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Supraorbital vs pterional keyhole for anterior circulation aneurysms: A systematic review and meta-analysis



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$A \ B \ S \ T \ R \ A \ C \ T$

Background: The supraorbital approach is a modification of the traditional pterional approach, and it offers the benefits of a shorter skin incision and a smaller craniotomy than the pterional approach. The purpose of this systemic review study was to compare the two surgical approaches for raptured and unruptured anterior cerebral circulation aneurysms.

Methods: We searched PubMed, EMBASE, Cochrane Library, SCOPUS, and MEDLINE, up to August 2021, for published studies on the supraorbital vs pterional keyhole approach for anterior cerebral circulation aneurysms, and reviewers performed a brief qualitative descriptive analysis of both approaches.

Results: Fourteen eligible studies were included in this systemic review. Results indicated that the supraorbital approach for anterior cerebral circulation aneurysms had fewer ischemic events compared to pterional approach. However, no significant difference between both groups in terms of complications such as intraoperative aneurysm rupture, brain hematoma, and postoperative infections for ruptured aneurysms.

Conclusion: The meta-analysis suggests that the supraorbital method for clipping anterior cerebral circulation aneurysms might be a viable alternative to the traditional pterional method as the supraorbital group had decreased ischemic events compared to the pterional group, however, the associated difficulties in utilizing this approach among ruptured aneurysms with cerebral oedema and midline shifts further needs to be understood.

1. Introduction

Since its introduction by Yasargil in the 1970s,¹ the pterional approach has been routinely used for lesions located in the anatomical areas such as sellar or suprasellar area, circle of Willis, and Sylvian fissure, for pathologies such as craniopharyngiomas, pituitary adenomas, meningiomas and, obviously anterior circulation aneurysms. This standard approach has become a familiar broadway passage for neurosurgeons to reach the area of interest quickly and safely. With the expansion of the concept of minimally invasive approaches in neurosurgery, the

keyhole approach has also been explored in vascular territories. It is based on the simple principle of "no exposure-no injury" to the normal brain parenchyma. Traditional standard pterional approach has been practiced for a long time to safely approach anterior cerebral circulation aneurysms (ACCAs), however recently supraorbital eyebrow incision² is being increasingly practiced due to its ability to provide smaller corridor thus reducing exposure of the brain to room air and any accidental trauma.³ Recently authors⁴ have reported no difficulty utilizing this approach, even among ruptured aneurysms. Based on these experiences among various neurosurgeons, in the present systematic review, we

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Abbreviations: ACCA, anterior cerebral circulation aneurysms; RCT, randomized clinical trial.

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attempt to understand the risk of poor neurological and clinical outcomes and complications related to supraorbital vs pterional keyhole approaches for ACCAs.

2. Methods

The scheme followed in accordance with the recommendations of the meta-analysis and the systematic reviews of MOOSE declaration for the presentation of the systematic reviews of observational studies, the meta-analyses, and the Cochrane manual of systematic reviews and meta-analyses.

2.1. Search

A search for RCT, not RCT, prospective and retrospective cohort studies will be carried out through PUBMED (until August 2021); SCO-PUS (until August 2021); Central Cochrane Registry of Controlled Trials (The Cochrane Library) (until March 2021); MEDLINE (Ovid) until August 2021; EMBASE (Ovid); PubMed [http://www.ncbi.nlm.nih. gov/sites/entrez] (until August 2021); in addition to the reference list of included studies and other relevant data in addition to potentially eligible studies.

2.2. Across the following search strategy

Anterior [All Fields] AND ("blood circulation"[MeSH Terms] OR circulation[Text Word]) AND ("cerebrum"[MeSH Terms] OR "brain"[-MeSH Terms] OR cerebral[Mesh Term]) AND "intracranial aneurysm"[MeSH Terms] OR "cerebral aneurysm" OR "Brain Aneurysm") AND ("Randomized clinical trials" OR "observational cohort study" OR "retrospective observational study") AND "Human" NOT "Animals".

2.3. Inclusion criteria

The studies to be included were screened separately using the following inclusion criteria:

- Patients with ACCAs treated with clipping across pterional keyhole and supraorbital approach
- All relevant RCT, not RCT, prospective and retrospective cohort studies.

Studies which did not fulfil the objectives, case reports, review articles were excluded. Study details including author, year of the study, type of study, sample size, patient population, demographic details, details of surgical approaches and outcome were collected. In addition, the following data is extracted: Poor outcome defined as Glasgow outcome scale (GOS) with a 3 point or less, Rankin modified Scale (mRS) with a 4 point or more. Complication: Intraoperative ruptured, Hematoma postoperative, ischemic complication and infection. All this analysis with sub-group in: Ruptured aneurysm and Unruptured Aneurysm. The authors of the included studies were contacted due to missing data. The doubts were clarified by consensus.

The quality of include studies was through Newcastle–Ottawa Quality Assessment Scale, studies

with scores of 7, were considered of high methodological quality. Those with scores in a range of 4–5 were considered of Moderate Quality. The risk of bias assessment was performed using the ROBINS-I tool, which evaluates the following 7 domains: D1: "Bias due to confounding"; D2: "Bias in selection of participants"; D3: "Bias in classification of interventions"; D4: "Bias due to deviations from intended intervention"; D5: "Bias due to missing data"; D6: "Bias in measurement of outcomes"; D7: "Bias in selection of the reported results, based on the presence or absence of some characteristic in "Low Risk", "moderate risk", "serious Risk", "critical Risk" and "no information".

2.4. Statistical analysis

Statistical analysis was performed through Odds ratio (OR) with the Mantel-Haenszel methodology and subgroup analysis for each variable Review Manager software version 5.3 (London, UK). with a fixed effect analysis model calculated using. Heterogeneity was assessed by calculating Chi square (I^2), 0%–50% was a low heterogeneity, 50–60% was a moderate heterogeneity, 60%–75% was a high heterogeneity and if is higher than 75% was a very high heterogeneity.

3. Results

We identified 2654 bibliographic citations based on the title or abstract, or both, and the full texts. After reviewing the complete text and screening of 1498, 17 studies were considered eligible, 3 were excluded^{5–7} because these did not meet the inclusion criteria and were assessing one approach, and only 14 studies^{4,8–20} included in the review (Fig. 1). All the studies included were retrospective cohort observational studies and the summary characteristics of included studies are summarized in Table 1. Details of excluded studies have been shown in Table 2. Overall, 1907 patients with brain aneurysms were treated with microsurgery, of which 1324 were ruptured aneurysms and 583 were unruptured. A total of 923 patients (643 ruptured and 280 unruptured ACCAs) were approached by the supraorbital route, and 981 patients



Fig. 1. PRISMA flow diagram for the meta-analysis. Study selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Table 1

Study	Country	Type of Study	Ν	Type of Aneurysm	Outcome assessed	Length Follow up
Alekseev et al, ⁸ 2019	Russia	Retrospective Cohort study	166 Supraorbital approach: 49 Pterional approach: 117	Unruptured	Poor outcome (mRS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	23.4 ± 12.3 months
Cha et al, ⁹ 2012	Korea	Retrospective Cohort study	132 Supraorbital approach: 61 Pterional approach: 71	Unruptured	Poor outcome (GOS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	In Hospital
Chaloui et al, ¹⁰ 2013	USA	Retrospective Cohort study	97 Supraorbital approach: 47 Pterional approach: 40	Ruptured	Poor outcome (GOS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	12 months
'onseca et al, ¹¹ 2021	Brazil	Retrospective Cohort study	100 Supraorbital approach: 40 Ruptured: 32 Unruptured:8 Pterional approach: 60 Ruptured:44 Unruptured: 16	Mixture Ruptured: 76 Unruptured:24	Poor outcome (GOS) Intraoperative Ruptured Infection	36 Months
Genesan et al, ¹² 2018	Malaysia	Retrospective Cohort study	121 Supraorbital approach: 40 Pterional approach: 81	Ruptured	Poor outcome (mRS) Postoperative hematoma Infection	6 months
.an et al, ¹⁴ 2006	China	Retrospective Cohort study	321 Supraorbital approach: 195 Ruptured: 175 Unruptured: 20 Pterional approach: 126 Ruptured: 108 Unruptured: 18	Mixture Ruptured: 283 Unruptured:38	Poor outcome (GOS) Postoperative hematoma Ischemic events	6 months
an et al, ¹⁵ 2017	China	Retrospective Cohort study	318 Supraorbital approach: 195 Pterional approach: 123	Ruptured	Poor outcome (GOS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	12 Months
arocca et al, ¹³ 2018.	Italy	Retrospective Cohort study	50 Supraorbital approach: 25 Pterional approach: 25	Unruptured	Poor outcome (mRS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	32.2 ± 4.33 month
ark et al, ¹⁶ 2009	Korea	Retrospective Cohort study	41 Supraorbital approach: 20 Ruptured: 10 Unruptured: 10 Pterional approach: 21 Ruptured: 10 Unruptured: 11	Mixture Ruptured: 20 Unruptured:21	Poor outcome (mRS) Postoperative hematoma Infection	12 Months
Park et al, ¹⁷ 2018	Korea	Retrospective Cohort study	42 Supraorbital approach: 21 Ruptured:5 Unruptured: 16 Pterional approach: 21 Ruptured: 18 Unruptured:3	Mixture Ruptured: 23 Unruptured:19	Poor outcome (mRS) Postoperative hematoma Ischemic events Infection	12 Months
Shin et al, ¹⁸ 2012	Korea	Retrospective Cohort study	94 Supraorbital approach: 71 Pterional approach: 23	Unruptured	Poor outcome (GOS) Intraoperative rupture Postoperative hematoma Ischemic events Infection	12 months
Tra et al, ⁴ 2018	Vietnam	Retrospective Cohort study	25 Supraorbital approach: 12 Pterional approach: 13	Ruptured	Poor outcome (GOS) Intraoperative rupture Postoperative hematoma Infection	18 months
Vu et al, ¹⁹ 2019	China	Retrospective Cohort study	260 Supraorbital approach: 77 Ruptured:64 Unruptured: 13 Pterional approach: 183 Ruptured: 157 Unruptured: 26	Mixture Ruptured: 221 Unruptured: 39	Poor outcome (mRS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	3 months

(continued on next page)

Table 1 (continued)

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Study	Country	Type of Study	Ν	Type of Aneurysm	Outcome assessed	Length Follow up
Yu et al, ²⁰ 2020	Germany	Retrospective Cohort study	140 Supraorbital approach: 70 Pterional approach: 70	Ruptured	Poor outcome (GOS) Intraoperative Ruptured Postoperative hematoma Ischemic events Infection	34.4 (11–67) Months

Table 2

1	Excluded studies with reason.	
	Excluded Study	Reason for exclusion
-	Noiphithak et al ⁷ 2020 Meng et al ⁶ 2017 Bhattarai et al ⁵ 2020	The Supraorbital approach was not assessed This study is a case report, only 2 case was reported The Pterional Approach was not assessed

(681 ruptured and 300 unruptured ACCAs) were treated using the pterional approach. These studies were found to have acceptable heterogeneity ($I^2 = 67\%$ and 0% for ruptured and unruptured aneurysm groups, respectively). as seen in the funnel (fig, 2) and forest plot (Fig. 3) for overall analysis among the two groups. Again, in the subgroup analysis of the ruptured and unruptured aneurysm group, as seen in Figs. 3 and 4, the overall heterogeneity ($I^2 = 40.8\%$ and 0% for ruptured and unruptured aneurysm group, respectively) was found to be acceptable (see Fig. 2).

Further studying the results shown in Fig. 3, it is clear that the incidence of events (IOR, post-op hematoma, ischemic, and infectious complications) among those ruptured aneurysms which were approached via the supraorbital keyhole craniotomy was significantly higher (OR 2.03 [95% CI 1.41–2.93] p = 0.0001) with moderate heterogeneity ($I^2 = 67\%$), when compared to standard pterional craniotomy. On the other hand, the incidence of events among the unruptured aneurysms approached via the supraorbital keyhole craniotomy was found to be lower (OR 0–69 [95% CI 0.39–1.24] p = 0.22) with no heterogeneity ($I^2 = 0\%$), when compared to standard pterional craniotomy, though this difference was statistically insignificant. Finally, the overall incidence (ruptured and unruptured combined) of unwanted events was found to be statistically significant and higher in the supraorbital approach

compared to the standard pterional approach ((OR 1.49 [95% CI 1.10–2.01] p = 0.01) with moderate heterogeneity ($I^2 = 56\%$).

Figs. 4 and 5 represent forest plots for sub-group analyses of these events, viz., intra-operative rupture, hematoma, ischemic events, and infectious complications among the patients whose aneurysm had ruptured (n = 643 and n = 681 were clipped via supra-orbital craniotomy and pterional, respectively) or unruptured (n = 280 and n = 300 were clipped via supra-orbital craniotomy and pterional, respectively) and approached via supra-orbital (n = 923) vs. pterional approach (n = 981), respectively. Among the group with ruptured aneurysms (Fig. 4), the differences in the incidences of intra-operative rupture (OR 1.30 [95% CI 0.72–2.36] p = 0.31) with no heterogeneity ($I^2 = 0\%$), hematoma (OR 1.34 [95% CI 0.76–2.36] p = 0.32) with no heterogeneity ($I^2 = 0$ %), and ischemia (OR 0.97 [95% CI 0.60–1.57] p = 0.90) with no heterogeneity $(I^2 = 0\%)$ were found to be statistically insignificant. The only parameter that was close to the significantly lower incidence for the supra-orbital approach was that of infectious complications (OR 0.55 [95% CI 0.29–1.05] p = 0.07) with no heterogeneity ($I^2 = 0$ %). It indicates that post-op infection was significantly less when ruptured aneurysms were clipped via supraorbital craniotomy instead of pterional craniotomy.

The complication with the most significant difference among the group of patients with unruptured aneurysms was ischemic complication (OR 0.33 [95% CI 0.31–0.81] p = 0.03) with mild heterogeneity (I2 = 19%), significantly lower for supra-orbital craniotomy approach. The difference in incidence of rest all the events viz. intra-operative rupture (OR 0.88 [95% CI 0.35–2.22] p = 0.79) with no heterogeneity (I2 = 0%), hematoma (OR 0.85 [95% CI 0.41–1.75] p = 0.66) with moderate heterogeneity (I2 = 33%), and infections (OR 0.65 [95% CI 0.0.31–1.36] p = 0.25) with no heterogeneity (I2 = 0%) were found to be statistically insignificant.



Fig. 2. Funnel Plot, representing publication bias, for studies analysing supraorbital vs pterional approach among ruptured and unruptured aneurysm group.

	Supraorb	itary	Pterio	nal		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 Ruptured Aneury	sm						
Chalouhi 2013	11	47	10	40	12.1%	0.92 [0.34, 2.45]	
Fonseca 2021	4	32	5	44	5.4%	1.11 [0.27, 4.53]	-
Genesan 2018	4	40	2	81	1.7%	4.39 [0.77, 25.07]	
Lan 2006	5	175	2	108	3.5%	1.56 [0.30, 8.18]	
Lan 2017	6	195	2	123	3.5%	1.92 [0.38, 9.67]	
Park 2009	0	10	1	10	2.1%	0.30 [0.01, 8.33]	
Park 2018	0	5	1	18	1.0%	1.06 [0.04, 29.96]	
Tra 2018	1	12	0	13	0.6%	3.52 [0.13, 95.09]	
VVu 2019	37	64	24	157	8.5%	7.59 [3.93, 14.69]	
Yu 2020	14	70	18	70	21.0%	0.72 [0.33, 1.60]	
Subtotal (95% CI)		650		664	59.3%	2.03 [1.41, 2.93]	
Total events	82		65				
Heterogeneity: Chi ² = 2				= 67%			
Test for overall effect: Z	.= 3.82 (F	' = 0.000	D1)				
1.1.2 Unruptured Aneu	irysm						
Alekseev 2019	0	49	5	117	4.7%	0.21 [0.01, 3.81]	
Cha 2012	1	61	0	71	0.7%	3.55 [0.14, 88.64]	
Fonseca 2021	1	8	7	16	5.9%	0.18 [0.02, 1.86]	
Lan 2006	2	20	1	18	1.4%	1.89 [0.16, 22.79]	
Larocca 2018	1	25	0	25	0.7%	3.12 [0.12, 80.39]	
Park 2009	1	103	3	110	4.2%	0.35 [0.04, 3.42]	
Park 2018	1	16	0	3	1.1%	0.68 [0.02, 20.39]	
Shin 2012	2	71	0	23	1.1%	1.69 [0.08, 36.50]	
VVu 2019	14	70	18	70	21.0%	0.72 [0.33, 1.60]	
Subtotal (95% CI)		423		453	40.7%	0.69 [0.39, 1.24]	
Total events	23		34				
Heterogeneity: Chi ² = 5)%			
Test for overall effect: Z	:= 1.24 (F	' = 0.22)					
Total (95% CI)		1073		1117	100.0%	1.49 [1.10, 2.01]	◆
Total events	105		99				
Heterogeneity: Chi ² = 4	0.86, df=	18 (P =	0.002); ł	² = 56%			0.01 0.1 1 10 100
Test for overall effect: Z	.= 2.58 (F	= 0.010))				0.01 0.1 1 10 100
Test for subgroup diffe		hiz - 0.4	0 46 4	~ ~ ·	0.000	00.50	

Fig. 3. Forest Plot analysing the overall significance of events among groups with ruptured and unruptured aneurysm approached for clipping via supra-orbital vs. pterional approaches.

When comparing the pterional technique to the supraorbital method, there was no discernible difference in the percentage of unruptured aneurysms that had a bad result after being treated with microsurgery (OR 0.69 [95% CI 0.39–1.24] p = 0.22], with a modest degree of heterogeneity $(I^2 = 0\%)$ (Fig. 5). In our subgroup analysis, the supraorbital approach was associated with a significantly higher probability of a poor outcome in the treatment of ruptured aneurysms (OR = 2.03, 95% confidence interval = 1.41.-2.93; p < 0.0001) with a high degree of heterogeneity (I2 = 67%). In comparison to the pterional keyhole method, the supraorbital approach was linked with a lower incidence of ischemia events (OR 0.33 [95% CI 0.13.-0.89] $p = 0.03 I^2 = 19\%$) with acceptable homogeneity. However, there were no changes in other sequelae. The likelihood of complications, such as intra-operative rupture, postoperative hematoma, ischemic complications, and infections, is compared between the two groups of patients with unruptured aneurysms and ruptured aneurysms in Figs. 4 and 5, respectively. Only two of the studies that were chosen showed significant biases when it came to the categorization of the interventions (Figs. 6 and 7). Three studies 8,11,12 had a score of 7/7, 4 studies^{4,9,10,19} had a score of 6/7, and 7 studies^{13-18,20} had a score of 5/7 on Newcastle-Ottawa Scale for quality assessment of studies included in this meta-analysis (Table-3).

4. Discussion

The supraorbital technique allows a smaller craniotomy than the conventional pterional technique through the shorter skin incision and generates minimal stress to the temporalis muscle and a much lesser risk of damaging the upper facial nerve branch. The post-operative sinking at the operative site and pain while chewing are the most common complications noted after standard pterional craniotomy. Poorly managed burr hole sites and temporalis muscle atrophy leads to bone flap sinking, resulting in post-op cosmetic deformity. As pterional craniotomy provides a more extensive vulnerability, over-exposure of the Brain increases the chances of iatrogenic injury to the non-lesion parenchyma. On the other hand, supra-orbital craniotomy minimizes this exposure and therefore reduces cosmetic and ischemic complications.

Many authors^{4,14} have concluded that among experienced neurosurgeons and in absence of brain swelling, diffuse subarachnoid haemorrhage, and Brain shifts, keyhole approaches are ideal craniotomy techniques for the treatment of intracranial aneurysms even for multiple and giant aneurysms. Therefore, careful selection of the patient gives better outcomes in the supraorbital approach.

In a comparative study¹⁰ involving 87 patients (40 and 47 among pterional and supraorbital craniotomy, respectively), procedural complications were found to be more in the supraorbital approach, but overall complications appear to be similar at 1-year follow-up. Various studies^{5,9,11,12,15,19} comparing the two approaches have concluded that the supraorbital craniotomy approach had shorter operative time, better cosmetic results, lower epileptic seizures,⁸ lower early clinical complications, and lower masticatory pain¹³ compared to standard pterional approach. A more direct comparison between the two groups was done by Park et al¹⁷ and concluded that in successful cases in which the primary surgical goal of complete aneurysm clipping without postoperative complications is achieved, a superciliary keyhole approach provides a much higher level of patient satisfaction than a pterional approach, despite a facial wound.

Study or Subgroup	Supraorb Events	-	Pterio		Moight	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl
.2.1 Intraoperative		TUTAL	Events	TUtal	weight	M-H, Fixed, 95% CI	M-n, Fixed, 95% Ci
				40	4 0.00		
Chalouhi 2013	5	47	1	40	1.0%	4.64 [0.52, 41.52]	
onseca 2021	1	32	1	44	0.8%	1.39 [0.08, 23.04]	
∋enesan 2018	2	40	2	81	1.3%	2.08 [0.28, 15.33]	
_an 2006	1	175	0	105	0.6%	1.81 [0.07, 44.93]	
_an 2017	2	195	0	103	0.7%	2.67 [0.13, 56.23]	
Park 2009	0	10	1	10	1.4%	0.30 [0.01, 8.33]	
Park 2018	0	5	1	18	0.7%	1.06 [0.04, 29.96]	
Fra 2018	0	12	1	13	1.4%	0.33 [0.01, 8.99]	
Vu 2019	0	64	1	157	0.9%	0.81 [0.03, 20.12]	
/u 2020	14	70	13	70	10.5%	1.10 [0.47, 2.54]	_
Subtotal (95% CI)		650		641	19.3%	1.30 [0.72, 2.36]	-
Fotal events	25		21			,,	-
Heterogeneity: Chi² =		/P = 0 (04			
Fest for overall effect			50), I = 0	70			
restior overall ellect	. Z = 0.86 (P	= 0.39)					
I.2.2 Postoperative	Hematoma						
				~		hist satissable	
Chalouhi 2013	0	0	0	0	4.000	Not estimable	
Genesan 2018	2	40	2	81	1.3%	2.08 [0.28, 15.33]	
_an 2006	1	175	0	105	0.6%	1.81 [0.07, 44.93]	
_an 2017	4	195	0	123	0.6%	5.80 [0.31, 108.75]	
Park 2009	1	10	0	10	0.4%	3.32 [0.12, 91.60]	
Park 2018	0	5	1	18	0.7%	1.06 [0.04, 29.96]	
Fra 2018	0	12	1	13	1.4%	0.33 [0.01, 8.99]	
Vu 2019	14	64	24	157	11.0%	1.55 [0.74, 3.24]	+•
/u 2020	0	70	4	70	4.5%	0.10 [0.01, 1.98]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		571		577	20.5%	1.34 [0.76, 2.36]	+
Fotal events	22		32				-
Heterogeneity: Chi² =		(P - 0.6		96			
Fest for overall effect			,,,, = 0				
	. 2 - 1.00 (i	- 0.52)					
1.2.3 Ischemic even	s						
		47		40	4.000	0.04/0.00.0.501	
Chalouhi 2013	4	47	4	40	4.0%	0.84 [0.20, 3.59]	
				81	1.0%	0.66 [0.03, 16.63]	
Genesan 2018	0	40	1				
_an 2006	7	175	1	105	1.2%	4.33 [0.53, 35.72]	
_an 2006	7	175	1	105	1.2%	4.33 [0.53, 35.72]	
∟an 2006 ∟an 2017	7 3	175 195	1 1	105 123	1.2% 1.2%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53]	
∟an 2006 ∟an 2017 Park 2018	7 3 0	175 195 5	1 1 1	105 123 18	1.2% 1.2% 0.7%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96]	
Lan 2006 Lan 2017 Park 2018 Wu 2019	7 3 0 10	175 195 5 64	1 1 1 30	105 123 18 157	1.2% 1.2% 0.7% 14.8%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72]	
Lan 2006 Lan 2017 Park 2018 Wu 2019 Yu 2020 Subtotal (95% CI)	7 3 0 10 11	175 195 5 64 70	1 1 30 13	105 123 18 157 70	1.2% 1.2% 0.7% 14.8% 11.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events	7 3 0 10 11 35	175 195 5 64 70 596	1 1 30 13 51	105 123 18 157 70 594	1.2% 1.2% 0.7% 14.8% 11.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97]	
_an 2006 _an 2017 ?ark 2018 Mu 2019 /u 2020 S ubtotal (95% CI) Fotal events Heterogeneity: Chi ^a =	7 3 0 10 11 35 : 2.80, df = 6	175 195 64 70 596	1 1 30 13 51	105 123 18 157 70 594	1.2% 1.2% 0.7% 14.8% 11.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events	7 3 0 10 11 35 : 2.80, df = 6	175 195 64 70 596	1 1 30 13 51	105 123 18 157 70 594	1.2% 1.2% 0.7% 14.8% 11.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97]	
Lan 2006 Lan 2017 Park 2018 Wu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ^a = Fest for overall effect	7 3 0 10 11 35 : 2.80, df = 6	175 195 64 70 596	1 1 30 13 51	105 123 18 157 70 594	1.2% 1.2% 0.7% 14.8% 11.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97]	
Lan 2006 Lan 2017 Park 2018 Wu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = Fest for overall effect I.2.4 Infection	7 3 0 10 11 35 : 2.80, df = 6 : Z = 0.12 (P	175 195 64 70 596 (P = 0.0	1 1 30 13 51 33); I ^z = 0	105 123 18 157 70 594 %	1.2% 1.2% 0.7% 14.8% 11.1% 34.0 %	4.33 (0.53, 35.72) 1.91 (0.20, 18.53) 1.06 (0.04, 29.96) 0.78 (0.36, 1.72) 0.82 (0.34, 1.97) 0.97 (0.60, 1.57)	
Lan 2006 Lan 2017 Park 2018 Wu 2019 Yu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect I.2.4 Infection Chalouhi 2013	7 3 0 10 11 35 : 2.80, df = 6 : Z = 0.12 (P	175 195 5 64 70 596 i (P = 0.1 = 0.90) 47	1 1 30 13 51 33); I ² = 0	105 123 18 157 70 594 %	1.2% 1.2% 0.7% 14.8% 11.1% 34.0 %	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.95 [0.05, 14.00]	
Lan 2006 Lan 2017 Park 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021	7 3 0 10 11 35 2.80, df = 6 Z = 0.12 (P	175 195 5 64 70 596 i (P = 0.1 = 0.90) 47 32	1 1 30 13 51 33); I ² = 0 1 0	105 123 18 157 70 594 % 40 44	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.95 [0.05, 14.00] 4.24 [0.17, 107.46]	
Lan 2006 Lan 2017 Park 2018 Avu 2019 Avu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chiª = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018	7 3 0 10 11 : 2.80, df = 6 : Z = 0.12 (P 1 1 1	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40	1 1 30 13 51 33); I ² = 0 1 0 2	105 123 18 157 594 % 40 44 81	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.95 [0.05, 14.00] 4.24 [0.17, 107.46] 1.01 [0.09, 11.51]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017	7 3 0 10 11 : 2.80, df = 6 : Z = 0.12 (P 1 1 1 1	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40 195	1 1 30 13 51 33); I ² = 0 1 0 2 0	105 123 18 157 594 % 40 44 81 123	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.85 [0.05, 14.00] 4.24 [0.17, 107.46] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017 Park 2009	7 3 0 10 11 35 : 2.80, df = 6 : Z = 0.12 (P 1 1 1 1 0	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40 195 10	1 1 30 13 51 33); I ² = 0 1 0 2 0 1	105 123 18 157 594 % 40 44 81 123 10	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 0.6% 1.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.85 [0.05, 14.00] 4.24 [0.17, 107.46] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017	7 3 0 10 11 : 2.80, df = 6 : Z = 0.12 (P 1 1 1 1	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40 195	1 1 30 13 51 33); I [#] = 0 1 0 2 0 1 1	105 123 18 157 594 % 40 44 81 123	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.85 [0.05, 14.00] 4.24 [0.17, 107.46] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017 Park 2009	7 3 0 10 11 35 : 2.80, df = 6 : Z = 0.12 (P 1 1 1 1 0	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40 195 10	1 1 30 13 51 33); I ² = 0 1 0 2 0 1	105 123 18 157 594 % 40 44 81 123 10	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 0.6% 1.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.85 [0.05, 14.00] 4.24 [0.17, 107.46] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33]	
Lan 2006 Lan 2017 Park 2018 Wu 2019 Vu 2020 Subtotal (95% CI) Total events Heterogeneity: Chi [#] = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017 Park 2009 Park 2018	7 3 0 10 11 35 2.80, df = 6 Z = 0.12 (P 1 1 1 1 1 0 0	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40 195 10 5	1 1 30 13 51 33); I [#] = 0 1 0 2 0 1 1	105 123 18 157 70 594 % 40 44 81 123 10 18	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.4% 0.7%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.96 [0.05, 14.00] 4.24 [0.17, 107.46] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017 Park 2009 Park 2018 Fra 2018	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 0 0 0 1	175 195 5 64 70 596 i (P = 0.1 = 0.90) 47 32 40 195 10 5 12	1 1 30 13 51 33); I [≠] = 0 1 0 2 0 1 1 0	105 123 18 157 70 594 % 40 44 81 123 10 18 13	1.2% 1.2% 0.7% 14.8% 11.1% 0.4% 1.3% 0.6% 1.3% 0.6% 1.4% 0.7% 0.4%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.09, 11.51] 1.01 [0.09, 11.51] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% Cl) Fotal events Heterogeneity: Chi ² = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Genesan 2018 Lan 2017 Park 2009 Park 2018 Fra 2018 Vu 2019	7 3 0 10 11 5 2.80, df = 6 Z = 0.12 (P 1 1 1 1 1 0 0 1 1	$\begin{array}{c} 175\\ 195\\ 5\\ 64\\ 70\\ 596\\ (P=0.8\\ =0.90)\\ 47\\ 32\\ 40\\ 195\\ 195\\ 195\\ 12\\ 64\\ \end{array}$	1 1 30 13 51 33); ² = 0 1 0 2 0 1 1 0 5	105 123 18 157 70 594 % 40 44 81 123 10 18 13 157	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.3% 0.6% 1.3% 0.6% 1.3% 0.6% 1.4% 0.7% 0.4% 2.9%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.60, 1.51] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Fest for overall effect I.2.4 Infection Chalouhi 2013 Conseca 2021 Denesan 2018 Lan 2017 Park 2009 Park 2018 Au 2018 Au 2019 Au 2020 Subtotal (95% Cl)	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 0 0 1 1 7	175 195 5 64 700 596 i (P = 0.1 = 0.90) 47 32 40 195 10 5 125 10 5 125 10 10 5 10 10 5 10	1 1 30 13 51 33); I [₽] = 0 1 0 2 0 1 1 1 0 5 19	105 123 18 157 594 % 40 44 81 123 10 18 13 157 70	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.4% 0.6% 1.4% 0.7% 0.4% 2.9% 17.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.60, 1.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Senesan 2018 Lan 2017 Park 2009 Park 2018 Fra 2018 Mu 2019 Au 2019 Au 2019 Au 2019 Au 2019 Au 2019 Au 2019 Cotal events Fotal events	7 3 0 10 11 : 2.80, df = 6 : Z = 0.12 (P 1 1 1 1 1 0 0 1 1 7 7	175 195 5 64 70 596 (P = 0.1 = 0.90) 47 32 40 195 10 5 12 64 70 475	1 1 30 13 51 33); ² = 0 1 0 2 0 1 1 0 5 9 9 9 9 29	105 123 18 157 70 594 % 40 44 81 123 10 18 13 157 70 556	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.4% 0.6% 1.4% 0.7% 0.4% 2.9% 17.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.60, 1.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Benesan 2018 Lan 2017 Park 2009 Park 2009 Park 2018 Fra 2018 Vu 2019 Vu 2019 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² =	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 0 0 1 1 7 5.57, df = 8	175 195 5 6 70 596 (P = 0.90) 47 32 40 195 12 64 70 475 12 64 70 475 12 64 70 475 12	1 1 30 13 51 33); ² = 0 1 0 2 0 1 1 0 5 9 9 9 9 29	105 123 18 157 70 594 % 40 44 81 123 10 18 13 157 70 556	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.4% 0.6% 1.4% 0.7% 0.4% 2.9% 17.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.60, 1.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi [#] = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Senesan 2018 Lan 2017 Park 2009 Park 2018 Fra 2018 Mu 2019 Au 2019 Au 2019 Au 2019 Au 2019 Au 2019 Au 2019 Cotal events Fotal events	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 0 0 1 1 7 5.57, df = 8	175 195 5 6 70 596 (P = 0.90) 47 32 40 195 12 64 70 475 12 64 70 475 12 64 70 475 12	1 1 30 13 51 33); ² = 0 1 0 2 0 1 1 0 5 9 9 9 9 29	105 123 18 157 70 594 % 40 44 81 123 10 18 13 157 70 556	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.4% 0.6% 1.4% 0.7% 0.4% 2.9% 17.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.60, 1.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Denesan 2018 Lan 2017 Park 2009 Park 2009 Park 2009 Park 2018 Au 2019 Au 2019 Au 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = Fest for overall effect	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 0 0 1 1 7 5.57, df = 8	$\begin{array}{c} 175\\ 195\\ 5\\ 64\\ 70\\ 596\\ \hline (P=0.(=0.90))\\ \hline 47\\ 32\\ 40\\ 195\\ 10\\ 5\\ 12\\ 64\\ 70\\ 475\\ \hline (P=0.(=0.7))\\ \hline (P=0.7)\\ \hline 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, $	1 1 30 13 51 33); ² = 0 1 0 2 0 1 1 0 5 9 9 9 9 29	105 123 18 157 594 % 40 44 81 123 10 18 13 157 556 %	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.3% 0.6% 1.4% 0.6% 1.4% 0.4% 2.9% 17.3% 26.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76] 0.55 [0.29, 1.05]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Denesan 2018 Lan 2017 Park 2009 Park 2009 Park 2018 Vu 2019 Vu 2019 Vu 2019 Vu 2019 Vu 2019 Fotal events Heterogeneity: Chi ² = Fest for overall effect Fotal (95% CI)	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 1 7 3 5.57, df = 8 2 = 1.82 (P	175 195 5 6 70 596 (P = 0.90) 47 32 40 195 12 64 70 475 12 64 70 475 12 64 70 475 12	1 1 30 13 51 33); I [₽] = 0 1 0 2 0 1 1 0 5 19 29 70); I [₽] = 0	105 123 18 157 594 % 40 44 81 123 10 18 13 157 556 %	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.4% 0.6% 1.4% 0.7% 0.4% 2.9% 17.3%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 0.97 [0.60, 1.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76]	
Lan 2006 Lan 2017 Park 2018 Au 2019 Au 2020 Subtotal (95% Cl) Fotal events Heterogeneity: Chi ² = Fest for overall effect I.2.4 Infection Chalouhi 2013 Fonseca 2021 Danesan 2018 Lan 2017 Park 2009 Park 2018 Au 2018 Au 2019 Au 2019 Au 2019 Fotal events Heterogeneity: Chi ² = Fest for overall effect Fotal (95% Cl) Fotal events	7 3 0 10 11 5 2.80, df = 6 2 = 0.12 (P 1 1 1 1 1 5.57, df = 8 2 = 1.82 (P 95	$\begin{array}{c} 175\\ 195\\ 5\\ 64\\ 70\\ 596\\ \hline (P=0.1\\ =0.90)\\ 47\\ 32\\ 40\\ 195\\ 10\\ 5\\ 12\\ 64\\ 70\\ 475\\ \hline (P=0.1\\ =0.07)\\ \hline 2292 \end{array}$	1 1 30 13 51 33); I ^P = 0 1 33); I ^P = 0 1 2 0 1 1 29 70); I ^P = 0 133	105 123 18 157 594 % 40 44 81 123 10 18 123 10 18 13 157 556 % 2368	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.3% 0.6% 1.4% 0.6% 1.4% 0.4% 2.9% 17.3% 26.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76] 0.55 [0.29, 1.05]	
Lan 2006 Lan 2017 Park 2018 Vu 2019 Vu 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = Fest for overall effect 1.2.4 Infection Chalouhi 2013 Fonseca 2021 Denesan 2018 Lan 2017 Park 2009 Park 2009 Park 2018 Vu 2019 Vu 2019 Vu 2019 Vu 2019 Vu 2019 Fotal events Heterogeneity: Chi ² = Fest for overall effect Fotal (95% CI)	7 3 0 10 11 35 2.80, df = 6 2.80, df = 6 2.80, df = 6 2.80, df = 6 1 1 1 1 0 0 1 1 5.57, df = 8 2.5, 7, df = 8 2.5, 7, df = 8 2.5, 2, 2, 2, 0, df = 1 2.5, 2, 2, 2, 0, df = 1 3.5, 2, 2, 2, 2, 2, 0, df = 1 3.5, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,	$\begin{array}{c} 175\\ 195\\ 5\\ 64\\ 70\\ 596\\ \end{array}\\ (P=0.)\\ =0.90)\\ \end{array}\\ \begin{array}{c} 47\\ 32\\ 40\\ 195\\ 10\\ 5\\ 12\\ 64\\ 70\\ 475\\ \end{array}\\ \begin{array}{c} 32\\ (P=0.)\\ \end{array}\\ \begin{array}{c} 33\\ (P=0.)\\ \end{array}$	1 1 30 13 51 33); I ^P = 0 1 33); I ^P = 0 1 2 0 1 1 29 70); I ^P = 0 133	105 123 18 157 594 % 40 44 81 123 10 18 123 10 18 13 157 556 % 2368	1.2% 1.2% 0.7% 14.8% 11.1% 34.0% 1.1% 0.4% 1.3% 0.6% 1.3% 0.6% 1.4% 0.6% 1.4% 0.4% 2.9% 17.3% 26.1%	4.33 [0.53, 35.72] 1.91 [0.20, 18.53] 1.06 [0.04, 29.96] 0.78 [0.36, 1.72] 0.82 [0.34, 1.97] 0.97 [0.60, 1.57] 0.97 [0.60, 1.57] 1.01 [0.09, 11.51] 1.90 [0.08, 47.13] 0.30 [0.01, 8.33] 1.06 [0.04, 29.96] 3.52 [0.13, 95.09] 0.48 [0.06, 4.21] 0.30 [0.12, 0.76] 0.55 [0.29, 1.05]	

Fig. 4. Forest Plot, with sub-group analysis, analysing the significance of events among groups with ruptured aneurysm approached for clipping via supra-orbital vs. pterional approaches.

For a pterional approach, the authors concluded, that the patient satisfaction level is affected by the cosmetic results, craniotomy-related pain, and numbness behind the hairline, in order of importance. Another study⁷ involving 102 matched pairs, concluded that the use of minimal invasive craniotomy for clipping aneurysms is a significant

predictive factor for a better outcome at a 1-month follow-up. This however may be attributed to the selection of lower WFNS grade patients for minimal invasive craniotomy. In an "aneurysm site-specific" study¹⁸ where authors studied the role of two different approaches for clipping unruptured supra-clinoid internal carotid artery aneurysms, the

Study or Subgroup	Supraorb Events	rtary Total	Pterio		Woigh*	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl
study of Subgroup 1.3.1 Introperative R			Events	TUtal	weight	m-n, rixeu, 95% Cl	M-n, rixeu, 95% Ci
	upture anet 1	-		117	3.8%	0.50.00.00.5.401	
Alekseev 2019		49	4			0.59 [0.06, 5.40]	
Cha 2012	1	61	1	71	1.5%	1.17 [0.07, 19.05]	
Fonseca 2021	1	8	2	16	1.9%	1.00 [0.08, 13.02]	
Larocca 2018	1	25	0	25	0.8%	3.12 [0.12, 80.39]	
Shin 2012	1	71	0	23	1.2%	1.00 [0.04, 25.39]	
Wu 2019	3	13	8	26	6.8%	0.68 [0.15, 3.13]	
Subtotal (95% CI)		227		278	16.0 %	0.88 [0.35, 2.22]	-
Total events	8		15				
Heterogeneity: Chi ^z =	0.88, df = 5	(P = 0.	97); I ^z = 0	%			
Test for overall effect:	Z = 0.26 (P	= 0.79)					
		•					
1.3.2 Postoperative I	Hematoma						
Alekseev 2019	1	49	7	117	6.7%	0.33 [0.04, 2.73]	
Cha 2012	4	61	2	71	2.9%	2.42 [0.43, 13.70]	
Lan 2006	1	20	Ó	18	0.8%	2.85 [0.11, 74.38]	
Lan 2000 Larocca 2018	4	20	1	25	1.4%	4.57 [0.47, 44.17]	
Park 2009	1	10	0	11	0.7%	3.63 [0.13, 99.85]	
Park 2018	1	16	0	3	1.2%	0.68 [0.02, 20.39]	
Shin 2012	0	71	4	23	11.1%	0.03 [0.00, 0.59]	
/Vu 2019	0	13	1	26	1.6%	0.63 [0.02, 16.53]	
Subtotal (95% CI)		265		294	26.3%	0.85 [0.41, 1.75]	-
Total events	12		15				
Heterogeneity: Chi ² =	10.46, df =	7 (P = 0	l.16); I ² = 1	33%			
Test for overall effect:	Z = 0.44 (P	= 0.66)					
1.3.3 Ischemic Event	s						
Alekseev 2019	0	49	11	117	11.2%	0.09 [0.01, 1.62]	· · · · · · · · · · · · · · · · · · ·
Lan 2006	0	20	1	18	2.5%	0.28 [0.01, 7.44]	
Larocca 2018	3	25	1	25	1.5%	3.27 [0.32, 33.84]	
Park 2018	Ő	16	1		3.9%	0.05 [0.00, 1.62]	← → → → → → → → → → → → → → → → → → → →
Shin 2012	Ő	71	1	23	3.7%	0.10 [0.00, 2.67]	·
Wu 2019	1	13	4	26	4.1%	0.46 [0.05, 4.58]	
Subtotal (95% CI)	1	194	4	212	4.1% 26.8%	0.33 [0.13, 0.89]	
		194	40	212	20.0%	0.55 [0.15, 0.69]	
Total events	4	-	19	~~			
Heterogeneity: Chi ² =			29); I* = 1	9%			
Test for overall effect	Z = 2.20 (P	= 0.03)					
1.3.4 Infection							
Alekseev 2019	6	49	16	117	13.7%	0.88 [0.32, 2.40]	
Cha 2012	1	61	5	71	7.5%	0.22 [0.02, 1.94]	
Fonseca 2021	0	8	1	16	1.6%	0.61 [0.02, 16.61]	
Larocca 2018	1	25	0	25	0.8%	3.12 [0.12, 80.39]	
Park 2009	0	10	1	10	2.4%	0.30 [0.01, 8.33]	
Park 2018	Õ	16	1	3	3.9%	0.05 [0.00, 1.62]	← – – – – –
Wu 2019	1	13	1	26	1.0%	2.08 [0.12, 36.23]	
Subtotal (95% CI)	1	182		268	30.9%	0.65 [0.31, 1.36]	-
Total events	q	.01	25	200	001070	5166 [516 I] 1100]	-
		n = 2		ov.			
Heterogeneity: Chi ² =				70			
Test for overall effect	.∠=1.14 (P	= 0.25)					
Total (95% CI)		868		1052	100.0%	0.66 [0.44, 0.98]	
		000	74	1052	100.0%	0.00 [0.44, 0.90]	•
Total events	33	ac /c		0.07			
	24.99, df=		0.52); l²=	= 0%			

Fig. 5. Forest Plot, with sub-group analysis, analysing the significance of events among groups with unruptured aneurysm approached for clipping via supra-orbital vs. pterional approaches.

superciliary approach demonstrated statistically significant advantages over the pterional approach, including a shorter operative duration (mean, 100 min), no intraoperative blood transfusions, and no postoperative epidural haemorrhages.

5. Limitations

functional outcomes, such as chewing pain, temporal muscle atrophy, and hyposmia, which severely impact the quality of life of our patients, were not compared among the two groups over a sufficiently long period of follow-up. We also tend not to compare cosmetic results and patient satisfaction in the long term.

6. Conclusions

Literature suggests that the supraorbital approach gives enough exposure to the aneurysm and for safe neurosurgical manipulation, with a substantially shorter surgical duration and a much smaller craniotomy, hence reducing surgical morbidity without compromise in technical manoeuvrability while clipping. When clipping ruptured ACCAs, supraorbital craniotomy significantly decreases the risk of ischemic events compared to standard pterional craniotomy. When clipping unruptured ACCAs, supra-orbital craniotomy significantly decreases the risk of infectious complications compared to standard pterional craniotomy. Our findings suggest that the supraorbital method for clipping ACCAs might

			Risk of bias domains									
		D1	D2	D3	D4	D5	D6	D7	Overall			
	Alekseev et al 2019	+	+	+	+	+	+	+	+			
	Cha et al 2012	+	+	+	-	+	+	+	+			
	Chaloui et al 2013	+	+	+	+	+	-	+	+			
	Fonseca et al 2021	+	+	+	+	+	+	+	+			
	Genesan et al 2018	+	+	+	+	+	+	+	+			
	Lan et al 2006	+	+	-	-	-	+	-	-			
Study	Lan et al 2017	+	+	-	-	-	+	+	-			
Sti	Larocca et al 2018	+	+	-	-	+	+	+	-			
	Park et al 2009	+	-	X	+	+	+	+	-			
	Park et al 2018	+	-	X	+	+	+	+	-			
	Shin et al 2012	+	-	-	-	-	+	+	-			
	Tra et al 2018	+	+	-	+	+	+	+	+			
	Wu et al 2019	+	+	+	-	+	+	+	+			
	Yu et al 2020	+	-	+	-	-	-	+	-			
		Domains	: due to cor	ofounding				Juc	dgement			
		D2: Bias	due to sel	ection of p	articipants terventions			X	Serious			
		D4: Bias	due to dev	iations fro	m intended	d intervent	ions.		Moderate			
		D6: Bias	in measur	ssing data. ement of c n of the re	outcomes. ported res	ult.		4	Low			
		27. 2.40										

Bias due to confounding

Fig. 6. Bias domains and their representative contribution among the studies selected for Meta-analysis.



Fig. 7. Bias domains and their representative contribution among the studies selected for Meta-analysis.

be a viable alternative to the traditional pterional method, however, the associated difficulties in utilizing this approach among ruptured

aneurysms with cerebral edema and midline shifts need to be further understood.

8

Table 3

Newcastle-Ottawa Scale for quality assessment of studies included in this meta-analysis.

Study	Representativeness of Sample	Size Sample	Source of information	Demonstration that outcome was not present at study start	Confusion variable control	Assessment of outcome	Enough follow-up period	Newcastle Ottawa Scale Score
Alekseev et al ⁸ 2019	*	*	*	*	*	*	*	7/7
Cha et al ⁹ 2012	*	*	*	*	*	*		6/7
Chaloui et al ¹⁰ 2013	*	*	*	*	*	*		6/7
Fonseca et al ¹¹ 2021	*	*	*	*	*	*	*	7/7
Genesan et al ¹² 2018	*	*	*	*	*	*	*	7/7
Lan et al ¹⁴ 2006	*	*	*			*	*	5/7
Lan et al ¹⁵ 2017	*	*	*			*		5/7
Larocca et al ¹³ 2018	*		*	*		*	*	5/7
Park et al ¹⁶ 2009	*		*	*		*	*	5/7
Park et al ¹⁷ 2018	*		*	*	*	*		5/7
Shin et al ¹⁸ 2012	*		*	*	*	*		5/7
Tra et al ⁴ 2018	*		*	*	*	*	*	6/7
Wu et al ¹⁹ 2019	*		*	*	*	*	*	6/7
Yu et al ²⁰ 2020	*		*	*	*	*		5/7

★ Indicates that it meets criteria in Newcastle–Ottawa Scale.

Credit author statement

Florez-Perdomo, W: Conceptualization, Methodology, Formal analysis. Zabala-Otero, C: Conceptualization, Methodology, Formal analysis. Herrea, H: Conceptualization, Methodology, Formal analysis. Moscote-Salazar, L: Review & editing, Formal analysis, Data curation, Visualization, Supervision. Abdulla, E: Writing – original draft, review & editing. Janjua, T: Writing – original draft, review & editing. Chaturvedi, J: Writing – original draft, review & editing. Chouksey, P: Writing – original draft, review & editing. Agrawal, A: Writing – original draft, review & editing, Supervision, Data curation, Visualization. All authors read and approved the final version of the manuscript.

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