

# The extracranial versus intracranial approach in fronthoethmoidal encephalocele corrective surgery a meta-analysis

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# The extracranial versus intracranial approach In frontoethmoidal encephalocele corrective surgery: a meta-analysis

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## Abstract

The debate between the extracranial and the intracranial approach for frontoethmoidal (FEE) encephalocele corrective surgery was not summarized yet. The extracranial approach is traditionally believed being inferior to the intracranial approach, but convincing evidence was missing. To provide robust evidence, we conducted a meta-analysis on the incidence of cerebrospinal fluid (CSF) leakage, its progression to infection, the reoperation to treat the leakage, and the recurrence rate between the two techniques. We performed a meta-proportion pooled analysis and meta-analysis on eligible literature following the recommendation of PRISMA guidelines. The outcome of interest was the incidence of CSF leakage, the CSF leakage that progressed into an infection, the reoperation rate to treat the leakage, and the recurrence rate. We included 28 studies comprising 1793 patients in the pooled prevalence calculations. Of the 28 studies, nine studies describing 730 patients were eligible for meta-analysis. The prevalence of CSF leakage was 8% (95% CI, 0.04–0.12) in the intracranial approach and 10% (95% CI, 0.01–0.23) in the extracranial approach. The subgroup analysis of the intracranial approach showed higher CSF leakage prevalence in the frontal craniotomy approach (9%; 95% CI, 0.03–0.16) than the subfrontal osteotomy (6%; 95% CI, 0.03–0.12). Meta-analysis study revealed a significantly higher risk of CSF leakage (OR 2.82; 95% CI, 1.03–7.72), a higher reoperation rate (OR 5.38; 95% CI: 1.13 – 25.76), and the recurrence rate (RR 4.63; 95% CI, 1.51–14.20) for the extracranial approach. The event of infected CSF leakage (OR 3.69; 95% CI, 0.52–26.37) was higher in the extracranial than intracranial approach without any statistical significance. The extracranial approach was associated with a higher risk of CSF leakage, reoperation rate to treat the CSF leakage, and the recurrence rates. The infected CSF leakage between the extracranial and intracranial approaches showed no significant difference.

**Keywords** Frontoethmoidal encephalocele · Extracranial approach · Intracranial approach · Complications · Meta-analysis

## Introduction

Frontoethmoidal encephalocele (FEE) remains a health problem in many Southeast Asian countries, including Burma, Cambodia, India, Indonesia, and the Philippines, with the prevalence of 1:3.500 to 1:7.500 in the population [22, 37]. It is characterized by a congenital bone defect between the frontal and the ethmoid bones that allow the protrusion of a sac containing brain parenchyma, dura,

and cerebrospinal fluid (CSF). The bony defect location and the prolapsing sac dictate the FEE type as nasofrontal, nasoethmoidal, and nasoorbital [39].

Children with increasing FEE size, impairment of binocular vision, airway problems, and at high risk of infection of the central nervous system should undergo early surgical treatment. The surgical strategy was classified as pure extracranial, intracranial, and combined approach. The combined approach was essentially an intracranial approach to some extent. General agreement exists that the intracranial approach combined with the extracranial approach, when necessary, is the best way to perform the corrective surgery for FEE. The intracranial approach provides a better view of the internal bony defect at the anterior skull base, giving broader and easier access to separate the FEE neck, close the dural, and plug the bone defect. However, it required special equipment to perform an intracranial approach, such as

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neurosurgical and craniofacial surgical sets. A well-equipped facility allows this strategy to be employed. The development of several new techniques to access the anterior cranial fossa without formal or large frontal craniotomy led to the concept of the subcranial approach, which was essentially an intracranial approach and should be classified accordingly [13, 42]. Looking at the facts and the nature of the surgical procedure, we agree to include the subcranial or subfrontal approach as a subgroup under the intracranial category. Including in the subcranial approaches were the Chula, modified Chula technique, minimal wedge craniotomy, and low frontal (subfrontal) osteotomy, to name a few [22, 27, 28, 31]. Their unique surgical nature permits the procedure to be done safely in a limited resources facility at a lower cost.

An extracranial approach alone is traditionally believed inferior to the intracranial approach. It is associated with an increased risk of CSF leakage and subsequent infection of the wound or central nervous system. Several authors, who developed and adopted this technique, claimed that CSF leakage incidence was lower than the initial encounter as the technique evolved. Avoiding the anterior fossa's opening would allow a surgical unit without craniofacial specialty to perform this simple procedure safely. However, convincing scientific evidence for the most appropriate surgical approach is missing.

Despite the techniques applied, CSF leakage remains one of the main complications of corrective surgery for FEE. In particular remote areas with poor hygiene, CSF leakage could lead to meningitis, arachnoiditis, encephalitis, infected pseudomeningocele, and abscess formation. It was not uncommon that the leakage did not stop spontaneously and needed a specific intervention to prevent further complications [1, 12, 21, 26, 32, 40]. The recurrence case was another problem that should be taken into account as it incurred higher costs and another burden of reoperation for the patients. There is no robust evidence reviewing the incidence of CSF leakage between the extracranial and intracranial approaches. This study aims to analyze the incidence of postoperative CSF leakage between the extracranial and intracranial approaches. We also analyzed the CSF leakage rate that turned into an infection, the intervention rate to treat the CSF leakage, and the recurrence rate between the extracranial and intracranial approaches in the corrective FEE surgery.

## Method

### Literature search and identification

This meta-analysis was conducted following the recommendation and guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [19]. The

study was registered in PROSPERO (CRD42021236515) and available for access at [https://www.crd.york.ac.uk/prosp/ero/display\\_record.php?ID=CRD42021236515](https://www.crd.york.ac.uk/prosp/ero/display_record.php?ID=CRD42021236515).

We performed a systematic literature search strategy on PubMed, Google Scholars' databases, and hand-picked reference lists around the PICO format: frontoethmoidal encephalocele (Patient/Population); intracranial (transcranial) approach (Intervention); extracranial (transfacial) approach (Comparison); and CSF leakage (Outcome). An electronic search was carried out by using the following terms: frontoethmoidal AND encephalocele OR encephalomeningocele OR cephalocele AND transfacial AND transcranial AND CSF OR cerebrospinal fluid AND leakage. We put the filter for "human" and "English" to limit the search results. Two investigators (W.S. and P.A.W.S.) systematically and independently assessed against the inclusion and exclusion criteria.

### Selection criteria

The inclusion criteria used for screening all identified articles' eligibility were as follows: (1) patients with frontoethmoidal encephalocele; (2) reported the detail of surgical technique; and (3) reported the number of patients with CSF leakage complications.

As the CSF leakage occurred during the first 2 weeks postoperatively, we included a study that followed up their patients for at least 2 weeks after surgery and reported the treatment needed to address the complication and the time to resolution.

The exclusion criteria applied to studies were as follows: (1) patients with encephalocele other than frontoethmoidal type, including basal and intranasal cavity encephalocele; (2) articles in the form of reviews, case reports, conference abstracts or presentations, editorials, and expert opinions; (3) endoscopic surgery; (4) insufficient data regarding CSF leakage complication; (5) and study that was not written in the English language.

### Data extraction

The full-text article that met the inclusion criteria was then thoroughly reviewed.

Two reviewers (W.S. and P.A.W.S.) independently extracted data from articles with any disagreement resolved by discussion to reach the final consensus. The following data were retrieved: author's name, affiliation country, year of publication, the setting of the surgery, number of patients, description of the surgical technique, occurrence of postoperative CSF leakage, treatment of the CSF leakage, number of infected CSF leakage, and the number of patients with recurrent lesion on follow-up.

The extracranial approach was defined as surgical procedures that did not involve anterior skull base opening to perform internal bony defect reconstruction. Any procedures that touched and rendered corrective surgery for the anterior part of the skull base were classified as the intracranial approach.

We further classified the intracranial approach based on the frontal bone opening into two subgroups: (1) subcranial or subfrontal and (2) pure intracranial or frontal approach. A subfrontal approach was defined as a FEE surgical procedure without any formal frontal craniotomy (opening more than half part of frontal bone) either through transfacial or bicoronal skin incision. Subfrontal osteotomy (opening only 1–2 cm above glabella to access the internal bone defect), subcranial osteotomy, very low frontal osteotomy, minimal wedge frontal osteotomy, and medial orbital bone osteotomy that was utilized in the Chula, modified Chula technique, and other techniques that met the definition were included under a subcranial approach. A frontal approach involved the formal or large frontal craniotomy and broad access to the frontal dura that employed bicoronal skin incision. The classic Tessier's operation, the HULA technique, and other procedures involving conventional frontal craniotomy were considered extensive or frontal approaches.

Postoperative CSF leakage was defined as any CSF leakage from intracranial to extracranial space, including leakage through a skin incision, wound dehiscence, or contained under the skin as pseudomeningocele. Reoperation for CSF leakage was defined as any intervention to treat the CSF leakage that failed with conservative medications, local aspiration and bandaging, and lumbar puncture. The intervention under this category was reopening of the surgical site, dural exploration, and implantation of a shunt (including the theco-peritoneal shunt). The recurrence rate was defined as any relapse that occurred during the follow-up period.

### Data analysis

Data were assessed for their quality to be included in the analysis. Descriptive analysis of the included studies was presented for all eligible studies, including those that were impossible to render in meta-analysis.

Studies that met the criteria for quantitative synthesis were undergone meta-analysis, which was carried out using the RevMan version 5.4.1 (the Cochrane Collaboration, 2020) and STATA 14 statistical software (StataCorp, College Station, Texas). Pooled proportion analysis of outcome (CSF leakage complication) for specific subgroups (subcranial and pure intracranial approach) was transformed using the Freeman-Tukey variant of the arcsine square and then combined using DerSimonian-Laird random-effects meta-analyses. A Mantel-Haenszel method for dichotomous data was employed to measure odds ratio (OR) with 95%

confidence interval. The inconsistency index ( $I^2$ ) statistic was conducted to estimate the percentage of heterogeneity across all studies, with values > 50% or p-value < 0.01 considered as substantial heterogeneity. The quality of nonrandomized studies included in the meta-analysis was assessed against the Newcastle–Ottawa Scale (NOS) by awarding stars in each domain, which justified selection, comparability, and outcome [41]. The risk of publication bias and the small sample effect of the nonrandomized study were evaluated using the risk of bias in nonrandomized studies of interventions (ROBINS-I) tool [36]. Regression-based Egger's test was employed to evaluate the risk of publication bias and small study effect.

## Results

### Search results

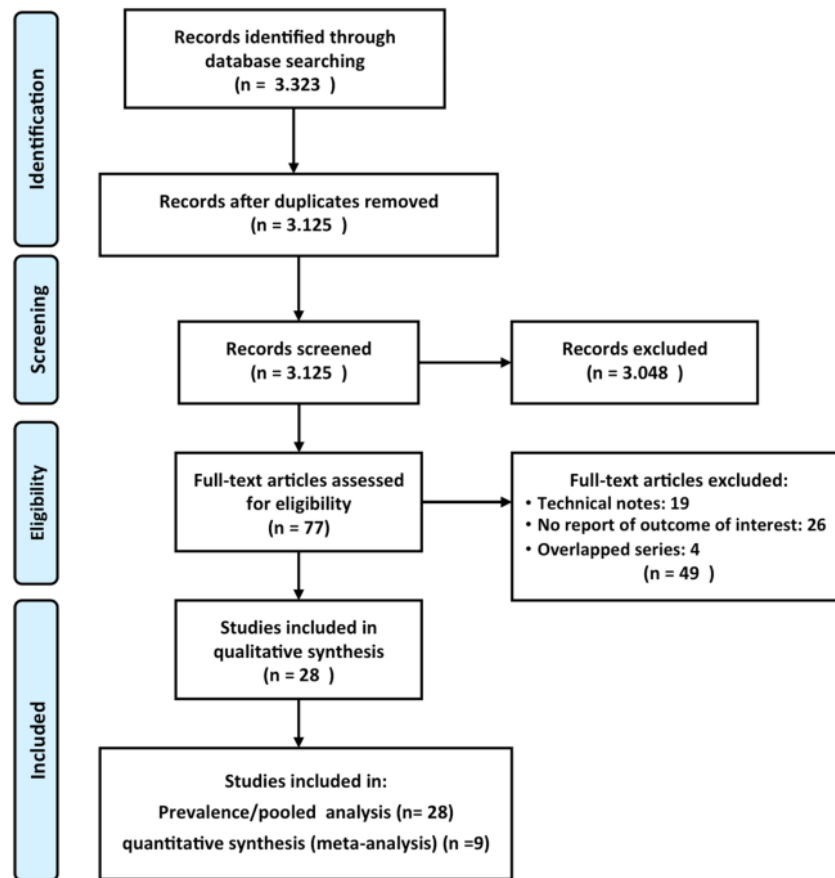
The summary of article selection for review is provided in Fig. 1. Initial database search results identified 3.323 records, which were then imported into reference manager software to filter duplicate articles. A total of 3.125 articles underwent title and abstract screening after removing duplicate articles. We excluded 3.048 articles that did not meet inclusion criteria such as case reports, review/editorial/letter, encephalocele other than frontoethmoidal, CSF leakage due to other etiology, and endoscopic surgery. Seventy-seven articles were selected for further eligibility thorough review. A thorough appraisal of these studies led to the elimination of 49 studies: 19 technical notes without the detail of patients and outcome of interest reported, 26 studies due to no outcome of interest reported, and four studies with an overlapped report (reported in several publications with the overlapped range of years at the same institution). Thus, a total of 28 studies were included in the incidence pooled analysis [1, 2, 6–9, 11–13, 16–18, 20–22, 24, 26–33, 35, 38, 40, 43], and 9 out of 28 studies were eligible for meta-analysis [1, 2, 6, 9, 17, 29, 30, 33, 38]. We reviewed one publication's raw data from our institution to retrieve the surgical detail and the outcome. According to the NOS scale, all studies had enough quality to be included in the pooled analysis and meta-analysis. The publication bias assessed using ROBINS-1 was presented as a traffic light visual plot (Fig. 2).

### Study population

The characteristic of the patients and studies is summarized in Table 1. A total of 1793 patients were included. The cohorts varied between 7 and 400 patients, with a median of 22 for individual study. The pure extracranial approach was used in 20% of study populations, while the



**Fig. 1** PRISMA flowchart for article selection



intracranial approaches consisted of 30% frontal craniotomy and 50% subcranial osteotomy. The length of surgery and the size of the lesion were reported in less than 50% of the studies. The amount of blood loss was not reported in almost all study except in three studies [24, 27, 28]. Follow-up time was varied from 2 weeks to 19 years. Most of the cases were followed up between 2 to 5 years.

The studied literature reported that most of the CSF leakage occurred immediately or in the early postoperative period, which in surgical term was within the first 24 h and during the hospitalization (1–7 days). Shokunbi reported the CSF leakage on day 1 and resolved spontaneously at day 4 [33]. In our series of 400 patients, the CSF leakage occurred within the first 2 weeks, with the peak at the first week postoperatively. We never found a late CSF leakage beyond the first-month follow-up [1]. The CSF leakage was stopped spontaneously or responded well to the first-line treatment (i.e., bed rest, acetazolamide, tight bandaging, multiple aspirations, or lumbar drainage) within 2 weeks [1, 12, 26, 27, 32, 35, 43]. The reoperation was warranted for persistent CSF leakage beyond 2 weeks

after the surgery. Dutta reported one infected CSF leakage case that occurred on day 8 after surgery [9]. Other authors did not state the exact onset of infection after the first day of CSF leakage.

The onset of recurrence varied from 2 months to 2.5 years, with the peak of onset in 3 to 4 months after surgery. Heiderkrueger et al. and Oucheng et al. reported a high recurrence rate (6 and 7%) during the 11 months and 4 months of follow-up, respectively [12, 26]. Our series found 7 recurrence cases (1.75%) between 3 and 6 months of follow-up [1]. Several patients in Holm's and Suwanwela's series came back due to the recurrence mass 2 years after the first surgery [13, 38].

## Meta-analysis

### Prevalence of CSF leakage

The weighted proportions for the prevalence of CSF leakage complications (the intracranial and extracranial approaches) are presented in Fig. 3A and B. In detail, the overall

**Fig. 2** Summary risk of bias for each included study based on ROB-INS-1 tool

weighted proportion of CSF leakage prevalence in the intracranial approach calculated by random-effects modeling was 8% (95% CI, 0.04–0.12;  $p < 0.01$ ;  $I^2 = 77.46\%$ ). The subgroup analysis of the intracranial approach showed the weighted proportion of CSF leakage prevalence was higher in the frontal craniotomy approach (9%; 95% CI, 0.03–0.16;  $p < 0.01$ ;  $I^2 = 74.58\%$ ) than the subfrontal osteotomy (6%; 95% CI, 0.03–0.12;  $p < 0.01$ ;  $I^2 = 79.76\%$ ) (Fig. 3A). The overall weighted proportion of CSF leakage prevalence in the extracranial approach was 10% (95% CI, 0.01–0.23;  $p < 0.01$ ;  $I^2 = 64.39\%$ ) (Fig. 3B). Regression-based Egger’s test confirmed no small study effects and publication bias in the intracranial group ( $p = 0.287$ ) and extracranial group ( $p = 0.340$ ).

A meta-analysis of postoperative CSF leakage complications was conducted in nine studies [1, 2, 6, 9, 17, 29, 30, 33, 38] comprising 730 patients. The rate of CSF leakage in the extracranial approach was 10/88 (11%), and it was 27/642 (4%) in the intracranial approach. The meta-analysis result revealed a significantly higher risk of CSF leakage from the extracranial approach (OR 2.82; 95% CI, 1.03–7.72;  $p = 0.04$ ;  $I^2 = 16\%$ ) (Fig. 4). The  $I^2$  statistic of 16% indicated no significant heterogeneity. No small study effects and publication bias were detected by Egger’s test ( $p = 0.709$ ).

**Infected CSF leakage**

A meta-analysis of postoperative CSF leakage that turns into infection was carried out in three studies [6, 9, 29] with 42 patients. The CSF leakage event that turned into infection was higher in the extracranial than intracranial approach without any significant difference (OR 3.69; 95% CI, 0.52–26.37;  $p = 0.19$ ;  $I^2 = 0\%$ ) (Fig. 5). The  $I^2$  statistic of 0% indicated no heterogeneity between studies. No small study effects and publication bias were identified by Egger’s test ( $p = 0.935$ ).

**Reoperation rate to treat CSF leakage**

A meta-analysis of postoperative CSF leakage that needed revision surgery or other interventional procedure was done for five studies [1, 2, 6, 29, 30] of 591 patients. The results showed that the event of repair surgery in the extracranial approach was significantly higher than the intracranial one (OR 5.38; 95% CI, 1.13–25.76;  $p = 0.04$ ;  $I^2 = 39\%$ ) (Fig. 6). No small study effects and publication bias were found on Egger’s test ( $p = 0.305$ ). Sensitivity analysis by removing Czech et al. study reduced the heterogeneity to zero and reached the significant difference (OR 8.98; 95% CI, 2.69–29.97;  $p = 0.0004$ ;  $I^2 = 0\%$ ).

	Confounding bias	Bias in classification of intervention	Missing data	Bias in measurement of outcomes	Selective reporting	Overall bias
Arifin 2018	+	+	+	+	+	+
Arshad 2008	?	+	+	+	+	+
Czech 1995	?	-	+	?	-	-
David 1984	?	+	+	+	+	+
Dhawan 1982	?	+	+	?	?	+
Dutta 2010	-	-	+	?	+	?
Hassanein 2016	?	+	+	+	+	+
Heiderkruger 2017	+	+	-	-	?	?
Holm 2008	?	+	+	?	+	+
Kumar 2009	?	+	+	+	+	+
Leelanukrom 2007	+	+	+	-	-	?
Lello 1989	?	+	+	?	?	?
Macfarlane 1995	+	+	+	+	+	+
Mahapatra 2011	-	+	?	?	+	?
Mahatumarat 2003	?	+	?	?	?	?
Marshall 2017	+	+	+	?	?	+
Oucheng 2010	+	+	+	?	+	+
Pascasio 2019	+	+	+	+	+	+
Pinzer 2006	?	+	-	-	?	-
Rahman 1979	+	+	+	+	+	+
Rapport 1981	?	+	+	+	+	+
Rifi 2015	-	+	?	?	?	-
Rojvachironanda 2006	+	+	+	+	+	+
Roux 2007	?	+	+	?	+	+
Shokunbi 1988	?	+	-	?	-	?
Songur 1999	?	+	-	-	?	?
Suwanwela 1966	?	+	?	+	+	+
Zabsonre 2014	+	+	+	+	+	+

**Table 1** Summarized characteristic of included studies

Study characteristic	All studies	Meta-analysis
Study design		
Retrospective	28	9
Number of patients included	1793	730
Number of patients in individual study	8–400	8–400
Gender distribution		
Male	876 <sup>a</sup>	360
Female	837 <sup>a</sup>	370
Age at presentation		
Mean	5.5 years old <sup>b</sup>	3.7 years old
Range	1 day to 38 years old <sup>b</sup>	7 days to 32 years old
Type of FEE <sup>c</sup>		
Nasofrontal (NF)	349 <sup>c</sup>	102 <sup>g</sup>
Nasoethmoidal (NE)	823 <sup>c</sup>	401 <sup>g</sup>
Nasoorbital (NO)	81 <sup>c</sup>	39 <sup>g</sup>
Combined NE-NO	264 <sup>c</sup>	82 <sup>g</sup>
Number of patients based on the approach		
Extracranial	330	88
Intracranial (frontal craniotomy)	528	298
Intracranial (subfrontal osteotomy)	945	344
Size of the lesion	1–40 cm <sup>d</sup>	2.5–25 cm
Surgical time		
Frontal craniotomy	3.5–9 hours <sup>e</sup>	3.83–9 h
Subfrontal osteotomy	2–7 hours <sup>e</sup>	2–3 h
Longest follow-up time <sup>f</sup>		
Less than 6 months	109 patients <sup>f</sup>	101 patients <sup>h</sup>
6–24 months	141 patients <sup>f</sup>	24 patients <sup>h</sup>
24 months to 5 years	760 patients <sup>f</sup>	414 patients <sup>h</sup>
more than 5 years	334 patients <sup>f</sup>	90 patients <sup>h</sup>

<sup>a</sup>Information available for 95% of patients (24 studies)

<sup>b</sup>Information available for 90% of patients (26 studies)

<sup>c</sup>Information available for 85% of patients (21 studies)

<sup>d</sup>Based on the range reported in individual study. Information available for 10 studies

<sup>e</sup>Based on the range reported in individual study. Information available for 11 studies

<sup>f</sup>Information available for 23 studies

<sup>g</sup>Information available for 8 out of 9 studies

<sup>h</sup>Information available for 8 out of 9 studies

There was no statistical difference on the reoperation rate for repairing the CSF leakage between subfrontal osteotomy and frontal craniotomy (OR 0.01; 95% CI, 0.00–0.02;  $I^2 = 1.17\%$ , versus OR 0.00; 95% CI, 0.00–0.01;  $I^2 = 0.00\%$ , for subfrontal osteotomy and frontal craniotomy, respectively;  $p = 0.70$ ) (Fig. 7).

### The recurrence rate

The recurrence rate analyzed from five studies [1, 29, 30, 33, 38] of 480 patients showed a significant higher rate in the extracranial than intracranial approach (RR 4.63; 95%

CI, 1.51–14.20;  $p = 0.007$ ;  $I^2 = 0\%$ ) (Fig. 8). The  $I^2$  statistic of 0% indicated no heterogeneity between studies. Egger's test resulted in no small study effects and publication bias ( $p = 0.052$ ).

### Discussion

We presented a meta-analysis comparing the extracranial and intracranial approaches for FEE corrective surgery in terms of the incidence of CSF leakage, risk of infection and reoperation rate due to CSF leakage, and the recurrence rate. After a rigorous screening process, 28 studies

were eligible for pooled analysis study, and 9 out of 28 studies were included for meta-analysis. Of these studies, it was evidenced that this disease's setting was mostly in low- and middle-income countries: Myanmar, Cambodia, Indonesia, Philippines, Malaysia, Thailand, Nigeria, Morocco, Burkina Faso, South Africa, Egypt, Pakistan, and India [1–9, 11, 13–18, 20, 24, 27]. The unique geographical and demographical distributions of FEE bring their challenge. In several areas, the orchestra of difficult access to the facility, limited resources health facility, poor hygiene and nutrition, and poverty play essential aspects in managing the patients. The extracranial approach, which avoided anterior fossa opening, offered a simple procedure and would allow without specialized craniofacial surgical units. However, the approach came with the higher risk of CSF leakage [12, 13].

The intracranial approach was further divided into two subgroups: frontal craniotomy and subcranial or subfrontal osteotomy approach. The first subgroup utilizes a formal frontal craniotomy to access the anterior skull base. It has been a mainstay technique in western countries. Broad exposures of the dura, direct access to the bony defect at the anterior skull base and the neck of the encephalocele, and a broader view for bony reconstruction are the advantages of the frontal craniotomy. Nevertheless, they carry several drawbacks such as longer surgical time, the risk of a higher amount of blood loss, and extensive use of disposable materials that incur higher costs [7, 8, 21]. In a one-stage surgery that involved an intracranial approach and orbito-facial reconstruction, the stakes were higher. While some surgeons believed that one-stage surgery in young children prevented the progression of facial deformities and restored binocular vision, others saw things otherwise, especially when looking at the higher risks [20].

At the end of the twentieth century, the Thailand craniofacial team introduced a simple one-stage extracranial repair and reconstruction technique for FEE surgery [22, 23]. This technique offered several advantages: (1) simultaneous correction of bone and soft tissue deformity; (2) good exposure for appropriate dural repair; and (3) more straightforward operation. Later, this technique was known as the Chula technique and was refined as a modified Chula technique [31]. This approach is actually an intracranial approach without formal frontal craniotomy. They access the anterior skull base and the internal bony defect from the subfrontal opening. The lower level of cribriform plate in several frontoethmoidal encephalocele effectively facilitates this access [14, 23]. Several other techniques were then developed to modify and refine this procedure [3, 27]. Recent literature reported using the subcranial technique in a limited resources' area [26–28, 32]. To address the limitation of the frontal craniotomy approach, a subcranial approach came with a shorter surgical time (average of 3 h; range 2–6 h) [1,

17, 22, 26, 27, 31], lower blood loss, and shorter hospital stay (4–7 days) [1, 27].

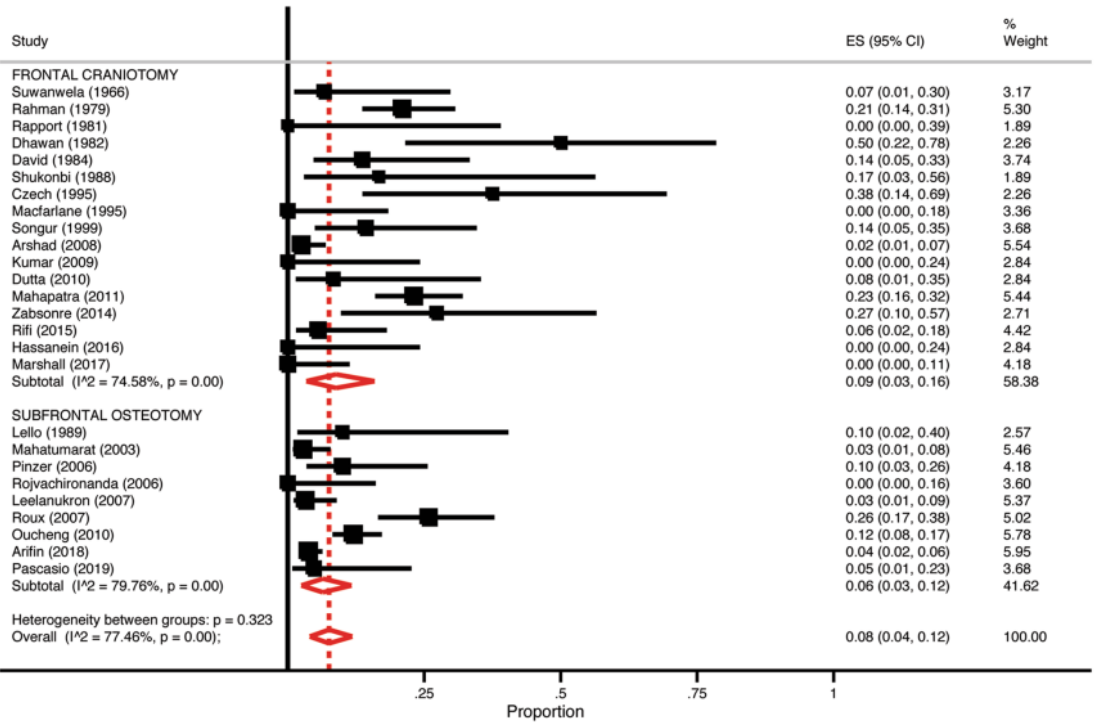
However, the present meta-analysis result revealed that the pure extracranial approach is associated with a higher risk of CSF leakage. Although the surgical techniques for FEE corrective procedures have evolved to provide the best results and lower complication rates, the CSF leakage risk in the pure extracranial approach was three times higher than the intracranial approach. The main factor for the higher prevalence of CSF leakage was the extracranial approach's technical difficulties [13]. The exposure to the encephalocele's neck was restricted by the size of the external bony defect, which in turn limiting the dural closure. As the CSF leaked, it would be hard to manage by conservative treatment alone. The evidence was revealed in the meta-analysis that the event of repair surgery due to CSF leakage was higher in the extracranial approach. CSF leakage might turn into an infection that complicated further treatment. The risk of repair surgery due to CSF leakage in the extracranial approach was five times higher in our meta-analysis study. This factor should be considered when choosing the extracranial approach since it might lead to higher treatment costs and more extended hospital stay and compromise the overall surgical result. The indications for reoperation were persistent leakage for more than 2 weeks, unresponsive to a medical or simple procedure (aspiration, bandaging, or lumbar puncture), and the occurrence of fistula or signs of inflammation around the leakage site [1, 40].

Regarding the reoperation rate for repairing the CSF leakage, there was no statistical difference between subfrontal osteotomy and frontal craniotomy. It means that the safety of the subcranial approach is comparable to the frontal approach. The reoperation rate is an important aspect to consider carefully, especially in limited resource facility settings. The consequences of corrective reoperation were increasing cost, surgical materials, and length of hospitalization. International non-government organizations (NGOs) that conducted the medical and surgical programs in some countries already put every aspect into accounts as they were not available all the time to follow up on the complications that might occur. Nevertheless, the cost was also an important aspect for the NGO. They would choose the simplest, low cost, safe, low complications rate, and teachable to local surgeons without compromising the results [10, 26, 28, 32].

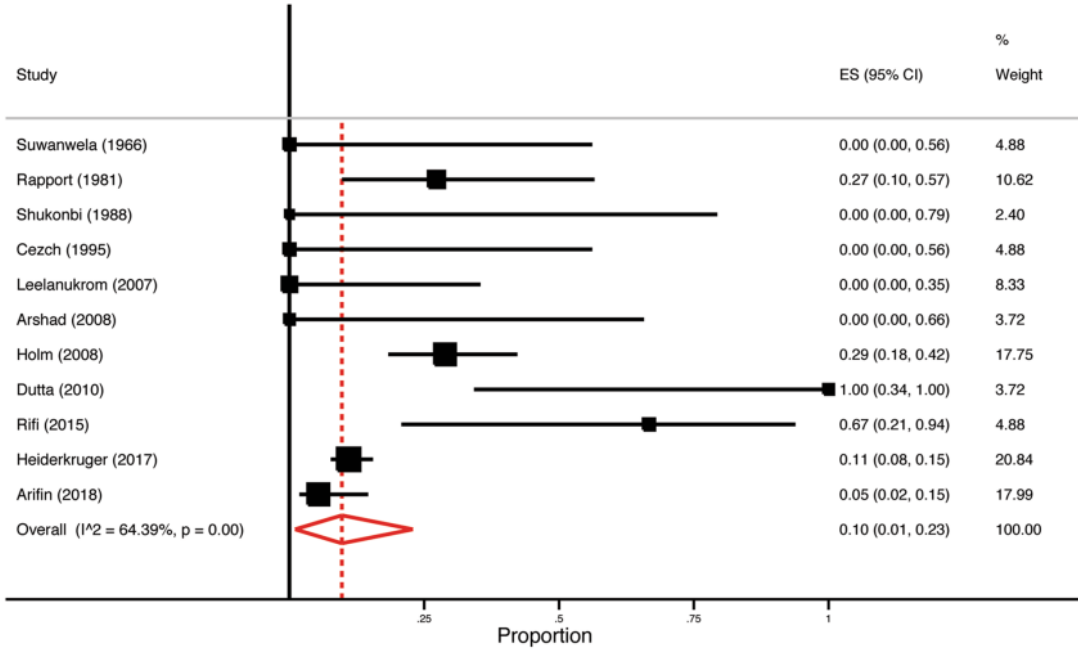
Our study showed no significant difference rate between the extracranial and intracranial approaches concerning the CSF leakage that turned into an infection. It is crucial to consider the rate of infected CSF leakage as it might complicate the operative results and increase the morbidity mortality rate. Prompt treatment of CSF leakage should prevent further complications of an infected wound, CSF fistulas, and intracranial infection.



# A CSF Leakage – Intracranial Approach



# B CSF Leakage – Extracranial Approach



**Fig. 3** Pooled prevalence of CSF leakage in **A** the intracranial approach (Frontal craniotomy, subfrontal osteotomy, and overall); **B** the extracranial approach

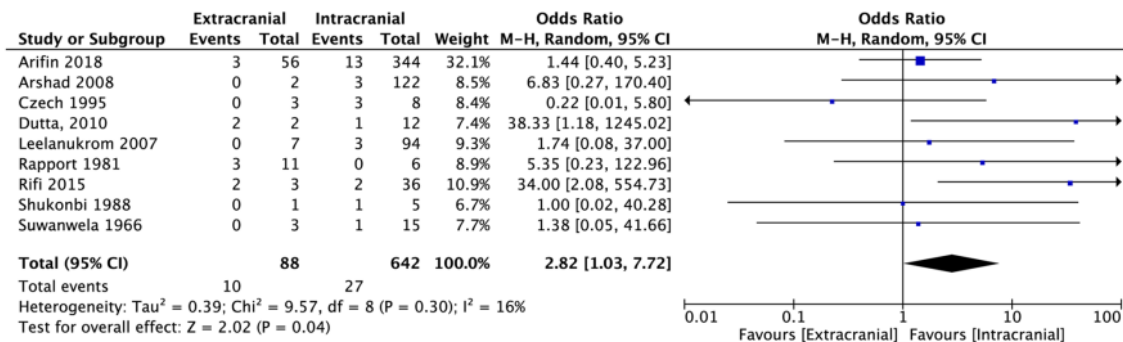
The recurrence rate was slightly higher in the extracranial approach. Heiderkrueger et al. reported the highest recurrence rate (6.1%) during their trip to Yangon, Myanmar [12]. This particular cause was not elaborated in detail except for their technical notes using the pure extracranial technique described by Holm et al. The mortality rate on both approaches was very low (approximate to zero) and showed no significant difference between groups. Frontoethmoidal encephalocele carried a better prognosis than their occipital counterpart [6, 25]. The mortality of occipital encephalocele was as high as 37.5% [15, 25], and the quality of life was significantly lower with respect to the cognitive function and dependency score [4, 34].

Despite the results of this study, the extracranial approach, with some of its advantages, may be utilized in carefully selected patients. Del Campo stratified the encephalocele into three degrees [5]. First-degree FEE has only mild facial distortion that needs no extensive reconstruction. Second-degree FEE is associated with redundant skin and “long nose” appearance that lead to employ transfacial incision. Third-degree FEE needs a comprehensive approach to

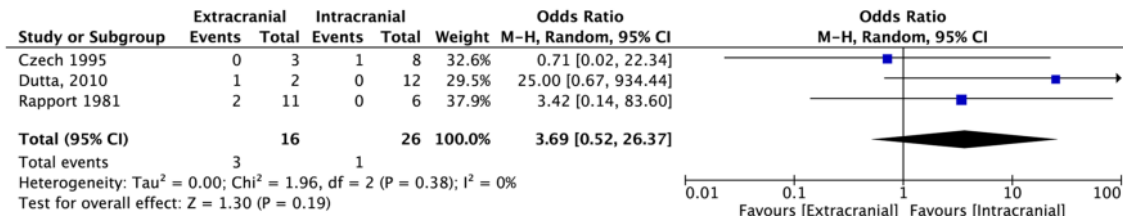
access the intracranial and facial reconstruction. The first-degree and some of second-degree FEE would be benefited from the extracranial approach.

Regarding patient safety, complications prevention, overall best results, and referring the patients to an established craniofacial center abroad incurred a high cost. Sending a patient to an established unit in Singapore (the nearest to Southeast Asian countries) would take up about US\$20,000 for hospital and surgical charges only. While performing the surgery by well-trained local surgeons in a government hospital would only cost US\$300–500 [10]. This expense was comparable to our experience in Indonesia [1]. When complications occurred, the cost was higher, the patient suffered longer, and the surgery results could be unsatisfactory, which caused a psychological burden for the patient. Thus, it is best to send the complex patient to the nearest local facility with a craniofacial team since the overall cost will be lower than the cost of complications, reoperation, and patient psychology.

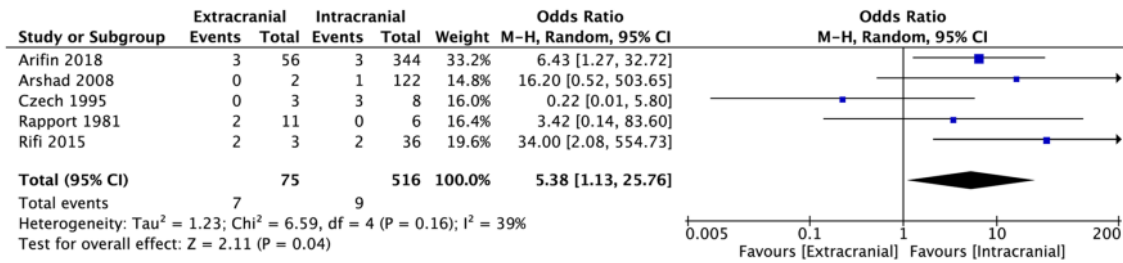
The precise etiology of the disease remains speculative. As the cause of this disease was linked to poverty and poor nutritional status during pregnancy, prevention with folic acid fortification program might help to decline the prevalence. It is wise for a hospital in a high-prevalence area of the disease to invest in well-trained surgeons and



**Fig. 4** Forest plot comparing the event of CSF leakage between the extracranial and intracranial approach with their respective OR (odds ratio) and 95% confidence interval



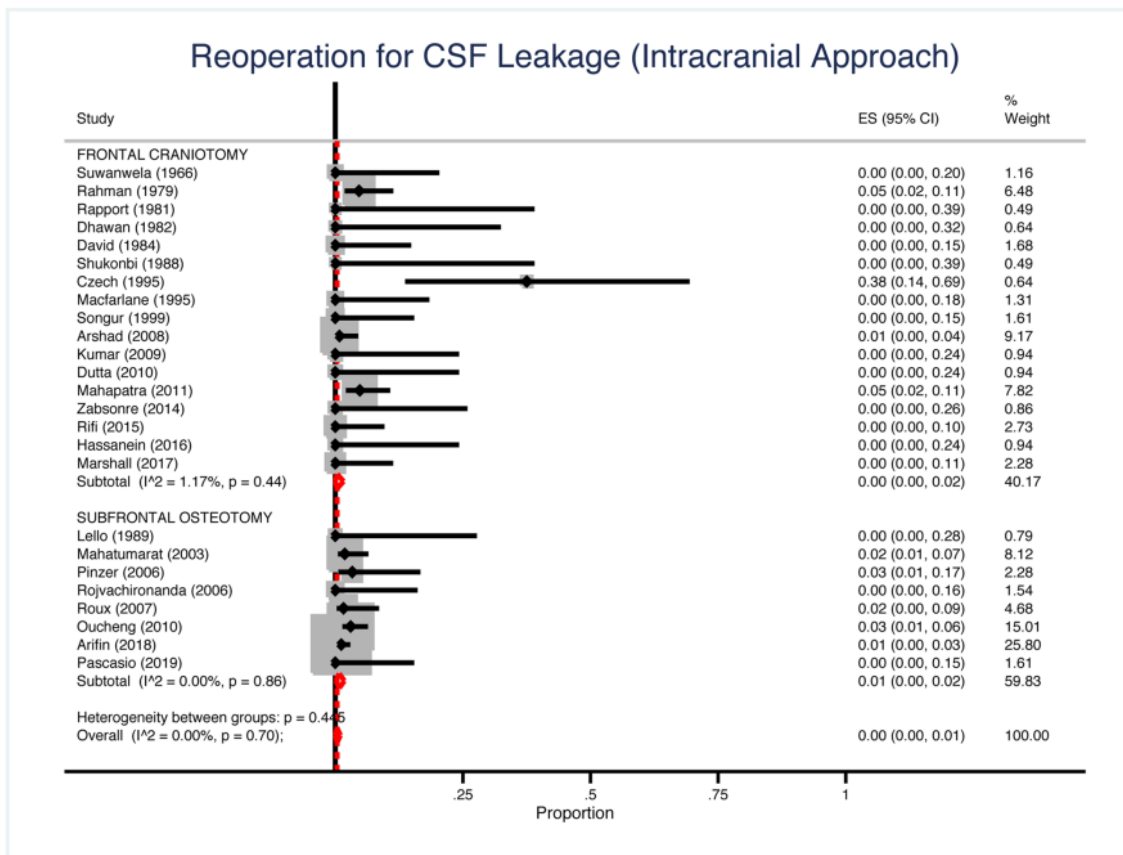
**Fig. 5** Forest plot comparing the event of CSF leakage progressing into infection between the extracranial and intracranial approach with their respective OR (odds ratio) and 95% confidence interval



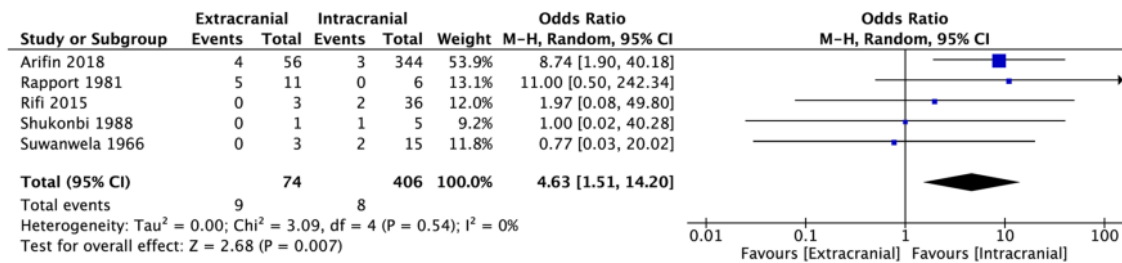
**Fig. 6** Forest plot comparing the reoperation rate to treat CSF leakage between the extracranial and intracranial approach with their respective OR (odds ratio) and 95% confidence interval

surgical equipment for the neurosurgical-craniofacial procedure. When the surgeon and equipment were unavailable at first, a charity program might help to initiate the service. International humanitarian mission in Cambodia was an exemplary instance that succeeded with local surgeons

training, lowered the cost of surgery, and performed surgery and follow-up for the FEE patients [10, 26, 32]. Strict patient selection for surgery based on age, body weight, and urgency should be applied before performing surgery in a limited resource area. Formal surgical training to



**Fig. 7** Pooled analysis of the reoperation rate to treat CSF leakage between the frontal and subfrontal approach with their respective OR (odds ratio) and 95% confidence interval



**Fig. 8** Forest plot comparing the encephalocele recurrence rate between the extracranial and intracranial approach with their respective OR (odds ratio) and 95% confidence interval

familiarize a surgeon with the safe approach for FEE corrective surgery is essential for the long-term availability of skilled surgeons.

### Study limitations

The present study had some limitations. First, despite the 28 studies that were eligible for the pooled analysis, only nine studies were eligible for meta-analysis. Of the nine studies, there was a number of the discrepancy of study participants on each arm. Second, all of the included studies were retrospective studies. The effect of lesion size, age, and the use of additional material on the prevalence of leakage were not well-reported. The condition of the covering skin and dura would give additional information in regard to the CSF leakage. Third, there was a methodological difference to judge the cosmetic results and the need for other repair surgery. While some authors used the Whittaker score, others used a qualitative method for the surgeon and patient satisfaction. Fourth, the authors of the included studies did not detail the exact onset time of the complications to occur, while it could be useful in the clinical setting. Despite the limitations, this meta-analysis provides convincing evidence in the selection of approaches for FEE corrective surgery.

### Conclusion

Despite the inherent limitations in this study, the extracranial approach had a three times higher risk of CSF leakage and was associated with a five times higher reoperation rate to treat the CSF leakage persistent complication. Under the intracranial approach group, the subcranial approach and extensive frontal approach provided a comparable result concerning the prevalence of CSF leakage and reoperation rate. When the CSF leakage occurred, the rate of progression to infection between the extracranial and intracranial approaches showed no significant difference. The recurrence rate was slightly higher in the extracranial approach, but

it failed to reach a significant difference. Referring a complex patient to a nearest established craniofacial unit with expertise in the intracranial approach will help to prevent the complications and overall cost of treatment.

7

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**Author contribution** WS, PAWS, and MAP contributed to the study conception and design. WS and PAWS performed literature search, collection, screening, and analysis. WS, PAWS, and MAP interpreted the results and assessed the risk of bias. WS wrote the draft of the manuscript. All authors critically reviewed, commented, and approved the final manuscript.

**Data availability** Not applicable.

**Code availability** Not applicable.

### Declarations

**Ethics approval** No medical ethical approval was needed for this study.

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**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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