Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis

Tao Xu, Xinyuan Yu, Shu Ou, Xi Liu, Jinxian Yuan, Hao Huang, Juan Yang, Liang He, Yangmei Chen*

Department of Neurology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

Tao Xu and Xinyuan Yu contributed equally to this work.

*Corresponding author. E-mail address: 757151961@qq.com (Y. Chen).

Abbreviations: PTE = posttraumatic epilepsy; RR = relative ratio; CI = confidence interval; TBI = traumatic brain injury; ASS = acute symptomatic seizure; GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia; CT = computed tomography; MRI = magnetic resonance imaging; MBI = mild brain injury; SBI = severe brain injury; SDH = subdural hemorrhage; EDH = epidural hemorrhage; SAH = subarachnoid hemorrhage; ICH = intracranial hemorrhage; IVH = intraventricular hemorrhage; CNS = central nervous system.

Abstract:

Objective: A systematic review and meta-analysis was performed to identify risk factors for posttraumatic epilepsy (PTE).

Methods: Two electronic databases (Medline and Embase) were searched to identify studies with a cohort, case-control, or cross-sectional design reporting on epidemiologic evidence regarding risk factors for PTE.

Results: Men had a higher risk of developing PTE than women [relative ratio (RR), 1.32; 95% confidence interval (CI), 1.10-1.59]. A history of alcohol abuse (RR, 2.18; 95% CI, 1.26-3.79), posttraumatic amnesia (RR, 1.31; 95% CI, 1.12-1.53), focal neurologic signs (RR, 1.42; 95% CI, 1.16-1.74), and loss of consciousness at initial traumatic brain injury (TBI) (RR, 1.62; 95% CI, 1.13-2.32) were associated with a greater risk of PTE. TBI-related abnormal neuroimaging findings, including skull fracture (RR, 2.27; 95% CI, 1.49-3.44), midline shift (RR, 1.46; 95% CI, 1.14-1.87), brain contusion (RR, 2.35; 95% CI, 1.69-3.28), subdural hemorrhage (RR, 2.00; 95% CI, 1.33-3.01), and intracranial hemorrhage (RR, 2.65; 95% CI, 1.83-3.82) were strong risk factors for PTE. The risk of developing PTE after skull fracture, mild brain injury, and severe brain injury peaked within the first year after TBI, and then gradually decreased. However, a high risk of PTE was sustained for more than 10 years.

Conclusion: The current meta-analysis identified potential risk factors for PTE. The results may contribute to better prevention strategies and treatments for PTE.

1. Introduction

Traumatic brain injury (TBI) is one of the most serious traumatic diseases, accounting for 1.1-1.7 million emergency room visits and 50,000 deaths every year [1, 2]. Posttraumatic epilepsy (PTE) is a well-known sequela of TBI [1, 3], and accounts for 5% of all epilepsy in the general population [4, 5]. Unfortunately, PTE is strongly associated with a high risk of mortality in children and adults compared to patients who do not experience PTE [6]. Individuals with PTE are also at a significant disadvantage regarding physical, cognitive, and mental issues, which negatively affects functional outcome following TBI [2, 4, 7].

To date there is no effective prophylaxis for PTE, and prophylactic anticonvulsant drugs do not reduce the risk of PTE [2, 5, 8]. Identifying risk factors associated with PTE may contribute to the development of new prevention and treatment strategies. Previous studies have reported a variety of risk factors involved in the development of PTE, including skull fracture, severity of TBI, abnormal neuroimaging findings, clinical features in patients with TBI, and time after TBI. However, due to differences in study design, demographics, definitions of PTE and follow-up duration, risk factors for predicting PTE remain unclear.

Here we report a systematic review and meta-analysis to determine PTE-related risk factors.

2. Methods

A systematic review and meta-analysis were conducted according to the guidelines previously published for a meta-analysis of observational studies in epidemiology (MOOSE) [9]. Ethics committee approval did not apply to this study.

2.1 Study Selection

Both Medline and Embase electronic databases were searched using predefined terms and search criteria. The inclusion criteria for the meta-analysis were: 1) English publications; 2) case-control, cohort or cross-sectional methodology; 3) epidemiologic evidence regarding the risk factors for PTE reported; and 4) original research with

full-text availability. Non-original articles, articles with insufficient data or irrelevant outcome, and single case reports were excluded. There were no restrictions on the time of publication. Two authors (T.X., X.Y.) independently evaluated the retrieved studies according to the selection criteria and manually reviewed the reference lists of retrieved articles to identify additional relevant studies. Discrepancies were resolved by discussion until consensus was reached.

2.2 Data Extraction and Quality Assessment

Data extracted from eligible studies included first author, publication year, country, study design, population demographics, and information [prevalence of PTE in patients with TBI, hazard ratio, risk ratio, odds ratio, and raw data to calculate relative risk (RR)] to evaluate PTE-related risk factors [e.g., gender, prior alcohol abuse, acute symptomatic seizure (ASS), TBI-related clinical findings, etiology of TBI, abnormal neuroimaging findings, clinical severity of TBI, and the Glasgow Coma Scale (GCS) score at initial TBI]. TBI-related clinical findings included posttraumatic amnesia (PTA), focal neurologic signs, and loss of consciousness at initial TBI. Abnormal neuroimaging findings were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) examination in patients with TBI. **Clinical severity of TBI was categorized into mild brain injury (MBI) and severe brain injury (SBI). MBI was defined as brain concussion without structural damage. By contrast, SBI was associated with brain structural damage**, including midline shift, brain contusion, subdural hemorrhage (SDH), epidural hemorrhage (EDH), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), and intraventricular hemorrhage (IVH).

For the purpose of the current analysis, ASSs were defined as seizures occurring within 7 days after TBI, while unprovoked seizures were defined as seizures occurring after this period [10]. According to the latest clinical definition of epilepsy proposed by the International League Against Epilepsy (ILAE) in 2014, a patient with one unprovoked seizure after TBI should be diagnosed with epilepsy[11]. This recommendation is based on the fact that a TBI patient with a single unprovoked seizure is at high risk of another unprovoked seizure in the next ten years [11].

A nine-star system based on the Newcastle-Ottawa Scale (NOS) was used to assess study quality [12].

2.3 Statistical Analysis

The overall prevalence of PTE in patients with TBI was assessed, and the RR for each risk factor for PTE was calculated. Additionally, the risk of PTE according to time since first admission with TBI was investigated by subgroup analyses. To assess between-study heterogeneity, the Cochran Q statistic was calculated. The I^2 statistic was used to quantify the magnitude of heterogeneity [13]. In the absence of statistically significant heterogeneity ($I^2 < 50\%$), the pooled estimate and 95% confidence intervals (CIs) were calculated with a fixed-effects model. Conversely, a random-effects model was used to calculate the pooled estimate when significant heterogeneity was present ($I^2 \geq 50\%$). Subgroup analyses were performed to explore sources of heterogeneity. STATA version 12.0 (StataCorp, College Station, TX, USA) was used for statistical analyses. A p-value less than 0.05 was considered statistically significant.

3. Results

After omitting duplicates (articles that were returned from both databases searched), 3,233 records were identified during our initial search. After omitting articles with non-relevant titles and abstracts, 167 articles with full text were selected for review. Finally, a total of 20 articles met our inclusion criteria [1, 3-7, 14-27] (Fig.1).

3.1 Description of studies and qualitative assessment

The 20 studies selected for meta-analysis were published between 1961 and 2015 and contained a total of 111,751 participants. The 20 studies included 16 prospective analyses [1, 3-7, 14, 16-21, 23, 24, 27] and 4 retrospective analyses [15, 22, 25, 26] (Table 1).

Quality scores of the included studies are listed in Table 1. The mean score of the included studies was 6.40 (standard deviation: 1.19; range: 4–8) (Table S1).

3.2 Pooled prevalence of PTE in patients with TBI

The pooled prevalence of PTE in patients with TBI ranged from 1.3% to 53.3%, with a high-level of heterogeneity between the 20 studies ($I^2 = 98.9\%$). According to the random-effects model, the pooled prevalence of PTE in patients with TBI was 15% (95% CI 14%–17%) (Fig.2).

3.3 Risk Factors for PTE

Male patients were more susceptible to PTE than female patients (RR, 1.32; 95% CI, 1.10-1.59). Prior alcohol abuse (RR, 2.18; 95% CI, 1.26-3.79) was associated with an increased risk of developing PTE. For clinical findings in TBI patients, PTA (RR, 1.31; 95% CI, 1.12-1.53), focal neurologic signs (RR, 1.42; 95% CI, 1.16-1.74), and loss of consciousness at initial TBI (RR, 1.62; 95% CI, 1.13-2.32) were associated with a greater probability of developing PTE. The risk of developing PTE in patients with ASS was five times greater than in those without ASS after TBI (RR, 5.14; 95% CI, 2.81-9.41). Although the pooled RRs of the GCS score at initial TBI were not statistically significant, there was an overall trend for an association between a low GCS score and a high risk of developing PTE. Subgroup analyses of abnormal neuroimaging findings found that skull fracture (RR, 2.27; 95% CI, 1.49-3.44), midline shift (RR, 1.46; 95% CI, 1.14-1.87), brain contusion (RR, 2.35; 95% CI, 1.69-3.28), SDH (RR, 2.00; 95% CI, 1.33-3.01), and ICH (RR, 2.65; 95% CI, 1.83-3.82) were associated with a higher risk of developing PTE.

Subgroup analyses of clinical severity of TBI indicated that both MBI (RR, 2.36; 95% CI, 1.96-2.84) and SBI (RR, 8.37; 95% CI, 5.21-13.45) were associated with a higher risk of developing PTE, but the risk of developing PTE in patients with SBI was higher than that in patients with MBI (Table 2). The risk of developing PTE after skull fracture, MBI, and SBI peaked within the first year after TBI, and then gradually decreased. However, the risk of PTE was sustained at a high level for more than 10 years after skull fracture (RR, 2.06; 95% CI, 1.37-3.10), MBI (RR, 1.59; 95% CI, 1.35-1.87), and SBI (RR, 3.72; 95% CI, 2.13-6.05) (Fig.3).

3.4 Publication bias and heterogeneity

Potential publication bias was assessed by visual inspection of funnel plots, and an asymmetric plot suggested risk of publication bias. (Fig. S1). Substantial heterogeneity of effect estimates between studies was observed for gender, clinical findings, abnormal neuroimaging findings, clinical severity of TBI, and ASS. Sources of heterogeneity were identified in reviewed studies, and included differences in sample size, study design, method of ascertaining risk factors for PTE, and follow-up duration.

4. Discussion

TBI is the cause of epilepsy in almost 30% of subjects who develop epilepsy between ages 15 and 34 years [2, 28]. Epilepsy that develops after TBI has several important features that make it distinct and particularly worthy of study. First, PTE is universally recognized as one of the most common forms of acquired epilepsies in young people, and it is strongly associated with poor functional outcomes and increased mortality [6]. Second, the increase in SBI associated with missile and blast injuries in modern warfare augments the necessity for further study of TBI and PTE. Severe TBI is among the most common injuries of the current conflicts in the Middle East and elsewhere, and it is likely that multiple cases of epilepsy will arise in soldiers and civilians as a result of these wars [21, 28]. Finally, PTE can be particularly difficult to treat medically and surgically, thereby increasing the burden of the illness on patients and family members [8, 28]. Although many TBI victims develop epilepsy months or years following initial injury, progress in this area of clinical research has been slow, due in part to a lack of known reliable and valid risk factors.

The current meta-analysis provides quantitative estimates of the magnitude of association between risk factors and PTE. With little heterogeneity between studies, a history of alcohol abuse, PTA, and midline shift were identified as strong risk factors for developing PTE after TBI. While there was substantial heterogeneity between studies in gender, focal neurologic signs, loss of consciousness at initial TBI, skull

fracture, brain contusion, SDH, ICH, SBI, and ASS, these factors were also strongly associated with an increased risk of PTE. The risk of developing PTE peaked within the first year after skull fracture, MBI, and SBI, and then gradually decreased and was sustained at a high level for more than 10 years.

Prior alcohol abuse was found to be significantly associated with an increased risk of PTE. This finding is consistent with several case-control studies reporting alcohol consumption as an independent risk factor for epilepsy [29, 30]. These previous studies identified alcohol's diverse effects on the structure and function of the central nervous system (CNS), which leads to hyperexcitability, as the main cause of epilepsy [29, 30]. Additionally, alcohol abuse was also associated with an increase in SBI, which significantly increases the risk of developing PTE [22]. Therefore, a TBI patient with a history of alcohol abuse may be more susceptible to PTE than those without a prior history.

The current meta-analysis found that men have a higher risk of developing PTE than women. Prior studies have found a higher incidence of TBI [1] and alcohol abuse among men compared to women [31], which may explain the increased risk of developing PTE in men with TBI.

The current meta-analysis identified skull fracture as a common and strong risk factor for PTE. Skull fractures lead to brain damage via cerebral compression which in turn leads to SBI [1, 5]. It is therefore understandable that patients with skull fractures have a higher risk of developing PTE. Subgroup analyses of abnormal neuroimaging findings indicated that TBI-related ICH, SDH, midline shift, and brain contusion are significantly associated with a higher risk of PTE. TBI-related ICH, SDH, midline shift, and brain contusion are associated with a high risk of devastating brain parenchyma injury leading to neuronal death and reactive gliosis. Ultimately, these conditions induce abnormal neuronal activity and subsequently increased epileptic activity [1, 32]. SBI was discovered to be a strong risk factor for PTE. Prior studies have found that patients with SBI are more likely to suffer from a loss of consciousness at initial TBI, PTA, and focal neurologic signs, thus these SBI-related symptoms were associated with a higher risk of developing PTE [17, 33]. GCS score

is commonly used to evaluate TBI severity. A low GCS score is correlated with severe brain damage [25], thus indicating a higher risk of developing PTE. Although the risk of developing PTE was lower in patients with MBI compared to SBI, MBI was still a significant risk factor for predicting PTE. Clinicians therefore, should alert patients with MBI of the potential risk of developing PTE. The overall trend of pooled estimates suggested that the risk of developing PTE peaks within the first year after skull fracture, MBI, and SBI, and then gradually decreases but is sustained at a high level for more than 10 years. ASS was one of the most relevant risk factors for PTE discovered in the current meta-analysis. This result indicates that effective prevention of ASS may decrease the risk of developing PTE. However, based on our comprehensive review of the literature, few studies to date have investigated the effects of ASS prevention on the risk of developing PTE [8]. Therefore, well-conducted prospective studies and randomized clinical trials are needed to assess the benefit of ASS prevention to decrease PTE risk.

While the results of the present meta-analysis are helpful to the overall understanding of risk factors in the development PTE, there are study limitations that must be considered. First, although we performed subgroup analyses to identify the sources of heterogeneity, there remains much heterogeneity among the included studies. Second, there was great variability in the quality of the included studies and more high quality original research studies are needed. Third, most of the included studies did not report treatment information for TBI and/or PTE, or for other TBI-related complications, which may have contributed to information bias. Fourth, most of the included studies did not report potential confounding variables of risk factors for PTE and whether they were adjusted for, and as such, the reliability of our results could be reduced to some extent.

In conclusion, male patients, a history of alcohol abuse, midline shift, SBI-related symptoms (PTA, focal neurologic signs, loss of consciousness at initial TBI, and skull fracture), brain contusion, SDH, ICH, SBI, and ASS were identified as strong risk factors for the development of PTE. Furthermore, the results of the meta-analysis indicate that the risk of developing PTE peaks within the first year after skull fracture,

MBI, and SBI, and then gradually decreases but remains at a sustained high level for more than 10 years.

Supplementary data to this article can be found online.

Acknowledgment

This work was supported by the National Science Foundation of China (No. 81571259).

References

- [1] Yeh CC, Chen TL, Hu CJ, Chiu WT, Liao CC. Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. *J Neurol Neurosurg Psychiatry* 2013;84: 441-5.
- [2] Christensen J. The Epidemiology of Posttraumatic Epilepsy. *Semin Neurol* 2015;35: 218-22.
- [3] Ferguson PL, Smith GM, Wannamaker BB, Thurman DJ, Pickelsimer EE, Selassie AW. A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. *Epilepsia* 2010;51: 891-8.
- [4] Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, Hughes R, Bergman W. Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. *Arch Phys Med Rehabil* 2003;84: 365-73.
- [5] Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet* 2009;373: 1105-10.
- [6] Englander J, Bushnik T, Wright JM, Jamison L, Duong TT. Mortality in late post-traumatic seizures. *J Neurotrauma* 2009;26: 1471-7.
- [7] Mazzini L, Cossa FM, Angelino E, Campini R, Pastore I, Monaco F. Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. *Epilepsia* 2003;44: 569-74.
- [8] Thompson K, Pohlmann-Eden B, Campbell LA, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst Rev* 2015;8: CD009900.
- [9] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283: 2008-12.
- [10] Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia* 1993;34: 592-6.
- [11] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Jr., Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Puccia E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55: 475-82.
- [12] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25: 603-5.
- [13] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327: 557-60.

- [14] Zhao Y, Wu H, Wang X, Li J, Zhang S. Clinical epidemiology of posttraumatic epilepsy in a group of Chinese patients. *Seizure* 2012;21: 322-6.
- [15] Skandsen T, Ivar Lund T, Fredrikli O, Vik A. Global outcome, productivity and epilepsy 3--8 years after severe head injury. The impact of injury severity. *Clin Rehabil* 2008;22: 653-62.
- [16] Messori A, Polonara G, Carle F, Gesuita R, Salvolini U. Predicting posttraumatic epilepsy with MRI: prospective longitudinal morphologic study in adults. *Epilepsia* 2005;46: 1472-81.
- [17] Angeleri F, Majkowski J, Cacchio G, Sobieszek A, D'Acunto S, Gesuita R, Bachleda A, Polonara G, Krolicki L, Signorino M, Salvolini U. Posttraumatic epilepsy risk factors: one-year prospective study after head injury. *Epilepsia* 1999;40: 1222-30.
- [18] Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 1998;338: 20-4.
- [19] Pohlmann-Eden B, Bruckmeir J. Predictors and dynamics of posttraumatic epilepsy. *Acta Neurol Scand* 1997;95: 257-62.
- [20] D'Alessandro R, Ferrara R, Benassi G, Lenzi PL, Sabattini L. Computed tomographic scans in posttraumatic epilepsy. *Arch Neurol* 1988;45: 42-3.
- [21] Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. *Neurology* 1985;35: 1406-14.
- [22] Mahler B, Carlsson S, Andersson T, Adelow C, Ahlbom A, Tomson T. Unprovoked seizures after traumatic brain injury: A population-based case-control study. *Epilepsia* 2015;56: 1438-44.
- [23] Bushnik T, Englander J, Wright J, Kolakowsky-Hayner SA. Traumatic brain injury with and without late posttraumatic seizures: what are the impacts in the post-acute phase: a NIDRR Traumatic Brain Injury Model Systems study. *J Head Trauma Rehabil* 2012;27: E36-44.
- [24] De Reuck J. Risk factors for late-onset seizures related to cerebral contusions in adults with a moderate traumatic brain injury. *Clin Neurol Neurosurg* 2011;113: 469-71.
- [25] Emanuelson I, Uvebrant P. Occurrence of epilepsy during the first 10 years after traumatic brain injury acquired in childhood up to the age of 18 years in the south western Swedish population-based series. *Brain Inj* 2009;23: 612-6.
- [26] Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia* 1999;40: 584-9.
- [27] Jennett WB. Late epilepsy after blunt head injuries: a clinical study based on 282 cases of traumatic epilepsy. *Ann R Coll Surg Engl* 1961;29: 370-84.
- [28] Lowenstein DH. Epilepsy after head injury: an overview. *Epilepsia* 2009;50 Suppl 2: 4-9.
- [29] Samokhvalov AV, Irving H, Mohapatra S, Rehm J. Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis. *Epilepsia* 2010;51: 1177-84.
- [30] Leone M, Bottacchi E, Beghi E, Morgando E, Mutani R, Cremo R, Ravagli Ceroni L, Floriani I. Risk factors for a first generalized tonic-clonic seizure in adult life. *Neurol Sci* 2002;23: 99-106.
- [31] Cubbins LA, Kasprzyk D, Montano D, Jordan LP, Woelk G. Alcohol use and abuse among rural Zimbabwean adults: a test of a community-level intervention. *Drug Alcohol Depend* 2012;124: 333-9.
- [32] Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA. Glia and epilepsy: excitability and inflammation. *Trends Neurosci* 2013;36: 174-84.
- [33] Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. *Seizure* 2000;9: 453-7.

Figure legends

Figure 1 Flowchart of the literature search performed.

Figure 2 Pooled analysis of the overall prevalence of PTE in patients with traumatic brain injury.

PTE = posttraumatic epilepsy.

Figure 3 Pooled analyses of onset time and the pooled RRs of developing PTE after first admission for skull fracture, mild brain injury, and severe brain injury.

RR = relative ratio; PTE = posttraumatic epilepsy.

Table 1. Characteristics of included studies in the meta-analysis

First author	Publication year	Country	Total number of patients with TBI	Prevalence of PTE (%)	Study design	Risk factors	Study quality*
Mahler et al. [22]	2015	Sweden	422	24.9%	R	Gender, history of alcohol abuse, neuroimaging findings	8
Yeh et al. [1]	2013	China	19,336	1.9%	P	Gender, clinical severity of TBI, neuroimaging findings; Onset time after MBI, SBI, and skull fracture	7
Bushnik et al. [23]	2012	USA	151	47.0%	P	Neuroimaging findings	7
Zhao et al. [14]	2012	China	2,826	5.0%	P	Gender, ASS, GCS, neuroimaging findings, etiology of TBI	5
De Reuck et al. [24]	2011	Belgium	39	35.9%	P	History of alcohol abuse	6
Ferguson et al. [3]	2010	USA	1,961	5.9%	P	Gender, etiology of TBI, ASS, loss of consciousness at initial TBI	7
Emanuelson et al. [25]	2009	Sweden	109	11.0%	R	ASS, GCS	5
Englander et al. [6]	2009	USA	508	14.0%	P	Gender, neuroimaging findings	5
Christensen et al. [5]	2009	Denmark	78,572	1.3%	P	Neuroimaging findings, clinical severity of TBI; Onset time after skull fracture, MBI, and SBI	8
Skandsen et al. [15]	2008	Norway	91	23.1%	R	Neuroimaging findings, loss of consciousness at initial TBI	6
Messori et al. [16]	2005	Italy	135	14.8%	P	Neuroimaging findings	5
Mazzini et al. [7]	2003	Italy	143	23.3%	P	Gender	7

Englander et al. [4]	2003	USA	647	10.2%	P	Gender, ASS, GCS, neuroimaging findings	7
Annegers et al. [18]	2000	USA	4,541	2.1%	P	Clinical severity of TBI, ASS, neuroimaging findings, PTA, loss of consciousness at initial TBI; Onset time after MBI and SBI,	7
Asikainen et al. [26]	1999	Finland	490	25.3%	R	ASS, GCS, neuroimaging findings, loss of consciousness at initial TBI	4
Angeleri et al. [17]	1999	Italy	137	13.1%	P	ASS, GCS, PTA	8
Pohlmann-Eden et al. [19]	1997	Germany	107	53.3%	P	Neuroimaging findings, PTA, loss of consciousness at initial TBI, focal neurologic signs	7
D'Alessandro et al. [20]	1998	Italy	219	5.9%	P	ASS, neuroimaging findings, loss of consciousness at initial TBI, focal neurologic signs	5
Salazar et al. [21]	1985	USA	421	53.2%	P	PTA, neuroimaging findings, loss of consciousness at initial TBI	7
Jennett et al. [27]	1961	UK	896	31.5%	P	ASS, neuroimaging findings	7

TBI= traumatic brain injury, PTE = posttraumatic epilepsy, MBI = mild brain injury, SBI = severe brain injury, PTA = posttraumatic amnesia, GCS = Glasgow Coma Scale, R = retrospective, P = prospective, ASS = acute symptomatic seizure.

* Study quality according to the Newcastle-Ottawa Scale.

Table 2. Pooled analyses of risk factors for PTE

Groups	No. studies	RR	95% CI	I^2 (%)
Sex (Ref = Female)				
Male*	7	1.32	1.10-1.59	88.9
History of alcohol abuse*	2	2.18	1.26-3.79	0.0
Etiology of TBI				
Fall accident	2	1.19	0.96-1.49	0.0
Traffic accident	2	0.89	0.73-1.08	56.7
Others	2	1.40	0.66-3.01	88.8
Clinical findings				
PTA*	4	1.31	1.12-1.53	31.6
Focal neurologic signs*	2	1.42	1.16-1.74	85.3
Loss of consciousness at initial TBI*	7	1.62	1.13-2.32	65.2
Initial GCS score				
13-15	3	0.73	0.56-0.94	52.1
9-12	4	1.23	0.72-2.11	61.4
3-8	5	1.34	0.67-2.69	90.2
Abnormal neuroimaging findings				
Skull fracture*	10	2.27	1.49-3.44	90.4
Midline shift*	3	1.46	1.14-1.87	0.0
Brain contusion*	6	2.35	1.69-3.28	91.2
EDH	2	1.74	0.47-6.44	69.7
SDH*	7	2.00	1.33-3.01	76.7
ICH*	7	2.65	1.83-3.82	60.7
SAH	2	1.13	0.15-8.33	82.1
Clinical severity of TBI				
Mild brain injury*	4	2.36	1.96-2.84	60.2
Severe brain injury*	4	8.37	5.21-13.45	94.0
Acute symptomatic seizure*	9	5.14	2.81-9.41	82.4

PTE = posttraumatic epilepsy; RR = relative risk, TBI = traumatic brain injury, EDH = epidural hemorrhage, SDH = subdural hemorrhage, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia.

* $p < 0.05$.

NOTE: Weights are from random effects analysis

NOTE: Weights are from random effects analysis