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Long-term outcome after severe traumatic brain injury: a systematic literature review

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Abstract

Background Expectation of long-term outcome is an important factor in treatment decision-making after severe traumatic brain injury (sTBI). Conclusive long-term outcome data substantiating these decisions is nowadays lacking. This systematic review aimed to provide an overview of the scientific literature on long-term outcome after sTBI.

Methods A systematic search was conducted using PubMed from 2008 to 2020. Studies were included when reporting long-term outcome ≥ 2 years after sTBI (GCS 3–8 or AIS head score ≥ 4), using standardized outcome measures. Study quality and risk of bias were assessed using the QUIPS tool.

Results Twenty observational studies were included. Studies showed substantial variation in study objectives and study methodology. GOS-E ($n = 12$) and GOS ($n = 8$) were the most frequently used outcome measures. Mortality was reported in 46% of patients (range 18–75%). Unfavourable outcome rates ranged from 29 to 100% and full recovery was seen in 21–27% of patients. Most surviving patients reported SF-36 scores lower than the general population.

Conclusion Literature on long-term outcome after sTBI was limited and heterogeneous. Mortality and unfavourable outcome rates were high and persisting sequelae on multiple domains common. Nonetheless, a considerable proportion of survivors achieved favourable outcome. Future studies should incorporate standardized multidimensional and temporal long-term outcome measures to strengthen the evidence-base for acute and subacute decision-making.

Highlights 1. Expectation of long-term outcome is an important factor in treatment decision-making for patients with severe traumatic brain injury (sTBI).

2. Favourable outcome and full recovery after sTBI are possible, but mortality and unfavourable outcome rates are high.

3. sTBI survivors are likely to suffer from a wide range of long-term consequences, underscoring the need for long-term and multi-modality outcome assessment in future studies.

4. The quality of the scientific literature on long-term outcome after sTBI can and should be improved to advance treatment decision-making.

Keywords Traumatic brain injury · Brain injury · Long-term outcomes · Head injury · Rehabilitation

Introduction

Severe traumatic brain injury (sTBI) is accompanied by high mortality rates in both the acute phase and the period following sTBI (35–75%) [16, 49, 67]. It can result in lifelong physical,

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cognitive and emotional impairments which cause an increasing global health and socioeconomic problem [49, 70, 72]. Physicians aim to minimize sTBI impact by selecting the most appropriate treatment strategy in the acute or subacute phase. This treatment decision-making process is complex due to clinical and moral dilemmas, and it is still poorly supported by scientific evidence. Prognostic models that show precise predictions on the population level are considered not precise enough for individual patient decision-making [13, 61, 74]. This results in poor guideline adherence and treatment variation [85–88].

Aiming at best patient long-term outcomes, many uncertainties on this subject remain to exist [14, 49, 75, 83]. Most high-impact studies, including those substantiating the most recent guidelines on the management of patients with sTBI, have focussed on 6 to 12-month short- to midterm outcome [13]. Likewise, validated prognostic models (IMPACT, CRASH) use mortality and Glasgow Outcome Score at 6 months post-injury [61, 74]. The use of this short-term follow-up period combined with inaccuracy on individual patient level predictions may explain why these models are not broadly used in clinical practice [34, 58, 59].

Despite the clinical credo that the greater part of recovery takes place within the first months to 1 year after the injury, it has long been recognized that improvements—especially on the cognitive, emotional and social domains—can continue to occur for several years after TBI [22, 29]. Because a physicians' intuitive prediction of patient outcome after sTBI typically influences acute treatment decisions, increased knowledge on long-term outcomes could improve clinical decision-making and reduce treatment variation [35, 49].

This systematic literature review aims to summarize current knowledge and gaps on long-term outcome in patients with severe TBI.

Methods

This systematic literature review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [48]. The study protocol was registered in the PROSPERO International Prospective Register of Systematic Review (registration number; CRD42020138030). The search was performed using PubMed on the 1st of June 2020 and focussed on the following terms: 'severe traumatic brain injury', 'long-term outcome' and 'adults'. The search strategy was designed and conducted with the assistance of an experienced medical librarian (Supplement 1).

Article selection criteria and procedure

Studies were eligible for inclusion when they reported on adult sTBI patients with documented outcomes ≥ 2 years after injury. The following inclusion criteria were used: (1) adults (aged ≥ 18 years); (2) patients sustained sTBI, defined by the two most commonly used definitions: Glasgow Coma Score (GCS) ≤ 8 or a head Abbreviated Injury Scale (AIS) ≥ 4 [24, 79]; (3) reported outcome at ≥ 2 years after injury and (4) cohort size > 10 patients. To improve comparability and to reduce heterogeneity, but also for pragmatic reasons, studies were included when published after January 2008 [5, 12] and when study patients were treated after 1996. This is the year the first TBI guideline was published [11].

Studies were excluded when: (1) non-standardized health outcome measures were used, including self-designed questionnaires, caregiver-based outcomes or rarely used functional outcome measures; (2) outcome of sTBI patients could not be distinguished from patients with other TBI severities; (3) written in non-English or non-Dutch language or irretrievable and (4) case reports or review articles.

Two researchers individually screened titles and abstracts in duplicate. Subsequently, full texts were retrieved and selected for inclusion based on the aforementioned eligibility criteria. Disagreements were discussed between the two researchers until consensus. A third reviewer was available to make a final decision in case consensus was not reached. A fourth reviewer independently repeated the screening process which did not change the final article selection.

Risk of bias

Study quality was assessed independently by two reviewers using the Quality in Prognosis Studies (QUIPS) tool [32]. This is a six-item questionnaire specifically designed to assess quality of observational follow-up studies and rates the risk of bias as 'low', 'moderate' or 'high' [33]. The QUIPS tool includes the following items: participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, analysis and reporting. All relevant information on the QUIPS tool and quality assessment scores can be found in Supplement 2.

Data extraction and reporting

Two researchers independently extracted data on study methodology and relevant outcome data in duplicate by using a standardized data extraction document. Disagreements were discussed until consensus. A third reviewer checked

all extracted data to correct any errors. The most frequently reported outcome measures were extracted and reported in this systematic review to ensure a comprehensive overview. Extracted outcome measures were the Glasgow Outcome Scale—Extended (GOS-E) [40], the Glasgow Outcome Scale (GOS) [39], mortality and the Short Form (36) (SF-36) [77]. Less frequently reported outcomes were the Quality of Life after Brain Injury (QOLIBRI) [89], the Barthel index [50], the hospital anxiety depression scale (HADS) [96], the Short Form (12) (SF-12) [91] and the Functional Independent Measure (FIM) [43]. GOS and GOS-E scores were dichotomized as favourable (4–5 and 5–8) and unfavourable (1–3 and 1–4) and recategorized accordingly when other cut-off values were used [92]. Mean mortality rates were calculated based on overall mortality scores, subgroup scores were excluded. All relevant information on these frequently reported and other less frequently reported outcome measures can be found in [Supplement 3](#).

Data analysis

All relevant data was reported in a descriptive manner using means and outcome ranges. A meta-analysis was considered but not performed due to the heterogeneity of study designs and outcome measures. When studies reported outcome data for different subgroups, this data was separately reported

for each subgroup. When studies only reported numbers of patients, a percentage was calculated. In addition, mean outcome percentages of patient groups combined were calculated and corrected for the number of patients per study, thereby providing a weighted mean percentage. All calculations, figures and tables were made using recent versions of Microsoft Excel and Microsoft Word.

Results

Literature search and study selection

Of 4287 identified records, 180 studies were retrieved for full text screening after title and abstract screening. A total of 20 studies with 1855 sTBI patients were included after full text screening (Fig. 1). Studies were mainly excluded for not reporting outcome for patients with sTBI separately ($n = 53$), not defining sTBI by using $GCS \leq 8$ or $AIS \geq 4$ ($n = 33$), not having a follow-up period of ≥ 2 years ($n = 17$) and not using standardized outcome measures ($n = 18$).

Study characteristics and study quality

Most studies were published between 2013 and 2020 ($n = 16$; 80%) and used a prospective design ($n = 14$; 70%). Studies

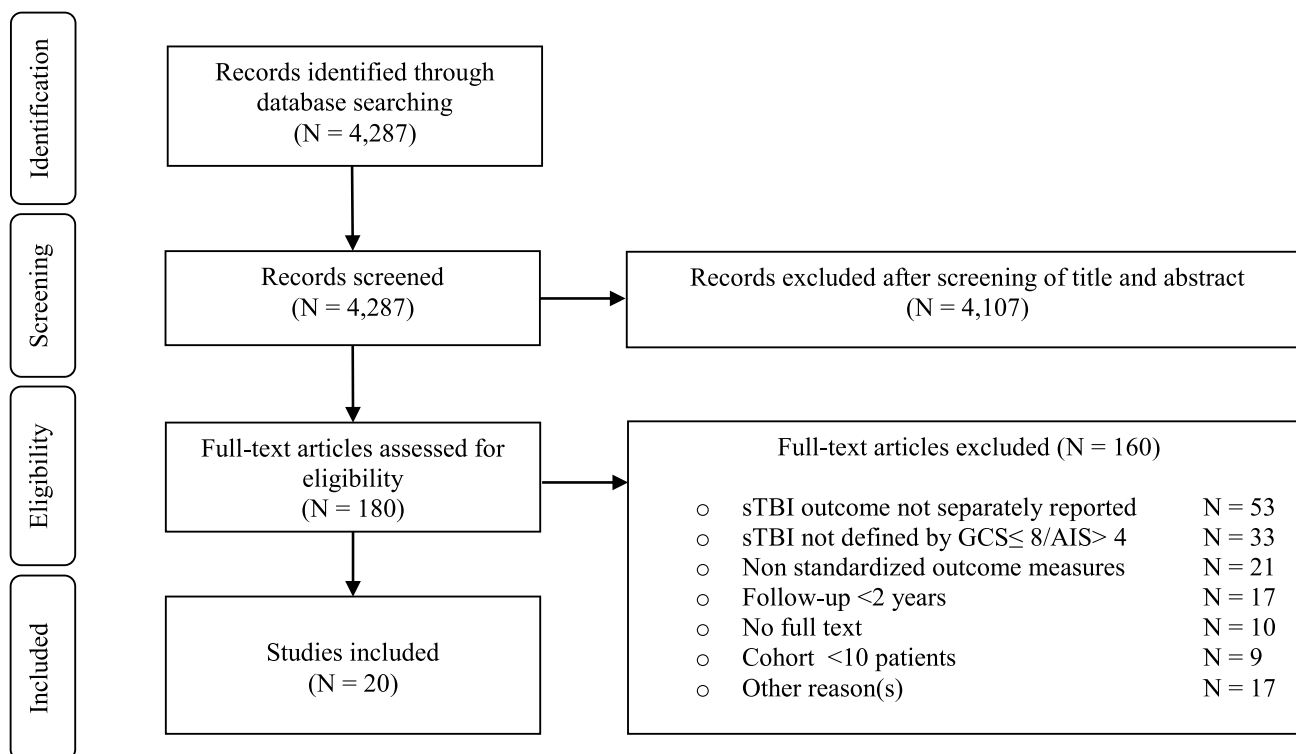


Fig. 1 Flowchart of article selection

were mostly conducted in France ($n=8$, 40%), the USA ($n=3$, 15%), Sweden ($n=3$, 15%) and Germany ($n=3$, 15%) (Table 1). Follow-up ranged from 2 to 15 years. Follow-up periods up to 5 years were reported in 13 studies (65%) [1, 4, 7, 8, 26, 38, 41, 42, 57, 78, 90, 92, 93], periods from 5 to 10 years in five studies (25%) [36, 47, 68, 73, 81], and a follow-up of more than 10 years was reported in two studies (10%) [2, 3].

Using the QUIPS tool, 12 studies (60%) showed an intermediate/moderate risk of bias, while six studies (30%) showed a low risk (Table 2). Two studies (10%) showed a high risk of bias due to inadequate confounder management and a high loss to follow-up (Supplement 2).

Used outcome measures

The GOS-E ($n=12$; 60%) and GOS scores ($n=8$; 40%) were the most frequently used outcome measures. Other commonly reported outcomes were mortality ($n=5$; 25%) and SF-36 scores ($n=3$; 15%) (Table 1).

Glasgow Outcome Scale—Extended

There was substantial variation in reported GOS-E scores (Table 1 and Fig. 2). Three studies differentiated between eight GOS-E categories [36, 78, 92], while four studies excluded mortality and vegetative state categories [1, 4, 47, 68]. Other studies used mean or median GOS-E scores [7, 73, 81] or dichotomized outcomes (favourable vs. unfavourable) [42, 73].

Unfavourable outcomes (GOS-E 1–4) ranged between 13 and 100% of patients. Favourable outcomes (GOS-E 5–8) between 0 and 86%. Reported mean GOS-E scores in two other studies were 4.7 ± 2.8 and 5.7 ± 1.5 [7, 73].

Glasgow Outcome Scale

Variation among reported GOS scores was also high (Table 1, Fig. 3). Some studies reported all five categories [1, 2, 26], while one study only mentioned GOS 3, 4 and 5 percentages [41]. Four studies used mean or median scores [3, 8, 38, 90]. Unfavourable outcomes ranged between 26 and 79% and favourable outcomes between 21 and 74%. Detailed outcomes of GOS scores are presented in Table 1 and Fig. 3. Reported mean GOS scores showed rather ‘favourable’ long-term outcome ranging from 3.8 to 4.4 [3, 8, 38].

Reported prognostic factors GOS/GOS-E

Factors associated with worse outcomes were lower GOS(-E) score at discharge or during rehabilitation, increased ICU length of stay [68, 78], unchanged ICP after decompression surgery [93], duration of coma, duration of post-traumatic

amnesia [4] and presence of a posttraumatic hydrocephalus [1]. Four studies found older age to correlate with worse outcomes [4, 68, 78, 93], but two studies reported no association [1, 42]. Longer duration of education was not found to be significantly associated with better outcomes [42, 68]. Gender did not seem to influence GOS(-E) outcomes [2, 42, 68, 93], just like time to craniectomy [26] and pituitary dysfunction [81].

Mortality

The weighted mean mortality rate of sTBI patients including both specifically reported mortality and GOS(E) scores of 1 was 46% (range 18–75%) (Table 1). Factors associated with higher mortality rates were initial GCS < 5 [26, 73, 93], bilaterally fixed and dilated pupils and poor outcome at 1-year follow-up [1], while lower post-decompression ICP levels were associated with decreased mortality rates [26, 93]. Four studies found older age to be associated with higher mortality [57, 73, 92, 93], whereas two others could not find this association [26, 78]. An attempt was made to identify any factors to clarify this conflict but predictors could not be retrieved from the included articles.

SF-36

Using the SF-36 (range 0–100, higher score indicating a better health), sTBI patients scored worse than the average population (Table 3). Mean physical scores (SF-36 #9) ranged from 33 to 48, while normative controls score around 51 [1, 36, 81]. Mean mental health scores (SF-36 #10) ranged from 46 to 49, which is slightly lower compared to the general population score of 52 [1, 36, 81]. Individual domain scores such as #2 role physical and #6 social functioning showed much lower scores, indicating higher rates of disabilities (Table 3).

Other outcomes

The long-term outcomes reported by using the QOLIBRI scale ($N=2$) showed mean scores (63.9 and 70.6 respectively) above the commonly used threshold of 60, reflecting a non-impaired health-related quality of life (HRQoL) [4, 38, 94]. The Barthel index showed average scores of 96.3 and 95 which corresponds to patients living at home with some help in daily activities [1, 15, 57] (Supplement 4).

The reported HADS scores (9.7, 11.7 and 11.7) [4, 42, 68] indicated that some patients (with a score of ≥ 11) could still be suffering from anxiety or depression [9]. Also, studies showed high rates of unemployment, 12.9% and 48% [3, 73].

Table 1 Study characteristics

| N | Study details* | Population** | Age*** | Male % | Follow-up# | Mortality % | Population at follow-up## | GOS % | GOS-E % | |
|---|---|--|---|----------------|--------------------|-------------|--|--|--|---------------------------------------|
| 1 | Ahmadi et al. [1] 2010, Germany 2005–2006 Prospective | 131 sTBI patients undergoing decompressive craniectomy | 35 ± 19.5 | 67 | 48.7 ± 24.9 months | NR | 124 (95%) patients recruited for GOS scoring at follow-up, 30 (24%) patients with GOS score ≥ 3 for extended examination and GOS-E scoring | 1: 60.5 2: 7.2 3: 11.3 4: 10.5 5: 10.5 | 1: NR### 3: 13.3 5: 6.7 7: 23.3 | 2: NR 4: 16.7 6: 33.3 8: 6.7 |
| 2 | Andersson et al. [2] 2017, Sweden 2000–2004 Prospective | 102 sTBI patients with intracranial pressure monitor- ing | Males: 39.5 ± 18.1 Females: 40.2 ± 21.2 | 71 | 10–15 years | NR | 95 (93%) patients | 1: 35.8 2: 0 3: 16.8 4: 30.5 5: 16.8 | | |
| 3 | Andruszkow et al. [3] 2013, Germany 2009–2011 Retrospective | 291 sTBI patients without any addi- tional injuries | 22.5 ± 16.4 | 74 | 14 ± 3.9 years | 39 | 54 (19%) surviving patients | Mean 4.3 ± 0.8 | | |
| 4 | Azouvi et al. [4] 2016, France 2005–2009 Prospective | 504 sTBI patients participating in the Paris-TBI study | 31.7 ± 12.9 | 81 | 50.9 months ± 6.4 | NR | 85 (58%) surviv- ing patients who completed assessment at follow-up (QOLIBRI and GOS-E) | | 1: NR 3: 1.2 5: 25.9 7: 23.5 | 2: NR 4: 16.5 6: 23.5 8: 9.4 |
| 5 | Bayen et al. [7] 2017, France 2005–2009 Prospective | 504 sTBI patients participating in the Paris-TBI study divided into two groups: A (with litigation procedure) and B (without litiga- tion procedure) | A: 31.7 ± 12.9 B: 33.9 ± 15.5 | A: 81 B: 81 | 4 years | 51 | A 53 (40%) surviv- ing patients who participated in the 4-year evalu- ation B 78 (60%) surviv- ing patients who participated in the 4-year evalu- ation | | A: Mean 5 ± 1.4 B: Mean 5.7 ± 1.5 | |

Table 1 (continued)

| N | Study details* | Population** | Age*** | Male % | Follow-up# | Mortality % | Population at follow-up## | GOS % | GOS-E % |
|---|---|---|---|------------------|----------------------|-------------|---|---|--------------------------------|
| 6 | Bivona et al. [8] 2014, Italy 2010–2011 Prospective | 28 sTBI patients divided into two groups: A (with reduced self-awareness based on the awareness questionnaire (AQ) measured at least 6 months after consciousness recovery) and B (with adequate awareness) | A: 37.2 ± 13.3 ^a B: 30.6 ± 8.9 ^a | A: 86° B: 64° | 2.2 years | NR | 28 patients | A: Mean 3.9 ± 0.73 B: Mean 4.4 ± 0.76 | |
| 7 | Gouello et al. [26] 2014, France 2005–2011 Retrospective | 60 sTBI patients undergoing decompressive craniectomy divided into two groups: A 40 patients (after refractory intracranial hypertension) B 20 patients (immediately after evacuation of acute mass lesion) | A: 31.5 B: 33.5 | A: 78 B: 75 | 30.7 months 24–78 | NR | 60 patients | A: 1: 18 2: 12 3: 10 4: 35 5: 25 B: 1: 50 2: 5 3: 15 4: 10 5: 20 | |
| 8 | Honeybul et al. [36] 2013, Australia 2004–2010 Prospective | 186 sTBI patients requiring decompressive craniectomy | 33 ± 15 | NR | 5 years | 21 | 27 (15%) sTBI patients assessed as severely disabled or in vegetative state at 18 months. With these patients, a GOS-E assessment was performed at a minimum of 3 years post-injury | 1: 26 3: 33 5: 0 7: 0 | 2: 19 4: 22 6: 0 8: 0 |

Table 1 (continued)

| N | Study details* | Population** | Age*** | Male % | Follow-up# | Mortality % | Population at follow-up## | GOS % | GOS-E % |
|----|--|--|--------------------------|--------|--------------------------|-------------|---|---|---------------------------------------|
| 9 | Jaeger et al. [38] 2014, France 2007–2008 Prospective | 151 sTBI patients | 37.3 ± 19.3 | NR | 2–4 years | NR | 18 (12%) sTBI patients hospitalized in a physical medicine and rehabilitation unit | Mean 3.8 ± 1.1 | |
| 10 | Jourdan et al. [41] 2015, France 2005–2009 Prospective | 504 sTBI patients participating in the Paris-TBI study | 32.5 ± 14.2 | 80 | 50.9 months ± 6.4 | NR | 147 (29%) sTBI surviving patients who participated in the 4-year evaluation | 1: NR 2: NR 3: 31 4: 39 5: 27 | |
| 11 | Jourdan et al. [42] 2017, France 2005–2009 Prospective | 504 sTBI patients participating in the Paris-TBI study | 35.2 ± 15.3 | 82 | 31.8 months 25.6–39.9 | NR | 93 (19%) sTBI surviving patients who completed an interview at 4-year follow-up | Unfavourable GOS-E ≤ 4 Favourable GOS-E ≥ 5 | 40 60 |
| 12 | Lesimple et al. [47] 2019, France 2005–2013 Retrospective | 63 sTBI patients admitted to the ICU | 35 ± 15 | 87 | 63.4 months ± 20.7 | NR | 63 surviving patients and exclusion of patients treated by DC or a ventriculoperitoneal drain | 1: NR 2: NR 3: 7.9 4: 6.4 5: 25.4 6: 31.8 7: 20.6 8: 7.9 | |
| 13 | Morgalla et al. [57] 2008, Germany 2000–2002 Prospective | 33 sTBI patients undergoing decompressive craniectomy | 36.3 13–60 | 60 | 3 years | 21.2 | 33 patients | | |
| 14 | Ruet et al. [68] 2019, France 2005–2007 Prospective | 504 sTBI patients participating in the Paris-TBI study | 34.1 ± 13.7 ^a | 79° | 8 years | NR | 86 (17%) sTBI surviving patients | 1: NR 2: NR 3: 9.3 4: 10.5 5: 9.3 6: 37.2 7: 17.4 | |
| 15 | Stålnacke et al. [73] 2019, Sweden 2010–2011 Prospective | 37 sTBI patients participating in the multicentre ProBrain study | 49 27–70 ^a | 66° | 7 years | 24 | 21 (57%) sTBI surviving patients | Median Mean Unfavourable GOS-E ≤ 4 Favourable GOS-E ≥ 5 | 5 1–8 4.7 ± 2.8 42 58 |
| 16 | Taw et al. [78] 2018, Hong Kong 2004–2008 Retrospective | 116 sTBI patients receiving intracranial pressure monitoring | 47.8 19–82 | 66 | 42 months 12–60 | 69 | 41 (35%) patients | 1: 12.2 3: 2.4 5: 2.4 7: 14.6 | 2: 4.9 4: 9.8 6: 7.3 8: 46.4 |

Table 1 (continued)

| N | Study details* | Population** | Age*** | Male % | Follow-up# | Mortality % | Population at follow-up### | GOS % | GOS-E % |
|----|---|---|----------------------------|-----------------|-----------------------------|-------------|--|---|---|
| 17 | Ulfarsson et al. [81] 2013, Sweden 1999–2002 Retrospective | 131 sTBI patients surviving until discharge from the NICU | 37.9 16–64 | 75 | 68.0 months 30–131 | NR | 51 (39%) surviving patients | Median 5.3 Unfavourable 26 Favourable 74 | 1: 74.8 2: 58 3: 75.3 4: 66.7 5: 52.7 6: 71.5 7: 68.7 8: 71.5 9: 45.4 10: 49.3 |
| 18 | Wabl et al. [90] 2018, USA 2008–2013 Retrospective | 129 patients with severe brain injury, with 17 sTBI patients | 57 ± 22 years | 50 | Median 845 days 766–1204 | 35 | 17 patients who underwent tracheostomy, admitted to the ICU and where full patient records were available | Median 5 (3–5) | |
| 19 | Wilkins et al. [92] 2019, USA 2003–2017 Prospective | 559 sTBI patients out of the brain trauma research centre (BTRC) database who survived the acute hospital setting | 35 ± 15 years ^a | 80 ^o | 24 months | 48 | 304 (54%) patients where at each follow-up moment only the surviving patients where included for the next follow-up, until final assessment at 48 months post-injury | | 1: 8.1 2: 1.2 3: 17.3 4: 14.5 5: 14.5 6: 17.3 7: 15 8: 12.2 |
| 20 | Williams et al. [93] 2008, USA 2002–2007 Prospective | 171 sTBI patients who underwent decompressive craniectomy | Median 35 15–90 | 80 | 37 months 8–77 | 32 | 111 (65%) surviving patients | | 1: NR 2: 1 3: 2.5 4: 9 5: 12.5 6: 15.5 7: 23.5 8: 30 |

* Author, year of publication, country, inclusion period, retrospective/prospective/unknown

** Included patient population

*** Mean age in years ± standard deviation or range at the time of trauma

^a Mean age ± standard deviation or range age at follow-up^o Percentage of males at follow-up[#] Average follow-up time ± standard deviation or range^{##} Part of original population included for follow-up^{###} NR, non-retrievable

Table 2 Risk of bias QUIPS tool

| Studies | QUIPS domain | | | | | | |
|-----------------------|------------------------|--------------------|----------------------------------|------------------------|----------------------|---------------------------------------|--------------------|
| | 1. Study participation | 2. Study attrition | 3. Prognostic factor measurement | 3. Outcome measurement | 4. Study confounding | 5. Statistical analysis and reporting | Total risk of bias |
| Ahmadi et al. [1] | Moderate | High | Moderate | Low | High | Low | Moderate |
| Andersson et al. [2] | Low | Moderate | Moderate | Low | High | Low | Moderate |
| Andruszkow et al. [3] | Low | Moderate | High | Low | High | Low | Moderate |
| Azouvi et al. [4] | Low | Low | Low | Low | Low | Low | Low |
| Bayen et al. [7] | Low | Low | Moderate | Low | Moderate | Low | Low |
| Bivona et al. [8] | Low | Low | High | Low | High | Low | Moderate |
| Gouello et al. [26] | Low | Low | Low | Low | Low | Low | Low |
| Honeybul et al. [36] | Low | High | Moderate | Low | High | Low | Moderate |
| Jaeger et al. [38] | Moderate | High | Moderate | Low | High | Low | Moderate |
| Jourdan et al. [41] | High | Low | Moderate | Low | Moderate | Low | Moderate |
| Jourdan et al. [42] | Low | High | Moderate | Low | Low | Low | Moderate |
| Lesimple et al. [47] | Moderate | Low | Moderate | Moderate | High | Low | Moderate |
| Morgalla et al. [57] | Low | High | High | Moderate | High | High | High |
| Ruet et al. [68] | Low | Low | Low | Low | Moderate | Low | Low |
| Stålnacke et al. [73] | Low | High | Moderate | Low | High | Low | Moderate |
| Taw et al. [78] | Low | Low | Moderate | Low | Moderate | Low | Low |
| Ulfarsson et al. [81] | Low | Low | Moderate | Low | Moderate | Low | Low |
| Wabl et al. [90] | Low | High | Low | Low | Moderate | Low | Moderate |
| Wilkins et al. [92] | High | Moderate | Moderate | Low | Moderate | Low | Moderate |
| Williams et al. [93] | Moderate | High | High | Low | High | High | High |

One study reported a FIM score of 87.4, which is below the threshold score of ≤ 108 that indicates limitations in activities of daily living (ADL) and need for assistance from another person [38].

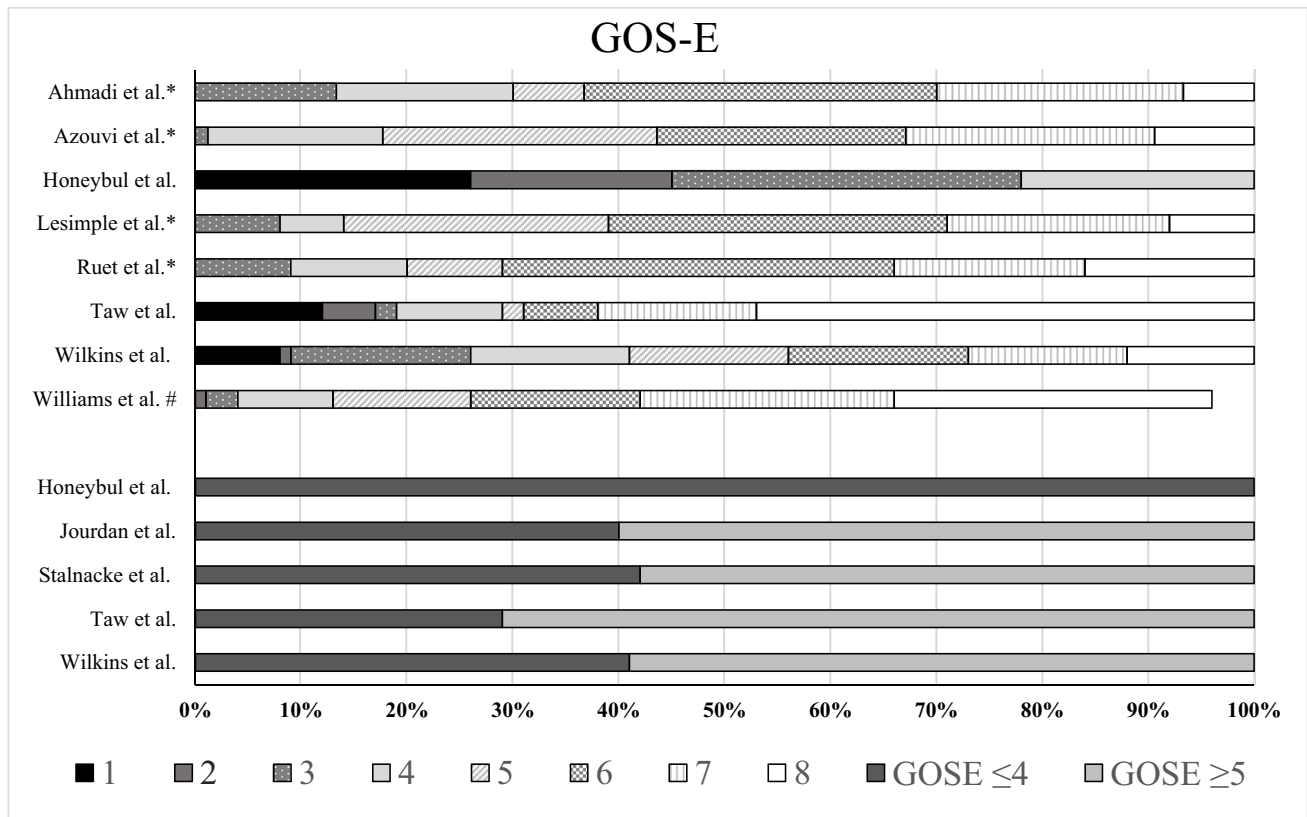
Temporal changes

Five of the included articles mentioned temporal outcome changes after sTBI [42, 73, 78, 90, 92]. The first study reported that favourable changes were more common than late loss of capacities between the first and fourth year post-injury [42]. Two studies reported an improvement in GOS-E score at follow-up, namely, an improvement in favourable outcome from 29% at 3 months to 59% at 2 years [92] and a good recovery increasing from 42 to 61%

respectively at 42 months [78]. One study found no significant improvement from 1 to 7 years in the mean GOS-E score [73]. The last study described a mean GOS score of 3 at 1 to 3 months post-injury and a score of 5 at 24 to 36 months post-injury [90].

Discussion

This systematic literature review found that data on long-term outcome after sTBI was limited and heterogenous. Although studies reported expected high mortality and ‘unfavourable’ outcome rates, a considerable number of patients achieved and maintained long-term ‘favourable’ outcome ≥ 2 years after sustaining sTBI.



GOS-E:

- | | |
|------------------------------|------------------------------|
| 1. Deceased | 2. Vegetative state |
| 3. Lower severe disability | 4. Upper severe disability |
| 5. Lower moderate disability | 6. Upper moderate disability |
| 7. Lower good recovery | 8. Upper good recovery |
| ≤4 Unfavourable outcome | ≥5 Favourable outcome |

* GOS-E 1 and 2 scores were not reported

GOS-E 1 score was not reported

Fig. 2 Glasgow Outcome Scale—Extended (GOS-E)

Long-term mortality rates based on reported mortality and GOS(E) scores of 1 (range 18–75%) were rather similar to previously reported short-term mortality rates after sTBI (range 24–37%) [16, 53, 65]. Although comparison between these results has several limitations, the relatively small difference between short and long-term mortality implies that early or in-hospital mortality accounts for the majority of deaths following sTBI. Additional post-discharge mortality is believed to be partly caused by sequelae and comorbidities attributable to the sustained brain injury, such as depression, cognitive impairment, substance misuse and physical disabilities [6, 23, 60]. In line with this, increased mortality rates for at least 10 to 13 years after sTBI have been reported [45, 55, 82], resulting in a reduced life expectancy of up to 7 years [31]. Initial worse neurological condition, low GOS(-E) scores, bilaterally fixed and dilated pupils, poor outcome at 1-year follow-up and high age, although

not unambiguously, were associated with higher long-term mortality rates [19, 52, 62]. Exact reasons for the increased long-term mortality are however still unknown and deserve further investigation [31, 55, 82]. Specifically, more detailed knowledge on the temporal pattern of outcome development after sTBI would be valuable for clinical decision-making.

In this regard, it is important to acknowledge that patients not only survived, but were also able to achieve so-called GOS(E) defined long-term ‘favourable outcome’ and even full recovery after sTBI [18, 20]. Despite the limitations of its definition, in cases where so-called ‘favourable outcome’ can be achieved, it seems proportional to initiate acute treatment. In case of likely ‘unfavourable outcome’, initiating or continuing treatment might be judged disproportional. As prediction of individual outcome is still inaccurate, and achieving ‘favourable outcome’ not impossible, withdrawal of acute treatment in these patients seems immoral [84]. To

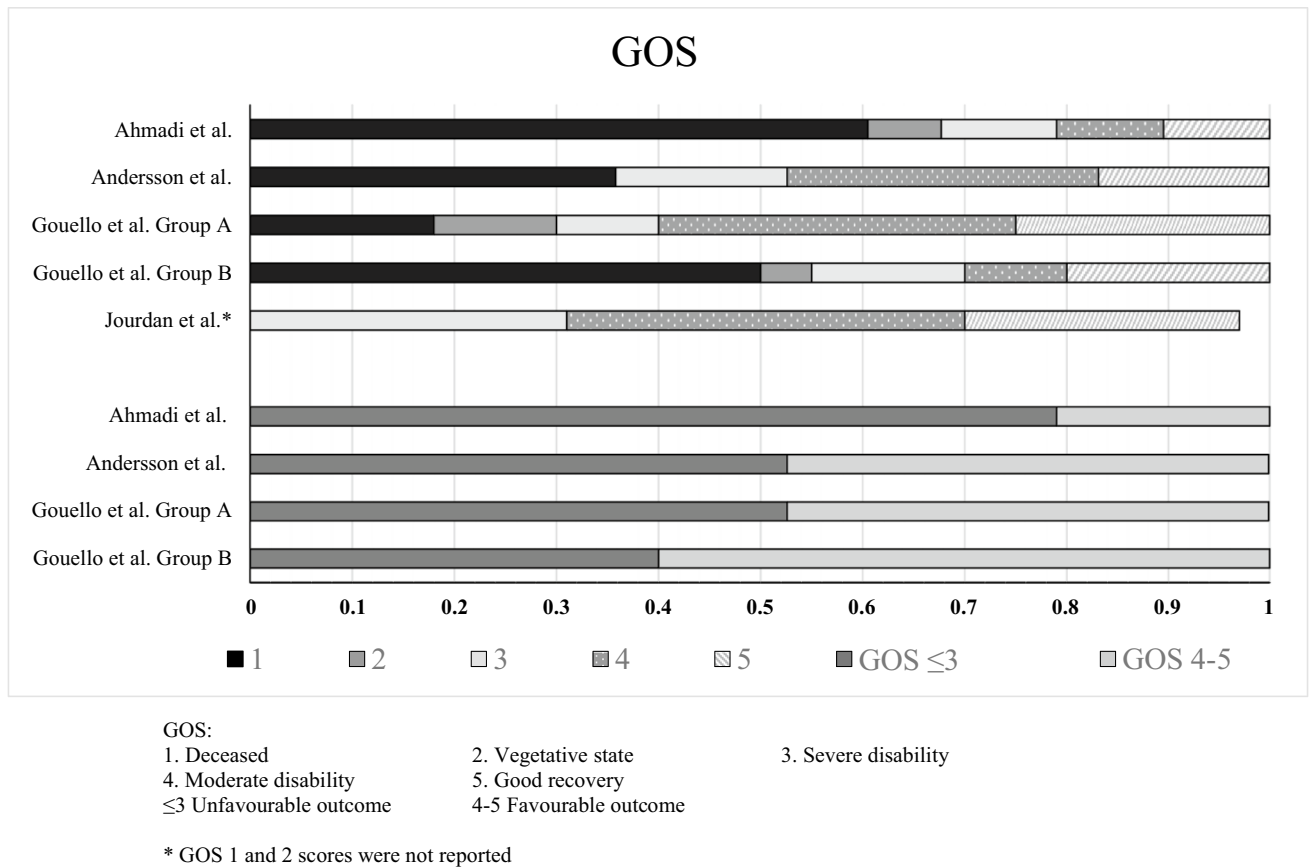


Fig. 3 Glasgow Outcome Scale (GOS)

Table 3 SF-36 score

| Patient population SF-36 score | Study | | | |
|-----------------------------------|---|---|--|----------------------------------|
| | Ahmadi et al. [1] 30 patients with GOS score ≥ 3 completed the SF-36 questionnaire at a mean of 49 months post-injury | Honeybul et al. [36] 27 sTBI patients assessed as severely disabled or in vegetative state at 18 months and then completed the SF-36 questionnaire at a minimum of 36 months post-injury | Ulfarsson et al. [81] 51 surviving patients assessed at a mean of 69 months post-injury | Mean population-based score [37] |
| 1. Physical functioning | 81.0 | 25 | 74.8 | 85.8 |
| 2. Role physical | 67.5 | 36 | 58 | 82.1 |
| 3. Bodily pain | 68.3 | 48 | 75.3 | 75.6 |
| 4. General health perceptions | 74.8 | 46 | 66.7 | 77.0 |
| 5. Energy/vitality | 82.2 | 49 | 52.7 | 65.8 |
| 6. Social functioning | 59.3 | 36 | 71.5 | 86.2 |
| 7. Role emotional | 83.8 | 32 | 68.7 | 84.0 |
| 8. Mental health | 68.9 | 47 | 71.5 | 77.5 |
| 9. Physical component scale | 48.0 | 33 | 45.4 | 50.5 |
| 10. Mental component scale | 49.3 | 46 | 49.3 | 51.7 |

improve outcome prediction in the acute phase after sTBI, future studies should aim to include patient data from the time of injury onwards.

In addition to mortality and functional outcome (GOS/GOS-E), there are many subtleties to the well-being of patients that require attention. Consistent with recent literature and SF-36 scores in this review, many long-term sTBI survivors suffered from multidimensional impairments on physical, cognitive and mental domains [21, 63, 66, 71, 76, 80]. Other outcome measures in this review, such as FIM and HADS scores, demonstrated lasting limitations in daily activities, depression, anxiety, headaches and high unemployment rates among long-term sTBI survivors. Also, sTBI survivors seemed more likely to be single or live alone, which may be linked to social isolation as a result of these impairments [25, 69]. The reported scores on the QOLIBRI and the Barthel index in this review were relatively, perhaps surprisingly, favourable. It should be noted, however, that three out of four studies reporting these outcomes included patients with relatively better clinical characteristics within the sTBI population [1, 4, 38].

The results of this review support the growing evidence that sTBI should be regarded as a chronic disease with common long-term sequelae on the physical, mental and social domain causing additional delayed morbidity and perhaps even mortality [76]. Long-term changes in patients' (dis)abilities have been described up to 14 years following sTBI. Both improvement (23%) and worsening (32%) have been reported [54]. Five studies included in this review assessed the temporal development of outcome after sTBI. It was however difficult to draw generic conclusions from these studies due to their retrospective nature, mostly small sample sizes and the heterogeneity of included patient cohorts.

Factors associated with worse long-term outcome were lower GOS(-E) scores at discharge or short-term follow-up, increased intensive care length of stay and older age. Although the precise impact of these factors could not be established in this review, most associations were also reported in literature on short-term outcome after TBI and thus seem to remain important in the long term [19, 30, 46, 52, 62]. This points out the need to support these patients by providing specialized rehabilitation or personalized chronic care for many years after the injury aiming to improve long-term life expectancy and quality of life [10, 17, 56, 95]. Recent publications have indeed reported that extended multidisciplinary rehabilitation programs and chronic care programs could improve sTBI patient outcomes [22, 44, 51, 64].

Additionally, currently available guidelines for the management of severe traumatic brain injury are based on evidence from 69 randomized controlled trials [13] of which only one (1.4%) used a follow-up period of more than 2 years. The results of this study emphasize the need for including multi-modality standardized long-term outcomes

in future sTBI studies to capture the impact of TBI on all relevant domains of life and strengthen the evidence base for both acute and chronic treatment decisions.

Strengths and limitations

Strict inclusion criteria resulted in a broad overview of available literature on long-term outcome after sTBI, while reducing heterogeneity and maintaining comparability between studies. By following the PRISMA recommendations and by assessing study quality with the QUIPS tool, we aimed to improve the quality of this systematic review.

There were several limitations. First, only PubMed was searched and the strict selection criteria could have resulted in missed studies. Not including non-standardized or rarely used outcome measures was expedient, but resulted in loss of information. This is especially problematic for outcomes such as 'return to work', which are very important for younger patients sustaining sTBI [27, 28]. Also, studies published before 2008, after two important guideline updates, were not included [5, 12]. This improved generalizability of results in a modern-day healthcare setting, but might have excluded older potentially relevant long-term outcome studies. Third, five included studies were based on patients from the Paris-TBI study [4, 7, 41, 42, 68]. These studies used different inclusion criteria as well as different outcome measures which minimized the implications of potential overlap, but did not eliminate this. Including these studies may thus have resulted in overrepresentation of a specific cohort and thereby hamper generalizability of the results. Not including these studies, however, would have resulted in disproportional loss of substantial relevant information. Fourth, we were dependent on the methodological quality and heterogeneity of the included studies. For example, many studies only included patients surviving the acute phase, which is likely to have resulted in biased outcome estimates. This only allowed us to analyse outcome using descriptive statistics instead of conducting a meta-analysis. Lastly, reported weighted mean percentage of outcomes of all studies aimed to provide a more general overview of collected data, but has its limitations and should be interpreted with caution.

Conclusions

Mortality and unfavourable outcome rates ≥ 2 years after sTBI are high, but a considerable number of sTBI patients also achieve long-term 'favourable' outcome or even a full recovery. Nonetheless, many surviving sTBI patients sustain substantial quality of life impacting long-term impairments that might benefit from specialized rehabilitation or chronic care. Future studies on sTBI should include long-term follow-up with standardized multi-modality outcomes

measures to strengthen the evidence base for both acute and chronic treatment decisions.

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Declarations

Conflict of interest WP reports to be part of the management team of CENTER-TBI study and to be the principal investigator of the Net-QuRe, Ciao@TBI, RESET-ASDH and the SPARTA trials. Other authors report no conflicts of interest.

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