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ORIGINAL RESEARCH

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Cut-off value for β-trace protein (β-TP) as a rapid diagnostic of cerebrospinal fluid (CSF) leak detection

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Abstract

Objective: To find an adequate cut-off point for beta trace protein (β-TP) in nasal secretion (NS) and validate this diagnostic test with a large sample of patients. Likewise, we evaluated β-TP test efficacy to confirm the cerebrospinal fluid (CSF) leakage closure after treatment.

Methods: We performed a retrospective analysis with 207 samples from 162 patients with suspected CSF leakage received in the Hospital Universitario Virgen de la Arrixaca between 2010 and 2016. Twenty-five samples were included in the control group. Samples were obtained from NS through a swab to determine β-TP using a nephelometry-based assay. Sensitivity, specificity, and area under the curve (AUC) for β-TP in NS were assessed using the receiver operator characteristic (ROC) analysis.

Results: Using imaging techniques, the diagnosis of CSF leak was confirmed in 57 patients (35.19%), while 105 had a negative diagnosis (64.81%). Patients with CSF leakage had significantly higher β-TP values in NS (16.07 ± 16.94 mg/L, $p < .001$) than the control group (0.33 ± 0.12 mg/L) and patients without CSF leakage (0.61 ± 2.34 mg/L). Applying a 1 mg/L cut-off point resulted in 96.5% sensitivity and 97.1% specificity. Positive and negative predictive values (PPV and NPV) at this cut-off were 94.9% and 98.6%, respectively. Finally, this cut-off point yields a test efficacy for CSF leak diagnosis of 97% (95% CI 92.9–98.9).

Conclusion: Our study has established a 1 mg/L β-TP concentration in NS as a cut-off point for CSF leakage diagnosis with high sensibility and specificity. These results suggest that β-TP analysis could be useful to check CSF leak resolution.

Level of Evidence: 4.

KEYWORDS
cerebrospinal fluid leakage, cut-off, nephelometry, rhinorrea, β-trace protein

1 | INTRODUCTION

Cerebrospinal fluid (CSF) leak is due to an osteodural defect leading to abnormal communications between the subarachnoid space and the adjacent paranasal sinus or the tympanomastoid cavity, presenting rhinorrhoea or otorrhoea.[1] CSF leaks are classified as traumatic, non-traumatic,[2] and spontaneous, which occur in the absence of trauma, surgery, or another inciting even.[3] Traumatic leaks account for about 80%–90% of CSF leaks.[4] CSF leaks are seen in about 30%–40% of accidental trauma due to skull base fractures, leading to an osteodural defect.[5] Another type of traumatic CSF leaks is iatrogenic leaks, which can be secondary to skull base or transnasal endoscopy surgery and are reported to account for about 16% of traumatic CSF leaks.[6] Non-traumatic CSF leaks represent 3%–4% of cases and most of them are produced by a non-congenital defect of the skull base.[7] Spontaneous CSF leaks present low frequency and are associated with obesity and idiopathic intracranial hypertension.[3,8] Persistent CSF leaks can result in chronic headaches and discomfort, as well as in increasing the patient's risk of developing life-threatening complications like bacterial meningitis.[9,10] Therefore, early diagnosis and subsequent repair of CSF leaks is imperative to prevent these complications.

CSF leak diagnosis involves the combination of clinical history, a skull base defect on high-resolution computed tomography (HRCT), and associated clear pulsatile otorrhoea or clear rhinorrhoea.[3] The most sensitive and specific laboratory tests for CSF leak diagnosis are beta-2-transferrin and beta trace protein (β-TP) assays. β-TP detection, also known as lipocalin-type prostaglandin D2-synthase, is a rapid and accessible nephelometric alternative for CSF leak diagnosis. This protein is located in high amounts in CSF; however, it is also present and can be measured in other biological fluids, such as serum and nasal secretion (NS). The mean β-TP concentration in CSF is approximately between 33 and 35 times higher than that in serum and 50 times higher than in NS. Besides, it presents the highest CSF/serum ratio of all CSF-specific proteins.[11] Several groups have investigated β-TP measurements used in secretions for CSF leakages detection and different cut-off values have been proposed.[12] Our study aims to find an adequate cut-off point for β-TP that can be applied to our population, together with the validation of this diagnostic test with a large sample of patients for which β-TP measurements in NS can be routinely performed. Likewise, we evaluate β-TP test efficacy to confirm CSF leakage closure after treatment.

2 | MATERIALS AND METHODS

2.1 | Patients selection

207 samples from 162 patients with suspected CSF leakage were investigated for β-TP detection between January 2010 and December 2016 at the Hospital Universitario Virgen de la Arrixaca (HUVA). We received informed consent from all subjects for this study. This study was approved by the Clinic Ethic Committee of our institution and performed in accordance with the ethical standards of the Institutional Research Committee.

Inclusion criteria comprised (1) patients over 18 years of age (not pregnant) presenting with repetitive rhinorrhoea after cranial traumatism, nasal or transpheniod base of the skull surgery; spontaneous unilateral rhinorrhoea without any objective improvement after medical treatment; and/or recurrent meningitis and (2) hospitalized patients with severe cranial traumatism and CSF leakage suspicion. Patients under 18, with acute meningitis, alterations of the facial mass that make it impossible to place the nasal packing, or patients with kidney disease, were excluded from the study.

Twenty-five NS samples from healthy volunteers without a history of nasal or skull base surgery, without rhinorrhoea, without history of head trauma or recurrent meningitis, and without kidney disease, were included as the control group.

2.2 | Biochemical analysis

NS was collected from patients with CSF leak suspicion and from healthy volunteers using $80 \times 15 \times 30$ mm sterile swabs (Mondomed®), inserted into each nostril. In 63.88% of cases, collection was simultaneously performed from both (left and right) nostrils and considered as individual samples for statistics. The infranatant was obtained from each nose tamponade by centrifugation (2500 rpm, 10 min). β-TP measurements were routinely performed by nephelometry BN-ProSpec® (Dade Behring) analyzers using the N Latex β-TP assay (Siemens Healthcare Diagnostics, Germany) according to the manufacturer's instructions. The measurement range was 0.25–15.8 mg/L, with a 1:100 initial dilution. Samples with higher or lower protein levels were analyzed again with an adequate dilution. Our internal quality control data showed an inter-day imprecision of 2.3%–6.5% at a β-TP level of 0.0025 mg/L.

2.3 | Assessment of using swabs for sample collection on β-TP concentration in patients with rhinorrhea

To investigate the effect of using swabs for sample collection on β-TP concentration, three pools were collected from non-altered CSF obtained by lumbar puncture and provided by the HUVA Clinical Analysis Service. These samples were diluted with physiological saline at 30%, 10%, 5%, and 1%. Two mL of each dilution were impregnated on Mondomed® swabs for 30 min. Later, samples were processed and analyzed by nephelometry as previously described.

2.4 | Evaluation of the influence of blood presence in β-TP concentration measurement in NS

To study blood presence influence in β-TP concentration in NS and CSF samples, we used a NS pool (patients from the HUVA ORL

TABLE 1 Patient characteristics.

Demographic variables	
Patient number (female/male)	162 (98/64)
Age, years (mean ± SD)	48.54 ± 18.91
Age range, years	18–86
Clinical history	
Traumatic brain, *n* (%)	73 (45.10)
Surgery, *n* (%)	49 (30.20)
Spontaneous rhinorrhoea, *n* (%)	40 (24.70)
Symptoms	
Spontaneous rhinorrhoea, *n* (%)	40 (24.70)
Rhinorrhoea after accidental trauma, *n* (%)	30 (18.50)
Rhinorrhoea after surgery, *n* (%)	29 (18)
Recurrent meningitis, *n* (%)	20 (12.30)
No symptoms	43 (26.50)

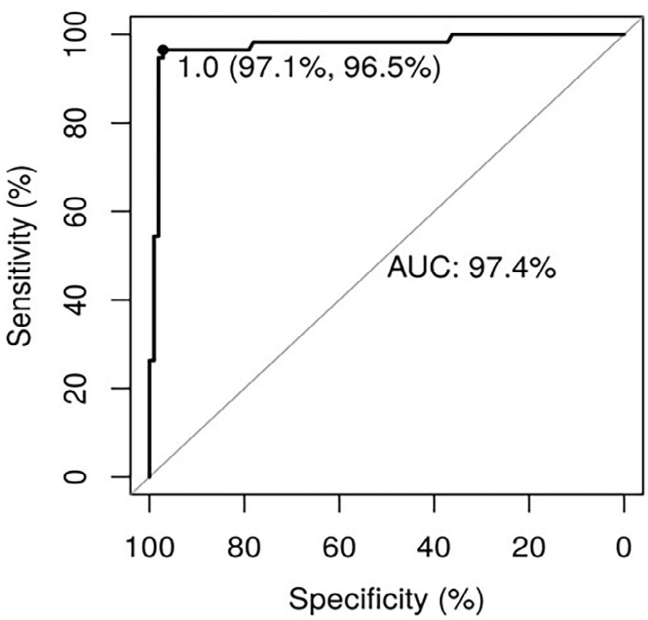

FIGURE 1 ROC analysis of β-TP measurements in nasal secretion.

Service) and a normal CSF pool from the HUVA Clinical Analysis Service that has been contaminated with a blood pool in serial dilutions from 1/2 to 1/1024. β-TP concentration was determined by nephelometry at each dilution.

2.5 | Statistical analysis

Statistical analyses were performed using the R software (Development Core Team) version 3.4.2. Sensitivity, specificity, and area under the cure (AUC) for β-TP were assessed using the receiver operator characteristic (ROC) analysis. Unpaired Student's t test was calculated when comparisons were restricted to two experimental groups with the GraphPad Prism software (GraphPad, San Diego, CA) version 6.0. Data are expressed as mean ± SD. P values of less than 0.05 were considered significant.

TABLE 2 Contingency table: Clinical interpretation versus β-TP results.

β-TP concentration	No CSF leakage	CSF leakage	Total
β-TP <1 mg/L	146	2	148
β-TP ≥1 mg/L	3	56	59
Total	149	58	207

3 | RESULTS

We have analyzed 207 samples from 162 patients with CSF leakage suspicion. The demographic characteristics as well as the clinical history and symptoms of the study population are summarized in Table 1.

CSF leak diagnosis involves the combination of clinical history, imaging studies, and associated clear pulsatile otorrhoea or clear rhinorrhoea. In our study, 175 imaging tests were performed on the 162 subjects with CSF leak suspicion. CSF leak diagnosis, using imaging techniques, was confirmed in 57 patients (35.19%), while 105 patients had a negative diagnosis (64.81%).

Patients with CSF leakage had significantly higher β-TP values in NS (16.07 ± 16.94 mg/L, $p < .001$) than the control group (0.33 ± 0.12 mg/L) and patients without CSF leakage (0.61 ± 2.34 mg/L). The ROC analysis using β-TP values yielded an area under the curve (AUC) of 0.974 (Figure 1). Applying a cut-off of 1 mg/L resulted in sensitivity and specificity of 96.5% and 97.1%, respectively. The positive and negative predictive values (PPV and NPV) at this cut-off were 94.9% and 98.6%, respectively. Therefore, establishing this cut-off point of 1 mg/L, the efficacy of the test for the diagnosis of CSF leak is 97% (95% CI 92.9–98.9).

As it can be seen in Table 2 and Figure 2, with a 1 mg/L cut-off point, 202 (97%) of 207 samples were correctly classified (56 samples from patients with CSF leakage and 146 from patients without CSF leakage). Two samples from patients with CSF leakage (red dots) and 3 samples from patients without CSF leakage (blue dots) were misclassified. The two samples in red dots correspond to 2 false negative cases and the three samples in blue dots to 3 false positive cases.

The most frequently performed imaging techniques have been HRCT and NMR. HRCT was performed in 128 patients out of 162 with suspected CSF leakage, being positive in 47 (36.7%) and negative in 81 (63.3%) patients. One hundred and nineteen samples were correctly classified while nine samples were misclassified (Table 3). Using HRCT as the unique criterion to identify CSF leakage resulted in a sensitivity of 85.2% and a specificity of 98.6%, while PPV and NPV were 97.9% and 90.1%, respectively, with a diagnostic efficiency of 93% (95% CI, 87.1–96.7). Similar results were obtained using NMR (Table 3). NMR was performed in 35 of the 162 patients

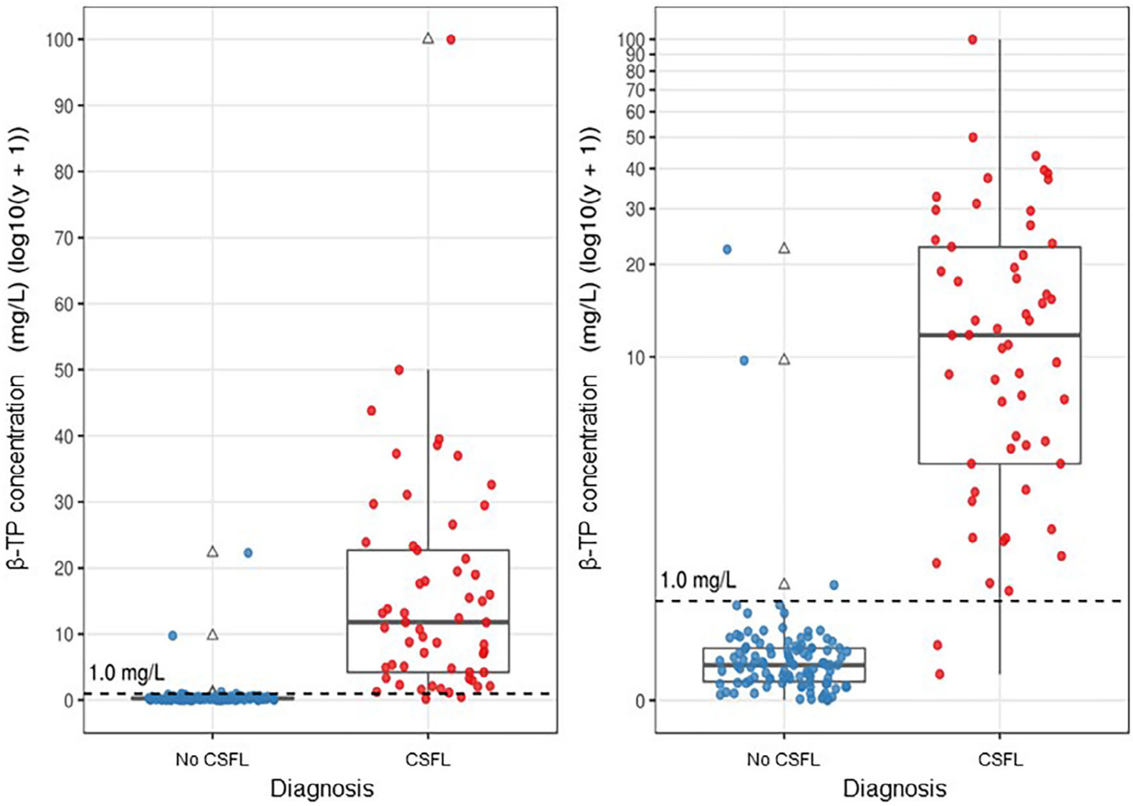

FIGURE 2 Box plots comparing β-TP values in NS in patients with or without CSF leakage. The striped line delineates the cut-off point of 1 mg/L. (A) Normal scale. (B) Logarithmic scale adding one.

TABLE 3 Contingency table: clinical diagnostic.

Imaging techniques	No CSF leakage	CSF leakage	Total
HRCT negative	73	8	81
HRCT positive	1	46	47
Total	74	54	128
NMR negative	15	8	23
NMR positive	1	11	12
Total	16	19	35

Abbreviations: HRCT, High resolution computed tomography; NMR, Nuclear magnetic resonance.

with suspected CSF leakage, being positive in 12 (34.3%) and negative in 23 (65.7%). Nine samples were misclassified. Based on these data, we obtained the following results: sensitivity 57.9%; specificity 93.7%; PPV 91.7%; NPPV 65.2%. The efficacy of this diagnostic technique was 74% (95% CI 56.7–87.5).

Twenty-one NS measurements were repeated within 1 week after surgical treatment to perform a clinical follow-up of the patients. Table 4 shows β-TP concentrations, diagnosis, treatment, and subsequent follow-up. The initial β-TP concentration could not be determined in two samples (8, 11) because respective NS were not provided. In the first case, after surgical treatment of CSF leakage, β-TP value is positive (>1 mg/L), coinciding with the diagnosis, and β-TP value became negative after a second surgical treatment. In the second case, β-TP value is negative (<1 mg/L) after surgical treatment, coinciding with the general diagnosis.

Samples 2–4, 7, 9, 10, 12, 13–17, 20, and 21 had a positive β-TP value, coinciding with the diagnosis of CSF leakage, and β-TP concentrations became negative after conservative or surgical treatment.

In samples 1, 5, and 18, β-TP concentration after surgical treatment was positive, according to our cut-off point, implying persistence of CSF leak. In these cases, β-TP value became negative after the second surgery.

Finally, samples 6 and 19, with a diagnosis of no CSF leakage, showed a concentration of β-TP <1 mg/L. However, in a second determination, we found an elevated β-TP concentration (>1 mg/L), coinciding with the diagnosis of CSF leakage. In these two patients, β-TP value became negative after surgical treatment, coinciding with the negative general diagnosis of the presence of CSF leak.

Regarding the effects of using swabs on β-TP concentration, we observed an increase in this protein concentration after swab centrifugation in all the established dilutions. It is important to note that the mean recovery is not proportional to the dilution degree of the CSF pool, and β-TP was detected even in 1% dilution. Therefore, we can affirm that sample collection using a swab produces an 8–34% increase in β-TP concentration (data not shown). Thus, we have protocolized in our hospital the methodology for collecting samples using swabs to implement our cut-off point.

β-TP concentration in blood is greater than in NS, while this concentration is lower in blood compared to CSF. Therefore, it is

TABLE 4 β-TP concentration, diagnosis, and treatments.

Patient	Initial β-TP concentration (mg/L)	Diagnosis	Treatment	Post-treatment β-TP concentration (mg/L)	Diagnosis	Post-treatment β-TP concentration (mg/L)	Diagnosis
1	LN 5.1 RN 2.95	CSFL	Surgery	13.8	CSFL surgery	0.47	No CSFL
2	LN 4.22 RN 1.8	CSFL	Surgery	0.82	No CSFL		
3	2.3	CSFL	Conservative	0.13	No CSFL		
4	LN 26.6 RN 27.8	CSFL	Surgery	0.20	No CSFL		
5	LN 39 RN 37.2	CSFL	Surgery	40	CSFL surgery	0.12	No CSFL
6	LN 0.42 RN 0.19	No CSFL	No treatment	LN 39.91 RN 25.33	CSFL surgery	0.16	No CSFL
7	LN 5.33 RN 6.18	CSFL	Surgery	0.31			
8		CSFL	Surgery	2.55	CSFL surgery	0.19	No CSFL
9	LN 12.5 RN 1.59	CSFL	Conservative	0.22	No CSFL		
10	38.2	CSFL	Surgery	LN 0.1 RN 0.1	No CSFL		
11		CSFL	Surgery	0.46	No CSFL		
12	31.1	CSFL	Conservative	LN 0.22 RN 0.19	No CSFL		
13	1.24	CSFL	Surgery	LN 0.29 RN 0.17	No CSFL		
14	3.28	CSFL	Conservative	0.21	No CSFL		
15	3.02	CSFL	Conservative	0.11	No CSFL		
16	11.8	CSFL	Conservative	0.23	No CSFL		
17	1.24	CSFL	Conservative	2.3	CSFL surgery	0.35	No CSFL
18	2.04	CSFL	Surgery	13.8	CSFL surgery	0.37	No CSFL
19	0.51	No CSFL	No treatment	5.2	CSFL surgery	0.24	No CSFL
20	18.02	CSFL	Surgery	LN 0.28 RN 0.14	No CSFL		
21	10.96	CSFL	Conservative	LN 0.15 RN 0.14	No CSFL		

Abbreviations: CSFL, Cerebrospinal fluid leakage; LN, Left nostril; RN, Right nostril.

important to consider blood as a possible contaminant in these secretions. For this purpose, we have measured β-TP in NS and CSF pools contaminated with a blood pool in serial dilutions. β-TP concentrations obtained were: 0.53 mg/L in blood pool, 0.12 mg/L in NS pool, and 6.97 mg/L in CSF pool. In addition, our results show that blood influence is greater in CSF than in NS samples since the difference in β-TP concentration between CSF and blood is greater than between NS and blood (data not shown).

4 | DISCUSSION

The early and accurate diagnosis of CSF leaks is vital for the prevention of life-threatening complications such as meningitis. The first laboratory tests used to evaluate a patient with clear watery nasal or ear discharge and suspected CSF leak include testing the fluid for the presence of β2-transferrin or β-TP. Both tests have the advantage of being non-invasive, free of complications and with a very easy sample to obtain. However, the reported sensitivity of β2-transferrine testing ranges 87%–100%, with specificities of 71%–94%,[13] while β-TP test, with lower cost and faster turnaround time, has a sensitive and specificity approaching 100%.[14–16] Altogether, these data supported that β-TP quantification in external body secretions using nephelometry is an effective method for CSF leak diagnosis.

Even though the β-TP cut-off has been a matter of debate during the last decade, the optimal limit decision for CSF leakage diagnosis is still controversial. In our study, the ROC analysis of patients with CSF leakage suspicion generated an optimal cut-off of 1 mg/L with excellent sensitivity (96.5%) and specificity (97.1%), which allows us to validate this cut-off point for CSF leakage diagnosis in our hospital with no need to establish a more complex diagnostic algorithm. This cut-off point is in the range of that proposed previously.[14,16,17]

The two false negative results that we found in our study correspond to two patients with a traumatic (β-TP 0.47 mg/L) or surgical (Β-TP 0.2 mg/L) history. It is difficult to establish a correct diagnosis of CSF leaks after trauma because radiological findings can indicate dural injury, but the presence of a blood clot, mucosal edema, herniated brain tissue, or bone fragments can temporarily close the injury so, there is not CSF in NS although the imaging test (HRCT) is positive.

Regarding the false positive results (3 patients), we found β-TP concentrations (22.3 mg/L, 1.24 mg/L, 9.74 mg/L) above our cut-off point. The first two data correspond to patients with a surgical history of skull base, rhinorrhoea, and negative HRCT scan. Probably, after sample collection, spontaneous closure of the leak occurred. The last data correspond to a patient without traumatic or surgical history and negative HRCT, but with rhinorrhoea. It may be a spontaneous fistula in which the HRCT scan has not found the bone defect. This case can also be explained by a spontaneous fistula closing since the rhinorrhoea was resolved spontaneously.

On the other hand, it is interesting to note that no statistically significant differences were found when comparing β-TP concentration (mean: 0.33 mg/L) in the control group (healthy volunteers) versus patients with negative diagnosis (mean: 0.61 mg/L) or between β-TP concentrations obtained from CSF samples (mean: 18.53 mg/L) versus β-TP concentrations from patients with a positive diagnosis (mean: 16.07 mg/L, NS).

An important consideration in studies measuring β-TP concentrations includes contamination of samples with other fluids like blood.[18] An uncontaminated NS sample is thus unlikely to be incorrectly diagnosed as containing CSF. Our results showed that β-TP concentration in blood is 0.53 mg/L, like that described previously.[16,19] Furthermore, β-TP concentration in NS is much lower than that in blood and CSF. Therefore, the presence of bleeding in the samples does not affect the critical values to differentiate CSF from NS, since a β-TP concentration higher than 1 mg/L indicates the presence of CSF, while a β-TP concentration lower than 1 mg/L indicates a lack of CSF in NS. These findings suggest that β-TP determination may have a powerful role in excluding CSF leaks in appropriately selected patient populations.

After the CSF leak confirmation, imaging is critical to localize and characterize the defect.[4,20] The initial imaging modalities in CSF leak evaluation, including HRCT and NMR, are usually non-invasive. Invasive studies including HRCT-cisternography, contrast-enhanced NMR-cisternography, and radionuclide-cisternography are utilized in selected cases.[5] In our study, the most frequently requested imaging tests have been HRCT and NMR, while HRCT-cisternography and RNM-cisternography have only been requested in 3 and 2 patients, respectively. It is known that HRCT fails to ascertain the concomitant dural defect in a patient with multiple bony defects.[4] It also fails to distinguish dehiscent and thin non-dehiscent bone.[5] Our data show that HRCT presents a 85.2% sensitivity and a 98.6% specificity, according with previous data that described a HRCT sensibility for CSF leaks between 84% and 95%, with specificity between 57% and 100%.[1,7,21] NMR (57.9% sensitivity and 93.7%, specificity) was less sensitive than HRCT for detecting CSF leak. Considering the sensitivity, specificity, and predictive values, we found that HRTC diagnostic efficacy (93%) was much higher than that of NRM (74%), being the most preferred imaging modality in our hospital.

Currently, there is not standardized protocol for following-up patients who present CSF leaks after surgical or conservative management. It has been suggested that β-TP test is a useful tool in postoperative screening and it can be used to monitor the spontaneous sealing of postoperative fistulas and to verify closure after placement lumbar drain or other conservative measures.[22] Twenty-one patients have been followed up with β-TP determination in NS. In these patients, the established general diagnosis coincided with the positive or negative value (above or below our cut-off point) of β-TP. These results support the reliability of the β-TP test for monitoring patients who have presented CSF leaks and for assessing success after surgical or conservative treatment.

The main limitations of this study result from patients with renal alteration or bacterial meningitis. In the first case, β-TP blood concentration is increased with end-stage renal disease but β-TP concentration in NS is much lower than that described in blood.[23] Moreover, patients with kidney disease were excluded. In the second case, patients with acute meningitis were excluded from the analysis. However, we have included patients with episodes of bacterial meningitis reflected in their clinical history since this background made us suspect a possible fistula and, therefore, request the determination of β-TP.

5 | CONCLUSION

Our study established a 1 mg/L β-TP concentration in NS as a cut-off point for CSF leakage diagnosis with high sensibility and specificity. Here, we also determined β-TP concentration in NS after conservative or surgery treatment to confirm the CSF leak closing. Our findings highlight that β-TP determination may have a powerful role in excluding CSF leaks in appropriately selected patient populations and suggest its usefulness in confirming the resolution of CSF leaks.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

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