Functional outcome, dependency and well-being after traumatic brain injury in the elderly population: A systematic review and meta-analysis

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ABSTRACT

Introduction: Traumatic brain injury (TBI) rates in the elderly are increasing worldwide, mainly due to fall accidents. However, TBI's impact on elderly patients' lives has not been thoroughly investigated.

Research question: This systematic review and meta-analysis aims at describing post-TBI incidence of functional decline, dependency, nursing home admission, reduced quality of life and depression in the elderly.

Materials and methods: A systematic literature search was performed in PubMed, EMBASE, Web Of Science, BIOSIS, Current Contents Connect, Data Citation Index, MEDLINE, Scielo, Cochrane library and CINAHL. Study selection was conducted by two independent reviewers. Meta-analysis was performed using a random-effects model.

Results: Twenty-seven studies were included in the qualitative synthesis and twenty-five in a random-effects meta-analysis. The prevalence of unfavorable functional outcomes after TBI was 65.2% (95% CI: 51.1–78.0). Admission to a nursing home had a pooled prevalence of 28.5% (95% CI: 17.1–41.6) and dependency rates ranged between 16.9% and 74.0%. A reduced quality of life was documented throughout follow-up with SF12/36 scores between 35.3 and 52.3/100.2.6–4.8% of the patients with mild TBI reported depressive symptoms. A large heterogeneity was found among studies for functional outcomes and discharge destination.

Discussion and conclusion: In conclusion, elderly patients have a significant risk for functional decline, dependency, nursing home admission and low quality of life following TBI. Moreover, more severe injuries lead to worse outcomes. These findings are important to provide accurate patient and family counseling, set realistic treatment targets and aim at relevant outcome variables in prognostic models for TBI in elderly patients.

1. Background

Traumatic brain injury (TBI) is defined as a physical and/or functional injury to the brain caused by an external force (Menon et al., 2010) and its incidence amongst elderly patients has been increasing in the last decades (Mosenthal et al., 2002; Steyerberg et al., 2019; Peeters et al., 2015). Most elderly cases of TBI are classified as mild TBI (Styrke et al., 2007), following the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). However, the term “mild TBI” could be a misnomer, as these patients are particularly at risk for injuries with delayed mass effect and secondary deterioration (Hofman et al., 2001; Stell et al., 2001; Hayden et al., 2009).

Elderly patients, conventionally defined as patients with a chronological age ≥65 years old in most TBI studies (Hawley et al., 2017; Choi et al., 2019; Rue et al., 2015; Susman et al., 2002; Mosenthal et al., 2004; Julien et al., 2017; Deb et al., 1998; Akbik et al., 2019; Erlebach et al., 2017; Haller et al., 2017; Wan et al., 2016; Brazinova et al., 2010), are at risk for a worse recovery after TBI (Mosenthal et al., 2002, 2004; Yu and Richmond, 2005; Thompson et al., 2012; Whitehouse et al., 2016; van Aalst et al., 1991). Poor premorbid condition, neurological sequelae and overall deconditioning lead to an increased risk for psychosocial changes (Rapoport and Feinstein, 2001), disability (Gardner et al., 2018) and secondary medical complications (Thompson et al., 2006).

The primary goal of medical management in TBI is to safeguard the patient's Quality of Life (QoL) (Scibert et al., 2002), which can be affected by TBI long after the initial medical treatment phase (Susman et al., 2002; de Guise et al., 2015). However, the lifelong impact of TBI on elderly patients' wellbeing remains a relatively neglected area in the field of TBI-related research to date (Gaastra et al., 2016).

Better insight into this matter may help (1) clinicians to set realistic treatment targets, (2) patients and families to gain understanding by...
improved counseling, and (3) researchers to underpin most relevant outcome determinants in the development of prognostic models for this population. We hypothesize that TBI in elderly patients is associated with a high likelihood of significant functional decline, which easily leads to dependency, and in turn is associated with reduced QoL and depression in this age group (Yu and Richmond, 2005; Rapoport and Feinstein, 2001; Gardner et al., 2018; Albrecht et al., 2015).

Therefore, the main objective of the current study is to document risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression and poor QoL in the elderly population.

2. Methods

2.1. Study registration

The protocol for this systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number [CRD42020212288]) and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) 2020 statement (Page et al., 2021) [Fig. 1] and the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019).

2.2. Search strategy and study selection

The systematic search was performed in October 2020 in PubMed, EMBASE, Web Of Science (WOS) Core Collection, BIOSIS Citation Index, Current Contents Connect, Data Citation Index, MEDLINE, SciELO Citation Index, the Cochrane Central Register of Controlled Trials and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Language was restricted to English. There was no restriction on publication date. The used MESH (Medical Subject Headings) terms were “Aged”, “Geriatrics”, “gerontology”, “Nursing Homes”, “Health Services for the Aged”, “Homes for the Aged”, “Housing for the Elderly”, “Brain Injuries, Traumatic”, “qualitative research” and ‘Case-Control Studies’.

Studies’ inclusion was limited to clinical, multi-center, case-control or qualitative studies; performed in hospitals, rehabilitation centers and health care facilities for the elderly; including ≥15 patients who sustained a TBI at ≥65 years (as a subset of a broader cohort or as an independent cohort of elderly patients); using one of the assessment instruments included in Appendix A or reporting nursing home admission rates. Studies were excluded if they included patients with a different pre-existing neurological condition or previous alcohol/drugs abuse or did not specifically associate outcomes to the TBI severity (given by the GCS).

Fig. 1. Prisma flow diagram.
2.3. Data extraction and analysis

First, references obtained from the systematic search were entered and deduplicated into EndNote X9 (Clarivate Analytics, Philadelphia). Second, titles and abstracts were screened for concordance with the inclusion and exclusion criteria using Rayyan QCRI software. Full texts of selected studies were then reviewed for final inclusion. The selection process was performed independently by two researchers blinded from each other. Disagreement in results was resolved through mutual discussion. When necessary, a third reviewer was consulted for arbitration. Data extraction was performed using a standardized data collection form, including the first author’s name, publication year, study design, sample size and number of dropouts, TBI injury severity, brain damage location, age of participants, sex of participants, number of months between TBI and assessment, metrics used and outcomes. In case of incomplete or ambiguous data, the corresponding author was contacted via e-mail. All included studies were subjected to descriptive analyses. For studies including a ≥16 years old cohort, only the results of the subset of patients ≥65 years were taken into account.

2.4. Quality assessment

The methodological quality of the studies was assessed using the Downs and Black Scale (Downs and Black, 1998) [Appendix B] and classified as excellent (26–27), good (20–25), fair (15–19) and poor (<14).

2.5. Statistical analysis

Two random-effects meta-analyses were conducted using tidyverse, meta and metafor packages in R 4.1.0, using the inverse variance weighted average method (IVW) (Lee et al., 2016), in order to calculate combined prevalences. The DerSimonian and Laird method was used to obtain Tau² (DerSimonian and Laird, 1986) and the Freeman-Turkey double arcsine transformation method to calculate combined prevalences (Freeman and Tukey, 1950). Clopper-Pearson confidence intervals for individual studies were reported (CLOPPER and PEARSON, 1934). Heterogeneity was quantified using I² and interpreted as low (0%–30%), moderate (30%–50%), substantial (50%–80%) and considerable (80%–100%) (Cochrane Handbook, 2021). Publication bias was assessed using funnel plots of the combined prevalences.

3. Results

The database search retrieved a total of 14,407 citations. 11,229 articles were screened by title and abstract and 1974 full-text articles were assessed for eligibility, of which 27 articles were included in the qualitative synthesis [Fig. 1 and Tables 1–5] and 25 were meta-analyzed. 40.7% of the included studies had a poor quality and 59.3% a fair quality [Appendix B].

3.1. Demographic and study characteristics

The included studies were retrospective or prospective observational studies performed in single or multi-center settings, or based on regional or national databases. The number of included patients ranged between 29 and 36,288. Follow-up duration across studies ranged from hospital discharge to 4 years post-TBI [Tables 1–5].

3.2. Functional outcome

Functional outcome was assessed using the Glasgow Outcome Score (GOS) and the Extended Glasgow Outcome Score (GOS-E) in 15 studies [Table 1], of which 14 could be meta-analyzed [Figs. 2 and 3].

GOS is scored following a scale where 1 corresponds to death, 2 to vegetative state, 3 to severe disability, 4 to moderate disability and 5 to good recovery (Jennett and Bond, 1975). GOS-E is scored as: 1 (death), 2 (vegetative state), 3 (lower severe disability), 4 (upper severe disability), 5 (lower moderate disability), 6 (upper moderate disability), 7 (lower good recovery) to 8 (upper good recovery) (Wilson et al., 1998). GOS 1–3 and GOS-E 1–4 are considered as unfavorable outcomes. Results are visualized in Fig. 4.

The pooled prevalence of unfavorable outcomes was 65.2% (95% CI: 51.1–78.0) at 12 months post TBI in mild, moderate and severe TBI patients. A significant heterogeneity between studies was found (I² = 97%, p < 0.01) [Figs. 2 and 3] and the asymmetric funnel plot indicates publication bias [Fig. 3].

In patients with mild TBI, 45.8% had unfavorable outcomes at hospital discharge, including 16.5% who died (Julien et al., 2017). Rates of good recovery at discharge after mild TBI varied between 2.4 and 71.0% (Hawley et al., 2017; Mosenthal et al., 2004; Julien et al., 2017). At 6 months post mild TBI, rates of unfavorable outcomes between 6.2 and 20% were reported (Choi et al., 2019; Mohindra et al., 2004), while these were of 2.5% at 1 year (Deb et al., 1998).

For moderate TBI, at 6 months FU, 53.3–85.7% had unfavorable outcomes (Choi et al., 2019; Mohindra et al., 2008), and for moderate and severe TBI combined the 6 months unfavorable outcome rate reportedly was 80.0% (Eblebach et al., 2017).

For patients who sustained severe TBI, outcomes were unfavorable in 79.3% at hospital discharge (Won et al., 2017), 41.8–89.9% 3–6 months post TBI (Choi et al., 2019; Wan et al., 2016; Tokutomi et al., 2008) and 72.2–89.0% 1 year post-TBI (Roe et al., 2015; Brazinova et al., 2010).

Differences regarding recovery in patients with mild TBI were observed across studies performed in different regions. While Mohindra et al. (2008) and Julien et al. (2017) reported very low or unexisting “good recovery” rates in India and Canada, respectively, higher recovery rates were reported by Hawley et al. (2017), Choi et al. (2019) and Mosenthal et al. (2004) in the United Kingdom (UK), Korea and United States (US).

3.3. Activities of daily living (ADL) dependency and social integration

ADL dependency was assessed in 8 studies using the Functional Independence Measure (FIM), Older Americans’ Resources and Services scale (OARS) (Milligan et al., 1988), the Community Integration Questionnaire (CIQ) (Willer et al., 1994) and non-standardized evaluations [Tables 2 and 3].

FIM is an 18-item functional assessment scale containing a motor and cognitive domain. Motor scores range between 13 (lowest) and 91 (highest level of independence), cognitive scores between 5 (lowest) and 126 (highest level of independence) (Linacre et al., 1994).

OARS is a 28-point questionnaire which assesses different ADL activities, scored on a 0–2 scale. Scores range between 0 (complete dependency) and 28 (complete independency) (Milligan et al., 1988).

The CIQ is a 15-item questionnaire which assesses home integration, social integration and productive activity. Total scores range from 0 (low integration) to 29 points (high integration), with a maximum score of 10 points for home integration, 12 points for social interaction and 7 points for productive activity (Willer et al., 1994).

In patients with mild TBI, at hospital discharge, a dependency rate of 38.6% was registered (Mosenthal et al., 2004). At 6 months follow-up, Brousseau et al. (2017) found a functional decline in 7.0% of the patients, defined as a reduction of 3 points on the OARS scale from their emergency department visit to FU, while on the other hand Mosenthal et al. (2004) showed an improvement in FIM scores in 20.5% of the patients at 6 months post mild TBI. At 1 year follow-up, 65–74 year-old patients had an average of 1.3 ADL difficulties and 75–84 year-old patients an average of 2.2 ADL difficulties (Thompson et al., 2012).

Considering patients with mild and moderate TBI, Miller et al. (2017) found that at hospital discharge 24.0% of the patients 70–79 years old, 33.0% of the patients 80–89 years old and 39.0% of the patients ≥90 years old were dependent.

For patients with moderate and severe TBI, at hospital discharge...
In patients with mild TBI, 5.8%–34.2% were discharged to a nursing home (Thompson et al., 2012; Schmidt et al., 2019; Velez et al., 2020; Khan et al., 2017) and 35.0% continued residence beyond one year of injury (Thompson et al., 2012; Schmidt et al., 2019; Velez et al., 2020; Khan et al., 2017).

Considering patients with mild and moderate TBI, Miller et al. (2017) found that 24.0% of the 70–79 years-old, 33.0% of the 80–89 years-old and 39.0% of the ≥85 years-old were discharged to a nursing home (Miller et al., 2017).

Rates of nursing homes discharge ranged between 28.3 and 54.0% in studies considering both moderate and severe TBI (Susman et al., 2002; Gorman et al., 2020). In patients with severe TBI, this rate was 67.8% at 4 years FU, 74.0% of the patients were discharged to an institution (Miller et al., 2017).

### Table 1
Summary of studies which assessed functional outcomes using GOS and GOS-E.

| Study (year) | TBI severity (given by GCS) | ISS | Type of study | Study settings | Country | N ≥ 65 years old | LOS (days) |
|--------------|-----------------------------|-----|---------------|----------------|---------|------------------|------------|
| Hawley et al. (2017) (Hawley et al., 2017) | All | NR | Retrospective | National database | UK | 575 (439 mild TBI and 136 moderate or severe TBI) | 65–74 years old: median (IQR)=11(15) 75–84 years old: median (IQR)=14(25) ≥85 years old: median (IQR)=16(23) |
| Mohindra et al. (2008) (Mohindra et al., 2008) | All | NR | Retrospective | Hospital | India | 45 ≥70 years old (5 mild TBI, 7 moderate TBI and 33 severe TBI) | NR |
| Choi et al. (2019) (Choi et al., 2019) | All | 21 patients minor (1–8); 53 moderate (9–15); 56 severe (16–24); 40 severely impaired (≥25) | Retrospective | Republic of Korea | NR | 170 (129 mild TBI, 15 moderate TBI and 26 severe TBI) | NR |
| Mosenthal et al. (2004) (Mosenthal et al., 2004) | Mild | NR | Retrospective | Multi-center | US | 44 | NR |
| Julien et al. (2017) (Julien et al., 2017) | Mild | Median–25 (results only reported for 952 patients) | Retrospective | Hospital | Canada | 982 | Median (IQR)=11 (17) |
| Deb et al. (1998) (Deb et al., 1998) | Mild | NR | Retrospective | Hospital | UK | 40 | NR |
| Abikh et al. (2019) (Abikh et al., 2019) | Moderate and severe | NR | Retrospective | Level I trauma center | US | 62 (31 GCS >9 and 31 GCS≤9) | Median−9 |
| Irlebach et al. (2017) (Irlebach et al., 2017) | Moderate and severe | Median (IQR)=20 (11) | Retrospective | Hospital | Switzerland | 50 | 9.2±8.5 (in ICU) |
| Gritt et al. (2019) (Gritt et al., 2019) | Moderate and severe | NR | Retrospective | Hospital | Italy | 38 ≥70 years old | NR |
| Won et al. (2017) (Won et al., 2017) | Severe | NR | Retrospective | Single center | Germany | 29 ≥80 years old | 9.1±6.2 |
| Tokutomi et al. (2008) (Tokutomi et al., 2008) | Severe | Mean (SD)= 26 (9) | Retrospective | National database | Japan | 189–70 years old | NR |
| Haller et al. (2017) (Haller et al., 2017) | Severe | Median (IQR)=25 (12) | Prospective observational | Multi-center | Switzerland | 97 | NR |
| Wan et al. (2016) (Wan et al., 2016) | Severe | NR | Retrospective | Hospital | China | 328 | NR |
| Brazinova et al. (2010) (Brazinova et al., 2010) | Severe | Median–20 | Prospective observational | Multi-center | Austria, Bonnia and Herzegovina, Croatia, Macedonia, and Slovakia | 100 | NR |
| Rue et al. (2015) (Rue et al., 2015) | Severe | NR | Prospective observational | Multi-center | Norway | 97 (46 patients 65–74 years old and 51 ≥71 years old) | NR |

N=number; GCS=Glasgow Coma Scale; All=Mild, moderate and severe TBI; ISS=Injury Severity Score; NR=not reported; LOS=length of hospital stay due to TBI; CVA=cerebrovascular accident; Severe disability=GOS of 3 or GOS-E of 3 or 4; Moderate disability=GOS of 4 or GOS-E of 5 or 6; Good recovery=GOS of 5 or GOS-E of 7 or 8; UK=United Kingdom; US=United States of America.

Susman et al. reported dependency rates of 35.8%, 16.9% and 33.6%, for motor function, expression and feeding, respectively (Susman et al., 2002). For severe TBI cases, Lilley et al. found that 67.8% of the patients were dependent for one or more ADL activities at hospital discharge (Lilley et al., 2016). At 2–4 years FU, 74.0% of the patients were dependent for mobility, of which 49.3% needed help for transfers and 41.9% needed help for climbing stairs, and 73.0% were dependent for self-care (Lecours et al., 2012).

### 3.4. Discharge destination

Discharge destination from hospital discharge to 4 years post TBI was reported in 12 articles [Table 4].
were reported by Khan et al. (2017), Velez et al. (2020) and Thompson et al. (2012) in the US, which were higher than the rate reported by Schmidt et al. (2019) in Switzerland. No similarities were found in studies conducted in the US for patients with moderate and severe TBI (Thompson et al., 2012; Gorman et al., 2020; Bhullar et al., 2010).

A high heterogeneity between studies was found in the 12 meta-

| Comorbidities                                    | Pre-injury anticoagulation (%) | Time post-TBI (months) | Outcome | Persistent vegetative state (%) | Severe disability (%) | Moderate disability (%) | Good recovery (%) |
|--------------------------------------------------|--------------------------------|------------------------|---------|---------------------------------|-----------------------|------------------------|-------------------|
| NR                                               | NR                             | Hospital discharge     | 143 (24.9%) patients: 35 patients 65–74 years old, 46 75–84 years old and 62 ≥85 years old. 80 of them had a moderate or severe TBI. | 29 (5.0%) patients: 11 patients 65–74 years old and 5 ≥85 years old. 14 of them had a moderate or severe TBI. | 79 (13.7%) patients: 27 patients 65–74 years old, 33 75–84 years old and 19 ≥85 years old. 10 of them had a moderate or severe TBI. | 358 (62.3%) patients: 127 patients 65–74 years old, 130 75–84 years old and 101 ≥85 years old. 32 of them had a moderate or severe TBI and 306 had a mild TBI. |
| NR                                               | NR                             | 6                      | 5 (71.4%) patients with moderate TBI and 24 (72.7%) of the patients with severe TBI. 8 (6.2%) patients with mild TBI, 8 (53.3%) with moderate TBI and 23 (88.5%) with severe TBI. | 1 (14.3%) patients with moderate TBI and 8 (24.2%) of the patients with severe TBI. 118 (91.5%) patients with mild TBI, 10 (66.7%) with moderate TBI and 3 (11.5%) with severe TBI. | 4(80.0%) patients with mild TBI, 1 (14.3%) of the patients with moderate TBI and 1 (3.0%) patient with severe TBI. |
| NR                                               | NR                             | 6                      | Unknown | Unknown | Unknown | Unknown | 13 (29.5%) |
| NR                                               | 439 (44.7%)                    | Hospital discharge     | 162 (16.5%) | 31 (3.2%) | 256 (26.1%) | 508 (51.7%) | 24 (2.4%) |
| NR                                               | 37 patients hypertension, 10 atrial fibrillation, 12 diabetes, 14 coronary artery disease, 8 CVA, 6 neoplastic process, 7 dementia | 1 patient stroke, 5 TBI, 1 epilepsy, 10 diabetes, 35 cardiovascular diseases, 4 psychiatric disorder and 8 alcohol/drug abuse | 27 | 6 | 40 (80.0%) | 10 (20.0%) |
| NR                                               | 35 patients hypertension, 27 hypertension | 15 patients diabetes and 27 hypertension | 35 | 12 | 15 (39.5%) | 1(2.6%) | 8 (21.0%) | 7(18.4%) | 7(18.4%) |
| NR                                               | 51 patients hypertension, 30 atrial fibrillation, 26 type 2 diabetes, 44 cardiovascular diseases, 20 respiratory insufficiency, 14 renal failure, 8 hematological disease, 51 metabolic disease, 8 previous stroke, 34 pneumonia, 3 sepsis | 59 patients hypertension, 30 atrial fibrillation, 26 type 2 diabetes, 44 cardiovascular diseases, 20 respiratory insufficiency, 14 renal failure, 8 hematological disease, 51 metabolic disease, 8 previous stroke, 34 pneumonia, 3 sepsis | 23 (79.3%) | 6 | 20 (67.2%) | 6 (20.7%) |
| NR                                               | 26 patients psychiatric disorders and 16 alcohol abuse | 52.4% of the cases | 60 (18.3%) | 77 (23.5%) | 35 (10.7%) | 11 (11.0%) |
| NR                                               | 51 patients                   | Present in 35 patients 65–74 years old and 45 patients ≥75 years old | 60 (18.3%) | 77 (23.5%) | 35 (10.7%) | 11 (11.0%) |
| NR                                               | 12 patients 65–74 years old and 21 patients 65–74 years old and 27 patients ≥75 years old | Present in 35 patients 65–74 years old and 45 patients ≥75 years old | 60 (18.3%) | 77 (23.5%) | 35 (10.7%) | 11 (11.0%) |
| NR                                               | 12 patients 65–74 years old and 21 patients 65–74 years old and 27 patients ≥75 years old | Present in 35 patients 65–74 years old and 45 patients ≥75 years old | 60 (18.3%) | 77 (23.5%) | 35 (10.7%) | 11 (11.0%) |
| NR                                               | 6 patients 65–74 years old and 21 patients 65–74 years old and 27 patients ≥75 years old | Present in 35 patients 65–74 years old and 45 patients ≥75 years old | 60 (18.3%) | 77 (23.5%) | 35 (10.7%) | 11 (11.0%) |
Table 2

Summary of studies which assessed ADL dependency after TBI using FIM.

| ISS Type of study | Study setting | Country | N | LOS (days) | Time post-TBI (months) | Outcomes | FIM motor (mean) | FIM cognition (mean) | FIM total | FIM locomotion | FIM expression | FIM feeding | FIM discharged |
|-------------------|---------------|---------|---|------------|------------------------|----------|-----------------|-------------------|-----------|----------------|--------------|-------------|---------------|
| /C21              | Multiple center | US     | 3244 | NR         | NR                     | Hospital discharge | 11.6 (SD 6.1) | 40.5 (SD 9.5) | 5.4 (SD 1.7) | 27 (61.4%) | 6.8%          | 11.6 (SD 6.1) | 11.6 (SD 6.1) | 27 (61.4%) |
| /C6               | Retrospective observational study | Canada | 95 (44 patients) | 42–48 | 4.8 (SD 1.5) | NR | NR | 5.4 (SD 1.7) | 27 (61.4%) | 6.8% | 11.6 (SD 6.1) | 11.6 (SD 6.1) | 27 (61.4%) |
| /C21              | Multiple center | US     | 3244 | NR         | NR                     | Hospital discharge | 11.6 (SD 6.1) | 40.5 (SD 9.5) | 5.4 (SD 1.7) | 27 (61.4%) | 6.8%          | 11.6 (SD 6.1) | 11.6 (SD 6.1) | 27 (61.4%) |

Note: ISS = Injury Severity Score; NR = Not reported; LOS = Length of hospital stay due to TBI; US = United States of America.

3.5. QoL

QoL was assessed using the 12-Item Short Form Survey (SF-12) (Ware et al., 1996), 36-Item Short Form Survey (SF-36) (Ware and Sherbourne, 1992) and Six-dimensional health state short form (SF-6D) (Ferreira et al., 2013) in 3 studies (Table 5 and Fig. 7).

SF-12 (Ware et al., 1996) and SF-36 (Ware and Sherbourne, 1992) assess the impact of health on patients’ everyday life on a scale ranging between 0 (low QoL) and 100 (high QoL). Both questionnaires contain a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (Ware et al., 1996; Ware and Sherbourne, 1992). The average reported population score is 50 (Huo et al., 2018; Maglinte et al., 2012). SF-6D evaluates role participation, social functioning, bodily pain, mental health and vitality (Ferreira et al., 2013). Scores range between 0.0 (worst health state) to 1.0 (best health state) (Ferreira et al., 2013).

In patients with mild TBI, Kinsella et al. reported an average PCS score of 36.7 (Kinsella et al., 2014), and average MCS of 52.1 at 6 months follow-up (Kinsella et al., 2014). At 12 months, Thompson et al. reported PCS SF-12 scores of 39.5 for the 65–74 year old patients and 35.3 for the 75–84 year olds (Thompson et al., 2012), while average MCS scores were 51.7 for the 65–74 year old patients and 48.2 for the 75–84 year olds (Thompson et al., 2012).

In severe TBI cases, Haller et al. found a mean SF-12 PCS score of 39.2 and a mean MCS score of 52.3 at 3 months, a mean PCS score of 42.3 and mean MCS score of 51.2 at 6 months, and a mean PCS score of 44.2 and mean MCS score of 52.3 at 12 months (Haller et al., 2017).

3.6. Depression

One study retrospectively studied depression 1 year post mild TBI in 309 patients ≥65 years old from a national database in US (Thompson et al., 2012). Assessment was performed through the self-report question: “Before your injury, did a doctor ever tell you that you had depression?” and through the Center for Epidemiologic Studies Depression Scale-Revised at follow-up, which is a 20-item questionnaire whose scores range from 0 to 60 (Eaton et al., 2004). Higher scores indicate the presence of more depressive symptomatology (Eaton et al., 2004).

One year after mild TBI, depressive symptoms were found in 4.8% of the 65–74 year old patients and 2.6% of the 75–84 years old patients (Thompson et al., 2012).

4. Discussion

This study assesses QoL, functional outcome, dependency, nursing home admission rate and incidence of depression in elderly patients of ≥65 years old who sustained TBI.

The results show a prevalence for unfavorable functional outcomes of 65.2% (95% CI: 51.1–78.0) and a prevalence of nursing home admission of 28.5% (95% CI: 17.1–41.6). Dependency rates range between 16.9% and 74.0%, with outcomes worsening with increasing severity and age and with unclear recovery over time. QoL was found to be particularly decreased as indicated by reported PCS scores ranging between 35.3 and 44.2/100 at 3–12 months post TBI. This is far below the population average scores (50/100 (Huo et al., 2018; Maglinte et al., 2012). In contrast, the MCS scores were similar to the population average scores, ranging between 48.2 and 52.3/100 at 6–12 months follow-up, 2.6–4.8% of patients with mild TBI reported depressive symptoms.

Higher injury severity was associated with poorer functional outcomes. However, this is not the case for QoL, where only subtle differences were observed between patients with mild and severe TBI and, in some cases, the reported QoL scores were lower for patients with mild TBI.

To date, there is a relative scarcity of evidence and lack of detail in...
| Study (year) | TBI severity (given by GCS) | ISS Type of study | Study settings | Country | N ≥ 65 years old | LOS (days) | Comorbidities | Pre-injury anticoagulation | Time post-TBI | Type of assessment | Outcomes |
|--------------|-----------------------------|------------------|----------------|---------|------------------|-----------|--------------|-----------------------|-------------|------------------|----------|
| Kinsella et al. (2014) (Kinsella et al., 2014) | Mild | NR | Retrospective | Hospital | Australia | 50 | Median (IQR)−4 (5) | NR | NR | 3 months | CIQ home mean 5.8 (SD 2.9); CIQ social 8.3 (SD 2.6) |
| Brousseau et al. (2017) (Brousseau et al., 2017) | Mild | NR | Prospective observational | Multi-center | Canada | 344 | NR | 0–1 comorbidities in 51 patients, 2–4 in 148 and 5–13 in 143 | NR | 6 months | OARS | 24 patients (7.9%) had functional decline |
| Thompson et al. (2012) (Thompson et al., 2012) | Mild | 65-74 years old: mean (SD)=17.9 (11.7) 75–84 years old: mean (SD)=7.5 (10.9) | Retrospective | National database | US | 309 | NR | In the 65–74 years group: 42.9% of the patients CCI<0, 28.4% CCI=1, 14.5% CCI=2 and 14.2% CCI>3 In the 75–84 years group: 28.8% CCI<0, 29.6% CCI=1, 17.0% CCI=2, 24.6% CCI>3 | NR | 12 months | Interview/non-standardized assessment | In the 65–74 years group patients had by mean 1.3 (SD 2.7) ADL difficulties and in the 75–84 years group a mean of 2.2 (SD 3.2). The number of ADL difficulties pre-injury was 0 in 87% of the 65-74 years old patients and 71.5% of the 75-84 years old patients 76.0% of the 70–79 years old group, 67.0% of the 80–89 years old group and 61.0% of the ≥90 years old group were independent at discharge 61 patients (67.8%) were dependent for one or more ADL activities. |
| Miller et al. (2017) (Miller et al., 2017) | Mild and moderate | NR | Retrospective | National database | US | 36288 | NR | NR | Hospital discharge | Interview/non-standardized assessment | |
| Lilley et al. (2016) (Lilley et al., 2016) | Severe | Median (IQR)= 5 (10) | Retrospective | National database | US | 90 | Median (IQR)=8 (14) | 41.9% CCI<0, 30.2% CCI=1, 16.3% CCI=2, 11.6% CCI>3 | 78.3% of the patients | Hospital discharge | Interview/non-standardized assessment | 69 of 136 participants (45 years old) needed no help to transfer to chair, wheelchair, or bed and 79 of 136 participants (≥55 years old) needed minimal help for going up or down the stairs |
| Lecours et al. (2012) (Lecours et al., 2012) | Severe | NR | Retrospective | Level I and level II trauma center | Canada | 95 | NR | NR | 24–48 months | Interview/non-standardized assessment | |

N=number; GCS=Glasgow Coma Scale; ISS=Injury Severity Score; NR=not reported; LOS=length of hospital stay due to TBI; CCI=Charlson Comorbidity Index; US=United States of America.
| Study (year) | TBI severity (given by GCS) | ISS Type of study | Study settings | Country | N ≥ 65 years old | LOS (days) | Comorbidities | Pre-injury anticoagulation (N) | Time post-TBI (months) | Outcomes | N patients discharged to a nursing home (%) |
|-------------|-----------------------------|-------------------|----------------|---------|-----------------|-----------|---------------|-----------------------------|----------------------|----------|------------------------------------|
| Khan et al. (2017) | Mild | Median (IQR)—17 (11) | Retrospective | National database | US | 8750 | NR | NR | NR | Hospital discharge | 2993 (34.2%) |
| Schmidt et al. (2019) | Mild | NR | Retrospective | Level I trauma center | Switzerland | 344 (141 patients 65–74 years old, 125 75–84 years old and 78 >85 years old) | Mean (SD)= (2) | 9.3% of the patients had diabetes, 22.7% psychiatric diseases and 5.2% musculoskeletal diseases | NR | Hospital discharge | 20 (5.8%); 1 patient 65–74 years old, 6 75–84 years old and 13 ≥85 years old |
| Velez et al. (2020) | Mild | Median—11 | Retrospective | National database | US | 19664 | NR | Median CCI=4 | NR | Hospital discharge | 5821(29.6%) |
| Thompson et al. (2012) | Mild | 65–74 years old: mean (SD)=17.9 (11.7) 75–84 years old: mean (SD)=7.5 (10.9) | Retrospective | National database | US | 309 | NR | In the 65–74 years group: 42.9% of the patients CCI=0, 28.4% CCI=1, 14.5% CCI=2 and 14.2% CCI≥3 In the 75-84 years group: 28.8% CCI=0, 29.6% CCI=1, 17.0% CCI=2, 24.6% ≥3 | NR | Hospital discharge | 12 | 108 (35.0%), of which 10.4% were 65–74 years old and 24.6 75–84 years old |
| Miller et al. (2017) | Mild and moderate | NR | Retrospective | National database | US | 36288 | NR | NR | NR | Hospital discharge | *76.0% of the 70–79 years old group, 67.0% of the 80–89 years old group and 61.0% of the ≥90 years old group were discharged to home or prison |
| Bhullar et al. (2010) | Moderate | 65-80 years old: mean=12 >80 years old: mean=11 | Retrospective | Level II trauma center | US | 328 | NR | NR | NR | Hospital discharge | 27 (8.2%) |
| Gorman et al. (2020) | Moderate and severe | Median (IQR)=–17 (9) | Retrospective | National database | US | 3292 | NR | Median CCI=4 | NR | Hospital discharge | 931 (28.3%) |
| Susman et al. (2002) | Moderate and severe (mean GCS=8.7) | Mean ± SD= 17.4± 8.7 | Retrospective | Database | US | 3244 | NR | NR | NR | Hospital discharge | 1752 (54.0%) |
| Lilley et al. (2016) | Severe | Median (IQR)= 5 (16–26) | Retrospective | National database | US | 90 | Median (IQR)=8 (14) | 41.9% CCI=0, 30.2% CCI=1, 16.3% CCI=2, 11.6 CCI ≥3 | 78.3% | Hospital discharge | 61 (67.8%) |
| Haller et al. (2017) | Severe | Median (IQR)=25 (12) | Prospective observational | Multi-center | Switzerland | 97 | NR | 10 patients psychiatric disorders and 16 alcohol abuse | 26 | 3 | 10 (10.3%) at 3 months, 14 (14.4%) at 6 months and 16 (16.5%) at 12 months |
| Rae et al. (2015) | Severe | NR | Prospective observational | Multi-center | Norway | 97 (46 65–74 years old and 51 >75 years old) | NR | 35 patients 65–74 years old and 45 patients ≥75 years old | 21 65–74 years old and 37 p ≥75 years old | 12 | 5 (5.2%); 4 patients 65–74 years old and 1 patient ≥75 years old |
| Lecours et al. (2012) | Severe | NR | Retrospective | Level I and level II trauma center | Canada | 95 | NR | NR | NR | Hospital discharge | 24–48 | 21 (22.1%) |

N=number; GCS=Glasgow Coma Scale; ISS—Ijury Severity Score; NR—not reported; LOS= length of hospital stay due to TBI; CCI=Charlson Comorbidity Index; US=United States of America.
| Study (year)           | TBI severity (given by GCS) | ISS | Type of study               | Study settings | Country | N ≥ 65 years old | LOS (days) | Comorbidities | Pre-injury anticoagulation | Time post-TBI (months) | Type of assessment | Outcomes                                                                 |
|-----------------------|-----------------------------|-----|----------------------------|----------------|---------|-----------------|------------|---------------|-------------------------|----------------------|----------------------|---------------------------------------------------------------------------|
| Kinsella et al. (2014) | Mild                        | NR  | Retrospective              | Hospital       | Australia | 50              | Median     | NR            | NR                      | 6                    | SF-12                | Mean SF-12 PCS score 36.71 (SD 10.7); mean SF-12 MCS score 53.2 (SD 8.8) |
| Haller et al. (2017)  | Severe                      | Median (IQR) = 25 (12) | Prospective observational | Multi-center study | Switzerland | 97               | NR         | 10 patients psychiatric disorders, 16 alcohol abuse | 26 patients          | 3, 6 and 12        | SF-12 Mean SF-12 PCS score 39.2 (range 30.7-50.0); mean SF-12 PCS score 52.3 (range 44.7-55.7) at 3 months, mean SF-12 MCS score 42.3 (34.9-52.8); mean SF-12 MCS score 51.2 (45.3-57.1) at 6 months and mean SF-12 PCS score 44.2 (34.5-52.8); mean SF-12 MCS score 52.3 (45.8-57.2) at 12 months |

N = number; GCS = Glasgow Coma Scale; ISS = Injury Severity Score; NR = not reported; LOS = length of hospital stay due to TBI; US = United States of America.
studies reporting on elderly TBI outcomes (Steyerberg et al., 2019; Peeters et al., 2015). Particularly, only three studies investigated QoL in elderly patients. While dependency in ADL is a strong predictor of declining QoL (Enkvist et al., 2012; Wilhelmson et al., 2005), the relation between mood changes and function is not straightforward. As the safeguarding of acceptable QoL is the primordial goal of any medical treatment, documented QoL outcomes following TBI in elderly are of major importance for treatment guidance and counseling. Nevertheless, to date, we could find no guidelines on the management of TBI in the elderly.

We hypothesized that TBI in elderly patients often results in significant functional decline and poor QoL, and the obtained results seem to confirm this. Moderate and severe TBI have a significant impact on dependency and QoL in elderly, while mild TBI has a potentially strong impact. Interestingly, Haller et al., Kinsella et al. and Thompson et al. found that health-related QoL was impaired to the same extent in mild as in severe TBI (Haller et al., 2017; Thompson et al., 2012; Kinsella et al., 2014). This might be explained by the definition of "mild TBI", following the GCS, not being sufficiently reliable in elderly patients. These patients are at a particular risk of deterioration after hospital admission (Hofman et al., 2001; Stiell et al., 2001; Haydel et al., 2000) and, therefore, the impact of mild TBI should not be underestimated. Furthermore, we believe that QoL depends on a large amount of factors about the patients' lives and not only the patients' status after TBI. This could lead, in some cases, to subjective results. Therefore, it could be that in some cases patients with mild TBI potentially perceive their limitations as a serious burden, while patients surviving moderate and severe TBI may be rather positive, outweighing the disabilities by their happiness to be still alive.

A limitation of the current study is the scarcity of published literature.
documenting outcomes of TBI in elderly, particularly in terms of QoL and depression. Moreover, the review was limited to studies written in English. However, the main limitation is the inter-study variability in outcome scales used, study settings and timings of assessment applied. Furthermore, the included studies generally contained insufficient detail to correct for patients’ heterogeneity, comorbidities, injury characteristics and clinical management in this population. An attempt to compare studies with similar characteristics has been performed. However, this has not been possible in all the cases due to the variability in outcome scoring, in combination with the impossibility for actual stratification. The establishment and application of an international reporting standard would be very useful.

Finally, if all the included studies would have contained more detail on patient and injury characteristics and management, this could have enabled a meta-analysis for all the included outcomes, which was not possible.

The results from this review illustrate the major burden of TBI in the elderly, primarily for the patients and their families. Second, to society, which is reflected in needs for outpatient supplies and residential care facilities and associated costs. In contrast, research in this field is, to date, rather limited and no clinical guidelines for the management of elderly TBI exist. Better insight into outcomes and risk factors for poor outcome, ideally resulting in the development of prognostic models specific for elderly TBI, can improve counseling of patients and their families, and help caregivers to set realistic treatment targets, particularly in situations of severe TBI where often surgical decisions need to be made fast and treatment withdrawal might be a humane alternative. Further clinical research in this field is therefore urgently needed in order to facilitate clinical guideline development.

5. Conclusion

TBI in the elderly has a major impact on patients’ lives, often leading to functional decline, dependency, nursing home admission and poor QoL. This is particularly true in moderate and severe TBI, but potentially
also true in mild TBI. Older age and injury severity are risk factors for poor functional outcome, while poor QoL is seen in all severities of TBI.

6. Authorship confirmation statement

All authors contributed to the study conception and design. The articles screening and selection was performed by Rebeca Alejandra Gavrila Laic and Liedewij Bogaert. Studies’ quality assessment and data extraction was performed by Rebeca Alejandra Gavrila Laic. The first draft of the manuscript was written by Rebeca Alejandra Gavrila Laic and Bart Depreitere. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

7. Author(s’) disclosure statement(s)

The authors declare that they have no competing interests.

Appendix A. Assessment techniques included in our study selection inclusion criteria

| Assessment technique                                                        | Outcome                                      |
|------------------------------------------------------------------------------|----------------------------------------------|
| WHO Disability Assessment Schedule (WHODAS)                                 | Functional outcome                          |
| Functional Independence Measure (FIM)                                        | Functional outcome                          |
| Glasgow Outcome Scale (GOS)                                                 | Functional outcome                          |
| GOS-Extended (GOS-E)                                                        | Functional outcome                          |
| Disability Rating Scale (DRS)                                                | Functional outcome                          |
| Functional Assessment Measure (FAM)                                          | Functional outcome                          |
| Functional Status Examination (FSE)                                          | Functional outcome                          |
| Community Integration Questionnaire (CIQ)                                    | Functional outcome                          |
| Barthel Index                                                                | Functional outcome                          |
| Patient Reported Outcomes Measurement Information System (PROMIS)           | Functional outcome/depression                |
| Rivermead Postconcussion Symptoms Questionnaire                             | Functional outcome/depression                |
| Trauma outcome profile (TOP)                                                 | Functional outcome/depression                |
| European Brain Injury Questionnaire (EBIQ)                                  | Functional outcome/QoL                       |
| General Health Questionnaire-30 (GHQ-30)                                    | Functional outcome/depression                |
| Hamilton Depression Rating Scale (HAM-D)                                    | Depression                                   |
| Mini International Neuropsychiatric Interview                               | Depression                                   |
| Wimbledon Self-Report Scale                                                 | Depression                                   |
| Beck’s Depression Inventory (BDI)                                            | Depression                                   |
| Patient Health Questionnaire 9-item depression scale (PHQ-9)                 | Depression                                   |
| Center for Epidemiologic Studies-Depression Scale (CES-D)                   | Depression                                   |
| Anxiety and depression scales from the Symptom Checklist-90                 | Depression and anxiety                       |
| Hospital anxiety and depression scale (HADS)                                | Depression and anxiety                       |
| Beck’s anxiety inventory (BAI)                                                | Anxiety                                      |
| 36-item Short Form Survey (SF-36)                                            | QoL                                          |
| 12-item Short Form Survey (SF-12)                                            | QoL                                          |
| Short-Form Six-Dimension (SF- 6D)                                            | QoL                                          |
| Quality of Life after Brain Injury (QOLIBRI)                                | QoL                                          |
| Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS)               | QoL                                          |
| Quality of Life Interview (QoLI)                                             | QoL                                          |
| QOLIBRI Proxy version (Q-Pro)                                                | QoL                                          |
| Traumatic Brain Injury Quality of Life (TBI-QOL)                             | QoL                                          |
| World Health Organization Quality of Life-BREF (WHOQOL-BREF)                | QoL                                          |
| World Health Organization Quality of Life 100 (WHOQOL-100)                  | QoL                                          |
| EuroQol-5D (EQ-5D)                                                          | QoL                                          |
| NeuroQol                                                                     | QoL                                          |
| Sickness Impact Profile (SIP)                                                | QoL                                          |
| Flanagan Quality of Life Scale (FQoLS)                                      | QoL                                          |
| Perceived Quality of Life Scale (PQoL)                                      | QoL                                          |
| Satisfaction With Life Scale (SWLS)                                         | QoL                                          |
| Life Satisfaction Questionnaire (LSSat-11)                                   | QoL                                          |
| Life Satisfaction Index I- A (LSI-A)                                        | QoL                                          |
| Freiburg Questionnaire of Coping with Illness (fqci)                        | QoL/depression                               |
| Profile of mood states (POMS)                                               | QoL/depression                               |
| Qualitative interviews                                                      | Functional outcome/depression/dependency/nursing home admissions |

Appendix B. Studies’ quality assessment based on the Downs and Blacks scale

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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| Author (year) | Reporting External validity | Internal validity-bias | Internal validity - confounding (selection bias) | Power | T | Quality |
|--------------|-----------------------------|------------------------|-----------------------------------------------|-------|---|--------|
| Akbik et al. (2019) | 1 1 1 1 0 1 0 0 1 0 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 1 0 16 Fair |
| Bhullar et al. (2010) | 0 0 0 1 0 1 0 0 0 1 1 0 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 11 Poor |
| Brazinova et al. (2010) | 1 1 1 1 0 1 0 0 0 1 1 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 14 Poor |
| Brousseau et al. (2017) | 1 1 1 1 0 1 1 0 1 0 1 0 1 0 0 0 0 0 1 1 1 1 1 0 0 0 0 0 14 Poor |
| Choi et al. (2019) | 1 1 1 1 0 1 1 0 1 0 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 16 Fair |
| Deb et al. (1998) | 1 1 1 1 0 1 1 0 1 0 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 17 Fair |
| Erlebach et al. (2017) | 1 1 1 1 0 1 0 0 1 0 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 17 Fair |
| Gorman et al. (2020) | 1 1 1 1 0 1 0 0 0 1 1 0 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 14 Poor |
| Gritt et al. (2019) | 1 1 1 1 0 1 1 0 1 0 1 0 0 0 1 1 1 1 1 1 0 0 0 0 1 17 Fair |
| Haller et al. (2017) | 1 1 1 1 0 1 1 0 1 0 1 0 0 0 1 1 1 1 1 1 0 0 0 0 1 16 Fair |
| Hawley et al. (2017) | 1 1 0 1 0 1 1 0 0 1 1 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 15 Fair |
| Julien et al. (2017) | 1 1 1 1 0 1 1 0 0 1 1 1 0 1 0 1 1 1 1 1 1 0 0 0 0 0 16 Fair |
| Khan et al. (2017) | 1 1 1 1 0 1 1 0 0 1 1 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 16 Fair |
| Kinsella et al. (2014) | 1 1 1 1 0 1 0 0 0 0 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 14 Fair |
| Lecours et al. (2012) | 1 1 0 1 0 1 1 0 1 1 0 1 0 1 0 0 1 1 1 1 1 1 0 0 0 0 0 15 Fair |
| Lilley et al. (2016) | 1 1 1 1 0 1 1 0 1 1 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 0 1 18 Fair |
| Miller et al. (2017) | 1 1 0 1 0 1 0 0 0 0 1 0 1 0 1 0 0 1 1 1 1 1 0 0 0 0 0 12 Poor |
| Mosenthal et al. (2004) | 1 1 0 1 0 1 1 0 1 1 0 1 0 1 0 0 0 1 1 1 1 1 0 0 0 0 1 16 Fair |
| Mohindra et al. (2008) | 0 0 0 1 0 1 0 0 0 1 0 1 0 0 0 1 0 1 1 1 1 1 0 0 0 0 0 10 Poor |
| Roe et al. (2015) | 1 1 1 1 1 1 0 0 0 1 0 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 15 Fair |
| Schmidt et al. (2019) | 1 1 1 1 1 1 0 0 1 1 0 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 16 Fair |
| Susman et al. (2002) | 1 1 0 1 0 1 0 0 0 1 1 1 0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 14 Poor |
| Thompson et al. (2012) | 1 1 0 1 0 1 0 0 0 1 1 0 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 13 Poor |
| Tokutomi et al. (2008) | 1 1 0 1 0 1 1 0 0 0 1 0 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 13 Poor |
| Velez et al. (2020) | 1 1 1 1 0 1 1 0 0 1 1 1 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 16 Fair |
| Wan et al. (2016) | 1 1 1 1 0 1 1 0 0 0 1 0 1 0 0 0 1 1 1 1 1 1 0 0 0 0 0 14 Poor |
| Won et al. (2017) | 1 1 1 1 0 1 1 0 0 0 1 0 0 0 0 0 1 1 1 1 1 1 0 0 0 0 0 13 Poor |

1-27 refer to questions 1–27 of the Downs and Blacks scale (Downs and Black, 1998); T=total score.
Downs and Blacks scale's questions (Downs and Black, 1998):

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dredging", was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/relievable?
20. Were the main outcome measures used accurate (valid and reliable)?
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
23. Were study subjects randomised to intervention groups?
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

All questions were scored on the following scale: yes=1, unable to determine=0 and no=0.

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