

# From postoperative cerebrospinal fluid leak to meningitis: unveiling the risk factors for meningitis after endoscopic skull base surgery

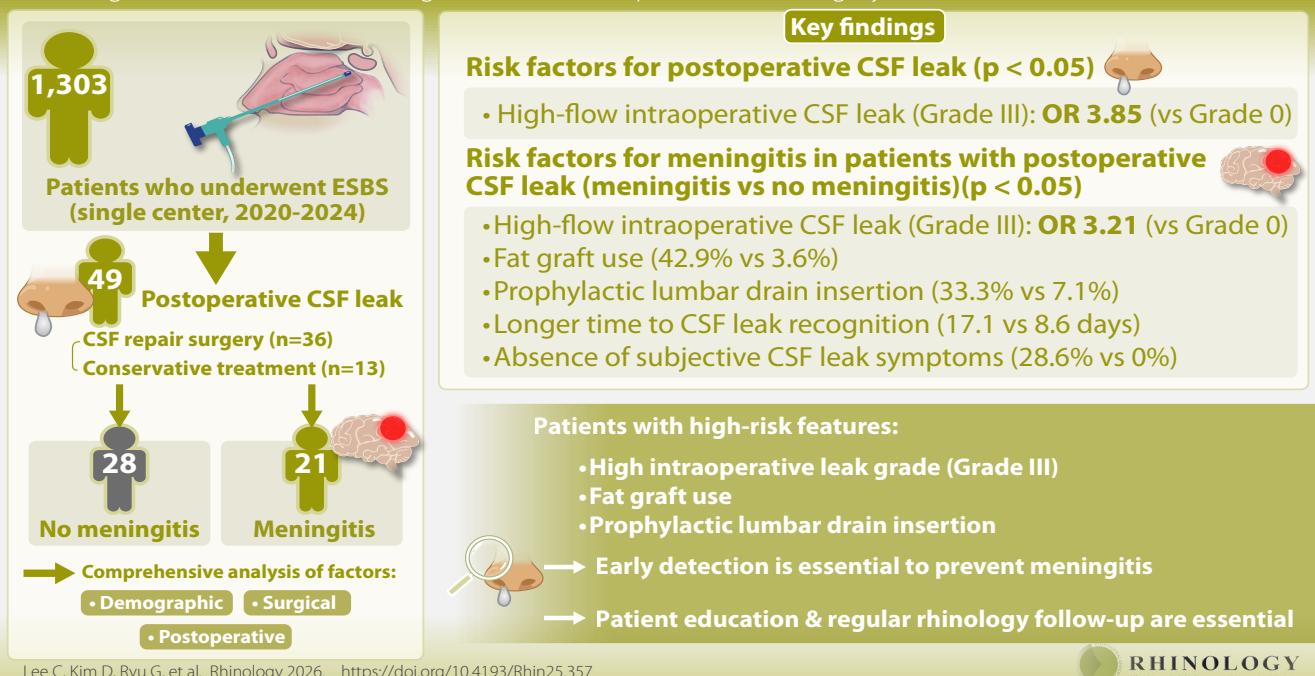
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## From postoperative cerebrospinal fluid leak to meningitis:

Unveiling the risk factors for meningitis after endoscopic skull base surgery (ESBS)



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## Abstract

**Background:** Postoperative cerebrospinal fluid (CSF) leak is a significant complication of endoscopic skull base surgery (ESBS) that increases meningitis risk, a serious and potentially life-threatening infection. This study aimed to delineate the risk factors associated with the development of meningitis in patients who experienced postoperative CSF leakage.

**Methodology:** We reviewed 1,303 ESBS cases for skull base lesion between January 2020 and July 2024 at a single tertiary center. Patient demographics, pathology, intraoperative CSF leak grade, reconstruction techniques, and postoperative CSF leak management strategies—including the use of nasoseptal flaps, fat grafts, and lumbar drains—were collected. Clinical and surgical factors were analyzed among patients with postoperative CSF leak to identify associations with the development of meningitis.

**Results:** Postoperative CSF leak was suspected in 49 patients (3.8%). Among them, 36 (2.8%) underwent repair surgery, while 13 (1.0%) were treated conservatively without surgical confirmation. Meningitis occurred in 21 of these patients. Multivariate analysis revealed that intraoperative CSF leak grade, use of fat grafts, lumbar drain insertion, and delayed CSF leak recognition were significantly associated with meningitis development. Patients with grade 3 intraoperative leaks had 3.21-fold increased odds of developing meningitis compared to grade 0. Tumor pathology, nasoseptal flap viability, and hydroxyapatite use were not significantly associated.

**Conclusions:** The transition from postoperative CSF leak to meningitis is influenced by the severity of intraoperative leakage, reconstructive choices, and the timing of leak detection. Restricting fat grafts and lumbar drains to selected cases and ensuring close postoperative rhinologic surveillance are critical in mitigating infectious complications following ESBS.

**Key words:** cerebrospinal fluid leak, meningitis, endoscopic skull base surgery

## Introduction

Endoscopic skull base surgery (ESBS) has become a widely adopted approach for managing skull base lesions, particularly in the sellar and parasellar regions<sup>(1)</sup>. Compared to conventional microscopic methods, ESBS minimizes brain manipulation and enables a less invasive approach to the lesion, making it a safer and effective surgical approach<sup>(2)</sup>. The superior visualization provided by ESBS allows for detailed endoscopic examination of adjacent structures<sup>(3)</sup> and avoids cosmetic concerns such as external scarring<sup>(4)</sup>. Consequently, ESBS has been increasingly utilized across a broader range of skull base pathologies over time<sup>(5)</sup>. Nonetheless, complications can still arise with ESBS.

Postoperative cerebrospinal fluid (CSF) leakage remains a significant concern, occurring approximately six times more frequently with ESBS than with conventional transcranial approaches (18% vs 3%)<sup>(4,6)</sup>. When CSF leakage occurs, it evokes direct communication between the septic nasal cavity and the sterile intracranial space, permitting nasal flora to enter and potentially cause central nervous system (CNS) infections, including meningitis<sup>(7,8)</sup>. Such infections not only prolong hospital stays but also pose life-threatening risks. Therefore, preventing these complications is a crucial consideration for skull base surgeons planning ESBS. Several studies have investigated risk factors associated with postoperative CSF leakage, identifying contributors such as high body mass index (BMI), posterior fossa tumors, perioperative radiotherapy, and high intraoperative CSF flow rates<sup>(9,10)</sup>. Additionally, increased intracranial pressure and the size of the skull base defect have been correlated with higher leakage risk<sup>(11,12)</sup>. In response, various reconstruction methods and surgical techniques have been proposed to reduce leakage rates, with the use of vascularized flaps, particularly nasoseptal flaps (NSFs), demonstrating a reduction in leakage rates from 15.6% to 6.7%<sup>(13,14)</sup>. Consequently, surgeons utilize vascularized pedicled NSFs and other techniques to achieve reliable skull base closure and minimize complications.

Despite the critical impact of meningitis on patient outcomes, systematic research on its risk factors remains limited. While postoperative CSF leakage is recognized as the crucial contributor to postoperative CNS infections, including meningitis<sup>(7,15)</sup>, other suggested risk factors, such as high BMI, complex tumors, the presence of external ventricular drains, prolonged lumbar drain (LD) placement, and revision surgery, are supported by relatively limited clinical evidence<sup>(8,16,17)</sup>. Comprehensive analyses of large patient cohorts and a broad range of variables remain scarce, highlighting the need for further research.

## Materials and methods

### Patient selection

We retrospectively collected data from patients who underwent ESBS at a single tertiary center, Samsung Medical Center in Seoul, Korea, between January 2020 and July 2024. The

surgeries addressed a broad spectrum of pathologies, including sellar and suprasellar tumors such as pituitary adenomas and craniopharyngiomas, as well as chordomas, Rathke's cleft cysts, and inflammatory lesions. Only tuberculum sellae meningiomas were included among meningiomas. Patients were excluded if they underwent only a biopsy or had additional surgical approaches, such as transorbital approaches or craniotomies. We also excluded four cases. These included two with immediate postoperative radiotherapy, one with metastatic cancer who received chemotherapy and developed meningitis with sepsis, and one with a burr-hole operation considered a confounding factor for meningitis (Table S1).

### Surgical technique and treatment course

All ESBS procedures were jointly performed by a neurosurgeon and a rhinologist. The rhinologist performed the approach to access the tumor, including suprasellar lesion, after which the neurosurgeon performed tumor removal. After intradural tumor resection, multilayer reconstruction was performed using various materials based on pathology and intraoperative findings, including autologous or allograft fascia lata, abdominal fat grafts, and 1 mm thick acellular dermal grafts (AlloDerm®, MegaDerm®). Hydroxyapatite (Hydroset®) and fibrinogen collagen sponges (TachoSil®) were also used as needed. Abdominal fat grafts were applied in cases with significant intradural dead space, such as large pituitary adenomas or posterior fossa defects, to reduce dead space.

Following primary reconstruction, either an NSF or a free mucosal graft was used to completely cover the skull base defect, ensuring direct adherence to the bone. Margins were reinforced with Surgicel® or TachoSil®, followed by compressive packing with Spongostan® or Merocel® to minimize dead space beneath the graft and control bleeding. To accommodate potential NSF contracture, the flap was designed larger than the defect and extended to the nasal floor mucosa if necessary. Abdominal fat grafts were harvested intraoperatively, while homologous fascia lata was utilized from the hospital's tissue bank.

Prophylactic LD was considered in cases with large posterior fossa defects, or high anticipated postoperative CSF leakage risk. When used, LD was maintained for 3–7 days with a controlled drainage rate of 5–10 cc/hr before removal.

Postoperatively, the rhinologist conducted evaluations three times a week, including symptom inquiry and endoscopic examination to monitor for CSF leakage or complications. Packing materials were partially removed on postoperative days 2–3 and fully removed within 7–14 days. After discharge, nasal endoscopy was performed at 1, 3, and 6 weeks, and at 3 months postoperatively. Imaging studies included contrast-enhanced CT on postoperative day 1 and sellar MRI with a 3D T2-weighted Vista sequence on postoperative day 2 to evaluate tumor resection and NSF viability. Partial NSF enhancement prompted

partial packing removal to prevent flap pedicle compression. If no enhancement or reduced viability was noted, packing was instead tightened, allowing the dead NSF to function at least as a free mucosal graft.

For antibiotic prophylaxis, unless antibiotic skin sensitivity testing indicated otherwise, a standardized empirical regimen was administered regardless of tumor type. IV ceftizoxime (1 g BID), levofloxacin (750 mg QD), and metronidazole (500 mg TID) were administered for approximately 5 days during hospitalization, followed by oral cefditoren (100 mg TID) for 2 weeks post-discharge. If postoperative CSF leakage was suspected or meningitis risk was high, a triple regimen of vancomycin, ceftizoxime, and metronidazole was initiated. Antibiotic regimens were adjusted per culture results, with antifungal agents added when necessary.

#### Assessment of intraoperative CSF leak grade

Intraoperative CSF leakage was assessed using Esposito's grading system<sup>(18)</sup>. Grade 0 indicated no leakage confirmed by Valsalva maneuver; Grade I was a small "weeping" leak detected by Valsalva without a visible diaphragmatic defect; Grade II was a moderate leak with a clear diaphragmatic defect; and Grade III was a large leak typically seen in suprasellar or transclival extended transsphenoidal approaches where intentional defects are created.

#### Postoperative CSF leakage repair surgery

If patients reported CSF rhinorrhea or exhibited meningitis symptoms (fever >38°C, headache, neck stiffness, meningeal signs), an endoscopic examination was performed to confirm CSF leakage. If leakage was suspected, CSF repair surgery was planned. For suspected meningitis, an LD was inserted preoperatively, and empirical triple antibiotics (vancomycin, ceftizoxime, metronidazole) were administered. During surgery, the site was irrigated with vancomycin before multilayer reconstruction. Fat grafts and fascia were used when necessary. If an NSF had not been used during initial ESBS, it was utilized for reconstruction. If previously used, management depended on viability and coverage. A non-enhancing or insufficiently covering NSF prompted harvesting of a new NSF from the contralateral side, while a viable NSF was only repositioned as needed to optimize closure.

#### Data collection

Data was collected through retrospective chart review, including electronic medical and operative records. Variables were categorized into demographic, surgical, and postoperative factors. Demographics included age, sex, BMI, obesity status, and comorbidities (hypertension, diabetes, dyslipidemia). Surgical factors included tumor pathology, recurrence status, NSF use, and reconstruction materials (fat grafts, fascia, hydroxyapatite).

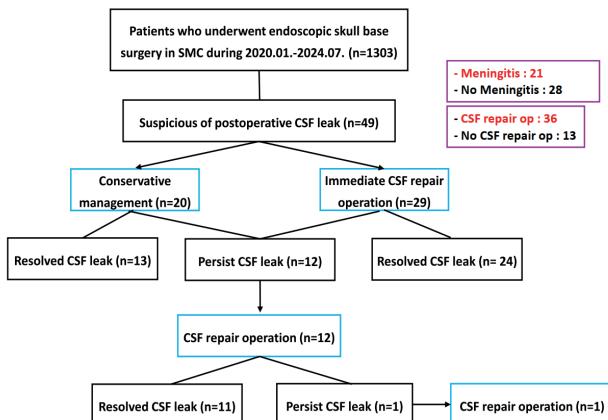


Figure 1. Schematic flow of 1,303 patients and postoperative management after endoscopic skull base surgery.

Tumor removal extent was classified as gross total resection (GTR), near-total resection (NTR), or subtotal resection (STR). Intraoperative CSF leak grades were documented per Esposito's system. For patients with NSF use, postoperative sellar MRI scans were reviewed to assess enhancement status systematically. Postoperative factors for CSF leakage cases included subjective leakage symptoms, rhinologist-confirmed objective leakage, and time from ESBS to symptom onset. For CSF repair surgeries, data included the interval from ESBS to repair and from symptom onset to repair. For patients with postoperative CSF leakage, meningitis-focused data were collected, including spinal tap results, and symptoms (fever >38°C, headache, neck stiffness, meningeal signs).

#### Statistical analysis

Statistical analyses were conducted using SPSS 26 (IBM, Armonk, NY, USA). Categorical variables were analyzed using Chi-square or Fisher's exact tests, and numerical variables with independent samples t-tests. Statistical significance was defined as  $p < 0.05$ . Odds ratios with 95% confidence intervals were calculated using univariate analysis with Fisher's exact test or logistic regression, with  $p$ -values used to determine statistical significance.

## Results

#### Patients' characteristics

A total of 1,303 patients were included in this study (Figure 1). Among them, 49 patients were suspected of postoperative CSF leakage, while 1,254 did not. Of the 49 patients with postoperative CSF leakage, 36 underwent CSF repair surgery, whereas 13 were managed conservatively without surgical intervention. Minimal leaks after pituitary surgery were sometimes managed conservatively, whereas high-grade leaks, especially grade III, usually required repair. Small defects with NSF could also be treated with tight packing instead of immediate surgery. Ad-

Table 1. Baseline characteristics of patients undergoing endoscopic skullbase surgery (N=1303).

Variables	No postoperative CSF leak group (N=1254)	Postoperative CSF leak group (N=49)	p-value
<b>Age (years, mean <math>\pm</math>SD)</b>	50.31 $\pm$ 15.43	51.90 $\pm$ 12.60	0.476
<b>Gender (Male, %)</b>	625 (49.8%)	30 (61.2%)	0.156
<b>BMI (kg/m<sup>2</sup>, mean <math>\pm</math>SD)</b>	25.44 $\pm$ 3.98	26.13 $\pm$ 4.19	0.236
<b>Obesity</b>	<30 (n, %)	1089 (86.8%)	42 (85.7%)
	30≤ (n, %)	165 (13.2%)	7 (14.3%)
<b>Underlying</b>	DL (yes, %)	188 (15.0%)	8 (16.3%)
	HTN (yes, %)	283 (22.6%)	10 (20.4%)
	DM (yes, %)	145 (11.6%)	10 (20.4%)
<b>Use of NSF (yes, %)</b>	513 (40.9%)	30 (61.2%)	<b>0.007</b>
	PA (n, %)	951 (75.8%)	34 (69.4%)
	CP (n, %)	89 (7.1%)	2 (4.1%)
	MNG (n, %)	55 (4.4%)	5 (10.2%)
	Rathke's Cleft (n, %)	63 (5.0%)	2 (4.1%)
	Chordoma (n, %)	30 (2.4%)	3 (6.1%)
	Schwannoma (n, %)	4 (0.3%)	0 (0%)
	Other tumors (n, %)	39 (3.1%)	1 (2.0%)
	Inflammatory lesion (n, %)	2 (0.1%)	0 (0%)
	Others (n, %)	21 (1.7%)	2 (4.1%)
<b>Recurrent tumor or not (yes, %)</b>	79 (6.3%)	3 (6.1%)	1.0
<b>Intra-op CSF leak grade</b>	0 (n, %)	637 (51.8%)	15 (31.9%)
	1 (n, %)	215 (17.5%)	5 (10.6%)
	2 (n, %)	122 (9.9%)	4 (8.5%)
	3 (n, %)	254 (20.6%)	23 (48.9%)

ditionally, 21 patients developed meningitis, while 28 did not. Among the 36 patients who underwent CSF repair surgery, 14 had not received an NSF during the initial ESBS, 14 had an NSF that remained viable, and 8 had an NSF that either showed no enhancement on MRI or was necrotic. All 14 patients who had not received an NSF during ESBS underwent reconstruction using a newly harvested NSF during the repair surgery. Meanwhile, in all 8 cases where the existing NSF was nonviable, the original NSF was taken down, and a new NSF was harvested from the contralateral side for reconstruction. Among the 14 patients whose NSF was harvested during ESBS and remained viable, 10 underwent simple repositioning of the existing NSF during CSF repair surgery. The remaining 4 patients required an additional contralateral NSF because the original NSF alone was insufficient to cover the defect site fully. In these cases, the original and contralateral NSF were utilized to achieve adequate reconstruction.

#### Factors related to postoperative CSF leakage

Patients were divided into two groups based on the presence of postoperative CSF leakage: those who developed postoperative

CSF leakage (n=49) and those who did not (n=1254). A statistical analysis was conducted to identify significant factors influencing postoperative CSF leakage (Table 1). The results showed that a higher intraoperative CSF leak grade was significantly associated with an increased incidence of postoperative CSF leakage (p<0.001). Additionally, the use of a NSF was more frequent in the postoperative CSF leakage group compared to the non-leakage group (40.9% vs. 61.2%, p=0.007). In univariate analysis, patients with intraoperative CSF leak grade 3 had an odds ratio of 3.85 for developing postoperative CSF leakage, compared to those with grade 0 (p<0.001). Although not statistically significant, patients with pre-existing diabetes mellitus showed a higher incidence of postoperative CSF leakage (11.6% vs. 20.5%, p=0.099). Other factors, including age, sex, BMI, obesity, tumor pathology, and tumor recurrence status, did not show statistically significant differences between the two groups.

#### Factors related to meningitis

The 49 patients who developed postoperative CSF leakage were further divided into two groups based on whether they developed meningitis: those who developed meningitis (n=21) and

Table 2. Comparison based on the occurrence of meningitis in the postoperative CSF leak group (N=49).

Variables	No meningitis (N=28)	Meningitis (N=21)	p-value
<b>Age (years, mean <math>\pm</math>SD)</b>	50.46 $\pm$ 11.46	53.81 $\pm$ 14.04	0.363
<b>Gender (Male, %)</b>	16 (57.1%)	14 (66.7%)	0.703
<b>BMI (kg/m<sup>2</sup>, mean <math>\pm</math>SD)</b>	26.22 $\pm$ 5.02	26.01 $\pm$ 2.84	0.862
<b>Obesity</b>	<30 (n, %)	23 (82.1%)	19 (90.5%)
	30 $\leq$ (n, %)	5 (17.9%)	2 (9.5%)
<b>Underlying</b>	DL (yes, %)	3 (10.7%)	5 (23.8%)
	HTN (yes, %)	6 (21.4%)	4 (19.1%)
	DM (yes, %)	5 (17.8%)	5 (23.8%)
<b>Pathology</b>	PA (n, %)	19 (67.9%)	15 (71.4%)
	CP (n, %)	2 (7.1%)	1 (4.8%)
	MNG (n, %)	4 (14.3%)	1 (4.8%)
	Rathke's Cleft (n, %)	1 (3.6%)	1 (4.8%)
	Chordoma (n, %)	1 (3.6%)	2 (9.5%)
	Schwannoma (n, %)	0 (0%)	0 (0%)
	Other tumors (n, %)	0 (0%)	0 (0%)
	Inflammatory lesion (n, %)	0 (0%)	0 (0%)
	Others (n, %)	1 (3.6%)	1 (4.8%)
<b>Recurrent tumor or not (yes, %)</b>	0 (0.0%)	3 (14.3%)	0.114
<b>Intra-op CSF leak grade</b>	0 (n, %)	4 (19.1%)	
	1 (n, %)	5 (17.9%)	2 (9.5%)
	2 (n, %)	3 (10.7%)	1 (4.8%)
	3 (n, %)	9 (32.1%)	14 (66.7%)
<b>Reconstruction</b>	NSF (n, %)	12 (42.9%)	17 (81.0%)
	- Viable (n, %)	- 7 (58.3%)	- 11 (65%)
	Fascia lata (n, %)	2 (7.1%)	6 (28.6%)
	Megaderm (n, %)	8 (28.6%)	10 (47.6%)
	Fat (n, %)	1 (3.6%)	9 (42.9%)
	Hydroxyapatite (n, %)	5 (17.9%)	6 (28.6%)
	LD insertion (n, %)	2 (7.1%)	7 (33.3%)
<b>Subjective CSF leak symptom (n, %)</b>	28 (100%)	15 (71.4%)	0.010
<b>Objective finding for CSF leak (n, %)</b>	18 (64.3%)	14 (66.7%)	1.000
<b>Intraop finding for CSF leak (n, %)</b>	16 (80%)	13 (86.7%)	0.948
<b>Time between the date of CSF leakage symptoms and endoscopic skullbase surgery (day)</b>	8.64 $\pm$ 7.17	17.14 $\pm$ 10.20	0.003
<b>Total hospitalization day</b>	14.36 $\pm$ 5.26	25.62 $\pm$ 20.84	0.024
<b>Degree of tumor removal</b>	27 (96.4%)	18 (85.7%)	0.407
	1 (3.6%)	3 (14.3%)	

those who did not (n=28). A statistical analysis was performed to identify significant factors associated with meningitis (Table 2). The results showed that demographic factors, including age, gender, BMI, and underlying comorbidities, as well as tumor pathology type, tumor recurrence status, and the degree of tumor removal, were not significantly associated with the development of meningitis. However, a higher intraoperative CSF leak grade

was significantly correlated with an increased incidence of meningitis (p=0.030). Additionally, the use of NSF and fat grafts was significantly more common in the meningitis group compared to the non-meningitis group (81.0% vs. 42.9%, p=0.017; 42.9% vs. 3.6%, p=0.003, respectively). Meningitis was also shown to be significantly more common in individuals who had received prophylactic LD insertion (33.3% vs. 7.1%, p=0.049). In the

# Corrected Proof

*Risk factors for meningitis in patients with postoperative CSF leakage*

Table 3. Comparison based on the occurrence of bacterial meningitis in the postoperative CSF leak group with Intraoperative CSF Leak Grade 3 (N=23).

Variables	No bacterial meningitis (N=9)	Bacterial meningitis (N=14)	p-value
<b>Age (years, mean <math>\pm</math>SD)</b>	54.11 $\pm$ 10.94	54.29 $\pm$ 15.68	0.975
<b>Gender (Male, %)</b>	6 (66.7%)	10 (71.4%)	1.000
<b>BMI (kg/m<sup>2</sup>, mean <math>\pm</math>SD)</b>	26.68 $\pm$ 2.97	26.03 $\pm$ 2.36	0.588
<b>Obesity</b>	<30 (n, %)	7 (77.8%)	
	30≤ (n, %)	2 (22.2%)	0.679
<b>Underlying</b>	DL (yes, %)	1 (11.1%)	0.636
	HTN (yes, %)	4 (44.4%)	0.480
	DM (yes, %)	1 (11.1%)	0.409
<b>Pathology</b>	PA (n, %)	3 (33.3%)	
	CP (n, %)	1 (11.1%)	0.193
	MNG (n, %)	4 (44.4%)	
	Rathke's Cleft (n, %)	0 (0%)	
	Chordoma (n, %)	1 (11.1%)	
	Schwannoma (n, %)	0 (0%)	
	Other tumors (n, %)	0 (0%)	
	Inflammatory lesion (n, %)	0 (0%)	
	Others (n, %)	0 (0%)	
<b>Recurrent tumor or not (yes, %)</b>	0 (0.0%)	3 (21.4%)	0.393
<b>Reconstruction</b>	NSF (n, %)	9 (100.0%)	1.000
	- Viable (n, %)	- 6 (66.7%)	0.882
	Fascia lata (n, %)	2 (22.2%)	1.000
	Megaderm (n, %)	6 (66.7%)	1.000
	Fat (n, %)	1 (11.1%)	0.250
	Hydroxyapatite (n, %)	5 (55.6%)	0.867
	LD insertion (n, %)	1 (11.1%)	0.144
<b>Subjective CSF leak symptom (n, %)</b>	9 (100%)	9 (64.3%)	0.131
<b>Objective finding for CSF leak (n, %)</b>	7 (77.8%)	11 (78.6%)	1.000
<b>Intraop finding for CSF leak (n, %)</b>	8 (100%)	10 (90.9%)	1.000
<b>Time between the date of CSF leakage symptoms and endoscopic skullbase surgery (day)</b>	8.56 $\pm$ 5.43	16.7 $\pm$ 8.45	<b>0.010</b>
<b>Total hospitalization day</b>	15.11 $\pm$ 4.91	28.93 $\pm$ 24.93	0.063
<b>Degree of tumor removal</b>	GTR/NTR (n, %)	8 (88.9%)	
	STR (n, %)	1 (11.1%)	1.000
		2 (14.3%)	

non-meningitis group, all patients subjectively recognized their symptoms of CSF leak. However, in the meningitis group, only 71.4% of patients reported subjective symptoms of a CSF leak, while 28.6% did not recognize any symptoms. This difference was statistically significant (p=0.01). Additionally, the time from ESBS to recognition of CSF leakage was significantly longer in the meningitis group compared to the non-meningitis group (17.14 days vs. 8.64 days, p=0.003). A subgroup analysis focusing on patients with intraoperative CSF leak grade 3 showed similar trends. Patients who did not subjectively perceive CSF leak symptoms or had a longer time to symptom recognition (16.7

days vs. 8.56 days) had a higher risk of developing meningitis (Table 3). Additionally, the total length of hospital stay was significantly longer in the meningitis group compared to the non-meningitis group (25.62 days vs. 14.36 days, p=0.024). Although not statistically significant, the rate of recurrent tumors was higher in the meningitis group compared to the non-meningitis group (14.3% vs. 0%, p=0.114) (Table 2).

## Discussion

### Factors related to postoperative CSF leakage

A higher intraoperative CSF leak grade and the use of NSF were

Table 4. Comparison based on the occurrence of bacterial meningitis after postoperative CSF leak among patients with unviable NSF (N=12).

Variables	No bacterial meningitis (N=6)	Bacterial meningitis (N=6)	p-value
<b>Age (years, mean <math>\pm</math>SD)</b>	53.33 $\pm$ 14.02	57.83 $\pm$ 13.17	0.579
<b>Gender (Male, %)</b>	4 (66.7%)	2 (33.3%)	0.564
<b>BMI (kg/m<sup>2</sup>, mean <math>\pm</math>SD)</b>	24.28 $\pm$ 2.88	24.81 $\pm$ 2.51	0.742
<b>Obesity</b>	<30 (n, %)	6 (100%)	
	30≤ (n, %)	0 (0%)	1.000
<b>Underlying</b>	DL (yes, %)	1 (16.7%)	1.000
	HTN (yes, %)	2 (33.3%)	1.000
	DM (yes, %)	1 (16.7%)	1.000
<b>Pathology</b>	PA (n, %)	3 (50.0%)	
	CP (n, %)	0 (0%)	1 (16.7%)
	MNG (n, %)	3 (50%)	1 (16.7%)
	Rathke's Cleft (n, %)	0 (0%)	0 (0%)
	Chordoma (n, %)	0 (0%)	1 (16.7%) 0.392
	Schwannoma (n, %)	0 (0%)	0 (0%)
	Other tumors (n, %)	0 (0%)	0 (0%)
	Inflammatory lesion (n, %)	0 (0%)	0 (0%)
	Others (n, %)	0 (0%)	0 (0%)
<b>Recurrent tumor or not (yes, %)</b>	0 (0%)	0 (0%)	1.000
<b>Intra-op CSF leak grade</b>	0 (n, %)	0 (0%)	
	1 (n, %)	3 (50.0%)	0 (0%)
	2 (n, %)	0 (0%)	1 (25.0%) 0.153
	3 (n, %)	3 (50.0%)	3 (75.0%)
<b>Reconstruction</b>	Fascia lata (n, %)	1 (16.7%)	0.242
	Megaderm (n, %)	2 (33.3%)	2 (33.3%)
	Fat (n, %)	0 (0%)	4 (66.7%)
	Hydroxyapatite (n, %)	2 (33.3%)	2 (33.3%)
	LD insertion (n, %)	0 (0.0%)	2 (33.3%) 0.455
<b>Subjective CSF leak symptom (n, %)</b>	4 (66.7%)	6 (100.0%)	0.454
<b>Objective finding for CSF leak (n, %)</b>	4 (66.7%)	6 (100.0%)	0.454
<b>Time between the date of CSF leakage symptoms and endoscopic skullbase surgery (day)</b>	3.83 $\pm$ 1.83	21.5 $\pm$ 8.55	<0.001
<b>Total hospitalization day</b>	15.00 $\pm$ 5.59	18.00 $\pm$ 4.65	0.336
<b>Degree of tumor removal</b>	GTR/NTR (n, %)	5 (83.3%)	
	STR (n, %)	1 (16.7%)	5 (83.3%) 1.000 1 (16.7%)

significantly associated with an increased incidence of postoperative CSF leakage. This aligns with prior studies<sup>(9,10)</sup>, as high-flow intraoperative leaks make achieving a watertight closure challenging, even when using vascularized flaps. High-flow intraoperative CSF flow compromises graft adherence, and high-grade leaks inherently remain at increased risk of postoperative leakage despite secure reconstruction.

The observation that NSF use was associated with higher postoperative CSF leakage may seem paradoxical, given that NSFs have been shown to reduce leakage rates significantly. However,

this likely reflects a selection bias, as NSFs are preferentially used in cases with high intraoperative leak grades or larger defects, both associated with higher leakage risk<sup>(19)</sup>. Thus, the association does not imply that NSF increases leakage risk but rather that it is used in higher-risk cases.

Although not statistically significant, patients with diabetes mellitus exhibited a higher risk of postoperative CSF leakage ( $p=0.099$ ). Diabetes-related factors, including microangiopathy, impaired oxygen delivery, chronic inflammation, macrophage dysfunction, and dysregulation of cytokines such as TNF- $\alpha$  and

IL-1 $\beta$ , can delay wound healing <sup>(19)</sup>. These factors may impair healing at the reconstruction site, increasing the risk of postoperative CSF leakage.

### Factors related to meningitis

Patients with meningitis were more likely to have higher intraoperative CSF leak grades, NSF reconstruction, fat graft placement, and prophylactic LD insertion. Additionally, delayed recognition or absence of subjective CSF leak symptoms was identified as a significant risk factor.

Higher intraoperative leak grades are associated with postoperative leakage, and when leakage occurs in these patients, the higher flow and pressure contribute to prolonged leakage, increasing infection risk. NSF reconstruction, fat grafting, and LD insertion are typically utilized in cases with higher leakage risk, complicating their interpretation as independent risk factors.

To clarify, a subgroup analysis focusing on grade 3 intraoperative leaks showed similar NSF use between the meningitis and non-meningitis groups, while fat grafting (50% vs. 11.1%) and LD usage (41.9% vs. 11.2%) remained significantly higher in the meningitis group (Table 3). This suggests that fat grafts and LDs may act as independent risk factors for meningitis.

Fat grafts are widely used in multilayer skull base reconstruction to reduce dead space and support closure, with minimal reported donor site morbidity <sup>(20,21)</sup>. However, large fat grafts may fail to integrate if insufficiently vascularized, leading to localized inflammation and potential infection. Infected fat grafts under NSFs may cause thrombosis in the flap pedicle, leading to flap necrosis and further leakage. Previous studies reported significantly higher fat graft use in necrotic NSF cases compared to viable ones (75% vs. 20%,  $p=0.004$ ) <sup>(22)</sup>, supporting a potential relationship between fat grafting and NSF viability. Additionally, early fat necrosis can lead to oily transudate leakage, which may persist and contribute to CSF leakage. If nasal flora enter the CNS through this persistent leak, the fat graft may act as a cause for infection, exacerbating inflammation and increasing the risk of meningitis.

Transudate leaks from fat grafts often resist conservative management, requiring early surgical intervention with necrotic fat removal to prevent prolonged leakage and infection <sup>(21)</sup>.

Prophylactic LD insertion, while intended to reduce CSF pressure and postoperative leakage, has shown conflicting results regarding its role in meningitis risk. While LDs can reduce CSF pressure, but may obscure CSF leak symptoms delaying recognition and intervention <sup>(23,24)</sup>, and serve as potential routes for ascending infection <sup>(7,8)</sup>. In our study, delayed detection and longer time to CSF repair surgery were observed in patients with fat grafts and LDs, suggesting that these interventions may contribute to meningitis risk by delaying CSF leak diagnosis.

### Correlation between unviable NSF and meningitis

NSF viability and its relationship with meningitis have been explored in previous studies, with some reporting that necrotic NSFs are strongly predictive of meningitis <sup>(22)</sup>. However, in our study, NSF viability alone was not significantly associated with meningitis risk. This supports our center's conservative management approach, where patients with non-enhancing NSFs on postoperative MRI are treated with reinforced nasal packing rather than immediate repair surgery, allowing the NSF to function as a free mucosal graft.

Nevertheless, in a subgroup analysis of 12 patients with non-enhancing or necrotic NSFs, all four patients who received fat grafts and both patients who underwent LD developed meningitis, suggesting a synergistic effect when NSF failure coexists with other risk factors. Additionally, the NSF failure rate among patients with postoperative CSF leakage was 30%, which is substantially higher than the commonly reported rate of 1–3% <sup>(22,25)</sup>, indicating that NSF failure may be associated with CSF leakage than with meningitis itself.

### Clinical diagnosis of meningitis

The reported incidence of CNS infections, including bacterial meningitis, post-ESBS ranges from 1–3% <sup>(16)</sup>, though higher rates have been reported in some studies <sup>(8)</sup>. Despite the occurrence of meningitis, mortality rates remain low, likely due to routine perioperative antibiotic administration, thorough intraoperative irrigation, and meticulous multilayer reconstruction <sup>(15)</sup>.

While the U.S. Centers for Disease Control and Prevention (CDC) define bacterial meningitis as requiring both positive CSF cultures and clinical symptoms <sup>(29)</sup>, false negatives are common, especially following antibiotic administration. The sensitivity of Gram stain and culture tests for CSF samples has been reported to vary widely across studies, ranging from 33% to 90% <sup>(26,27)</sup>. For example, one study found that when intravenous antibiotics were administered before CSF sampling, the yield of culture tests from CSF samples decreased by 10–20%, complicating the diagnosis of bacterial meningitis.

Typical CSF findings in bacterial meningitis include WBC counts  $\geq 1,000/\mu\text{L}$ , but some cases show lower counts or lymphocyte predominance <sup>(27,30)</sup>. Alternative diagnostic criteria include CSF WBC  $>1,000/\mu\text{L}$ , CSF-to-serum glucose ratio  $<0.3$ , elevated lactate, and high protein levels ( $>100 \text{ mg/dL}$ ) <sup>(32)</sup>, yet these criteria can also result in false negatives, particularly after prophylactic antibiotic use <sup>(28,34)</sup>.

Recognizing these limitations, our center adopts a proactive approach by initiating empirical treatment in patients with suspected postoperative meningitis based on clinical symptoms and endoscopic examination, even if CSF cultures are negative. In this study, 21 patients were treated empirically, with 11 culture-positive, 7 meeting CSF criteria despite negative cultures, and 3 neither culture nor CSF-criteria positive but treated

due to clinical presentation (Table S2). None of these last three patients had fat grafts, indicating that their condition was unlikely to be lipoid meningitis. Instead, their cases were more likely attributable to chemical or viral meningitis, or possibly bacterial meningitis with false-negative test results.

#### Subgroup analysis: delayed recognition and surgical timing

A key finding of this study was that patients who either failed to recognize CSF leak symptoms or experienced significant delays in recognizing them were at a notably higher risk of developing meningitis. CSF leaks are diagnosed based on patient-reported symptoms and endoscopic findings, and undetected leaks prolong exposure to nasal flora, increasing infection risk. Our subgroup analysis showed that patients with both subjective symptoms and objective findings had a meningitis incidence of 37.9% (11/29), while those with symptoms but no objective findings had a 40% incidence (4/10). Notably, all six patients with no subjective symptoms developed meningitis, highlighting the importance of early symptom recognition.

Further analysis showed that fat grafting delayed symptom recognition (11.3 vs. 6.3 days,  $p=0.012$ ) and prolonged the time to CSF repair surgery (28.5 vs. 17.7 days,  $p=0.002$ ). LD use showed similar trends, delaying recognition (15.1 vs. 11.6 days,  $p=0.254$ ) and repair (24.4 vs. 18.4 days,  $p=0.213$ ). It implies that these interventions may obscure CSF leak detection, increasing meningitis risk.

#### Strengths and limitations

The strengths of this study include a comprehensive evaluation of risk factors for meningitis following ESBS, an emphasis on the importance of early symptom detection, and analysis of a large cohort of 1,303 patients at a single tertiary center, which enhances its statistical power and clinical relevance.

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However, the study's single-center retrospective design, and potential for selection and information biases may limit the generalizability of the results. Tumor location, size, and defect extent were not analyzed in detail, potentially influencing leakage and infection risk. Additionally, variations in surgeon expertise may have influenced postoperative CSF leak rates and subsequent meningitis risk.

#### Conclusion

A higher intraoperative CSF leak grade significantly increases the risk of postoperative leakage and is strongly associated with meningitis. Fat grafts and prophylactic LDs also correlate with higher meningitis incidence. Additionally, patients who fail to promptly recognize CSF leak symptoms are at greater meningitis risk. Clinicians should adopt a more proactive strategy in patients with these risk factors, including detailed history-taking and frequent short-term endoscopic evaluations to ensure early detection and timely intervention.

#### Author contributions

Conceptualization: CHL, and SDH; Data curation: CHL; Formal analysis; Methodology: CHL and SDH; Project administration: CHL and SDH; Visualization: CHL; Writing – original draft: CHL; Writing - review & editing: CHL, DK, GR, W-JL, D-SK and SDH collectively contributed to reviewing and editing the manuscript. All authors have thoroughly reviewed and approved the final manuscript.

#### Conflict of interest

The authors have no conflicts of interest to declare.

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# Corrected Proof

*Risk factors for meningitis in patients with postoperative CSF leakage*

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## SUPPLEMENTARY MATERIAL

Table S1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients who underwent endoscopic skull base surgery (ESBS) between January 2015 and December 2021 at our institution	Patients with multiple postoperative complications (hemorrhage, sepsis, etc.)
Age ≥ 18 years	Patients who underwent immediate postoperative radiotherapy due to tumor extent or rapid progression (n=2)
Availability of complete medical records and follow-up data	Patients with metastatic cancer receiving concurrent chemotherapy that affected the operative bed and led to postoperative CSF leakage with sepsis (n=1)
	Patients who underwent burr-hole operation and developed meningitis without CSF leakage (n=1)

Table S2. Detailed data of patients who were suspicious of postoperative CSF leakage (N=49).

No.	Pa-thol-ogy	Patient information		Information about ESBS				Complica-tion				Findings related to CSF leak				
		BMI/kg/m <sup>2</sup>	intraop CSF leak grade (0,1,2,3)	NSF 0=no, 1=yes	postop NSF vi-ability 0=no, 1=yes	Lum-bar drain 0=no, 1=yes	Fat graft 0=no, 1=yes	Postop men-ingitis 0=no, 1=yes	Spinal lab (when suspicious of meningitis)				sub-jective CSF leak symp-tom 0=no, 1=yes	objec-tive find-ing for CSF leak 0=no, 1=yes	Tx for CSF leak 0=re-pair op, 1=con-serva-tive Mx	
1	1	23.4	3	1	1	1	1	1	3350	187	33	Positive	1	1	0	
2	1	27.2	3	1	0	0	1	1	1	37.4	73	Positive	1	1	0	
3	4	24.9	3	1	1	1	1	1	30	335	54	Negative	1	0	0	
4	1	27.9	3	1	1	1	1	1	180	623	88	Positive	1	1	0	
5	1	23.7	NA	1	0	1	0	1	2160	95.8	56	Negative	1	1	0	
6	1	26.1	3	1	1	0	0	1	380	113	28	Positive	0	1	1	
7	2	20.2	NA	1	0	1	0	1	1400	127	42	Positive	1	0	1	
8	1	25.8	3	1	1	0	0	1	1080	873	15	Negative	1	1	0	
9	7	26.3	3	1	1	0	1	1	226	161	48	Positive	1	1	1	
10	1	25.7	2	1	0	1	0	1	90	28.7	63	Negative	1	1	0	
11	3	26.1	3	1	0	0	0	1	1400	55	46	Positive	0	0	0	
12	1	28.1	0	0	NA	0	0	1	268	75	46	Positive	0	0	0	
13	1	32.3	3	1	1	1	0	1	2	57.4	42	Negative	1	1	1	
14	1	26.1	0	0	NA	0	0	1	1	63.9	47	Negative	1	0	1	
15	1	32.7	0	0	NA	0	0	1	380	395	34	Negative	1	0	0	
16	1	25.1	0	0	NA	0	0	1	10	76	40	Negative	1	1	0	
17	1	25.4	3	1	1	0	0	1	178	108	52	Negative	0	1	0	
18	5	25.9	3	1	0	1	1	1	1969	65	54	Positive	0	1	0	
19	1	26.4	3	1	1	0	0	1	7050	685	51	Positive	0	0	0	
20	5	24.9	3	1	1	1	1	1	3854	260	72	Positive	1	1	0	
21	1	21.8	3	1	1	0	0	1	7	205	77	Negative	1	1	0	
22	3	25.6	3	1	0	0	0	0					1	1	0	

# Corrected Proof

Risk factors for meningitis in patients with postoperative CSF leakage

Patient information				Information about ESBS					Complication				Findings related to CSF leak			
No.	Pathology	BMI kg/m <sup>2</sup>	intraop CSF leak grade (0,1,2,3)	NSF 0=no, 1=yes	postop NSF viability 0=no, 1=yes	Lumbar drain 0=no, 1=yes	Fat graft 0=no, 1=yes	Postop meningitis 0=no, 1=yes	Spinal lab (when suspicious of meningitis)			Culture	subjective CSF leak symptom 0=no, 1=yes	objective finding for CSF leak 0=no, 1=yes	Tx for CSF leak 0=repair op, 1=conservative Mx	
23	1	19.4	0	0	NA	0	0	0	WBC (cells/µL)	protein (mg/dL)	glucose (mg/dL)		1	1	0	
24	1	28.0	0	0	NA	0	0	0					1	1	1	
25	3	31.1	3	1	1	0	0	0					1	1	0	
26	1	23.9	2	1	1	0	0	0					1	1	0	
27	1	34.4	0	0	NA	0	0	0					1	0	1	
28	1	34.1	0	0	NA	0	0	0					1	1	0	
29	1	23.2	0	0	NA	0	0	0					1	0	0	
30	11	21.1	2	0	NA	0	0	0					1	1	0	
31	1	24.6	3	1	1	1	0	0					1	0	1	
32	5	31.6	3	1	1	0	1	0					1	1	0	
33	2	27.8	3	1	1	0	0	0					1	1	0	
34	1	24.5	1	0	NA	0	0	0					1	1	0	
35	1	28.4	1	0	NA	0	0	0					1	1	0	
36	1	24.0	0	0	NA	0	0	0					1	1	1	
37	1	29.4	0	0	NA	0	0	0					1	1	1	
38	1	28.7	2	0	NA	0	1	0					1	1	0	
39	1	41.0	0	0	NA	0	0	0					1	0	0	
40	3	24.5	3	1	0	0	0	0					1	1	0	
41	1	27.3	1	0	0	0	0	0					1	0	1	
42	1	21.4	0	0	NA	0	0	0					1	1	0	
43	1	18.8	1	1	0	0	0	0					1	0	1	
44	1	23.2	3	1	1	0	0	0					1	1	0	
45	2	21.1	0	0	NA	0	0	0					1	0	0	
46	1	24.7	1	1	0	0	0	0					1	0	1	
47	4	20.7	0	0	NA	0	0	0					1	0	0	
48	3	24.8	3	1	0	0	0	0					1	0	0	
49	1	26.8	3	1	1	0	0	0					1	1	0	

Pathology : 1=PA, 2=CP, 3=MNG, 4=Rathke's Cleft Cyst 5=Chordoma, 6=schwannoma, 7=other tumor, 10=inflammatory (Brain abscess), 11=other.