Risk factors for postoperative CSF leakage after endonasal endoscopic skull base surgery: a meta-analysis and systematic review*

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Abstract

Background: Cerebrospinal fluid (CSF) leakage is a complication that any surgeon working in the field of skull base surgery does not wish to encounter. The surgical approach to the skull base often varies, and the various sizes and locations of skull base lesions make it difficult to determine the cause of CSF leakage. However, it is useful to investigate which factors contribute to postoperative CSF leakage.

Methods: Related studies were identified by searching the following databases: PubMed/Medline, Embase, and Web of Sciences through December 2019. Random-effects models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The Newcastle-Ottawa scale was used to evaluate the quality of observational studies.

Results: Our search yielded 56 retrospective cohort studies involving a total of 11,826 skull base surgical procedures. The overall rate of postoperative CSF leakage was 7.2%. The effect of obesity on postoperative CSF leakage had an OR of 1.88, and the effect of perioperative radiotherapy on postoperative CSF leakage yielded an OR of 1.87. High intraoperative CSF flow rate also had a significant OR of 2.98. On the other hand, a pedicled vascularized flap efficiently reduced the risk of postoperative CSF leakage. Defect size and the presence or absence of a lumbar drain had no effect on postoperative CSF leakage.

Conclusions: This comprehensive quantitative assessment of postoperative CSF leakage showed that obesity, perioperative radiotherapy, and high intraoperative CSF flow rate raised the risk of CSF leakage; however, a pedicled vascularized flap can effectively reduce the risk of postoperative CSF leakage.

Level of Evidence: level NA

Key words: cerebrospinal fluid leakage, skull base, obese; radiotherapy, vascularized flap

Introduction

The endoscope was first introduced into the field of sinus surgery in the late 1980s, but the application of this instrument in skull base surgery has been relatively recent [(1)]. The greatest advantage of this technique over transcranial surgery is that it does not lead to brain retraction, resulting in fewer complications and shorter hospital stays, which greatly improves patient quality of life [(2)]. However, the most significant criticism of endoscopic skull base surgery is the risk of cerebrospinal fluid (CSF) leakage and this remains a challenge for skull base surgeons. Understanding the risk factors for CSF leakage after endoscopic skull base surgery is important to surgeons. A high body mass index (BMI) could impair venous drainage because of increased intraabdominal and thoracic pressure, therefore, obesity

is generally considered to be a risk factor for postoperative CSF leakage [3]. However, a recent study showed no correlation between obesity and the rate of CSF leakage [4]. A larger defect size induced more postoperative CSF leakage in one study [5], whereas another study reported that there was no correlation between defect size and postoperative CSF leakage [6]. A lumbar drain can be applied to reduce postoperative CSF leakage, but its efficiency has been considered debatable among several studies [4,7,8]. Vascularized flaps, introduced to prevent skull base defects, are known to prevent significant postoperative CSF leakage; however, results of their ability to reduce postoperative CSF leakage are also discordant [9,10].

These variable and inconclusive results might be the result of heterogenous inclusion criteria and small sample sizes. In addition, there is no comprehensive meta-analysis of the factors influencing CSF leakage after endoscopic skull base surgery. Therefore, we aimed to systematically review the potential risk factors such as radiation history, defect size, the presence of obesity, use of CSF diversion, or the application of vascularized flaps.

Materials and methods

Search strategy

Two investigators (JSK, SDH) independently searched all of the relevant studies published to November 2019 in the PubMed/Medline, Embase, and Web of Science databases. The search details for PubMed/Medline were as follows: (("skull base"[MeSH Terms] OR ("skull"[All Fields] AND "base"[All Fields]) OR "skull base"[All Fields]) AND ("cerebrospinal fluid leak"[MeSH Terms] OR ("cerebrospinal"[All Fields] AND "fluid"[All Fields] AND "leak"[All Fields]) OR "cerebrospinal fluid leak"[All Fields])) AND (("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "operation"[All Fields]) OR ("reconstructive surgical procedures"[MeSH Terms] OR ("reconstructive"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "reconstructive surgical procedures"[All Fields] OR "reconstruction"[All Fields])). We used similar key terms to search the other databases.

Selection of literature

The definition of skull base surgery or reconstruction included the following conditions: skull base tumor, preoperative or intraoperative CSF leakage, and cystic lesions. Skull base tumors included craniopharyngioma, meningioma, pituitary adenoma, chordoma, neuroblastoma, germinoma, etc, and cystic lesions included arachnoid cyst, Rathke's cyst, and encephalocele. The inclusion criteria were as follows: 1) studies mentioning CSF leakage after skull base surgery or reconstruction; 2) studies including data on endonasal endoscopic surgery; 3) prospective or retrospective studies; 4) studies dealing with a human

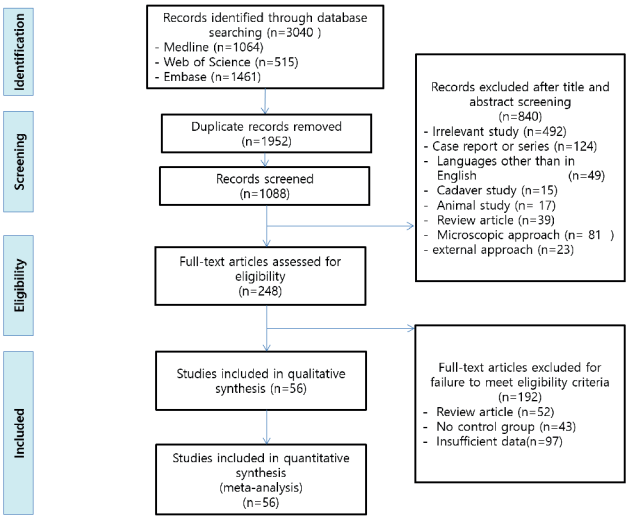

Figure 1. Flow chart for identification, screening, and eligibility of the studies included in this meta-analysis (n=number of studies).

population.

The exclusion criteria were as follows: 1) spontaneous CSF leakage; 2) no data regarding CSF leakage; 3) language other than English; 4) review article; 5) case report; 6) cadaver or animal study; 7) skull base surgery through an external or microscopic approach; 8) studies without relevant data.

Data extraction

Relevant data were collected by the two authors independently. Any discrepancy between the two authors was discussed until agreement was reached. The following information was collected from each paper: publication year, author names, study setting, method of surgical approach, age, sex, body mass index, size of defect, CSF leakage flow rate, use of vascularized flap, presence or absence of a lumbar drain, and perioperative radiotherapy. High flow CSF leakage was taken to include those cases mentioned in the original article as having high flow as well as the following cases: 1) all craniopharyngioma; 2) tuberculum sella, planum or olfactory groove meningioma; 3) intradural clival chordoma. Pituitary adenoma was considered to be low flow unless otherwise noted. To minimize selection bias, we only analyzed the efficacy of vascularized flaps in patients with intraoperative CSF leakage. In the case of pituitary adenoma, intraoperative CSF leakage was rare, and vascularized flaps were rarely used, so these cases were excluded from the analysis of vascularized flaps.

Methodological quality

For non-randomized controlled trials, the Newcastle-Ottawa score was used to assess methodological quality. A maximum of 9 stars was attainable. The Cochrane risk of bias tool was applied to assess the quality of randomized controlled trials (RCT).

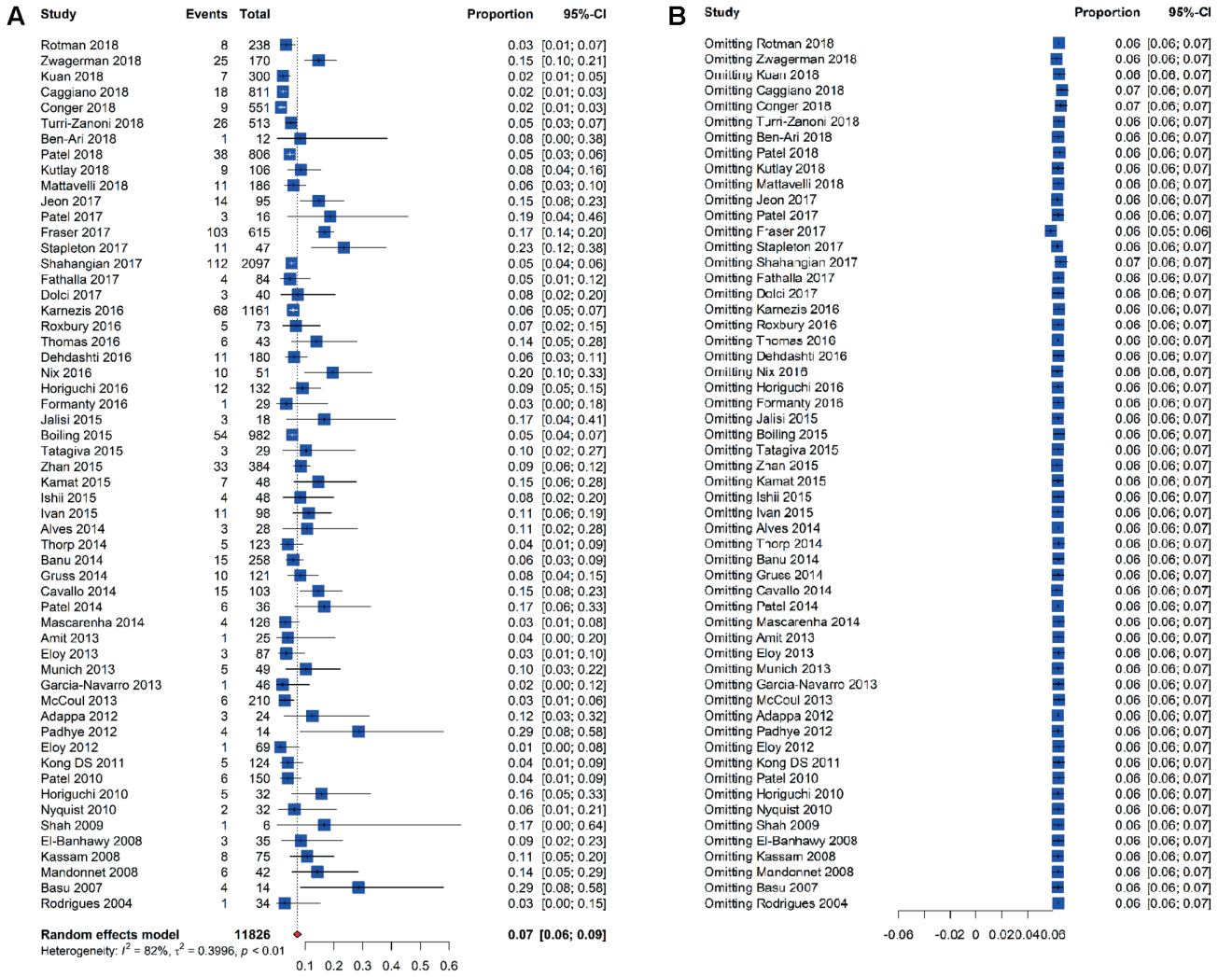

Figure 2. A) Forest plot of overall rate of CSF leakage after skull base surgery using single proportion analysis. B) Sensitivity analysis according to publication year.

Statistics

A meta-analysis of the selected studies was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). We also used Comprehensive Meta-Analysis software (version 2.0, Biostat Inc., Englewood, NJ, USA). Dichotomous variables were analyzed using the inverse variance method and a random effects model. This particular model was selected because it considers heterogeneity among studies with regard to different clinical environments or methodologies, and thus enables a more strict and detailed analysis than the fixed effects model.

We used the PRISMA methodologies [11]. The I^2-statistic was used to assess heterogeneity across the studies. An I^2 value of 0% indicated no heterogeneity, while values less than 50% indicated low heterogeneity, values less than 75% indicated moderate heterogeneity and values above 75% indicated substantial heterogeneity. Egger's test and funnel plots were used to view the publication bias [12].

We calculated the odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous variables, and finally performed pooled analyses with R statistical software. All authors were qualified to combine and analyze data. Ethics committee or institutional review board approval was not required for systematic reviews and meta-analysis.

The Duval and Tweedie trim and fill method was used as a method to adjust the effect size, assuming that unpublished missing studies were published [13].

Results

Literature retrieval

A PRISMA reporting diagram of the study selection process and the main reasons for exclusion can be found in Figure 1. A total of 3,040 articles were identified from the PubMed/Medline, Embase and Web of Science databases. We removed 1,952

Table 1. Characteristics of the 56 studies included in this meta-analysis.

Publication year	First author and reference	Primary outcome	Methodology	Newcastle-Ottawa Scale Or Cochrane Risk Of Bias tool	No. of cases with postop CSF leakage	Total no. of patients	Follow-up (years)
2018	Rotman [14]	Flap	Retrospective	7	8	238	2009–2017
2018	Zwagerman [4]	LD	RCT	Low	25	170	2011–2015
2018	Kuan [15]	Flap	Retrospective	6	7	300	2013–2016
2018	Caggiano [16]	Obesity, LD, RTx	Retrospective	8	18	811	2008–2017
2018	Conger [10]	Flap	Retrospective	7	9	551	2010–2017
2018	Turri-Zanoni [6]	Flap, RTx, size	Retrospective	9	26	513	1998–2017
2018	Ben-Ari [17]	LD, sella	Retrospective	7	1	12	2011–2016
2018	Patel [18]	Flap, RTx	Retrospective	8	38	806	2004–2016
2018	Kutlay [19]	TC	Retrospective	5	9	106	2010–2017
2018	Mattavelli [20]	RTx	Retrospective	9	11	186	2007–2015
2017	Jeon [21]	Flap, TC	Retrospective	8	14	95	2009–2014
2017	Patel [22]	Obesity, flap	Retrospective	7	3	16	1995–2016
2017	Fraser [3]	Obesity, flap, LD,	Retrospective	8	103	615	1997–2012
2017	Stapleton [9]	Obesity, flap, sella, TC	Retrospective	7	11	47	1999–2014
2017	Shahangian [23]	Flap, LD, RTx	Retrospective, multicenter	9	112	2097	2002–2014
2017	Fathalla [24]	Size, sella, TC, FR	Retrospective	7	4	84	1999–2014
2017	Dolci [25]	FR, sella	Retrospective	7	3	40	2012–2014
2016	Karnezis [26]	Flap, LD, RTx, sella, FR	Retrospective	8	68	1161	2002–2014
2016	Roxbury [27]	Obesity, FR	Retrospective	6	5	73	2008–2014
2016	Thomas [28]	FR, sella	Retrospective	7	6	43	2011–2015
2016	Dehdashti [29]	FR	Retrospective	8	11	180	2009–2013
2016	Nix [30]	FR, sella, TC	Retrospective	8	10	51	2009–2015
2016	Horiguchi [31]	Flap	Retrospective	9	12	132	1990–2014
2016	Formanty [302	RTx	Retrospective	8	1	29	2009–2014
2015	Jalisi [5]	Flap, LD, size	Retrospective	8	3	18	2005–2008
2015	Boiling [33]	Obesity	Retrospective multicenter	8	54	982	2002–2014
2015	Tatagiva [34]	Size	Retrospective	7	3	29	2005–2013
2015	Zhan [35]	LD	Retrospective	7	33	384	2012–2014
2015	Kamat [36]	FR, LD, TC	Retrospective	7	7	48	2008–2012
2015	Ishii [37]	FR, flap, sella, TC	Retrospective	6	4	48	2001–2014
2015	Ivan [2]	Obesity, flap, RTx	Retrospective	8	11	98	2008–2012
2014	Alves [38]	RTx	Retrospective	7	3	28	1992–2011
2014	Thorp [39]	FR, RTx, sella, TC	Retrospective	6	5	123	NA
2014	Banu [40]	LD, sella, TC	Retrospective	8	15	258	2003–2012
2014	Gruss [41]	LD, RTx, size	Retrospective	7	10	121	2005–2012
2014	Cavallo [42]	Flap, LD	Retrospective	9	15	103	1997–2012
2014	Patel [43]	LD, size	Retrospective	8	6	36	2005–2010
2014	Mascarenha [44]	FR, Flap, sella, TC	Retrospective	7	4	126	2004–2012
2013	Amit [45]	Flap, RTx	Retrospective	6	1	25	2008–2011
2013	Eloy [46]	Sella, TC	Retrospective	7	3	87	2008–2012
2013	Munich [47]	FR, sella	Retrospective	7	5	49	NA
2013	Garcia-Navarro [48]	FR, LD, flap	Retrospective	7	1	46	2005–2010

Publication year	First author and reference	Primary outcome	Methodology	Newcastle-Ottawa Scale Or Cochrane Risk Of Bias tool	No. of cases with postop CSF leakage	Total no. of patients	Follow-up (years)
2013	McCoul [48]	Flap	Retrospective	8	6	210	2003–2011
2012	Adappa [7]	LD, size	Retrospective	7	3	24	2008–2011
2012	Padhye [49]	Size	Retrospective	7	4	14	2004–2010
2012	Eloy [50]	Sella, TC	Retrospective	7	1	69	2008–2011
2011	Kong DS [51]	FR	Retrospective	8	5	124	2008–2009
2010	Patel [52]	FR, TC, sella	Retrospective	6	6	150	2007–2008
2010	Horiguchi [53]	Flap	Retrospective	8	5	32	2005–2009
2010	Nyquist [54]	Obesity	Retrospective	7	2	32	2004–2009
2009	Shah [55]	FR, sella	Retrospective	7	1	6	2007–2008
2008	El-Banhawy [56]	Sella	Retrospective	8	3	35	1997–2006
2008	Kassam [57]	FR, sella, TC	Retrospective	8	8	75	2006–2007
2008	Mandonnet [58]	RTx, TC	Retrospective	7	6	42	1992–2002
2007	Basu [59]	Obesity, sella, TC	Retrospective	6	4	14	1996–2004
2004	Rodrigues [60]	RTx	Retrospective	7	1	34	1995–2000

Flap: vascularized flap reconstruction; LD: lumbar drain; TC: transclival; sella, transsellar; RTx: radiotherapy; Size: defect size; FR: flow rate; RCT: randomized controlled trial; NA: not available; N, number

duplicate papers and analyzed the titles and abstracts in the remaining 1,088 papers.

After screening the title with abstract and reviewing the full texts, we excluded 1,032 publications because they failed to meet our eligibility criteria. These articles were excluded because they were review articles (n=91), insufficient data (n=97), case reports (n=124), language other than English (n=49), cadaver studies (n=15), animal studies (n=17), microscopic approach (n=81), external approach (n=23), irrelevant studies (n=492), and no control group (n=43).

Thus, 56 articles were included in our quantitative analysis and the characteristics of the 56 studies are summarized in Table 1 [2,4-10,14-61]. The study populations in the studies included did not overlap. For all analyses, a random effects model was used to evaluate the variation among and within the studies.

Overall postoperative CSF leakage

In a total of 56 studies, 753 out of 11,826 patients had CSF leakage after skull base surgery. The overall rate of postoperative CSF leakage was 7.2% [95% CI: 5.9–8.7%, I2=82.3%] (Figure 2A). In a sensitivity analysis, the rate of postoperative CSF leakage did not change in relation to the publication year (Figure 2B).

Obesity

Seven studies concerning obesity and comprising a total sample of 1,687 patients were included. We defined overweight as BMI over 25 and obese as BMI over 30. Analysis of postoperative CSF leakages across overweight and obesity revealed an odds ratio of 1.88 [95% CI, 1.35 to 2.63, p<0.01] with no heterogeneity (I2=0%) (Figure 3A). Egger's regression test was not performed due to the low sample size. In a funnel plot of obesity in relation to CSF leakage, the studies were spread at the top and center of the plot, which indicated no publication bias (Figure 4A). Using Duval and Tweedie's trim and fill to adjust for potentially unpublished reports revealed no change in the pooled OR (Figure 4B) (OR: 1.88 [95% CI, 1.34 to 2.63, p<0.01]. In a subgroup analysis, in an obese group in whom the BMI was over 30, the OR was 1.90 [95% CI, 1.22 to 2.97, p<0.01] (Figure 3B).

Reconstruction method: vascularized flap vs. free graft

Sixteen studies were included which examined the reconstruction method after tumor resection with a total sample of 3,579 patients. Analysis of CSF leakage across pedicled vascularized flap revealed an odds ratio of 0.62 [95% CI, 0.46 to 0.85, p<0.01] with low heterogeneity (I2=9%) (Figure 3C). Egger's regression test showed significant publication bias (p<0.10). In a funnel plot of reconstruction method in relation to CSF leakage, the studies were spread at the center of the plot, which indicates low publication bias (Figure 4C). Using Duval and Tweedie's trim and fill to adjust for potentially unpublished reports revealed a significant change in the pooled OR (Figure 4D) (OR: 0.54 [95% CI, 0.37 to 0.78, p<0.01]).

Lumbar drain

Fifteen studies concerning lumbar drains with a total sample of 2,604 patients were included in our study. Analysis of CSF leakage across lumbar drains revealed an odds ratio of 1.13 [95% CI, 0.73 to 1.77, p=0.41] with moderate heterogeneity (I2=51.1%)

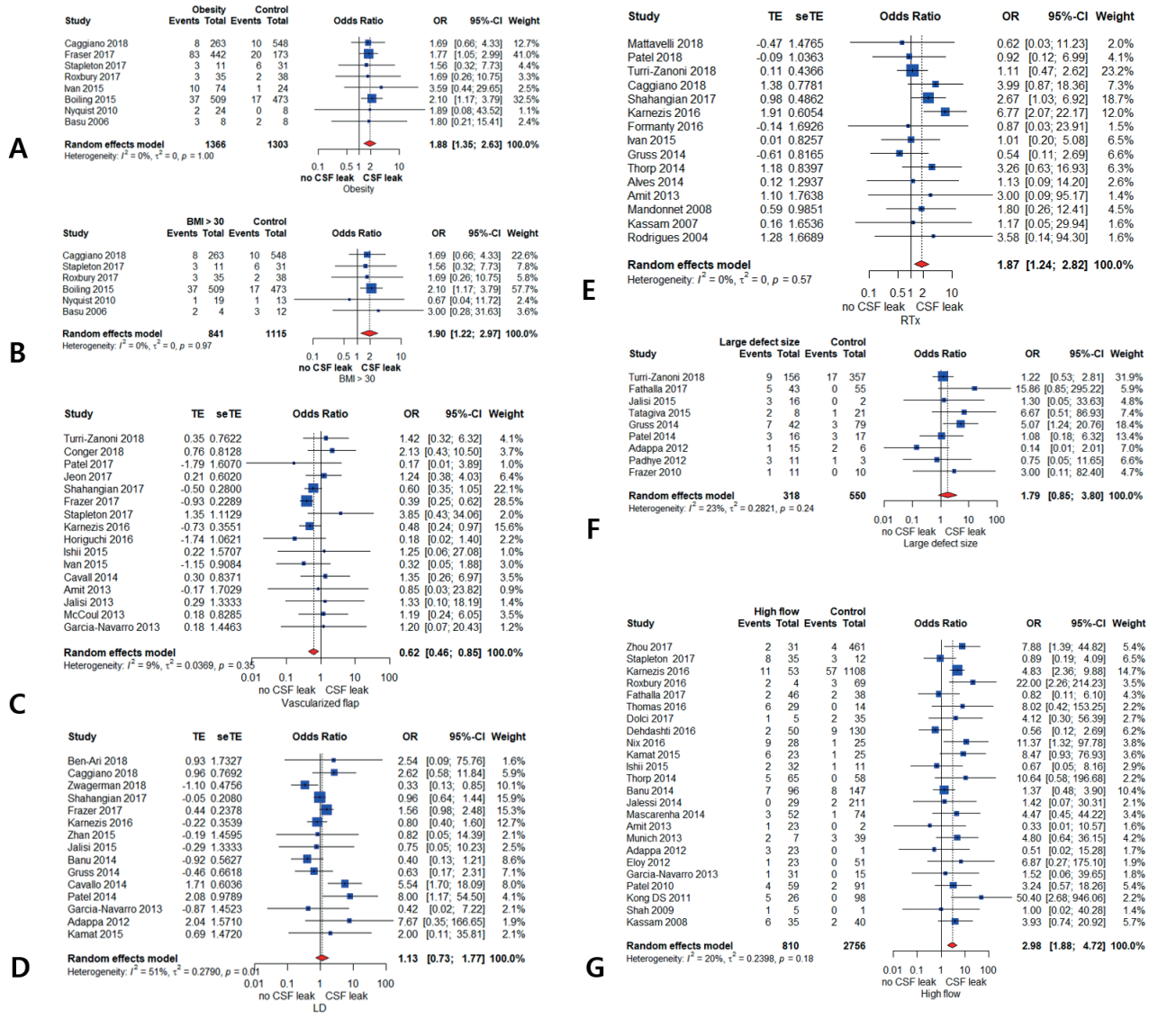

Figure 3. Forest plot of postoperative CSF leakage for each factor. A) Overweight and obesity with BMI over 25; B) obesity subgroup with BMI over 30; C) pedicled vascularized flap; D) lumbar drain; E) perioperative radiotherapy; F) defect size; G) high/low intraoperative flow rate.

(Figure 3D). Egger's regression test did not detect any significant evidence of publication bias (p=0.59). Using a funnel plot, most studies were distributed in the center and top portion of the plot, indicating little publication bias (Figure 4E). There was no difference in OR when using Duval and Tweedie's trim and fill method (Figure 4F) (1.01 [95% CI, 0.64 to 1.59, p=0.97]).

History of perioperative radiotherapy

Fifteen studies regarding perioperative radiotherapy with a total sample of 4,028 patients were included. Analysis of CSF leakage across perioperative radiotherapy revealed an odds ratio of 1.87 [95% CI, 1.24 to 2.82, p=0.002] with no heterogeneity (I2=0%) (Figure 3E). Egger's regression test detected no significant evidence of publication bias (p=0.58). Using a funnel plot, most studies were distributed in the center and top of the plot, indicating little publication bias (Figure 4G). When using Duval and Tweedie's trim and fill method, there was no significant difference in OR (Figure 4H) (OR: 2.21 [95% CI, 1.51 to 3.26, p<0.01]).

Defect size

Nine studies regarding defect size with a total sample of 355 patients were included. Analysis of CSF leakage across defect size revealed an odds ratio of 1.79 [95% CI, 0.85 to 3.80, p=0.13] with low heterogeneity (I2=23%) (Figure 3F). Egger's regression test was not performed due to the low sample size. Using a funnel plot, most studies showed an even distribution over the entire plot (Figure 4I). When using Duval and Tweedie's trim and fill method, there was no difference in OR (Figure 4J) (OR: 1.56 [95% CI, 0.71 to 3.43, p=0.27]).

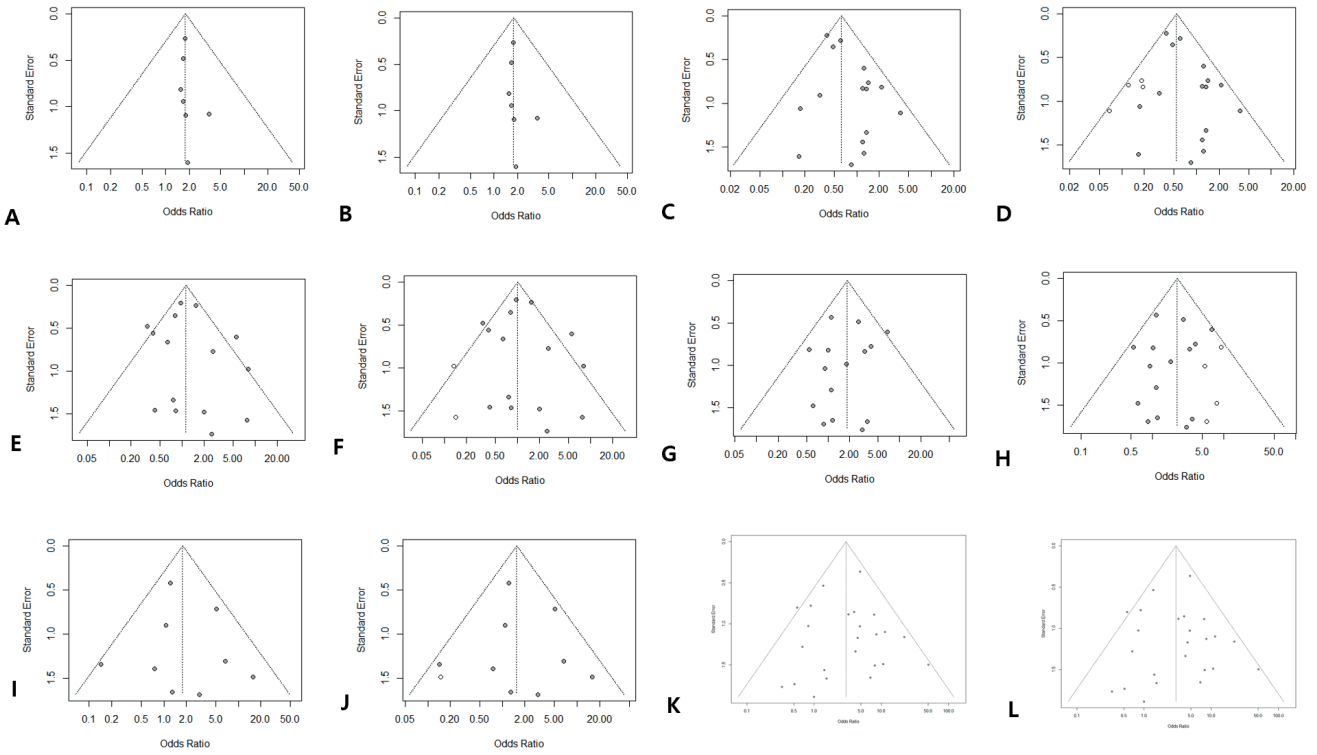

Figure 4. Funnel plots to indicate publication bias and their correction using Duval and Tweedie's trim and fill method to adjust for potentially unpublished reports. A) Obesity; B) obesity after correction using Duval and Tweedie's trim and fill method; C) vascularized pedicled flap; D) vascularized pedicled flap after correction using Duval and Tweedie's trim and fill method; E) lumbar drain; F) lumbar drain after correction using Duval and Tweedie's trim and fill method; G) radiotherapy; H) radiotherapy after correction using Duval and Tweedie's trim and fill method; I) defect size; J) defect size after correction using Duval and Tweedie's trim and fill method; K) intraoperative flow rate; L) intraoperative flow rate after correction using Duval and Tweedie's trim and fill method.

High flow vs. Low flow

Twenty four studies concerning CSF pressure with a total sample of 3566 patients were included. Analysis of CSF leakage across high flow rates revealed an odds ratio of 2.98 [95% CI, 1.88 to 4.72, p<0.01] with low heterogeneity (I2=20.4%) (Figure 3G). Egger's regression test detected no significant evidence of publication bias (p=0.28). Using a funnel plot, most studies showed an even distribution over the entire plot, indicating little publication bias (Figure 4K). There was no significant difference in OR when using Duval and Tweedie's trim and fill method (Figure 4L) (OR: 2.98 [95% CI, 1.88 to 4.72, p<0.01]).

Discussion

Postoperative CSF leakage remains a major cause of morbidity in endoscopic endonasal skull base surgery. Identifying the risk factors is important when performing reconstructions and consulting patients. However, there is little published data dealing with this.

CSF leakage can largely be divided into spontaneous and secondary causes. Among these, we have focused only on postoperative CSF leakage that occurred after skull base tumor surgery because spontaneous leakage is rare and has a unique pathophysiology that is different from that in tumor cases.

A total of 56 studies showed that the rate of postoperative CSF leakage after endonasal skull base surgery was 7.2%. This finding is presented as a whole, regardless of patient weight, radiation history, tumor size, and lumbar drain placement. The percentage of postoperative CSF leakage, as shown in Figure 2, does not seem to increase or decrease significantly over time, even when compared by year (Figure 2B). Some studies have shown the importance of learning curves in individual centers [14,62], but our data showed that there was no significant improvement with time.

Empty sella syndrome is frequently observed in normal obese people, and elevated intracranial pressure may be the underlying mechanism [63]. This obesity has been confirmed in individual studies where there is not only increased probability of spontaneous CSF leakage but also increased probability of postoperative CSF leakage in skull base procedures [60].

The vascularized flaps used included the middle turbinate flap, inferior turbinate flap, pericranial flap, nasoseptal flap (NSF), etc. A free tissue graft such as fascia or fat required about 7 days for

neovascularization and sometimes some portion of the graft material would be necrotized. On the other hand, a vascularized flap can quickly progress to the vascularization phase and rarely become necrotic. Therefore, it is reasonable that a vascularized flap can have a better outcome when reconstructing a skull base defect. The vascularized flap is usually only used in CSF leakage with a high flow rate, so we excluded pituitary surgery for this comparison because of selection bias. Because there is usually no intraoperative CSF leakage or low flow CSF leakage in pituitary surgery, a free graft is usually used and inevitably, low postoperative CSF leakage is encountered. As a result, with the exception of pituitary adenoma, the use of a vascularized flap reduced postoperative CSF leakage by a factor of 0.62 compared to a free graft (Figure 3C).

There is a debate regarding the effect of lumbar drainage (LD) on postoperative CSF leakage. Cavallo et al. noted that, in 103 craniopharyngioma cases, LD had no role in reducing postoperative CSF leakage [43]. Caggiano et al., analyzing 811 cases of endonasal skull base surgical procedures, found that LD did not have much effect in preventing postoperative CSF leakage [17]. However, a recent RCT reported that LD reduced postoperative CSF leakage (LD vs. no LD: 8.2% vs 21.2%) [4]. In our meta-analysis, the OR of LD was 1.13 with moderate heterogeneity (I2=51%, p=0.41). There was little publication bias and the result was quite convincing. However, surgeons tend to perform LD in higher risk patients or when the surgeon feels that the reconstruction was not completely successful. So, retrospective studies, whether using LD or not, have their own bias, and meta-analysis using mostly these retrospective studies also show some bias. We have to interpret these results carefully.

Radiation works by damaging the DNA of normal and cancerous tissue [64]. Although Intensity-Modulated Radiation Therapy has recently been introduced to prevent damage to surrounding tissue, there is still no guarantee that radioactive beams will not encroach on that tissue. Therefore, radiation is likely to damage normal tissue around the tumor, and so there may be more CSF leakage in patients with a history of radiation therapy. In our results, patients who received radiation therapy were 1.87 times more likely to have postoperative CSF leakage.

There has been controversy about whether a larger defect size could increase the possibility of CSF leakage after endoscopic skull base surgery. Our results showed that larger defect sizes did not increase postoperative CSF leakage (p=0.13). However, a higher flow rate could lead to more CSF leakage (Figure 3I; OR: 2.98, p<0.01). The results for this high flow rate have little publication bias, indicating that the results are robust and more reliable.

There are several limitations in our study. First, histologic factors and surgical approach methods were not considered in our study. Because not all studies included data on the surgical approach or histologic factors for all individuals, the final results of our meta-analysis cannot be complete without the data for all these individuals. Second, due to the lack of RCTs, the results of our study may be less persuasive than results originating from purely RCTs. In the future, further studies from RCTs can enrich and substantiate our results.

Despite these limitations, this is the first known meta-analysis regarding the risk factors for postoperative CSF leakage after endonasal endoscopic skull base surgery. This study could provide important information for the endoscopic skull base surgeon who manages and counsels a diverse group of patients who may be undergoing this surgical procedure.

Conclusion

The risk factors for postoperative CSF leakage after endonasal endoscopic skull base surgery are obesity, perioperative radiotherapy, high intraoperative CSF pressure and free grafts. However, CSF diversion and defect size were not significant risk factors in this meta-analysis. Further prospective studies could validate our data.

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None.

Authorship contribution

Acquisition of data: JSK, SDH; analysis and interpretation of data: JSK, SDH; drafting the manuscript for critical intellectual content: JSK, SDH; review and improvement of the manuscript: SDH; conception and design of the study: JSK, SDH.

Conflict of interest

None.

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