Clinical and technical factors in endoscopic skull base surgery associated with reconstructive success*

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Abstract

Background: In this study, we identified key discrete clinical and technical factors that may correlate with primary reconstructive success in endoscopic skull base surgery (ESBS).

Methods: ESBS cases with intraoperative cerebrospinal fluid (CSF) leaks at four tertiary academic rhinology programs were retrospectively reviewed. Logistic regression identified factors associated with surgical outcomes by defect subsite (anterior cranial fossa [ACF], suprasellar [SS], purely sellar, posterior cranial fossa [PCF]).

Results: Of 706 patients (50.4% female), 61.9% had pituitary adenomas, 73.4% had sellar or SS defects, and 20.5% had high-flow intraoperative CSF leaks. The postoperative CSF leak rate was 7.8%. Larger defect size predicted ACF postoperative leaks; use of rigid reconstruction and older age protected against sellar postoperative leaks; and use of dural sealants compared to fibrin glue protected against PCF postoperative leaks. SS postoperative leaks occurred less frequently with the use of dural onlay. Body-mass index, intraoperative CSF leak flow rate, and the use of lumbar drain were not significantly associated with postoperative CSF leak. Meningitis was associated with larger tumors in ACF defects, nondissolvable nasal packing in SS defects, and high-flow intraoperative leaks in PCF defects. Sinus infections were more common in sellar defects with synthetic grafts and nondissolvable nasal packing.

Conclusions: Depending on defect subsite, reconstructive success following ESBS may be influenced by factors, such as age, defect size, and the use of rigid reconstruction, dural onlay, and tissue sealants.

Key words: endoscopic skull base surgery, skull base reconstruction, skull base repair, risk factors, CSF leak

Introduction

Over the past two decades, advancements in endoscopic skull base surgery (ESBS) have made it possible to manage many skull base pathologies via a minimally invasive approach that

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otherwise previously required open resection [1]. Furthermore, for properly selected patients, ESBS is associated with decreased surgical morbidity, shorter hospital stays, and faster recovery times, which has facilitated the adoption of endoscopic approaches among otolaryngologists and neurosurgeons at high-volume skull base surgery centers [2-4]. However, the incidence of postoperative cerebrospinal fluid (CSF) leak following reconstruction presents a major technical challenge and serves as the primary cause of morbidity following ESBS [5,6].

Various factors, such as defect site, defect size, and intraoperative CSF leak flow rate have been found to predict reconstructive outcomes [1]. Numerous surgical techniques and materials have been proposed over the years to improve the likelihood of successful skull base repair and reduce postoperative complications [1,7,8]. However, systematic reviews examining ESBS techniques have demonstrated a high degree of heterogeneity across studies, with limited high-quality comparative evidence to suggest an optimal repair technique [9-11]. Additionally, there is a paucity of studies investigating the influence of specific reconstruction layers, materials, and adjunctive measures on reconstructive outcomes following ESBS.

In this study, we present one of the largest series to date of endonasal intradural skull base defect repairs. We aimed to identify patient-specific factors (e.g., sex, body mass index, defect site and size), technical factors (e.g., reconstruction layers and materials), and perioperative interventions and adjunctive measures (e.g., lumbar drain, nasal packing) that predict major reconstructive outcomes, including postoperative CSF leak, meningitis, and sinus infection.

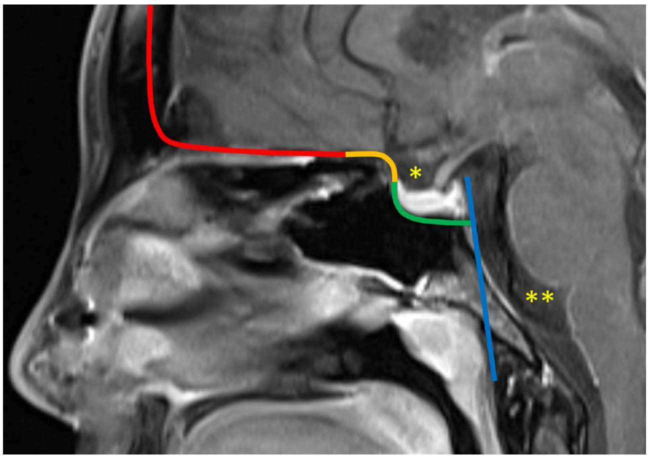

Figure 1. Boundaries of skull base defect sites analyzed in the current study: anterior cranial fossa (red), suprasellar (orange), sellar (green), and posterior cranial fossa (blue). The suprasellar (*) and prepontine (**) cisterns are indicated.

Materials and methods

Study population

A retrospective chart review of ESBS cases spanning from December 7, 2007 to December 21, 2022 was conducted at four tertiary academic rhinology programs (University of California, Irvine, Orange, CA, USA; University of California, Los Angeles, Los Angeles, CA, USA; University of Pennsylvania, Philadelphia, PA, USA; University of Cincinnati, Cincinnati, OH, USA) in accordance with each institution's corresponding Institutional Review Board. Inclusion criteria included any adult patient (age ≥18 years) who underwent ESBS and exhibited an intraoperative CSF leak (Table 1).

Study variables

Independent covariates used for analysis included overall patient demographics, intraoperative CSF leak flow rate (i.e., low-flow vs. high-flow), defect site, lumbar drain (LD) placement, nasal packing use (none/dissolvable vs. nondissolvable), and technical factors, including use of rigid reconstruction, multilayer inlay grafts (subdural/epidural placement), dural onlay (none vs. autologous vs. synthetic), mucosal coverage (none vs. free mucosal graft [FMG] vs. vascularized flap, including nasoseptal flap [NSF]), and tissue sealant use (none vs. fibrin glue vs. dural sealant). CSF leaks were classified based on the scale described by Esposito et al., with low-flow leaks as grade 1 or 2 and high-flow leaks as grade 3 (defect with direct extension to suprasellar/prepontine cistern and/or dural defect > 1 x 1 cm) [12]. Figure 1 provides definitions of the skull base defect sites as it pertains to this study. Anterior cranial fossa (ACF) defects were defined as those involving the posterior table of the frontal sinus and/or ethmoid roof (e.g., fovea ethmoidalis, lateral lamella, cribriform plate). Suprasellar (SS) defects were defined as those involving the planum sphenoidale and/or tuberculum sella with continuity with the suprasellar cistern, or sellar pathologies requiring removal of bone in those areas. Purely sellar defects only involved the sellar floor. Posterior cranial fossa (PCF) defects were defined as those involving the clivus or craniocervical junction with continuity with the prepontine cistern. For pathologies which overlapped multiple defect subsites, the subsite with highest CSF flow rate and/or largest defect was used (e.g., invasive pituitary adenoma with inferior clival extension was classified as PCF). Primary measured outcomes were postoperative CSF leaks, meningitis, and sinonasal infections (defined as endoscopic evidence of mucopurulence with positive culture with possible treatment with culture-directed antibiotics within 3 months postoperatively).

Statistical analysis

Statistical analyses were performed using R (version 4.2.2; The R Foundation for Statistical Computing) in RStudio (version 2022.12.0). A p-value of <0.05 was considered statistically significant. Wilcoxon rank sum and chi-square tests were conducted for continuous and categorical variables, respectively,

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Table 1. Summary of demographics, reconstruction technical factors, and postoperative measures and complications (N=706).

Demographics	No. (%)	Reconstruction Factors	No. (%)	Postoperative Measures	No. (%)	Postoperative Complications	No. (%)
Age, yr (mean ± SD)	51.2 ± 17.1	**Rigid Reconstruction**		**Nasal Packing**		**CSF Leak**	
Sex		No	499 (70.7)	None/ Dissolvable	520 (73.9)	No	651 (92.2)
Male	350 (49.6)	Yes	207 (29.3)	Non-dissolvable	184 (26.1)	Yes	55 (7.8)
Female	356 (50.4)	**Multi-Layer Inlay**		**Lumbar Drain**		**Meningitis**	
BMI, kg/m² (mean ± SD)	29.9 ± 7.4	No	504 (71.4)	No	482 (70.5)	No	687 (97.3)
Tumor Size, cm (mean ± SD)	2.36 ± 1.33	Yes	202 (28.6)	Yes	202 (29.5)	Yes	19 (2.7)
Defect Site		**Dural Onlay**		**Bedrest Days**	2.8 ± 4.3	**Sinus Infection**	
ACF	58 (9.6)	None	514 (79.4)	**POD of Debridement**	17.6 ± 16.0	No	674 (95.6)
Sella	262 (43.4)	Autologous	14 (2.2)			Yes	31 (4.4)
Suprasellar	181 (30.0)	Synthetic	119 (18.4)				
PCF	103 (17.1)	**Mucosal Coverage**					
Defect Size, cm² (mean ± SD)	3.27 ± 2.24	None	49 (7.0)				
ACF	3.81 ± 3.46	FMG	77 (11.0)				
Sella	2.96 ± 1.71	Vascularized Flap	576 (82.1)				
Suprasellar	3.11 ± 2.08	**All Synthetic Grafts**					
PCF	4.29 ± 2.17	No	505 (81.3)				
Intraoperative CSF Leak Flow		Yes	116 (18.7)				
Low	561 (79.5)	**Tissue Sealant**					
High	145 (20.5)	None	279 (40.8)				
Pathologies		Fibrin Glue	72 (10.5)				
Pituitary Adenoma	437 (61.9)	Dural Sealant	291 (42.6)				
Craniopharyngioma	56 (7.9)	Fibrin Glue + Dural Sealant	41 (6.0)				
Meningioma	52 (7.4)						
Rathke's Cleft Cyst	41 (5.8)						
ENB	17 (2.4)						
Chordoma	15 (2.1)						
Encephalocele	15 (2.1)						
Cushing Disease	8 (1.1)						
Other*	65 (9.2)						

ACF: Anterior Cranial Fossa; BMI: Body Mass Index; CSF: Cerebrospinal Fluid; ENB: Esthesioneuroblastoma; FMG: Free Mucosal Graft; POD: Postoperative Day; PCF: Posterior Cranial Fossa; Postoperative Day; SD: Standard Deviation. * Pathologies representing less than 0.5% of the study population.

to assess differences in demographics and outcomes between patients with different skull base defects. Logistic regression was conducted to identify predictors of postoperative CSF leak, meningitis, and sinus infection. For analysis of the entire cohort, variables with p-values of <0.1 on univariate logistic regression or those considered clinically significant (e.g., intraoperative leak flow, multilayer inlay, mucosal coverage) based on a priori causal knowledge were included as covariates in multivariable models [13]. Models were checked for multicollinearity by ensuring that covariates had variance inflation factors less than 10 [14]. For site-specific analysis, due to limits in sample size, only univariate logistic regression was performed.

Results

A total of 706 ESBS (50.4% female) patients were studied. The mean age was 51.2 ± 17.1 years. Table 1 lists the sociodemographic and clinical characteristics of this cohort. Overall, 61.9% had pituitary adenomas, 73.4% had sellar or SS defects, and 20.5% had high-flow intraoperative CSF leaks. The average defect size was 3.27 ± 2.24 cm^2. PCF defects were larger than sella

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Table 2. Demographics and reconstruction technical factors in patients with and without postoperative CSF leaks, stratified by defect site.

Variables	Anterior Cranial Fossa			Sellar			Suprasellar			Posterior Cranial Fossa		
	No Leak (N = 53)	Leak (N = 5)	P	No Leak (N = 238)	Leak (N = 24)	P	No Leak (N = 166)	Leak (N = 15)	P	No Leak (N = 94)	Leak (N = 9)	P
Age, yr	56.0 ± 15.4	46.2 ± 20.8	0.360	50.7 ± 17.7	41.5 ± 15.7	**0.013**	52.8 ± 15.5	53.2 ± 19.1	0.859	52.6 ± 17.1	49.7 ± 10.7	0.344
Sex, No. (%)												
Male	33 (62.3)	4 (80.0)	0.644	121 (50.8)	10 (41.7)	0.521	78 (47.0)	6 (40.0)	0.788	45 (47.9)	4 (44.4)	>0.99
Female	20 (37.7)	1 (20.0)		117 (49.2)	14 (58.3)		88 (53.0)	9 (60.0)		49 (52.1)	5 (55.6)	
BMI, kg/m²	30.1 ± 6.8	24.3 ± 0.2	0.128	31.6 ± 8.8	35.2 ± 7.3	0.178	28.0 ± 5.6	31.9 ± 7.9	0.174	29.6 ± 7.0	38.1 ± NA	0.198
Tumor Size, cm	3.78 ± 2.07	4.32 ± 2.02	0.481	1.78 ± 1.12	1.88 ± 1.33	0.831	2.42 ± 0.97	2.83 ± 1.44	0.180	2.96 ± 1.28	2.95 ± 0.84	0.756
Defect Size, cm²	3.35 ± 2.65	7.71 ± 6.75	0.095	2.88 ± 1.72	3.68 ± 1.56	**0.044**	3.01 ± 2.02	4.03 ± 2.49	0.101	4.22 ± 2.18	4.87 ± 2.18	0.450
Intraop Leak Flow, No. (%)												
Low	30 (56.6)	4 (80.0)	0.392	213 (89.5)	23 (95.8)	0.485	106 (63.9)	9 (60.0)	0.784	76 (80.9)	6 (66.7)	0.384
High	23 (43.4)	1 (20.0)		25 (10.5)	1 (4.2)		60 (36.1)	6 (40.0)		18 (19.1)	3 (33.3)	
Rigid Reconstruction, No. (%)												
No	50 (94.3)	5 (100.0)	>0.99	166 (69.7)	22 (91.7)	**0.029**	123 (74.1)	14 (93.3)	0.122	69 (73.4)	7 (77.8)	>0.99
Yes	3 (5.7)	0 (0.0)		72 (30.3)	2 (8.3)		43 (25.9)	1 (6.7)		25 (26.6)	2 (22.2)	
Multi-Layer Inlay, No. (%)												
No	32 (60.4)	5 (100.0)	0.148	198 (83.2)	23 (95.8)	0.141	99 (59.6)	11 (73.3)	0.411	72 (76.6)	7 (77.8)	>0.99
Yes	21 (39.6)	0 (0.0)		40 (16.8)	1 (4.2)		67 (40.4)	4 (26.7)		22 (23.4)	2 (22.2)	
Dural Onlay, No. (%)												
None	37 (72.5)	3 (60.0)	0.370	202 (84.9)	22 (91.7)	0.815	104 (67.1)	14 (93.3)	**0.008**	67 (75.3)	6 (75.0)	0.285
Autologous	3 (5.9)	1 (20.0)		3 (1.3)	0 (0.0)		3 (1.9)	1 (6.7)		2 (2.2)	1 (12.5)	
Synthetic	11 (21.6)	1 (20.0)		33 (13.9)	2 (8.3)		48 (31.0)	0 (0.0)		20 (22.5)	1 (12.5)	
Mucosal Coverage, No. (%)												
None	13 (24.5)	2 (40.0)	0.711	23 (9.7)	2 (8.3)	0.337	0 (0.0)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	0.576
FMG	16 (30.2)	1 (20.0)		18 (7.6)	4 (16.7)		11 (6.6)	1 (6.7)		8 (8.5)	1 (11.1)	
Vascularized Flap	24 (45.3)	2 (40.0)		197 (82.8)	18 (75.0)		155 (93.4)	14 (93.3)		86 (91.5)	8 (88.9)	
Synthetic Grafts, No. (%)												
No	29 (60.4)	5 (100.0)	0.147	185 (80.8)	24 (100.0)	**0.011**	96 (69.1)	12 (85.7)	0.235	79 (90.8)	9 (100.0)	>0.99

BMI: Body Mass Index; FMG: Free Mucosal Graft. Percentages reflect the number of patients with available data.

Bold indicates statistically significant, p<0.05

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Table 2. *continued*

Variables	Anterior Cranial Fossa			Sellar			Suprasellar			Posterior Cranial Fossa		
	No Leak (N = 53)	Leak (N = 5)	P	No Leak (N = 238)	Leak (N = 24)	P	No Leak (N = 166)	Leak (N = 15)	P	No Leak (N = 94)	Leak (N = 9)	P
Yes	19 (39.6)	0 (0.0)		44 (19.2)	0 (0.0)		43 (30.9)	2 (14.3)		8 (9.2)	0 (0.0)	
Tissue Sealant, No. (%)												
None	5 (10.6)	2 (40.0)	0.084	82 (38.1)	10 (43.5)	0.882	74 (50.3)	5 (33.3)	**0.044**	48 (53.9)	4 (50.0)	**0.005**
Fibrin Glue	11 (23.4)	2 (40.0)		21 (9.8)	2 (8.7)		11 (7.5)	4 (26.7)		5 (5.6)	3 (37.5)	
Dural Sealant	31 (66.0)	1 (20.0)		112 (52.1)	11 (47.8)		62 (42.2)	6 (40.0)		36 (40.4)	1 (12.5)	
Nasal Packing, No. (%)												
None/Dissolvable	22 (41.5)	3 (60.0)	0.643	172 (72.3)	21 (87.5)	0.144	119 (71.7)	11 (73.3)	>0.99	70 (74.5)	9 (100.0)	0.112
Nondissolvable	31 (58.5)	2 (40.0)		66 (27.7)	3 (12.5)		47 (28.3)	4 (26.7)		24 (25.5)	0 (0.0)	
Lumbar Drain, No. (%)												
No	24 (49.0)	2 (40.0)	>0.99	155 (67.7)	16 (66.7)	>0.99	106 (65.8)	8 (57.1)	0.564	71 (77.2)	6 (75.0)	>0.99
Yes	25 (51.0)	3 (60.0)		74 (32.3)	8 (33.3)		55 (34.2)	6 (42.9)		21 (22.8)	2 (25.0)	

and suprasellar defects (all p<0.05). Postoperatively, 7.8% had CSF leaks, 2.7% had meningitis, and 4.4% had sinus infections. Of the 55 patients with postoperative CSF leaks, 80% had initially presented with low-flow intraoperative leaks and 20% with high-flow leaks.

There were no significant differences in rates of postoperative CSF leak, meningitis, or sinus infection between defect sites (all p>0.05). Defect site-specific differences in demographic and technical reconstruction factors between patients with and without postoperative CSF leak are listed in Table 2. Among sellar defects, larger defects and repairs not involving rigid reconstruction or synthetic grafts more often exhibited postoperative CSF leaks (all p<0.05). The use of dural onlay in SS defect repair and the use of tissue sealants in SS and PCF defect repairs exhibited fewer postoperative leaks (all p<0.05).

Multivariable logistic regression on the entire cohort was used to identify risk factors for postoperative CSF leaks (Table 3). Increased defect size predicted postoperative leak (OR 1.26; 95% CI, 1.04-1.57; p=0.028). Use of rigid reconstruction (OR 0.17; 95% CI, 0.04-0.59; p=0.011), synthetic grafts (OR 0.10; 95% CI, 0.01-0.72; p=0.047), dural sealant (OR 0.14; 95% CI, 0.03-0.50; p=0.005) , and nondissolvable nasal packing (OR 0.22; 95% CI, 0.07-0.60; p=0.005) was protective of postoperative leaks. Sub-analyses stratified by defect site demonstrated that BMI and intraoperative CSF leak flow rate as well as the use of nasal packing, fibrin glue, and lumbar drain were not significantly associated with postoperative CSF leak (all p>0.05).

Anterior cranial fossa defects

Of 58 patients with ACF defects, 8.6% had postoperative CSF leak, 5.2% meningitis, and 5.2% sinus infection. On logistic regression, larger defect size was associated with increased risk for postoperative CSF leaks (OR 1.32; 95% CI: 1.04-1.89; p=0.049). Larger tumors were associated with increased risk for meningitis (OR 1.94; 95% CI: 1.14-4.06; p=0.028). There were no significant predictors of sinus infection in ACF defects (all p>0.05).

Purely sellar defects

Of 262 patients with sellar defects, 9.2% had postoperative CSF leak, 2.3% meningitis, and 3.8% sinus infection. Older age (OR 0.97; 95% CI: 0.95-0.99; p=0.017) and rigid reconstruction (OR 0.21; 95% CI: 0.03-0.74; p=0.038) were associated with decreased risk for postoperative CSF leaks. There were no significant predictors of meningitis in sellar defects (all p>0.05). Use of synthetic grafts (OR 8.15; 95% CI: 1.79-57.28; p=0.012) and nondissolvable nasal packing (OR 8.53; 95% CI: 1.89-59.70; p=0.010) were associated with increased risk for sinus infection.

Suprasellar defects

Of 181 patients with SS defects, 8.3% had postoperative CSF leak, 1.7% meningitis, and 4.4% sinus infection. The rate of

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Table 3. Logistic regression identifying predictors of postoperative CSF leak.

Variables	Univariate		Multivariable	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age, yr	0.98 (0.97-0.99)	**0.034**	0.98 (0.95-1.01)	0.126
Sex				
Male	1 [Reference]		1 [Reference]	
Female	1.20 (0.69-2.09)	0.525	~	~
BMI, kg/m²	1.04 (0.98-1.09)	0.189	~	~
Tumor Size, cm	1.10 (0.89-1.33)	0.370	~	~
Defect Size, cm²	1.22 (1.08-1.39)	**0.001**	1.26 (1.04-1.57)	**0.028**
Defect Site				
ACF	1 [Reference]		1 [Reference]	
Sella	1.07 (0.42-3.29)	0.897	0.64 (0.13-3.46)	0.590
SS	0.96 (0.35-3.06)	0.936	0.83 (0.15-3.92)	0.836
PCF	1.02 (0.33-3.45)	0.980	0.24 (0.03-1.65)	0.145
Intraoperative CSF Leak Flow Rate				
Low	1 [Reference]		1 [Reference]	
High	0.97 (0.46-1.85)	0.918	1.46 (0.41-4.91)	0.542
Rigid Reconstruction				
No	1 [Reference]		1 [Reference]	
Yes	0.27 (0.10-0.60)	**0.003**	0.17 (0.04-0.59)	**0.011**
Multi-Layer Inlay				
No	1 [Reference]		1 [Reference]	
Yes	0.40 (0.17-0.82)	**0.020**	0.60 (0.12-2.44)	0.501
Dural Onlay				
None	1 [Reference]		1 [Reference]	
Autologous	2.71 (0.60-9.05)	0.136	1.14 (0.11-8.70)	0.90
Synthetic	0.35 (0.10-0.87)	**0.045**	0.40 (0.03-2.63)	0.41
Mucosal Coverage				
No Flap	1 [Reference]		1 [Reference]	
Vascularized Flap	0.87 (0.45-1.81)	0.680	1.09 (0.25-5.33)	0.909
All Synthetic Grafts				
No	1 [Reference]		1 [Reference]	
Yes	0.15 (0.03-0.50)	**0.010**	0.10 (0.01-0.72)	**0.047**
Tissue Sealant				
None	1 [Reference]		1 [Reference]	
Fibrin Glue	2.34 (1.07-4.92)	**0.028**	0.45 (0.11-1.77)	0.266
Dural Sealant	0.82 (0.43-1.54)	0.532	0.14 (0.03-0.50)	**0.005**
Nasal Packing				
None/Dissolvable	1 [Reference]		1 [Reference]	
Nondissolvable	0.53 (0.24-1.06)	0.090	0.22 (0.07-0.60)	**0.005**
Lumbar Drain				
No	1 [Reference]		1 [Reference]	
Yes	1.495 (0.82-2.65)	0.175	1.86 (0.53-6.95)	0.342

ACF: Anterior Cranial Fossa; BMI: Body Mass Index; CI: Confidence Interval; CSF: Cerebrospinal Fluid; OR: Odds Ratio; PCF: Posterior Cranial Fossa; SS: Suprasellar. Bold indicates statistically significant, $p<0.05$

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postoperative CSF leak was significantly lower in reconstructions that used a dural onlay (1.9% vs. 11.9%, p=0.035). Use of nondissolvable nasal packing was associated with increased risk for meningitis (OR 5.88; 95% CI: 1.12-43.11; p=0.044). There were no significant predictors of sinus infection in SS defects (all p>0.05).

Posterior cranial fossa defects

Of 103 patients with PCF defects, 8.7% had postoperative CSF leak, 4.9% meningitis, and 2.0% sinus infection. Fifteen (14.6%) patients presented with chordomas, 5 of whom had high-flow intraoperative leaks, 3 had postoperative CSF leaks, and 2 had meningitis. Compared to fibrin glue, use of dural sealant was associated with reduced risk for postoperative CSF leaks (OR 0.05; 95% CI: 0.01-0.44; p=0.014). High-flow intraoperative CSF leak was associated with increased risk for meningitis (OR 19.06; 95% CI: 2.62-385.61; p=0.010). There were no significant predictors of sinus infection in PCF defects (all p>0.05).

Discussion

Postoperative CSF leak remains one of the most challenging complications encountered following ESBS. Many reconstructive surgical techniques have therefore been introduced to reduce the incidence of CSF leak, albeit, with variable results. This multicenter study sought to leverage the large number of patients and use of different techniques at four tertiary care rhinology/anterior skull base surgery programs to investigate patient and technical factors that may be associated with reconstructive success in ESBS. Overall, the incidence of postoperative CSF leak regardless of reconstructive technique used or location of skull base defect was comparable to the current literature, with an overall rate of 7.8%, of which 80% occurred in patients with intraoperative low-flow CSF leaks. This suggests overall highly favorable outcomes with modern techniques and repair strategies. Additionally, there was no difference in CSF leak rate between ACF (8.6%), sella (9.2%), SS (8.3%), or PCF (8.7%) defect locations. Multivariable logistic regression that accounted for potential confounders, such as differences in defect size between subsites, similarly supported a lack of association between defect subsite and CSF leak incidence. Soudry et al.'s systematic review evaluating repair techniques of 673 endoscopically created skull base defects similarly showed that the overall postoperative CSF leak rate after intraoperative skull base repair was 8.5% (57/673) [15]. Moreover, this review also demonstrated the location of the skull base defect does not significantly affect the risk of postoperative CSF leak, excluding clival defects (though the sample size was small).

Anterior cranial fossa defects

When evaluating factors associated with surgical outcomes by defect subsite, larger ACF defect size was associated with increased risk for postoperative CSF leak. ACF defects can be as large as extending from the posterior table of the frontal sinus to the planum sphenoidale, requiring significant area for coverage, thus increasing the risk for postoperative CSF leaks [16–21]. These defects often also require a multilayer reconstruction technique which may include the use of a NSF. With a larger area requiring reconstruction in an anti-gravity configuration, it is conceivable that the forces created by intracranial pressure (ICP) may need to be countered by stiffer materials or bolstering (e.g., nasal packing). Our study does not show any association with onlay used (e.g., NSF vs. FMG) when reconstructing the ACF. The current literature shows variable success with ACF reconstruction; although, recently, rates of postoperative CSF leak are much more consistent and generally low regardless of material used [19,20,22–24]. Germani et al. used a nonvascularized single layer to reconstruct the skull base defect with a 3% postoperative CSF leak rate while Eloy et al. reconstructed the ACF with multiple layers including a vascularized flap with a postoperative CSF leak rate of 0% [22,23]. Given the variations in reconstructive technique with comparable postoperative outcomes, the success of ACF reconstruction may, in fact, rely on the ability to cover the entire defect regardless of the reconstructive technique used.

Sellar defects

There are a myriad of reconstruction options for repairing sellar defects, the most common of ESBS defects, most of which include multiple layers; however, there is no consensus on the optimal reconstructive technique or material [25–27]. Some propose graded reconstruction based on the presence of an intraoperative leak and leak flow rate (e.g., high- vs. low-flow) [25,27–35]. Most intraoperative CSF leaks following resection of sellar pathologies are low-flow, as demonstrated in this study, with a rate of 90.1% compared to high-flow leaks. In the current study, rigid reconstruction was statistically associated with decreased risk for postoperative CSF leak comprising a rate of 2.7% when used to reconstruct sellar defects compared to a rate of 11.7% when no rigid reconstruction was used. The "gasket seal" technique is one method of rigid reconstruction used for such defects [36,37]. It typically consists of a soft overlay (e.g., fascia lata) with a rigid buttress (e.g., bone, synthetic plate) placed into the bony defect and over the overlay creating a gasket that accommodates defect irregularities, thereby creating a watertight seal [36,37]. Garcia-Navarro et al. demonstrated success in a larger cohort of 46 patients with a postoperative leak rate of 4.3% [38]. Excluding use of rigid reconstruction, no other materials or techniques were associated with reducing CSF leak. This suggests surgical success is largely independent of specific materials or technique used as long as meticulous technique is employed.

Suprasellar defects

Reconstruction of SS defects poses a unique set of challenges. SS defects are typically associated with intraoperative high-flow

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CSF leaks with continuity with the suprasellar cistern and, in some cases, the third ventricle [39]. Difficulty repairing these high-flow CSF leaks is amplified when the defect involves multiple skull base planes including the planum sphenoidale, tuberculum sella, and/or sella turcica. Additionally, as the SS defect extends to its limits, the defect border may abut vital structures including the internal carotid arteries and the optic nerves, partially limiting the ability to place inlays [15]. In our study, the single most important SS reconstructive technique was the use of a dural onlay, which was associated with a significantly lower rate of postoperative CSF leak. We hypothesize that a dural onlay, which may take the form of autologous (e.g., fascia lata) or synthetic (e.g., porcine small intestine submucosa) graft, may provide an additional layer of watertight coverage over the SS defect, which is commonly irregularly shaped due to exposure of the optic canals and carotid arteries.

Posterior cranial fossa defects

PCF defects pose unique surgical challenges compared to other skull base defects due to the vertical orientation, limited bony or dural edges, as well as the anatomic proximity to the anterior brain cisterns and ventricles. Reconstruction often requires the use of a vascularized flap for mucosal coverage [8,40–42]. Multiple studies have shown clival defects to be particularly difficult to reconstruct; in fact, it has been demonstrated to be the only skull base subsite with improved outcomes using a vascularized flap compared to nonvascularized repair [15,43]. One study demonstrated a 60% success rate with multilayer free graft alone whereas the use of a pedicled flap improved success rate to 100% [44]. Saito et al. used a fascia lata inlay and NSF onlay with a 100% success rate [45]. Two series evaluating resection of clival chordomas with PCF reconstruction with a Duragen inlay and a NSF onlay showed a 90% (9/10) and 75% (15/20) success rate, although the second series comprised more complex patients who were either received prior radiation, had recurrence of disease, or significant intradural extension [16,46]. A vascularized flap was used for reconstruction in 91.2% (94/103) of our PCF defects; however, there was no difference in rate of postoperative leak and whether a FMG or vascularized flap was used with leak rates of 11.1% (1/9) and 8.5% (8/94), respectively.

Support materials and adjuncts for reconstruction

The benefit of ancillary reconstructive techniques including the use of nasal packing, tissue sealants, and lumbar drains (LD) have long been debated with conflicting outcomes in the literature [47–79]. Our data demonstrates a decrease in the risk of CSF leak with the use of dural sealants and nondissolvable nasal packing. Eloy et al. analyzed different tissue sealants including Duraseal® and Tisseel® when applied over a NSF in patients undergoing endoscopic skull base repair for high-flow CSF leaks and compared the incidence of postoperative CSF leak to patients without tissue sealant use [63]. This study found there to be no significant difference in the incidence of CSF leak between the two groups. A comprehensive meta-analysis by Ahmed et al. evaluated perioperative LD use following endonasal endoscopic CSF leak repair and found that LD use did not significantly lower postoperative CSF leak recurrence rates [48]. There may, however, be certain circumstances in which a LD may be beneficial, most notably high-flow CSF leak in the setting of large ACF and PCF defects [58]. Lastly, nasal packing is often used to bolster the reconstruction while the surgical wound heals. The value of packing has been questioned recently with the use of sound techniques and other adjuncts [59,82]. Given each of these factors as well as flow rate or other general repair technique did not significantly impact the rate of postoperative CSF leak, success of skull base repair may hinge largely on surgeon adherence to basic principles and necessary elements of skull base reconstruction [83]. This is further emphasized by the lack of effect of patient factors including BMI and sex on a success of skull base reconstruction regardless of subsite.

Postoperative meningitis and sinusitis

When considering skull base reconstruction and risk of postoperative infections, sinusitis and meningitis are fortunately uncommon complications. In the present study, there was an overall meningitis rate of 2.7% (19/687), which is comparable to the current literature. In a recent systematic review evaluating risk of meningitis following expanded ESBS, the overall incidence of meningitis was found to be 1.8% (80). Unsurprisingly, when postoperative CSF leak was encountered, the risk of meningitis increased compared to those without a postoperative CSF leak (13% vs 0.1%). This emphasizes the importance of successful skull base reconstruction preventing postoperative CSF leak. In the subanalysis comparing ACF and PCF, rates of postoperative meningitis were not statistically different (1.7% vs 1.0%). In the present study, ACF (5.2%) and PCF (4.9%) defects had the highest meningitis rates, but the difference was not significantly different from meningitis arising from sellar (2.3%) and SS (1.7%) surgery. Additionally, we found there were inconsistent factors associated with meningitis, including large tumor size for ACF defects, use of dissolvable nasal packing in SS defects, and high-flow intraoperative CSF leaks in PCF defects.

Our study demonstrated an incidence of postoperative sinusitis occurred in 4.4% of cases and was statistically associated with sellar defects when synthetic grafts or nondissolvable packing was used as part of the reconstruction. Importantly, no factors predicted increased risk of sinonasal infection in ACF, SS, or PCF reconstruction. Nondissolvable packing may act as a foreign bodies, with associated risk of local infection. Little et al. examined factors associated with sinonasal quality of life following endoscopic transsphenoidal surgery in 100 patients and found

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that nasal packing was associated with a higher incidence of postoperative mucopurulence [81]. Additionally, mucopurulence resolution in patients with nasal packing occurred significantly later postoperatively (6 weeks) compared to patients without (2 weeks), with presumed impact on patient quality of life. Additionally, Asmaro et al. evaluated 73 consecutive patients after skull base reconstruction without sinonasal packing for CSF leak [69]. Infectious sinusitis occurred in 2.7% of patients in the first 3 months postoperatively which is less than the incidence in the present study. Ultimately, there remains a paucity of data exploring the use of these materials in skull base reconstruction and association of sinusitis among other outcomes, thereby warranting further investigation [7,10].

Limitations

Although this study leveraged data from four different tertiary rhinology centers, it was still limited by its retrospective nature. Certain pathologies, such as pituitary adenoma, were overrepresented as compared to other rarer pathologies (e.g., chordoma). Moreover, certain factors such as history of previous radiation treatment or comorbid sinusitis were not accounted for in our analysis. Finally, our rates of meningitis and sinus infection were low in our cohort, thereby limiting our statistical analyses of these outcomes. However, notable strengths of this study include a larger sample size across different tertiary skull base programs of wide geographic distribution (U.S. West, Midwest, and Northeast) and diversity in surgical techniques and management principles, which permits for comparison groups, as well as granular data collection with consistent reporting of specific layers of reconstruction, which has not been compiled previously.

Conclusion

In this multicenter observational study of 706 ESBS patients, we found technical factors, such as the use of rigid reconstruction, dural onlay, and tissue sealants, to be independent predictors of postoperative CSF leak in certain skull base subsites. Perioperative factors, such as the use of synthetic grafts for reconstruction and nondissolvable nasal packing postoperatively, may also incur increased risk for meningitis or sinus infection. Success of skull base reconstruction may largely depend on surgeon adherence to basic principles and necessary elements of skull base reconstruction, and to do so in a meticulous and thoughtful manner.

Authorship contribution

Data acquisition: AA, BFB, TVN, JCP, KMR, MV, DDC, SHT, JCH, NK, RMS, MK, JEM; Data analysis: AA; Data interpretation: AA, BFB, JED, DJL, JGE, RSK, KMP, ARS, MB, MBW, JNP, NDA, FPKH, ECK; Drafting Article: AA, BFB, TVN, JCP; Final Approval: AA, BFB, TVN, JCP, KMR, MV, DDC, SHT, JCH, NK, RMS, MK, JEM, JED, DJL, JGE, RSK, KMP, ARS, MB, MBW, JNP, NDA, FPKH, ECK

Conflict of interest

There are no relevant conflicts of interest.

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Ethics approval

This study was conducted in accordance with the Institutional Review Boards at University of California - Irvine, University of California - Los Angeles, University of Pennsylvania, University of Cincinnati.

Availability of data and materials

Data used in this study is available from the corresponding author (ECK) on reasonable request.

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