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Original article

Prognostic factors for unfavorable outcome after mild traumatic brain injury. A review of literature

Facteurs pronostiques d'évolution défavorable après un traumatisme cranio cérébral léger

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ABSTRACT

Background. – Unfavorable outcomes occur in 15–20% of patients with mild traumatic brain injury (mTBI). Early identification of patients at risk of unfavorable outcome is crucial for suitable management to be initiated, increasing the chances of full recovery. Many studies have been published on prognostic factors, but are not of a high level of evidence and certainty. A number of factors have been proposed and predictive models have been constructed that, although attractive, have not yet been externally validated.
Objectives. – A review of literature (systematic search of PubMed and Google Scholar) assembled relevant available information about prognostic factors for unfavorable outcome after mTBI. We discuss the consistency of these findings, and the possibility and difficulty of using these factors in a daily practice.
Results. – It appears that the strongest and most consistent predictors are the number, severity and duration of symptoms present in the first few days after the trauma.
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Mots clés :
Traumatisme cranio-cérébral léger
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RÉSUMÉ

Une évolution défavorable survient chez 15 à 20 % des patients victime d'un traumatisme cranio cérébral léger. L'identification précoce des patients présentant un risque élevé d'évolution défavorable est cruciale pour une prise en charge adaptée, augmentant les chances de guérison complète. De nombreuses études ont été publiées sur les facteurs pronostiques mais ne présentent pas un niveau élevé de preuve et de certitude. Un certain nombre de facteurs ont été proposés et des modèles prédictifs ont été construits qui, bien qu'attrayants, n'ont pas encore été validés de manière externe.
Objectives. – Dans cette revue de la littérature (recherche systématique de PubMed et de Google Scholar), nous avons essayé de rassembler les informations pertinentes disponibles sur les facteurs pronostiques de l'évolution défavorable. Nous discutons leur cohérence, la possibilité mais aussi de la difficulté d'utiliser ces données dans une pratique quotidienne.
Résultats. – Il semble que les prédicteurs les plus puissants et les plus cohérents soient le nombre, la gravité et la durée des symptômes présents au cours des premiers jours suivant le traumatisme.
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1. Introduction

Symptoms that appear after mTBI tend to decrease within 10 days of trauma and usually disappear within 3 months. A "miserable minority", to use Wood's expression [1], which is nonetheless as much as 15–25% [1–9], is still symptomatic or worsens beyond 3 months. All dimensions, cognitive, somatic, emotional and behavioral, can be disrupted. The consequences of

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these persistent symptoms can affect the future of patients in each dimension of life and can have serious consequences in terms of public health costs [10,11].

Many studies have highlighted the relevance of early management of mTBI to prevent these poor outcomes [12–14]. It is therefore important to have tools to identify patients at risk of poor outcome at an early stage, in order to offer them appropriate care.

It is important to highlight the problem of the relevance and inhomogeneity of these studies: several problems make it difficult to generalize the conclusions of each. To mention only the most important ones: the problem of defining mTBI itself, the lack of a common definition of poor progression, and the tools used for monitoring and classifying patients. An essential element of all these studies is that the majority of patients with mTBI never consult and this necessarily biases any statistical conclusion.

There is a debate about the origin of these symptoms: are they due to brain damage or are they related to individual psychological factors? Over the past decade, several studies have been published on this issue. These studies showed that risk factors can be related to individual characteristics, personal, medical or psychosocial history, the characteristics of the accident itself, and the environmental context (family, occupational, etc.) [15,16]. To better understand this phenomenon, we can draw inspiration from "biopsychosocial" models.

The biopsychosocial model was first formulated by the psychiatrist George Engel [17]. In the biopsychosocial model, illness is viewed as the result of interaction between a multitude of causal factors, operating at different levels in different phases of the disease process. In the biopsychosocial model it is customary to describe the determinants of the disease process in terms of predisposing (pretraumatic), precipitating (traumatic) and perpetuating factors

The onset and persistence of this symptomatology should therefore be considered as the result of a complex interaction between a person (physical and medical factor) at a given time in their life (environmental and psychological factors) and the accidental event (factors related to the accident).

Based on a review of literature, we tried to assemble available information about prognostic factors for unfavorable outcome after mTBI.

2. Material and methods

A review of literature was performed using following search-terms on PubMed and Google Scholar: mild traumatic brain injury, prognostic factor, outcome. Only English articles published in peer reviewed journals, focusing on prognostic factors after mTBI and based on a series of at least 100 patients, for the period 1975–2010, were considered. Following these criteria, 40 articles were analyzed.

3. Results

For clarity of presentation, we segregated the prognostic factors into two categories: pre-existing and those related to the accident.

3.1. Pre-existing factors

3.1.1. Gender

Many studies mentioned female gender as a factor for poor prognosis [6,18,19], without confirming it as an independent factor.

3.1.2. Age

The literature is ambiguous and relatively difficult to interpret with regard to the contribution of the "age" factor to recovery rate. Symptoms observed in young children (under eight years of age) appear to persist for a shorter period of time than in older children (adolescents). The sports literature reports that adolescent athletes appear to be particularly vulnerable to persistent symptoms compared to adult athletes, a phenomenon that may be related to the fact that a young adolescent's brain is less developed and has fewer reserves to deal with trauma [20,21]. Although evidence is still incomplete, some studies indicate that young girls, particularly athletes, generally have more symptoms than their male colleagues and that these symptoms persist longer [16,20,21]. A number of publications suggest that advanced age (>65 years) is a negative factor [22–24]. Two more recent studies attempting to develop predictive systems also found age to be an important prognostic factor [25,26].

There were several case series or descriptive studies that suggested that elderly people have poorer recovery after mTBI [22–24]. Unfortunately, none of these studies reported information that could distinguish disabilities due to the head injury versus other injuries.

3.1.3. Educational level

Several studies reported educational level to be a reliable predictor of incomplete recovery (6, 25, 26). It appears that higher education contributes positively to complete recovery after mTBI.

3.1.4. Personal psychological, societal considerations and comorbidities

Prospective studies also revealed that pre-injury mental health problems and previous mTBI significantly increase the risk of persistent symptoms in both adults and children beyond three months after the initial trauma [16,26–28]. In these publications, mental health problems were defined by psychiatric or psychological symptoms necessitating treatment by a psychologist or psychiatrist or use of psychotropic medication, without further details. In a recent prospective study of 910 patients, van der Naalt et al. showed that "Emotional distress experienced early after injury, in combination with a maladaptive coping style and demographic variables (pre-injury mental health problems and education) were significant factors for incomplete recovery." [26]

In children in particular, family socio-economic status is reported to be a moderating factor in recovery from mTBI, while history of hyperactivity and learning disabilities complicate recovery of activities, but are not associated with more persistent symptoms over time [28,29].

Higher levels of parental stress were consistently associated with greater PCS (post-concussion syndrome) across both acute and late post-injury periods [30]. This may suggest either that parental stress leads to greater endorsement of PCS by parents, or alternatively that environmental stress somehow influences the development or expression of PCS within the child [31,32].

In a paper based on an exhaustive literature review published by the World Health Organization collaboration center task force on mild traumatic brain injury in 2004, one of the most powerful factors was the existence of litigation or compensation issues [13]. Studies that examined the relationship between litigation and/or compensation issues and slower recovery after mTBI consistently reported an association between the two. For example, a meta-analysis of 17 studies found that financial compensation was a strong risk factor for long-term disability, symptoms and objective findings after mTBI [36]. Subsequently, Paniak et al. [37,38] found that compensation-seeking strongly predicted delayed return to work, more long-term symptoms and greater symptom severity, independently of mTBI severity.

Comorbid somatic conditions (history of previous head injury and neurological problems) were also found to be more common in PCS cases in the study by Ponsford [6] and, in another study, pre-existing physical limitations and history of brain illness were independent predictors of poor outcome after mild head injury [33].

3.1.5. Alcohol consumption

It is clear that alcohol is an important risk factor for the occurrence of injury. However, the role of alcohol as a predictor of poor prognosis is an under-studied area, and no conclusions can be drawn as to its importance. Only one study specifically examined this question in a systematic manner, and concluded that blood alcohol level testing was performed too selectively to be able to accurately determine the relationship between blood alcohol concentration and outcome at discharge [34]. Alcoholism is likely to be associated with markers of poor outcome, even in the absence of injury. However, a high blood alcohol level at presentation to the emergency department after a head injury appears to be a marker for a history of problem drinking [35]. Clearly, the question of whether alcohol use is a determining factor in outcome after MTBI deserves further study [13].

3.1.6. Genetic factors

There is limited preliminary evidence from one study [46] that, in the presence of a positive APOE ε4 allele, mTBI may lead to slight long-term decreases in certain cognitive functions, comparing pre- and post-mTBI scores. However, these findings need to be replicated, because individuals with positive or negative APOE ε4 allele were not shown to be impaired compared with controls, and the clinical importance of the cognitive changes was questionable [46].

3.2. Factors related to the accident

No association was found between loss of consciousness and increased persistent deficits in cognitive functioning after mTBI. Concerning post-traumatic amnesia (PTA), the literature is more ambiguous: several authors found that PTA duration did not predict long-term PCS, while others reported that acute symptoms had strong predictive value for the development of PCS. [39–41] Surprisingly, Van der Naalt et al. [26] found that a duration of less than 1 h was associated with worse outcome.

There is some evidence from a phase I study that there is a lower rate of good recovery as assessed by the GOS (Glasgow outcome scale) when mTBI is complicated by a focal brain lesion and/or depressed skull fracture than when such complications are not present [27,42,43] In a recent review of the literature, Studerus-Germann et al. pointed out that "from the evaluated diagnostic approaches to predict PTS after mild traumatic brain injury, DTI (Diffusion tensor imaging), SWI (Susceptibility weighted imaging), MRS (MR spectroscopy) and fMRI (functional MRI) (resting-state condition) seem to have adequate sensitivity and specificity as predictive diagnostic tools according to the current literature". However they advocated larger clinical trials to validate prognostic applicability and practicability in daily clinical practice [44]. Several studies reported that mTBI with an etiology of assault was associated with worse outcome [18,38].

There is little evidence about the role of biological markers in predicting the extent or persistence of cognitive impairment after mTBI. Limited evidence suggests no association between S100B or S100A1B proteins and subsequent cognitive function [45]. Therefore, despite the frequent presence of this protein in the early stages of mTBI, it may not have value as a marker for prolonged cognitive dysfunction in that population.

The role of severe associated injuries in recovery from mTBI has not been well studied. One series of patients hospitalized for mTBI with severe associated injuries suggested poor outcome (only 62% had good outcome at 4–5 years post-injury). However, it was unclear whether these residual disabilities were attributable to the head injury [47].

4. Predictive models

We retrieved four publications that focused on the development of a prediction model for outcome after mTBI [25,26,48,49].

The study by Stulemeijer et al. [48] comprised 201 patients and identified absence of premorbid physical problems, low number and severity of symptoms and post-traumatic stress early after injury as predictors of good recovery. A score chart for the early prediction of low post-concussional symptoms (favorable outcome) 6 months after mTBI was proposed (AUC 0·73) (Table 1).

The study by Jacobs et al. [25] reported a consecutive series of patients over a period of 8 years (2,784 patients). Outcome was assessed at 6 months post-trauma using the Glasgow Outcome Scale- Extended (GOSE), dichotomized into unfavorable (GOSE score 1–6) and favorable (GOSE score 7–8). The predictive value of several variables was determined using multivariate binary logistic regression analysis. Age, extracranial injury and day-of-injury alcohol intoxication proved to be the strongest outcome predictors. The presence of facial fractures and the number of hemorrhagic contusions emerged as predictors of CT abnormalities. The authors proposed two schemes with equal predictive value: one based on a modified Injury Severity Score (ISS), alcohol intoxication and age, and one that also included CT abnormalities and proved superior to one based on CT abnormalities alone. The "clinical" models demonstrated the highest predictive values. Combination of clinical and CT variables ("combination" models) did not improve the performance of the "clinical" models (Table 2).

Cnossen et al., based on a series of 277 mTBI patients, developed a prediction model for the RPQ total scale. Thy found that years of education, pre-injury psychiatric disorder and prior TBI were the strongest predictors of 6-month post-concussive symptoms. Baseline demographic and clinical variables were predictive of 6-month post-concussive symptoms following mTBI, but explained less than one-fifth of the total variance in outcome. The authors concluded that model refinement with larger datasets, more granular variables and objective biomarkers is needed before implementation in clinical practice [50].

Lingsma et al. [49] aimed to externally validate all available studies and found that existing prognostic models for mTBI were unsatisfactory, with risk of model overfit, and suggested that larger cohorts of patients with more specific predictors for outcome were required.

Caplain et al. [51] assessed the value of a comprehensive neuropsychological complaints and quality of life evaluation to identify early prognostic factors for mTBI patients, and to establish short clinical assessment tools applicable during the early stage of mTBI for patients liable to develop PCS. They performed a multicenter open prospective longitudinal study that included 72 mTBI patients and 42 healthy volunteers matched for age, gender and socioeconomic status. mTBI patients were evaluated 8–21 days and 6 months after injury, with full neurological and psychological examination and brain MRI. At 6 months' follow-up, patients were categorized into two subgroups according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as having either favorable or unfavorable evolution (UE), corresponding to the presence of major or mild neurocognitive disorder due to traumatic brain injury. Univariate and multivariate logistical regression analysis demonstrated the importance of patient complaints, quality of life and cognition in the outcome of mTBI patients, but only 6/23 UE patients were detected early via the multivariate logistic regression model. Using several variables from each of these three categories of variables, they built a model that assigned a score

Table 1
Stulemeijer et al. Score chart for the early prediction of low post-concussional symptoms 6 months after mild traumatic brain injury.

Premorbid physical comorbidities		−1	
Severe post-concussional symptoms within weeks after injury		−1	
Severe post-traumatic stress within weeks after injury		−2	
Total score			
Score	Observed probabilities	Predicted probabilities[a]	Predicted probabilities after bootstrap[b]
0	0.96	0.95	0.90
−1	0.77	0.80	0.90
−2	0.47	0.50	0.60
≥3	0.21	0.15	0.35

If a predictor is scored positively, the given weight needs to be filled in. Subsequently, the scores are added to calculate the "total score". Using the score chart, the chance (%) of good recovery for an individual patient can be determined based on this total score.
[a] Predicted probabilities of low post-concussional symptoms 6 months after injury based on the multivariate logistic regression analysis (AUC = 0.82).
[b] Predicted probabilities after shrinkage and correction for optimism (AUC = 0.73).

Table 2
Jacobs and al. Rules for Predicting Unfavorable Outcome at 6 Months After mTBI.

A. Clinical variables	A = -2.8 + 0.017 × age + 0.30 × AISH + 0.070 × ISSe − 0.80 × alcohol intoxication
B. CT characteristics	B = −1.3 + 0.58 × number of hemorrhagic contusions + 0.52 × presence of facial fracture
C. Combined	C = −2.2 + 0.018 × age + 0.065 × ISSe + 0.65 × number of hemorrhagic contusions − 0.75 × alcohol intoxication

Age in years; ISSe, and AISH in points; alcohol intoxication and presence of facial fracture: 1 present, 0 absent. To calculate the probability of unfavorable outcome the value of A, B, or C is inserted in the formula: $1 = (1 + e^{-A,\ B,\ or\ C})$. mTBI, mild traumatic brain injury; CT, Computed tomography; AISH, Abbreviated Injury Scale Head score; ISSe, Injury Severity Scale- Extracranial score.

to each patient for risk of UE. Statistical analyses showed this last model to be reliable and sensitive, allowing early identification of patients at risk of developing PCS, with 95.7% sensitivity and 77.6% specificity.

The difficulty in using this model is that it is based on the results of neuropsychological tests and assessments that are difficult to obtain in emergency departments.

Van der Naalt [26] reported a consecutive series of 910 patients 2 weeks after head injury. 764 of these patients (84%) had post-traumatic complaints and 414 (45%) showed emotional distress. At 6 months after injury, outcome data were available for 671 patients; complete recovery (GOSE = 8) was observed in 373 (56%) patients and incomplete recovery (GOSE ≤ 7) in 298 (44%). Logistic regression analyses identified several predictors for 6-month outcome, including education and age, with significantly greater value for indicators of emotional distress and coping obtained at 2 weeks (area under the curve [AUC] = 0·79, optimism 0·02; Nagelkerke R2 = 0·32, optimism 0·05) than only emergency department predictors at time of admission (AUC = 0·72, optimism 0·03; Nagelkerke R2 = 0·19, optimism 0·05). Based on these variables, the authors proposed a nomogram to estimate the probability of complete recovery at 6 months.

5. Discussion

The present literature review identified several prognostic factors for unfavorable outcome after mTBI (Table 3). Individual factors such as age, gender, neuropsychiatric history emerged, but their value in daily clinical practice is uncertain. The identification of risk factors might be especially useful for clinical practice when combined in a prognostic model predicting patients at risk of poor outcome. The value of having models that combine predictive factors to predict individual patient outcome is obvious. These models, although fairly well constructed, are based on single-center series, have not yet obtained external validation and must therefore be considered with uncertainty.

It appears that the strongest and most consistent predictors of poor prognosis are the number, severity and duration of symptoms present in the first few days following mTBI [21,28,52,53]. To this end, post-concussion symptom tools and grids make it possible to

Table 3
Summary of prognostic factors for unfavorable outcome after mTBI.

Pre-existing factors
Age
Gender
Education level
Neuropsychological history and medical comorbidities
Previous mTBI
Factors related to the accident
Litigation or compensation issues
Assault
GCS
PTA?
Focal brain lesion
Post-trauma period
High score on the Post-Concussion Symptom Scale OR Rivermead
Post-Concussion Symptoms Questionnaire
Nausea, memory problem, dizziness

"quantify" the relative severity of the initial symptoms and compare them to certain norms in order to judge the risk incurred by the patient. Two of the most frequently used tools in this context are the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) [54] and the Post-Concussion Symptom Scale (PCSS) [55].

The RPQ lists 16 symptoms commonly experienced following mTBI. Using a scale ranging from 0 (no longer a problem) to 4 (severe problem), patients identify symptoms that have been more of a problem over the previous 24 hours than they were premorbidly. These items' scores are summed to yield a total score out of 64. The RPQ has been shown to be a valid measure of PCS, with high reliability, and has been widely used in PCS research. Thompson et al. [56], employing receiver-operating characteristics curve analysis, suggested a total score of ≥ 16 as the optimal cut-off point for PCS, with 97% sensitivity and 87% specificity. It should be noted that this study still needs to be replicated in order to establish generalizability.

The PCSSS is a 97-item PCS checklist composed of common neuropsychological complaints, such as "noise sensitivity" and "trouble remembering things", with distractor items. Drawing on symptoms related to cognitive, emotional, and somatic disorders, items are consistent with DSM-IV-TR PCS criteria. Symptom severity is graded on a 5-point Likert scale, with "A" being never descriptive of the patient, and "E" being always descriptive of the patient; scale points between "A" and "E" are not specifically defined. "A" to "E" responses were converted to a score of 1–5, and scores of 3 or more were categorized as endorsement of that particular symptom. This measure has been used in several PCS studies.

6. Conclusion

It has become clear over the years that the persistence of post-mTBI symptomatology is the result of complex interaction between pre-existing factors (related to the person and/or their environment), accident typology and perpetuating factors. Many studies have been published on prognostic factors but are not of a high level of certainty. A number of factors have been proposed and predictive models have been constructed that, although attractive, have not yet been externally validated. It appears that the strongest and most consistent predictors are the number, severity and duration of symptoms present in the first few days after the trauma. It is therefore essential to have and use tools that allow accurate recording of these symptoms and, above all, to monitor their progression. Patients with poor scores according to these tools require special attention and appropriate multidisciplinary management.

Disclosure of interest

The authors declare that they have no competing interest.

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