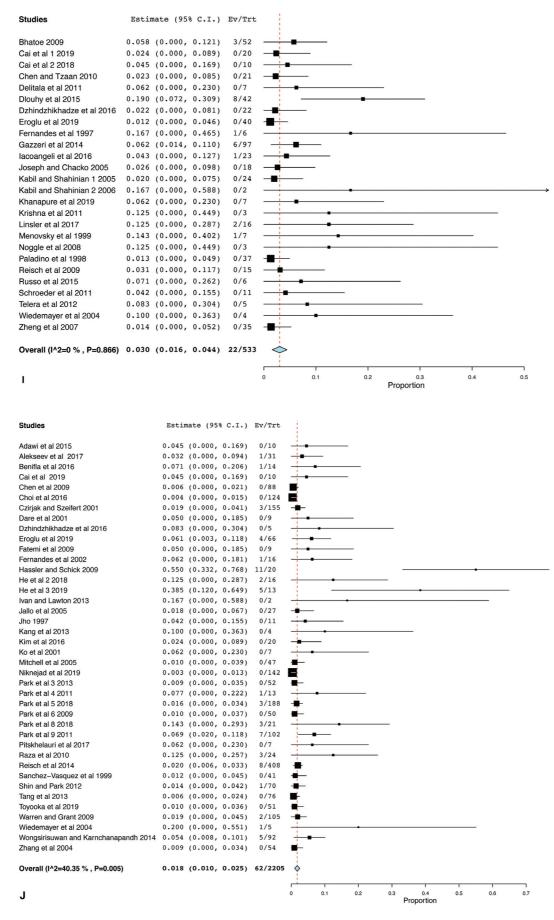
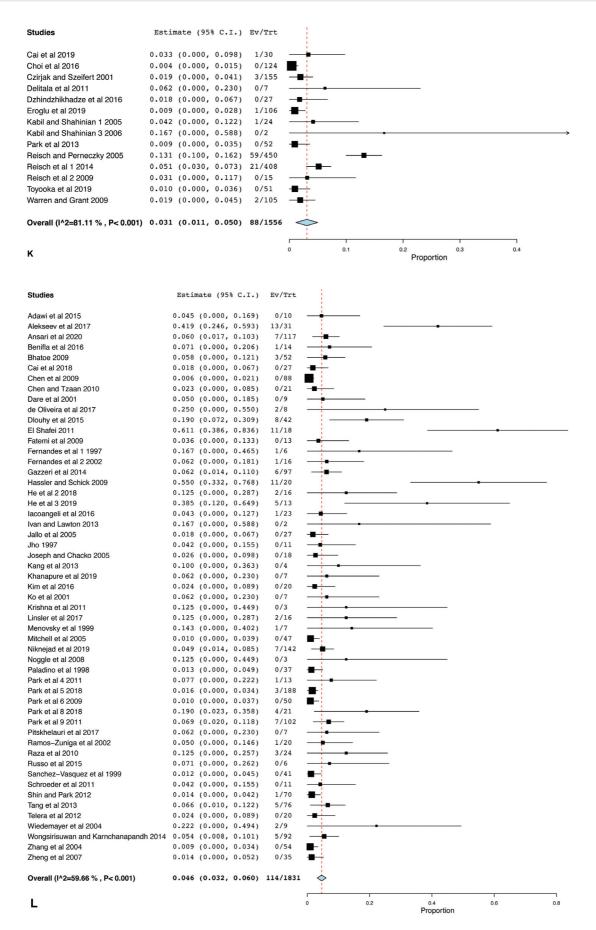


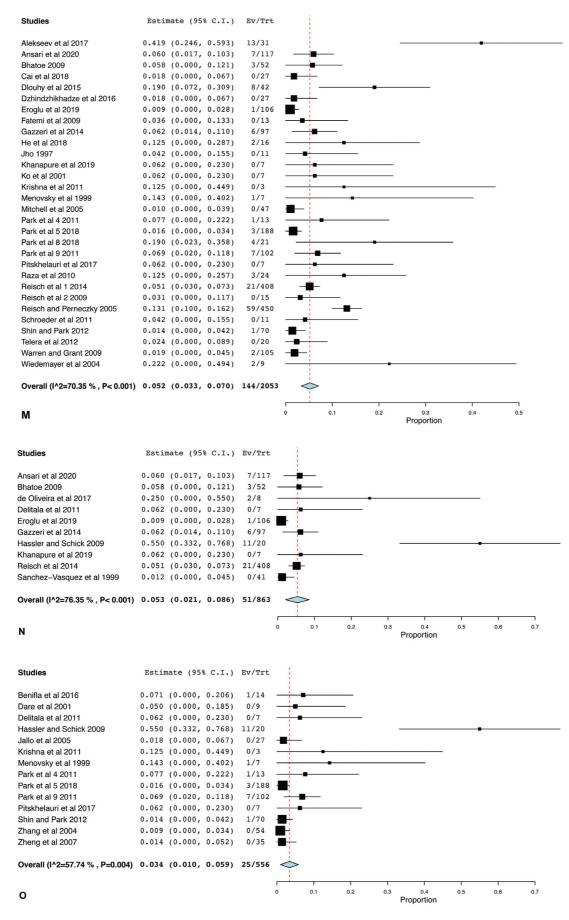
Fig. 3 (Continued)



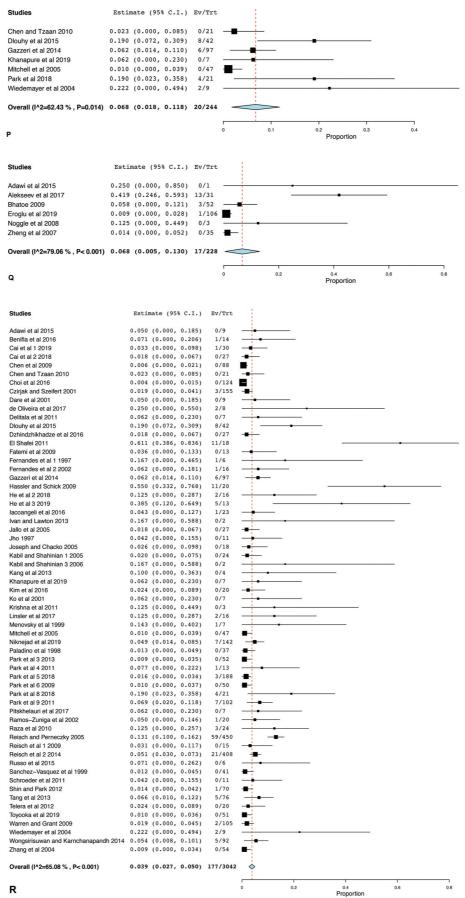




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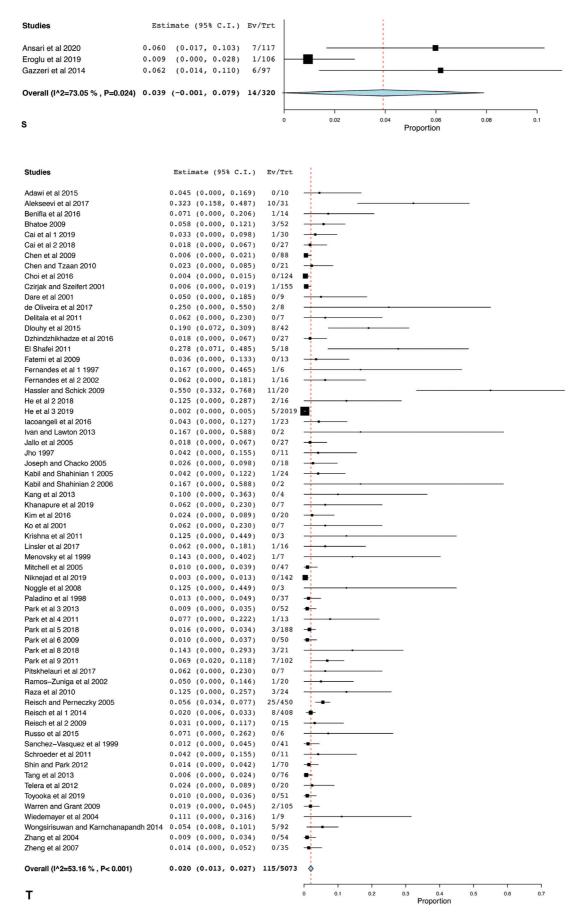
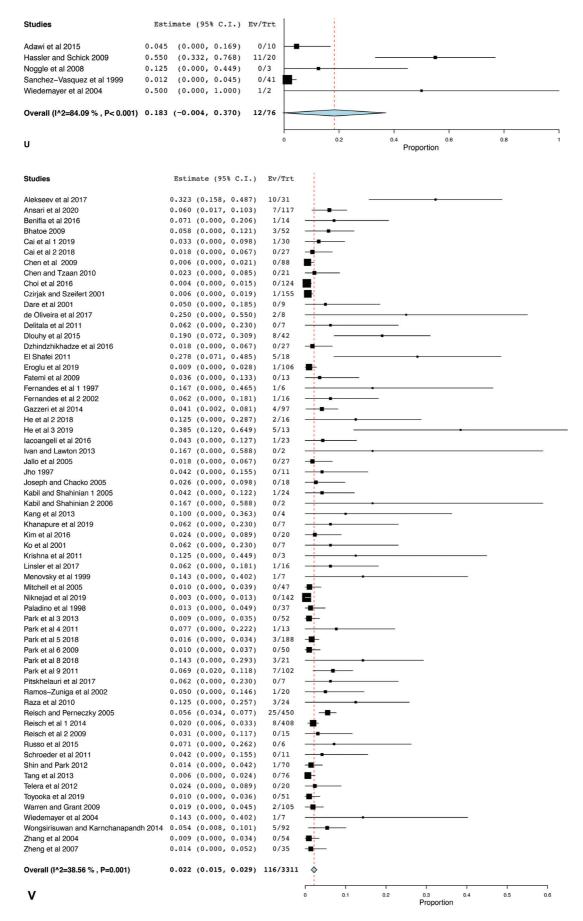


Fig. 3 (Continued)



cosmetic complications. The location of the incision, extent of exposure, utilization of an endoscope, type of cranial reconstruction, method of skin closure, and the addition of pressure dressing do not seem to affect cosmetic outcomes. However, the addition of an orbital osteotomy and use of a subgaleal drain were found to be associated with an increased risk of permanent cosmetic complications. Vascular cases or clipped aneurysms also tended to have better cosmetic outcomes than tumor cases.

Technique Variations

As mentioned, several variations to the supraorbital eyebrow keyhole have been described. First, the placement of the skin incision may be within the eyebrow (transciliary), along the superior border of the eyebrow (superciliary), within the eyelid crease, or through a skin crease in the forehead. Additionally, a lateral supraorbital variant has also been recently introduced and involves a more laterally placed skin incision. In this approach, the craniotomy is also extended more laterally up to the sphenoid ridge.¹³¹ An orbital osteotomy can be added to the supraorbital craniotomy to increase the angle of exposure, and is necessary if using an eyelid incision.¹³² In patients with prominent frontal sinuses, the craniotomy can purposefully enter the sinus and a soft tissue graft is often needed to obliterate the lateral sinus and maintain its patency/function.

Once intradural, the primary variation described is the use of an endoscope. The supraorbital eyebrow approach can be performed as a purely endoscopic^{13,32} or endoscopicassisted^{24,29,42} operation, and some authors report improved visualization which is particularly advantageous for deepseated lesions.¹³³

During closure and repair, a dural substitute may or may not be used in addition to primary dural closure. Type of craniotomy repair technique also varies, with some advocating for standard bone plating with titanium screws and plates, whereas others use bone plating with sutures, dissolvable plates, mesh and cement or bone filler for gaps. Some even forgo the use of the bone flap and repair the craniotomy defect entirely with bone substitute.⁴⁸ When titanium plates are used, it may be prudent to minimize hardware to reduce the likelihood of subcutaneous palpable irregularities that can cause patient discomfort. The kerf defect between the craniotomy flap and native skull may be filled with collagen sponge, bone dust, pre-made prosthetics (e.g., Medpor Gap Wedge), or numerous bone substitute.⁴ After repairing the craniotomy defect, the galea, muscles, and skin are typically closed in layers although some forgo muscular layer closure.^{17,68} Although most authors report skin closure using dissolvable suture, non-dissolvable suture and skin glue have also been reported.^{14,34} There is also variability in the use of postoperative pressure dressings.¹³⁴

Factors Affecting Patient Cosmesis

In this systematic review and meta-analysis, we found that the addition of an orbital rim osteotomy, use of a subgaleal drain, and tumor indication for surgery were each associated with worse cosmetic outcome. When applied to the supraorbital keyhole approach, orbital rim osteotomy increases of the periosteum encasing the periorbita and lateral orbital rim, bone drilling, and addition of more hardware for craniotomy repair. All this contributes to the complexity of achieving a symmetric repair of the surgical site. Orbital rim osteotomy is incorporated by some authors to increase the vertical working space afforded by the approach. In a cadaveric study by Rychen and colleagues, the authors found that addition of orbital rim osteotomy to a trans-eyebrow approach increased the vertical extent of the craniotomy from 1.5 to 2.5 cm.¹³² Cavalcanti and colleagues performed supraorbital keyhole craniotomy on cadaveric heads and found that addition of orbital rim osteotomy significantly increased surgical freedom and working angles to common sites of anterior circulation aneurysms, with the greatest increases for anterior communicating artery and posterior communicating artery targets.¹³⁵ Rychen and colleagues reported that the transpalpebral approach requires removal of the orbital rim, because without orbital osteotomy the skin can be retracted superiorly to provide only 0.5 cm of vertical working space, but a trans-eyebrow approach without additional orbital rim osteotomy affords wider working angles toward the anterior clinoid process compared with the transpalpebral approach with orbital rim osteotomy.¹³² Despite the increased working angles afforded by this modification, orbital osteotomy is infrequently used and was reported in only 8.1% of cases. In our recent systematic review of supraorbital keyhole craniotomy via eyebrow incision, an 83.6% technical success rate, defined as gross total tumor resection or complete aneurysm obliteration via clipping, was achieved despite rare inclusion of orbital osteotomy.² The increased working angles achieved with orbital osteotomy must be balanced against the increased tissue manipulation and worsened cosmetic outcomes. Ultimately, inclusion of orbital osteotomy is left to the surgeon's discretion and may be maximally beneficial when using a supraorbital transpalpebral approach instead.

soft tissue dissection, necessitating the need for mobilization

Another factor found to influence cosmetic outcomes in this meta-analysis is the utilization of a subgaleal drain. Subgaleal drain placement is a widespread practice across many surgical fields, and closed-suction drains are frequently left after cranial neurosurgery despite limited data to support their benefit. Drains are often used after cranial procedures in hopes of evacuating blood and serous fluid, which can interfere with wound healing and serve as a nidus for infection.^{35,136} Despite this, Choi and colleagues conducted a retrospective review of 607 patients who had undergone pterional craniotomy and compared outcomes stratified by postoperative drain placement.³⁵ The non-drain group had a lower incidence of postoperative epidural hematomas and less postoperative increase in thickness of the myocutaneous flap compared with the drain group. The authors hypothesize that the negative suction from the drain increased exudate accumulation and soft tissue edema, impairing wound healing and increasing incidence of epidural fluid accumulation. Other proposed mechanisms for the difference in outcomes include decreased intraoperative hemostasis in the drain group compared with the non-drain group, and subclinical infection from the drain causing

inflammation and impaired wound healing.³⁵ In a prospective study of 150 patients undergoing craniotomy, Hamou and colleagues found no difference in periorbital edema, subgaleal swelling, impaired wound healing, non-adequate pain control, or need for re-operation between patients with and without subgaleal drains.¹³⁶ The authors did find that longer, curved incisions and larger craniotomies were associated with a significantly higher rate of subgaleal swelling. Although the underlying mechanism behind the inferior cosmetic outcomes in patients with postoperative drains in our systematic review are unclear, given the small size of the space created with this approach, the lack of data supporting benefit of postoperative drains in cranial neurosurgery, and the association with poor cosmetic outcome in this report, the potential risks of a subgaleal drain placement outweigh the benefits. Further research is needed to guide drain placement after craniotomies in general.

Lastly, inferior cosmetic outcomes were also associated with supraorbital eyebrow craniotomy for tumor resection compared with aneurysm clipping in our systematic review and meta-analysis. This may be due to the fact that tumors may be more infiltrative and larger in nature compared with aneurysms. Hence, tumor surgery may have required greater exposure and soft tissue manipulation than cases with clipped aneurysms. The authors found that orbital osteotomy was not a confounding variable as similar percentage of patients undergoing aneurysm clipping and tumor resection incorporated orbital osteotomy. However, we did find that tumor cases tended to be longer in operative time compared with aneurysm cases, although the trend was not statistically significant. Additionally, patients undergoing craniotomy for tumor resection may have had higher rates of confounding comorbidities or adjuvant chemoradiation related to their underlying diagnosis that might have affected postoperative wound healing. Beside length of operative time, there are too few cases to extract data such as chemoradiation to perform sufficient analysis.

Cosmetic Complaints after Supraorbital Craniotomy

The most commonly reported cosmetic complaints in the literature following supraorbital craniotomy are deformity related to the craniotomy site, frontalis palsy, and visible/ unattractive scar. Surgical site deformity is typically caused by depression at the site of the burr hole, depression along the kerf between the bone flap and native skull, or depression of the craniotomy flap itself. Based on the results of our systematic review, orbital osteotomy is associated with significantly worse cosmetic outcomes, possibly by causing surgical site deformity. The placement of the single burr hole below the superior temporal line, allowing for the site to be covered when the temporalis is re-approximated during closure, helps decrease burr hole-related deformity compared with other approaches; however, depression may still occur due to atrophy of the overlying temporalis muscle.³ As mentioned above, a variety of gap-filling techniques have been described and may warrant consideration. Consistent with the results of our review, no single study demonstrates the superiority of one bone flap fixation

technique or gap filling technique in avoiding the above complications or improving cosmetic outcomes.

It is important to note that frontalis palsy can result in a significant cosmetic deformity. The frontalis branch of the facial nerve supplies the frontalis muscle, and postoperative palsy results in facial asymmetry. Permanent nerve damage is rare, as the incision's curve along the orbital rim avoids the frontalis nerve as it courses superiorly and medially above the orbit. Transient palsy may result from stretching of the nerve during retraction and use of electrocautery nearby. In a large series by Park et al, 5.9% of patients had a frontalis palsy at 6-month follow-up, but the deficit resolved in all patients by 2 years.⁹⁸ Use of gentle retraction and minimization of monopolar electrocautery along the superolateral aspect of the surgical field are considerations to help prevent transient frontalis palsy.

The conspicuous location of the supraorbital incision places increased importance in cosmetic wound healing. Alopecia, scar hypertrophy, and overall scar visibility are potential incision-related complaints. To avoid alopecia, many emphasize aligning the scalpel with the hair follicles during initial incision and minimizing electrocautery to avoid damage to nearby hair follicles and blood vessels.¹³⁰ Alternate incision locations, including superciliary, transpalpebral, behind-the-hairline, and forehead crease have been endorsed to avoid eyebrow alopecia and decrease scar visibility.⁶⁵ Incisions behind the hairline have been promoted in patients with a history of scar hypertrophy or keloid formation.⁹⁸ Previously, absorbable sutures for skin closure were thought to cause inflammation from suture breakdown products leading to scar hypertrophy and damage to hair follicles, prompting many to discourage their use.^{10,73} In a study of 41 patients undergoing face skin cancer excision, Parell and Becker compared skin closure with absorbable Rapide suture to nonabsorbable Prolene suture by closing half of each incision with each suture.¹³⁷ No difference in scar formation between techniques was noted after 6 months of follow-up. Studies directly comparing differences in cosmetic outcome following supraorbital keyhole craniotomy by incision location, closure technique and other variations mentioned above are rare, and the above-described variations and recommendations are based on surgeon preference. Our systematic review found no significant difference in cosmetic results by suture type or incision location.

Recommendations

To minimize postoperative cosmetic complications, a transciliary incision allows for the hair to conceal the incisional scar. Avoidance of monopolar electrocautery may prevent thermal injury to nearby nerves, hair follicles, and blood vessels. Preservation of the peri-incisional microvasculature may also help decrease scar size and reduce the likelihood of alopecia. Avoidance of an orbital osteotomy may reduce the likelihood of an associated cosmetic deformity. With respect to closure, watertight dural closure and a collagen onlay may reduce the likelihood of CSF leak and pseudomeningocele. Closing the kerf at the superior and medial edges of the craniotomy defect may reduce the likelihood of a cosmetic defect that is most noticeable on the patient's forehead. Furthermore, filling kerfs with collagen and/or bone cement may help prevent palpable irregularities. A multilayer soft tissue closure may decrease the likelihood of a cosmetic deformity due to thinning of the incision site and discontinuity of the muscle layers. Avoidance of wound drains may be prudent, and a pressure dressing, if used, should be carefully monitored to prevent skin injury. There does not seem to be a role for postoperative antibiotics in routine cases. In general, the supraorbital eyebrow keyhole craniotomy is an approach with high postoperative patient satisfaction and positive cosmetic outcome, and should be considered as a viable alternative to the pterional approach for select patients.

Study Limitations

One limitation of this study is the inherent risk of systematic reviews to selection biases. Not all studies with unfavorable results are published in the literature, and hence a systematic review may favor more positive outcomes and conclusions. Another limitation is the lack of prospective data available in the current literature, as all studies included in this review were retrospective case series and cohort studies. This resulted in high heterogeneity (I^2) for several primary end points assessed in the meta-analysis. Since high heterogeneity was expected, the DerSimonian–Laird random effects model was used for our meta-analysis.

Another major limitation of this study is our inability to evaluate other variables that may have contributed to poorer cosmetic outcomes due to lack of sufficient data; these include use of forehead crease incision, mesh for cranial reconstruction, use of dural substitute, muscular closure technique, use of skin glue, administration of steroids, patient-specific risk factors, use of lumbar drain, perioperative steroids, use of ice packs and specific patient activity instructions, among others. More research would be needed to investigate possible relationships between these underreported variables and cosmetic outcomes.

Conclusion

This systematic review and meta-analysis analyzes the impact of technical variations of the supraorbital keyhole eyebrow approach on postoperative patient cosmetic outcomes. We found that the addition of an orbital osteotomy, use of a subgaleal drain, and surgical indication of tumor resection each are associated with worse cosmetic outcome. On the other hand, location of the incision, extent of exposure, use of endoscope, cautery, type of cranial reconstruction, skin closure method, and the addition of a pressure dressing did not affect cosmetic outcomes. The eyebrow supraorbital keyhole approach is a safe and effective approach for management of vascular etiologies and tumors. Careful planning of the incision, minimalization of soft tissue and muscle manipulation, avoidance of an orbital osteotomy, minimalization of blood loss, cranial reconstruction, and avoidance of subgaleal drains are recommended to achieve favorable cosmetic outcomes.

Conflict of Interest None declared.

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