Factors influencing timing of cerebrospinal fluid leak after endoscopic skull base surgery: a multicenter study

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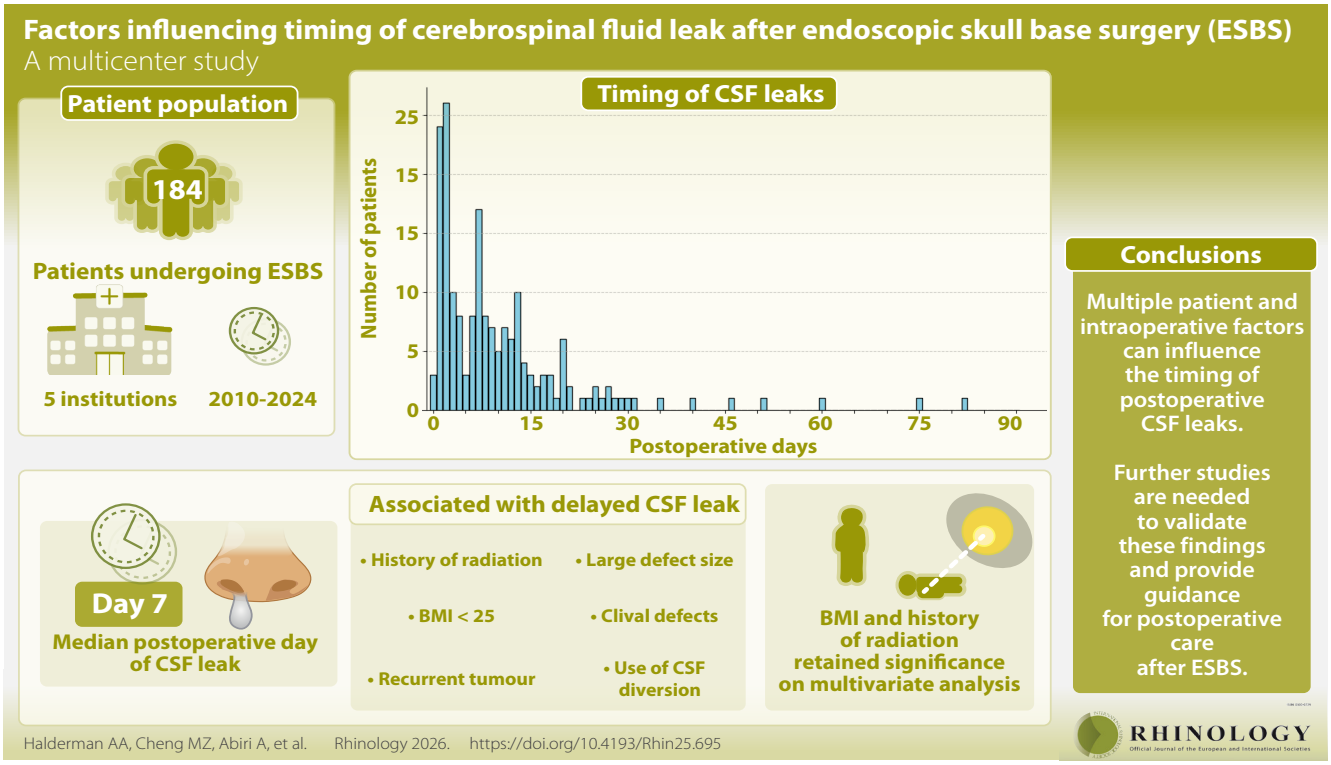

Abstract

Introduction: Considerable work has been done to delineate risk factors for cerebrospinal fluid (CSF) leak after endoscopic skull base surgery (ESBS). Little work has been done to evaluate factors that influence the timing of CSF leaks after ESBS. The timing of when CSF leaks occur may have important implications on postoperative precautions and managing the underlying etiology. The aim of this multi-institutional study was to evaluate postoperative CSF leaks after ESBS to determine timing of occurrence and factors that influence when leaks occur. **Methods**: Data were collected retrospectively on patients diagnosed with CSF leak after ESBS at 5 institutions from 2010 to 2024. Variables including patient demographics, tumour and defect dimensions, defect location, reconstruction, timing of CSF leak, management of leak, and rates of meningitis were collected. **Results**: A total of 184 patients were analysed. The median postoperative day (POD) when CSF leak occurred was 7. Prior radiation, BMI<25, recurrent tumours, large defect size, defects located in the clivus, and CSF diversion were all associated with delays in presentation of postoperative CSF leak (all $p<0.05$). On multivariate analysis, BMI and history of radiation retained significance in association with delayed CSF leak. Timing of leak also appeared to be impacted by the number of, and specific layers used in reconstruction. **Conclusions**: Several factors were found to impact the timing of CSF leak after ESBS including patient, intraoperative, and postoperative factors. Understanding timing of postoperative CSF leaks may provide insights for prevention and secondary management.

Key words: cerebrospinal fluid leak, meningitis, postoperative management, skull base reconstruction, timing

Introduction

Considerable work has been done to delineate risk factors for cerebrospinal fluid (CSF) leak incidence after endoscopic skull base surgery (ESBS). Thus far, obesity/body mass index (BMI) >25, presence of preoperative hydrocephalus and/or elevated intracranial pressure (ICP), larger defect size, presence of intraoperative leak, use of vascularized flaps and/or multilayer reconstructions, and surgeon experience have been shown to influence the rate of postoperative CSF leaks in this patient population [1-14]. Little work, however, has been done to evaluate factors which might influence the timing of CSF leaks after ESBS. This is despite the fact that CSF leaks are the most common complication of ESBS, occurring at an overall rate of 8.9% (range 0-40%) in one systematic review [15]. Of the studies that provided information regarding timing of CSF leak after ESBS, the range has been reported as between postoperative days (POD) 0-32 [4,16,17]. One study defined delayed leaks as those occurring after POD7 [18]. Another study found that patients with obstructive sleep apnea (OSA) trended towards developing postoperative CSF leaks earlier than patients without OSA, although it must be noted that the sample size of this study was small and may have prevented the difference from attaining significance [3].

The timing of postoperative CSF leaks and factors which may influence that timing have important implications on hospital length of stay, postoperative monitoring, nasal hygiene routines, and activity restrictions, for which there is no consensus [19]. The aim of this multicenter study was to evaluate postoperative CSF leaks after ESBS to determine timing of CSF leaks and factors that may influence when leaks occur.

Materials and methods

Five academic rhinology and skull base surgery programs (University of Texas Southwestern, University of California Irvine, Oregon Health and Science University, University of Pittsburgh, University of Pennsylvania) participated in this study. Institutional review board approval was obtained at each participating institution. Data were collected retrospectively on patients who underwent ESBS for resection of a neoplasm complicated by a subsequent postoperative CSF leak between January 1, 2010 through April 1, 2024. Inclusion criteria included all ages, index ESBS case corresponding to the postoperative leak performed at one of the participating institutions, and development of a CSF leak postoperatively. Exclusion criteria included index surgery done at an outside institution or no postoperative CSF leak. Primary CSF leak repairs (such as for traumatic, congenital, and spontaneous etiologies), meningoceles, and meningoencephaloceles were excluded from analysis.

Patient data including demographic information, tumour and defect dimensions, history of prior radiation, presence of elevated ICP before surgery (defined as presence of hydrocephalus requiring intervention or confirmed intracranial hypertension on diagnostic testing), defect location (anterior cranial fossa [ACF], suprasellar, sellar, posterior cranial fossa [PCF]), Esposito grade of leak for sellar defects [20], CSF flow rate for non-sellar defects (low-flow leak was defined as <1 cm^2 dural defect, high-flow leak was defined as >1 cm^2 dural defect and/or communication with a ventricle or cistern) [21], layers of reconstruction (subdural layer [graft placed in the subdural space], epidural underlay [graft placed in the epidural space], bony/dural onlay, mucosal coverage with free graft or vascularized flap), CSF diversion via lumbar drain (LD) or external ventricular drain (EVD), use of dural sealant, and use of nasal packing to bolster the reconstruction (non-absorbable [i.e., requiring formal removal; e.g., strip gauze] versus absorbable [i.e., not requiring formal removal; e.g., Nasopore]). Outcome variables included timing (POD) of CSF leak, management strategy of postoperative CSF leak, and development of meningitis. A total of 184 patients were included in the analysis. This was a very heterogeneous population in terms of its age, history of prior tumour resection or radiation, tumour size, and tumour location.

Statistical analysis

GraphPad statistical software (Boston, MA, USA) was used for univariate analysis. Each patient and surgical variable was evaluated in univariate analysis for an association with timing of the postoperative CSF leak (Table 2). Continuous variables were analysed using Student's t-test and categorical variables were analysed with the χ^2 test or Fisher's exact test where appropriate. Multivariate analyses were performed using R (version 4.2.2; The R Foundation for Statistical Computing) in RStudio (version 2022.12.0). For logistic regression, a generalized linear model with a gamma distribution and log link was used to evaluate associations between covariates and POD of CSF leak. A p-value of <0.05 was considered statistically significant. Linear regression was used to identify associations between clinical factors and POD of CSF leak. For continuous variables, the median was used to divide the cohort into two groups. This was done to improve stability in regression models and to represent typical risk strata that resemble factors that influence postoperative decision making in practice. Covariates included in multivariable models were based on a combination of a priori information and univariate analyses where p-values were <0.1. Interactions between defect site, defect size, elevated ICP, number of reconstruction layers, and LD use were included in multivariable models.

Results

Table 1 provides an overview of the characteristics of the study population. Table 2 demonstrates the univariate analysis of associations between patient and surgical variables with timing of CSF leak. Notably, history of radiation, elevated ICP, revision surgery, non-sellar defect location, and larger bony defect size

Table 1. Data for the overall group (n=184).

Variable	n or Average
Demographic Information	
Gender	
Male	89 (48.4%)
Female	95 (51.6%)
Age (years)	51.4 (range 5-88)
Average BMI	32.3 (range 13.7-61)
BMI <25	39 (21.2%)
BMI >25	145 (78.8%)
History of Radiation	19 (10.3%)
Preoperative Hydrocephalus/Elevated ICP	12(6.5%)
Tumour Information	
Tumour Location/Defect Site	
Sella	52 (28.3%)
Suprasellar	22 (12%)
Tuberculum	14 (7.6%)
Planum	28 (15.2%)
Posterior Cranial Fossa	55 (29.9%)
Anterior Cranial Fossa	13 (7.1%)
Tumour Type	
New	121 (65.7%)
Recurrent	45 (24.5%)
Unspecified / Missing data	18 (9.8%)
Tumour Dimensions	
Cranio-Caudal (cm)	2.5 (range 0.2-7.1)
Anterior-Posterior (cm)	2.4 (range 0.2-10.4)
Transverse (cm)	2.5 (range 0.2-8.6)
Maximum Diameter (cm)	2.9 (range 0.2-10.4)
Volume (cm^3)	26.8 (range 0.008-635)
Defect Dimensions	
Maximum Bony Defect, lateral (cm)	2.1 (range 0.7-5.6)
Maximum Bony Defect, anteroposterior (cm)	2.5(range 0.14-6.7)
Bony Defect Area (cm^2)	5.9 (range 0.3-27.5)
CSF Leak Information	
Intraoperative Leak Grade	
No leak	15 (8%)
Low flow*	33 (18%)
High flow	137(74%)
Reconstruction	
Subdural Layer	159 (86%)
Epidural Underlay	18 (10%)
Bony/Dural Onlay	62 (34%)
Mucosal Coverage	160 (87%)
Free mucosal graft	18 (11%)
Vascularized Graft	159 (89%)
Dural Sealant	168 (90%)
Dissolvable Nasal Packing	51 (27.7%)
Non-dissolvable Nasal Packing	15 (8.2%)
Number of reconstructive layers	2.3 (range 0-5)
Bedrest	29 (16%)
CSF Diversion	52 (31%)
Day Post-op Leak Diagnosed	10.2 (range 0-82)
Method of Management of Leak	
Bedrest	1 (0.5%)_
Lumbar Drain	32 (17.4%)
Surgery	29 (15.8%)
Lumbar Drain + Surgery	115 (62.5%)
Extraventricular drain + Surgery	7 (3.8%)
Meningitis	52 (28%)

* Defined as Esposito Grade 1 or 2, or <1 cm defect and no communication with ventricle or cistern. Legend: BMI=Body mass index, ICP=Intracranial pressure, CSF=Cerebrospinal fluid leak.

were all associated with later development of postoperative CSF leak (Table 2). BMI >25 was associated with significantly earlier, rather than later, presentation of postoperative CSF leaks compared to BMI <25 (8.6 days vs 16.2 days p<0.001, 95% CI 3.6 to 11.7 days for BMI≥25). Said another way, BMI<25 was associated with later presentation of CSF leak.

The method of reconstruction also appeared to be strongly associated with the timing of postoperative CSF leaks. Use of epidural underlay (p=0.01), mucosal coverage (p=0.03), and increasing number of layers used for reconstruction (p=0.02) were all associated with later CSF leak (Table 2). Finally, use of CSF diversion in the postoperative period versus no CSF diversion was associated with later leak presentation (p<0.001).

On multivariable linear regression, BMI <25 and history of radiation retained significance for association with delayed CSF leaks (Table 3). The findings of this table were plotted on a forest plot as a visual summary (Figure 1). The distribution of timing of postoperative CSF leaks was plotted on a scatter plot (Figure 2). Most leaks occurred within the first 2 weeks postoperatively, but other patients experienced a leak more than 2 months after their surgery. Analysing the overall cohort, several time points stood out as peaks in time when CSF leaks were diagnosed including peaks at postoperative days 2, 7, 13, and 20.

Table 2. Univariate analysis.

Variable (n, %)	Average POD of Leak	p	95% CI (POD of earlier leak)
Gender (n=184)			
Male (89, 48.4%)	8.8	0.1	
Female (95, 51.6%)	11.6		
Age (n=184)			
<52 (90, 48.9%)	10.6	0.7	
>52 (94, 51.1%)	9.8		
BMI (n=184)			
<25 (39, 21.2%)	16.2	<0.001	
>25 (145, 78.8%)	8.6		[3.6 - 11.7]
History of Radiation (n=184)			
Yes (19, 10.3%)	24.1	<0.001	
No (165, 89.7%)	8.6		[10.2 - 20.7]
Elevated ICP (n=184)			
Yes (12, 6.5%)	17.3	0.03	
No (172, 93.5%)	9.7		[0.54 - 14.5]
C/C Diameter (n=174)			
<2.3 cm (92, 50%)	10.2	0.9	
>2.3 cm (82, 44.6%)	10.4		
A/P Diameter (n=174)			
<2.1 cm (89, 48.4%)	9.2	0.2	
>2.1 cm (85, 46.2%)	11.5		
Transverse Diameter (n=173)			
<2.2 cm (89, 48.4%)	9.2	0.2	
>2.2 cm (84, 45.7%)	11.7		
Maximum Diameter (n=175)			
<2.6 cm (97, 52.7%)	9.2	0.2	
>2.6cm (78, 42.4%)	11.8		
Volume (n=173)			
<10.2 cm^3 (87, 47.3%)	9.4	0.3	
>10.2 cm^3 (86, 46.7%)	11.4		
Maximum Bony Defect, lateral (n=180)			
<1.95 cm (90, 48.9%)	8	0.012	1.01 to 8.01
>1.95 cm (90, 48.9%)	12.5		
Maximum Bony Defect, anteroposterior (n=173)			
<2 cm (87, 47.3%)	7.2	0.001	2.41 to 9.61
>2cm (86, 46.7%)	13.2		
Bony Defect Area (n=176)			
<3.8 cm^2 (88, 47.8%)	7.2	<0.001	2.99 to 9.98
>3.8 cm^2 (88, 47.8%)	13.7		
Defect Location (n=184)			
Sella (52, 28.3%)	5.6	<0.001	2.64 to 10.2
Not Sella (132, 71.7%)	12		
Suprasellar (22, 12%)	10.9	0.77	
Not Suprasellar (162, 91.3%)	10.1		
Tuberculum (14, 7.6%)	7.8	0.5	

Table 2 *continued.* Univariate analysis.

Variable (n, %)	Average POD of Leak	p	95% CI (POD of earlier leak)
Not Tuberculum (170, 92.4%)	10.2		
Planum (28, 15.2%)	11.3	0.7	
Not Planum (156, 84.8%)	10.2		
Posterior Cranial Fossa (55, 29.9%)	14.1	0.03	
Not Posterior Cranial Fossa (129, 70.1%)	10.2		[0.25 - 7.44]
Anterior Cranial Fossa (13, 7.1%)	11.5	0.7	
Not Anterior Cranial Fossa (171, 92.9%)	10.2		
Tumour Type (n=166)			
New (121, 65.8%)	8.5	0.009	[1.42 - 9.86]
Recurrent (45, 44.2%)	14.2		
Esposito Grade* (n=27)			
1 (18, 9.8%)	3.5	0.03	[0.53 - 8.91]
2 (9, 4.9%)	8.2		
Non-Sellar Leak Grade (n=122)			
Low (6, 3.3%)	22.7	0.5	
High (116, 63%)	11.7		
Subdural Layer (n=184)			
Yes (159, 86%)	9.3	0.7	
No (25, 14%)	10.4		
Epidural Underlay (n=184)			
Yes (18, 9.8%)	16.9	0.01	
No (166, 90.2%)	9.4		[1.6 - 13.3]
Bony/Dural Onlay (n=184)			
Yes (62, 33.7%)	10.9	0.6	
No (122, 66.3%)	9.9		
Mucosal Coverage (n=184)			
Yes (160, 87%)	11	0.03	
No (24, 13%)	5.3		[0.59 - 10.8]
Free mucosal graft (18, 11%)	6.9	0.3	
Nasoseptal flap (159, 89%)	10		
Number of Layers In Reconstruction# (n=110)			
1 (28, 20.7%)	6.2	0.003	[2.2 - 10.4]
3 (53, 48.2%)	12.5		
1 (28, 20.7%)	6.2	0.02	[0.71 - 8.6]
4 (19, 10.3%)	10.8		
Dural Sealant (n=184)			
Yes (168, 91.3%)	10.1	0.04	
No (16, 8.7%)	4.1		[0.12 - 12]
Nasal Packing (n=66)			
Dissolvable (51, 27.7%)	8.2	0.05	
Non-dissolvable (15, 8.2%)	11.9		
Bedrest (Initial Surgery) (n=184)			
Yes (29, 15.8%)	12.2	0.3	
No (155, 84.2%)	9.8		

Table 2 *continued.* Univariate analysis.

Variable (n, %)	Average POD of Leak	p	95% CI (POD of earlier leak)
Lumbar Drain (Initial Surgery) (n=180)			
Yes (66, 35.9%)	13.7	<0.001	
No (114, 62%)	7.5		[2.83 - 9.6]
External Ventricular Drain (Initial Surgery) (n=180)			
Yes (13, 7.1%)	20.1	<0.001	
No (167, 90.8%)	7.5		[6.02 - 19.2]

* Comparisons between all other Esposito grades did not reach statistical significance. # Comparisons between all other number of layers did not reach statistical significance.

Discussion

Much work has been done to delineate risk factors for developing CSF leak after ESBS [1-14]. It has been well established that use of a multilayer closure and vascularized flaps significantly reduce the rate of postoperative CSF leak [1,9,10]. The 2019 International Consensus Statement, recent American Rhinologic Society Expert Practice Statement, and recent Expert Strategies document all advocate for the use of such methods for reconstruction in cases of high-flow leaks (e.g., intra-arachnoid dissection, craniopharyngioma, meningioma, etc), for cases with dural defects >1 cm^2, and for regions requiring more complex reconstructions such as the PCF [1,21,28].

Little work has been done to better delineate factors that may influence the timing of CSF leak after surgery. The timing of potential CSF leak after ESBS has important implications on when patients can resume use of positive airway pressure (PAP), return to work and normal activities, travel, and in guiding recommendations for postoperative care such as debridements and when to initiate saline sprays or irrigations. However, very little literature exists to guide these decisions [19,22]. Each of the above factors could theoretically displace the skull base reconstruction if initiated too early in the postoperative course and potentially lead to the development of a postoperative CSF leak and/or pneumocephalus. What little information does exist is generally in the form of surveys of practice patterns and shows a significant degree of heterogeneity [23,24]. In reviewing the literature, it appears that many surgeons are guided by factors such as location of the skull base defect, extent of surgery, and presence/grade of intraoperative CSF leak when counseling patients regarding postoperative care [23,24].

Based on the current study, a history of radiation is the main factor that may be worth taking into consideration when counseling patients on being conservative with postoperative precautions. A history of prior radiation appears to be associated with significantly later presentation of CSF leak on multivariate analysis, and therefore patients with this history could potentially benefit from a more prolonged period of refraining from strenuous activities or other ICP-shifting maneuvers. Prior radiation likely contributes to delayed CSF leaks due to impairment of healing in the wound bed, which presents an added stress over time and leads to delayed failure in a reconstruction that may otherwise be successful in a patient without prior radiation. Interestingly, in our analysis elevated BMI was associated with earlier, rather than later CSF leak. The reason for this is not immediately clear within our data. It may be that patients with elevated BMI may have elevated ICP, which imposes a higher pressure gradient across the defect reconstruction and causes earlier failure. ICP elevation itself was found to be associated with delayed CSF leak on univariate analysis, but this association did not hold in multivariate analysis. Only 6.5% of patients in this cohort had a preoperative diagnosis of ICP elevation, while over 78% of patients had BMI over 25, so it is possible that there were many patients in the cohort with undiagnosed ICP elevation. This makes it difficult to draw conclusions regarding the role of BMI and ICP in the timing of CSF leak after skull base surgery.

Factors that compromise skull base reconstruction can be mitigated to some degree with the use of vascularized reconstructive options, which promote more robust healing due to a richer blood supply [22,25,26]. Patients with elevated ICP may also benefit from more aggressive or prolonged management of ICP elevation after ESBS to prevent delayed CSF leaks from occurring. In such patients, short-term CSF diversion and/or postoperative treatment with acetazolamide for several weeks may be beneficial to lower ICP and potentially prevent delayed development of CSF leak [6,8,27]. Further study is needed to determine the most appropriate management of patients with elevated ICP after ESBS.

Interestingly, in patients with postoperative CSF leak after ESBS, a greater number of layers used in reconstruction and the use of an epidural underlay appeared to delay the presentation of the leak. The former inherently makes sense. We hypothesize that in such cases, each layer must fail, presumably in a successive fashion, and the cumulative effect of each subsequent layer failing adds to prolongation of the CSF leak presenting clinically.

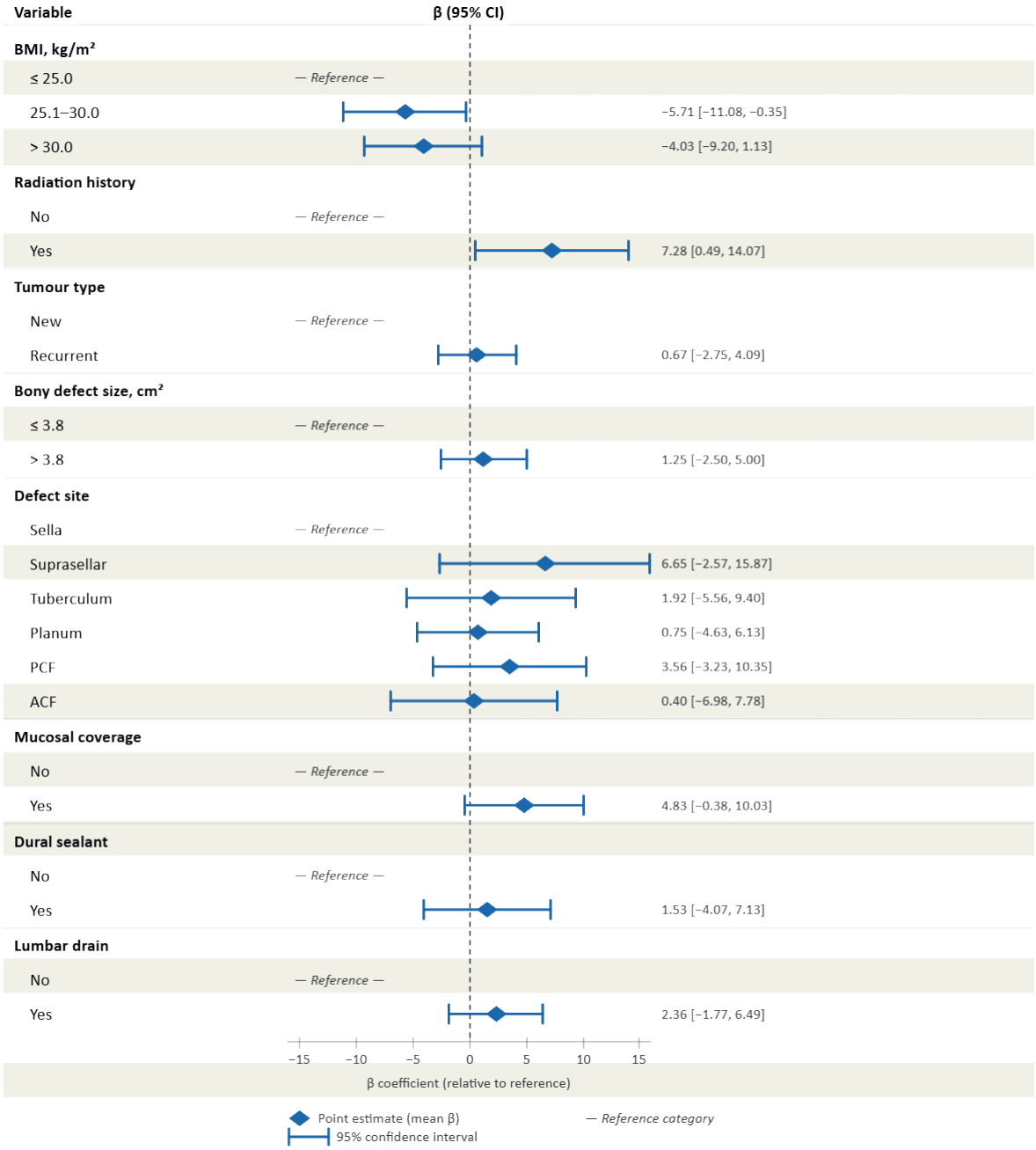

Figure 1. Forest plot summary of multivariable analysis.

The use of an epidural underlay was significantly associated with later CSF leak presentation even on multivariate analysis, but other reconstructive maneuvers such as defect coverage with a mucosal flap were not. It is unclear why exactly this might be the case. When used in a reconstruction, the epidural underlay is unique in that it is placed deep to bone and therefore has a rigid surface to anchor against ICP shifts. Perhaps this is the reason that when an epidural underlay is part of a failed reconstruction, it takes significantly longer to present with a clinically apparent CSF leak than reconstructions without.

The level of complexity of the reconstruction has previously been identified as a risk factor for developing CSF leak after ESBS. Factors that contribute to the complexity of reconstruction include the location and size of the defect, grade of intraoperative leak, tissue quality (as determined by prior radiation), intracranial pressure, and more nuanced factors that are difficult to quantify such as the three-dimensional shape of the defect and its relationship with critical neurovascular structures. These may impact the timing of CSF leak after ESBS when taken in aggregate. It is interesting that several of these factors have previously been identified as risk factors for developing CSF leak after ESBS in general, but this is the first study to evaluate how

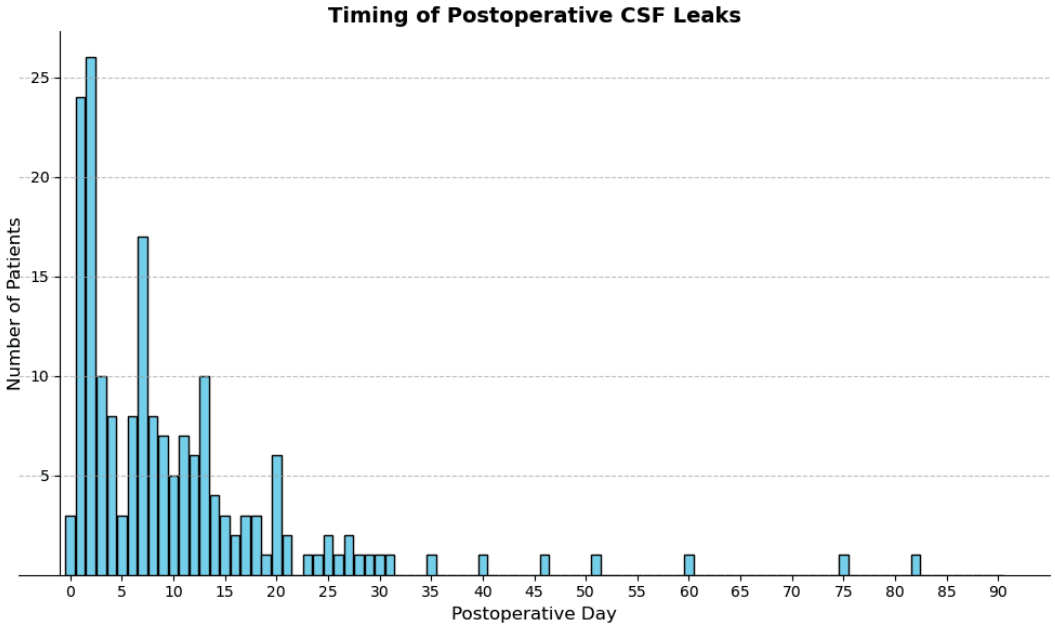

Figure 2. Scatter plot of the timing for all CSF leaks in the current study.

these factors influence the timing. Many of these factors would also dictate the choice of reconstructive method, and with increasing complexity, a greater number of reconstructive layers may be utilized which could delay a CSF leak presentation when CSF leaks do occur. This may partially explain the effect that epidural underlays have on timing of the leak: it may be that their use is a signifier of a higher complexity defect.

The same could be said for the association between CSF diversion after the initial surgery and late CSF leaks. CSF diversion is typically performed on a case-by-case basis in patients considered to be at high risk for postoperative CSF leak. CSF diversion is also usually considered in patients with ACF or PCF pathologies where LD has been shown to significantly reduce the rate of postoperative CSF leaks [2,8]. The decision to use a LD after ESBS may again be an indicator of more complex defects explaining the more delayed leak presentation. The lowering of CSF volume by CSF diversion also likely delays clinical presentation of CSF leak, as leaks may remain occult until a sufficient reservoir of CSF has been produced following clamping or removal of the CSF diversion.

Regarding the specific time points when CSF leaks were detected (Figure 1), there were peaks on postoperative days 2, 7, 13, and 20. The CSF leaks diagnosed on postoperative days 1 and 2 were likely detected during the index admission following ESBS. The CSF leaks diagnosed on days 7, 13, and 20 were likely detected on regularly scheduled postoperative clinic visits following discharge. As such it should be noted that the time points of CSF leaks in this study likely do not reflect the exact day on which the leaks began, but rather the day that they were detected and these are constrained by the logistics of clinical practice.

There are several limitations to the current study. First, it is retrospective, and therefore subject to bias by recall and confounding variables. Additionally, not all variables were documented for each patient, and this study was reliant on the accurate recording of information in the medical record. Tumour diagnosis was not captured, which could have introduced a significant confounding factor as different pathologies such as malignancies may have an impact on the timing of CSF leak. Other potentially significant factors that may impede healing such as tobacco use or diabetes were also not captured. Furthermore, postoperative factors such as timing of initiation of positive airway pressure therapy or nasal saline irrigations were not analyzed. Different institutions and surgeons may have different practices which were pooled for analysis, though this may in fact be a strength in presenting a pragmatic set of data. Finally, causality cannot be established through a retrospective study, and this study could only evaluate associations between factors and the timing of CSF leaks.

Conclusion

In this large retrospective study of patients who developed a CSF leak after ESBS, the timing of CSF leak appeared to be influenced by several factors. History of radiation, lower BMI, and number and type of layers used in reconstruction was associated with a delayed presentation of CSF leak. Such patients may benefit from closer postoperative follow up for a longer duration to detect a leak. This is the first study to evaluate factors that influence the timing of CSF leak after ESBS, and further research is needed to validate the findings of the current study and provide

Table 3. Multivariable linear regression with interaction terms.

Variable (n, %)	Univariate		Multivariable (with interaction terms*)	
	β (95% CI)	P-Value	β (95% CI)	P-Value
BMI, kg/m² (n=184)				
≤ 25.0 (40, 21.7%)	0 [Reference]		0 [Reference]	
25.1-30.0 (55, 29.9%)	-7.56 [-13.96 - -1.17]	**0.017**	-5.71 [-11.08 - -0.35]	**0.035**
> 30.0 (89, 48.4%)	-7.71 [-13.88 - -1.53]	**0.011**	-4.03 [-9.20 - 1.13]	0.149
Radiation History (n=184)				
No (165, 89.7%)	0 [Reference]		0 [Reference]	
Yes (19, 10.3%)	15.43 [4.26 - 26.61]	**0.007**	7.28 [0.49 - 14.07]	**0.036**
Elevated ICP (n=184)				
No (172, 93.5%)	0 [Reference]		0 [Reference]	
Yes (12, 6.5%)	7.53 [-3.73 - 18.79]	0.189	~	~
Tumour Type (n=166)				
New (121, 65.8%)	0 [Reference]		0 [Reference]	
Recurrent (45, 44.2%)	5.64 [0.36 - 10.91]	**0.036**	0.67 [-2.75 - 4.09]	0.698
Bony Defect Size, cm² (n=176)				
≤ 3.8 (88, 47.8%)	0 [Reference]		0 [Reference]	
> 3.8 (88, 47.8%)	6.49 [2.97 - 10.01]	**<0.001**	1.25 [-2.50 - 5.00]	0.510
Defect Site (n=184)				
Sella (52, 28.3%)	0 [Reference]		0 [Reference]	
Suprasellar (22, 12%)	5.29 [-1.67 - 12.26]	0.201	6.65 [-2.57 - 15.87]	0.242
Tuberculum (14, 7.6%)	2.17 [-4.14 - 8.48]	0.804	1.92 [-5.56 - 9.40]	0.903
Planum (28, 15.2%)	5.67 [-0.78 - 12.12]	0.106	0.75 [-4.63 - 6.13]	0.98
PCF (55, 29.9%)	8.44 [2.62 - 14.26]	**0.001**	3.56 [-3.23 - 10.35]	0.523
ACF (13, 7.1%)	5.85 [-3.45 - 15.14]	0.362	0.40 [-6.98 - 7.78]	0.998
Epidural Underlay (n=184)				
No (166, 90.2%)	0 [Reference]		0 [Reference]	
Yes (18, 9.8%)	7.46 [-2.01 - 16.93]	0.122	~	~
Bony/Dural Onlay (n=184)				
No (122, 66.3%)	0 [Reference]		0 [Reference]	
Yes (62, 33.7%)	5.71 [2.49 - 8.92]	0.594	~	~
Mucosal Coverage (n=184)				
No (24, 13%)	0 [Reference]		0 [Reference]	
Yes (160, 87%)	5.71 [2.49 - 8.92]	**<0.001**	4.83 [-0.38 - 10.03]	0.069
Number of Layers (n=284)				
≤ 2 (109, 59.2%)	0 [Reference]		0 [Reference]	
> 2 (75, 40.8%)	3.11 [-0.90 7.11]	0.128	~	~
Dural Sealant (n=184)				
No (16, 8.7%)	0 [Reference]		0 [Reference]	
Yes (168, 91.3%)	6.82 [4.04 9.61]	**<0.001**	1.53 [-4.07 - 7.13]	0.59
Nasal Packing (n=66)				
Dissolvable (51, 27.7%)	0 [Reference]		0 [Reference]	
Non-Dissolvable (15, 8.2%)	3.70 [-0.07 - 7.46]	0.054	~	~
Lumbar Drain (n=180)				
No (114, 62%)	0 [Reference]		0 [Reference]	~
Yes (66, 35.9%)	7.38 [2.86 - 11.91]	**0.002**	2.36 [-1.77 - 6.49]	0.260

*Interaction terms: Number of layers/defect site, Number of layers/lumbar drain, Elevated ICP/lumbar drain, Defect size/lumbar drain. Legend: BMI=Body mass index, 95% CI=95% Confidence interval, ICP=Intracranial pressure.

more detailed guidance on the postoperative evaluation and care of patients undergoing ESBS.

Author contributions

AAH contributed to study design, data gathering, data analysis, and manuscript writing. MZC contributed to data analysis, manuscript editing and writing. AA contributed to data gathering, data analysis, and manuscript editing. KED, VP, ADW, SC, SLB, NDA, GC, PAG, MG, JNP, CHS, EWW, and GAZ contributed to data gathering. ECK contributed to study design, data analysis, manuscript editing and writing.

Conflict of interest

NDA and JNP: Consultant for Acclarent, Optinose, 3-D Matrix. ECK: Consultant for Stryker and 3-D Matrix; receives royalties from Springer. The other authors declare that there are no relevant conflicts of interest.

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