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Original Article

Risk of death in patients with post-traumatic cerebrospinal fluid leakage—Analysis of 1773 cases

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Abstract

Background: Post-traumatic cerebrospinal fluid (CSF) leakage is one of the most troublesome conditions associated with head trauma. CSF fistulae, meningitis/central nervous infection, or even death may accompany it. Few studies have discussed post-traumatic CSF leakage as a risk factor in mortality following head trauma. We conducted this cohort study to examine the issue.

Methods: We reviewed the records in the Taiwan Traumatic Brain Injury (TBI) Registry System between 1993 and 2008. The study group included patients with acute TBI and post-traumatic CSF leakage, and the control group included cases with TBI but without CSF leakage, selected randomly at a 5:1 ratio with respect to the study group. The demographic data, Glasgow Coma Scale, brain computerized tomography, association of skull fractures and intracranial lesions, and 1-year mortality rates between these two cohorts were reviewed meticulously and analyzed statistically.

Results: Of 174,236 cases, 1773 with post-traumatic CSF leakage were included in the study group, and 8865 cases in the control group. Of the total 10,638 sampled cases, 406 (3.8%) died during the 1-year follow-up period, 159 (9.0%) cases in the CSF leakages group, and 247 (2.8%) in the control group. The patients with CSF leakage had a significantly higher mortality rate within 1 year (adjusted hazard ratio = 1.44, $p < 0.001$) than those without. We divided the CSF leakage group into three subgroups: otorrhea ($n = 568$), rhinorrhea ($n = 302$), and tension pneumocephalus ($n = 903$). The mortality rates were 8.5% (48/568) in the otorrhea subgroup, 10.9% (33/302) in the rhinorrhea subgroup, and 8.6% (78/903) in the tension pneumocephalus subgroup. The cases with CSF rhinorrhea had a significantly higher mortality rate than the other two subgroups ($p < 0.05$). All three subgroups had significantly higher mortality rates than the control group during the 1-year follow-up period (adjusted hazard ratios = 2.29, 1.35, and 1.32 in the rhinorrhea, tension pneumocephalus, and otorrhea subgroups, respectively).

Conclusion: Post-traumatic CSF leakages had higher mortality rates than those without CSF leakages in TBI cases, and the cases with CSF rhinorrhea had worse outcomes compared with CSF leakages with pneumocephalus or otorrhea.

Keywords: cerebrospinal fluid; leakage; mortality; skull fracture; traumatic brain injury

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Traumatic brain injury (TBI) is a major cause of morbidity and mortality,[1−3] and post-traumatic cerebrospinal fluid (CSF) leakage is a complication of TBI. Approximately 84% of cases of CSF leakage are caused by head injuries involving skull fractures,[4] and up to 30% of patients with skull base fractures develop CSF fistulae.[5−7]

CSF rhinorrhea and otorrhea can potentially lead to fatal complications such as persistent CSF fistulae, central nervous system infections, and meningitis. The occurrence rate of meningitis among patients with post-traumatic CSF leakage has been reported to range from 10% to 37%.[4,8] These complications usually cause prolonged hospital stays and even higher mortality rates.

However, the occurrence rate, fracture sites, and mortality rates in patients of TBI with post-traumatic CSF leakage have seldom been reported. Therefore, we conducted this case-control cohort study to compare TBI patients with and without post-traumatic CSF leakage drawn from the Traumatic Brain Injury Registry database of Taiwan. We hypothesized that cases with post-traumatic CSF leakage after TBI would have increased intracranial damage and a higher mortality rate compared with those without CSF leakage.

2. Methods

2.1. Data collection

From January 1st, 1993, to December 31st, 2008, a survey on TBI was conducted by the Head & Spinal Cord Injury Research Group of the Taiwan Neurosurgical Society. The data of patients from 24 major hospitals (80% of the hospitals in Taiwan capable of treating TBI) were retrospectively collected in this study. The Head & Spinal Cord Injury Research Group of the Taiwan Neurosurgical Society then created a database, named the Traumatic Brain Injury Registry (TBIR). Data in the TBIR were recorded by experienced neurosurgeons from each hospital and extracted by research assistants. International Classification of Diseases, Ninth Revision (ICD-9) codes 800−804 (fracture of the skull or facial bones), 850.0 (concussion without loss of consciousness), 850.1−850.2 (concussion with loss of consciousness), 851−851.1 (cerebral/cerebellar/brain stem contusion or laceration), 852.0−853 (extracerebral and/or intracerebral hematoma, subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage, intracranial hemorrhage), 854.0 (unspecified intracranial injury), 900.0 (injury to blood vessels of the head and neck), and 950.0−951.5 (injury to cranial nerves) were used to identify TBI cases. In total, 174,236 cases were included in the database. The principles outlined in the Declaration of Helsinki were followed strictly, and there was no patient consent sought because the retrospective data were analyzed anonymously and no personal information could be connected in this study.

2.2. Study population

We retrospectively analyzed the database of the TBIR. The inclusion criteria for the study cohort were cases who had sustained a closed TBI, and who were diagnosed with new-onset CSF leakage and tension pneumocephalus associated with the injury. Cases that sustained a penetration brain injury, died at the scene, suffered out-of-hospital cardiac arrest, or underwent cardio-pulmonary cerebral resuscitation were excluded. A total of 1773 cases matched these criteria and were included as the study cohort.

The comparison cohort (control group) was those patients who had sustained a closed TBI without CSF leakage or tension pneumocephalus during the same period. The control cohort cases were randomly selected at a ratio of 5:1 to the study cohort matched by age (<18 years, 18−30 years, 31−45 years, 46−65 years, and >65 years) and sex. In total, 8865 cases were included in the control cohort.

The demographic data, mechanisms of injury, Glasgow Coma Scale (GCS) score on admission and discharge, brain computerized tomography, cranial nerve injury, associated injury other than central nervous system, skull fractures, intracranial hemorrhage, and management were recorded. All cases were followed for 1 year, and the survival for each at the end of the year was assessed and recorded.

2.3. Statistical analysis

Pearson χ^2 tests were used to explore the differences in the characteristics (age, sex, GCS, cranial nerve lesion, fracture of the skull, associated injuries, and intracranial hemorrhage) between the two cohorts. We calculated the 1-year survival rate using a Cox regression plot to examine the differences in the survival rate between the two cohorts. Cox proportional hazard regression analysis was performed to compute the 1-year survival rate, after adjusting for TBI characteristics and selecting comorbid medical disorders. Each dichotomous variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log−log survival plots. Multinomial logistic regression models were performed to analyze the risk factors of the 1-year death or vegetative outcome in patients with traumatic brain injuries. A significance level of $p < 0.05$ was used to determine the significance of predictors in the models. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) Version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study group

Of the 174,236 cases in the TBIR database, we identified 1773 patients with post-traumatic CSF leakages and tension pneumocephalus as the study cohort. The occurrence rate of

post-traumatic CSF leakages was 1.0% (1773/174,236) in our series. In the study group, there were 1364 (76.9%) males and 409 (23.1%) females. We also divided the study cohort into five age subgroups, as follows: <18 years, 18–30 years, 31–45 years, 46–65 years, and >65 years. They were 202 (11.4%) cases, 609 (34.3%) cases, 387 (21.8%) cases, 359 (20.2%) cases, and 216 (12.1%) cases, respectively, in each of the five subgroups. More than half of the injury cases (56.1%) were aged 18–45 years (Table 1).

3.2. Severity of injury

In TBI, cases with CSF leakage commonly have more damage to their neurological system. In the study cohort, 50.0% had mild TBI (GCS ≥ 13), 21.8% moderate TBI (GCS 9–12), and 28.2% severe TBI (GCS ≤ 8). In the comparison group (n = 8865), 79.9%, 10.2%, and 9.9% had mild, moderate, and severe TBI, respectively. There were significantly higher rates of moderate and severe TBI in the CSF leakage group than in the control group ($p < 0.001$). In addition, cases in the CSF leakage group had more cranial nerve injuries (26.5% vs. 9.0%, $p < 0.001$) and intracranial hemorrhage (64.7% vs. 28.8%, $p < 0.001$) than did cases in the comparison group (Table 1).

3.3. Higher mortality rate in the CSF leakage group

There were more severe neurological injuries in the CSF leakage group, with higher morbidity and lower survival rates.

Table 1
Demographic characteristics of patients with cerebrospinal fluid leakage and patients in the comparison cohort.

Variable	Cerebrospinal fluid leak or pneumocephalus n = 1773		Control n = 8865		p
	Total no.	%	Total no.	%	
Sex					>0.99
Male	1364	76.9	6820	76.9	
Female	409	23.1	2045	23.1	
Age (y)					>0.99
<18	202	11.4	1010	11.4	
18–30	609	34.3	3045	34.3	
31–45	387	21.8	1935	21.8	
46–65	359	20.2	1795	20.2	
>65	216	12.2	1080	12.2	
Glasgow Coma Scale					<0.001
Score of ≥13	886	50.0	7086	79.9	
Score of 9–12	387	21.8	902	10.2	
Score of ≤8	500	28.2	877	9.9	
Cranial nerve lesions					<0.001
Yes	470	26.5	800	9.0	
No	1303	73.5	8065	91.0	
Associated injuries[a]					<0.001
Yes	955	53.9	5267	59.4	
No	818	46.1	3598	40.6	
Intracranial hemorrhage					<0.001
Yes	1147	64.7	2551	28.8	
No	626	35.3	6314	71.2	

[a] Injuries of body beyond the head and brain followed by accident.

Of the total 10,638 sampled cases, 406 (3.8%) died during the 1-year follow-up period. In the CSF leakage group, 159 (9.0%) cases died and 1614 (91.0%) cases were still alive, compared with 247 (2.8%) and 8618 (97.2%) cases respectively, in the comparison group. The crude hazard ratios for death between these two cohorts showed a significant difference. The hazard ratio of death in the CSF leakage group during the 1-year follow-up period was 3.35-fold [95% confidence interval (CI) = 2.75–4.09, $p < 0.001$] greater than for those in the control group. After adjusting for age, sex, GCS, cranial nerve lesion, associated injuries and intracranial hemorrhage, the adjusted hazard ratio of death in the CSF leakage group was still 1.44-fold (95% CI = 1.16–1.79, $p < 0.001$) higher compared with the control cohort. The CSF leakage group had a significantly higher 1-year mortality rate than the comparison group ($p < 0.001$; Table 2).

3.4. Mortality rates in the CSF otorrhea, rhinorrhea, and tension pneumocephalus subgroups

We divided the CSF leakage group into three subgroups: otorrhea (n = 568), rhinorrhea (n = 302), and tension pneumocephalus (n = 903). During the 1-year follow-up period, the mortality rates were 8.5% (48/568) in the otorrhea subgroup, 10.9% (33/302) in the rhinorrhea subgroup, and 8.6% (78/903) in the tension pneumocephalus subgroup (Table 3).

We compared the crude hazard ratios for death between these three subgroups to the control group. During the 1-year follow-up period, the hazard ratios of death were 3.17 (95% CI = 2.33–4.32, $p < 0.001$) in the otorrhea subgroup, 4.14 (95% CI = 2.88–5.95, $p < 0.001$) in the rhinorrhea subgroup, and 3.44 (95% CI = 2.72–4.36, $p < 0.001$) in the tension pneumocephalus subgroup, compared with the control group.

Similarly, after adjusting for age, sex, GCS, cranial nerve lesion, associated injuries, and intracranial hemorrhage, the adjusted hazard ratios of death during the 1-year follow-up period were 1.32 (95% CI = 1.02–1.95, $p < 0.05$) in the otorrhea subgroup, 2.29 (95% CI = 1.55–3.38, $p < 0.001$) in the rhinorrhea subgroup, and 1.35 (95% CI = 1.04–1.74, $p < 0.05$) in the pneumocephalus subgroup (Table 3). All three subgroups had significantly lower 1-year survival rates than

Table 2
Crude and adjusted hazard ratios for death among sample patients during the 1-year follow-up period starting from the index ambulatory care visit (n = 10,638).

Presence of death	All cases		Control		CSF leakage	
	No.	%	No.	%	No.	%
1-y follow-up period						
Dead	406	3.8	247	2.8	159	9.0
Alive	10232	96.2	8618	97.2	1614	91.0
Crude HR (95% CI)	—		1.00		3.35 (2.75–4.09)*	
Adjusted HR (95% CI)[a]	—		1.00		1.49 (1.21–1.83)*	

*$p < 0.001$.
CI = confidence interval; CSF = cerebrospinal fluid; HR = hazard ratio.
[a] Adjustments were made for age, sex, Glasgow Coma Scale, cranial nerve lesions, associated injuries and intracranial hemorrhage.

Table 3
Crude and adjusted hazard ratios for death among sample patients during the 1-year follow-up period starting from the index ambulatory care visit.

Presence of death	Control		Otorrhea		Rhinorrhea		Pneumocephalus	
	No.	%	No.	%	No.	%	No.	%
1-y follow-up period								
Yes	247	2.8	48	8.5	33	10.9	78	8.6
No	8618	97.2	520	91.5	269	89.1	825	91.4
Crude HR (95% CI)	1.00		3.17 (2.33–4.32)*		4.14 (2.88–5.95)*		3.44 (2.72–4.36)*	
Adjusted HR (95% CI)[a]	1.00		1.32 (1.02–1.95)		2.29 (1.55–3.38)*		1.35 (1.04–1.74)**	

*$p < 0.001$.
**$p < 0.05$.
CI = confidence interval; HR = hazard ratio.
[a] Adjustments were made for age, sex, Glasgow Coma Scale, cranial nerve lesions, associated injuries and intracranial hemorrhage.

the control group during the 1-year follow-up period, and the rhinorrhea subgroup had the lowest survival rate among three CSF leakage subgroups (Fig. 1).

3.5. Skull fracture sites

The locations of the skull fractures had a significant impact on the types of CSF leakage. In the CSF leakage group, 1305 (73.6%) cases had skull fractures. Among them, 347 (26.6%) cases were in the otorrhea subgroup, 185 (14.2%) in the rhinorrhea subgroup, and 773 cases in the pneumocephalus subgroup (59.2%). We then analyzed the relationship between the fracture sites and CSF leakage. In the otorrhea subgroup, the two most common fracture sites were the temporal bone and skull base with odds ratios (ORs) of 2.31 (95% CI = 1.70–3.12, $p < 0.001$) and 3.04 (95% CI = 2.15–4.29, $p < 0.001$), respectively. In the rhinorrhea subgroup, the two most common fractures sites were the frontal bone (OR 1.51, 95% CI = 1.01–2.25, $p < 0.05$) and skull bases (OR 3.58, 95% CI = 2.34–5.47, $p < 0.001$), although the frontal bone was the most common fracture site in the pneumocephalus subgroup (OR 1.72, 95% CI = 1.38–2.15, $p < 0.001$; Table 4).

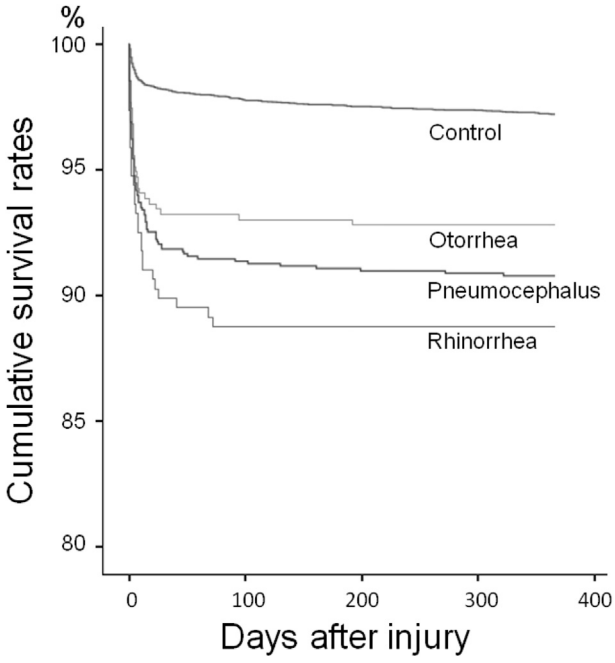

Fig. 1. Cumulative survival rates of enrolled cases with post-traumatic cerebrospinal fluid leakage (rhinorrhea, otorrhea, and pneumocephalus subgroups) and comparison cohort (control group) during the 1-year follow-up period.

3.6. Risk factors for 1-year death or vegetative outcome

After multivariate analysis, the significant risk factors for 1-year death or vegetative outcome compared with those for full recovery or moderate disability in patients with TBIs were found to include age, intracranial hemorrhage, cranial nerve lesion, GCS, and CSF leakage, including otorrhea, rhinorrhea, and pneumocephalus (Table 5). Risk factors for severe disability compared with those for full recovery or moderate disability were significant in age, intracranial hemorrhage, cranial nerve lesion, GCS, and pneumocephalus (Table 5).

4. Discussion

4.1. The occurrence of post-traumatic CSF leakage

Head trauma is a frequent cause of CSF leakage, and 30–80% of cases of CSF leakage are caused by closed head injuries and skull base fractures.[5–7,9] Bell et al[10] reported that 4.6% of 735 traumatic cases developed post-traumatic CSF leakage over a 10-year study period, among whom post-traumatic otorrhea (75.8%) was more common than post-traumatic rhinorrhea (26.5%). Friedman et al[4] also reported that approximately 2% of 51 cases treated for TBI had post-trauma CSF leakage. However, these previous studies were limited by the small number of cases or being localized to a single institute or particular region. Conversely, the TBIR database in Taiwan is one of the biggest TBI registry databases in the world (n = 174,236).[1,3,11] Our cases were collected from multiple centers nationwide, including rural and urban areas, covering approximately 80% of the 23-million population of Taiwan.

Furthermore, this study did not only focus on a particular TBI group, such as those patients with severe (GCS $\leq$ 8) or moderate (GCS 9–12) TBI, but also covered the whole TBI population, including mild (GCS $\geq$ 13), moderate, and severe TBI. Therefore, we believe that the results of this study reflect the real occurrence of post-traumatic CSF leakage in patients

Table 4
Relationships between cerebrospinal fluid leakage subtypes and anatomic locations of skull fractures and the odds ratio.

Fracture sites	Otorrhea (n = 347)		Rhinorrhea (n = 185)		Pneumocephalus (n = 773)	
	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Frontal (n = 388)	48 (13.9)	0.45* (0.32–0.64)	68 (36.8)	1.51** (1.01–2.25)	272 (35.2)	1.72* (1.38–2.15)
Temporal (n = 367)	140 (40.3)	2.31* (1.70–3.12)	29 (15.7)	0.53*** (0.33–0.84)	198 (25.6)	0.98 (0.78–1.22)
Parietal (n = 153)	31 (8.9)	0.62** (0.41–0.92)	12 (6.5)	0.50** (0.26–0.94)	110 (14.2)	1.22 (0.94–1.58)
Occipital (n = 123)	36 (10.4)	1.16 (0.77–1.75)	9 (4.9)	0.38** (0.17–0.85)	78 (10.1)	1.14 (0.84–1.55)
Skull base (n = 274)	92 (26.5)	3.04* (2.15–4.29)	67 (36.2)	3.58* (2.34–5.47)	115 (14.9)	1.29 (0.97–1.72)

*$p < 0.001$.
**$p < 0.05$.
***$p < 0.01$.
CI = confidence interval; OR = odds ratio.

with TBI. In addition, the number of cases with post-traumatic CSF leakage (n = 1773) was larger than in previous studies. The occurrence rate of post-traumatic CSF leakage was 1.0%, which is far less than in other series.[10,12] However, we believe this rate more closely reflects the actual clinical situation because the cases in our study were distributed nationally, not locally, and the severity of injury was studied more wholly, not partially.

4.2. More intracranial hemorrhage and cranial nerve injuries in the CSF leakage group

Few reports have discussed intracranial damage and cranial injuries in patients with post-traumatic CSF leakage. Our results showed that the traumatic CSF leakage group had a higher rate of intracranial hemorrhage (64.7%) compared with the group without CSF leakage (28.8%;) ($p < 0.001$). There were two potential explanations for this finding: (1) the presence of post-traumatic CSF leakage or tension pneumocephalus means a loss of integrity of the skull bone and skull base. An impact strong enough to break a solid skull bone involves more energy than that which does not break the skull bone. This also means more damage to the brain parenchyma and vulnerable cranial nerves; and (2) the presence of post-traumatic CSF leakage or tension pneumocephalus reflects the dural tearing and breakdown of the subarachnoid space. In this situation, both the loss of the protection of brain parenchyma from firm dura matter and the loss of the cushion effect of the subarachnoid CSF system would cause more damage to parenchyma and cranial nerves, thereby leading to the increased intracranial hemorrhage and cranial nerve injuries in our series. This is consistent with the recent report by Neville et al,[13] who reported that 90% of their patients with frontal depressed skull fractures had concomitant focal lesions, 82.5% had subarachnoid hemorrhage, and 70% presented with pneumocephalus.

Table 5
Odds ratios (ORs) based on multinomial logistic regression models for risk factors of identified variables between post-traumatic cerebrospinal fluid leakages and different GOS after 1-year follow up.

Variables	GOS 1–2 versus GOS 4–5	GOS 3 versus GOS 4–5
	OR (95% CI)	OR (95% CI)
Age	1.024 (1.017–1.030)*	1.019 (1.015–1.023)*
Sex (female)	0.874 (0.712–1.071)	0.858 (0.666–1.104)
Associated injuries[a]	0.833 (0.658–1.053)	0.861 (0.702–1.055)
Intracranial hemorrhage	2.346 (1.748–3.147)*	2.736 (2.162–3.461)*
Cranial nerve lesion	7.744 (6.121–9.797)*	1.803 (1.397–2.326)*
GCS	4.437 (3.807–5.169)*	1.777 (1.561–2.022)*
Otorrhea	1.649 (1.158–2.346)**	1.300 (0.913–1.849)
Rhinorrhea	2.476 (1.577–3.886)*	1.246 (0.748–2.074)
Pneumocephalus	1.426 (1.083–1.876)***	1.424 (1.082–1.873)***

*$p < 0.001$.
**$p < 0.05$.
***$p < 0.01$.
CI = confidence interval; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale, classified as Grade 1–5 (1 = death, 2 = vegetative, 3 = severe disability, 4 = moderate disability, 5 = full recovery).
[a] Injuries of body beyond the head and brain following accident.

4.3. The association between fracture sites and pattern of CSF leakage

The association between fracture sites and pattern of CSF leakage in TBI has not been thoroughly studied to date. Choi et al[14] reported 115 cases who presented with post-traumatic CSF leakage, and concluded that the patients with CSF rhinorrhea had a significantly greater incidence of periorbital hematoma. In addition, frontal/ethmoid bone fractures were particularly associated with dural tearing and CSF leakage. Friedman et al[4] reported that 84% of their cases with post-traumatic CSF leakage presented with skull fractures, and the frontal sinus was most commonly involved. Anterior skull base leaks are more common than middle or posterior leaks, due to the firm adherence of the dura to the anterior basilar skull. The most commonly reported sites in CSF rhinorrhea after accidental trauma are the sphenoid sinus (30%), frontal sinus (30%), and ethmoid/cribriform (23%).[15,16]

In our study, 73.6% of post-traumatic CSF leakages presented with skull fractures, mildly lower than the Friedman's series,[4] however, we had a similar trend of more vulnerable injuries in frontal bone. In our post-traumatic CSF rhinorrhea group, the frontal bone and skull base were the two most commonly involved fracture sites (36.8% and 36.2%, respectively). The presence of frontal bone and skull base fractures had a greater risk of dural tearing and CSF rhinorrhea (OR, 1.51 and 3.58, respectively) compared with those patients

without such fractures. There were similar findings in the post-traumatic CSF otorrhea group, in which temporal bone was the most commonly involved fracture site (40.3%), and the OR was 2.31, significantly higher than for those cases without temporal bone fracture ($p < 0.001$).

Approximately 75−80% of cases of pneumocephalus are caused by trauma.[17] In our series, the frontal bone was the most common fracture site causing tension pneumocephalus (272 cases, 35.2%), compared with the other skull bone/base fractures. There were also more frontal bone fractures (OR 1.72, $p < 0.001$) in the tension pneumocephalus group than other skull fractures. There are two possible mechanisms to explain these findings: (1) the relationship of anatomy between the frontal/ethmoid sinus and frontal bone causes codamage of the frontal/ethmoid sinus in cases of frontal bone fractures[18]; and (2) motorcycle accidents were the most common cause of TBI in our database.[11,19] Even with helmet protection, the anterior frontal-facial parts of these patients are the most vulnerable.

4.4. The risks of death in the CSF leakage group

For all sampled cases of TBI (10,638), the 1-year mortality rate was 3.8%. The mortality rate of those with CSF leakage was significantly higher than for those without CSF leakage (9.0% vs. 2.8%, respectively), and the crude hazard ratio of death between these two groups was 3.35 (95% CI = 2.75−4.09, $p < 0.001$). After adjusting for age, sex, GCS, cranial nerve lesions, associated injuries, and intracranial hemorrhage, the hazard ratio was still significant between these two groups (1.49). This means that patients with post-traumatic CSF leakage had a higher association with death than those without post-traumatic CSF leakage.

Among the three subgroups of post-traumatic CSF leakage, CSF rhinorrhea had a greater association with death than the other two subgroups after 1-year of follow-up. There are two possible explanations for this finding: (1) craniofacial trauma was a common injury in our TBIR database, in which motorcycle accidents are predominant. This trauma type causes complicated frontal base fractures and para-sinus injuries, and it is more difficult to repair these complicated fractures involving multiple sites. This may also be associated with a higher risk of CNS infections, such as meningitis and brain abscess, and also the recurrence of CSF rhinorrhea even after surgical repair[16]; and (2) the occurrence of CSF rhinorrhea may reflect the release of intracranial pressure via CSF leakage, regardless of post-traumatic CSF leakage or spontaneous CSF leakages,[20,21] and intracranial hypertension leads to higher mortality and morbidity in TBI cases. This may also explain the outcomes in the post-traumatic CSF leakage group being poorer than in those cases without CSF leakage in the current study.

To the best of our knowledge, this study is the first population-based cohort study to assess the risk for death in patients with CSF leakage. In addition, the large sample size of our dataset allowed us to determine the risk of death for patients with different categories of CSF leakage, while controlling for major potential confounding factors.

In conclusion, TBI patients with post-traumatic CSF leakage had significantly higher mortality rates than those cases without CSF leakages, and the cases with CSF rhinorrhea had worse outcomes compared with pneumocephalus or otorrhea among CSF leakages. Therefore, neurosurgeons should pay more careful attention to TBI cases with CSF leakage, especially those with the presence of CSF rhinorrhea.

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