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REVIEW ARTICLE

PROGNOSIS OF SIX-MONTH FUNCTIONING AFTER MODERATE TO SEVERE TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW OF PROSPECTIVE COHORT STUDIES

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Objective: **To systematically review which determinants, assessed within the first month after a moderate to severe traumatic brain injury, predict 6-month functional outcome.**

Methods: **Databases were searched for relevant publications between 1995 and August 2008. Selection criteria were: prospective cohort studies; determinants associated with functional outcome 6 months after moderate to severe traumatic brain injury in adult patients; determinants assessed within the first month post-injury. Two reviewers independently performed the selection and quality assessment. A best-evidence synthesis was performed for prognostic factors assessed in 2 or more studies.**

Results: **Twenty-eight studies were included, 27 of which were high quality. Most studies used the Glasgow Outcome Score at 6 months post-injury as outcome measure, sometimes in combination with other outcome measures. Strong evidence for predicting outcome at 6 months was found for the Glasgow Coma Scale (GCS), GCS admission, motor score, midline shift on computed tomography scan, subdural haematoma and pulsatility index. Strong evidence of no association was found for gender and intraventricular haemorrhage. For other determinants, inconclusive or no evidence was found.**

Conclusion: **GCS, GCS on admission, motor score, midline shift, subdural haematoma and pulsatility index predicted outcome 6 months after traumatic brain injury. Gender and intraventricular haemorrhage did not have predictive value.**

Key words: traumatic brain injury; outcome; systematic review; rehabilitation; prognosis.

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INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability. The incidence rate in Europe, reporting hospitalized patients and patients who die before reaching hospital, is approximately 243 per 100,000 per year (1). The majority is discharged home, often without any follow-up treatment, and many experience long-term consequences without receiving adequate help (1–3).

In the hospital phase, a global prognosis on outcome is made and follow-up treatment is initiated. Early prognostication of outcome is relevant for directing rehabilitation treatment and for informing patients and relatives about the prognosis. A broad variety of possible determinants of prognosis after TBI has been investigated. However, the studies are of varying quality and often generate conflicting results. In a systematic review on prognostic models, the authors established that: (*i*) as many as 89 determinants were included in prognostic models; (*ii*) the methodological quality of many of these models was poor; and (*iii*) that they were rarely validated on external populations (4). Therefore, well-accepted algorithms to determine which patients will recover well and which will be at risk for long-term disabilities are currently not available. Little is known about predicting outcome at the level of resuming daily activities and social participation.

In a systematic review of long-term prognosis after TBI, Willemse-van Son et al. (5) established that the level of disability at discharge from rehabilitation predicts ongoing disability 1 year or more after TBI. In a second study Willemse-van Son et al. (6) established that the Barthel Index at hospital discharge predicts community integration 3 years post-onset. Optimizing a patient's level of activities may contribute to an optimal level of participation in the longer run. From this perspective it may be pivotal to identify those patients who are in need of subacute rehabilitation.

The objective of the present systematic review was therefore to identify which determinants, assessed within the first month post-injury, predict functioning 6 months post-injury.

METHODS

Search strategy

In 1995 the Brain Trauma Foundation in the United States developed the first TBI Guidelines with the assistance of a group of international experts (7). This set the benchmark for evidence-based guidelines in neurosurgery and other surgical specialties regarding TBI. After an update in 2000 and 2007, the guidelines were endorsed by the American Association of Neurological Surgeons and the World Health Organi-

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zation's Committee on Neurotrauma. We performed a computerized literature search of PubMed and PsychINFO from 1995 to August 2008. Additionally, reference lists of identified publications were checked.

The search strategy was developed and tested for PubMed and adapted for PsychINFO. To describe the population the MeSH term "craniocerebral trauma" was used. To describe the design the following key terms were used: the MeSH term "predictive value of tests", prognos* and predict*. To select the adult population the MeSH terms "adult" and "middle aged" were used. Two reviewers independently screened titles and abstracts to identify relevant articles. Relevant articles were retrieved in full text. Full papers were also retrieved when abstracts were absent or if they provided insufficient information to enable selection.

Selection criteria

A study was included if all of the following criteria were met: (*i*) the study investigated determinants of functional outcome after TBI; (*ii*) TBI was defined as "an alteration in brain function as a result of an acute external violent force to the head"; (*iii*) outcome was described as functional outcome, measured with at least the Glasgow Outcome Score (GOS) (8) or a comparable measure describing activity limitations or participation restrictions; (*iv*) the study investigated the association between determinants, measured in the first month post-injury, and outcome measures as defined; (*v*) outcome was assessed at 6 months post-injury; (*vi*) the study population consisted of moderate and/or severe TBI patients or a separately analysed subgroup of moderate to severe TBI patients (Glasgow Coma Scale (GCS) 3–12 (9)); (*vii*) the majority (at least 80%) of the patients in the studies was in the age range 18–65 years; (*viii*) the article was written in English, French, German or Dutch; (*ix*) the article was a full-text article; (*x*) the study design was a prospective cohort study.

A study was excluded if: (*i*) the study population had additional serious neurological, oncological or systemic impairments; (*ii*) outcome was presented only as a dichotomous distinction on the GOS between "death/vegetative state" and "severe disability/moderate disability/good recovery".

Two reviewers assessed all criteria independently in the full-text articles. Reviewers were not blinded as to the names of author(s), institution(s) or journal. In case of disagreement, consensus was sought. If disagreements were not resolved a third reviewer made the final decision.

Quality assessment

The methodological quality of the articles was assessed with a modified version of an established criteria list for prospective cohort studies (10). The criteria list was modified for the topic of the review in concordance with the framework for assessing validity in prognostic studies (11).

The criteria list consisted of 16 items (footnote Table I). The item was scored positive (yes), if it fulfilled the criterion. If a criterion was not fulfilled, the item was scored negative (no). If there was insufficient information, the item was scored unclear (?). The total sum of positive items was calculated as the quality score (maximum 16 points). A study that scored 8 or more points was considered high quality.

Table I. *Results of methodological assessment*

Article	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	Quality score
Wang et al. (27)	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	0	11
Signoretti et al. (12)	1	0	0	1	0	0	1	0	1	1	1	0	1	0	0	0	7
Fabbri et al. (36)	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	12
Hebb et al. (37)	1	0	1	1	1	0	1	1	1	1	1	0	1	0	0	0	10
IMPACT study (13–23)	1	1	0	1	1	0	1	0	1	1	1	0	1	0	1	1	11
Pang et al. (50)	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	11
Tanriverdi et al. (63)	1	1	0	1	1	1	1	1	1	1	0	0	1	1	0	1	12
Oh et al. (29)	1	0	0	1	0	0	1	0	1	1	1	0	1	0	0	1	8
Hiler et al. (24)	1	1	0	1	1	0	1	1	0	1	0	0	1	1	0	1	10
Shutter et al. (30, 33)	1	0	1	1	1	0	1	1	1	1	1	1	1	1	0	0	12
Vos et al. (44)	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	15
Glenn et al. (34)	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	13
Lew et al. (28)	0	0	1	1	1	1	1	0	1	1	1	0	1	1	0	0	10
Mattioli et al. (40)	1	1	1	1	1	0	1	0	0	1	0	0	1	0	0	1	9
Tan et al. (32)	1	1	0	1	1	1	1	0	1	1	1	0	1	1	0	1	12
Sarrafzadeh et al. (51)	1	1	1	1	1	0	1	1	1	1	1	0	1	1	0	0	12
Rovlias & Kotsou (39)	1	1	1	1	0	0	1	0	1	1	1	0	1	1	0	1	11
Moreno et al. (38)	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	15
Struchen et al. (25)	1	0	1	1	0	0	1	0	1	1	1	1	1	1	0	1	11
Theilen et al. (31)	1	0	0	1	0	0	1	1	0	1	0	1	1	1	0	0	8
Lannoo et al. (26)	1	0	1	1	1	0	1	0	1	1	1	1	1	1	0	1	12
Van den Brink et al. (52)	1	1	0	1	1	1	1	1	1	1	1	0	1	1	0	1	13
Lubillo et al. (41)	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	14
Della Corte et al. (48)	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	13
Le Roux et al. (43)	1	0	1	1	1	1	1	1	1	1	1	0	1	1	0	0	12
Kelly et al. (42)	1	1	0	1	1	0	1	1	1	1	1	0	1	1	0	0	11
Ellenberg et al. (35)	1	1	1	1	1	1	1	0	1	1	0	0	1	0	0	0	10
Rae-Grant et al. (49)	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	12

Criteria; yes = 1, no/? = 0: (a) inception cohort; (b) description of source population; (c) description of relevant inclusion and exclusion criteria; (d) follow-up at least 6 months; (e) drop-outs/loss to follow-up < 20%; (f) information completers vs loss to follow-up/drop-outs; (g) prospective data collection; (h) treatment in cohort is fully described/standardized; (i) clinically relevant potential prognostic factors; (j) standardized or valid measurements; (k) data presentation of most important prognostic factors; (l) clinically relevant outcome measures; (m) standardized or valid measurements; (n) data presentation of most important outcome measures; (o) appropriate univariate crude estimates; (p) appropriate multivariate analysis techniques.

Two reviewers independently scored the quality. In case of disagreement, consensus was sought. If consensus could not be reached, a third reviewer made the final decision. Overall inter-observer agreement was tested with kappa statistics; the agreement on the 448 individual items was compared with the expected agreement.

Data extraction

Data on study cohort, inclusion and exclusion criteria, number of participants, time post-injury, loss to follow-up, outcome measurements, prognostic factors, and results on associations were extracted, using a standardized form.

Analysis

A best-evidence synthesis was performed, in which 4 levels of evidence (10) (Table II) were defined to determine the strength of the association of prognostic factors with functioning after 6 months. Significant relative risk ratios (RRs), odds ratios (ORs), or significant associations ($p < 0.05$) that were provided by the studies were used to determine the levels of evidence. We used the results of multivariate analyses preferentially to establish levels of evidence. When multivariate data on a determinant were not available, we used the univariate results. We also checked all studies for univariate results to rule out the chance that we missed relevant information. For our conclusion and analysis we only present results on determinants investigated in 2 or more studies.

RESULTS

Selection of studies

In total, 770 non-duplicate citations were identified and 106 full-text articles were retrieved. Agreement was initially reached in 85% (90 of 106) of articles, and consensus was sought and reached for 16 articles. Finally, 39 articles were selected, investigating 28 cohorts.

Methodological quality

The overall inter-observer agreement of the methodological quality assessment was $K = 0.61$, representing substantial agreement. Disagreement occurred mainly because of reading errors and was easily resolved. For 9 individual items disagreement persisted and a third reviewer made the final decision. Table I shows the final results of the methodological assessment. One study was of lower quality and scored 7 points (12); all other studies were of high quality.

Study characteristics

The study characteristics are presented in Table III. All studies were prospective observational cohort studies except for one (13–23), which used the data of several randomized controlled trials (RCT) and observational cohorts. We included studies with patients with moderate to severe TBI (GCS 3–12). Some studies used other classifications for severity: the necessity of full intensive care unit (ICU) treatment (24), a motor GCS < 6 (25), or a motor GCS < 6 for more than 24 h (26). These populations were considered to meet the inclusion criteria and were therefore included in this review. More than 40 prognostic determinants were studied. All studies used the GOS at 6 months after injury as an outcome measure, except for 2 studies that used the extended GOS (GOS(E)) (27, 28), and 1 study that used the Disability Rating Scale (DRS) (29). Several studies used additional outcome measures besides the GOS(E): the DRS (25, 29–31), the employability component of the DRS (EMP) (30) the Sickness Impact Profile (SIP) (26), a neuropsychological test battery (26) the Cognitive Ability Scale (29) and mortality. For this review only the GOS(E) and DRS were considered. Many of the articles did not report descriptive statistics regarding the determinants, or effect sizes such as an odds ratio. This complicated the estimation of the impact of the determinants.

Table II. *Levels of evidence*

Strong	Consistent findings (≥ 80%) in at least 2 high-quality cohorts
Moderate	One high-quality cohort and consistent findings (≥ 80%) in one or more low-quality cohorts
Limited	Findings of one cohort or consistent findings (≥ 80%) in one or more low-quality cohorts
Inconclusive	Inconsistent findings irrespective of study quality

Levels of evidence

We only established the levels of evidence for prognostic factors analysed in 2 or more studies. Table IV presents the results of the best-evidence synthesis.

Patient characteristics

There was strong evidence of no relationship between gender and outcome. Gender was analysed in 9 studies (21, 22, 27, 32–38), 5 of which used gender as a determinant in the multivariate analysis (21, 22, 32, 35–37). None of these 9 studies found a relationship between gender and outcome.

The evidence for the prognostic value of age was inconclusive. Nine studies found that an older age was related to a worse outcome (21, 22, 24–26, 29, 35, 37, 39, 40), and 4 studies found no relationship between age and outcome (31, 32, 36, 41). In contrast, one study found an inverse relationship; an older age was associated with a better outcome (33). After taking the univariate results into account, a larger proportion of studies found no association between age and outcome (27, 31–34, 38, 42–44).

Cerebral oxygenation

The evidence for the predictive value of pulsatility index (PI, difference between systolic and diastolic blood flow velocities divided by mean blood flow velocity) on transcranial Doppler (TCD) was strong. Two high-quality studies found an association between higher PI and worse outcome. ORs were high: 21.42 (95% confidence interval (CI) 3.81–183.08) (38) and 25.69 (95% CI 4.95–113.26) (32).

The evidence for the prognostic value of cerebral blood flow (CBF), blood flow velocity, cerebral perfusion pressure (CPP) and intracranial pressure (ICP) was inconclusive.

CPP and ICP were analysed in 7 studies (24, 25, 32, 34, 38, 42, 43), 4 of which presented a multivariate analysis (24, 25,

Table III. *Data extraction*

Article	Patient characteristics	Outcome	Univariate results	Multivariate results
Wang et al. 2008 (27)	US, 12 patients, 11 completing. Mean age 26 years. Inclusion: severe closed head TBI, injury mechanism consistent with DAI, informed consent (legal guardian), 8th grade education level, at least 16 years old. Exclusion: previous TBI or neurological disorder.	GOSE	Significant ($p<0.005$): mean FA CC, mean FA CC splenium, fibre count CC, mean length CC anterior body, FDI CC anterior body. Age ($p=0.046$) Non-significant: DAI index in FLAIR imaging ($p=0.010$), sex, initial GCS, TCDB, all other fibre measurements.	Significant ($p<0.005$): mean FA CC, mean FA CC splenium, fibre count CC anterior body, mean length CC anterior body, FDI CC anterior body, fibre volume PVF. Non-significant: all other fibre measurements.
Signoretti et al. 2008 (12)	US, 25 patients, ? completing. Inclusion: severe TBI.	GOS 1–3 vs 4–5	Significant: single voxel and multi voxel MRS ratios (15 patients) NAA/Cho, NAA/Cr.	
Fabbri et al. 2008 (36)	Italy, 309 patients, 289 completing. Median age 50 years. Inclusion: Moderate TBI, time since injury < 24 h, age > 10 years, local inhabitants. Exclusion: sedation/ intubation before ER, hypotension through extra cranial injuries, cardiopulmonary resuscitation, penetrating head injury.	GOS 1–3 vs 4–5	Significant: GCS, age, high-risk mechanism, ISS, CT Marshall category. Non-significant: Gender, co morbidity, door-to-CT time, injury-to-CT time, road accidents, falls.	Significant: Basal skull fracture (OR 8.89), SAH (OR 4.50), coagulopathy (OR 4.48), subdural haematoma (OR 3.04), CT Marshall category (OR 1.82), GCS (OR 0.58). Non-significant: Gender, age, co morbidity, ISS, drugs/alcohol, high risk mechanism, hypotension, hypoxia, depressed skull fracture, intracranial haematoma, epidural haematoma, intraventricular haematoma.
Hebb et al. 2007 (37)	US, 53 patients, no dropouts. Mean age 41.5 years. Inclusion: GCS 3–13, age 16–85 years, abnormal CT scan, direct admission to study hospital with diagnosis TBI. Exclusion: pentobarbital/propofol induced burst suppression, pre-existing neurological disorder, hepatic/ metabolic encephalopathy, brain death, GCS increase to 14/15 within 8 h.	GOS (PAV 3 days, 7 days, brain injury profiles)	Significant: 3 day PAV I and II vs III and IV and correlation, diffuse oedema, multiple subcortical lesions, brain stem injuries. Non-significant: basal ganglia, thalamus, deep white matter.	Significant: age, pupillary reaction, presenting GCS, diffuse oedema, multiple lesion sites, white matter, 3 day PAV. Non-significant: gender, basal ganglia, thalamus, brain stem injuries.
IMPACT study 2007 (13–23)	Different countries, 8989 patients. Number of patients analysed were different for the various determinants. Median age (8,719 patients) 30 years. Inclusion: patients from 8 RCTs and 3 observational studies, moderate-severe TBI. Exclusion: penetrating head injury, not surviving transport to hospital.	GOS	Significant: (proportional ORs) age (2.14), Black vs Caucasian (1.30), education >12 years vs < 8 years (0.70), CT Marshall score (reference class II) I (0.45), III (2.50), IV (3.03), V/VI (2.18), compressed/absent cisterns (2.45), midline shift 1–5 mm (1.36), midline shift > 5 mm (2.20), tSAH (2.64), EDH (0.64), SDH (2.14, contusion (1.34), SBP < 120 mmHg (1.53), SBP >150 mmHg (1.42), MBP < 85 mmHg (1.30), MBP > 110 mmHg (1.45), hypoxia (2.08), hypotension (2.67), hypothermia (2.21), GCS motor (vs localizes/obeys) enrolment (1.74–7.48), pre-hospital (1.71–3.82), 1st in hospital (1.30–4.14), GCS eye enrolment (0.36), pre-hospital (0.37), 1st in hospital (0.53), GCS verbal enrolment (0.38), pre-hospital (0.39), 1st in hospital (0.48), pupil reactivity (vs both reacting) 1 reacting enrolment (2.71), pre-hospital (2.70), 1st in hospital (2.49), neither reacting enrolment (7.31), pre-hospital (4.77), 1st in hospital (5.50), cause (vs falls) road traffic (0.66), assault (0.66), sports (0.45), glucose (1.68), sodium low (1.40), pH. (0.80) platelets (0.70), Hb (0.69)	Results Model A: adjusted for age, motor score, pupils. Significant: $p<0.01$: age, GCS motor, pupillary reactions, hypoxia (1.65), hypotension (2.06), Marshall class I (0.47), III/IV (2.23), V/VI (1.48)), compressed/absent cisterns (1.83), midline shift 1–5 mm (1.31), tSAH (2.01), EDH (0.63), SDH (1.33), contusion (1.40), GCS eye (none) (1.54), GCS verbal (none) (1.51), SBP < 120 mmHg (1.28), SBP >150 mmHg (1.30), pH (0.84), Hb (0.76), glucose (1.45), platelets (0.79), prothrombin time (1.63) $p<0.05$: black race (1.44), >12 years education (0.74), hypothermia (1.63), midline shift > 5 mm, (1.38), MBP < 85 mmHg (1.14), MBP >110 mmHg (1.27). Non-significant: Asian race, gender, education 9–12 years, cause of injury (falls, road, assault, work, sports, other), high/low sodium.

Table III. *contd.*

Article	Patient characteristics	Outcome	Univariate results	Multivariate results
			Non-significant: gender, Asian vs Caucasian, education 9–12 years vs < 8 years, cause work-related, other causes, sodium high, prothrombin time.	
Pang et al. 2007 (50)	Singapore, 513 patients, no dropouts. Mean age 44.4 years. Inclusion: severe TBI, GCS 3–8.	GOS	No analysis of individual determinants.	No analysis of individual determinants.
Tanriverdi et al. 2006 (63)	Turkey, 71 patients, no dropouts. Inclusion: acute head injury.	GOS 1–3 vs 4–5	Non-significant: IL1A gene.	Non-significant: IL1A gene.
Oh et al. 2006 (29)	Korea, 82 patients, no dropouts? Mean age 50 years. Inclusion: brain injury, admission to ICU.	DRS (Cognitive ability)	No analysis.	Subgroup of severe TBI Significant: 6 month DRS: systolic blood pressure, age, intracranial haematoma, GCS motor score, heart rate. Non-significant: DRS: pupils.
Hiler et al. 2006 (64)	United Kingdom, 126 patients, 107 completing. Age 14–74 years. Inclusion: head injury, necessity of full ICU.	GOS	Significant: correlations: CT Marshall class, midline shift, volume of lesion, 1st 24 h: CPP, PRx, total period: ICP, CPP, PRx. Non-significant: 1st 24 h: ICP, total period: GCS.	Significant: age, midline shift, PRx (1st 24 h). GOS = 3.99–0.0086 × age – 0.947 × midline shift – 1.54 × PRx. Non-significant: admission GCS, CT scan type, ICP and CPP (1st 24 h)
Shutter et al. 2004 (65) Shutter et al. 2006 (30)	US, 45 patients, 42 completing. Mean age 30 years. Inclusion >14 years, presenting in ER, severe TBI (GCS 3–8). Exclusion: previous TBI, other neurological disease, ineligibility for MRI scanning.	GOS 1–3 vs 4–5 DRS EMP	Significant for GOS: motor GCS, SSEP present†, MRS variables‡ Non-significant: age, gender, field GCS, admission GCS, ER pupil, diffuse axonal injury on MRI, contusion on MRI. MRS variables‡ Significant for DRS: motor GCS, SSEP present†, MRS variables‡ Significant for EMP: motor GCS, SSEP present†, MRS variables‡.	Significant for GOS: admission GCS (χ^2 12.4), Motor GCS (χ^2 13.3), age (χ^2 18.7), best early MRS levels. Non-significant: field GCS, best early MRS ratios Significant DRS: PWM Cho, PWM Cho/Cr.
Vos et al. 2004 (44)	The Netherlands, 85 patients, no dropouts. Median age 32 years. Inclusion within 36 h, severe TBI (GCS < 8). Exclusion: penetrating injury, no possibility for follow-up, no blood sample, no informed consent	GOS 1–3 vs 4–5	Significant: GCS (OR 0.65), Injury severity score (OR 1.05), CT (OR 1.79), hypotension (OR 2.85), hypoxia (OR 1.74), GFAP, S100b, NSE Non-significant: age, pupillary reactions.	Significant: GFAP, GCS after resuscitation (OR 0.51), CT (OR 2.15), S100b. NSE, S100b, ISS equals CT (in model, no OR). Non-significant: hypotension, hypoxia.
Glenn et al. 2003 (66)	US, 49 patients, no dropouts. Mean age 36 years. Inclusion > 14 years, within 24 h, moderate-severe TBI (GCS ≤ 13 or deterioration to GCS ≤ 13 within 24 h) requiring mechanical ventilation and ICP monitoring. Exclusion: terminal illness, severe neurological illness, acute complete SCI.	GOS 1–3 vs 4–5 GOS linear trend	Significant: linear trend: $artO_2sat$, $CMRO_2$, art glucose, metabolic ratio, art lactate, AVDlac, CMRlac, CBF, CSFlac, pupils %any abnormal, GCS, CT score. Good/bad: $artO_2sat$, $CMRO_2$, art glucose, art lactate, CBF, CSFlac, pupils %any abnormal, GCS, CT score BBB damage. Non-significant: linear trend: hypotension-hypoxia episode, CT score BBB damage, ISS, age, gender, mean CPP, %CPP < 60 mmHg, mean ICP, %ICP>20 mmHg, $JugO_2sat$, $artpO_2$, $AVDO_2$, AVDglc, CMRglc, CSFglc. Good/bad: hypotension-hypoxia, episode, ISS, age, gender, mean CPP, %CPP < 60 mmHg, mean ICP,	Significant: linear trend: $CMRO_2$, art glucose, art lactate, CSFlac. Good/bad: $artO_2sat$, art glucose, art lactate, CSFlac Non-significant: Linear trend: $JugO_2sat$, $artO_2sat$, $artpO_2$, $AVDO_2$, AVDglc, CMRglc, metabolic ratio, AVDlac, CMRlac, CBF, CSFglc. Good/bad: $CMRO_2$, $JugO_2sat$, $artpO_2$, $AVDO_2$, AVDglc, CMRglc, metabolic ratio, AVDlac, CMRlac, CBF, CSFglc. (controlled for age, injury, ICP, CPP).

Table III. *contd.*

Article	Patient characteristics	Outcome	Univariate results	Multivariate results
			%ICP>20 mmHg, $JugO_2$sat, $artpO_2$, $AVDO_2$, AVDglc, CMRglc, CSFglc, metabolic ratio, AVDlac, CMRlac, CT score.	
Lew et al. 2003 (28)	US, 22 patients, no dropouts. Mean age 36 years. Inclusion: acute severe TBI (GCS ≤ 8), 17–70 years. Exclusion: pre-existing neurological disorder, median neuropathy, hearing loss, dementia, psychiatric disorder, SCI, barbiturate use.	GOSE (mean)	Significant: SEP bilaterally absent vs normal/present but abnormal, ERP absent vs normal/present but abnormal Non-significant: SEP present but abnormal vs bilaterally normal, ERP present but abnormal vs normal.	No analysis.
Mattioli et al. 2003 (40)	Italy, 169 patients (out of 282 eligible), subgroup of 117 with severe TBI (GCS < 9). 5 dropouts. Mean age 42 years. Inclusion: head injured patients in ICU. Exclusion: gunshot, SCI, CT scan not available.	GOS: 1- step-worsening	Subgroup with GCS < 9: no univariate results.	Significant: age (OR 1.051), admission GCS (OR 1.723), compressed/absent cisterns (OR 2.914), major lesions on CT (OR 1.790). Non-significant: tSAH, Morris-Marshall-grade (distribution of haemorrhage).
Tan et al. 2001 (32)	China, 96 patients, no dropouts. Median age 35 years. Inclusion: Severe TBI (GCS 3–8).	GOS 1–3 vs 4–5	Significant: non-reactive pupils at admission, GCS < 5 at admission, shock at admission, CT class 5/6 (not Marshall classification), multiple sites of tSAH, initial ICP, initial CPP, mean blood flow velocity, PI, high-density lesions. Non-significant: age, gender, convulsions, hyperglycaemia, pO_2, pCO_2, Hb.	Significant: non-reactive pupils at admission (OR 1.32), GCS < 5 at admission (OR 4.56), CT class 5/6 (OR 5.24), initial ICP (OR 11.78), initial CPP (OR 3.54), mean blood flow velocity (OR 15.43), PI (25.69). Non-significant: age, gender, convulsions, hyperglycaemia, pO_2, pCO_2, Hb, tSAH, high-density lesions. Shock?
Sarrafzadeh et al. 2001 (51)	Germany, 119 patients, of which 39 non head injury (control), 110 completing. Median age 32 years. Inclusion: severe TBI (GCS < 8), age 6–75 years, Exclusion: haemodynamically unstable, death within 24 h, penetrating head injury, fixed, dilated pupils on admission.	GOS 1–2 vs 3 vs 4–5	GOS: no difference between head injured patients with or without extra cranial injuries.	No analysis for GOS, only for mortality.
Rovlias et al. 2001 (39)	Greece, 125 patients, all completing. Mean age 42 years. Inclusion: non-penetrating head injury, age 16–70 years. Exclusion: previous TBI, drug/alcohol abuse, brain death, factors that might alter WBC count, associated trauma.	GOS 1–3 vs 4–5	Significant: mean WBC count in favourable vs unfavourable outcome.	Significant: GCS after resuscitation (OR 1.7818), pupillary reaction (OR 0.2833), age (OR 0.9622), intracranial diagnosis, WBC count.
Moreno et al. 2000 (38)	Spain, 125 patients, no dropouts. Mean age 34 years. Inclusion: severe head injury, GCS < 9, cranial lesions on CT, stay in hospital > 24 h. Exclusion: inability to perform TCD, irregular left ventricle ejection volume, heart rate > 140 bpm.	GOS 1–3 vs 4–5	Significant: pupillary reaction (OR 16.74), shock (OR 0.20), CT class III (cisterns) (OR 17.23), SAH absent (OR 0.45), APACHE II (OR 1.35), GCS (OR 0.25), ICP (OR 1.08), CPP (OR 0.94), blood flow velocity (OR 0.96), PI (OR 8.50), Hb (OR 0.76). Non-significant: gender, associated lesions, focal injury, convulsions, otorrhagia, surgery, age, pH, $PaCO_2$, PaO_2, glucose.	Significant: GCS (OR 0.24), pupillary reaction (OR 3.86), shock (OR 0.13), PI (OR 21.42) Non-significant: CT class III, SAH, Hb, APACHE II, ICP, CPP, blood flow velocity.
Struchen et al. 2001 (25)	USA, 184 patients, 99 completing for DRS, 127 for GOS. Mean age 34 years. Inclusion: GCS motor < 6, non-penetrating TBI. Exclusion: unstable cardiopulmonary status, brain death, participation in experimental condition of clinical trial.	GOS DRS	Significant for GOS: duration of: intracranial hypertension (χ^2 14.2), systemic hypotension (χ^2 8.8), cerebral perfusion hypotension (χ^2 16.2), jugular venous oxygen desaturation.	Significant for DRS (Sr^2, incremental explained variance) Age (0.084–0.101), ER-GCS (0.084–0.090), log-ICP (0.244), log-MAP (0,044), log-CPP (0.197), log-VO_2 (0.063).

Table III. *contd.*

Article	Patient characteristics	Outcome	Univariate results	Multivariate results
Theilen et al. 2000 (31)	Germany, 45 patients, 32 completing. Mean age 35,3 years (range 18–75). Inclusion: Severe TBI (GCS 3–8) after resuscitation or deteriorating within 6 h. Exclusion: penetrating head injury, EEG inactivity or burst-suppression pattern.	GOS DRS	Significant: ESR (r^2 GOS 0.67, DRS 0.66, PPV 0.83) Non-significant: age. GCS no analysis SSEP (PPV 0.66), BAEP (PPV 0.47) no p-value.	Significant: ESR (accuracy 90.6%), SSEP (accuracy 84.4%) Non-significant: age, GCS after resuscitation.
Lannoo et al. 2000 (26)	Belgium, 158 patients, no dropouts for GOS, 80 patients died, completing impairment index 64, SIP 68. Inclusion: closed head injury, coma duration (GCS motor < 6) at least 24 h, age > 15 years, no medical history of CNS disease or mental retardation.	GOS (SIP, Neuro-psychological test battery (impairment index))	No analysis.	Significant: age (r^2 0.159, F 7.92) Non-significant: GCS (lowest before sedation), pupils, base excess, platelet count, temperature, ventricular haemorrhage, PaO_2.
Van den Brink et al. 2000 (52)	The Netherlands, 101 patients, no dropouts. Mean age 34 years (range 11–82). Inclusion: GCS ≤ 8, non-penetrating head injury.	GOS 1–3 vs 4–5	Significant: low $PbrO_2$ >30 min (unfavourable outcome, OR 2.8).	Significant: low $PbrO_2$> 30 min, remains independent prognostic factor in logistic regression models, only status of perimesencephalic cisterns reduced prognostic value.
Lubillo et al. 1999 (41)	Spain, 82 patients, no dropouts. Mean age 36 years. Inclusion: GCS ≤ 8, non-penetrating head injury, removal of intracranial haematoma.	GOS 1–3 vs 4–5	Significant: motor GCS ≤ 3 (OR 25.6), pupils (OR 51.1; 0.57), systolic blood pressure (OR 11.81), CT score post-operative I/II (OR 0.04), III/IV (OR 21.95), associated intracranial lesions (OR 7.15). Non-significant: unilaterally reactive pupils, basal cisterns status.	Significant: Motor GCS (OR 10.8), bilaterally non-reactive pupils (OR 31.8), post-operative CT III/IV (OR 8.9). Non-significant: hypotension, intracranial lesions, age.
Della Corte et al. 1998 (67)	Italy, 22 patients, no dropouts. Mean age 29 years. Inclusion: severe head injury. Exclusion: females, age < 16 years or > 60 years, GCS 3, steroid use, endocrine abnormalities, severe cardiac/pulmonary disorders, requirement of dopamine or > 2 units of blood.	GOS 1–3 vs 4–5	Significant: GH response to GHRH on day 7, GH response to TRH, TSH response to TRH, PRL response to GHRH on day 7 and 15 Non-significant: basal values of hormones, GH response to GHRH on day 2 and 15, PRL response to TRH, PRL response to GHRH on day 2.	No analysis.
Le Roux et al. 1997 (43)	US, 32 patients, no dropouts. Median age 35 years. Inclusion: GCS ≤ 8, admission within 8 h, isolated non-penetrating head injury, normal blood pressure, normothermia, haematocrit > 30%, survival > 24 h.	GOS 1–3 vs 4–5	Significant: delayed cerebral infarction, elevated $AVDO_2$ post- treatment, limited improvement in $AVDO_2$ post-treatment, admission GCS. Non-significant: age, ICP (post-treatment), CPP (post-treatment), $AVDO_2$ pre-treatment.	No analysis.
Kelly et al. 1997 (42)	US, 54 patients, no dropouts. Mean age 35. Inclusion: GCS ≤ 13, serial CBF measurement and ICP monitoring.	GOS 1–3 vs 4–5	Significant: CBF (3 groups), age, h of high ICP, CPP. Non-significant: GCS, no of CT diagnoses, mean ICP, CBF (mean).	No analysis.
Ellenberg et al. 1996 (68)	US, 314 patients, 259 completing. Mean age 29 years. Inclusion: initial GCS ≤ 8, age > 16 years, survival of initial evaluation, out of coma before hospital discharge. Exclusion: penetrating injury.	GOS 1–3 vs 4–5	No analysis.	Significant: age (OR 0.96), time in coma (OR 0.93), time in PTA (OR 0.98), dexamethason use (OR 0.29). Non-significant: first GCS score, race, sex, pupillary response, CT abnormalities, use of phenytoin, use of morphine sulphate.

Table III. *contd.*

Article	Patient characteristics	Outcome	Univariate results	Multivariate results
Rae-Grant et al. 1996 (49)	US, 69 patients, 3 completing. Mean age 36 years. Inclusion: GCS ≤ 8, age ≥ 15 years, coma > 48 h, closed head injury, consent form, no brain death.	GOS	Significant: GCS day 7 (LR 34.04) Non-significant: CT, age, (hypertension (1 patient)).	Significant: EEG, TCD (R = 0.54), GCS day 7. Non-significant: BAEP, SSEP, OPG.

*ORs are mentioned for determinants that are investigated in more than one study. Combinations of factors or models are not mentioned, except when details about the contribution of the individual determinants are reported. Only outcome measures relevant to this review are mentioned.
†Data on SSEP: the study reported a significant relationship in the univariate analysis, but the presented figures of 1 month and 6 month outcomes differed in the total number of abnormal SSEPs. We have assumed that this was due to a typing error, and that the p-value of < 0.001 was correct.
‡Specified in article, too detailed for this table.
§Studies also report results on subgroups, not specified in this table. Results regard all patients together.
Art: arterial; AVD: arteriovenous difference; BAEP: brainstem auditory evoked potentials; BBB: blood brain barrier; CC: corpus callosum; CMR: cerebral metabolic ratio; CSF: cerebral spinal fluid; DAI: diffuse axonal injury; EEG: electro-encephalogram; ER: emergency room; ERP: cognitive event related potentials; ESR: electroencephalogram silence ratio; FA: fractional anisotropy; FDI: fibre intensity index; FLAIR: fluid attenuation and inversion recovery; GFAP: glial fibrillary acidic protein; GH: growth hormone; GHRH: growth hormone releasing hormone; Glc: glucose; Hb: haemoglobin; Jug: jugular; Lac: lactate; MAP: mean arterial pressure; MBP: mean arterial blood pressure; MRS: magnetic resonance spectroscopy; NSE: neuron specific enolase; OPG: ocular plethysmography; PaO_2: arterial oxygen pressure; PAV: percent alpha variability; $PbrO_2$: brain oxygen pressure; PRL: prolactin; PRx: pressure reactivity; PVF peduncular projections to ventral frontal cortex; S100b: calcium-binding protein; Sat: saturation; SBP: systolic blood pressure; SCI: spinal cord injury; TCDB: trauma coma data bank; TRH: thyrotropin releasing hormone; tSAH: traumatic SAH; TSH: thyroid stimulating hormone; WBC: white blood cell.
GOS: 1 = death, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, 5 = good recovery.

32, 38). Two studies found a lower CPP and a higher ICP to be associated with worse outcome (25, 32). Univariate results were consistent with multivariate results.

The evidence for the prognostic value of hypotension and hypoxia was also inconclusive. In the multivariate analysis of 4 studies, hypotension was associated with a worse outcome (21, 25, 29, 38). However, in 4 other studies no significant relationship was found (32, 36, 41, 44). Hypoxia was tested in a multivariate model in 6 studies (21, 26, 32, 34, 36, 44). One study found a correlation between hypoxia and unfavourable outcome (45), and another study reported a significant result for oxygen saturation, but not for oxygen pressure (34). The others found no significant results.

Imaging studies

Computed tomography (CT) scanning was assessed in most studies. Different classification methods were used, but the Marshall classification (46) was used most commonly. Therefore, we made subgroups corresponding to this classification. For the separate category midline shift (Marshall IV) we found strong evidence. Midline shift was analysed in 2 studies and both found an association with worse outcome (16, 21, 24).

The evidence for the prognostic value of the total Marshall classification and for the separate categories mass lesion (corresponding to Marshall V/VI) and compressed/absent cisterns (Marshall III) was inconclusive, in the analysis of multivariate results. In the univariate analysis, however, compressed/absent cisterns were associated with worse outcome in all 3 studies (16, 21, 38, 40).

The evidence for the prognostic value of subdural haematoma (SDH) was strong. Two studies found an association with worse outcome (16, 21, 47). There was strong evidence of no relationship between intraventricular haemorrhage (IVH) and outcome. Two studies found no association (26, 47). The evidence for subarachnoid haemorrhage (SAH), epidural haematoma (EDH) and intracranial haemorrhage (ICH) was inconclusive (Tables III and IV).

Magnetic resonance spectroscopy (MRS) was investigated in 2 studies (12, 30, 33). Regarding the items investigated in both studies, only univariate data were available. These items were N-acetylaspartate/creatine (NAA/Cho) and N-acetylaspartate/choline (NAA/Cr) ratios. NAA/Cho had an association with outcome in both studies. Because one study was of low quality (12), this evidence was moderate. The evidence for NAA/Cr was inconclusive.

Physical examination

We found strong evidence for the prognostic value of the GCS overall (all GCS measurements together), the GCS on admission to the hospital and the GCS motor score. The GCS was analysed in 21 different studies (17, 21, 24–27, 29, 31–34, 37–44, 47–49), 5 of which presented only univariate results (27, 34, 42, 43, 48). Of the remaining 16 studies, 13 found that a lower GCS was related to worse outcome. All 4 studies on motor GCS (17, 21, 29, 33, 41) found that lower motor score was related to worse outcome. Five studies (32, 33, 37, 40,

47) found an association between lower admission GCS and worse outcome, 1 found no association (24). The evidence for the prognostic value of GCS after resuscitation and field GCS was inconclusive (Tables III and IV). There was inconclusive evidence for the prognostic value of pupillary reactions. Six studies found a relation between absence of or abnormal pupillary reactions and worse outcome in the multivariate analysis, (17, 21, 32, 37–39, 41), 3 studies found no association (26). However, univariate analysis showed an association in 6 out of 7 studies.

The evidence for the prognostic value of body temperature and injury severity score (ISS) was inconclusive (Tables III and IV).

Electrophysiological data

The evidence for the prognostic value of somatosensory evoked potentials (SSEP) was inconclusive. In a multivariate analysis, a relation between normal SSEP and better outcome was found in 1 of 2 studies (31, 49). Two other studies presented only a univariate analysis (28, 33), one found a relationship between presence of abnormal SSEP and worse outcome, and one found a relationship between absent vs (ab)normal SSEP and lower mortality, but not for abnormal vs normal SSEP.

Laboratory parameters

The evidence for haemoglobin, platelet count and hyperglycaemia was inconclusive (Tables III and IV).

Subgroup analysis of larger studies

To estimate the influence of sample size on our results, a subgroup analysis of studies including more than 100 patients was performed. In these 12 studies (21, 24–26, 35, 38–40, 47, 50–52) we found strong evidence that midline shift and subdural haematoma predict outcome. Strong evidence of no association was found for gender and intraventricular haemor-

Table IV. *Results of qualitative analysis*

Determinant	Number of studies	Association with better outcome	Non-significant	Association with worse outcome	Inconsistent	Level of evidence
Older age	14	1	4	9	0	Inconclusive
Body temperature	2	0	1	1	0	Inconclusive
Lower blood flow velocity	3	0	1	2	0	Inconclusive
Lower CBF*	2	0	0	1	1	Inconclusive
Lower CPP	4	0	2	2	0	Inconclusive
CT	21	–	–	–	–	
Marshall ordinal	4	0	2	2	0	Inconclusive
Compressed/absent cisterns	3	0	1	2	0	Inconclusive
Midline shift	2	0	0	2	0	Strong
Mass lesion	4	0	3	1	0	Inconclusive
Traumatic SAH	6	0	4	2	0	Inconclusive
EDH	2	1	1	0	0	Inconclusive
SDH	2	0	0	2	0	Strong
ICH	2	0	1	1	0	Inconclusive
IVH	2	0	2	0	0	Strong no
Lower GCS	16	0	3	13	0	Strong
Admission	6	0	1	5	0	Strong
After resuscitation	3	0	1	2	0	Inconclusive
Motor	4	0	0	4	0	Strong
Field	2	0	1	1	0	Inconclusive
Male gender	5	0	5	0	0	Strong no
MRS NAA/Cr*	2	0	1	1	0	Inconclusive
MRS NAA/Cho*	2	0	0	2	0	Moderate
Haemoglobin low	3	0	2	1	0	Inconclusive
Hyperglycaemia	3	0	1	2	0	Inconclusive
Hypotension	8	0	4	4	0	Inconclusive
Hypoxia	6	0	4	1	1	Inconclusive
Higher ICP	4	0	2	2	0	Inconclusive
Lower ISS	2	1	1	0	0	Inconclusive
Higher PI	2	0	0	2	0	Strong
Platelet count low	2	0	1	1	0	Inconclusive
Abnormal/absent pupillary reactions	9	0	3	6	0	Inconclusive
Abnormal SSEP	2	0	1	1	0	Inconclusive

*Univariate analysis.

CBF: cerebral blood flow; CPP: cerebral perfusion pressure; CT: computed tomography; EDH: epidural haematoma; SDH: subdural haematoma; ICH: intracranial haemorrhage; IVH: intraventricular haemorrhage; GCS: Glasgow Coma Scale; MRS: Magnetic resonance spectroscopy; NAA/Cr: N-acetylaspartate/choline; NAA/Cho: N-acetylaspartate/creatine ; ICP: intracranial pressure; ISS: injury severity score; PI: pulsatility index ; SSEP: somatosensory evoked potentials.

rhage. Inconclusive evidence was found for GCS, age, hypotension, hypoxia, epidural haematoma, SAH, pupillary reactions, state of basal cisterns, haemoglobin, platelet count, body temperature, ICP and CPP. In a subgroup analysis of studies with more than 300 patients (3 studies (21, 35, 47)) we found strong evidence for the predictive value of subarachnoid haemorrhage and subdural haematoma. We found strong evidence of no association between gender and outcome. Inconclusive evidence was found for GCS, age, hypotension, hypoxia, epidural haematoma, and pupillary reactions.

DISCUSSION

The objective of this systematic review was to identify which determinants, assessed within the first month after TBI, predict functioning 6 months post-onset. Providing new information or explaining the findings in terms of pathophysiology is not the primary goal of a systematic review. Therefore, although relevant for clinicians, we were cautious not to speculate about underlying mechanisms or explanations for which no evidence was given in the included studies.

Our study established strong evidence that low GCS overall, low GCS on admission, low motor score, presence of midline shift on CT scan, presence of subdural haematoma and high PI on transcranial Doppler were predictors of poor outcome 6 months post-TBI. We found strong evidence that gender and intraventricular haemorrhage do not predict outcome. We found moderate evidence that a lower ratio NAA/Cho on MRS predicts poor outcome. However, this was based on univariate data. For all other determinants the evidence was inconclusive.

Comparison with other literature

We compared our findings with several other reviews and relevant publications on prognostic factors and prognostic models after TBI. In a systematic review on the long-term prognosis (1 year or more) after TBI, Willemse et al. (5) established that older age, pre-injury unemployment, substance abuse, and more severe disability at rehabilitation discharge were strong predictors for ongoing disability. Inconclusive evidence was found for female gender, and lower GCS. Our results were different with regard to age and GCS. Possibly long-term functioning depends less on initial severity scores such as the GCS and more on psychosocial variables such as age, coping style, social support and, for example, financial resources. In the studies included in the current review, few other sociodemographic factors were investigated besides age. In contrast, the studies included in the review on the longer term by Willemse et al., investigated primarily sociodemographic factors, and few basic medical and neurological variables.

As mentioned in the introduction, several prognostic models have been developed. Most models predict mortality or GOS after 6 or 12 months and include age, GCS or motor score, pupillary reactivity and some other factors, such as CT parameters, hypotension or hypoxia (45, 53–55). Our findings, however, suggest that age might not be a strong predictor of outcome. PI has not been included in previous prognostic models as far as we know. Given the high odds ratios found in 2 studies in this review, the PI may well be a promising determinant of outcome.

In a systematic review on SSEP, the authors concluded that SSEP are the best single overall predictor of outcome after TBI (56). We could not find any evidence to support this conclusion. It is possible that SSEP are more useful for predicting mortality than for predicting functional outcome.

Limitations of the review

We searched studies published between the presentation of the TBI guidelines in 1995 and August 2008. It is possible that relevant publications before or after that time were not included in this review, such as the Traumatic Coma Data Bank studies (57). However, we think that it would be inappropriate to include older studies in a review on prognostic factors, because there have been substantial changes in treatment over the last decades (7, 58). This most likely has had an effect on the general prognosis after TBI, thus hampering comparability between older and more recent studies. Furthermore, publication bias might have occurred. Studies with significant results might be easier to publish and therefore easier to find. Also, we did not include studies published in languages other than English, French, German or Dutch. We studied only moderate to severe TBI patients. Therefore it is not clear whether the findings can also be generalized to mild TBI patients.

Besides the GOS, only a few other measures of functional outcome were used. The GOS is a rather crude measure, with limited sensitivity to change (59, 60). There is some observer variation in outcome assessment with the GOS(E), which might have influenced the results of the studies (61, 62). The effect of this on our results is not clear. The prognostic value of a determinant might be underestimated by using such a crude measure. However, underestimation might also happen when more categories are used, as a result of a higher misclassification rate (61). In planning individualized long-term rehabilitation programmes more detailed information on outcome is pivotal.

Some of the included studies excluded penetrating head injury, other studies did not. Little information was given in the studies about how many patients had closed or open head injuries, or about the prognosis of these subgroups. It is not clear whether this has influenced our results.

Some variables might have a U-shape correlation with outcome. For example: in the IMPACT study both very high and very low blood pressure were associated with a worse outcome (13). In many other studies, blood pressure was dichotomized on a certain threshold. Therefore, the adverse effect of a very high blood pressure might obscure the prognostic value of hypotension in the studies analysed in this review. It was not possible to calculate a correction for this effect.

In the analysis, the results of large studies were given equal weight to the results of small studies. Therefore negative findings in smaller studies might influence the results disproportionately. However, based on the separate analysis of the

results of studies with more than 100 and 300 patients, this has not resulted in false negative conclusions. The evidence for determinants such as age, pupillary reactions, hypotension and hypoxia remained inconclusive in both subgroup analyses, indicating that our results are robust.

Recommendations

In predicting outcome after brain injury there is a reasonable amount of uncertainty. A multitude of determinants may contribute to the prognosis. In planning rehabilitation treatment, clinicians should pay attention to the contextual factors as well as to the early medical information. Because TBI is a lifelong disorder in which changing contextual demands may generate new needs for professional support, and because we are unable to accurately predict who is at risk of incurring restrictions of activities or participation, TBI patients should be involved in a life-long, well-coordinated programme.

Furthermore, outcome measurement should be more specific than just the GOS(E) and should encompass more detailed functional outcome measures, for instance on participation in leisure and professional activities, caregiver strain and the risk of developing mood disorders.

Much of the literature available is written from an isolated neurological, neurosurgical or rehabilitation perspective. To improve outcome prediction, multidisciplinary research should take place, and knowledge should be integrated.

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