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Transsphenoidal resection for pituitary adenoma in elderly versus younger

patients: a systematic review and meta-analysis

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Abstract

Introduction: Pituitary adenomas (PA) are common intracranial tumors. In the context of the ageing of the population, the question is whether postsurgical outcomes are comparable to the younger ones. The primary objective of the present study was to review published resection and recurrence rates after transsphenoidal resection. The secondary aim was to evaluate visual improvement and complication rates.

Methods:

The authors searched PubMed and Medline databases, of published English series, with no time frame limit, evaluating outcomes of transsphenoidal resection in populations aged more or less than 65, 70 and 80 years. We performed a systematic review and meta-analysis.

Results:

Median overall resection rates for younger population was 70.7% (range 54-76.8) and for elderly one was 65.7% (range 16.6-78.2) (two sample t test, p= 0.35). The only statistically significant difference for gross total resection rates (GTR) favored patients aged less than 80 (p=0.01). There was no statistically significant difference among recurrence rates. There was a statistically significant difference for visual improvement favoring patients aged more than 80 (p=0.03). For the age groups of less versus more than 70, there was a statistically significant difference for overall complication rate favoring younger groups (p<0.05).

Conclusion:

Present data shows GTR rates favoring younger patients. Recurrence rates remain similar over mean follow-up period. Moreover, visual improvement favors patients aged more than 80. Overall complications rates favors patients younger than 70, which might be also related to additional comorbidities, frequently present in seniors. Transsphenoidal surgery is safe and effective even for older patients.

Introduction

Pituitary adenomas (PAs) is a common benign intracranial neoplasm. The prevalence is as high as 16.7%, ranging between 14.4% in autopsic series and 22.5% in radiological studies[21]. The incidence is estimated at 18.1/100.000 per year[34]. They are mainly classified as non-functional and functional (or secreting), the former being biologically active by excess hormone secretion. Nowadays, PAs are also categorized depending on histological, immunocytochemical and ultrastructural characteristics, with prognostic implications, while strongly predicting the probability of post-operative complete remission or tumor progression[57].

The number of people aged 65 years or older is considered to nearly double from 52 million in 2018 to 95 million in 2060, while there will be also an increase at the 65-and-older age group's from 16 to 23 percent in USA. The same applies for Europe and other continents, where the ageing population will become one of the main challenges of the 21-st century[12]. There are several key questions with regards to the functional limitations and disability that accompany the ageing population. One major aspect is whether medical and technological developments will be able to face these challenges[12]. A second aspect is related to the incidence of associated ocular pathologies in the elderly population, which could interfere with the presence of specific visual symptoms related to PAs presence. Specifically, open-angle glaucoma incidence rises significantly with age, and passes from 1% at 60 years old to 3% at 80 years old[19]. Furthermore, cumulative incidence of nuclear cataract increases from 2.9% in persons aged 43 to 54 years to 40% in those aged 75 years or older[33]. Moreover, macular degeneration is less than 1% for people aged 60 years or less and increases to 10% for people aged 80 or more[37].

The majority of PA in the elderly are non functional[42], followed by incidental microadenomas[35]. An important aspect is that many of these benign tumors will remain stable during time, due to their slow-growing process. They will eventually become symptomatic either by mass effects, frequently on the optic chiasm (but not only), and/or by their biological activity (with their specific syndromes)[8]. In this context, (i.e. symptomatic mass effect and/or uncontrolled biological activity) primary treatment is microsurgery, so as to achieve decompression of vital structures, or to slow the biological activity. However, the unique exception to this rule are prolactinomas, where first line therapy is pharmacological[43]. Although transcranial approaches to pituitary gland can be performed, commonly used is the transsphenoidal one, either endoscopically most or microscopically[60]. The former avoids any brain or cranial nerve retraction during tumor removal. The risk of complication of such procedures is low, ranging between 0 to 9%. The risk of death or major disability is considered as low as 0.26%[1].

Elderly patients have the same expectancies in terms of morbidity and mortality as the overall population. In this context, one open question is whether they are subject to more complications after surgery and if their outcome in terms of safety and efficacy is comparable to the others. The purpose of the present study is to assess the current literature on elderly patients with PA operated by transsphenoidal approach, as compared with younger patients, in terms of reported resection rates and complication occurrence. To achieve this, we performed a meta-analysis of all comparative studies addressing this issue. Our findings should be valuable for decision-making process and also to be able to offer correct information to this specific group of patients.

Methods

Literature search

A systematic search has been performed using the Pubmed, Embase and Cochrane Library databases, from March 1909 (date of the first online publication of a PA) up-to-date for studies evaluating the safety and efficacy of transsphenoidal resection of PA in elderly patients (whatever the definition of elderly in terms of cut-off in the individual studies), as compared with younger ones. The PubMed and other databases were queried using the following word combinations in the "title" or "title/abstract" item: ("elderly" AND "pituitary" AND "adenoma"), ("transsphenoidal" AND "elderly" AND "pituitary") etc.

Additional articles were identified by hand search. In fact, we also used the Google search engine to expand our list of studies, including abstracts, but we considered in the final analysis only peer-reviewed papers. No age limit as expressing the word "elderly" has been defined, accepting variation of this age (i.e. 60, 65, 70, 75, 80 etc). Studies were included if all the defined outcomes were reported.

Study selection

Inclusions criteria were: 1- transsphenoidal resection performed in elderly population; 2- comparison of outcomes to a younger group of age; 3- resection rates were reported; 4complication rates described. This was independent of the fact that the microsurgical technique was performed via an endoscopic or transcranial approach. Exclusion criteria were: non-English studies, articles reporting outcomes in a single group (either elderly, either younger), studies reporting only part of the researched outcomes.

Titles and abstracts were screened by two different persons (CT, YD). Potentially relevant articles were selected for a full-text screening evaluation, which was independently performed by 3 investigators (CT, YD, FP). Discrepancies were resolved by the corresponding and senior authors (CT, FP).

Data Extraction

Were included for further analysis 8 studies[9, 11, 24, 26, 38, 49, 59, 61], containing a total of 2387 patients (table 1). The flow-chart describing the study selection is displayed in figure 1. Moreover and by microsurgical technique, one study concerns only microscopic transsphenoidal approach, 1 both techniques and the remaining six only endoscopic approaches (please see table 1 for further details).

Extracted data included study characteristics, such as publication year, sample size, resection rate, postoperative complication rates (and their subsequent description), type of surgery, clinical improvement after the intervention, reintervention rates.

The cut-off of the "elderly" population has varied from one study to another, being defined as either 65, 70, 75 and 80 years. For consistency reasons, the funnel-plots (see below) were performed for patients having the same cut-off. Data extraction was conducted, as stated by the 2 investigators (CT, YD) and discrepancy was resolved by the senior author (FP).

The analyzed outcomes were: resection rates, overall complication rates (1-cranialmeningitis, hematoma, 2-sinus related-infection, epistaxis, 3-medical, 4-visual), panhypopituitarism, diabetes insipidus, CSF leak, visual improvement and recurrence (with eventual second surgery).

Data Analysis

First data analysis using RevMan and fixed effects methodology

For all nonrandomized studies, the generic inverse variance method and fixed effects model in Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) were used to pool data. The outcome measures used the OR and 95% confidence intervals, which were estimated using the hazard ratio meta-analysis toolbox[45].

Second data analysis using OpenMeta (Analyst) and random-effects model

Due to the high variation in study characteristics, a second statistical analysis was performed. The former included a binary random-effects model (DerSimonian-Laird method) We used OpenMeta (Analyst) from the Agency for Healthcare Research and Quality. Pooled estimates using meta-analytical techniques were obtained for all the outcome previously described.

Statistical heterogeneity

In the context of the present study, it is important to undeline the statistical heterogeneity, which is a consequence of clinical or methodological diversity, or both, among the selected reports. Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect due to random error alone. This is the reason why the data analysis was performed using two different types of statistical analysis.

Results

The overall median follow-up period was 33.2 months (mean 39.5, range 15.5-85.2). The median follow-up for the younger population was 35.5 months (mean 46.2, range 15.5-85.2) and for the elderly one was 32 months (mean 33.2, range 16.9-62.4) (p>0.05).

Resection rates (figure 2)

The median overall resection rates for the younger population was 70.7% (mean 68.8%, range 54-76.8) and for the elderly one was 65.7% (mean 59.2, range 16.6-78.2) (two sample t test, p=0.35).

RevMan funnel plots were possible for 3 different comparisons, respectively less and more than 65, 70, and 80, with all situations including 2 studies.

For the age groups of less versus more than 65 and 70, there was no statistically significant difference. In fact: for less versus more than 65 the p values was 0.16, with OR= 1.31 (CI 0.90, 1.89); for less versus more than 70 the p values was 0.37, with OR= 0.8 (CI 0.49, 1.30).

There was a statistically significant difference for gross total resection rates (GTR) favoring patients aged less than 80, with a p value of 0.01 and OR 3.37 (CI 1.33, 8.56).

Recurrence rates (figure 2)

The median overall recurrence rates for the younger population was 12.3% (mean 14.2%, range 1-32) and for the elderly one was 3.7% (mean 5.4, range 1.3-13) (two sample t test, p=0.27).

For the age groups of less versus more than 65 and 70, there was no statistically significant difference. In fact: for less versus more than 65 the p values was 0.08, with OR= 12.29 (CI 0.91, 5.76); for less versus more than 70 the p values was 0.35, with OR= 1.74 (CI 0.55, 5.5).

Postoperative visual improvement (figure 3)

The median overall visual improvement rates for the younger population was 81.3% (mean 78.8%, range 36.7-93.8) and for the elderly one was 86.6% (mean 85.3, range 78.5-91.7) (two sample t test, p= 0.46).

For the age groups of less versus more than 65, there was no statistically significant difference in visual improvement, with a p value of 0.25 and a OR of 1.29 (0.84-1.97).

For the age groups of less versus more than 70 only one series reported their result (table 1).

There was a statistically significant difference for visual improvement favoring patients aged more than 80, with a p value of 0.03 and a OR 0.27 (CI 0.08, 0.87). Using binary random effects, the p value was 0.39 (data from OpenMeta).

Overall complication (except CSF leak) (figure 3)

The median overall complication rates (cranial- meningitis, hematoma, sinus relatedinfection, epistaxis, medical and visual) for the younger population was 4% (mean 6,8%, range 0-33) and for the elderly one was 8% (mean 10,5, range 0-33) (two sample t test, p=0.36).

For the age groups of less versus more than 70, there was a statistically significant difference for the overall complication rate favoring the younger groups: p value was 0.009, with OR=0.38 (CI 0.18, 0.79).

For the age groups of less versus more than 65 or 80, there was no statistically significant difference in the overall complication rate, with a p value of 0.08 and 0.22, respectively and a OR of 0.46 (0.19-1.10) and 0.89 (0.34-2.38), respectively.

Panhypopituitarism (figure 4)

The median panhypopituitarism rates for the younger population was 8% (mean 7,8%, range 2-17) and for the elderly one was 7% (mean 7,9, range 2-20) (two sample t test, p= 0,94).

There was no statistically significant difference for panhypopituitarism rates independently of the compared groups of age: less or more than 65- with a p value of 0.90, OR= 0.23 (CI 0.15, 0.35); less or more than 70- with a p value of 0.92, OR= 0.97 (CI 0.53, 1.77); less or more than 80- with a p value of 0.36, OR= 1.79 (CI 0.52, 6.17).

Diabetes insipidus (figure 4)

The median diabetes insipidus rates for the younger population was 6,5% (mean 6,25%, range 0-16) and for the elderly one was 6% (mean 6,6, range 0-22) (two sample t test, p=0,86)

For the age groups of less versus more than 65, 70 and 80 there was no statistically significant difference. In fact: for less versus more than 65 the p values was 0.20, with HR= 0.75 (CI 0.47, 1.17); for less versus more than 70 the p values was 0.94, with OR= 0.95 (CI 0.29, 3.10); for less versus more than 80 the p values was 0.87, with OR= 1.16 (CI 0.19, 7.05).

CSF leak (figure 5)

The median CSF leak rates for the younger population was 3.5% (mean 4.3%, range 0-9) and for the elderly one was 3% (mean 6.3, range 0-7) (two sample t test, p=0,49)

For the less versus more than 65 the results seem to be favoring the more than 65 but without statistically significant difference the p value was 0.20, with OR= 1.78 (CI 0.70; 4.53)

For the less versus more than 70 the results seem to be favoring the less than 70 but without statistically significant difference the p value was 0.07, with OR=0.40 (CI 0.15; 1.09).

There was a statistically significant difference for CSF leak rates favoring patients aged less than 80, with a p value of 0.003 and a OR= 0.0.09 (CI 0.02, 0.45).

Discussion

To the best of our knowledge, this is the first meta-analysis showing outcome of transsphenoidal surgery for PA in elderly patients versus younger patients. In fact, the results are intriguing and support the use of such approach even for seniors, as their postsurgical

assessment globally show no inferiority as compared to the younger ones. Individually taken, many studies show no statistically significant differences in terms of outcome.

This meta-analysis shows overall results for comparable populations that are further to be discussed on each relevant aspect. The first one is that resection rates for patients aged more than 80's are less important as compared with the younger ones. Recurrence rates were not statistically significantly different among groups after an overall median follow-up period of 33.2 months (mean 39.5, range 15.5-85.2). The second aspect is that visual improvement favor elderly patients in the same age group. This former aspect was not statistically significant while using the random effects methodology. In other words and to overall conclude, even if gross total resection might be lower, their symptomatic recovery is higher. In terms of postoperative complications, they do have more CSF leaks. Of course, it is supposed that these patients have less presurgical comorbidities. For diabetes insipidus, there is no statistically significant difference.

One should remember that with the unique exception of prolactinomas[7, 40, 56], the primary treatment for all other symptomatic PA[8] is surgery[3, 5, 10, 16, 22, 27, 28, 32, 46, 48]. The endocrinological and oncological result following surgery primarily depends on the extensions of the tumor[2, 44]. The majority of the sellar and suprasellar tumors can be treated with surgery only[29]. The endoscopic transsphenoidal approach has as main advantage an enhanced visualization of the sellar and suprasellar structures, while performing improved gross total removal[39, 41], decrease of nasal swelling, avoidance of the use of fluoroscopy[18] and shorter hospital stay[15]. Its major drawbacks are the lack of binocular vision and the narrow nasal corridor. Furthermore, the results in terms of functional recovery, complication rates and biological remission are, in elderly patients, comparable to what has been published in general series. In fact, with regards to postoperative outcomes, gross total removal is achieved for non-functioning PA in 56% to 93% [4, 31, 41] in endoscopic series.

If resection rates for patients aged more than 80's are lower, this is not a problem per se. One aspect is that endoscopy procedures allow easy reoperation. A second aspect is that the approach should be, however, different, between secreting and non-secreting residual PA. For non-functional ones, the primary endpoint remains tumor control and function preservation, especially visual. They are most commonly encountered in this age group and they can be considered as slowly growing lesions. In this context, one could advocate for a wait-and-scan policy for any residual tumor, especially if no aggressive pathological behavior is present[57]. If eventual tumor growth would be observed during follow-up course, repeat resection versus radiation therapy could be than applied. Single fraction radiosurgery, usually

by Gamma Knife (Elekta Instruments, AB, Sweden)[51, 54] could be a valuable option. This type of approach is well tolerated by patients, with high levels of safety and efficacy[6, 14, 52, 53]. Its only limiting factor in terms of therapeutic delivered dose is related to the proximity with the optic apparatus, and the dose received by the former, which should not overpass 8 Gy in older studies[25] or, more recently, more than 12 Gy[36, 47]. In case of larger residual progressive lesions or those invading the optic pathways, hypofractionnated radiosurgery by Leksell Gamma Knife ICON[58] can be used. Functional PA are a different case scenario. Primary endpoints are tumor control, but also biological remission. In this context, a "wait-and-scan" policy might not be the best option. Here, multimodal management is necessary. The remaining options are, beside reintervention, medical therapy or radiation therapy.

Another important aspect is that visual dysfunction may be present at the time of surgical management[60]. With both microscopic and endoscopic techniques, all patients with preoperative visual impairment recover enough vision to resume a normal life, with the unique exception of those having had a long preoperative evolution causing an optic atrophy. Overall, in the current literature, overall postoperative visual improvement or normalization rates are as high 92%, with very little (exceptional even) worsening across some of the large series[20, 23, 41, 55].

The most usual complication of transsphenoidal approach are CSF leaks, reported in 1.2% to 6% of endoscopic series, as compared to 0.9% to 3 % of microsurgical series[4, 20, 23, 30]. This is comparable to what our meta-analysis shows in the analyzed series. Furthermore, people aged more than 80's, had more CSF leaks, yet remaining less than 1%. This risk is amplified in cases of suprasellar and/or parasellar extensions.

A last relevant aspect concerns the risk of endocrinological impairment, such as transient or permanent diabetes insipidus and hypopituitarism. Permanent diabetes insipidus is reported in 1% to 5% in endoscopic series[4, 13, 20, 23, 30, 50]. Postoperative hypopituitarism may be eluded by cautious tumor resection[17] but appears in around 14% of cases[4].

Our meta-analysis has several limitations. The first is the number included in each forest plot (i.e. two studies), for each outcome. To avoid flows related to heterogeneity among age groups, we only included for each analysis populations of similar ages. A second limitation is related to inter-patients variability in the same study and across them. This applies to personal co-morbidities, preoperative characteristiques of PA etc. It also relates to functional or non-functional PA included in the same comparison, for uniformity reasons. A

third limitation is related to the learning curve, with surgeon's experience not being necessary the same among studies. This could potentially have an impact on the extent of resection and postoperative outcomes. A fourth limitation is related to the cut-off of age in these populations. In a context of the increase of the elderly population, how elderly is elderly remains to be further defined. A fifth limitation is related to the molecular profile in individual cases, which might be different. A sixth limitation is the absence of postoperative details concerning the biological remission in functional PA among series. Moreover, both functional and non-functional PA were reported inside the same group of patients. Another potential limitation is that medical comorbidities related to age might have been a limited factor, in some series, biasing the surgical decision. However, how these aspects influence patients selection and outcomes remains to be discussed by further studies. With regards to postoperative visual improvement, the included studies do not detail the preoperative ophtalmological comorbidities, especially in elderly patients. Moreover and in this context, this is one of the limitations with regards to this outcome. Another limitation is the fact that a vast majority of these outcomes have been reported in nonfunctional PA and might be applied only to this particular tumor's profile. Another important aspect is heterogenity in general, which is frequently underestimated in meta-analysis. The present one might present clinical heterogeneity (among the populations of patients included in each study), methodological heterogeneity, which further might bring statistical heterogeneity. However, we tried to overwhelm this limitatiom by using two different approaches. The vast majority of studies included endoscopic approaches. This can be further consider as a limitation of our analysis.

Conclusions

Our present meta-analysis shows GTR rates favoring younger patients. However, recurrence rates remain similar over the mean follow-up period. Transsphenoidal surgery is so considered feasible even in elderly patients. Surgical re-exploration is rather easy by this approach. Additionally, visual improvement favors patients aged more than 80. Overall complications rates favor patients younger than 70's, which might be also related to additional comorbidities, which are naturally, present in seniors. Multidisciplinary management is mandatory for safe and effective pre- and postoperative care. In conclusion, transsphenoidal surgery is safe and effective even for older patients.

Figures:

Figure 1: Prisma 2009 Flow diagram illustrating the study selection
Figure 2: Forest plots for resection rates (A) and for recurrence rates (B)
Figure 3: Forest plots for visual improvement rates (A) and complication rates (B)
Figure 4: Forest plots for panhypopituitarism (A) and diabetes insipidus (B)
Figure 5: Forest plots for CSF leak

Table 1: Series illustration in the present literature

Compliance with Ethical Standards: yes

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Fig. 2 Forest plots for resection rates (A) and for recurrence rates (B)

	< 6	5	>6	5		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			d, 95% CI	
Liu (2015)	781	1035	46	69	44.3%	1.54 [0.91, 2.59]			-	
Zhan (2015)	120	155	119	158	55.7%	1.12 [0.67, 1.89]		-	-	
Total (95% CI)		1190		227	100.0%	1.31 [0.90, 1.89]			•	
Total events	901		165							
Heterogeneity. Chi2 =	0.70, df	= 1 (P	= 0.40);	$ ^2 = 0.9$			0.01	0'1	10	100
Test for overall effect.	Z = 1.41	I(P = 0)	0.16)				0.01		Favours [<65]	100
	<70)	>70)		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Gondim (2015)	212	319	43	55	66.4%	0.55 [0.28, 1.09]			-	
Wilson (2018)	57	81	35	54	33.6%	1.29 [0.62, 2.69]		-	•	
Total (95% CI)		400		109	100.0%	0.80 [0.49, 1.30]		-	-	
Total events	269		78							
Heterogeneity. Chi2 =	2.75, df	= 1 (P	= 0.10);	$ ^2 = 64$	%		0.01	0 1	10	100
Test for overall effect	Z = 0.90	(P = 0)	.37)				0.01		Favours [<70]	100
	<80)	>80)		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Chinezu (2017)	36	49	8	15	65.1%	2.42 [0.73, 8.02]		-		
Fujimoto (2017)	80	150	2	11	34.9%	5.14 [1.07, 24.61]				
Total (95% CI)		199		26	100.0%	3.37 [1.33, 8.56]			-	
Total events	116		10							
Heterogeneity. Chi ² =	0.57, df	= 1 (P	= 0.45);	$ ^2 = 0.9$			0.01	01	10	100
Test for overall effect.	Z = 2.56	5 (P = 0	011				0.01		Favours [<80]	100

	<6	5	>6	5		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
Robenshtok 2014	19	67	5	38	70.2%	2.61 [0.89, 7.69]	1			
Zhan 2015	3	155	2	158	29.8%	1.54 [0.25, 9.34]			-	
Total (95% CI)		222		196	100.0%	2.29 [0.91, 5.76]			-	
Total events	22		7							
Heterogeneity. Chi ² =		= 1 (P	= 0.62);	$ ^2 = 0.9$	6				1 10	
Heterogeneity: Chi ² = Test for overall effect	0.24, df			l ² = 09	8		0.01	0.1 Favours [<65]	1 10 Favours [>65]	100
	0.24, df	7 (P = 0			8	Odds Ratio	0.01	Favours [<65]		100
	0.24, df : Z = 1.77	7 (P = 0	>70	0	Weight		0.01	Favours [<65] Odds	Favours [>65]	100
Test for overall effect	0.24, df Z = 1.77	r (P = 0 Total	>70 Events	0		M-H, Fixed, 95% CI	0.01	Favours [<65] Odds	Favours [>65] s Ratio	100
Test for overall effect Study or Subgroup	0.24, df 2 = 1.77 <70 Events	Total	>70 Events) Total	Weight	M-H, Fixed, 95% CI 0.51 [0.05, 5.02]	0.01	Favours [<65] Odds	Favours [>65] s Ratio	100
Test for overall effect Study or Subgroup Gondim 2015	0.24, df 2 = 1.77 <70 Events 3	7 (P = 0 Total 319	>70 Events 1	0 Total 55 54	Weight 34.9%	M-H, Fixed, 95% CI 0.51 [0.05, 5.02]	0.01	Favours [<65] Odds	Favours [>65] s Ratio	100
Test for overall effect Study or Subgroup Gondim 2015 Wilson 2018	0.24, df 2 = 1.77 <70 Events 3 10	7 (P = 0 Total 319 81 400	0.08) >7(Events 1 3 4	0 Total 55 54 109	Weight 34.9% 65.1% 100.0%	M-H, Fixed, 95% CI 0.51 [0.05, 5.02] 2.39 [0.63, 9.14]	0.01	Favours [<65] Odds	Favours [>65] s Ratio	100

Fig. 3 Forest plots for visual improvement rates (A) and complication rates (B)

		č	I Fore	est pl	lots fo	r visual impro	vemer	nt		
al all college	<65		>65		Sector States	Odds Ratio		Odds		
Study or Subgroup						M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
Liu (2015)	970		61	69	19.7%	1.96 [0.90, 4.26]			-	
Robenshtok (2014)	57	67	33	38	17.2%	0.86 [0.27, 2.74]			1	
Zhan (2015)	126	155	124	158	63.0%	1.19 [0.68, 2.07]		-	-	
Total (95% CI)		1257		265	100.0%	1.29 [0.84, 1.97]		1	•	
Total events	1153		218				20			
Heterogeneity. Chi ² =				12 = 09	6		0.01	0.1	10	100
Test for overall effect:	Z = 1.15	P = 0).25)					Favours [>65]	Favours [<65]	
de marco en	<80	0	>80)		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
Chinezu (2017)	18	49	12	15	90.4%	0.15 [0.04, 0.58]	-	_		
Fujimoto (2017)	125	134	10	11	9.6%	1.39 [0.16, 12.09]				
Total (95% CI)		183		26	100.0%	0.27 [0.08, 0.87]		-		
Total events	143		22				21	0.28		
Heterogeneity. Chi ² =				r = 66	5%		0.01	0.1	1 10	100
Test for overall effect:	2 = 2.19	f(P) = 0	1.031					Favours [>80]	Favours [<80]	
			b For	rest r	olots f	or complicatio	on rate			
	<65		>65			Odds Ratio		Odds	Ratio	
Study or Subgroup					Weight	M-H, Fixed, 95% CI		M-H. Fixed		
Liu (2015)	4	1035	4	69	51.0%	0.06 [0.02, 0.26]	-		,	
Robenshtok (2014)	1	38	0	38	3.3%	3.08 [0.12, 78.02]				_
Zhan (2015)	5	155	7	158	45.8%	0.72 [0.22, 2.32]		-		
Zilan (2015)	5	155		156	43.0%	0.72 [0.22, 2.32]				
Total (95% CI)		1228		265	100.0%	0.46 [0.19, 1.10]		-		
Total events	10		11							
		2(P = 1)		= 79%		F .		+		
						(0.1 1	10	100
Heterogeneity: Chi ² = Test for overall effect		'P = 0.0						Favours [<65]	Favours (>65)	
		(P = 0.0	8)						aroust col	
			>70)	_	Odds Ratio		Odds		
Test for overall effect.	Z = 1.74 (<70 Events	D Total	>70		Weight	Odds Ratio M-H, Fixed, 95% CI		Odds		
Test for overall effect.	Z= 1.74 (D	>70		Weight 46.7%			Odds	Ratio	
Test for overall effect Study or Subgroup Gondim (2015)	Z = 1.74 (<70 Events	D Total	>70 Events	Total		M-H, Fixed, 95% CI		Odds	Ratio	
Test for overall effect Study or Subgroup Gondim (2015) Wilson (2018)	Z = 1.74 (<70 Events 15	0 Total 319 81	>70 Events 6	Total 55 54	46.7% 53.3%	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03]		Odds	Ratio	
Test for overall effect Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI)	Z = 1.74 (<70 Events 15 6	0 Total 319	>70 Events 6 10	Total 55 54	46.7%	M-H, Fixed, 95% CI 0.40 [0.15, 1.09]		Odds	Ratio	
Test for overall effect Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI) Total events	Z = 1.74 (<70 Events 15 6 21	0 Total 319 81 400	>70 Events 6 10	Total 55 54 109	46.7% 53.3% 100.0%	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03]		Odds M-H, Fixe	Ratio	
Test for overall effect Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² =	Z = 1.74 (Events 15 6 21 0.03, df	0 Total 319 81 400 = 1 (P	>70 Events 6 10 16 = 0.86);	Total 55 54 109	46.7% 53.3% 100.0%	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03]	0.01	Odds M-H, Fixe	Ratio d, 95% Cl	100
Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity. Chi ² =	Z = 1.74 (Events 15 6 21 0.03, df	0 Total 319 81 400 = 1 (P	>70 Events 6 10 16 = 0.86);	Total 55 54 109	46.7% 53.3% 100.0%	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03]	0.01	Odds M-H, Fixe	Ratio d, 95% Cl	100
Test for overall effect Study or Subgroup Gandim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	Z = 1.74 (Events 15 6 21 0.03, df Z = 2.62 <80	0 Total 319 81 400 = 1 (P 2 (P = C	>70 Events 6 10 16 = 0.861; 0.009) >80	Total 55 54 109 ² = 0%	46.7% 53.3% 100.0%	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03] 0.38 [0.18, 0.78] Odds Ratio	0.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI 10 Favours [>70] Ratio	100
Test for overall effect Study or Subgroup Gendim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity. Chi ² = Test for overall effect. Study or Subgroup	Z = 1.74 (Events 15 6 21 0.03, df Z = 2.62 <80 Events	D Total 319 81 400 = 1 (P 2 (P = C D Total	>7(Events 6 10 16 = 0.86); 0.009) >8(Events	Total 55 54 109 ² = 0% Total	46.7% 53.3% 100.0% Weight	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03] 0.38 [0.18, 0.78] Odds Ratio M-H, Fixed, 95% CI	0.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI	100
Test for overall effect Study or Subgroup Gendim (2015) Wilson (2018) Total (95% CI) Total (95% CI) Total vents Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Chinezu (2017)	Z = 1.74 (<70 Events 15 6 21 0.03, df Z = 2.62 <80 Events 16	D Total 319 81 400 = 1 (P 2 (P = C D Total 49	>7(Events 6 10 16 = 0.86); 0.009) >8(Events 5	Total 55 54 109 ² = 0% Total 15	46.7% 53.3% 100.0% 6 Weight 61.9%	M-H, Fixed, 95% CI 0.40 [0.15, 1 09] 0.35 [0.12, 1 03] 0.38 [0.18, 0.78] Odds Ratio M-H, Fixed, 95% CI 0.97 [0.28, 3 31]	b.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI 10 Favours [>70] Ratio	100
Test for overall effect Study or Subgroup Gendim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Chinezu (2017)	Z = 1.74 (Events 15 6 21 0.03, df Z = 2.62 <80 Events	D Total 319 81 400 = 1 (P 2 (P = C D Total	>7(Events 6 10 16 = 0.86); 0.009) >8(Events 5	Total 55 54 109 ² = 0% Total	46.7% 53.3% 100.0% Weight	M-H, Fixed, 95% CI 0.40 [0.15, 1.09] 0.35 [0.12, 1.03] 0.38 [0.18, 0.78] Odds Ratio M-H, Fixed, 95% CI	b.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI 10 Favours [>70] Ratio	100
Test for overall effect: Study or Subgroup Gendim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Chinezu (2017) Fujimoto (2017)	Z = 1.74 (<70 Events 15 6 21 0.03, df Z = 2.62 <80 Events 16	D Total 319 81 400 = 1 (P 2 (P = C D Total 49	>7(Events 6 10 16 = 0.86); 0.009) >8(Events 5	Total 55 54 109 ² = 0% Total 15 11	46.7% 53.3% 100.0% 6 Weight 61.9%	M-H, Fixed, 95% CI 0.40 [0.15, 1 09] 0.35 [0.12, 1 03] 0.38 [0.18, 0.78] Odds Ratio M-H, Fixed, 95% CI 0.97 [0.28, 3 31]	0.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI 10 Favours [>70] Ratio	100
Test for overall effect Study or Subgroup Gandim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	Z = 1.74 (<70 Events 15 6 21 0.03, df Z = 2.62 <80 Events 16	D Total 319 81 400 = 1 (P 2 (P = C D Total 49 150	>7(Events 6 10 16 = 0.86); 0.009) >8(Events 5	Total 55 54 109 ² = 0% Total 15 11	46.7% 53.3% 100.0% 6 <u>Weight</u> 61.9% 38.1%	M-H, Fixed, 95% CI 0.40 [0.15, 1 09] 0.35 [0.12, 1 03] 0.38 [0.18, 0.78] 0.38 [0.18, 0.78] 0.38 [0.18, 0.78] 0.48 [0.18, 0.78] 0.97 [0.28, 3.31] 0.77 [0.16, 3.82]	0.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI 10 Favours [>70] Ratio	100
Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity, Chi ² = Test for overall effect: Study or Subgroup Chinezu (2017) Total (95% CI) Total (95% CI)	Z = 1.74 (Events 15 6 21 0.03, df Z = 2.62 80 Events 16 22 38	D Total 319 81 400 = 1 (P 2 (P = C D Total 49 150 199	>7(Events 6 10 16 = 0.86); 0.009) >8(Events 5 2 7	Total 55 54 109 1 ² = 0% Total 15 11 26	46.7% 53.3% 100.0% Weight 61.9% 38.1% 100.0%	M-H, Fixed, 95% CI 0.40 [0.15, 1 09] 0.35 [0.12, 1 03] 0.38 [0.18, 0.78] 0.38 [0.18, 0.78] 0.38 [0.18, 0.78] 0.48 [0.18, 0.78] 0.97 [0.28, 3.31] 0.77 [0.16, 3.82]	0.01	Odds M-H, Fixe 0.1 Favours [<70] Odds	Ratio d, 95% CI 10 Favours [>70] Ratio	100

Fig. 4 Forest plots for panhypopituitarism (A) and diabetes insipidus (B)

		6	Fore	est p	ots fo	r panhypopitu	litari	sm		
	<65		>65	-		Odds Ratio		Odds Ratio		_
Study or Subgroup	Events	Total		Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl		
Liu (2015)		1035	3	69	26.9%	0.77 (0.23, 2.57)				_
Robenshtok (2014)	7	67	1	38	5.7%	4.32 [0.51, 36.51]				
Zhan (2015)	13	155	15	158	67.4%	0.87 [0.40, 1.90]				
Total (95% CI)		1257		265	100.0%	1.04 [0.56, 1.92]		•		
Total events	55		19							
Heterogeneity: Chi ² =				7%		5	.01	0.1 1	10	1
Test for overall effect.	Z = 0.13 (P = 0.9	0)					Favours [<65] Favours		
	<70)	>70)		Odds Ratio		Odds Ratio		-
Study or Subgroup					Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95%	CI	
Gondim (2015)15	56	319	7	55	46.0%	1.46 [0.63, 3.39]	6			
Wilson (2018)	10	81	11	54	54.0%	0.55 [0.22, 1.40]				
Total (95% CI)		400		100	100.0%	0.07 /0 53 1 77				
Total (95% CI)	66	400	18	109	100.0%	0.97 [0.53, 1.77]		-		
Heterogeneity: Chi ² =		- 1 (9		1	NC		-	_	-	_
Test for overall effect:				1. # 27	70		0.01	0.1 1	10	1
- est tot oretain enteet		8						Favours [<70] Favours	[>70]	
Study or Subgroup	<80		>80		Walaht	Odds Ratio M-H, Fixed, 95% CI		Odds Ratio M-H, Fixed, 95%	C1	
Chinezu (2017)	6	49	1	49		6.70 [0.78, 57.88]		m-n, rixeu, 93/6		_
Fujimoto (2017)	15	150	2	11	79.3%					
10,111010 (2027)	17				12.274	0.50 [0.10, 2.55]		-		
Total (95% CI)		199		60	100.0%	1.79 [0.52, 6.17]			-	
Total events	21		3					1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		
Heterogeneity. Chi ² =	3.81, df		= 0.05);	$ ^2 = 74$	1%		0.01	0'1 1	10	1
	3.81, df		= 0.05);	² = 74	1%		0.01	0.1 Favours [<80] Favours		1
Heterogeneity. Chi ² =	3.81, df	? (P = 0	= 0.05); 0.36)			or diabetes ins	0.00	Favours [<80] Favours		1
Heterogeneity. Chi ² =	3.81, df Z = 0.92	? (P = 0	= 0.05); 0.36) b For	est p		or diabetes ins	0.00	Favours [<80] Favours		1
Heterogeneity: Chi ² = Test for overall effect:	3.81, df Z = 0.92	2 (P = 0	= 0.05); 0.36) b For >65	est p	olots f	Odds Ratio	0.00	Favours [<80] Favours	[>80]	1
Heterogeneity. Chi ² =	3.81, df Z = 0.92 <65 Events	2 (P = 0	= 0.05); 0.36) b For >65	est p	olots f	Odds Ratio M-H, Fixed, 95% CI	0.00	Favours [<80] Favours	[>80]	1
Heterogeneity. Chi ² = Test for overall effect: Study or Subgroup	3.81, df Z = 0.92 <65 Events	2 (P = 0 5 Total	= 0.05); 0.36) b For >65 Events	est p 5 Total	olots fo	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77]	0.00	Favours [<80] Favours	[>80]	1
Heterogeneity. Chi ² = Test for overall effect: Study or Subgroup Llu (2015) Zhan (2015)	3.81, df Z = 0.92 <65 Events 101	7 (P = 0 Total 1035 155	= 0.05); 0.36) b For >65 Events 8	Total	010ts fo Weight 31.9% 68.1%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25]	0.00	Favours [<80] Favours	[>80]	1
Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Liu (2015) Zhan (2015) Total (95% CI)	3.81, df Z = 0.92 <65 Events 101 26	(P = 0 5 Total 1035	= 0.05); 0.36) b For >65 Events 8 35	Total	Weight 31.9%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25]	0.00	Favours [<80] Favours	[>80]	1
Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Uu (2015) Zhan (2015) Total (95% CI) Total events	3.81, df Z = 0.92 <65 Events 101 26 127	5 Total 1035 155 1190	= 0.05); 0.36) b For >65 Events 8 35 43	est p Total 69 158 227	0lots fo Weight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25]	0.00	Favours [<80] Favours	[>80]	1
Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Liu (2015) Than (2015) Total (95% CI) Total events Heterogeneity: Chi ² =	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df	5 Total 1035 155 1190 = 1 (P	= 0.05); .36) b For >65 <u>Events</u> 8 35 43 = 0.75);	est p Total 69 158 227	0lots fo Weight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25]	0.00	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95%	(>80) CI	
Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Liu (2015) Than (2015) Total (95% CI) Total events Heterogeneity: Chi ² =	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df	5 Total 1035 155 1190 = 1 (P	= 0.05); .36) b For >65 <u>Events</u> 8 35 43 = 0.75);	est p Total 69 158 227	0lots fo Weight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25]	sipidu	Favours [<80] Favours	(>80) CI	1
Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Uu (2015) Zhan (2015) Total (95% CI) Total events	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df	5 Total 1035 155 1190 = 1 (P 8 (P = C	= 0.05); .36) b For >65 <u>Events</u> 8 35 43 = 0.75);	est p Total 69 158 227	0lots fo Weight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25]	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95%	(>80) CI	
Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Liu (2015) Than (2015) Total (95% CI) Total events Heterogeneity: Chi ² =	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df Z = 1.28 <70	Total 1035 155 1190 = 1 (P 3 (P = C	= 0.05); 0.36) b For >65 Events 8 35 43 = 0.751; 0.20) >70	est p Total 69 158 227	Weight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17]	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% 0 ^t 1 1 Favours [>65] Favours	CI 10 5 [>65]	
Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Zhan (2015) Total (95% CI) Total (95% CI) Total (95% CI) Total overnis Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Gondim (2015)	3.81, df Z = 0.92 (65) Events 101 26 127 0.10, df Z = 1.28 (70) Events 8	Total 1035 155 1190 = 1 (P 3 (P = C Total 319	= 0.05); 0.36) b For >65 Events 43 = 0.751; 0.20) >70 Events 2	rest p Total 69 158 227 I ² = 09 Total 55	Veight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3.30]	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% 	CI 10 5 [>65]	
Heterogeneity, Chi ² = Test for overall effect: Study or Subgroup Liu (2015) Total (95% CI) Total (95% CI) Total events Heterogeneity, Chi ² = Test for overall effect:	3.81, df Z = 0.92 <53 Events 101 26 127 0.10, df Z = 1.28 <70 Events	5 Total 1035 155 1190 = 1 (P 3 (P = C) Total	= 0.05); 0.36) b For >65 Events 8 35 43 = 0.75); 0.20) >70 Events	rest p Total 69 158 227 1 ² = 09 Total	Veight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.88, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% 	CI 10 5 [>65]	
Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Gendim (2015) Wilson (2018)	3.81, df Z = 0.92 (65) Events 101 26 127 0.10, df Z = 1.28 (70) Events 8	5 Total 1035 155 1190 = 1 (P 3 (P = C) Total 319 81	= 0.05); 0.36) b For >65 Events 43 = 0.751; 0.20) >70 Events 2	est p Total 69 158 227 ² = 09 Total 55 54	Weight 31.9% 68.1% 100.0% 100.0% Weight 59.3% 40.7% 107.1%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3:30] 1.35 [0.24, 7.64]	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% 	CI 10 5 [>65]	
Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (2015) Total events Heterogeneity, Chi ² = Test for overall effect: Study or Subgroup Gendim (2015) Wilson (2015) Total (95% CI)	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df Z = 1.28 <7(Events 8 4	Total 1035 155 1190 = 1 (P 3 (P = C Total 319	= 0.05); .36) b For >65 Events 8 35 43 = 0.75); .20) >70 Events 2 2	est p Total 69 158 227 ² = 09 Total 55 54	Veight 31.9% 68.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3:30] 1.35 [0.24, 7.64]	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% 	CI 10 5 [>65]	
Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (95% CI) Total (95% CI) Total ovents Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Gendim (2015) Wilson (2018) Total (95% CI) Total events	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df Z = 1.28 <70 Events 8 4 12	5 Total 1035 155 1190 = 1 (P 3 (P = C Total 319 81 400	= 0.05); 0.36) b For >65 Events 8 35 - 43 = 0.75); 0.20) >70 Events 2 2 4 4 4 - 4 - 4 - 4 - 4 - 4 - 4	rest p Total 69 158 227 1 ² = 09 Total 55 54 109	Weight 31.9% 68.1% 100.0% Weight 59.3% 40.7% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3:30] 1.35 [0.24, 7.64]	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95%. Favours [>65] Favours Odds Ratio M-H, Fixed, 95%.	ci (>80]	1
Heterogeneitry. Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (2015) Total events Heterogeneitry. Ch ² = Test for overall effect: Study or Subgroup Gendim (2015) Total (95% CI) Total events Heterogeneitry. Ch ² =	3.81, df Z = 0.92 Events 127 0.10, df Z = 1.28 4 12 0.33, df	5 Total 1035 155 1190 = 1 (P 3 (P = C Total 3 19 81 400 = 1 (P	= 0.05); .36) b For >65 <u>Events</u> 8 35 = 0.75); .20) >70 <u>Events</u> 2 2 4 = 0.57);	rest p Total 69 158 227 1 ² = 09 Total 55 54 109	Weight 31.9% 68.1% 100.0% Weight 59.3% 40.7% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3:30] 1.35 [0.24, 7.64]	sipidu	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95%	ci [>80] ci [>65] ci -	1
Heterogeneitry. Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (2015) Total events Heterogeneitry. Ch ² = Test for overall effect: Study or Subgroup Gendim (2015) Total (95% CI) Total events Heterogeneitry. Ch ² =	3.81, df Z = 0.92 Events 101 26 127 0.10, df Z = 1.28 CVENTS 8 4 0.32, df Z = 0.08	$\begin{array}{c} 5 \\ 7 \\ $	= 0.05); .36) b For >63 Events 43 = 0.75); .20) >76 Events 2 2 4 = 0.57); .94)	Total Total 227 Total 5 5 4 109 1 ² = 00	Weight 31.9% 68.1% 100.0% Weight 59.3% 40.7% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3.30] 1.35 [0.24, 7.64] 0.95 [0.29, 3.10]	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Favours [<70] Favours	ci [>80] ci [>65] ci -	1
Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Uiu (2015) Total events Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Gendim (2015) Total events Heterogeneity: Chi ² = Test for overall effect	3.81, df Z = 0.92 <65 Events 101 26 127 0.10, df Z = 1.28 <77 Events 4 4 12 0.33, df Z = 0.08 <80	$\begin{array}{c} 5 \\ \mathbf{Total} \\ 1035 \\ 155 \\ 1190 \\ 0 \\ 7 \\ 7 \\ 190$	= 0.05); .36) b For >65 Events 8 35 -43 = 0.751; .20) >70 Events 2 2 4 = 0.57; .94) >80	Total 5 Total 158 227 Total 55 54 109 1 ² = 00	Weight 31.9% 68.1% 100.0% Weight 59.3% 40.7% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77) 0.71 (0.40, 1.25) 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3.30] 1.35 [0.24, 7.64] 0.95 [0.29, 3.10] Odds Ratio	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o ¹ 1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio	ci ; [>80] ; [>65] ci ; [>65]	1
Heterogeneity: Chi ² = Test for overall effect: Uiu (2015) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup	3.81, df Z = 0.92 Events 101 26 127 0.10, df Z = 1.28 CVENTS 8 4 12 0.33, df Z = 0.08 CVENTS CVENTS	Total 1035 155 1190 - 1 (P) 8 (P = C) Total 319 81 400 = 1 (P) 8 (P = C) Total 400 = 1 (P) 8 (P = C) Total	= 0.05); .36) b For >65 Events 35 43 = 0.75); .20) >70 Events 2 2 4 = 0.57); .94) >80 Events 2 2 2 2 2 2 2 2 2 2 2 2 2	est p Total 227 Total 55 54 109 Total 109 Total	Weight 31.9% 68.1% 100.0% 59.3% 40.7% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 [0.38, 1.77] 0.71 [0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 [0.14, 3.30] 1.35 [0.24, 7.64] 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Odds Ratio M-H, Fixed, 95% Favours [<70] Favours	ci ; [>80] ; [>65] ci ; [>65]	1
Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (2015) Total events Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total events Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Chinezu (2017)	3.81, df Z = 0.92 <52 Events 101 26 127 0.10, df Z = 1.28 (2 = 1.28 (2 = 0.08 3 4 4 2 2 = 0.08 (2 = 0.08 (2 = 0.92) 2 (2 = 0.92) (2	$\frac{5}{1000} \frac{1}{1000} \frac{1}{1000$	= 0.05); .36) b For >65 Events 8 35 -43 = 0.75); .20) >70 Events 2 2 -4 = 0.571; .94) >88 Events -88 Events -88 -88 -88 -88 -88 -88 -88 -8	est p Total 69 158 227 Total 55 54 109 1 ² = 09 Total 109 1 ² = 09 Total 109 158	Weight 31.9% 68.1% 100.0% * Weight 59.3% 40.7% 100.0% * weight 59.3% 40.7% 100.0% *	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI 1.24 (0.13, 12.07)	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o ¹ 1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio	ci ; [>80] ; [>65] ci ; [>65]	1
Heterogeneity: Chi ² = Test for overall effect: Uiu (2015) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup	3.81, df Z = 0.92 Events 101 26 127 0.10, df Z = 1.28 CVENTS 8 4 12 0.33, df Z = 0.08 CVENTS CVENTS	Total 1035 155 1190 - 1 (P) 8 (P = C) Total 319 81 400 = 1 (P) 8 (P = C) Total 400 = 1 (P) 8 (P = C) Total	= 0.05); .36) b For >65 Events 35 43 = 0.75); .20) >70 Events 2 2 4 = 0.57); .94) >80 Events 2 2 2 2 2 2 2 2 2 2 2 2 2	est p Total 227 Total 55 54 109 Total 109 Total	Weight 31.9% 68.1% 100.0% 59.3% 40.7% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 [0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI 1.24 (0.13, 12.07)	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o ¹ 1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio	ci ; [>80] ; [>65] ci ; [>65]	1
Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (2015) Total events Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total events Heterogeneity, Ch ² = Test for overall effect: Study or Subgroup Chinezu (2017)	3.81, df Z = 0.92 <52 Events 101 26 127 0.10, df Z = 1.28 (2 = 1.28 (2 = 0.08 3 4 4 2 2 = 0.08 (2 = 0.08 (2 = 0.92) 2 (2 = 0.92) (2	$\frac{5}{1000} \frac{1}{1000} \frac{1}{1000$	= 0.05); .36) b For >65 Events 8 35 -43 = 0.75); .20) >70 Events 2 2 -4 = 0.571; .94) >88 Events -88 Events -88 -88 -88 -88 -88 -88 -88 -8	est p <u>Total</u> 69 158 227 <u>Total</u> 55 54 109 <u>Total</u> 15 10 <u>Total</u> 10 <u>15</u> 11	Weight 31.9% 68.1% 100.0% * Weight 59.3% 40.7% 100.0% * weight 59.3% 40.7% 100.0% *	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 (0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.68 (0.14, 3.30) 1.35 (0.24, 7.64] 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI 1.24 (0.13, 12.07] 1.24 (0.13, 12.07] 1.24 (0.13, 12.07] 1.24 (0.13, 12.07] 1.24 (0.13, 12.07] 1.24 (0.13, 12.07] 1.03 (0.05, 19.54)	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o ¹ 1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio	ci ; [>80] ; [>65] ci ; [>65]	
Heterogeneity: Ch ² = Test for overall effect: Uiu (2015) Zhan (2015) Total (2015) Total events Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Gondim (2015) Wilson (2018) Total events Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Chinezu (2017) Total (95% CI) Total events Study or Subgroup Chinezu (2017) Total (95% CI) Total events	3.81, df Z = 0.92 (65) Events 127 0.10, df Z = 1.28 8 8 8 4 12 12, df Z = 0.08 8 8 8 8 8 14 6 10 10 11 12 12, df Z = 0.08 12 12 12, df Z = 0.08 12 12 12, df Z = 0.08 14 4 10 10 10 10	$\begin{array}{c} 5\\ \hline Total\\ 1035\\ 155\\ 1190\\ \hline 8(P=0)\\ \hline Total\\ 319\\ 81\\ 400\\ \hline 8(P=0)\\ \hline Total\\ 400\\ \hline 7\\ Total\\ 98\\ 19\\ 9150\\ 199\\ \end{array}$	= 0.05);	est p Total 69 158 227 Total 55 54 109 Total 15 11 15 11 26	Weight 59.3% Weight 100.0% Weight 63.3% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 (0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI 1.24 [0.13, 12.07] 1.24 [0.13, 12.07] 0.05 [10.05, 19.54]	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o ¹ 1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio	ci ; [>80] ; [>65] ci ; [>65]	1
Heterogeneity: Ch ² = Test for overall effect: Study or Subgroup Liu (2015) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Gondim (2015) Milson (2015) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Chinezu (2017) Total (95% CI) Total (95% CI)	3.81, df df Z = 0.92 <b< td=""><td><math display="block">\begin{array}{c} 5 \\ 7 \\ </math></td><td>= 0.05); > 360 b For > 65 Events 8 3 5 5 2 2 2 2 2 2 2 2 2 2 2 2 2</td><td>est p Total 69 158 227 Total 55 54 109 Total 15 11 15 11 26</td><td>Weight 59.3% Weight 100.0% Weight 63.3% 100.0%</td><td>Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 (0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI 1.24 [0.13, 12.07] 1.24 [0.13, 12</td><td>5.01</td><td>Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o¹1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio</td><td>ci ; [>80] ; [>65] ci ; [>65]</td><td>1</td></b<>	$\begin{array}{c} 5 \\ 7 \\ $	= 0.05); > 360 b For > 65 Events 8 3 5 5 2 2 2 2 2 2 2 2 2 2 2 2 2	est p Total 69 158 227 Total 55 54 109 Total 15 11 15 11 26	Weight 59.3% Weight 100.0% Weight 63.3% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.82 (0.38, 1.77] 0.71 (0.40, 1.25] 0.75 (0.47, 1.17] Odds Ratio M-H, Fixed, 95% CI 0.95 [0.29, 3.10] Odds Ratio M-H, Fixed, 95% CI 1.24 [0.13, 12.07] 1.24 [0.13, 12	5.01	Favours [<80] Favours IS Odds Ratio M-H, Fixed, 95% o ¹ 1 1 Favours [>65] Favours Odds Ratio M-H, Fixed, 95% IS Odds Ratio Odds Ratio Odds Ratio Odds Ratio	ci ; [>80] ; [>65] ci ; [>65]	1

Fig. 5 Forest plots for CSF leak

				Fore	est plo	ts for CSF leal	ĸ			
	Experim	ental	Cont	rol		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	1, 95% CI	
Liu (2015)	61	1035	1	69	23.6%	4.26 [0.58, 31.19]				-
Zhan (2015)	6	155	6	158	76.4%	1.02 [0.32, 3.23]			<u> </u>	
Total (95% CI)		1190		227	100.0%	1.78 [0.70, 4.53]		-	-	
Total events	67		7							
Heterogeneity: Chi2=	1.64. df =	1 (P = 0)	20): F=	39%				1	1	
Test for overall effect							0.01	0.1 1 Favours [65]	10 Favours [>65]	10
	<70)	>70	6		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% CI	
Gondim (2015)	15	319	6	55	100.0%	0.40 [0.15, 1.09]	1		-	
Wilson (2018)	0	81	0	54		Not estimable				
Total (95% CI)		400		109	100.0%	0.40 [0.15, 1.09]	i	-	1	
Total events	15		6					200		
Heterogeneity. Not ap	plicable						0.01	01	10	10
Test for overall effect	Z = 1.75	P = 0	.07)				0.01		Favours [>70]	10
WARNESS AND AND AND	<80)	>80)		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixe	ed, 95% CI	
Chinezu (2017)	0	49	0	15		Not estimable		100	100 C 100 C 100 C	
Fujimoto (2017)	5	150	3	11	100.0%	0.09 [0.02, 0.45]	-			
Total (95% CI)		199		26	100.0%	0.09 [0.02, 0.45]	-			
Total events	5		3							
Heterogeneity. Not ap	plicable						0.01	0 1	10	10
Test for overall effect	Z = 2.93	(P = 0)	.003)				0.01		Favours [>80]	10