Short Communication

Economic burden of readmission due to postoperative cerebrospinal fluid leak in Chinese patients

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Aim: This real-world data study investigated the economic burden and associated factors of readmissions for cerebrospinal fluid leakage (CSFL) post-cranial, transsphenoidal, or spinal index surgeries. **Methods:** Costs of CSFL readmissions and index hospitalizations during 2014–2018 were collected. Readmission cost was measured as absolute cost and as percentage of index hospitalization cost. Factors associated with readmission cost were explored using generalized linear models. **Results:** Readmission cost averaged US$2407–6106, 35–94% of index hospitalization cost. Pharmacy costs were the leading contributor. Generalized linear models showed transsphenoidal index surgery and surgical treatment for CSFL were associated with higher readmission costs. **Conclusion:** CSFL readmissions are a significant economic burden in China. Factors associated with higher readmission cost should be monitored.

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Keywords: 30-day readmission • cerebrospinal fluid leakage • economic burden • real-world study • surgical complications

Cerebrospinal fluid leakage (CSFL) is a serious complication of cranial, spinal and transsphenoidal surgeries. The incidence rate of CSFL varies from 0.3 to 14.3%, depending on the types of the underlying neuro- and spinal surgery [1–6]. Postoperative CSFL may present as headaches, projectile vomiting, neck stiffness or other signs of meningeal irritation [7]. Serious sequelae, such as meningitis, seizures, hemorrhage, cerebral abscess or death have also been reported [7–9].

Postoperative CSFL may prolong hospital stay or lead to reoperation and increase healthcare costs [7,8,10–16]. Postoperative CSFLs were also reported as a common cause of readmission after neuro- and spinal surgeries [10]. Thirty-day readmission has been demonstrated as a major driver of total hospitalization expenditure growth [17–20]. Most of the aforementioned disease burden studies were conducted in the US or European countries [12,13,15,16]. These studies primarily focused on the burden of CSFLs during the same hospital stay as the initial neuro- or spinal surgery. Our literature review found only one study involving postoperative CSFL patients in China [11]. The healthcare system in China differs significantly from those in the US and Europe. It is difficult to estimate the economic burden of CSFLs in China based on the published results from developed countries.

As control of healthcare expenditure is a major policy priority in China, it is important to gain a better understanding of CSFL readmission costs. Cao *et al.* examined patients readmitted for CSFL after surgery for cerebellopontine angle tumors. They reported the average readmission costs of RMB 18,140 to 28,894 (approximately US$2800–4500) [11]. However, the study was a single-center study with limited representativeness. The published manuscript did not report any healthcare resource utilization details. To address the information needs for public health decision makers, we conducted this real-world data (RWD) study to investigate the detailed cost

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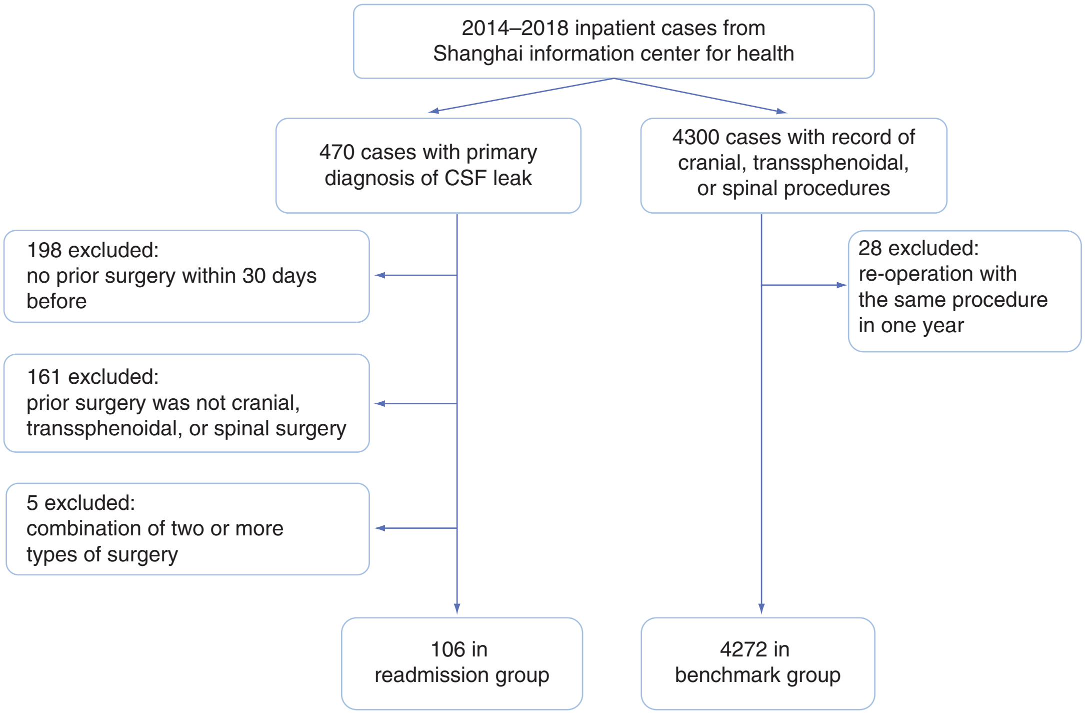

Figure 1. Attrition flow of Readmission Group and Benchmark Group patients.
CSF: Cerebrospinal fluid.

structure of CSFL readmissions within 30 days after cranial, transsphenoidal and spinal surgery. Statistical analysis was performed to identify potential influencing factors associated with readmission costs and length of stay (LOS).

Materials & methods

Study population & analysis set selection

This retrospective RWD study used data extracted from the electronic medical record and medical claim databases managed by the Shanghai Information Center for Health. The databases collect patient records from more than 450 public health institutions throughout Shanghai. During the study period of 2014–2018, the databases covered 6 million uniquely identifiable patients, with 10.5 million inpatient records. The database contains patient demographic information, hospitalization details (diagnosis, operations in the same hospitalization, date of visit, LOS and health insurance type) and categorized costs (such as surgery service costs, pharmacy costs, medical supply costs, etc.). The data used in this study were fully de-identified for patient privacy protection and were exempt from an institutional review board approval.

Two cohorts were analyzed in this study: a Readmission Group and a Benchmark Group. The Readmission Group included patients readmitted for CSFL after index surgery discharge during 2014–2018. The types of index surgeries involved in this study were cranial, spinal and transsphenoidal surgeries that were originally performed. The Benchmark Group included patients who underwent one of the index surgeries during 2014–2018. The attrition flows for both cohorts were shown in Figure 1.

Index surgeries were selected using the standardized operation names in the database. We manually categorized the surgeries as cranial, transsphenoidal or spinal. Specifically, 'resection of skull base tumor,' 'resection of sellar region tumor,' 'resection of meningioma,' 'decompression of optic nerve,' 'decompression of trigeminal nerve,' 'removal of intracranial hematoma,' 'removal of intracerebral hematoma,' 'craniotomy for decompression' and 'cranioplasty' were classified as the cranial surgery subgroup; transsphenoidal hypophysectomy surgeries were classified as transsphenoidal surgery; "spinal fixation" was classified as spinal surgery. Patients who underwent more than one type of the index surgeries were excluded.

CSFL readmissions were first selected using International Classification of Diseases, tenth edition (ICD-10) codes [21]. The primary diagnosis codes for readmission must have had one of the codes under Cerebrospinal Fluid

Leak [G96.0]. The initial hits were further filtered by excluding cases with multiple index surgery types, cases without any of the index surgery types and cases with CSFL hospitalization more than 30 days after previous discharge.

The index hospitalization was defined as the hospitalization in which one of the index surgeries occurred. In this study, index hospitalization costs were estimated using the Benchmark Group. This was because the total case count in the Readmission Group was relatively small. Estimation of index hospitalization costs using only Readmission Group would introduce large variation. Therefore, the Benchmark Group was created to leverage a much larger sample size for a more stable and accurate estimation of the index hospitalization costs.

Patients in both groups were classified into subgroups based on index surgery categories. To ensure that the subgroups in both cohorts were comparable, propensity score matching (PSM) was performed prior to statistical comparison.

Cost definition

The economic burden of readmission due to CSFL was defined as the direct medical cost of readmission, in other words, all itemized charges billed to patients and insurance by hospitals. Readmission costs were calculated from the Readmission Group data, while index hospitalization costs were calculated using the Benchmark Group data. All costs reported were converted to USD based on the currency exchange rate of RMB 6.8 to USD 1 on December 31, 2018. No inflation adjustment was applied to the costs in this study.

Study variables

The primary outcome was the total cost of readmission for CSFL. We further examined components of the total CSFL readmission cost, including pharmacy costs, supply costs and surgery service costs. LOS for CSFL readmission was also investigated.

Factors which might be predictive of readmission burden were analyzed using the Readmission Group exclusively. These included three major categories: patient characteristics, index surgery type and readmission characteristics. Patient characteristics included age, gender and comorbidities (diabetes and hypertension). Readmission characteristics included discharge-to-readmission days (number of days between readmission and index hospitalization discharge), CSFL treatment types (conservative care or surgical intervention) and number of surgical interventions for CSFL.

Statistical analysis

Descriptive statistics of patient characteristics were calculated for the Readmission Group and Benchmark Group; descriptive statistics of readmission characteristics were computed for the Readmission Group only. The mean and standard deviation (SD) were calculated for quantitative variables. The distributions for categorical variables were captured using proportions. Patient characteristics were compared between the two groups per index surgery type. Two-sided Welch's t-test was used for comparing quantitative variables since we did not assume equal variances between groups [22]. Pearson's chi-square test was used to compare gender composition between groups because there were no expected probabilities less than 5, and Fisher's exact test was used to compare comorbidity proportions (diabetes and hypertension) [22]. Matching was deemed necessary when the p-value between groups was less than 0.1. PSM was performed using the MatchIt package for R 3.5.1 [23]. Nearest neighbor matching was applied, with a matching ratio of 1 to 10.

In addition to the absolute values of readmission costs, relative costs were reported. For each index surgery type, the costs of CSFL readmission were compared with index hospitalization costs. For each readmission component cost, we report the relative magnitude as a percentage of corresponding index hospitalization component cost:

$$\Delta\%\text{cost} = \frac{\text{Readmission Mean Cost}}{\text{Index Hospitalization Mean Cost}} \times 100\%$$

Within the Readmission Group, generalized linear models (GLMs) [24] were used to investigate the relationship of a selected group of factors with each healthcare resource utilization outcome separately. Utilization outcomes included total cost, total pharmacy costs, disposable medical supply costs and LOS.

The independent variables in the GLMs were patient age and gender, type of index surgery, time to readmission and CSFL treatment type.

GLMs were performed using the GLM function in base R 3.5.1 [25] and the glm.nb function in the MASS package [26]. Distributions of the dependent variables were shown in Supplementary Figure 1. GLMs were fitted

Table 1. Patient characteristics of Readmission and Benchmark Groups by initial surgery type.

Charactetistics	Readmission group	Benchmark group	p-value
Cranial surgery†			
– N	56	2974	–
– Age (years, mean ± SD)	46.6 ± 14.20	46.5 ± 20.05	0.944
Gender (%)			
– Male	53.15	55.50	0.274
– Female	46.85	44.50	
Comorbidities (%)			
– Diabetes	0.90	2.55	0.637
– Hypertension	6.31	8.82	0.169
Spinal surgery (matched)‡			
– N	18	180	–
– Age (years, mean ± SD)	52.9 ± 19.22	50.6 ± 12.37	0.625
Gender (%)			
– Male	50.00	58.33	0.666
– Female	50.00	41.67	
Comorbidities (%)			
– Diabetes	0	0	1
– Hypertension	1.67	6.11	0.121
Transsphenoidal surgery (matched)‡			
– N	32	320	
Age (years, mean ± SD)	53.7 ± 11.16	54.6 ± 11.35	0.676
Gender (%)			
– Male	37.50	43.13	0.670
– Female	62.50	56.88	
Comorbidities (%)			
– Diabetes	3.13	2.82	1
– Hypertension	6.25	5.00	0.673

†The cranial surgery subgroup was balanced, and no matching was applied.
‡The spinal and transsphenoidal surgery subgroups were matched using age, gender and comorbidities with a ratio of 10. The unmatched results are shown in Supplementary Table 1.
SD: Standard deviation.

with a gamma distribution and log link for cost outcomes [27–29], while a negative binomial distribution and log link were applied to LOS [30–32]. For ease of interpretation, we applied the natural exponential function to the coefficients for reporting.

For the independent variables, continuous variables were scaled by their standard deviations, with resulting standard deviations equal to 1. Centering was not applied as no interaction terms were used [33].

Results

The Readmission Group included a total of 106 patients, with 56 in the cranial surgery subgroup, 18 in the spinal surgery subgroup and 32 in the transsphenoidal surgery subgroup.

After PSM, the Benchmark Group included 3474 patients, with 2974, 180 and 320 in the cranial, spinal and transsphenoidal subgroups, respectively.

Descriptive statistics

Patient characteristics of both groups are shown in Table 1. according to index surgery subgroups. In the cranial surgery subgroup, patient characteristics were comparable between the Readmission and Benchmark Groups. Matching was applied to the transsphenoidal surgery and spinal surgery subgroups because of unmatched baseline characteristics. Overall, patient age ranged from 43 to 54 years. Patient gender was mostly balanced. Cases of diabetes and hypertension were few in both groups.

Readmission characteristics of the Readmission Group are shown in Table 2. In all, 61% of spinal surgery patients received only conservative therapy, and 28 and 32% of cranial surgery and transsphenoidal surgery patients

Table 2. Characteristics of readmissions after three types of prior surgery (n = 106).

Characterisics	Cranial (n = 56)	Spinal (n = 18)	Transsphenoidal (n = 32)
Type of therapy (%)			
– Conservative therapy	32%	61%	28%
– Surgical intervention	68%	39%	72%
N surgical interventions (n, mean)	0.89	0.50	0.91
Duration before readmission (days, mean)	17.25	15.44	20.34
Length of stay (days, mean)	17.5	17.9	19.2

Table 3. Readmission Group and Benchmark Group cost comparison (US$).†

Surgery type	Readmission group		Benchmark group		Δ % cost
	N	CSFL readmission costs (mean ± SD)	N	Index hospitalization costs (mean ± SD)	
Cranial surgery‡					
– Total cost	56	3753 ± 4678	2974	10,740 ± 6223	34.94
– Surgery service cost		427 ± 705		1472 ± 1687	29.02
– Pharmacy cost		1674 ± 2863		2725 ± 2892	61.43
– Supply cost		739 ± 1006		2999 ± 2594	24.63
Spinal surgery (matched)§					
– Total cost	18	2407 ± 2805	180	5133 ± 5433	46.90
– Surgery service cost		112 ± 215		589 ± 378	19.07
– Pharmacy cost		1383 ± 2039		688 ± 646	200.99
– Supply cost		264 ± 291		3191 ± 3193	8.29
Transsphenoidal surgery (matched)§					
– Total cost	32	6106 ± 4022	96	6486 ± 2012	94.14
– Surgery service cost		679 ± 812		1198 ± 654	56.68
– Pharmacy cost		2614 ± 2118		1742 ± 1064	150.04
– Supply cost		1155 ± 1019		3309 ± 3129	34.91

†The costs reported as central values are shown in Supplementary Tables 2 & 3.
‡The cranial surgery subgroup was balanced, and no matching was applied.
§The spinal and transsphenoidal surgery subgroups were matched using age, gender and comorbidities with a ratio of 10.
Readmission Group and Benchmark Group cost comparison (US$).
CSFL: Cerebrospinal fluid leakage; SD: Standard deviation.

received conservative therapy, respectively. The average time from index hospitalization discharge to readmission was 15, 20 and 17 days in the subgroups of spinal surgery, transsphenoidal surgery and cranial surgery, respectively. Readmission LOS was similar between cranial and spinal surgery patients, with an average of 17 days, while transsphenoidal surgery patients had a slightly longer LOS, with an average of 19 days.

Hospitalization costs

Readmission costs for CSFL after the three different types of index surgery are shown in Table 3. Patients who received transsphenoidal index surgery incurred the highest total readmission costs (US$6106/RMB 41,521), followed by cranial surgery (US$3753/RMB 25,520) and spinal surgery (US$2407/RMB 16,370). Compared with index hospitalization costs, the economic burden for CSFL was quite substantial. In particular, the readmission cost after transsphenoidal index surgery reached 94.14% of the index hospitalization cost. For spinal and cranial index surgeries, readmission costs reached 46.90% and 34.94% of index hospitalization costs, respectively. Notably, pharmacy costs for readmission after transsphenoidal index surgery were equivalent to 150.04% of pharmacy costs for the index hospitalization itself. Pharmacy costs for readmission after spinal surgery were also much higher compared with those of the index hospitalization, with an increase of 200.99%.

Factors associated with economic burden

Exponentially transformed coefficients of independent variables from GLM fitting are reported in Table 4. Com-

Table 4. Exponentiation results of significant coefficients of generalized linear models (n = 106).

Factor	Total cost	Pharmacy costs	Supply costs	Length of stay
Therapy for CSFL†				
– Conservative therapy‡	0.28***	0.26***	0.17***	0.55***
Prior surgery				
– Spinal surgery§	0.95	1.59	0.82	1.17
– Transsphenoidal surgery§	1.84**	1.99*	1.43	1.05
Duration before readmission¶	1.14	1.30*	1.05	1.06
Gender	0.91	0.87	1.14	0.95
Age	1.02	1.07	0.84	1.03

†Therapy for CSFL during readmission.
‡Compared with surgical intervention for CSFL treatment.
§Compared with cranial surgery.
¶Days between readmission and prior discharge (scaled).
Significance values: ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.
CSFL: Cerebrospinal fluid leakage.

pared with cranial index surgery, transsphenoidal index surgery was associated with significantly higher readmission total cost and pharmacy costs, but not supply costs. Surgical treatments in CSFL readmission was associated with significantly increased total cost, pharmacy costs, supply costs and LOS. Delayed readmission, which meant longer time from index hospitalization discharge to readmission, was associated with an increased pharmacy cost.

Discussion

This RWD study demonstrated the economic burden of readmission for CSFLs after cranial surgery, transsphenoidal surgery or spinal surgery in China. The excess burden of readmission has been widely recognized in the US. Thirty-day readmission is used as a healthcare quality measures [17–20]. The characteristics of 30-day readmission costs for postoperative CSFL in China had not been extensively investigated thus far.

Total readmission costs for the treatment of postoperative CSFLs were high, and most of these increased costs came from pharmacy costs rather than surgery service or supply costs. Total CSFL readmission costs ranged from US$2407 (RMB 16,370) to US$6106 (RMB 41,521), equivalent to 35–94% of the index hospitalization cost. These results are in line with those reported by Cao and his colleagues [11], who reported that the total economic cost for readmission ranged from RMB 18,140 to 28,894 (equivalent to US$2668 and US$4248, respectively, using the exchange rate of 6.8 in this study), and the LOS ranged from 18.2 to 19.8 days.

The economic burden of postoperative CSFLs varied by index surgery type. We found that readmission cost for CSFLs after transsphenoidal index surgery was almost equal to the total index hospitalization cost. This means that CSFL readmission could double the economic burden of a transsphenoidal surgery. For cranial and spinal index surgeries, readmission costs were also substantial relative to the index hospitalization cost. These phenomena are also consistent with other studies [12,13].

The relatively higher costs of readmission for post-transsphenoidal surgery CSFL readmission may be related to the risk of surgical site infection or meningitis. Transsphenoidal surgery is a clean-contaminated surgery because this approach traverses the nasal cavity [34]. To prevent infection, surgeons tend to use antibiotics [35,36], specifically in transsphenoidal surgery [37–39]. This may suggest higher antibiotic usage also occurs in cases of CSFLs post-transsphenoidal surgery to prevent or treat infection. Our data also showed that transsphenoidal index surgery is associated with increased pharmacy costs (Tables 2 & 3).

Type of treatment used for CSFL was related to index surgery type, as shown in Table 1. The transsphenoidal index surgery subgroup had the highest rate of surgical intervention. Several studies reported the rates of surgical intervention for postoperative CSFL after spinal [42–45], transsphenoidal [46–50] and cranial surgery [51–53]. These studies also confirmed that surgery treatment for CSFL was used more frequently after transsphenoidal surgery. One potential explanation is that prompt surgery treatment of CSFL was deemed more appropriate clinically to reduce the risk of infection [48,54–57].

Selection of CSFL treatment was an important factor affecting total readmission costs. Some authors have recommended a step-wise approach [40,41], though this may not be suitable for all index surgery types, such as transsphenoidal surgery. In the stepwise approach, the first choice is usually conservative therapy, such as bed rest with a reversed Trendelenburg position, caffeine, antibiotic therapy, etc. Lumbar drainage or other types of drainage are recommended if conservative therapy fails. Patients will be treated by surgical intervention if CSFL persists [11]. Cao and his colleagues demonstrated that patients who underwent surgical repair for CSFL incurred higher total costs than those who underwent conservative methods [11]. Our study showed that surgical intervention was associated with significantly increased total costs, and pharmacy costs specifically. This result may be because surgical intervention could necessitate the use of higher antibiotic dosages and other medication. It may also be that more severe cases of CSFL undergo surgical repair, as well as patients that have failed conservative therapy. In addition, due to the high risk of meningitis and low cure rate of conservative therapy [46,48], surgical repair is generally the first option for CSFL after transsphenoidal surgery. Therefore, the clinical need of surgical repair may outweigh financial considerations.

The burdens associated with the required surgical repairs for some cases of CSFL highlight the need for CSFL prevention. This is especially important for transsphenoidal surgery, as the data showed that transsphenoidal index surgery had the highest readmission costs among the three types of index surgeries. Closure of the surgical defect is the key to preventing postoperative CSFLs. Various closure techniques have been reported. Small dural tears may be repaired by watertight sutures, along with hemostyptic or hemostatic agents [40,58,59]. Where dural sutures are not sufficient or feasible, more sophisticated techniques can be applied. These techniques usually involve sealing the dura with suitable materials and supporting these materials with a buttress [14]. Autologous tissue, such as abdominal fat, thigh fat or nasoseptal flaps, can be used along with fibrin sealant or synthetic materials, including collagen sponges, gelfoam, dural substitutes or resorbable meshes [8,14,15,60].

In the US., researchers have also recognized CSFL as a concern for surgeons, particularly because of potential sequelae [8,10,16,52,54,61–64]. Multiple US studies documented CSFL incidence rates of 6.2–17.2% in cranial surgeries [52,54], 7.4–11.7% in spinal surgeries [61–63] and 3.9–13.5% in transsphenoidal surgeries [8,16,64, 66]. Cote *et al.* reported that CSFL was the most common reason for reoperation after transsphenoidal surgery (63.6%), and the second most common reason for readmission (16.0%) [10].

The mean costs for treating CSFL during the index hospitalization were reported as US$46,026 after transsphenoidal surgery, about 86% of the index surgery itself [65]. CSFL were also linked to prolonged LOS of the index hospitalization, by 2.8–4 days on average, after transsphenoidal surgery. Chern *et al.* reported the median cost of CSFL repair to be US$50,401 after cranial surgery, including treatment during the index hospitalization and outpatient visits [15]. Studies from Germany reported an increase of EUR 10,350 and 10,643 (or US$9079 and 9336, based on the exchange rate of EUR 1 to US$1.14 on December 31, 2018) in DRG reimbursement after spinal and cranial surgery, respectively [12,13].

Our study suggested that the economic burdens of CSFL readmission are substantial relative to the index surgery. While healthcare systems vary between countries, this finding is consistent with similar studies in other countries. The financial consequences of CSFL readmission warrant serious consideration for healthcare systems globally. The association between index surgery type and CSFL readmission cost may be of interest for further investigations. Our results showed that the cost of CSFL readmission following transsphenoidal surgery was the highest among the three types of index surgeries. Marchiano *et al.* also reported that surgical repair for CSF rhinorrhea significantly increased costs of CSFL treatment [67]. As surgical repair for CSFL after transsphenoidal surgery is generally more common compared with other index surgeries, CSFL readmission following transsphenoidal surgery may also lead to significant increase in cost in other healthcare systems.

Limitations

Our study had several limitations. We focused on CSFLs readmissions and did not cover CSFLs which occurred in the same hospitalization period as the index surgery. In addition, our study excluded patients when CSFL was not their primary diagnosis for hospitalization. This may have biased the sample toward patients with more serious CSFL symptoms.

Conclusion

The economic burden of readmission due to CSFL readmission is substantial in China. Prevention measures of CSFL must be emphasized to reduce the economic burden caused by readmission. This is especially important for transsphenoidal surgery.

Summary points

- Postoperative cerebrospinal fluid leakage (CSFL) is a serious neuro- and spinal surgery complication that may lead to readmission.
- Medical records of 30-day readmissions for CSFL during 2014–2018, as well as those of cranial, spinal and transsphenoidal index surgeries, were collected from a Shanghai municipal platform for hospital management.
- The average total costs of the Readmission Group (n = 106) after cranial, transsphenoidal and spinal index surgeries were RMB 25,520 (US$3753), RMB 41,521 (US$6106), and RMB 16,370 (US$2407), respectively.
- Compared with the Benchmark Group, these costs mean that readmission for CSFL increased the economic burden by 35, 94 and 47% for patients who underwent cranial, transsphenoidal and spinal index surgeries, respectively.
- Across all three types of index surgery, pharmacy costs were the main contributors to CSFL readmission costs.
- CSFL caused by transsphenoidal surgery was associated with increased total and pharmacy costs during readmission.
- Surgical repair for CSFL was also associated with increased costs, however surgery may be clinically required.
- Aside from controlling readmission costs, reduction of readmissions by taking preventive measures should also be emphasized.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0067

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Author contributions

Y Han and Y Wu were responsible for study conception and design; X Cui, S Zhang, W Tian and J Liu were responsible for data acquisition and management; S Wu was responsible for data analysis; S Wu, X Cui, Y Wu, M Wu and Y Han were responsible for drafting and revision of the manuscript.

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