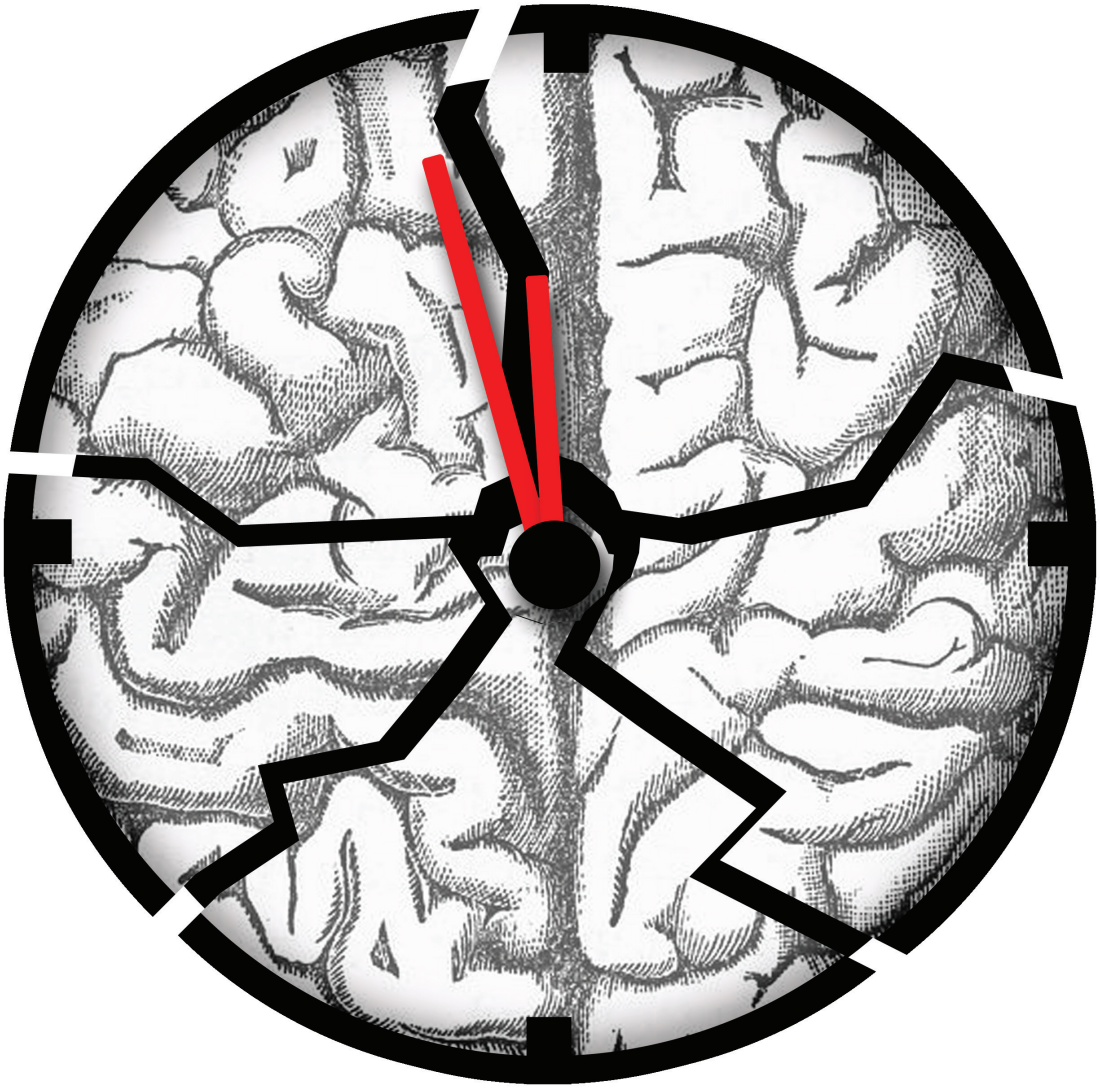

Long-term Impact of Moderate to Severe Traumatic Brain Injury

Erik Grauwmeijer

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Langetermijngevolgen van middelzwaar tot ernstig traumatisch hersenletsel

Proefschrift

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Contents

Chapter 1

General introduction

Worldwide, traumatic brain injury (TBI) is the foremost cause of injury-related death and disability.[1] It is to be expected that TBI will be the largest global contributor to neurological disability until the end of the next decade, with a projected burden of disability that surpasses that of conditions such as cerebrovascular disease and dementia.[2] The incidence rates of TBI vary considerably. Higher incidence rates are found in population based studies that often use broad definitions of TBI (811–979 per 100,000 people per year).[1,3,4] Studies based on hospital discharge rates tend to report lower incidence rates (47,5–643,5 per 100,000 people per year).[1,4,5] Past years show a trend towards an increase of TBI in high-income countries for elderly people, as a result of falls, while in low-income countries the incidence of TBI is growing due to road traffic incidents.[1] The mortality rate of severe TBI is estimated at 30–40% in observational studies on unselected populations.[6] On a global scale an estimated 50 million people have a TBI each year.[1] In the Netherlands TBI incidence is 213.6 per 100,000 per year, total costs mount up to €314.6 (USD $433.8) million per year with a disease burden of 171,200 Disability Adjusted Life Years (DALYs, on average 7.1 DALYs per case).[7] Fifteen international prevalence studies showed that in a total sample of 25,134 adults, 12% had experienced a serious TBI with men being at more than double the risk of women.[8] A population based survey in Colorado (USA) showed that 42% of respondents experienced at least one TBI in their lifetime (36% mild and 6% moderate-severe).[9] About half of the world's population is expected to suffer one or more TBIs over lifetime.[1] Further, TBI might be a major risk factor for late neurodegenerative disorders such as dementia and Parkinson's disease. Which illustrates that TBI can also evolve into a progressive lifelong illness.[10]

The outcome after TBI may range from complete recovery to death, with many survivors having long-term disabilities. Due to a dose response relationship the (long-term) consequences of TBI are partly determined by injury characteristics such as the pattern and extent of the damage.[1] Environmental and personal factors have an impact on outcome too. For example, the presence or absence of a primary caregiver may determine whether a patient can be discharged home or needs to be discharged to a sheltered living situation. The more adept caregivers deal with the situation, the better the patients recover.[11] When the caregiver has a passive way of coping, the patient is at higher risk to restrictions in participation. Therefore, the long-term physical, cognitive, emotional and behavioural problems after TBI are determined by injury characteristics as well as by contextual factors of the patient and the caregiver. Such issues are not covered in outcome studies such as the CRASH and IMPACT studies that focus on mortality and severe disability at 6 months post injury.[12,13] Although helpful in estimating survival and decision making in acute care, these models do not cover outcomes such as the independence in daily living in the long

run. After surviving the critical acute phase, we are facing questions like will the patient be able to live independently or return to work? Such long-term outcomes may guide rehabilitation treatment and facilitate adequate counselling of patients and relatives.

This thesis therefore focuses on long-term consequences after moderate-severe TBI. The study was performed as part of the Rotterdam TBI project within the 'Long-term prognosis of functional outcome in neurological disorders' research program (FuPro). The FuPro research program studied four neurological disorders, multiple sclerosis (MS), stroke, amyotrophic lateral sclerosis (ALS) and traumatic brain injury, which was supervised by the Department of Rehabilitation Medicine of the VU Medical center in Amsterdam and was supported by the Netherlands Organization for Health Research and Development (grant no. 1435.0001). The department of Rehabilitation Medicine of the Erasmus MC, Rotterdam coordinated the TBI study. The aim of the study was to establish the most optimal set of measurement instruments for the evaluation of the consequences of TBI and to identify determinants of functional outcome, which was published in the thesis 'Clinimetrics and functional outcome one year after TBI' by B. van Baalen.[11,14-16] A second thesis 'Functional prognosis of long-term outcome after TBI' by A. Willemse-van Son focused on the course of functional outcome and determinants of functional outcome over three years.[17-20] These studies emphasize that outcome after TBI is not static and stabile after a predetermined period of time but rather dynamic, changing with transition stages (e.g. discharge from hospital, return to leisure activities or return to work) and with contextual demands.

AIM OF THIS THESIS

The primary aim of this thesis is to describe and evaluate long-term consequences of moderate to severe Traumatic Brain Injury (TBI) regarding employment, Health-Related Quality of Life (HRQoL), cognition, and mood. A cohort of 113 patients was therefore prospectively followed up with baseline measurements at hospital admission, and follow-up measurements at 3, 6, 12, 18, 24, and 36 months and 10 years post injury. **Chapter 2** is an introduction to the subject describing the lack of prognostic models on functional outcome and illustrating the need of organizing follow-up visits in the chain of care, and illustrates with two clinical cases that TBI is not an incident but should be considered a chronic condition. **Chapter 3** aims to evaluate the course of HRQoL in home-dwelling patients up to 3 years after moderate or severe TBI (as measured with the SF-36), and to identify which determinants are associated with the physical and mental components of HRQoL in the long-term. The focus of **chapter 4** is to evaluate the employment outcome up to 3 years after moderate and severe TBI and to identify which patients are at risk

of unemployment in the long-term. **Chapter 5** evaluates employment outcome and determines its predictors up to 10 years after injury. In the literature, no studies were found on HRQoL and depression in relation to cognitive outcome in the long-term (more than five years) in moderate-severe TBI. **Chapter 6** therefore aims to evaluate cognitive function ten years after moderate-severe TBI and to investigate the associations between cognitive function, depression and HRQoL in these patients. **Chapter 7** presents the general discussion of the main findings, several methodological considerations, some future research perspectives, and the general conclusion of this study.

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Chapter 2

Chronic problems after traumatic brain injury – TBI is not an incident

Adapted from:
Grauwmeijer E, van der Naalt J, Heijenbrok-Kal MH, Ribbers GM. Chronische problemen na Traumatisch Hersenletsel: Traumatisch Hersenletsel is geen incident. Ned Tijdschr Geneeskd. 2016;160:A8949.

INTRODUCTION

Traumatic Brain Injury (TBI) is an important cause of life-long disability. Nevertheless it is frequently appraised as an acute incident rather than a chronic condition. Patients consequentially only receive treatment by a medical specialist for a limited period of time without long-term follow-up. Both patients surviving a stroke or a TBI may suffer from long-term consequences such as intolerance to light or noise, memory, attention, and mood disorders. These are problems that may interfere with daily activities and quality of life until years after the incident. However, stroke patients are more likely to be on the radar of the general practitioner than TBI patients because of the need for managing cardiovascular risk factors and other comorbidity. In patients with TBI the risk of late or no recognition of TBI-related problems is therefore higher. Two case studies are discussed to address these issues both in mild and in severe TBI.

Patient A, a 45-year old woman, is referred to a neurologist by the general practitioner as a result of complaints of headaches and concentration problems. Six months earlier she had been hit by a car while cycling. As a result she suffered a skull base fracture, CT-scanning revealed no intraparenchymal abnormalities. On admission to the hospital she was disoriented with a Glasgow Coma Scale (GCS) score of 14 (E4-M6-V4). The posttraumatic amnesia phase lasted for 12 hours. The patient did not sustain any other injuries and was discharged the day after, with the advice to 'take it easy'. At home the patient experienced headaches and dizziness which decreased after a couple of weeks. After six weeks she gradually resumed her work duties as a teacher after consulting her company's practitioner. She developed headaches, memory complaints and impaired concentration, especially after continuously teaching several hours or teaching large classes. After three months she fully resumed her work. Several weeks later she was compelled to reduce her workload as a result of increasing complaints. As a result of this relapse she was referred to a neurologist. At the outpatient Neurology department, the patient explained that she experienced cognitive complaints, especially at the end of the day. She reported feeling run down and consequentially going to sleep early. As a result of her low energy levels, she had not yet managed to resume her sports and other hobbies. On neurological examination no abnormalities were found. For further evaluation a neuropsychological examination and MRI was performed. The neuropsychological examination showed an average intelligence with a diminished divided attention, particularly under time pressure. The results of the memory tests fell within the aged adjusted norm. There were indications of slightly increased anxiety and depression levels, as well as a passive coping style. The MRI-scan did not display clear abnormalities on the T2- and FLAIR-sequences; 'susceptibility weighted imaging' (SWI)-sequences demonstrated a number of dispersed punctuated

bleedings, most profound in the left frontal and temporal areas (Figure 2.1). Based on these additional findings it was concluded that the symptoms and complaints of this patient could be related to the accident. Subsequently, she was referred to a psychologist for cognitive behavioural therapy. Furthermore she was advised to gradually resume her work activities. Twelve months after the accident, the patient resumed her work duties for 80%. She still has complaints of fatigue when busy or after long working days.

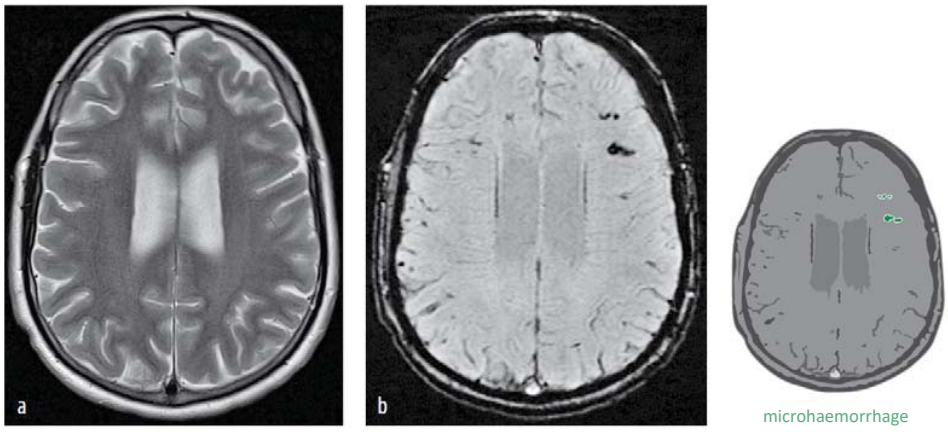

Figure 2.1: MRI-scan of the cerebrum of patient A, 4 months after sustaining a skull base fracture (transversal coupes).
(a) T2-weighted in which no clear pathology is visible. (b) 'Susceptibility weighted imaging' (SWI), sequence in which hypo-intense pathological findings are visible at the transition from white to grey matter left frontal, in accordance with microhaemorrhage.

Patient B is 36-year old man referred to the outpatient department of the rehabilitation centre, 5 years after being hit by a car as a pedestrian which resulted in a severe traumatic brain injury with bilateral frontotemporal cerebral contusions and subdural hematomas. No information was provided about the Glasgow coma score, the duration of the posttraumatic amnesia or coma. Six days after injury a clinical decline was observed and with vital functions in danger due to increased intracerebral pressure caused by cerebral edema, a bifrontal craniotomy was performed.

After clinical recovery the patient was discharged from the acute hospital and referred to an inpatient psychiatric hospital because of a frontal syndrome with disinhibition and runaway tendency. After 4 weeks the psychiatrist concluded that this patient suffered from 'transient cognitive impairments with complete recovery'. Neuropsychological examination was not performed, nor behavioural observation during activities of daily life, and the patient was discharged home without subsequent treatment or after care.

Once at home it became apparent that the patient was highly dependent on external structure for his personal care and financial administration. He became socially derailed, not paying his bills nor taking care of his personal hygiene and was not able to return to work. In a short period of time he lost his job, created debts, developed alcohol abuse and displayed characteristics of depression with suicidal expressions. The patient was not in a formal after care program and his problems remained unnoticed, except to an uncle who also had immigrated to the Netherlands. He took him into his home, restructured his debts and initiated support for his alcohol abuse. Four years after the accident, the patient moved into a supervised housing project. The patient was referred to us for an expert opinion regarding the question whether his symptoms, complaints and social downfall were to be related to the prior traumatic brain injury or to a psychiatric condition with mood problems and substance abuse.

On evaluation we saw an adipose, North-African man with a language barrier. Previously he had completed an applied-science degree. According to his uncle, up until the accident, he was a 'dedicated worker in his father's company in Morocco in the electro technique sector, athletic and with a completely different personality compared to now'. He now suffers from a lack of initiative, without external stimulation spending his days in bed or watching TV. He is unable to structure his days or even to independently follow an imposed day structure and still tends to neglect his personal care. The alcohol issue is under control with disulfiram and psychiatric consultation. However he disinhibited with regard to eating sweets and has put on much weight with a BMI of 34.7. He receives both requested and unrequested supervision and support in his assisted living arrangement. Upon physical examination no abnormalities were observed except for a divergent eye positioning with limited elevation and adduction of the left eye, and a scar resulting from the bifrontal craniotomy. A MRI-scan reveals severe atrophy of the frontal lobes, most noticeably frontobasal and temporal (Figure 2.2). Due to the language barrier extensive neuropsychological testing cannot be performed. At bedside testing we observe severely disturbed attentional functions that worsen rapidly when fatigued, semantic and episodic memory disorders and severely impaired visual-constructive abilities. During a supervised practical assignment, in which the patient has to take the subway to the train station to buy a magazine, and then return to the rehabilitation centre, the patient becomes disoriented, forgets the tasks and lacks problem solving strategies. He panics and because of acting out to passers-by the assignment has to be terminated. We conclude that the symptoms, especially the executive problems, but also the mood problems and substance abuse, should be regarded as consequences of the traumatic brain injury.

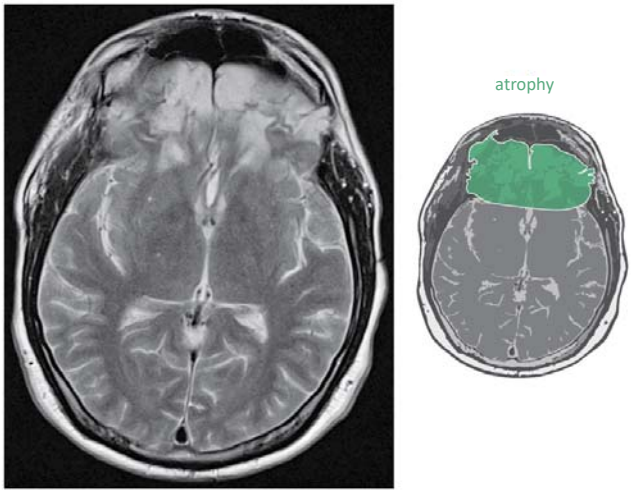

Figure 2.2: MRI-scan of the cerebrum of patient B (transversal coupe).
Severe atrophy of the frontal lobes can be observed, most pronounced frontobasal and temporal.

CONSIDERATION

About 21,000 patients with TBI are admitted to hospitals in the Netherlands every year. The actual number of people who sustain a TBI per year is estimated to be around 85,000. The majority of these patients are not entered into the national health registry system as they only visit the emergency department or general practitioner. Moreover, some of these patients do not seek help at all.[1] It is estimated that in the Netherlands approximately 200,000 people below the age of 65 are functioning in their home environment after sustaining traumatic brain injury between the ages of 12 to 45. The exact numbers are unknown, but it is estimated that of this group approximately 80,000 to a 100,000 people have unmet needs.[2]

Classification of TBI

Traumatic brain injury is categorized based on the Glasgow Coma Scale (GCS) score, in mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS 3–8) TBI. Other measures for the determination of the severity of brain injury are the duration of the posttraumatic amnesia and the loss of consciousness. A dose response relationship explains that with increasing TBI severity lasting physical and cognitive deficits become more frequent. The clinical manifestation of TBI, however, is heterogeneous and related to age, the presence and extend of focal and diffuse neurological damage, additional injuries, such as fractures

or pulmonary damage, and the medical history, including for example depression or substance abuse. Sociodemographic characteristics such as educational level, marital and employment status, and for example coping style may also be important. Even patients with mild TBI may have long-term consequences.

The ICF conceptual framework of the 'International classification of functioning, disability and health' (ICF model) can be used to clarify the consequences of TBI. In this model human functioning can be described at 3 different levels:

1. Bodily functions such as for example spasticity, contractures, aphasia, dysarthria, memory- or attention disorders, incontinence, pressure sores, and diabetes mellitus.
2. Activities such as walking, getting dressed, structuring the day, and communication.
3. Social participation such as family role, leisure activities, or work.

There is no linear relationship between, for example, the severity of disorders of bodily functions and the consequences for social participation. External and personal factors are important. For example, the presence of a caregiver, the coping style of the patient, or the possibility to adjust work or work setting to altered physical or cognitive abilities may affect outcome at the level of social participation.

Mild traumatic brain injury

Patients with mild traumatic brain injury often do not experience physical limitations and, in general, no cognitive deficits are observed during neuropsychological examinations either. An initial CT-scan frequently does not display pathology. With persistent complaints an MRI-scan may nevertheless display pathological findings. The majority of patients with mild traumatic brain injury recover spontaneously although cognitive complaints can be present up until several months after the injury. However a small part of this group may experience complaints, especially in the cognitive domain. It is estimated that 10–15% uses specialised care after the injury.[3] Patients with mild TBI often experience fatigue, headaches and intolerance to noise and light. A reduced capacity to perform normal activities may interfere with work or the fulfilment of the partner- or family-role. 6 months after injury, approximately 75% of the patients, have fully resumed their work.[4] For patients with mild traumatic brain injury it is important to optimise the balance between workload and work capacity, which can be accomplished through 'graded activity'. This is a structured treatment focused on a gradual increase in the level of functioning usually provided by an occupational or physical therapist.

Moderate and severe traumatic brain injury

Patients with moderate and severe TBI often show focal and diffuse pathology on imaging techniques, such as diffuse axonal injury, epidural or subdural hematoma's, and intracerebral haemorrhages. Neurologic examination can be abnormal with reduced motor strength, sensory loss, or spasticity. Epilepsy and heterotopic ossification, especially in the case of lengthy IC-admission, are well known problems, as are challenging behavioural problems and cognitive deficits. The heterogeneous clinical manifestation is strongly associated with the focal and diffuse neurological damage. Part of these patients do not survive and some may not return home and remain dependent on professional care. Of all patients that survive moderate to severe TBI 94% will return home while 1 per 4 patients is likely to suffer from severe limitations.[5] One year after moderate to severe TBI approximately 50% of the patients has a paid job. The most important predictors of unemployment are limitations in cognitive functioning and psychiatric symptoms such as anxiety and depression at hospital discharge.[6]

Prognostic models

There is a dose relationship between the severity of the initial trauma and the extent of the consequences. However, in combination with unfavourable contextual and personal factors, even minor physical and cognitive impairments may have severe consequences at the level of societal participation, for example in family role, study or work. Reliable prognostic models aimed at the long-term consequences of TBI are currently unavailable.

The CRASH- and IMPACT-models predict mortality after 14 days or predict severe limitations after 6 months based on age, GCS, absent pupil reactions, and the presence of extracranial damage.[7,8]

These models are focused on treatment in the acute phase and are mainly related to prediction of survival. Furthermore, cerebral imaging in the early phase has limited predictive power for functioning on the long-term of the patient. In case of diffuse axonal injury the findings with imaging are subtle, while the outcome can be very poor. In case of large cerebral contusions, with extensive pathology on imaging, the recovery may be good.

The location of the injury and neuropsychological examination in the subacute phase do not contribute to a reliable prognostic model either. Nevertheless, there is, for example, an association between frontal cerebral pathology on CT-scans and behavioural changes.[9] Besides, a dysexecutive syndrome is associated with diminished reintegration in work.[10] Little is known about which patients are at increased risk of late complications such as

dementia or parkinsonism, or who is at increased risk of social derailment. Because reliable prognostic models for long-term functioning are not available it is of essential importance to provide care based on the individual TBI patient. The lack of these long-term prognostic models are a hindrance in designing efficient and effective long-term care models for TBI patients.

ORGANISATION OF CARE

Traumatic brain injury is not an incident but a chronic condition.[2] Patients can suffer the consequences for the rest of their life and new complaints can arise even years after the incident. To guarantee patient access to the right type of care at the right time is a major challenge.

The 'Zorgstandaard Traumatisch Herstenletsel', published under auspices of the 'Hersenstichting', attempts to describe the multidisciplinary chain of care for traumatic brain injury. The involvement of general practitioners in recognising complaints that are related to traumatic brain injury is pivotal. They can refer patients with TBI in their medical history to a rehabilitation physician or neurologist for consultation, treatment, or further referral. In addition to this, the role of the patient organisation cannot be left unmentioned. For example, various patient organisations have merged into 'Hersenletsel.nl', as a result of which information provision, education, lobbying, and consulting can be further professionalised.

Discussion/What could have gone differently?

For both patient A and B, early coordination between the treating specialists and the general practitioner, with attention for the long-term perspective, could have prevented the patient's stagnation. Patient A stagnated in her work resumption before she was referred. Early onset support, for example in a multidisciplinary rehabilitation team, could have potentially prevented this outcome. The medical history of patient B illustrates the consequences of a referral to a non-specialised clinic, in which the severe cognitive deficits were not recognised and the patient was discharged without any form of aftercare. These cases serve as clear examples that the chain of care and long-term follow-up of patients with TBI need to be improved.

Conclusion

The long-term consequences of TBI often remain unrecognised and are underestimated. TBI should be considered as a chronic condition rather than an incident. Our health care system is not properly set up for this, resulting in many patients with unrecognised problems becoming dysfunctional at home. Cognitive deficits and behavioural changes in particular, are not recognised and can have major consequences on the patient's level of participation in work, family role or otherwise. The general practitioner has an important role in signalling these problems and can refer to for example the rehabilitation physician or neurologist for diagnosis, explanation and advise about a rehabilitation trajectory. Furthermore, patients and caregivers should be informed about patient organisations such as 'Hersenletsel.nl' and the services they provide.

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Chapter 3

Health-related quality of life 3 years after moderate to severe traumatic brain injury: a prospective cohort study

Erik Grauwmeijer
Majanka H. Heijenbrok-Kal
Gerard M. Ribbers

Arch Phys Med Rehabil. 2014;95:1268-76

ABSTRACT

Objectives To evaluate the time course of health-related quality of life (HRQoL) after moderate to severe traumatic brain injury (TBI) and to identify its predictors.

Design Prospective cohort study with follow-up measurements at 3, 6, 12, 18, 24, and 36 months after TBI.

Setting Patients with moderate to severe TBI discharged from 3 level-1 trauma centers.

Participants Patients (N=97, 72% men) with a mean age ± SD of 32.8±13.0 years (range, 18–65y), hospitalized with moderate (23%) or severe (77%) TBI.

Interventions Not applicable.

Main outcome measures HRQoL was measured with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), functional outcomes with the Glasgow Outcome Scale (GOS), Barthel Index, FIM, and Functional Assessment Measure, and mood with the Wimbledon Self-Report Scale.

Results The SF-36 domains showed significant improvement over time for Physical Functioning (P<.001), Role Physical (P<.001), Bodily Pain (P<.001), Social Functioning (P<.001), and Role Emotional (P=.024), but not for General Health (P=.263), Vitality (P=.530), and Mental Health (P=.138). Over time there was significant improvement in the Physical Component Summary (PCS) score, whereas the Mental Component Summary (MCS) score remained stable. At 3-year follow-up, HRQoL of patients with TBI was the same as that in the Dutch normative population. Time after TBI, hospital length of stay (LOS), FIM, and GOS were independent predictors of the PCS, whereas LOS and mood were predictors of the MCS.

Conclusions After TBI, the physical component of HRQoL showed significant improvement over time, whereas the mental component remained stable. Problems of disease awareness seem to play a role in self-reported mental HRQoL. After TBI, mood status is a better predictor of the mental component of HRQoL than functional outcome, implying that mood should be closely monitored during and after rehabilitation.

INTRODUCTION

Long-term outcome after traumatic brain injury (TBI) is commonly described in terms of activities and participation according to the International Classification of Functioning, Disability and Health of the World Health Organization.[1] In addition, subjective well-being or health-related quality of life (HRQoL) is an important outcome, providing information on impairments, disabilities, and the need for rehabilitation interventions.[2,3] HRQoL questionnaires measure the impact of a disease or disability, or its treatment, on physical, emotional, and social health, including participation in the community and level of everyday functioning.[4] Because the consequences of TBI may vary between individuals (depending on, e.g., TBI severity and/or personal circumstances), insight into the impact of TBI on quality of life, as experienced by the patient, is required.

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), frequently used to assess HRQoL, is validated for the assessment of patients with TBI.[5-8] Evaluating HRQoL at multiple points over time provides insight into how and when HRQoL may change after sustaining a TBI in relation to physical and mental recovery.

The SF-36 scores of persons after mild, moderate, and severe TBI have been reported to be lower compared with those of control subjects.[7,9,10] On the different subdomains of the SF-36, poor scores are often related to lower intelligence, more postconcussion symptoms, more posttraumatic fatigue, female sex, Medicaid coverage, not having health insurance, inadequate or moderate social support, comorbidities, cognitive complaints, and limitations in activities of daily living.[10-13] In a selected sample of 37 patients with mild TBI, SF-36 scores improved to normative values at 3 months postinjury and did not change thereafter; this suggests that most of the self-reported problems are present in moderate to severe TBI.[11]

Recovery after TBI is a long and complex process in which physical and psychosocial well-being may change over time. Studies on HRQoL after TBI often have shortcomings because of methodological issues such as a retrospective or cross-sectional design, small numbers of patients, or a focus only on patients with mild TBI.[9,11]

Therefore, the current study has a prospective design, in which patients with moderate or severe TBI are followed up from hospital admission until 3 years postinjury. The multiple measurements that are obtained make it possible to determine which variables change over time, and at which moment in time. The extensive measurements, recorded 6 times during a 3-year period (with 3 measurements in the first year), provide extensive insight into recovery patterns after TBI.

This study aims to evaluate the course of HRQoL in home dwelling patients up to 3 years after moderate or severe TBI (as measured with the SF-36), and to identify which determinants are associated with the physical and mental components of HRQoL in the long-term. We hypothesized that HRQoL will improve over time (with most improvement during the first year postinjury) and that the physical and mental components will likely have different determinants.

METHODS

Procedure

Details of the study design are published elsewhere.[14-16] In short, consecutive patients with moderate or severe TBI were enrolled between January 1999 and April 2004 at 3 acute care hospitals (all supraregional level-1 trauma centers): the Erasmus MC, University Medical Center Rotterdam (January 1999 to April 2004); the Medical Center Haaglanden, The Hague (January 2003 to February 2004); and the University Medical Center Utrecht, Utrecht (April 2003 to February 2004). Patients were prospectively followed up for 3 years.

Acute treatment of the patients was in accordance with the guidelines of the European Brain Injury Consortium.[17] If possible, informed consent was obtained from the patient; otherwise, informed consent was obtained from a family member, and patients were asked to give consent later. The study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam.

After baseline measurements were completed on hospital admission, patients were followed up prospectively at 3, 6, 12, 18, 24, and 36 months postinjury. After hospital discharge, potential destinations for patients are the home setting (with/without outpatient rehabilitation), inpatient rehabilitation centers, or nursing homes.[18]

Measurement of HRQoL and mood started from the time at which the patient was discharged home only. These self-report questionnaires were not administered during admission to the hospital or to the rehabilitation center or nursing home.

Participants

For the present study, inclusion criteria were admission to a hospital for moderate (Glasgow Coma Scale [GCS] score, 9–12) or severe (GCS score, 3–8) TBI caused by a nonpenetrating trauma. Exclusion criteria were inadequate knowledge of the Dutch language or important

pretraumatic neurologic, oncologic, or systemic impairments (e.g., spinal cord injury, psychiatric disorder, or cancer) that may interfere with TBI-related assessment of disability.

Outcome measure

The Dutch version of the SF-36 was used to assess HRQoL in the home setting only.[5,6,19] This is a valid and reliable instrument for use in various conditions, including TBI.[6-8] The SF-36 consists of 36 items measuring 8 domains: Physical Functioning; Role Physical (the extent to which physical health interferes with daily activities); Bodily Pain; General Health; Vitality; Social Functioning; Role Emotional (the extent to which emotional health interferes with daily activities); and Mental Health. All domains are transformed into a scale from 0 to 100, with 100 indicating the best possible condition. The 8 domain scores can be summarized into a Physical Component Summary (PCS) score (to which Physical Functioning, Role Physical, Bodily Pain, and General Health contribute most) and a Mental Component Summary (MCS) score (to which Mental Health, Social Functioning, Role Emotional, and Vitality contribute most). The PCS and MCS are scored using norm-based methods (T scores); for example, in the general United States population, the PCS and MCS have a mean ± SD of 50±10.[20] For the present study, age-adjusted norm values from the Dutch normative population were used.[6]

In this study, the internal consistency of the PCS and MCS subscales was adequate (α=.72 and α=.76, respectively). Correlation between the summary scales and the associated subscales was highly significant (PCS: r>.55 and MCS: r>.56; P<.001), whereas correlation between the PCS and MCS was not (r=-.13; P>.300), indicating that the construction of the summary scores was valid.

Determinants of HRQoL

In the acute care hospital, patient and clinical characteristics were recorded by the medical staff using a standardized patient record form, which included age at injury (in years), sex, marital status (alone vs living with others), the lowest GCS score in the first 24 hours after TBI measured in the hospital, the presence (yes/no) and type of psychiatric symptoms (depression, anxiety, or other serious psychiatric symptoms), the hospital length of stay (LOS), and the hospital discharge destination (home vs institution). Follow-up measures included change in marital status, employment status (yes/no), type of work and workload (full-time, part-time, unemployed), self-reported psychiatric symptoms and other comorbidities, and functional outcomes. Follow-up measures were recorded by 1 of the 2 research psychologists using structured face-to-face interviews.

Functional outcomes, assessed at hospital discharge and at 3, 6, 12, 18, 24, and 36 months postinjury, included the FIM and the Functional Assessment Measure (FAM) (FIM+FAM), the Barthel Index (BI), the Glasgow Outcome Scale (GOS), and the Wimbledon Self-Report Scale (WSRS).[21-26] The FIM+FAM is a (combined) 30-item scale in which each item is evaluated on a 7-point scale (ranging from totally dependent to completely independent). The 18 FIM items evaluate motor functioning with regard to locomotion, transfers, self-care, and sphincter control; scores range from 18 (completely dependent) to 126 (totally independent). The 12 FAM items evaluate cognitive and communication functioning, and psychosocial adjustment; scores range from 12 to 84. The 2 research psychologists were qualified FIM+FAM assessors. The reliability and validity of the FIM, FAM, and BI are good.[24-27] The BI encompasses 10 items of daily living (dressing, grooming, bathing, and bladder and bowel status); scores range from 20 (no restrictions) to 0 (severely restricted). The GOS is frequently used to assess general outcome after TBI; the 5 outcome categories range from death to good recovery.[28,29] The WSRS was used to assess mood in the home setting; this scale is suitable for neurologic patients.[30]

Although patients' feelings are explored, somatic symptoms and memory and concentration problems are not analyzed. This scale is unaffected by sex or age, and false-positive (4%) and false-negative (6%) scores are relatively low.[30] Of the 30 adjectives/phrases used to describe feelings, 24 are related to unpleasant feelings and 6 to feelings of happiness. The WSRS score ranges from 0 to 30; scores of 0 to 7 are considered normative, scores of 8 to 10 are borderline, and scores ≥11 indicate a mood disorder.[30]

Statistical analysis

Descriptive analyses were performed for the SF-36 scores over time, both for its subdomains and for the PCS and MCS scores separately. A linear mixed-model analysis with repeated measurements was completed, taking into account correlations of measurements within the same patient. By estimating the covariance structure, this method is very flexible in handling missing values.

Using univariable analyses in 2 separate linear mixed models, we evaluated the effect of potential fixed and time-varying predictors on the dependent variables PCS and MCS, respectively. Time after TBI was entered as a factor to each model to evaluate changes over the total follow-up period and to compare changes between all individual time points in the post hoc analyses.

After the univariable analyses, the significant variables were tested in a multivariable mixed model for PCS and MCS, separately. Potential fixed predictors included patient

characteristics (age, sex, educational level), injury severity variables (LOS, discharge destination, TBI severity), and time-varying predictors that included living with a partner (yes/no), the presence of psychiatric symptoms (yes/no), employment status (yes/no), and all functional outcomes (GOS, BI, FIM, FAM, WSRS). The time varying predictors were measured at the same measurement times as the dependent variables, that is, at 3, 6, 12, 18, 24, and 36 months after TBI.

For the model that included all significant variables, the covariance structure was estimated starting with an unstructured matrix. Simpler covariance structures for this model were tested using the restricted likelihood ratio test and were adopted if the differences were not significant. The final covariance structure for the PCS model was the homogenous autoregressive matrix, and for the MCS model, the compound symmetry matrix. Subsequently, nonsignificant determinants were omitted from the multivariable models using the likelihood ratio test for comparison of the models. The model fit was also checked using the Akaike Information Criterion; lower model fit values indicate a better fit.

SPSS version 19 was used for all analyses; a P-value <.05 was considered statistically significant.

RESULTS

Patient population

Of the 549 patients screened, 153 died and 229 were not included based on the exclusion criteria -that is, 90 patients were outside the age range, 46 had mild TBI, 45 had severe comorbidity, 42 had relocated to another area, and 6 patients had insufficient mastery of the Dutch language. Of the remaining 167 eligible patients, 113 were willing to participate.

During the 3-year follow-up, multiple SF-36 scores were available for 97 (86%) of the 113 patients, who were included in the present analyses. Of these 97 patients, 86 were from the Erasmus MC, University Medical Center Rotterdam; 9 from the University Medical Centre Utrecht; and 2 patients were from the Medical Center Haaglanden.

The mean age ± SD of the participants was 32.8±13.0 years; 72% were men; and the mean GCS score ± SD was 6.6 ± 2.6 (Table 3.1). Patients who completed the 3-year follow-up (n=66) showed no significant difference, compared with patients not assessed at that point in time (n=31), for age at injury, sex, GCS score, LOS, TBI severity, GOS, and FIM+FAM, as well as for the BI score at hospital discharge and the WSRS score measured at home.

Table 3.1: Characteristics of patients with moderate or severe traumatic brain injury (TBI)

Patient characteristics	Total group N=97
Age (y)	32.8±13.0
Sex (men)	70 (72)
Living with partner	46 (47)
Educational level, higher	51 (53)
Psychiatric symptoms	9 (10)
Hospital LOS (d)	38.6±27.3
TBI severity	
Moderate (GCS 9–12)	22 (23)
Severe (GCS 3–8)	75 (77)
Hospital discharge destination	
Rehabilitation center/nursing home	52 (54)
Home	45 (46)
GOS at hospital discharge	
Vegetative	1 (1)
Severe	48 (62)
Moderate	29 (37)
FIM at hospital discharge	102.4±24.1
FAM at hospital discharge	62.0±15.0
BI at hospital discharge	15.7±6.0
WSRS measured at home	4.8±4.9

Note. Values are mean ± SD or n (%). LOS, length of stay; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; FIM, Functional Independence Measure; FAM, Functional Assessment Measure; BI, Barthel Index; WSRS, Wimbledon Self-Report Scale.

HRQoL: change over time

Table 3.2 presents the estimated means and SEs for the SF-36 at 3, 6, 12, 18, 24, and 36 months. During the 3-year follow-up period, a significant change was found for Physical Functioning (P<.001), Role Physical (P<.001), Bodily Pain (P<.001), Social Functioning (P<.001), and Role Emotional (P=.024), but not for General Health (P=.263), Vitality (P=.530), and Mental Health (P=.138).

After TBI, the Physical Functioning score showed a gradual increase from 72 at 3 months to 86 at 3 years, with a significant increase in the first 3 to 6 months (P=.001) and also from 6 to 36 months (P=.003). The Role Physical score showed a significant increase from 39 at 6 months to 53 at 12 months (P=.004), after which it increased to 66 at 3 years (P=.010). Bodily Pain showed a significant improvement in the first 3 to 6 months (P=.019), stabilized, and then showed a further increase from 24 to 36 months (P=.017). Vitality

Table 3.2: SF-36 outcomes of the Dutch normative population (norms) and estimated SF-36 outcomes over time of the TBI population, including significance level of change over time

	Dutch norms*	3mo†	6mo†	12mo†	18mo†	24mo†	36mo†	P-value Change over time
SF-36								
PF	93±12	72±2.9	80±2.3	82±2.3	82±2.4	84±2.3	86±2.3	.000‡
RP	86±28	30±4.7	39±4.6	53±4.5	54±4.6	58±4.7	66±4.3	.000‡
BP	80±19	70±3.2	77±2.7	80±2.7	79±2.6	75±2.9	83±2.5	.004‡
GH	78±17	71±2.3	74±2.1	76±1.9	76±1.9	77±2.1	77±2.3	.263
VT	71±16	59±2.1	61±2.3	62±2.0	63±1.9	64±2.0	64±2.0	.530
SF	88±19	70±3.2	76±2.8	84±2.4	82±2.7	82±2.7	85±2.2	.001‡
RE	85±30	69±5.7	74±4.5	76±4.0	77±3.9	86±3.3	80±4.1	.024‡
MH	79±15	72±2.0	76±2.0	74±1.8	73±1.7	77±1.7	75±1.5	.138
PCS§	50±10	34±1.8	39±1.6	42±1.6	42±1.5	42±1.5	46±1.3	.000‡
MCS§	50±10	49±1.6	49±1.3	49±1.2	49±1.3	51±1.2	49±1.2	.139

PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health; PCS, Physical Component Summary; MCS, Mental Component Summary.
* Values are mean ± SD.
† Values are mean ± SE.
‡ Statistically significant data.
§ T-scores.

remained stable, ranging from 59 to 64 during the entire follow-up. Social Functioning showed a significant increase during the first 12 months (3–6mo, P=.048; 6–12mo, P=.022) and then stabilized. The Role Emotional score showed a significant increase at 18 to 24 months (P=.024), whereas the Mental Health showed no significant improvement over time (range, 72 at 3mo to 75 at 3y).

The PCS score showed a significant improvement from 3 to 6 months (P=.002), 6 to 12 months (P=.046), and from 24 to 36 months (P=.008), with T scores ranging from 34 to 46. In contrast, the MCS score remained stable over the 3-year follow-up (T score, 49 at almost each measurement time).

HRQoL compared with Dutch norm values

Figure 3.1 shows that, at 3 months after TBI, scores on the SF-36 domains of the patient group were significantly lower compared with those of the age-adjusted Dutch normative population. Differences between the TBI population and the Dutch norms were still significant at 3-year follow-up for the subdomains Physical Functioning (P<.001), Role Physical (P<.001), Vitality (P<.001), and Mental Health (P=.014), but not for Bodily Pain (P=.353), General Health (P=.604), Social Functioning (P=.153), and Role Emotional (P=.144) (see Figure 3.1).

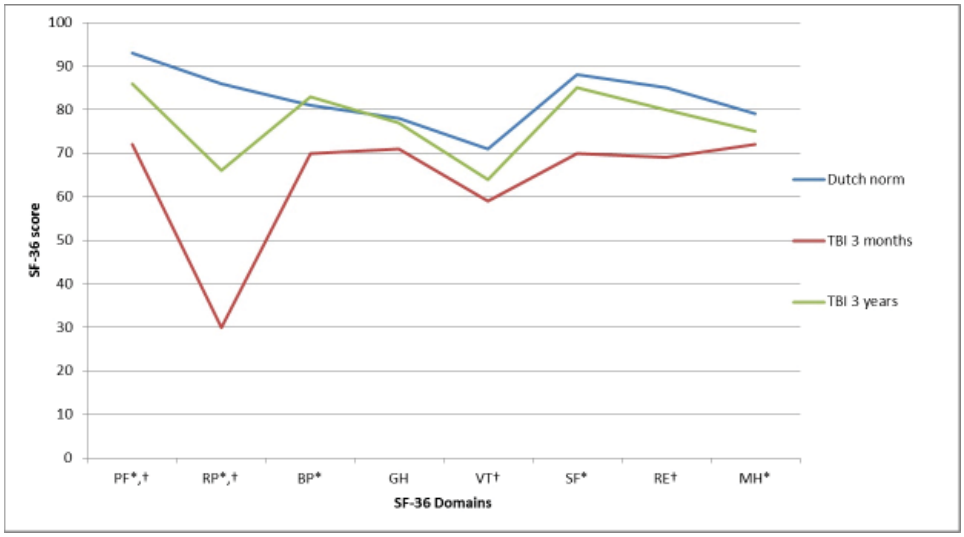

Figure 3.1: SF-36 domain scores at 3 months and 3 years after TBI compared with the age-adjusted Dutch normative population (norm) (Dutch norms obtained from Aaronson et al.[6]).
* Differences between 3 months and 3 years after TBI were significant for Physical Functioning (P<.001), Role Physical (P<.001), Bodily Pain (P<.001), Social Functioning (P<.001), and Role Emotional (P=.024).
† Differences between the normative population and TBI after 3 years were significant for Physical Functioning (P<.001), Role Physical (P<.001), Vitality (P<.001), and Mental Health (P=.014).

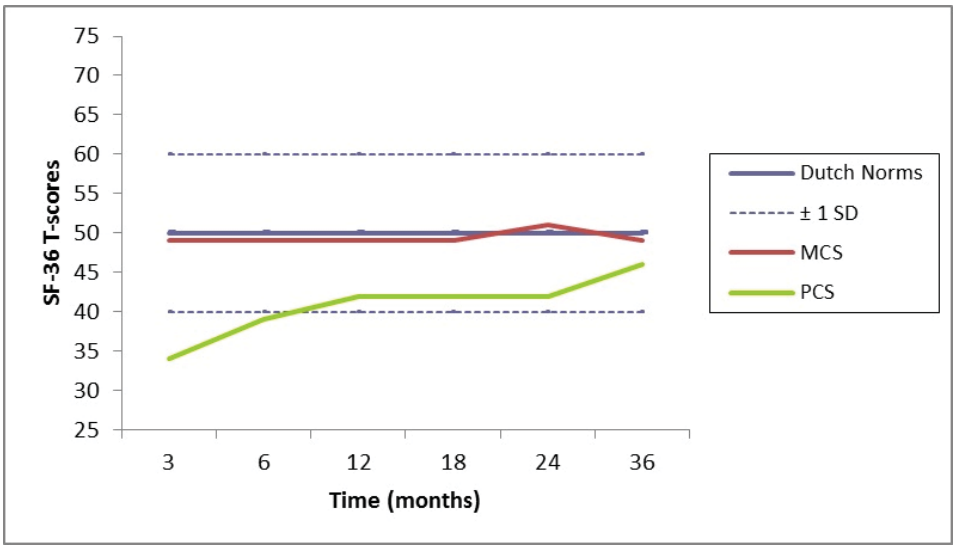

Figure 3.2: Course of PCS and MCS of the TBI population over time (Dutch Norms obtained from Aaronson et al.[6]), T scores based on the age-adjusted Dutch normative population (Norms).

Figure 3.2 presents data on the PCS and MCS over time. During the first year after TBI the PCS improved, after which it differed by ≤1 SD from that of the Dutch normative population. In contrast, the MCS remained stable over time at the same level as that of the normative population.

Determinants of HRQoL

To determine significant predictors for HRQoL we used the PCS and MCS scores as outcome measures. Time after TBI, hospital discharge destination, age, LOS, FIM, FAM, BI, and GOS were significant determinants for the PCS score in the univariable analysis (Table 3.3). In

Table 3.3: Results of the linear mixed models analyses for prediction of the PCS score (n=97)

	Univariable		Multivariable	
Predictors	β	P-value	β	P-value
Time after TBI:				
3mo	-11.61	.000	-10.30	.000
6mo	-6.52	.000	-6.92	.000
12mo	-3.76	.008	-3.45	.021
18mo	-3.37	.006	-3.39	.012
24mo	-3.44	.008	-3.22	.010
36mo (reference)	0	NA	0	NA
Hospital discharge destination				
Home	7.7	.001	Excluded	NS
Rehabilitation center/nursing home (reference)	0	NA		
Age	-0.19	.037	Excluded	NS
LOS	-0.19	.000	-0.10	.006
FIM	0.72	.000	0.60	.000
FAM	0.58	.000	Excluded	NS
BI	0.8	.035	Excluded	NS
GOS				
Severe	-12.18	.000	-7.32	.003
Moderate	-4.32	.001	-2.67	.037
Good	0	NA	0	NA
Model fit statistics	Full model	No. of parameters	Final model	No. of parameters
-2 Log likelihood	2766.8	14	2770.3	10
AIC	2808.8	14	2804.3	10

Note. Lower model fit statistics indicate a better fit. Model comparisons were performed using the likelihood ratio test. PCS, Physical Component Summary; LOS, length of hospital stay; FIM, Functional Independence Measure; FAM, Functional Assessment Measure; BI, Barthel Index score; GOS, Glasgow Outcome Score; AIC, Akaike's Information Criterion; NA, not applicable; NS, not significant.

the multivariable analysis, the variables LOS, FIM, and GOS were independent predictors of the PCS. Sex, living with a partner, educational level, psychiatric symptoms, and TBI severity (as measured with the GCS) did not predict the PCS score.

For prediction of the MCS score, TBI severity (P=.024), LOS (P=.005), FIM (P=.036), FAM (P=.002), and WSRS (P<.001) were significant variables in the univariable analysis. Patients with moderate TBI perceived a lower mental HRQoL than patients with severe TBI. In the multivariable analysis, LOS (P<.001) and WSRS (P<.001) were independent predictors of the MCS (Table 3.4). Patients with more symptoms of depression perceived a lower mental HRQoL, whereas a longer LOS was related to a higher HRQoL. Time after TBI, hospital discharge destination, and age were not predictive for the MCS score; neither were the factors that were also not predictive for the PCS score.

Table 3.4: Results of the linear mixed models analyses for the prediction of the MCS (n=97)

	Univariable		Multivariable	
Predictors	β	P-value	β	P-value
TBI severity				
Moderate	-4.58	.024	Excluded	NS
Severe (reference)	0	NA		
LOS	0.09	.005	0.11	.000
FIM	0.17	.036	Excluded	NS
FAM	0.27	.002	Excluded	NS
WSRS	-1.10	.000	-1.20	.000
Model fit statistics	Full model	No. of parameters	Final model	No. of parameters
-2 Log likelihood	2548.5	6	2544.3	3
AIC	2564.5	6	2554.3	3

Note: Lower model fit statistics indicate a better fit. Model comparisons were performed using the likelihood ratio test. MCS, Mental Component Summary; TBI, traumatic brain injury; LOS, length of hospital stay; FIM, Functional Independence Measure; FAM, Functional Assessment Measure; WSRS, Wimbledon Self-Report Scale; AIC, Akaike's Information Criterion; MA, not applicable; NS, not significant.

DISCUSSION

This prospective study in patients with moderate and severe TBI underlines that physical HRQoL shows a significant improvement up to 3 years after TBI, with most improvement occurring in the first year. At 3 years postonset, compared with the Dutch normative population, differences were no longer significant for either of the summary scores of

HRQoL. On the subdomain level, at 3-year follow-up, significant differences compared with the normative population were found for only 4 subdomains (Physical Functioning, Role Physical, Vitality, Mental Health). Bearing in mind the severity of the injury, this seems a remarkable finding.

The studies of Andelic,[31] Forslund,[32] and Jacobsson[33] and colleagues (all conducted in Scandinavia) report lower scores on the SF-36 domains compared with those of their general population. Regarding the mean PCS score, our physical findings at 2-year follow-up replicated those of Forslund,[32] whereas our mean MCS score was higher. However, a possible explanation for this difference is that in our study, physical scores improved during the third year of follow-up, whereas the follow-up period in the study of Forslund[32] was limited to 2 years. Also, Andelic[31] and Jacobsson[33] retrospectively assessed HRQoL 10 years after moderate to severe TBI, which may have resulted in some selection bias. Jacobsson[33] also reported that HRQoL improved over time after sustaining a TBI; this is supported by our findings of continued improvement. Similar to the present study, in the Scandinavian studies the MCS scores were higher than the PCS scores; this result may be due to the limited awareness of mental disorders among patients with severe TBI.[32,33] However, this was not the case in an Australian retrospective study investigating mild to severe TBI; this latter study reported PCS scores similar to those in our study, but lower MCS scores. This discrepancy between the studies might be explained by the large proportion of patients with mild TBI in the Australian study as opposed to our study population with moderate and severe TBI.[34]

In the present study, the most improvement in physical HRQoL was found during the first year after TBI. Other prospective studies also reported a similar trend regarding the recovery pattern over time, even when using other instruments to measure HRQoL. For example, Lin et al.[35] followed up 158 patients with mild to severe TBI over 1 year and found that scores on all domains of the brief version of the World Health Organization Quality of Life (except for Social Relationships) greatly improved during the first 6 months, with continued improvement up to 12 months postinjury. In our study, a similar trend was seen on the physical domains (except for General Health).

Furthermore, Pagulayan et al.[36] examined HRQoL in 133 patients with mild to severe TBI from 1 month up to 3 to 5 years after TBI using the Sickness Impact Profile. Their patients with TBI reported significant limitations at 1 month postinjury but with substantial improvement occurring at 6 months, especially in the physical domain. This result is similar to that in our study.[36] Moreover, Pagulayan et al.[36] reported that psychosocial improvement was smaller and that perceived cognitive, emotional, and communication difficulties remained stable over time. These trends are also largely in agreement with our findings.

In the present study, a longer LOS was associated with higher mental HRQoL. This might be explained by a reduced disease awareness related to the severity of the TBI, as also reported by Dijkers.[37] Being unaware of deficits may interfere with reporting them, whereas evaluation by a proxy might have provided more realistic information. In addition, we found that LOS was negatively associated with physical HRQoL and positively associated with mental HRQoL; this indicates that patients with more severe TBI (i.e., longer LOS) reported worse physical HRQoL but better mental HRQoL. These findings also suggest a limited disease awareness with respect to mental health in patients with more severe TBI. Similar associations between physical and mental health were reported by others for injury severity based on the GOS, or on the length of posttraumatic amnesia.[32,33]

We also found that mood independently affected the course of mental health. The presence of mood disorders and the influence of mood on HRQoL have also been reported by others. The psychiatric diagnoses most frequently reported after TBI are depressive disorders (23%-30%)[31,32,34,38] and (in case of severe TBI) changes in personality (33%).[38] Lin[35] reported that depressive status significantly influenced longitudinal changes in the psychological and social domains of the brief version of the World Health Organization Quality of Life over a 1-year period after TBI, which is in accordance with our findings. Furthermore, Hart et al.[39] concluded that severity of depression after TBI is associated with reduced participation and quality of life. Therefore, after TBI, it seems advisable to place more focus on screening and treatment of mood disorders and at an early stage.

Study limitations

Some study limitations need to be addressed. A total of 97 participants may not be sufficient to detect small but important differences. Also, only 66 of this group could be followed up until the 3-year measurement point; this 32% loss to follow-up might have affected the outcomes. Moreover, because HRQoL and mood were measured in the home environment only, this may have resulted in missing data during the first measurements if the patients were still in the hospital, rehabilitation center, or nursing home at that time. If these self-report questionnaires had also been administered during admission, the data would have been more complete.

TBI severity was measured using the lowest GCS score measured during the first 24 hours in the hospital; therefore, potential bias resulting from the influence of, for example, medications or shock, cannot be completely ruled out.

Furthermore, HRQoL is not a static phenomenon and is known to change in response to individual lifetime developments, priorities, and alterations in the outside world (e.g.,

winning the lottery or sustaining an accident). Thus, being a dynamic phenomenon, HRQoL is difficult to objectively measure in each individual.

The PCS and MCS scores were used to define the physical and mental subdomains of HRQoL; this may lead to simplification because not all 8 subdomains were studied in detail. A considerable number of analyses would be needed to study all potential predictors for each outcome separately; however, this would not add to the interpretation and readability of the present results.

Moreover, it is reported that the PCS and MCS scores should be interpreted with caution in patients with TBI (n=514) because of different loading patterns when compared with United Kingdom and United States normative populations.[40] However, in the present study, the construction of the MCS and PCS appeared to be valid.

Finally, (health-related) quality of life is a multidimensional concept. Although the SF-36 is widely applied, its use may be questioned. For example, it is a generic measure and not specifically designed to measure HRQoL after a specific disease such as TBI. Therefore, it may not capture all the necessary dimensions of HRQoL for patients with TBI. Unfortunately, the TBI-specific Quality of Life after Brain Injury questionnaire was not available at the start of data collection for the present study.[41]

CONCLUSIONS

In this population of patients with moderate and severe TBI, physical HRQoL showed a significant improvement over time. Although these individuals initially indicated more physical functioning difficulties compared with the normative Dutch population, these differences were no longer present at 3-year follow-up. In contrast, mental HRQoL of the TBI group showed no significant change over time and, from the first measurement, was comparable with that of the Dutch normative population. It seems that after TBI, problems related to disease awareness play a role in self-reported levels of mental HRQoL.

On the physical domain, the most important significant predictors for HRQoL were time after TBI, LOS, and physical functioning, whereas the most influential factors for mental health were LOS and mood. Therefore, in individuals who are more aware of their disabilities after TBI, for optimal mental HRQoL it seems necessary to focus on early screening and treatment of mood disorders.

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Chapter 4

A prospective study on employment outcome 3 years after moderate to severe traumatic brain injury

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ABSTRACT

Objectives To evaluate the employment outcome in patients with moderate to severe traumatic brain injury (TBI) and to identify which patients are at risk of unemployment 3 years after injury.

Design Prospective cohort study.

Setting Patients with moderate and severe TBI discharged from the neurosurgery departments of 3 level 1 trauma centers in The Netherlands.

Participants Patients aged 18 to 65 years (N=113; mean age ± SD, 33.2±13.1y; 73% men) who were hospitalized with moderate (26% of patients) to severe (74% of patients) TBI.

Interventions Not applicable.

Main outcome measures The main outcome measure was employment status. Potential predictors included patient characteristics, injury severity factors, functional outcome measured at discharge from the acute hospital with the Glasgow Outcome Scale (GOS), Barthel Index (BI), and FIM, and cognitive functioning measured with the Functional Assessment Measure (FAM).

Results Ninety-four patients (83%) completed the 3-year follow-up. The employment rate dropped from 80% preinjury to 15% at 3 months postinjury and gradually increased to 55% after 3 years. The employment rate significantly increased from 3 months up to 1 year, but it did not change significantly from 1 to 3 years postinjury. Age, length of hospital stay, discharge to a nursing home (vs home), psychiatric symptoms, and BI, GOS, FIM, and FAM scores were found to be significant univariate determinants for employment status. By using multiple logistic regression analysis, the FAM score (adjusted odds ratio 1.1; P<.000) and psychiatric symptoms (adjusted odds ratio .08; P<.019) were selected as independent predictors for employment status. A FAM cutoff score of less than 65 to identify patients at risk of long-term unemployment had a good diagnostic value.

Conclusions Patients with TBI with psychiatric symptoms and impaired cognitive functioning at hospital discharge are at the highest risk of long-term unemployment. These factors should be the focus of vocational rehabilitation.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. It is 3 times more common in men than in women; young people and the elderly are at the highest risk. The most common mechanisms of injury are traffic accidents, falls, and violence.[1,2] Approximately 1.6 million patients with TBI are admitted to hospitals each year in Europe.[3,4] In the United States, the incidence of TBI is estimated to be 200 per 100,000 people per year.[1]

The outcome after TBI can vary from complete recovery to death, with many patients having long-term physical, cognitive, and psychosocial disabilities. An otherwise successful medical rehabilitation may end unsuccessfully because of the failure to return to work (RTW), with severe consequences to the patient and the patient's family, both economic and psychosocial.[1] Several medical, physical, and psychosocial therapies that improve the chances of returning to work are currently being implemented in rehabilitation settings. In order to treat patients in an optimal way, it is important to identify which patients are at high risk of long-term unemployment and which patients are not.

Many studies have been performed on the prediction of TBI outcomes with many candidate predictors available, varying from preinjury sociodemographic factors and clinical variables related to injury severity to postinjury behavioral and psychosocial variables.[5] However, the outcomes of these studies may vary considerably, because of patient mix, differences in definitions of outcome variables, assessment methods, and study design. The majority of studies on employment outcomes are performed at 1 or more points in time, in a retrospective, cross-sectional study design.[6-8] Changes over time cannot be studied in these study designs. Only a few studies have been published in which a cohort of patients with TBI has been followed prospectively. Unfortunately, follow-up time often ends 1 year after TBI.[9,10]

Prospective follow-up studies with a more than 1-year follow-up time after injury are scarce.[11] Exceptions are the large prospective database studies, such as the Traumatic Brain Injury Model Systems. These database studies have their own methodologic difficulties, such as missing values and high losses to follow-up (42% after 1 year and 68% after 5 years), which could be a threat to the validity of the results.[12]

Many measures of early functional status and global outcomes have been found to be predictive of unemployment after TBI. What is often missing in these studies is the calculation of the optimal cutoff value of the measurement instrument to decide which patient is at risk and which patient is not. The diagnostic value of a measurement instrument

and the optimal cutoff score can be evaluated by using receiver operating characteristics (ROC) analysis.[13] The cutoff value helps clinicians and rehabilitation professionals in deciding which patients should be selected for a specific treatment. The current study is a prospective study in which a cohort of patients with moderate to severe TBI was followed from hospital admission until 3 years postinjury at regular time intervals. The aim of the study was to evaluate the employment rate up to 3 years after moderate and severe TBI and to identify which patients are at risk of unemployment in the long term.

METHODS

Procedure

Patients with TBI were consecutively enrolled between January 1999 and April 2004 at 3 Dutch acute care hospitals, which were all level 1 trauma centers—Erasmus Medical Centre, Rotterdam (January 1999 to April 2004); Medical Centre Haaglanden, The Hague (January 2003 to February 2004); and University Medical Centre Utrecht, Utrecht (April 2003 to February 2004)—and prospectively followed for 3 years. All study centers served as treatment centers for acute hospital care for all patients with moderate to severe TBI within their regions. Patients were treated in accordance with the European Brain Injury Consortium guidelines.[14] In The Netherlands patients are discharged from the acute care hospitals to the initially referring neurology department of local hospitals, to their homes (with or without outpatient rehabilitation), to inpatient rehabilitation centers, or to a nursing home.[15] Upon admission, patients with acute TBI or family members were asked whether they were willing to participate in the study. When possible, informed consent was obtained from the patient. Otherwise, informed consent was obtained from a family member and patients were asked to give consent at a later time. The medical ethics committee of Erasmus Medical Centre approved this study. Baseline measurements were performed at hospital admission, and patients were followed prospectively at 3, 6, 12, 18, 24, and 36 months postinjury.

Participants

Inclusion criteria were admission to a hospital for moderate (Glasgow Coma Scale [GCS] score of 9–12) or severe (GCS score of 3–8) TBI due to a nonpenetrating trauma. Exclusion criteria were insufficient knowledge of the Dutch language to participate in the study or serious pretraumatic neurologic, oncologic, or systemic impairments (e.g., spinal cord injury, psychiatric disorder, and cancer) that may interfere with TBI-related disability assessment.

Data collection

Data were collected from the patient and/or a significant other or primary caregiver. Baseline sociodemographic and clinical data were obtained by the treating physicians in collaboration with the neurosurgery department of each participating hospital. The lowest GCS score within 24 hours of admission was recorded. Other baseline and follow-up data were gathered at different locations, including the department of neurosurgery, rehabilitation centers and various nursing homes in the area, and at the patients' homes. All follow-up data were collected by 2 trained research psychologists, who visited the patients at the medical institution or at their homes for each measurement. In The Netherlands, patients with severe deficits who suffer from posttraumatic amnesia, recover slowly, and have a poor physical condition are transferred to nursing homes. Patients with some anterograde memory function, sufficient attention span, and a physical condition that allows for a minimum of 2 to 3 therapy sessions of 15 minutes per day are transferred to specialized inpatient rehabilitation clinics.[15]

Measurement instruments

Employment outcome was recorded during each visit by means of structured interviews. Employment outcome included questions on employment status (yes/no), type of work, and workload (full-time, part-time, unemployed). The type of work was classified into 4 categories: professional/managerial, skilled, manual labor, and unemployed or student. The first category included executive, administrative, and managerial functions and professional specialties. The second category included technicians and administrative support, precision production, craft, and repair personnel. The third group incorporated people working as machine operators, assemblers, transporters, and cleaners. This classification is largely based on the article of Walker et al.[16] We did not exclude previously unemployed persons or students, but we analyzed these patients separately in a fourth category.

The presence (yes/no) and type of psychiatric symptoms were observed during hospitalization by the medical staff and also recorded at each visit by the research psychologist in a structured interview, which included self-reported depression, anxiety, and other serious psychiatric symptoms.

Functional outcome was assessed with the FIM and the Barthel Index (BI) at hospital discharge.[17,18] Cognitive outcome was measured with the Functional Assessment Measure (FAM). The FIM and FAM have a good reliability and validity.[19-22] They consist of 30 items that are evaluated on a 7-point scale (completely independent to totally dependent). The FIM evaluates motor functioning with respect to self-care, sphincter control, transfers,

and locomotion, whereas FAM evaluates cognitive and communication functioning and psychosocial adjustment. The FIM motor scale score ranges from 18 (totally dependent) to 126 (totally independent), and the FAM cognitive scale score ranges from 12 (totally dependent) to 84 (totally independent). The research psychologists were qualified FIM/FAM assessors. The BI also has a good reliability and validity.[23] This instrument consists of 10 items on activities of daily living (grooming, dressing, bathing, and bowel and bladder status), each with 2 or 4 response categories (0–3 points). Total scores range from 0 (severely restricted) to 20 (no restrictions).

The Glasgow Outcome Scale (GOS) is a widely accepted measure for general outcome after TBI. The full GOS encompasses 5 outcome categories: death, vegetative state, severe disability, moderate disability, and good recovery.[24,25]

Statistical analysis

Descriptive analyses were performed for the total group and for 2 subgroups that were defined as the persons who were employed preinjury and the persons who were unemployed preinjury. The course of employment status over time was calculated by using generalized estimating equations to fit a logistic regression analysis with repeated measurements. This analysis takes into account that multiple measurements within subjects are correlated.

By using univariable and multiple logistic regression methods, we evaluated the effect of potential predictors, which were measured at baseline, on employment status (unemployed vs employed) at 36-month follow-up. Potential predictors included patient characteristics (age, sex, partner, educational level), injury severity variables (length of hospital stay, TBI severity [moderate (GCS score 9–12) or severe (GCS score 3–8)]), presence of psychiatric symptoms (yes/no), employment variables (preinjury employment, occupational category, preinjury workload [full-time, part-time, unemployed]), and functional outcomes at hospital discharge (GOS, BI, FIM, FAM).

ROC analysis was performed to evaluate the diagnostic value of the measurement instrument selected. The area under the ROC curve was calculated, which indicates how well the test discriminates between diseased and nondiseased patients. An area of 100% indicates perfect diagnostic value, whereas an area of 50% is equal to flipping a coin, which means no diagnostic value. The optimal cutoff score was defined as the point on the ROC curve that maximizes sensitivity and specificity.

For all statistical analyses, we used the Statistical Package for the Social Sciences, version 16.

RESULTS

In total, 549 patients were screened. Of these patients, 153 patients died and 229 patients were excluded on the basis of exclusion criteria (90 patients were out of the age range, 46 patients showed mild TBI, 45 patients had severe comorbidity, 42 patients were transferred to another area, and 6 patients did not master the Dutch language). This left 167 eligible patients, from which 113 were willing to take part in this study. No patient refused to participate after informed consent from a family member was obtained. After 3 years, 19 patients were lost to follow-up (17%). Patients who were lost to follow-up did not differ significantly from patients with complete follow-up in baseline characteristics, except for GCS score, educational level, and preinjury employment status. Patients who were lost to follow-up compared with patients with complete follow-up had a higher mean GCS score

Table 4.1: Characteristics of patients with moderate to severe TBI for the total group and subgroups of employed and unemployed patients pre-injury

	Employment status pre-injury		
Patient characteristics	Employed N=88	Unemployed N=22	Total group N=113
Mean age ± SD (y)	34.0±11.9	29.4±15.5	33.2±13.1
Sex: male, n (%)	68 (77)	12 (54)	82 (73)
Living with partner, n (%)	47 (53)	4 (18)	52 (46)
Educational level, higher, n (%)	49 (56)	4 (18)	54 (50)
Psychiatric symptoms, n (%)	9 (11)	0 (0)	9 (8)
Mean length ± SD of hospital stay (d)	41.2±30.5	31.7±18.1	39.7±28.4
TBI severity, n (%)			
Moderate (GCS score 9–12)	23 (26)	6 (27)	29 (26)
Severe (GCS score 3–8)	65 (74)	16 (73)	84 (74)
Hospital discharge destination, n (%)			
Rehabilitation centre	35 (40)	7 (32)	42 (38)
Nursing home	14 (16)	2 (9)	16 (15)
Home	39 (44)	13 (59)	52 (47)
Occupational category preinjury, n (%)			
Professional/managerial	14 (16)	NA	14 (12)
Skilled	25 (28)	NA	25 (22)
Manual labour	47 (53)	NA	47 (42)
Unemployed/student	NA	22 (100)	22 (19)
Work load pre-injury, n (%)			
Full-time	66 (75)	NA	66 (60)
Part-time	22 (25)	NA	22 (20)
Unemployed	NA	22 (100)	22 (20)

GCS, Glasgow Coma Scale; NA, not applicable.

(7.95 vs 6.52; P<.035), had more often a low educational level (88% vs 44%; P<.001), and were more often unemployed preinjury (53% vs 14%; P<.001).

The mean age ± SD of the study population was 33.2±13.1 years, the majority (73%) were men, and 74% had severe TBI. The employment rate preinjury was 80%. For comparison, in The Netherlands, the employment rate of the total working population varied from 74% to 77% for men and from 51% to 57% for women, respectively, during the study period.[26] Patient characteristics are listed in Table 4.1.

Course of employment rate

The mean employment rate at different time points during follow-up is presented in Figure 4.1. This figure shows that the employment rate dropped from 80% preinjury to a level of 12% at 3-month follow-up and then gradually increased to 55% at 3-year follow-up. The employment rate significantly increased from 3 months up to 1 year (P<.000), but it did not change significantly from 1 to 3 years postinjury (P<.097).

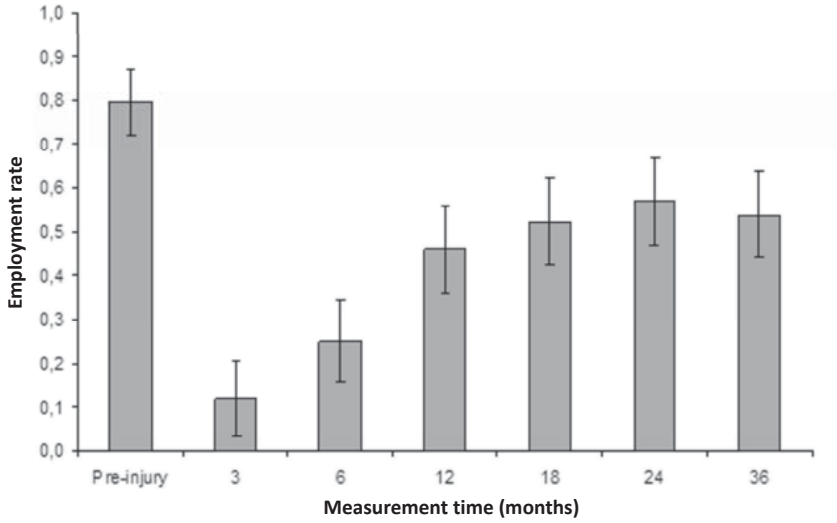

Figure 4.1: Mean employment rate over time.
The error bars indicate the upper and lower bounds of the 95% confidence intervals. The employment rate significantly improved until 12 months postinjury and then remained stable over time.

Employment status preinjury

The descriptive statistics of the total population and the 2 subgroups of previously employed versus unemployed are listed in Table 4.1. The patients who were employed preinjury had

a mean age of 34 years, were mostly men (77%), and were mostly married or living with partner or family (53%); the majority of these had a high educational level (at least high school; 56%). There were 9 patients (11%) with new or recurrent psychiatric symptoms during acute hospitalization, such as symptoms of depression or anxiety, which did not interfere with study inclusion criteria. The severity of TBI was equally distributed over the previously employed and unemployed patients. The smallest percentage (16%) of employed patients in this study was working on a managerial level, and the largest percentage (53%) included manual laborers. A quarter of the employed persons were part-time workers.

Employment outcome 3 years after TBI

Table 4.2 shows the characteristics and outcomes of patients who were employed versus unemployed 3 years after TBI. At this time, 53 patients (56%) were employed and 41 patients (44%) were unemployed. The mean age of the employed patients was 29.5 years, which is almost 5 years younger than the mean age of patients employed before the TBI (see Table 4.1). Only 1 of the 9 patients with psychiatric symptoms during hospitalization was employed 3 years after TBI. Of the 22 previously unemployed, 4 patients found employment during follow-up (18%), 9 remained unemployed (41%), and 9 were lost to follow-up (41%). From the 88 previously employed, 33 patients lost their job (38%), 34 kept the same job (39%), 19 patients changed their employment (22%), and 2 patients were lost to follow-up (2%). From the 19 patients who changed their employment, 7 had a positive career change (37%) and 12 were demoted to a lower job status (63%). Thirteen patients changed from full-time to part-time jobs, and 5 part-timers became full-time workers over time (data not shown). The occupational categories were almost equally distributed over the employed and unemployed patients 3 years after TBI.

Determinants of employment status

The patients employed at 3 years after TBI differed significantly from those who were unemployed regarding indices of severity of initial trauma and residual deficits (see Table 4.2). Employed persons were significantly younger, less often demonstrated psychiatric symptoms, and were less impaired, with a shorter length of hospital stay and higher scores on the GOS, BI, FIM, and FAM at hospital discharge than unemployed patients.

There were no significant differences at 36 months when the 2 groups were compared based on sex, educational level (high school or not), living with partner or family or not, and the 4 professional categories listed in Table 4.2.

Table 4.2: Differences in characteristics and outcomes between patients who were employed versus unemployed 3 years after TBI

	Employment status 3y after TBI		
Characteristics/outcomes	Employed N=53	Unemployed N=41	P-value
Age ± SD (y)	29.5 (10.7)	37.9 (14.2)	.000
Sex: male, n (%)	38 (72)	28 (68)	.720
Living with partner, n (%)	25 (47)	21 (49)	.697
Educational level, high, n (%)	30 (57)	22 (55)	.877
Psychiatric symptoms, n (%)	1 (2)	8 (21)	.003
Mean length ± SD of hospital stay (d)	30.5±17.6	56.2±35.2	.002
TBI severity, n (%)			
Moderate (GCS score 9–12)	13 (24)	7 (17)	.381
Severe (GCS score 3–8)	40 (76)	34 (83)	
Hospital discharge destination, n (%)			
Rehabilitation centre	21 (40)	18 (44)	.001
Nursing home	2 (4)	12 (29)	
Home	30 (57)	11 (27)	
Occupational category preinjury, n (%)			
Professional/managerial	7 (13)	6 (15)	.340
Skilled	14 (26)	9 (23)	
Manual labour	27 (51)	16 (39)	
Unemployed/student	5 (9)	9 (23)	
Work load pre-injury, n (%)			
Full-time	33 (62)	24 (59)	.119
Part-time	15 (28)	8 (20)	
Unemployed/student	4 (8)	9 (22)	
GOS score <4, n (%)			
Hospital discharge	22 (50)	26 (87)	.001
3 yrs after TBI	1 (2)	6 (15)	.041
BI, mean ± SD			
Hospital discharge	17.2±4.5	12.3±7.6	.001
3 yrs after TBI	19.6±2.3	18.4±4.5	.116
FIM, mean ± SD			
Hospital discharge	109±16.8	86±32.7	.000
3 yrs after TBI	122±3.6	110±23.5	.002
FAM, mean ± SD			
Hospital discharge	68±9.1	52±18.8	.000
3 yrs after TBI	79±4.7	70±14.3	.001

GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; BI, Barthel Index; FIM, Functional Independence Measure; FAM, Functional Assessment Measure.

Using multiple logistic regression analysis (Table 4.3), the FAM (adjusted odds ratio 0.92; P<.002) and psychiatric symptoms (adjusted odds ratio 10.6; P<.019) were selected as independent predictors of unemployment 3 years after TBI, indicating that patients with better cognitive function score and no psychiatric symptoms during hospitalization had a significantly higher chance of being employed during follow-up.

Table 4.3: Significant risk factors, measured at hospital discharge, for long-term unemployment

	Univariable		Multivariable	
Risk factor	OR	P-value	OR	P-value
Age (per year)	1.06	.003		
Length of hospital stay (per day)	1.04	.000		
Hospital discharge destination				
Rehabilitation centre (vs home)	2.33	.075		
Nursing home (vs home)	16.67	.001		
Psychiatric symptoms (yes)	13.90	.015	10.6	.049
GOS score (<4)	6.50	.002		
BI score	0.86	.001		
FIM score	0.96	.001		
FAM score	0.92	.000	0.92	.002

OR, odds ratio; GOS, Glasgow Outcome Scale; BI, Barthel Index; FIM, Functional Independence Measure; FAM, Functional Assessment Measure.

Selecting patients at risk of long-term unemployment using the FAM

Figure 4.2 shows the ROC curve of the FAM instrument. The area under the curve was 79.3% (95% confidence interval, 68.1–90.5), indicating a reasonable diagnostic value. A FAM score of less than 65 at hospital discharge was selected as the optimal cutoff score to identify patients at risk of long-term unemployment. Patients with a FAM score of less than 65 had a 6.9 times greater chance of long-term unemployment than did patients with a score of ≥65 (odds ratio 6.9; 95% confidence interval, 2.5–19.4). The FAM cutoff score of less than 65 had a sensitivity of 75%, specificity of 70%, positive predictive value of 65%, and negative predictive value of 79%.

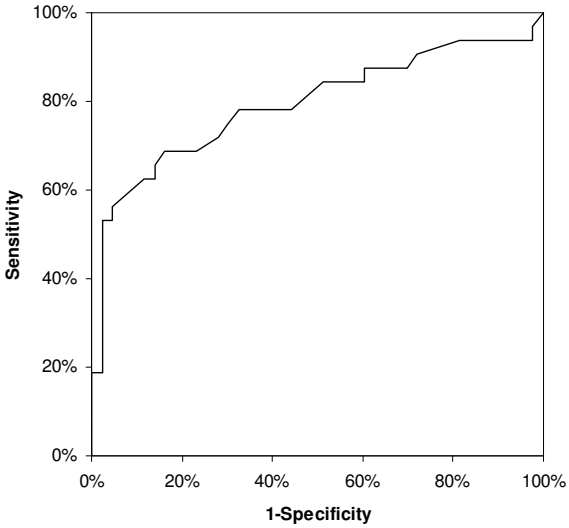

Figure 4.2: ROC curve: sensitivity and specificity of the FAM for identification of long-term unemployment.

DISCUSSION

In this prospective study on patients with moderate and severe TBI we found that age, length of hospital stay, discharge to a nursing home (vs home), psychiatric symptoms, a relatively low BI score, GOS score of less than 4, and relatively low FIM and FAM scores at hospital discharge are risk factors of unemployment at 3-year follow-up. Earlier studies showed that the Disability Rating Scale,[27,28] the FIM, and the length of hospital stay show a consistent correlation with the ability to RTW.[29] Age older than 40 years has been shown to be a significant negative predictor of RTW.[29,30] The most important predictors for long-term unemployment in our study were cognitive functioning as measured with FAM and the presence of psychiatric symptoms, such as depression and anxiety. We found that the FAM score was more predictive of employment outcome than the FIM score, which is in agreement with the study of Gurka et al.[31] In previously published studies, cognitive impairments were also predictive of RTW in patients with moderate to severe TBI at 1 year postinjury.[10,32]

Furthermore, we found that patients with psychiatric symptoms at hospital discharge were at risk of long-term unemployment, adjusting for the FAM score. Depression and anxiety are the most common psychiatric problems in patients with TBI. Our findings suggest that cognitive rehabilitation and adequate treatment of psychiatric symptoms are important targets for vocational rehabilitation programs in rehabilitation centers. In

The Netherlands, vocational rehabilitation programs are offered to patients who are not able to work for more than 6 to 12 months. Patients are eligible for this program if they have physical complaints in combination with psychosocial problems. The patient will be examined by a rehabilitation doctor and will receive a work-related training of 12 to 15 weeks. The costs are paid by the employer. If suited for the program, generally every employee has access to this program.

This study focuses on preinjury and early recovery factors to identify patients at risk of unemployment in the long term. This is of value because it can help to target persons at risk for poor outcomes early in the recovery process so that a tailored rehabilitation program can be offered to each individual. Concurrent factors, such as emotional functioning and family support, could also influence the employment outcome, but these were not assessed in this study.

FAM cutoff scores to identify patients at risk of long-term unemployment have not been published before to our knowledge. We showed that a FAM score of less than 65 is a cutoff score with reasonable diagnostic value for the prediction of unemployment 3 years after TBI. Our results may help rehabilitation professionals in the early selection of patients who may benefit most from vocational rehabilitation programs.

TBI severity based on the GCS score did not predict employment outcome in our study. Patients with mild TBI were not included in our sample, and the group with moderate TBI was relatively small. Shames et al.[1] state that TBI classification in mild, moderate, or severe may not be sufficiently sensitive to appropriately describe and therefore predict outcomes. Some authors have suggested that the "motor component" of the GCS may yield a higher predictive value.[33] Marion and Carlier[34] point out the difficulty of determining the initial GCS score in a reproducible manner. More aggressive prehospital treatment (involving early sedation and intubation) leads to more difficulty in obtaining a valid neurologic examination in the first 24 hours after trauma as well as progress in clinical management.

In our sample, 3 months after TBI the employment rate dropped from 80% preinjury to 12%. Thereafter, it increased, especially in the first year, reaching a level of 55% at 3-year follow-up. In a recent review, the overall estimate of RTW 1 year after TBI was found to be 40.7%, ranging from 0% to 84%.[35] In the review of Shames,[1] RTW rates were in the 12% to 70% range. These wide ranges are caused by the heterogeneity between studies included in the reviews. The studies reviewed showed a wide variety of patient populations (ranging from including patients with severe TBI only to excluding patients with severe TBI), different follow-up times, different study designs (both retrospective and prospective), and different thresholds of determining the success of RTW outcomes.

Some studies include sheltered work and unpaid work while other studies focus on competitively employed individuals and amount of income.[1] The employment rate in our study was on the high side compared with that in other studies. Although the loss to follow-up rate was low, we found that unemployed persons were more likely than employed persons to be lost to follow-up. Moreover, not only heterogeneity between studies but also country-specific economic factors will influence employment outcomes. In The Netherlands, the general unemployment rate is one of the lowest in Europe. Furthermore, in the Dutch social security system employers are encouraged to employ disabled persons by financial compensation regulations. Employers are fully compensated in the case of illness of a disabled person, receive financial compensation for adjusting the work space, and are allowed to pay less than the minimum salary (the government supplements the employee's salary).

Furthermore, we found that the mean employment rates remained quite stable after the first year postinjury. Kreutzer et al.[36] followed patients over a period of 4 years and found that 34% of the patients in the study were stably employed. Possl et al.[37] found an overall 53% RTW rate, but 28% of patients retired within a 2-year period after an unsuccessful work trial (the study contained both patients with TBI and those with no trauma).

The occupational categories and workload preinjury (fulltime, part-time, unemployed) turned out not to be predictors for being employed 3 years after TBI. Prior research has shown that preinjury employment status (employed vs unemployed) greatly influences the odds of successful RTW. Walker et al.[16] found that the type of occupation also influences RTW outcome, with the best prospect for RTW among patients with professional/managerial jobs. We could not reproduce these results, which might be due to the difference in study size (113 vs 1341 patients) and different distribution of patients over the different categories. Walker et al.[16] used a different definition of returning to work and excluded unemployed patients and students from their study sample, whereas we analyzed those in an extra category. The percentage of patients with managerial jobs in both studies was comparable (14% each), but the skilled and manual labor categories differed (21% vs 56% for the skilled category and 45% vs 29% for the manual labor category).

Patients in our study were not selected on employment status preinjury. In many studies on RTW or employment outcomes, only employed patients are included. In our study, unemployed patients were followed over time. In this way, we found that some of the previously unemployed patients or students were able to find employment after TBI.

Study limitations

Some limitations of this study should be noted. The study population of 113 patients might not be large enough to detect small but important differences. Of the 113 patients, 95 completed the 3-year follow-up. A percentage of patients lost to follow-up of 17% could have had an effect on the outcomes. However, a successful follow-up rate of 83% of the population over 3 years' time is much higher than the follow-up rates in other prospective cohort studies. In the Traumatic Brain Injury Model Systems, for example, the 1-year follow-up rate was 58% and the 5-year follow-up rate was 32%.[12]

Another limitation is that the collected data did not allow detailed conclusions such as whether a patient returned to his previous work, whether the level and extent of employment preinjury differed from follow-up, and whether there was a change in income over the years.

Reviewing statistical data on employment rates of the general Dutch working population, we found that the employment rates varied during the years of inclusion and follow-up, and employment rates among men were higher than among women (patients with TBI are mainly men).[26] We did not adjust our data for these effects.

In summary, local economic factors, such as general unemployment effects and financial arrangements for companies to employ disabled persons, might have had their effect on our study results, limiting the generalizability of the results.

CONCLUSIONS

The complex consequences of moderate and severe TBI may cause hindrances for finding employment or RTW. However, as in earlier work, our results show that is no reason for therapeutic nihilisms. Further studies are needed to identify the pivotal determinants and timing of a successful vocational rehabilitation program. Cognitive ability and psychiatric symptoms, such as depression, seem to be important targets.

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Chapter 5

Employment outcome ten years after moderate to severe traumatic brain injury: a prospective cohort study

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ABSTRACT

Objective The objective of this prospective cohort study was to evaluate the probability of employment and predictors of employment in patients with moderate-to- severe traumatic brain injury (TBI) over 10-year follow-up.

Methods One hundred nine patients (18–67 years) were included with follow-up measurements 3, 6, 12, 18, 24, and 36 months and 10 years post-TBI. Potential predictors of employment probability included patient characteristics, injury severity factors, functional outcome measured at discharge from the hospital with the Glasgow Outcome Scale (GOS), Barthel Index (BI), Functional Independence Measure (FIM), and the Functional Assessment Measure (FAM).

Results Forty-eight patients (42%) completed the 10-year follow-up. Three months post-TBI, 12% were employed, which gradually, but significantly, increased to 57% after 2-years follow-up (P<.001), followed by a significant decrease to 43% (P=.041) after 10 years. Ten years post-TBI, we found that employed persons had less-severe TBI, shorter length of hospital stay (LOS), and higher scores on the GOS, BI, FIM, and FAM at hospital discharge than unemployed persons. No significant differences in age, sex, educational level, living with partner/family or not, pre-injury employment, professional category, psychiatric symptoms, or discharge destination were found. Longitudinal multivariable analysis showed that time, pre-injury employment, FAM, and LOS were independent predictors of employment probability.

Conclusions We concluded that employment probability 10 years after moderate or severe TBI is related to injury severity and pre-injury employment. Future studies on vocational rehabilitation should focus on modifiable factors and take into consideration the effects of national legislation and national labor market forces.

INTRODUCTION

Worldwide almost 10 million people suffer a traumatic brain injury (TBI) each year.[1] A recent meta-analysis from 16 European countries estimated that the incidence of TBI is 262 per 100,000 persons per year, causing a total of direct and indirect health care costs of 33 billion euros (approximately USD $45.4 billion).[2,3] TBI is fatal in 20–35% of cases, and 52% of survivors suffer some level of disability at 1 year post-injury.[4–6] Especially after moderate and severe injury, serious cognitive, behavioral, emotional, and sensorimotor impairments may occur.[3] These impairments can have major consequences for activity patterns, social participation, and quality of life.[7] Over time, the loss of life roles and meaningful social engagement may cause further decline of quality of life. As such, employment and income not only are economic necessities, but they also facilitate social engagement and can positively impact quality of life.[8] The success of returning to work (RTW) post-TBI depends on a variety of factors, such as national legislation, support provided in the workplace, the interplay of pre-injury and injury-related factors, and occupational demands.

The current study focuses on employment status 10 years after sustaining moderate or severe TBI. Many studies on employment post-TBI have been published with mixed results. Patient mix, definitions of outcome variables, assessment methods, and study design may differ substantially between studies, which may hinder comparing the outcomes. Several studies use a retrospective or cross-sectional design.[9–11] Prospective studies often have a follow-up limited to 1 year post-TBI or sometimes to 3 or 5 years post-TBI.[12–16] Prospective studies with a 10-year follow-up are scarce.

Cuthbert and colleagues prospectively followed 3618 moderate-to-severe TBI patients up to 10 years post-onset.[17] The patients in this study were not retired at injury, received inpatient rehabilitation at a Traumatic Brain Injury Model System center, were discharged between 1989 and 2009, and had at least three complete follow-up interviews at post-injury years 1, 2, 5, and 10. The researchers developed a model to predict individual employment outcome.[17] They describe an overall decline in trajectories of probability of employment between 5 and 10 years post-injury.[17] Age, sex, race/ethnicity, education, pre-injury substance abuse, pre-injury vocational status, and days of post-traumatic amnesia (PTA) were identified as predictors of being employed in the long term.[17] In Dahm and colleagues, shorter PTA and younger age were associated with higher employment rates in a prospectively followed cohort of 97 mild-to-severe TBI patients (who were compared with 91 patients with orthopedic injuries) over 10-year follow-up.[18] They reported a 10-year employment rate of 50.5%.

We previously reported the 3-year outcomes of the Rotterdam TBI study, a prospective cohort study of outcome after moderate and severe TBI. [7,16,19] We found that employment rate dropped from 80% pre-injury to 55% over 3-year follow-up and that unemployment could be predicted using the Functional Assessment Measure (FAM) at hospital discharge.[16] The aim of the present study was to evaluate employment outcome and its predictors up to 10 years post-injury.

METHODS

Procedure

The design of the Rotterdam TBI study has been described before.[7,16,19] In short, after informed consent and with approval of the Medical Ethics Committee (MEC), patients with moderate or severe TBI were consecutively enrolled between January 1999 and April 2004 at three Dutch level 1 trauma centers and prospectively followed. Measurements were completed at hospital discharge and at 3, 6, 12, 18, 24, and 36 months post-TBI. In 2012, the Rotterdam TBI Study was extended with a 10-year follow-up visit, which was approved by the MEC. New informed consent was obtained from all participants.

Participants

Inclusion criteria were admission to a hospital for moderate (Glasgow Coma Scale [GCS] score of 9–12) or severe (GCS score of 3–8) TBI attributed to a nonpenetrating trauma and age at injury between 16 and 67 years. Exclusion criteria were inadequate knowledge of the Dutch language to participate in the study or important pre-traumatic neurological, oncological, or systemic impairments (e.g., spinal cord injury, psychiatric disorder, and cancer) that may interfere with TBI-related disability assessment. Follow-up measurements were excluded from patients who reached the age of 67 during follow-up.

Measurement instruments

Primary outcome

The primary outcome measure was status of employment. Data on employment outcome were collected at each visit by means of a structured interview by a trained research psychologist. This interview included questions on employment status (yes/no) and type of work. Employment included all payed vocational activities at the time of measurement.

Unemployment was defined as any voluntary vocation without payment, including students, homemakers, early retirement, sick leave, and other. The type of work was classified into four categories: professional/managerial (executive, administrative, and managerial functions and professional specialties); skilled (technicians and administrative support, precision production, craft, and repair personnel); manual labor (machine operators, assemblers, transporters, and cleaners); and unemployed or student.[20]

Covariates

Sociodemographic data were collected at enrollment in the study and during follow-up. Sociodemographic data included age at injury, sex, marital status (living together vs. alone), education (at least high school vs. less), and pre-injury employment status (employed vs. unemployed). Clinical data were collected from the medical records during hospitalization and at hospital discharge. Severity of TBI was based on the GCS, defining moderate TBI as a GCS of 9–12 and severe TBI as a score of 8 or less. The GCS was determined as the lowest score in the first 24 hours post-TBI measured in the hospital. Presence (yes/no) and type of psychiatric symptoms were observed during hospitalization by the medical staff and also recorded at each follow-up visit by the research psychologist in a structured interview, which included self-reported depression, anxiety, and other serious psychiatric symptoms.

Functional outcome was assessed with the Functional Independence Measure (FIM), FAM, Glasgow Outcome Scale (GOS) and the Barthel Index (BI) at hospital discharge.[21,22] The FIM and FAM have a good reliability and validity.[22,23] The FIM evaluates motor functioning with respect to self-care, sphincter control, transfers, and locomotion, whereas FAM evaluates cognitive and communication functioning and psychosocial adjustment. Together, they consist of 30 items, 18 of the FIM and 12 of the FAM, that are evaluated on a 7-point scale. The FIM score ranges from 18 (totally dependent) to 126 (totally independent), and the FAM score ranges from 12 (totally dependent) to 84 (totally independent). The research psychologists were qualified FIM/FAM assessors. The GOS measures general outcome post-TBI and consists of five categories: death, vegetative state, severe disability, moderate disability, and good recovery.[23,24] The BI also has a good reliability and validity.[25] It consists of 10 items on activities of daily living (e.g., making transfers, dressing, bathing, and bowel and bladder status), each with two, three, or four response categories (0–3 points). Total scores range from 0 (severely restricted) to 20 (no restrictions). Finally, the hospital discharge destination (home, rehabilitation institute, or nursery home) was recorded.

Statistical analysis

Descriptive data are presented as the means and standard deviations (SDs) of interval variables and the numbers and proportions of categorical variables. Variables of interest included patient characteristics (age, sex, partner, educational level, and injury severity variables: length of hospital stay [LOS], TBI severity [moderate {GCS 9–12} or severe {GCS 3–8}], presence of psychiatric symptoms [yes/no], and employment variables [pre-injury employment, occupational category]) and functional outcomes at hospital discharge (GOS, BI, FIM, and FAM). Differences between patients that were included and patients that were lost to follow-up were analysed using X^2 or exact tests for categorical data and independent-samples t-tests for interval variables. The same statistical tests were used to compare the two subgroups of persons who were employed and those who were unemployed in a cross-sectional analysis at 10 years post-injury.

The longitudinal pattern of the probability of employment over 10-year follow-up time was estimated using generalized estimating equations (GEEs) to fit a logistic regression analysis with repeated measurements. This analysis takes into account that multiple measurements within subjects are correlated using an unstructured covariance structure. This method is very flexible in handling missing values. Thus, all available measurements of the total cohort (N=109) were included in this GEE analysis, in which employment status depended on the measurement time post-TBI in years (0.25, 0.5, 1, 1.5, 2, 3, and 10 years, respectively). In post-hoc analyses, the differences between measurements were evaluated using pairwise comparisons.

We also used GEE analyses to evaluate the effect of potential predictors, that were measured at baseline, on the probability of employment over 10-year follow-up. We first fitted a quadratic unconditional model to the data by adding time and time squared as predictors of employment status to the model. Next, we evaluated the effects of the covariates that differed significantly between the employed and unemployed subgroups on employment outcome over time. Because of missing values in some of the covariates at hospital discharge, the first follow-up outcomes of the FIM, FAM, BI, and GOS were used instead in some cases. Variables that were not significant were removed from the multivariable model one by one. The final multivariable model included all significant predictors.

Statistical analyses were performed using SPSS for Windows software (version 21.0; SPSS, Inc., Chicago, IL). A significance level of .05 was used in all analyses.

RESULTS

Study population

Of 549 patients screened, 153 patients died and 229 were excluded (Figure 5.1), which left 167 eligible patients, from which 113 were willing to take part in the Rotterdam TBI study.[16] Four patients (4%) were excluded because they reached the age of retirement during follow-up. Thus, 109 patients remained in the cohort. After 3 years, 19 patients were lost to follow-up (17%). Between 3- and 10-year follow-up, 7 patients died (7%), 20

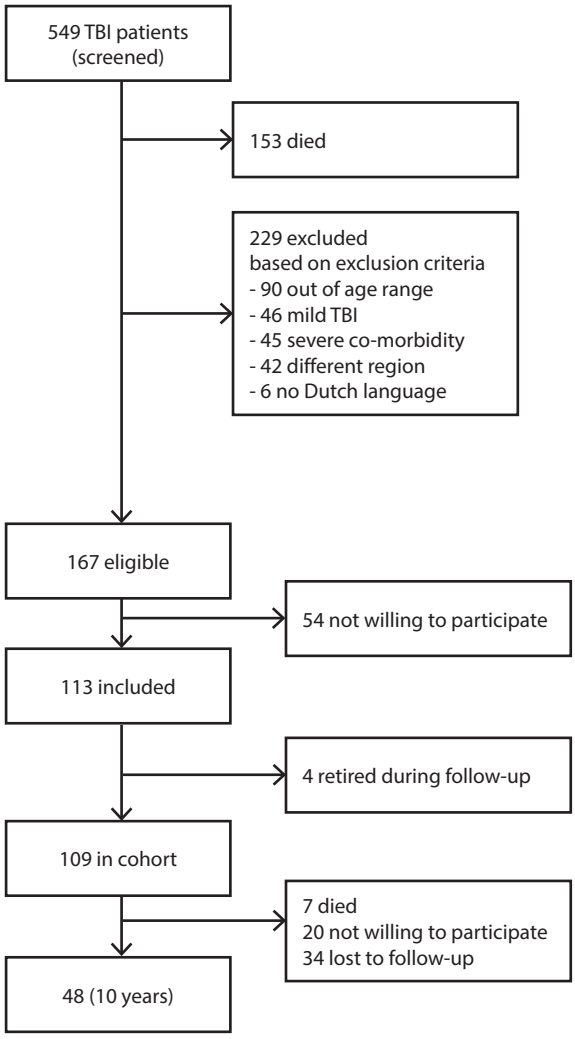

Figure 5.1: Flow chart of patient inclusion and participation.
TBI, traumatic brain injury.

were no longer willing to participate (21%), and 15 could not be traced (16%). Thus, 48 patients participated in 10-year follow-up. Patients who were lost to follow-up (n=61) did not differ significantly from patients with complete follow-up in baseline characteristics, except for pre-injury employment status (Table 5.1). Patients with complete follow-up were more often employed pre-injury than those who were lost to follow-up (90% vs. 75%; P<.048). Baseline characteristics, hospital discharge outcomes, and discharge destinations are presented in Table 5.1.

Table 5.1: Comparison of baseline characteristics and hospital discharge outcomes of patients with moderate to severe TBI, who were included versus lost to follow-up 10 years post- injury

	Patients included n=48[a]	Patients lost to FU n=61[a]
Age at injury, mean (SD)	34.3±12.7	30.2±11.0
Time post TBI in years, mean (SD)	9.9±1.8	10.2±1.8
Sex: male, n (%)	32 (67)	47 (77)
Living with partner, n (%)	24 (50)	24 (40)
Educational level, higher, n (%)	27 (56)	27 (47)
Employed pre-injury, yes n (%)	43 (90)	44 (75)*
Occupational category pre-injury, n (%)		
Unemployed/student	5 (10)	16 (28)
Executive/managerial	8 (17)	6 (10)
Skilled	12 (25)	13 (22)
Manual labor	23 (48)	23 (40)
GCS, mean (SD)	6.5±2.8	6.9±2.6
TBI severity, n (%)		
Moderate (GCS 9–12)	10 (21)	18 (30)
Severe (GCS 3–8)	38 (79)	43 (70)
Psychiatric symptoms, n (%)	4 (8)	4 (7)
Length of hospital stay (days), mean (SD)	37.6±24.7	41.3±31.5
Discharge FIM, mean (SD)	103.4±23.4	97.5±30.2
Discharge FAM, mean (SD)	63.0±14.6	59.4±17.8
Discharge BI, mean (SD)	15.9±6.0	15.0±6.8
Discharge GOS score <4, n (%)	25 (63)	31 (65)
Hospital discharge destination, n (%)		
Rehabilitation center	21 (44)	22 (36)
Nursing home	5 (10)	11 (18)
Home	22 (46)	28 (46)

[a] Number of missings in included and lost patients, respectively: employed pre-injury: 0, 2; occupational category pre-injury: 0, 3; FIM: 7, 11; FAM: 8, 11; BI: 11, 13; GOS score: 8, 13.

* P<.048 included versus lost.

TBI, traumatic brain injury; SD, standard deviation; GCS, Glasgow Coma Scale; FIM, Functional Independence Measure; FAM, Functional Assessment Measure; BI, Barthel Index; GOS, Glasgow Outcome Scale; FU, follow-up.

Cross-sectional employment outcome 10 years after traumatic brain injury

In the cross-sectional analysis of the 10-year follow-up data, we found that 26 persons of 48 (55%) were employed. Further, we found that patients who were employed 10 years post-TBI differed significantly from those who were unemployed regarding severity of TBI and hospital discharge outcomes (Table 5.2). Employed persons had significantly less-severe TBI, a shorter LOS, and higher scores on the GOS, BI, FIM, and FAM at hospital discharge than persons without employment in the long term. Cross-sectionally, there were no significant differences between the groups in age, sex, educational level (high school or not), living with partner or family or not, pre-injury employment, professional

Table 5.2: Differences in characteristics and outcomes at hospital discharge between patients who were employed versus unemployed 10 years post-injury

	Employed n=26[a]	Unemployed n=22[a]	P-value
Age at injury, mean (SD), y	32.7±11.5	36.2±14.0	.338
Sex: male, n (%)	19 (73)	13 (59)	.322
Living with partner, n (%)	12 (46)	12 (55)	.322
Educational level, high, n (%)	16 (62)	11 (44)	.210
Employed pre-injury, yes n (%)	25 (96)	18 (82)	.165
Occupational category pre-injury, n (%)			
Unemployed	1 (4)	4 (18)	.439
Executive/managerial	5 (19)	3 (14)	
Skilled	7 (27)	5 (23)	
Manual labor	13 (50)	10 (46)	
TBI Severity, n (%)			
Moderate (GCS 9–12)	9 (35)	1 (5)	.013*
Severe (GCS 3–8)	17 (65)	21 (95)	
Psychiatric symptoms, n (%)	1 (4)	3 (14)	.320
Length of hospital stay (d), mean (SD)	30.9±19.9	45.6±27.7	.038*
Discharge FIM, mean (SD)	111.9±19.5	93.5±24.0	.016*
Discharge FAM, mean (SD)	68.4±11.6	57.0±15.5	.023*
Discharge BI, mean (SD)	18.0±4.6	13.4±6.5	.029*
Discharge GOS score <4, n (%)	9 (41)	16 (89)	.002*
Hospital discharge destination, n (%)			
Rehabilitation center	8 (31)	13 (59)	.060
Nursing home	2 (8)	3 (14)	
Home	16 (62)	6 (27)	

[a] Number of missings in employed and unemployed respectively: FIM: 4, 3; FAM: 5, 3; BI: 6, 5; GOS score: 4, 4.
* P-value <.05.
SD, standard deviation; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; FIM, Functional Independence Measure; FAM, Functional Assessment Measure; BI, Barthel Index; GOS, Glasgow Outcome Scale.

category, psychiatric symptoms, or the different hospital discharge destinations (home, rehabilitation center, or nursing home).

Longitudinal analysis of employment status and its predictors

In the longitudinal GEE analysis with repeated measurements, taking into account all available data of the cohort (N=109) and the covariance between measurements, we found that the estimated employment probability at 10-year follow-up was 43%. The estimated employment probabilities at each follow-up time are presented in Figure 5.2. This figure shows that the probability of employment dropped from 80% pre-injury to 12% at 3-month follow-up and gradually increased to 57% at 2-year follow-up, after which it decreased to 43% at 10 years post-TBI. The employment probability significantly increased between 3 months and 1 year (mean difference, 0.34; P<.001) and decreased significantly between 2 and 10 years post- injury (mean difference, 0.14; P=.041). In Figure 5.2, also the quadratic model without covariates is presented.

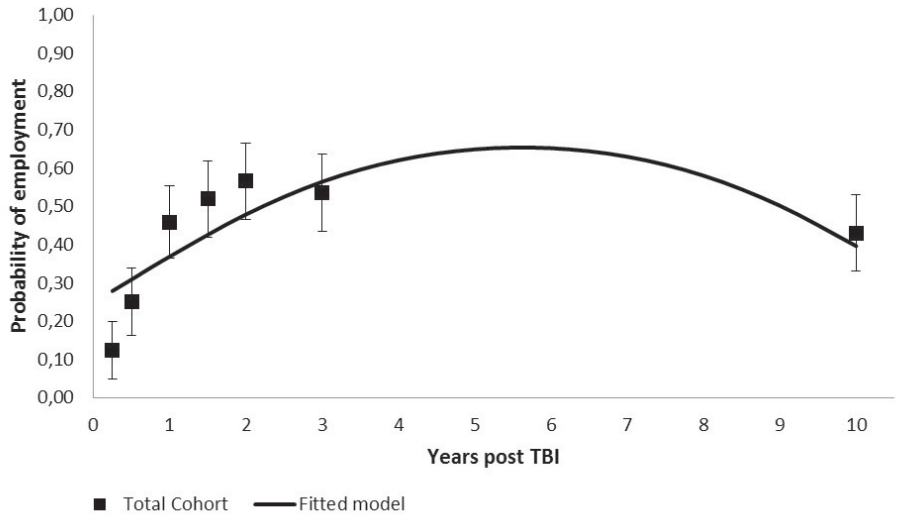

Figure 5.2: Probability of employment (estimated means and 95% confidence intervals) over 10-year follow-up and fitted model for the total cohort.
TBI, traumatic brain injury.

Table 5.3 presents the parameters of the final multivariable GEE model. Time post-TBI, pre-injury employment, the FAM and LOS were found to be independent predictors of the probability of employment 10 years post-TBI. The model shows that the probability

of being employed was significantly better for patients with preinjury employment, higher cognitive functioning score at hospital discharge, or shorter LOS (Table 5.3). In Figure 5.3, the trajectories for two subgroups of pre-injury employment are presented, in which the solid line presents a subgroup of persons who were employed pre-injury, with a mean FAM score of 68.4 and a mean LOS of 30.9 days, whereas the dotted line presents a subgroup of unemployed persons pre-injury with a mean FAM score of 57.0 and a mean LOS of 45.6 days.

Table 5.3: Parameters of the multivariable prediction model estimating the probability of employment over 10 years follow-up (N=109)

Parameter	Estimate	Odds	95% confidence interval	P-value
Intercept	-5.479	0.004	0.000; 0.043	<.001
Time	0.961	2.614	1.950; 3.505	<.001
Time*Time	-0.083	0.920	0.896; 0.944	<.001
Employment pre-injury (yes)	2.105	8.210	3.383; 19.922	<.001
Employment pre-injury (no)	0	1	NA	NA
Length of hospital stay (days)	-0.023	0.978	0.964; 0.991	.001
FAM score	0.047	1.049	1.019; 1.079	.001

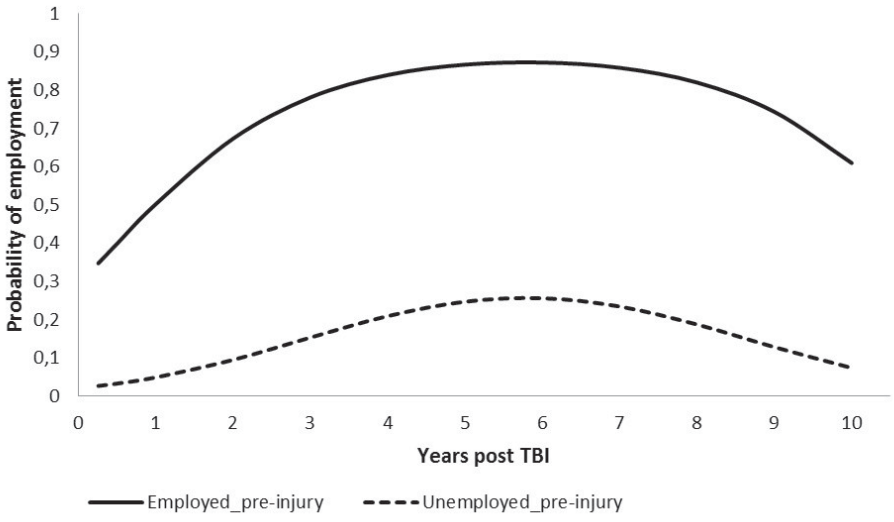

Figure 5.3: Probability of employment for persons who were employed pre-injury (solid line) and unemployed pre-injury (dotted line).
TBI, traumatic brain injury.

DISCUSSION

In this prospective 10-year follow-up study on patients with moderate and severe TBI, we found that, after an initial increase in the first 2 years post-TBI, the probability of employment stabilizes and decreases in the long term. The current study is unique for the fact that it contains many measurements in the first 3 years, in which most recovery takes place. These early extensive measurements enabled us to accurately predict outcome over 10 years despite the inevitable loss to follow-up in a 10-year follow-up study. Taking into account all measurements of the initial cohort, we estimated the 10-year probability of employment to be 43%, which is lower than the employment probability we found in cross-sectional analysis (55%). This study shows that the 10-year employment rate in a cross-sectional analysis will be overestimated if more persons who were unemployed pre-injury dropped out.

Using statistical modeling, we found that a quadratic model best fitted these data, indicating an increase of the probability of employment in the first 2 years, which levels off and is followed by a decrease later in time. Forslund and colleagues found no relationship between employment probability and time in a similar cohort in Norway with measurements at 1, 2, and 5 years post-TBI.[15] This is not in conflict with our results, because most of the improvement over time was found in the first year in our study, when no measurements were done in the Norwegian study. Our long-term results are in accord with the large American cohort study described by Cuthbert and colleagues, who demonstrated a decline in trajectories of employment between 5 and 10 years post-injury.[17]

Comparing our study with the results by Cuthbert and colleagues, we provide more-detailed information and more-extensive measurements in the first 3 years, which is important for long-term statistical modeling. This study concerns Dutch/European patients and confirms the results found in the American population investigated by Cuthbert and colleagues.

Comparing those who were employed 10 years post-injury with those who were unemployed in a cross-sectional analysis, we found that the latter group had more-severe TBI, a longer LOS, and worse functional outcomes at hospital discharge, as measured by the FIM, FAM, BI, and GOS. We did not find significant differences in age, sex, partner status, educational level, or type of occupation. A higher injury severity and poorer outcome in terms of impairments were predictive of long-term unemployment. This is in line with earlier findings that identified low GCS scores and longer PTA as predictors of employment probability.[15,17,18] In longitudinal analyses, we demonstrated that from the functional outcome measures, the FAM, measuring cognitive functioning, was the best predictor of long-term probability of employment, in addition to LOS and pre-injury employment

status, which confirms the findings of our previous study.[16] Based on these predictors, two different scenarios illustrated how these variables impact the probability of employment in the long term. In other long-term follow-up studies, functional outcomes at hospital discharge are not often used as potential predictors of employment outcome. In a recent systematic review, there was weak evidence that the Disability Rating Scale has predictive value for RTW.[26]

The current study shows that injury severity and functional factors, rather than personal and contextual factors (such as age, sex, being single, type of occupation, and education level), independently predicted employment status over 10 years follow-up. Previous studies did show that contextual factors, such as type of medical insurance, may be associated with long-term employment status.[15,17] Cuthbert and colleagues suggest that employment status after moderate and severe TBI is also influenced by national labor market forces, which may explain different outcomes between countries.[17] Age (older than 40 years) has been shown to be a significant predictor of unemployment.[18,27,28] Age may both be related to a poorer outcome post-TBI, in terms of survival and disability, and may be considered a contextual determinant given that employment rates may also drop with increasing age for healthy persons.[29,30] The employment rate in the general Dutch population is lower for those between 55–65, compared to 45–55, years of age. The difference varies from 25–40% over the study years, with a consistently lower employment rate for the eldest group.[31]

National regulations and labor market forces have to be taken into account in planning vocational rehabilitation programs and should also be considered in interpreting the employment rate in nationally oriented research/literature. Global, but also local, economic factors might influence the employment rate, especially if a longer time period is being investigated. To rule out national regulations, labor market forces, and local economic factors as much as possible, internationally oriented TBI research on employment outcome is needed.

The prospective study design and long-term follow-up are a strength of this study. However, in cross-sectional analyses, selection bias may be a limitation. Of 167 eligible patients, 113 agreed to participate with a loss to follow-up of 17% after 3 years and 56% after 10 years. Patients who were lost to follow-up were more often unemployed pre-injury. Taking into account the within person correlations between measurements, we found that the estimated 10-year employment probability was overestimated in the cross-sectional analysis. Although we adjusted our longitudinal analyses for pre-injury employment status and covariance between measurements, the 10-year employment rates may still be optimistic. Further, the data did not allow for detailed conclusions, such as whether a patient

returned to his previous work, whether the level and extent of preinjury employment differed from follow-up, and whether there was a change in income over the years.

CONCLUSION

A dose-response relationship between TBI severity and mortality or long-term disability has been described before.[15–17,27,29,30] The results of our study underscore that this relation also accounts for employment outcome 10 years after sustaining a moderate or severe TBI. Employment probability over a long follow-up time may be influenced by national regulations, labor market forces, and local, but also global, economic factors, which pleads for internationally oriented TBI research on employment outcome. Future studies on vocational rehabilitation should focus on modifiable factors and take into consideration the effects of national legislation and national labor market forces.

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Chapter 6

Cognition, health-related quality of life, and depression ten years after moderate to severe traumatic brain injury: a prospective cohort study

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ABSTRACT

Objective The aim of this study was to evaluate cognitive function ten years after moderate-severe TBI and to investigate the associations between cognitive function, depression and Health-Related Quality of Life (HRQoL).

Methods In this prospective cohort study, with measurements at 3, 6, 12, 18, 24, 36, and 120 months post-TBI, patients aged 18–67 years (N=113) with moderate-severe TBI were recruited. Main outcome measures were depression (CES-D), subjective cognitive functioning (CFQ), objective cognitive functioning, and HRQoL (SF-36).

Results Fifty of the initial 113 patients completed the ten-year follow-up. Twenty percent showed symptoms of depression (CES-D≥16). These patients had more psychiatric symptoms at hospital discharge (P=.048) and were more often referred to rehabilitation or nursing homes (P=.015) than non-depressed patients. Furthermore, they also had significantly lower scores in 6 of the 8 subdomains of the SF-36. The non-depressed patients had equivalent scores compared with the Dutch norm-population on all subdomains of the SF-36. Cognitive problems at hospital discharge were related with worse cognitive outcome ten years post-TBI, but not with depression or HRQoL. Ten years after moderate-severe TBI, only weak associations (P<.05) between depression scores and two objective cognitive functioning scores were found. However, there were moderate associations (P<.01) between depression scores, HRQoL, and subjective cognitive functioning.

Conclusions Signaling and treatment of depressive symptoms after moderate-severe TBI may be of major importance for optimizing HRQoL in the long-term. We did not find strong evidence for associations between depression and objective cognitive functioning in the long-term post-TBI. Disease awareness and selective drop-out may play a role in long-term follow-up studies in moderate-severe TBI. More long-term research is needed in this field.

INTRODUCTION

Traumatic brain injury (TBI) continues to be a major health and socio-economic problem throughout the world, despite major advances in prevention and treatment of TBI, which has resulted in a substantial decrease in mortality. The problems resulting from TBI are frequently not directly discernible, and therefore this is called a 'silent epidemic'.[1] The incidence of TBI-related disability is underestimated and society is usually unacquainted with the impact of TBI in the long-term.[1] There are several perspectives from which TBI can be viewed. Moderate and severe TBI are, for example, associated with numerous medical, functional, and cognitive concerns. TBI outcome is fatal in 27% to 37% of cases.[2-4] Approximately 43% of TBI survivors suffer some level of disability at 1 year postinjury.[5]

Cognitive dysfunction is a major cause of TBI-related disability and affects approximately 54% of patients with severe TBI after one year.[6] Because of interference with work, relationships, leisure, and activities of daily living, cognitive dysfunction causes a personal and economic cost that is difficult to quantify.[7] The cognitive domains that are most often affected in mild-moderate TBI include memory, attention, processing speed, and executive functioning. In moderate-severe TBI, other functions, such as communication, visuospatial processing, intellectual ability, and awareness of deficit, may also be affected.[7] Many studies have concentrated on cognitive outcomes in the first year post-TBI, suggesting that cognitive functions may improve during one year follow-up.[6] Studies on long-term cognitive outcomes (5 to 10 years follow-up) that may give insight into the problems patients face, are scarce.[8-11]

Long-term cognitive functioning was investigated by Ponsford et al., who followed 141 mild-severe TBI patients at 2, 5, and ten-years post injury, with the Structured Outcome Questionnaire, a patient-reported outcome measurement instrument, and found that more than 60% of the participants reported memory problems and more than 50% reported difficulty concentrating, slowed thinking, cognitive fatigue, and word-finding difficulties.[8] Problems with planning, initiative, self-centeredness, and impulsivity were reported by 25–45% of the sample.[8] In the TBI Model Systems Database was found that of the 292 patients followed up to 5 years after TBI only 16% reached the maximum score on the Cognitive subdomain of the Functional Independence Measure (FIM) at 1 year, after which 26% improved, 61% stayed the same, and 14% worsened at 5 years postinjury.[9] Marsh et al. performed neuropsychological tests on the domains of: intelligence, attention, verbal and visual memory, visual-spatial construction, and executive functions, 5 years after moderate-severe TBI.[10] While the prevalence of impairment varied across the cognitive domains, the data showed deficits in all six domains and pointed out that complete cognitive recovery

in the long-term is unlikely.[10] In a review article performed by Dikmen et al. the association between severity of TBI and cognitive deficits was investigated in the available literature.[12] The authors found clear evidence for an association between severe TBI and cognitive deficits 6 to 12 months post-injury. Only one study was performed six years after injury, and established that 70% of the severe TBI patients had clinically significant impairments, with learning and memory problems as the most common problem (56%).[12] For moderate TBI they concluded that the evidence is limited/suggestive for an association with cognitive impairments.[12]

The above mentioned studies agree that severity of TBI is related to cognitive deficits. Although depression is an important factor that may have a negative influence on cognitive functioning, the literature on the relationship between cognitive outcome and emotional state is limited, especially in the long-term. Ponsford et al. compared cognitive functioning and emotional state between patients with good outcome and those with poor outcome based on the GOSE ten-years post-TBI, but did not directly study the relationship between cognitive outcome and emotion.[13]

Two review articles describe the increased prevalence of depression post-TBI, therefore the presence of depression may influence the assessment of cognitive function.[14,15] However, it remains unclear whether cognitive function and emotional state are related in the long-term post-TBI. From previous studies we do know that health-related quality of life is affected by symptoms of depression in the general population.[16] Also in TBI patients, relationships between symptoms of depression and HRQOL have been described.[17-19]

To our knowledge, no studies were performed on HRQoL and depression in relation to cognitive outcome in the long-term (more than five years) in moderate-severe TBI. Therefore, the aim of the present study was to evaluate cognitive functioning ten-years after moderate-severe TBI and to investigate the associations between cognitive function, depression, and HRQoL in these patients.

METHODS

Procedure

The design of the Rotterdam TBI study has been described in detail elsewhere.[20,21] In short, after informed consent and with approval of the Medical Ethics Committee (MEC), patients with moderate or severe TBI were consecutively enrolled between January 1999 and April 2004 at 3 Dutch level-1 trauma centers and prospectively followed. Measurements were completed at hospital discharge, and at 3, 6, 12, 18, 24, and 36 months post-TBI. In 2012

the Rotterdam TBI Study was extended with a ten-year-follow-up visit, which was approved by the MEC. New informed consent was obtained from all participants.

Participants

Inclusion criteria for the Rotterdam TBI study were admission to a hospital for moderate (Glasgow Coma Scale [GCS] score of 9–12) or severe (GCS score of 3–8) TBI due to a non-penetrating trauma and age at injury between 16 and 67 years. Exclusion criteria were insufficient knowledge of the Dutch language to participate in the study or important pre-traumatic neurologic, oncologic, or systemic impairments (e.g., spinal cord injury, psychiatric disorder, and cancer) that may interfere with TBI-related disability assessment. For the extended ten-year follow-up measurement, all patients that were originally included were approached and asked for participation.

Measurement instruments

Primary outcome

Questionnaires

Ten years post-injury, depression was measured with the Center for Epidemiologic Studies-Depression scale (CES-D). The scale consists of 20-items, and scores range from 0–60, the higher the score, the more depressive symptoms are present. Scores of 16 or higher are considered a depression.[22] Up to 3 years after TBI, depression was measured with the Wimbledon Self Report Scale, on which a score >8 was considered symptomatic for depression.[23]

The Cognitive Failure Questionnaire (CFQ) measures self-perceived cognitive mistakes in daily life based on 25 items.[24] Test-subjects answer on a 5 point scale (range 0–4) how often they experience cognitive failures in daily life. A total score is calculated (range 0–100). The higher the score, the more cognitive mistakes are perceived. 'Normal' scores range from 21 up to 43 (mean 31.8, SD 11.1), a cut off score >43 was used to distinguish normal from abnormal scores.[25]

The Functional Assessment Measure (FAM) was used to measure cognitive functioning at hospital discharge. The FAM was developed as an adjunct to the FIM to specifically address cognitive, behavioral, communication, and community functioning measures. The FAM consists of 12 items and total scores range from 12 (totally dependent) to 84 (totally independent).[26]

Neuropsychological tests

The Trail Making Test (TMT- A and B) measures processing speed (TMT-A) and divided attention (TMT-B).[27] The test subject is asked to draw a line, in consecutive order, between numbers (TMT-A). On the TMT-B test-subjects need to switch between numbers and letters. The time needed to complete both these tasks is corrected for age and education and converted into T-scores. T-scores <40, e.g. 1 standard deviation below the mean, are defined as lowered scores.

The Digit Span (DS) is a subtest of the Wechsler Adult Intelligence Scale-III and measures attention and working memory.[28] Subjects are instructed to repeat numbers forward and backward. Raw scores are obtained for span length forward (DS-F) and backward (DS-B). Lowered span lengths are defined as <5 digits on the DS-F and <4, digits on the DS-B.

The Fifteen Word Task (15WT), the Dutch version of the Auditory Verbal Learning Test, was used to measure short and long-term memory and memory recognition.[29,30] Subjects were instructed to recall 15 unrelated words immediately after listening to them (repeated 5 times). After 20 minutes a delayed recall and a recognition task is performed. Raw scores are calculated for the immediate total recall (15WT-TR; range 0–75), and delayed recall (15WT-DR; range 0–15). Raw scores are converted into decile scores corrected for age, gender and education for both subscores. Decile scores <2.0 are defined as lowered scores.

The modified Six Elements Test (6ET) was used to measure executive function, and is part of the Behavior assessment of dysexecutive syndrome test (BADS).[31] Test-subjects are instructed to work on 6 tasks within 10 minutes, taking into account 2 rules. Based on the number of attempts and rules broken, a score of 1 to 4 is given.

The D2 test of attention was used to measure visual selective attention, processing speed and concentration. Participants need to identify as many as possible 'D' symbols in a specified period of time. A total performance score and a concentration performance score are calculated. The total performance score is calculated from the total of processed items minus total missed items and total wrong items; the concentration performance score is based on the total identified correct items minus total identified wrong items.[32]

HRQoL

To assess HRQoL the Dutch version of the SF-36 was used.[33-35] This is a reliable and valid instrument for several medical disorders, including TBI.[34,36,37] The SF-36 consists of 36 items measuring 8 domains: Physical Functioning; Role Physical (the extent to which physical health interferes with daily activities); Bodily Pain; General Health; Vitality; Social Functioning; Role Emotional (the extent to which emotional health interferes with daily

activities); and Mental Health. All domains are converted into a scale from 0 to 100, with 100 indicating the best potential condition. The eight domain scores were summarized into a physical component summary score (PCS) and a mental component summary score (MCS). The PCS and MCS are scored using norm based methods; they both have a mean of 50 and a standard deviation of 10 in the general U.S. population.[38] Age-adjusted norm values from the Dutch normative population were used.[34]

Statistical analysis

Descriptive data of interval variables are presented with means and standard deviations and for categorical variables with numbers and proportions. Variables of interest included patient characteristics (age, gender, partner, educational level, pre-injury employment status), injury severity variables (length of hospital stay, TBI severity (moderate (GCS 9–12) or severe (GCS 3–8)), functional outcomes at hospital discharge (psychiatric symptoms (yes/no), GOS, BI, FIM, FAM) and hospital discharge destination (home, rehabilitation center, nursing home). Differences between patients that were included and patients that were lost-to-follow-up were analyzed using X^2 or exact tests for categorical data and independent-samples t-tests for interval variables. The same statistical tests were used to compare patient characteristics, HRQoL, and cognitive functioning between two subgroups of persons with and without symptoms of depression.

Bivariate two-tailed Pearson (for interval scales) and Spearman (for ordinal scales) correlations were used to study associations between the depression score (CES-D), HRQoL (PCS and MCS), cognitive functioning at hospital discharge (FAM), and subjective (CFQ) and objective cognitive functioning scores (D2, DS, TMT, 15WT, 6ET). Correlation coefficients <0.5 are considered to be weak, between 0.5 and 0.7 moderate, and >0.7 strong.

P-values <.05 were considered significant in all analyses. All statistical analyses were performed using SPSS for Windows version 21.0.

RESULTS

Study population

All patients who previously participated in the Rotterdam TBI study (N=113) were contacted by mail or phone. From these patients, 7 patients died during follow-up, 16 patients were untraceable, 20 refused to participate in the long-term-follow-up, and 19 were unable to participate due to logistical reasons (work obligations, on holiday, or long-term abroad).

Thus, 51 patients were able to take part in the ten-year-follow-up measurement. The drop-out rate was 17% after 3 years and 56% after ten years follow-up, of which 6% died. In one patient, no scores were available for depression and cognition and was therefore excluded.

Patients who were included (n=50) did not differ significantly from patients without ten year follow-up (n=63) in baseline characteristics, except for age at injury. Patients that participated were significantly older at the time of injury compared to those who were lost-to-follow-up (respectively 36.2±14.2 vs 30.7±11.7, P=.029).

Estimated changes over ten years follow-up in the total cohort

Depression scores (WSRS) and cognitive functioning scores (FAM) up to 3 years post-TBI have been reported elsewhere; cognitive functioning significantly improved during the first year post-injury and stabilized thereafter, whereas depression scores started to improve after 18 months up to 3 years post TBI.[39] The proportion of patients with depression also improved from 19% at 3 months post TBI to 14 % after 3 years follow-up. Between 3 and 10 years after TBI the proportion of depressed patients increased from 14% to 20%, which was not significant (P<.291).

HRQoL scores up to 3 years post TBI have also been reported before; the domain scores increased up to 2 years and stabilized between 2 and 3 years post TBI.[40] Between 3 and 10 years after TBI none of the domain scores changed significantly (Figure 6.1). The PCS and MCS did not change significantly either; PCS decreased from 46 (SE 1.3) at 3 years follow-up to 45 (SE 1.5) at 10 years follow-up (P<.700), whereas MCS increased from 49 (SE 1.2) at 3 years to 51 (SE 1.5) at 10 years follow-up (P<.221).

Depression and HRQOL ten-years-post-TBI

Ten of 50 patients (20%) showed symptoms of depression (CES-D≥16). We found that patients with depressive symptoms ten-years-post-TBI differed significantly from those without symptoms regarding hospital discharge destination (P=.015) and psychiatric symptoms at hospital discharge (P=.048, Table 6.1). Patients with depressive symptoms were more frequently admitted to clinical rehabilitation or nursing homes or had psychiatric symptoms at hospital discharge, whereas patients without depressive symptoms were more often discharged home after the initial hospitalization. Differences between the groups in age, sex, living with partner or family, educational level (% high school), pre-injury employment, length of hospital stay, discharge FIM, FAM, BI, and GOS did not reach statistical significance (Table 6.1).

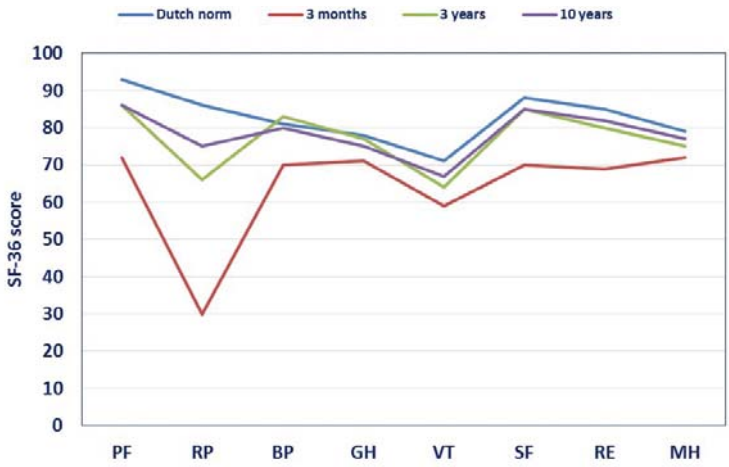

Figure 6.1: Change over time in HR-QoL for each domain of the SF-36, from 3 months (red line), to 3 years (green line), up to 10 years post TBI (purple line), in comparison with Dutch norms (blue line).[34]
PF, Physical Functioning; RF, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health.

Table 6.1: Comparison of baseline characteristics and hospital discharge outcomes of patients with moderate to severe TBI, who were depressed versus no depression

	No depression CES-D<16 n=40	Depression CES-D≥16 n=10	P-value
Age at injury, mean (SD), y	36.6±14.7	34.6±12.9	.765
Gender: male, n (%)	27 (68)	7 (70)	1.00
Living with partner, n (%)	27 (69)	6 (60)	.709
Educational level, high, n (%)	19 (48)	5 (56)	.725
Employed pre-injury, yes n (%)	34 (85)	9 (90)	1.00
TBI severity, n (%)			
Moderate (GCS 9–12)	29 (73)	0 (0)	.092
Severe (GCS 3–8)	11 (27)	10 (100)	
Length of hospital stay (days), mean (SD)	36.9±26.3	40.3±18.4	.344
Discharge FIM, mean (SD)	108.4±18.8	91.4±30.2	.064
Discharge FAM, mean (SD)	65.3±13.5	57.8±17.0	.143
Discharge BI, mean (SD)	17.2±4.7	12.4±8.1	.076
Discharge GOS score <4, n (%)	18 (56)	8 (88)	.068
Discharge psychiatric symptoms, n (%)	2 (5)	3 (30)	.048
Hospital discharge destination, n (%)			
Rehabilitation center	14 (35)	6 (60)	.015
Nursing home	3 (7)	3 (30)	
Home	23 (58)	1 (10)	

TBI, traumatic brain injury; CES-D, Center for Epidemiologic Studies-Depression Scale; GCS, Glasgow Coma Scale; FIM, Functional Independence Measure; FAM, Functional Assessment Measure; BI, Barthel Index; GOS, Glasgow Outcome Scale.

Comparing the two groups concerning HRQoL, measured with the SF-36, significantly worse scores were found in the subgroup of patients with depressive symptoms with regard to the following subdomains: role physical (P≤.001), general health (P=.005), vitality (P≤.001), social functioning (P≤.001), role emotional (P=.021) and mental health (P≤.001). Differences in physical functioning (P=.072) and bodily pain (P=.059) did not reach statistical significance, but the PCS (P=.001) and MCS (P=.008) did (Table 6.2). The group that showed no signs of depression had equivalent scores compared with the Dutch norm-population on all the subdomains of the SF-36 (Figure 6.2).

Depression and cognitive function ten-years-post-TBI

Patients with depressive symptoms reported more subjective cognitive complaints (measured with the CFQ) than patients without depressive symptoms (P=.013). Level of cognitive functioning was assessed through a series objectively measured neuropsychological tests including tests of attention and concentration, speed of information processing, memory, and executive functioning (Table 6.3).

No significant differences were found between the subgroups with and without depressive symptoms on any of the cognitive-tests, except for some measures of the D2 test. Patients with depressive symptoms had a lower number of items completed (P=.047). Furthermore,

Table 6.2: Comparison of HRQoL in the depression versus the no depression group based on the CES-D and a Dutch norm population[34]

	Dutch norm mean±SD	No depression CES-D<16 n=40 mean±SD	Depression CES-D≥16 n=10 mean±SD	P-value
Physical Functioning	93±12	88.7±19.3	61.3±32.5	.072
Role Physical	86±28	86.5±24.2	21.9±36.4	.000*
Bodily Pain	80±19	83.7±21.2	61.5±31.3	.059
General Health	78±17	80.4±16.8	53.3±27.5	.005*
Vitality	71±16	72.8±16.9	42.5±11.9	.000*
Social Functioning	88±19	90.4±13.6	59.4±17.4	.000*
Role Emotional	85±30	89.7±25.5	41.7±49.6	.021*
Mental Health	79±15	82.9±12.1	55.0±22.8	.000*
PCS	50±10	48.4±10.9	29.4±13.5	.001*
MCS	50±10	53.3±9.3	38.3±14.7	.008*

HRQoL, health-related quality of life; CES-D, Center for Epidemiologic Studies-Depression Scale; PCS, Physical Component Summary Score; MCS, Mental Component Summary Score. * P<.05.

Table 6.3: Comparison of subjective and objective cognitive functioning in the depression versus the no depression group based on the CES-D

	No depression CES-D<16 n=40	Depression CES-D≥16 n=10	P-value
Subjective cognitive functioning			
CFQ, mean (SD)	28.0 (12.3)	39.0 (11.7)	.013*
CFQ, score >43, n/N (%)	4/39 (10)	3/10 (30)	.140
Attention and concentration			
DS-F, mean (SD)	8.0 (2.5)	8.4 (1.9)	.373
DS-F, span <4, n/N (%)	1/38 (3)	1/10 (10)	.377
D2-CP, mean (SD)	148 (36.1)	120 (41.)	.082
D2-CP, T-score <40, n/N (%)	8/37 (22)	6/8 (75)	.007*
Speed of information processing			
D2-TP, mean (SD)	386 (84.5)	314 (86.1)	.047*
D2-TP, T-score <40, n/N (%)	12/37 (32)	6/8 (75)	.045*
TMT-A, mean (SD)	34.2 (15.2)	29.7 (15.4)	.164
TMT-A, T-score <40, n/N (%)	7/39 (18)	1/9 (11)	1.00
Memory			
15WT-TR, mean (SD)	39.8 (11.0)	33.6 (13.0)	.213
15WT-TR, decile <2, n/N (%)	10/38 (26)	5/9 (55)	.121
15WT-DR, mean (SD)	7.5 (3.4)	6.1 (4.0)	.386
15WT-DR, decile <2, n/N (%)	10/38 (26)	5/9 (55)	.121
DS-B, mean (SD)	6.2 (1.7)	5.3 (1.8)	.169
DS-B, span <3, n/N (%)	1/38 (3)	2/10 (20)	.106
DS-Total, mean (SD)	14.3 (3.6)	13.7 (3.0)	.891
DS-Total, span <7, n/N (%)	1/38 (3)	1/10 (10)	.377
Executive functioning			
6-ET, mean (SD)	3.42 (0.94)	2.88 (1.36)	.376
6-ET, Profile Score 1, n/N (%)	3/36 (8)	2/8 (25)	.178
2, n/N (%)	2/36 (6)	1/8 (13)	
3, n/N (%)	8/36 (22)	1/8 (13)	
4, n/N (%)	23/36 (64)	4/8 (50)	
TMT-B, mean (SD)	86.1 (38.4)	76.9 (31.0)	.621
TMT-B, T-score <40, n/N (%)	8/39 (21)	1/9 (11)	1.00

CES-D, Center for Epidemiologic Studies-Depression Scale; CFQ, Cognitive Failure Questionnaire; DS-F, Digit Span Forward, D2-CP, D2 Concentration Performance; D2-TP, D2 Total Performance; TMT, Trail Making Test, 15WT-TR, 15 Word Task Total Recall, 15WT-DR, 15 Word Task Delayed Recall, DS-B, Digit Span Backward, 6ET, Six Elements Test. * P<.05.

a larger proportion of the group with depressive symptoms had T-scores <40 compared with the group without symptoms, both on the D2 Concentration (P=.045) and the D2 Total performance tests (P=.007).

Focusing on the total group of patients, we found that 12% of patients was not able to perform the total cognitive test battery; especially, executive functioning (6ET) could not

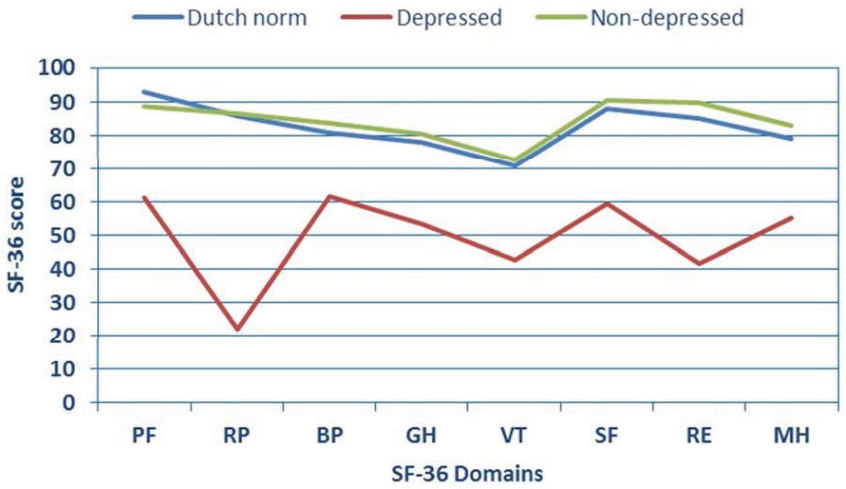

Figure 6.2: HRQoL domain scores for patients with (red line) and without (green line) symptoms of depression, ten-years-post-TBI, in comparison to the Dutch norms (blue line).[34]
PF, Physical Functioning; RF, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health.

Table 6.4: Correlations between depression score, HRQoL, subjective and objective cognitive functioning

	CES-D	PCS	MCS	FAM	CFQ
HRQOL					
PCS	-.502**	1			
MCS	-.694**	.054	1		
Hospital discharge Cognitive Functioning					
FAM	-.304	.150	.179	1	
10Y FU Subjective Cognitive Functioning					
CFQ	.468**	-.348*	-.332*	-.372*	1
10Y FU Objective Cognitive Functioning					
DS-F	-.112	-.013	.104	.042	.08
DS-B	-.294*	.073	.181	.241	-.025
15WT-TR	-.210	-.124	.244	.426**	-.141
15WT-DR	-.215	-.188	.314*	.482**	-.145
D2-CP	-.341*	.251	.216	.380*	-.164
D2-TP	-.331*	.271	.122	.270	-.117
TMT-A	.150	.109	-.283	.452**	.109
TMT-B	.155	.229	-.327*	.573**	.051
6ET	-.249	.243	.054	.331	-.054

** Correlation is significant at the .01 level (2-tailed). * Correlation is significant at the .05 level (2-tailed).
HRQoL, health-related quality of life; CES-D, Center for Epidemiologic Studies-Depression Scale; PCS, Physical Component Summary Score; MCS, Mental Component Summary Score; FAM, Functional Assessment Measure; CFQ, Cognitive Failure Questionnaire; DS-F, Digit Span Forward; DS-B, Digit Span Backward; 15WT-TR, 15 Word Task Total Recall; 15WT-DR, 15 Word Task Delayed Recall; D2-CP, D2 Concentration Performance; D2-TP, D2 Total Performance; TMT, Trail Making Test; 6ET, Six Elements Test.

be assessed. Furthermore, we found that the proportion of lowered test scores ranged from 4–6% for the DS, 17–19% for the TMT, 21–32% for the 15WT and 31–40% for the D2 test. In the general population about 15.9% has scores of 1 standard deviation below the mean. Thus, patients with TBI scored relatively low on memory tests (15WT), information processing speed (D2) and concentration (D2) compared with reference values.

Associations between depression score, HRQoL, and cognitive functioning scores

Depression scores, were significantly (P<.001) associated with HRQoL, and subjective cognitive functioning scores at 10 years post-TBI (Table 6.4). Cognitive functioning at hospital discharge (FAM) was significantly associated with multiple objective cognitive test outcomes (P<.001) and with subjective cognitive functioning (P<.05) at 10 years follow-up, but not with depression or HRQoL. Both depression scores and mental health scores were weakly associated with part of the objective tests of cognitive functioning (P<.05). Subjective cognitive functioning scores were not associated with any of the objective cognitive test results.

DISCUSSION

In this prospective ten-year-follow-up study in patients with moderate-severe TBI, we investigated the associations between depression, HRQoL and cognition. In general, we found a prevalence of depressive symptoms of 20% in our study population, which is comparable with the prevalence of 17% reported by Scholten et al., but is not in line with Zgaljardic et al. who reported a prevalence of 30–38%.[14,15] Remarkably, we found no reduction in HRQoL, but we found some underperformance on the cognitive test-battery in the total group of patients, ten-years after moderate-severe TBI. About 12% of patients was not able to perform the 6ET test of executive functioning and up to 40% had low scores (>1SD) on one or more tests of memory, concentration, or information processing speed.

Focusing on patients with depressive symptoms we found significantly worse scores on six of the eight HRQoL subdomains of the SF-36 compared to those without symptoms. Patients with symptoms of depression also reported more subjective cognitive failures, which could not be confirmed by the scores on the neuropsychological tests, as patients did not perform worse on these tests, except for the D2 test, which measures concentration and speed of information processing.

These findings are not in line with the hypothesis that depression would be related, not only to HRQoL, but also to problems of cognitive functioning. As the group of patients

with depressive symptoms was small, we may not have had enough power to detect more subtle, but important differences. Therefore, we also looked for associations between depression score, HRQoL and cognition scores on a continuous scale in the total group of patients. We only found weak correlations between the depression score and some of the cognitive test results ten-years-post-TBI, whereas interrelations between depression score, HRQoL, and subjective cognitive functioning were clearly present.

Furthermore, cognitive functioning at hospital discharge was significantly related with objective cognitive functioning 10 years later. More specifically, a low hospital discharge FAM score was related with low scores on memory tasks, information processing speed, and executive functioning in the long term. However, discharge cognitive functioning was not related with HRQoL, or depression in the long term.

Moreover, subjective cognitive functioning was not related to objective cognitive functioning. Disease awareness may explain these contradictions in moderate-severe TBI; patients with reduced disease awareness may report good HRQoL. These patients may not have cognitive complaints or symptoms of depression, whereas cognitive outcome may be (severely) compromised.[41]

The relationship between depression and HRQoL seems obvious, however, this study makes clear that this relationship is still present in the long-term post-TBI. The longitudinal course of HRQoL has been described before, but not in relation to depression and cognition in the long-term post-TBI.[40,42,43]

Studies that objectively investigated cognitive function after moderate-severe TBI by means of standardized neuropsychological tests are often limited to a shorter follow-up period and show various results. For example, Spitz et al. studied 111 individuals with moderate-severe TBI and objectively assessed the patients with a neuropsychological test-battery at 3, 6, and 12 months post-injury and compared them with healthy subjects.[44] The participants scored significantly worse on all cognitive measures at 3 and 6 months.[44] At 12 months 6 out of 8 tests still were significantly worse compared to healthy subjects, but all cognitive measures showed gradual improvement over time.[44] Previously, we also found gradual improvement over time in the FAM score, which stabilized 1 year post TBI.[39] In the study by Stenberg et al., the clinical course of cognitive functioning, measured with the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS), and depression, measured with the Hospital Anxiety and Depression Scale (HADS), was assessed in 78 patients with severe TBI up to one year.[6] They also concluded that cognition improved over time and appeared to be rather stable from 3 months to 1 year.[6] Significant correlations were found between cognitive functioning and HADS depression scores at 3 months and

one year post TBI.[6] In another study on neuropsychological functioning after severe TBI (n=105) by Sigurdardottir et al., the authors concluded that nearly two-thirds of patients showed cognitive impairments in at least 1 of 3 cognitive domains one year after injury.[45]

In a retrospective study ten-years-post-TBI, Ponsford et al. compared cognitive functioning and emotional state between 60 patients with mild-severe TBI.[13] Two groups were made based on the GOSE, one group with good and one group with poor outcome. The patients with poor outcome performed more poorly on cognitive measures, such as information processing speed, attention, memory, and executive function, and showed higher levels of anxiety on the HADS.[13] Another retrospective study performed by Hoofien et al. evaluated 76 patients with severe TBI by means of standardized scales and neuropsychological tests at an average of 14.1 years post-injury.[46] This study indicates primarily severe long-term psychiatric problems, such as depression, anxiety and hostility.[46] On the cognitive domain a lower range of intellectual ability and slower psychomotor ability and processing speed was reported.[46]

The above mentioned studies describe cognitive impairments mainly up to one year. The study with a longer follow-up period also described cognitive disorders in poor GOSE patients. A strength of our study is that it provides some insight in the course of cognitive functioning in the period beyond one year post onset. Our results suggest that cognitive problems at hospital discharge gradually improve and stabilize one year post TBI and are related with cognitive outcome 10 years later, but not with depression or HRQoL.

In our study cognitive difficulties were objectively detected in a subgroup of patients, ten-years-post-TBI, whereas HRQoL was equivalent with Dutch norms. Therefore, this study suggests that most of the moderate-severe patients with TBI function rather well in the long-term, but also that a subset of these patients suffers from depression, reduced quality of life, and subjective cognitive complaints. We found that almost all these patients already are referred to rehabilitation centers/nursing homes. It will be a challenge to predict which patients need extra attention during rehabilitation to prevent these long-term problems. We found that patients with cognitive problems at hospital discharge are at risk for long-term problems, but other factors may also play a role. The current study is unique, to our knowledge, for studying this subject ten-years-post-TBI in a prospective cohort study.

Limitations

The long-term-follow-up and prospective study design are a strength of this study. Nevertheless, selection bias may be a limitation, because of the large drop out after 10 years follow-up. Of the 113 patients who agreed to participate 17% were lost-to-follow-up

after three years and 56% after ten-years. However, our drop-out rates are comparable to other long-term prospective cohort studies.[9,47,48]

The CES-D is a self-report scale not specifically designed for use with TBI patients, but it was originally intended for use in the general population. However, in the meta-analysis performed by Osborn et al. 8 studies on TBI, which used the CES-D, could be identified.[49] In this meta-analysis a higher prevalence of depression post-TBI was found, when using the CES-D (prevalence=0.48) compared to, for example, the HADS (0.32) or BDI (0.43), which might have had its effect on our results.[49] In our study, however, the proportion of patients with depression was rather small (20%).

The neuropsychological test-battery consisted of tests that comprised several cognitive domains. However, due to time constraints we chose only one test per domain, instead of two or more. This may have caused a less differentiated picture than a more comprehensive neuropsychological test-battery.

Finally, we studied symptoms of depression but we did not look into the use of antidepressants.[50] Failla et al. investigated the effect of depression and use of antidepressants on cognitive recovery after severe TBI.[51] No difference was found between patients with or without posttraumatic depression.[51] The use of antidepressants was associated with cognitive impairment one year post-TBI, a factor we did not consider. Post-Traumatic Stress Disorder might also be of influence on cognition and depressive symptoms, this effect was not investigated either.[50]

Other factors we did not consider and that might have been of influence are degenerative disease and decreased life-span and their potential association with depression.[52-54]

CONCLUSION

The majority of patients had good HRQoL, ten-years after moderate-severe TBI. Cognitive problems at hospital discharge were associated with cognitive deficits in the long term, but not with depression or HRQoL, which is possibly a result of reduced disease awareness. Depression score was significantly associated with HRQoL and subjective cognitive complaints, ten-years after moderate-severe TBI.

Therefore, signaling and treatment of depressive symptoms during rehabilitation is of major importance for optimal functioning in the long-term post-TBI. We did not find that these associations could be extended to objective cognitive functioning. However, selective drop-out may have been of influence, therefore the results should be interpreted with

caution. More long-term research is needed to clarify the role of disease awareness in moderate-severe TBI.

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Chapter 7

General discussion and summary

INTRODUCTION

Traumatic brain injury is a leading cause of death and disability worldwide. It is 3 times more common in men than in women; young people and the elderly are at the highest risk. The most common mechanisms of injury are traffic accidents, falls, and violence.[1,2]

A recent meta-analysis from 16 European countries estimated that the incidence of hospital admitted TBI is 262 per 100,000 persons per year,[3] causing a total of direct and indirect healthcare costs of 33 billion euros (approximately USD $45.4 billion).[4]

Especially after moderate and severe brain injury, serious cognitive, behavioral, emotional and sensorimotor impairments may occur.[4] These impairments can have major and long-term consequences for activity patterns, social participation, and quality of life.[5]

Despite a dose response relationship between TBI severity and its consequences, long-term sequelae may occur in mild TBI too.[6]

This thesis focuses at long-term outcome in patients with moderate/severe TBI included in the Rotterdam TBI study described by van Baalen (2008) and Willemse-van Son (2009) in which moderate/severe TBI patients were consecutively enrolled from January 1999 to April 2004. All patients were prospectively followed-up at 3, 6, 12, 18, 24, 36 months and at 10 years post onset with structured interviews at the participant's home or institution of admittance. In cases where patients suffered from serious communication impairments, a significant other or professional caregiver was interviewed. Inclusion criteria of the Rotterdam TBI study were: 1) admittance in hospital for moderate or severe TBI due to blunt or penetrating trauma (Glasgow Coma Scale (GCS) score of 9–13 or 3–8, respectively); 2) age at onset between 16 and 67 years; 3) survival until discharge from hospital. Exclusion criteria were: 1) insufficient knowledge of the Dutch language to participate in the study; 2) serious pre-traumatic neurological, oncological or systemic impairment (e.g. spinal cord injury, psychiatric disorders, cancer) that might interfere with the assessment of TBI-related disability.

The aim of this thesis is to study long-term consequences of moderate/severe TBI on HRQoL (chapter 3), employment (chapters 4 and 5) and cognitive function and the associations between cognitive function, depression and HRQoL (chapter 6).

This chapter summarizes the main findings, strengths and limitations of the studies and presents clinical implications and recommendations for future research.

MAIN FINDINGS

Chapter 2 provides a general introduction on the classification of severity and some figures and facts on epidemiology. With two clinical cases this chapter also illustrates the importance of well-coordinated case management after acute care and that TBI is not an incident but should be considered a chronic condition.[7] The first case suffered mild TBI and failed to successfully return to work as a teacher. After several months she was referred to the neurologist who performed additional analysis and provided the needed care.

The second case concerns a young man who had a severe TBI and was discharged after acute care to a non-specialized clinic in which the severe cognitive deficits were not recognized. He was discharged home without any form of aftercare and developed challenging behavior at home, with alcohol abuse and depression with suicidal expressions. The patient was dependent on external support which was provided by his family. After 4 years his family was able to move the patient into a supervised housing project run by professionals.

These cases illustrate that 'TBI rehabilitation should be a lifelong, well-coordinated process with the client and his or her family in the focus' and that both patients with mild as with moderate/severe TBI may suffer from long-term consequences.[7] A well-organized chain of care may be hindered by national and municipal legislation, health insurance policies and reimbursement practices, but also by a lack of collaboration between healthcare organizations.

Chapter 3 evaluates HRQoL during three years after TBI and identifies its predictors. HRQoL was measured with the SF-36, of which five of the eight subdomains showed significant improvement over three years. Whereas the Physical Component Summary (PCS) improved significantly, the Mental Component Summary (MCS) score remained stable. After three years HRQoL equaled the score of the healthy Dutch norm population which we considered a remarkable finding in perspective of the severity of the injury. Reduced disease awareness might have been of influence, being unaware of deficits may interfere with reporting them. Caregiver evaluations might have led to different scores.[8] Three Scandinavian studies on HRQoL after TBI reported lower scores on the SF-36 compared to the general population.[9-11] Concerning the mean PCS score, our physical findings at 2-year follow-up were comparable with those of Forslund et al. whereas our mean MCS score was higher.[10] A possible explanation for this difference is that in our study, physical scores improved during the third year of follow-up, whereas the follow-up period in the study of Forslund was limited to 2 years.[10] Jacobsson et al. also reported that HRQoL improved over time after sustaining a TBI; which is in line with our findings.[11]

Time after TBI, length of hospital stay (LOS), FIM, and GOS were independent predictors of the PCS, whereas LOS and depressive symptoms were predictors of the MCS. After TBI depressive symptoms are a better predictor of the mental component of HRQoL than functional outcome, implying that depressive symptoms should be closely monitored during and after rehabilitation.

The ability to return to work is an important aspect of community integration. Consequences of TBI that interfere with return to work are multifold encompassing any combination of cognitive, physical, emotional or behavioral problems. Social barriers such as concerns about employing a person with TBI or difficulties with transportation to and from work may be important too. Chapters 4 and 5 focus on return to work after moderate and severe TBI.

In **chapter 4** the employment outcome three years after moderate and severe TBI in 113 patients was prospectively investigated. The employment rate dropped from 80% preinjury to 15% at 3 months post injury and gradually increased to 47% after 1 year and 55% after 3 years. No significant change occurred from 1 to 3 years post injury. Employment rates remained quite stable after the first year post injury, which is in line with other studies on employment.[12,13] An employment rate of 55% after moderate to severe TBI is somewhat higher than reported in a review by van Velzen et al. with 40.7% of patents employed after one year and 40.8% after two years. However reported employment rates are very variable ranging from 0–84%.[14] The review of Shames showed similar ranges of employment (12% to 70%).[1] Variability in employment rates may be due to methodological issues such as a wide variety of patient populations, different follow-up times, different study designs and different outcome measures.[1] Some studies included sheltered work and unpaid work while other studies focus on competitively employed individuals and income.[1]

Using multiple logistic regression analysis, the FAM score and psychiatric symptoms were selected as independent predictors for employment status. A FAM cutoff score of less than 65 to identify patients at risk of long-term unemployment had a good diagnostic value. Thus patients with psychiatric symptoms and impaired cognitive functioning at hospital discharge are at the highest risk of long-term unemployment. These factors should be in the focus of vocational rehabilitation.

Chapter 5 was a follow-up on employment 10 years after injury. Of the initial cohort forty-eight patients (42%) completed the 10-year follow-up. After an initial increase in employment rates a significant decrease to 43% after ten years was observed. These results are in line with Cuthbert et al., who described a large American cohort which also showed a decline in employment between 5 and 10 years post-injury.[15]

Our study further showed that employed patients had a significantly less severe TBI, a shorter length of hospital stay (LOS) and higher scores on the GOS, BI, FIM, and FAM at hospital discharge. A multivariable analysis showed that time, pre-injury employment, FAM at discharge and LOS are independent predictors of employment. Being employed ten years after moderate/severe TBI is related to injury severity and functional factors rather than personal and contextual factors (such as age, sex, being single, type of occupation, and education level). National legislation and economy driven factors should be taken into account too.

Chapter 6 studied cognitive functioning ten years after TBI and the associations between cognitive function, depression and HRQoL. Fifty of the initial 113 patients completed the ten-year follow-up. The drop-out rate was 17% after 3 years and 56% after ten years of which 6% died. Patients who were included (n=50) did not differ significantly from patients without follow-up (n=63) in baseline characteristics, except for age at injury. Patients that participated were significantly older at the time of injury compared to those who were lost-to-follow-up.

Ten years after TBI, we found that 12% of participants was not able to perform the total cognitive test battery; especially, executive functioning (6ET) could not be assessed. Patients with TBI scored relatively low on memory tests (15WT), information processing speed (D2) and concentration (D2) compared with reference values. Over time cognitive functioning significantly improved during the first year post-injury and stabilized thereafter (measured with the FAM up to three years).

Ten patients (20%) showed symptoms of depression. Compared to non-depressed patients significantly worse scores were found in 6 of the 8 subdomains of the SF-36 for the depressed patients. Patients with depressive symptoms reported more subjective cognitive complaints than patients without depressive symptoms. However, no significant differences were found between depressed and non-depressed patients on any of the cognitive-tests, except for the D2 test.

Depression scores were significantly associated with HRQoL, and subjective cognitive functioning scores 10 years after TBI. Cognitive functioning at hospital discharge (FAM) was significantly associated with performance on cognitive tests and with subjective cognitive functioning at 10 years follow-up, but not with depression or HRQoL.

Therefore, signaling and treatment of depressive symptoms after moderate-severe TBI may be of major importance for optimizing HRQoL in the long-term. We did not find strong evidence for reduced cognitive functioning or associations between depression

and objective cognitive functioning, which could have been influenced by reduced disease awareness or possible selective drop-out.

The findings described in chapters 3–6 show relatively positive results on long-term outcome with regard to employment, HRQoL and cognitive functioning after moderate to severe TBI. The absence of reliable prognostic models on these outcomes hampers clinical decision making in the acute care setting leading to complex ethical choices for clinicians involved.[16,17]

METHODOLOGICAL CONSIDERATIONS

Study design

The longitudinal design of the Rotterdam TBI study is its major strength and allows detailed exploration of the course over time.

However, the sample size is small and the loss to follow-up increases over the years (17% and 34% after three years, 56% after ten years). Although patients who were lost to follow-up were comparable to included patients, selection bias cannot be ruled out. Including more patients would probably not have changed our results, but might have led to smaller confidence intervals, which means more precise results. The small sample size combined with the loss to follow-up, especially after ten years, reduces generalizability. The data were collected by trained psychologists doing home visits. Different psychologists performed the measurements within the first year, after three years and at 10 years follow-up. Errors due to inaccurate registration cannot be excluded. Further mood was assessed with the WSRS in chapter 3. The WSRS was replaced in chapter 5 by the CES-D because of the limited use of the WSRS in the international literature. The lack of use of the WSRS hinders comparison with other studies.

Participants with insufficient knowledge of the Dutch language were excluded from the study which may have led to a 'differential nonresponse'. A factor which could not be prevented due to the nature and the way of collecting the data.

In the studies regarding employment, National regulations and labor market forces were not considered in interpreting the employment rate. Global, but also local, economic factors might influence the employment rate, especially if a longer time period is being investigated.

Outcome measures

Outcome measures in this long-term follow-up study shifted from injury related outcomes in the (sub) acute phase to participation oriented outcomes in (long-term) follow-up measurements. This shift sometimes hampered follow-up over time.

Another topic that concerns all measurements is possible reduced disease awareness after TBI.[8] Being unaware of deficits may interfere with adequately reporting deficits. Thus evaluation by a proxy could have added important information.[8,18]

Functional outcome

In this thesis several injury related/functional outcome measures were used. The GOS, for example, is a widely accepted measure for general outcome after TBI but due to its generic nature detailed information is lost. This needs to be taken into account when interpreting the changes or the lack of changes when considering the GOS.

The length of hospital stay (LOS) is another important injury related factor, it is a numerical instrument that can easily be compared. However, clinical motivation to end or prolong stay in acute hospital or to choose the discharge destination is not available. Information on which grounds a clinician decides the discharge destination to be a rehabilitation center, nursing home or home can broaden the perspective on clinical reasoning after TBI.

The Barthel Index (BI) is a measurement instrument not specifically designed for TBI patients, but has several advantages. It is easy to administer and does not require formal training, takes little time to complete, which reduces patient burden. The widespread familiarity contributes to its interpretability. On the other hand, the test is relatively insensitive for changes, and the lack of comprehensiveness results in problems with ceiling/floor effects.[19]

Cognitive functioning was measured in chapters 3–6 with the FAM. Although the FAM has a high internal consistency and reliability and is widely used in TBI research there are more detailed and extensive tools to measure cognition.[20] FIM/FAM also suffer from ceiling effects, which could have had its effect particularly in long-term follow-up.[21]

Employment

Employment outcome was recorded during each visit by means of structured interviews. Employment outcome included questions on employment status (yes/no), type of work, and workload (full-time, part-time, unemployed). The type of work was classified into 4

categories based on the article by Walker et al.[22] Detailed information, such as whether a patient returned to his previous work, whether the level and extent of employment preinjury differed from follow-up, and whether there was a change in income over the years would have positively contributed to these articles.

Health-Related Quality of Life

The SF-36 was used to measure HRQoL. It is widely used after TBI, is available in several languages, and has population norms for many countries.[18] However it is a generic instrument with known floor and ceiling effects and it may not capture all disease specific dimensions of HRQoL after TBI. The TBI-specific Quality of Life after Brain Injury questionnaire was not available at the start of data collection for the present study.[18,23] In regression and correlation analyses the PCS and MCS scores of the SF-36 were used to define the physical and mental subdomains of HRQoL, because it was not practical to study relationships in all 8 subdomains in detail. This may have led to simplification.

Depression

The presence (yes/no) and type of psychiatric symptoms were observed during hospitalization by the medical staff and also recorded at each visit by the research psychologist in a structured interview. Mood was measured in the home environment only which may have resulted in missing data during the first measurements if the patients still were in the hospital, rehabilitation center or nursing home at that time. The use of anti-depressant medication could also have been of influence and may result in lower prevalence estimates, making this an important variable to consider in future research.[24,25]

At the start of the study the WSRS was chosen to measure depression, during follow-up this was converted to the CES-D which impedes evaluation of these data during follow-up.

Cognition

In the first three years of the study the FAM was used to measure cognition. At ten years the FAM was not administered, due to the large number of other cognitive tests.

In chapter 6 the CFQ was used to measure subjective cognitive complaints. Reduced disease awareness and ceiling/floor effects may be of importance.

FUTURE RESEARCH/PERSPECTIVES

To learn more about TBI related outcome in the future it seems important to prevent possible misclassification. Technological advances in modern medicine will most likely provide new (imaging) techniques (or extended use of current techniques) that enables physicians, together with the clinical presentation of the patient, to determine a more reliable and easy to use classifying system. The development of such a system will pose a challenge, but seems essential.

Future research should strive for large cohorts of patients such as in the Traumatic Brain Injury Model Systems (TBIMS) in the US and CENTER –TBI in Europe.[15,26] In the Netherlands the NeuroTraumatology Quality Registry (NetQuRe) will allow systematic and long-term follow-up of TBI patients.[27] When investigating employment after TBI national regulations, labor market forces, and local, but also global, economic factors should be taken into account. Another option might be performing a correction for local and global economics, which will be difficult and time-consuming, if even possible.

Patient reported outcome measures are imported in long-term value-based health care. However, in patients with moderate-severe TBI, patient-reported outcomes may not always be in line with objectively measured outcomes, due to lack of awareness of disease. Future studies should also incorporate questionnaires measuring the level of disease awareness, in which patient-reported outcomes are compared with those from proxies and health care professionals.

Furthermore, this thesis did not focus on exacerbated cognitive decline as a precursor for Alzheimer's disease and other forms of dementia or on reduced life expectancy.[28,29] These themes might need attention in future studies.

GENERAL CONCLUSION

This thesis showed that a large percentage (43%) of patients, despite the severity of TBI, is able to perform work related activities after ten years, and has a normal HRQoL after three and ten years. Emotional status and cognitive performance after ten years were also found to be reasonably optimistic.

However, there are subgroups that perform worse in the long term, for example 12% of the patients was not able to perform the total cognitive test battery, and 20% showed symptoms of depression.

At hospital discharge the cognitive status is predictive for long-term outcome with respect to employment and cognitive function after ten years. Depressive symptoms at hospital discharge or during follow-up have important negative impact on overall outcome, but most off all on HRQoL.

Taking the severity of TBI into account, these findings are relatively positive and should be taken into account in clinical decision making in both acute and subacute care settings.

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Samenvatting

Hoofdstuk 1 vormt een algemene introductie op de problematiek rondom traumatisch hersenletsel (THL), met name op de lange termijn. In dit hoofdstuk worden de achtergronden en het doel van de Rotterdam THL studie besproken.

Hoofdstuk 2 beschrijft de noodzaak van het organiseren van adequate follow-up van patiënten met THL in de keten van zorg. Twee klinische casussen illustreren dat THL geen incident is, maar als een chronische aandoening moet worden beschouwd. Eén casus betreft een patiënt met licht THL, de tweede casus betreft een patiënt met ernstig THL. Beide casussen illustreren dat revalidatie een levenslang, goed gecoördineerd proces, met aandacht voor de patiënt en zijn familie dient te zijn. Deze casussen laten tevens zien dat, zowel licht als middelzwaar/ernstig THL-patiënten, kampen met de langetermijngevolgen van THL. Het ontbreken van goede prognostische modellen van functionele uitkomsten op de lange termijn wordt besproken. Verder illustreert dit hoofdstuk dat een goed georganiseerde keten van zorg voor patiënten met THL wordt gehinderd door nationale en gemeentelijke wetgeving, beleid van de ziektekostenverzekeraars, maar ook door een gebrek aan samenwerking tussen zorgorganisaties.

Het evalueren van het tijdsverloop van gezondheidsgerelateerde kwaliteit van leven bij 97 THL-patiënten en het identificeren van de voorspellers hiervan was het doel van **hoofdstuk 3**. Gezondheidsgerelateerde kwaliteit van leven (HRQoL) werd gemeten met de SF-36, waarvan 5 van de 8 subdomeinen een significante verbetering vertoonden over 3 jaar. Voor de 'fysieke component' van de SF-36 (PCS) was er eveneens een significante verbetering in de tijd, terwijl de score van de 'mentale component' van de SF-36 (MCS) stabiel bleef. Na drie jaar was gezondheidsgerelateerde kwaliteit van leven ongeveer hetzelfde als in de Nederlandse normatieve populatie. Tijd na THL, de verblijfsduur in het ziekenhuis, FIM en GOS waren onafhankelijke voorspellers van de 'fysieke component' van de SF-36 (PCS), terwijl verblijfsduur in het ziekenhuis en depressieve symptomen voorspellers van de 'mentale component' van de SF-36 (MCS) waren. Na THL zijn depressieve symptomen een betere voorspeller van de 'mentale component' van gezondheidsgerelateerde kwaliteit van leven (HRQoL) dan functionele uitkomstmaten, wat impliceert dat depressieve symptomen nauwlettend gevolgd moeten worden tijdens en na revalidatie.

In **hoofdstuk 4** zijn de uitkomsten ten aanzien van de mogelijkheid tot werken over een periode van 3 jaar bij 113 middelzwaar/ernstig THL-patiënten prospectief onderzocht. Het percentage werkenden daalde van 80% voor het ongeval, naar 15% op 3 maanden na het ongeval en nam geleidelijk toe tot 55% na 3 jaar. Het percentage werkenden steeg significant in de periode van 3 maanden tot 1 jaar, maar het veranderde niet significant meer in de periode van 1 tot 3 jaar na het ongeval. Na logistische regressieanalyse

werden de FAM-score en psychiatrische symptomen geselecteerd als onafhankelijke voorspellers voor het hebben van werk 3 jaar na THL. Een FAM-score van minder dan 65 had een goede diagnostische waarde om patiënten te identificeren die het risico lopen op langdurige werkloosheid. Patiënten met psychiatrische symptomen en een verminderd cognitief functioneren bij ontslag uit het ziekenhuis hebben daarom het grootste risico op langdurige werkloosheid. Deze factoren zouden belangrijke aandachtspunten moeten zijn bij revalidatie gericht op terugkeer naar werk.

Het doel van **hoofdstuk 5** was om de kans op werk en voorspellers van werk 10 jaar na THL te evalueren. Van het initiële cohort voltooiden 48 patiënten (42%) de 10-jarige follow-up. Na 3 maanden was 12% werkzaam, wat geleidelijk, maar significant steeg tot 57% na 2 jaar follow-up, gevolgd door een significante afname tot 43% na 10 jaar. Patiënten die 10 jaar na THL werkten, hadden een significant minder ernstig THL, een kortere verblijfsduur in het ziekenhuis (LOS) en hogere scores op de GOS, BI, FIM en FAM bij ontslag uit het ziekenhuis. Multivariabele analyse toonde dat tijd, werkzaam zijn voor het ongeval, cognitie (FAM-score) en verblijfsduur in het ziekenhuis (LOS) onafhankelijke voorspellers zijn voor de kans op werk op de lange termijn. Hieruit kan worden geconcludeerd dat de kans op werk 10 jaar na THL vooral gerelateerd is aan ernst van het letsel en minder aan contextuele factoren. Toekomstige studies met betrekking tot arbeidsrevalidatie moeten zich daarom vooral richten op beïnvloedbare factoren en daarbij rekening houden met de effecten van nationale wetgeving en de invloed van werkgelegenheid binnen een land.

Hoofdstuk 6 bestudeerde het cognitief functioneren 10 jaar na THL en de associaties tussen cognitief functioneren, depressie en gezondheidsgerelateerde kwaliteit van leven (HRQoL). Vijftig van de initiële 113 patiënten voltooiden de follow-up van 10 jaar. Patiënten die konden worden geïncludeerd (n=50) verschilden niet significant van patiënten die niet konden worden geïncludeerd (n=63) wat betreft de basiskenmerken, met uitzondering van de leeftijd ten tijde van het ongeval. Tien jaar na THL vonden we dat 12% van de deelnemers de totale cognitieve testbatterij niet kon uitvoeren; vooral het executief functioneren (6ET) kon niet worden beoordeeld. Patiënten met THL scoorden relatief laag op geheugentests (15WT), snelheid van informatieverwerking (D2) en concentratie (D2) vergeleken met referentiewaarden. Over de tijd verbeterde het cognitief functioneren aanzienlijk gedurende het eerste jaar na het ongeval en stabiliseerde daarna (gemeten met de FAM tot 3 jaar). Tien patiënten (20%) vertoonden symptomen van depressie. Bij 6 van de 8 subdomeinen van de SF-36 scoorden de depressieve patiënten significant slechter in vergelijking met niet depressieve patiënten. Patiënten met depressieve symptomen rapporteerden meer subjectieve cognitieve klachten dan patiënten zonder depressieve symptomen. Er werden echter geen significante verschillen gevonden tussen depressieve en niet depressieve

patiënten bij de objectieve cognitieve testen, behalve de D2-test. Depressiescores waren significant geassocieerd met gezondheidsgerelateerde kwaliteit van leven (HRQoL) en het subjectief cognitief functioneren 10 jaar na THL. Cognitief functioneren bij ontslag uit het ziekenhuis (gemeten met de FAM) was significant geassocieerd met de prestaties op cognitieve tests en met het subjectief cognitief functioneren na 10 jaar follow-up, maar niet met depressie of gezondheidsgerelateerde kwaliteit van leven (HRQoL). Daarom lijkt signalering en behandeling van depressieve symptomen na middelzwaar/ernstig THL van groot belang te zijn voor het optimaliseren van gezondheidsgerelateerde kwaliteit van leven (HRQoL) op de lange termijn. We vonden geen sterk bewijs voor verminderd cognitief functioneren of associaties tussen depressie en objectief cognitief functioneren. Dit kan beïnvloed zijn door een verminderd ziekte-inzicht of mogelijk selectieve uitval van patiënten gedurende follow-up.

Hoofdstuk 7 is een algemene discussie van dit proefschrift, waarin de belangrijkste bevindingen worden samengevat, methodologische aspecten van de studie worden besproken en overwegingen voor toekomstige onderzoek worden beschreven.

Dankwoord

Bij het tot stand komen van dit proefschrift hebben diverse mensen een bijdrage geleverd. Een aantal hiervan wil ik er extra uitlichten.

Allereerst de deelnemende patiënten, zonder de door hen geleverde inspanning, over een lange periode, was dit proefschrift niet mogelijk geweest. Het zal niet altijd even eenvoudig zijn geweest om de uitgebreide metingen te ondergaan bij deze ernstige aandoening, zonder daar direct beter van te gaan functioneren.

Dr. M.H. Heijenbrok-Kal mijn copromotor, Majanka je bent zeer intensief betrokken geweest bij dit proefschrift. Je prettige en tevens kritische houding hebben een essentiële bijdrage geleverd aan mijn wetenschappelijk vorming en het uiteindelijke resultaat (dit proefschrift). Majanka, het uitvoeren van statistische analyses lijkt bijna eenvoudig met jouw hulp. Dank voor je steun en toewijding en het altijd beschikbaar zijn ondanks je drukke agenda.

Prof. dr. G.M. Ribbers, mijn promotor en tevens directe collega. Ik kan aansluiten bij de in eerdere proefschriften geroemde capaciteiten: het zicht houden op de grote lijnen, kritische en stimulerende commentaren, de snelle, en kernachtige manier van formuleren. Gerard, dank daarvoor, maar bovenal waardeer ik je zeer als directe collega met meer kennis en ervaring. Je analytische vermogen en humor geeft regelmatig een andere kijk op patiëntenzorg gerelateerde onderwerpen, operationele kwesties (die mijn dagelijkse werkzaamheden beïnvloeden), alsmede mijn wetenschappelijke inzichten. Je hebt wat dat betreft voor mij een voorbeeldfunctie, wat betreft arbeidsethos en inhoudelijke kennis.

De leden van de kleine commissie, prof. dr. C.M.F. Dirven, prof. dr. C.A.M. Bennekom en prof. dr. R.W.H.M. Ponds, wil ik bedanken voor het beoordelen van mijn manuscript en het plaatsnemen in mijn oppositie. Ik wil ook prof. dr. A.I.R. Maas, prof. dr. W.C. Peul, prof. dr. J. van der Naalt en prof. dr. S.M.A. Bierma-Zeinstra danken voor het plaatsnemen in de grote promotiecommissie.

Graag wil ik ook de overige mede-auteurs drs. I.K. Haitsma en dr. I. de Koning bedanken, zonder jullie medewerking hadden de artikelen er anders uit gezien. Ditzelfde geldt voor L.D. Peppel en C.J. Hartjes, zij zijn daarnaast verantwoordelijk voor het verzamelen van de data na tien jaar.

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Loes Knoope wil ik eveneens bedanken, jij creëerde als dit nodig was altijd ruimte in mijn agenda voor het uitwerken van verschillende onderdelen van dit proefschrift.

Mijn paranimfen Christian Riksen en Maaike Dorresteijn-Grauwmeijer wil ik op deze wijze bedanken. Chris ik ken je al vanaf de brugklas, wij hebben vooral heel veel leuke dingen beleefd. Je positieve instelling en enthousiasme werken aanstekelijk. Onze levens vertonen veel parallellen, ik hoop daarom vooral nog veel mooie dingen samen met je te mogen meemaken. Maaike, bedankt voor alle hulp, je nuchtere kijk en vrolijke inbreng. Ondanks je drukke werk en gezinsleven ben je altijd bereid om mee te denken en te relativeren, dank daarvoor.

Mijn vrienden en familie wil ik bedanken voor de interesse en de nodige ontspanning en gezelligheid die het mogelijk maakten om dit proefschrift te kunnen schrijven.

In het bijzonder wil ik mijn ouders bedanken. Jullie onvoorwaardelijke steun, niet alleen bij dit proefschrift, maar bij alles wat ik doe is op alle fronten heel bijzonder en koester ik. Jullie hebben regelmatig op Mitchell gepast, zodat ik mij kon focussen op dit proefschrift. Dit was niet alleen praktisch maar ook heel gezellig. Mijn dank voor dit alles is lastig om in woorden om te zetten.

Mitchell jij bent één brok energie en enthousiasme. Je vrolijkheid en je nu inmiddels drie jaar durende ontdekkingstocht werken aanstekelijk en zijn een constante bron van inspiratie (en gratis entertainment). Bellina, zonder jouw steun en liefde en constante aansporing was dit proefschrift niet mogelijk geweest. Dank voor je begrip en geduld. Ik ben bevoorrecht om door jullie beiden omringd te worden en kijk uit naar onze verdere toekomst.

About the author

CURRICULUM VITAE

Erik Grauwmeijer was born on 27th of February 1978 in Rotterdam, the Netherlands. He attended secondary school at the Vallei College (VWO) in Amersfoort, where he graduated in 1996. Because he could not start his Medical study due to numerus fixus (lottery) he started his Physical Therapy study at the 'Hoge School van Utrecht' faculty of Health Care, as an alternative for his future Medical study. In 2001 he graduated cum laude on the faculty of Health Care and became a physical therapist. The same year, after six unsuccessful attempts because of the numerus fixus system, he was eventually selected through 'decentrale selectie' (admission apart from the numerus fixus after assessment) and started with his Medical study at Utrecht University.

During his study he worked as a physical therapist at Medicort/Tamminga in Utrecht in the evenings and weekends. In 2007 he obtained his degree of Doctor of Medicine from the Medical faculty of Utrecht University. He worked as a surgical resident between 2008 and 2009 at the IJsselland Hospital. In 2009 he started his training in Rehabilitation Medicine at Rijndam Rehabilitation and the department of Rehabilitation Medicine and Physical Therapy, of the Erasmus University MC in Rotterdam. He obtained the degree of Medical Doctor in Physical and Rehabilitation Medicine in 2013.

In 2013 he started working as a rehabilitation physician at Rijndam Rehabilitation center, location Dordrecht, and continued his work as a PhD researcher which already started during his residency. The research described in this thesis is part of the research line of the Rotterdam Traumatic Brain Injury (TBI) study on outcome after moderate/severe Traumatic Brain Injury with theses of B. van Baalen on outcome after the first year post onset, A. Willemse-van Son on outcome three years post onset and the current project on outcome 10 years post onset. At the end of 2013 he started working as a staff member at the adult in- and outpatient clinic of neurorehabilitation of Rijndam rehabilitation Centre in Rotterdam (location Westersingel), in which he continues to work at this moment.

SUMMARY OF PHD TRAINING AND TEACHING

Name PhD student: Erik Grauwmeijer
PhD Period: 2012–2017
Erasmus MC Department: Rehabilitation Medicine
Promotor: Prof. Dr. G.M. Ribbers
Co-promotor: Dr. M.H. Heijenbrok

	Year	Workload (Hours/ECTS)
1. PhD Training		
General courses		
BROK Course (Basiscursus Regelgeving Klinisch Onderzoek)	2014	30 Hours/1
PhD day	2015	5 Hours/0.25
Teach the Teacher 3, Erasmus MC, Rotterdam, The Netherlands	2015	16 Hours/0.5
Seminars and workshops		
Cognitive Rehabilitation Training, ACRM, Toronto	2014	16 Hours/0.5
Presentations		
Poster Presentation 'Return to work after TBI', Ontwikkelingen in Onderzoek, Nijmegen, The Netherlands	2011	30 Hours/1
Poster Presentation: A prospective study on return to work three years after moderate-severe TBI, American Congress of Rehabilitation medicine, ACRM-ASNR, annual conference, Atlanta, USA	2011	30 Hours/1
Oral Presentation 'Return to work after TBI', Basiscursus THL, Rotterdam, The Netherlands	2012	30 Hours/1
Oral Presentation 'Neuropsychiatric consequences after Stroke/TBI', Refereeravond, Rotterdam (Rijndam/Erasmus MC), The Netherlands	2012	30 Hours/1
Poster presentation: Health-Related Quality of Life 3 Years After Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. American Congress of Rehabilitation medicine, ACRM-ASNR, annual conference, Toronto, Canada.	2014	30 Hours/1
Oral Presentation: 'Traumatic Brain Injury and Longterm consequences', cursorisch onderwijs, Rijndam Rotterdam, The Netherlands	2015	30 Hours/1
Poster Presentation: Health-Related Quality of Life 3 Years After Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. 11th World Congress on Brain Injury, Den Haag, The Netherlands	2016	30 Hours/1
Poster Presentation: Employment Outcome Ten Years After Moderate to Severe Traumatic Brain Injury: a Prospective Cohort Study. 12th World Congress on Brain Injury (IBIA 2017), New Orleans, USA	2017	30 Hours/1
Oral Presentation: Lange termijn effecten van THL. Hersenletselcongres, Ede, The Netherlands	2017	30 Hours/1
Oral Presentation: Licht THL, cursorisch onderwijs, Rijndam Rotterdam, The Netherlands	2017	30 Hours/1

	Year	Workload (Hours/ECTS)
(Inter)national conferences		
American Congress of Rehabilitation medicine, ACRM-ASNR, annual conference, Atlanta, USA	2011	40 Hours/1
VRA Annual Congress, Noordwijkerhout, The Netherlands	2012	16 Hours/0.5
VRA Colloquium, Arnhem, The Netherlands	2012	8 Hours/0.25
VRA course on TBI, Rotterdam, The Netherlands	2012	16 Hours/0.5
VRA Annual Congress, Ermelo, The Netherlands	2013	16 Hours/0.5
VRA Colloquium,	2013	8 Hours/0.5
American Congress of Rehabilitation medicine, ACRM-ASNR, annual conference, Toronto, Canada	2014	36 hours/1
Dutch Congress of rehabilitation Medicine, Rotterdam, The Netherlands	2014	16 Hours/0.5
Dutch Colloquium of rehabilitation Medicine, Zwolle, The Netherlands	2014	8 Hours/0.25
International Neurorehabilitation Symposium (INRS/ICRAN/ICVR), Valencia, Spain	2015	36 Hours/1
Congres on Neurorehabilitation and Neural Repair, Maastricht, The Netherlands	2015	16 Hours/0.5
Dutch Congress of rehabilitation Medicine, Rotterdam, The Netherlands	2015	16 Hours/0.5
11th World Congress on Brain Injury, Den Haag, The Netherlands	2016	36 Hours/1
12th World Congress on Brain Injury (IBIA 2017), New Orleans, USA	2017	36 Hours/1
Hersenletselcongres, Ede, The Netherlands	2017	8 Hours/0.25
Other		
Participating in RoNeRes meetings, dept. of Rotterdam Neurorehabilitation Research	2013-2017	40 Hours/1
Participating and advise on 'patient information Brochure' on mild and moderate-severe TBI (Folders Hersenstichting Hersenschudding en Hersenkneuzing)	2017	30 Hours/1
2. Teaching		
Organizing and participating teaching program Rehabilitation Medicine Residents, Rijndam rehabilitation Centre	2013	60 Hours/2
Supervising Medical students, on neurorehabilitation Department Rijndam, Rotterdam, The Netherlands	2012-2017	100 Hours/3
Supervising Rehabilitation Medicine Residents on neurorehabilitation Department Rijndam, Rotterdam, The Netherlands	2013-2017	400 Hours/12
Participating in teaching program of Rehabilitation Medicine Residents, Rijndam Rehabilitation Centre, Rotterdam, The Netherlands	2014-2017	130 Hours/4