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Patients with Diffuse Axonal Injury Can Recover to a Favorable Long-Term Functional and Quality of Life Outcome

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Abstract

Functional outcome and quality of life are difficult to predict in patients with diffuse axonal injury (DAI) after traumatic brain injury (TBI). The primary aim of this cross-sectional cohort study was to assess the long-term functional outcome in patients with DAI and to identify prognostic factors. Second, health-related quality of life (HRQL) at long-term follow-up was assessed. Patients ≥16 years of age with TBI and DAI (admitted 2008–2014) were included. Clinical and imaging data were collected. The primary outcome parameter was the Glasgow Outcome Scale Extended (GOSE) at long-term follow-up. Second, the HRQL was assessed with the Quality Of Life after Brain Injury (QOLIBRI) questionnaire. DAI was diagnosed in 185 patients. Long-term functional outcome was obtained in 134 patients (72%), median follow-up was 54 months (range 14–100); and 51% had a favorable outcome (GOSE 6–8). Independent prognostic factors were age, pupillary reaction, Hb, DAI grading, and return of consciousness ≤7 days. Sixty-two percent had a good HRQL, after a median follow-up of 57 months (range 14–100) with age as an independent prognostic factor. More than half of patients with DAI had a favorable functional outcome and a good HRQL at long-term follow-up. Also in patients with a DAI grade 3, a favorable outcome was seen. HRQL is a clinically relevant outcome measure because it reflects perceived outcome by patients. Independent prognostic variables for functional outcome were factors obtained in the acute phase after injury, whereas age was an independent prognostic factor for HRQL.

Keywords: DAI; GOSE; HRQL; QOLIBRI; TBI

Introduction

For patients with diffuse axonal injury (DAI) after traumatic brain injury (TBI), prognosis, in terms of functional outcome and quality of life, is not clear. It is uncertain whether the patient will remain in a vegetative state, or will be able to participate in a working environment again. In the (sub)acute phase after injury, patients and their relatives are in need of more individualized information concerning long-term prognosis.

DAI is the result of tearing of axons caused by acceleration-deceleration forces during trauma.[1] After sustaining fatal TBI, DAI is present in all patients; however, it occurs also in mild, moderate, and severe TBI.[2,3] DAI can be diagnosed with MRI. The most used MRI grading for DAI represents the depth of the lesions in three grades: (1) cortical, (2) corpus callosum, and (3) brainstem.[4] Prior research indicates DAI to be a prognostic factor for an unfavorable outcome.[5] A higher grade of DAI is associated with a higher mortality rateand a higher risk of an unfavorable functional outcome.[6–8] However, this association does not result in a reliable individual prognosis assessment in clinical practice.

The use of prognostic models, such as the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) and Corticosteroid Randomization After Significant Head Injury (CRASH), have improved prognosis estimates in patients with TBI.[9,10] Both models use clinical data and CT imaging data to predict outcome after TBI. Although the presence of DAI on the MRI is a prognostic factor, in neither of these models were MRI-specific factors included. Because DAI specific clinical or MRI features may affect prognosis, a prognostic model focusing solely on DAI patients would provide the opportunity to more specifically predict functional outcome and quality of life for the individual patient with DAI.

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Outcome is often defined as functional outcome or as the scores on neurocognitive tests. The ''Quality of Life After Brain Injury'' (QOLIBRI) questionnaire provides the opportunity to assess disease-specific health-related quality of life (HRQL) in patients with brain injury.[11] With this instrument, the perceived patient outcome can be measured. Outcome defined as HRQL after TBI in patients with MRI-proven DAI has not yet been addressed.

The primary aim of this cross-sectional cohort study was to assess long-term functional outcome in patients with DAI and to identify prognostic factors. Second, we aimed to assess the perceived outcome of patients with DAI by determining the HRQL at the long-term follow-up.

Methods

Study design

In this cross-sectional study, we studied all patients with DAI admitted to one of the participating Dutch level I trauma centers (St. Elisabeth Hospital [EH] or University Medical Centre Groningen [UMCG]) during a 7 year period (January 1, 2008, to December 31, 2014). Patients with TBI, ≥16 years of age at the time of the injury, and with DAI on the MRI (which was performed <6 months after the injury) were included. DAI was defined as microbleeds on the MRI, either on fast field echography (FFE) or on T2 stir gradient echo resonance (T2*GRE). Exclusion criteria were MRI artefacts impairing diagnostics, large cerebral infarction, preexistent mental retardation, and other neurological conditions that affect long-term follow-up.

Data collection and analysis

Clinical data were extracted from the electronic medical records, comprising: age, trauma mechanism, initial Glasgow Coma Score (GCS), length of intensive care unit (ICU) stay, return of consciousness (defined as a motor score of M6), and hospital admittance. Also, the imaging data such as the Marshall score of the first performed CT scan, the timing and field strength of the MRI, and the result of the MRI were obtained. The long-term follow-up was assessed prospectively and consisted of the Glasgow Outcome Scale Extended (GOSE) and the QOLIBRI.

The GOSE is a functional outcome scale with eight categories, from 1 = death to 8 = good recovery. A score ≥6 indicates participation in a working environment, and is considered a favourable outcome.[12] The QOLIBRI is a validated questionnaire assessing HRQL in patients with TBI. With 37 questions, a maximum score of 100 can be obtained, from 0 = very poor quality of life to 100 = very good quality of life.[11,13] A total score of ≥60 indicates a good quality of life.[14]

The patients were contacted by telephone and a structured telephone interview was assessed to complete the GOSE. The QOLIBRI was sent by mail after the telephone interview. The GOSE could be obtained either from the patient or a relative, whereas the QOLIBRI had to be filled out by the patient. The researcher was blinded for the DAI grading of the patients. When patients repeatedly could not be contacted by telephone, both the QOLIBRI and GOSE were sent by mail.

Imaging technique

In the EH, the MRI scans were performed on a 1 Tesla (T) MRI (only in 2008), a 1.5 T MRI (2009–2014), and a 3 T MRI (2011–2014) (all Phillips Medical Systems). The scanning protocol differed over time and per MRI scanner, however in all patients, FFE imaging was performed as well as T2 sagittal imaging. Diffusion weighed imaging was performed when cerebral ischemia was suspected. In the UMCG, all the MRI scans were performed on a 1.5 T scanner (Siemens Medical Systems). T2*GRE and T2 sagittal imaging were performed in all patients.

All MRI scans were initially assessed by a neuroradiologist and reassessed for DAI grading by a researcher (M.v.E.). In cases of inconclusive assessment, a neuroradiologist (J.P.) was consulted.

Ethical approval

The study did not meet the criteria for medical scientific research, according to the Dutch Medical Research Involving Human Subject Act (1998). The study protocol was presented to the Medical Ethical Committee Brabant in The Netherlands, which on these grounds deemed no further ethical evaluation necessary. Patients and/or their representatives were asked for written informed consent for participation in the study.

Statistical analysis

First, a univariable analysis comparing putative risk factors with the functional outcome, GOSE, as ordinal outcome measure was performed. Proportional odds logistical regression was used to calculate the odds ratio (OR) with 95% confidence interval (CI).[15] Next, a multivariable proportional odds logistical regression analysis was performed. Variables with a p value of $p < 0.20$ in the univariable analyses were included in the multivariable analysis. For the multivariable analyses, a backward elimination procedure was performed to define the final independent risk factors. Variables were eliminated from the model if the p value was >0.10.[16]

Second, univariable linear regression analysis with the HRQL (QOLIBRI) as continuous dependent factor was performed. The β coefficient with 95% CI was calculated. A step backward multivariable linear regression analysis was performed on variables with a p value of <0.20 in the univariable analysis. Variables were eliminated from the model if the p value was >0.10.

Finally, we explored the relationship between the functional outcome and the HRQL in the surviving patients. The GOSE and QOLIBRI outcomes were dichotomized as favorable and unfavorable outcomes. First, a Pearson correlation was calculated. Second, a binary logistical regression with the GOSE as dependant variable was performed to calculate the OR with 95% CI.

Statistical analyses were performed with IBM SPSS Statistics version 24.

Missing data

The data were checked and missing variables were provided when possible. After assessment of the randomness of the missing data, multiple imputation was performed. The putative prognostic variables were included in the multiple imputation model and missing data were imputed. The outcome variables (GOSE and QOLIBRI) were included as a predictor in the imputation model; these values were not imputed.[17] The number of imputations (m) was defined by the highest percentage of missing data per variable.[18] This was 13% in the variable pupillary reaction; therefore, we imputed the data 15 times (m = 15).

Results

Patients

A total of 714 patients with TBI had an MRI scan of the brain. In 185 patients, DAI was proven on an MRI scan performed within 6 months after trauma. Eight patients were excluded for further analysis. In Figure 1 the selection process and outcomes were presented. Within this DAI cohort, 63% of patients had severe TBI (admission GCS 3–8), 22% had moderate TBI (GCS 9–12), and 15% had mild TBI (GCS 13–15). The main cause of the TBI was high energy trauma in traffic. Cranial neurosurgical intervention

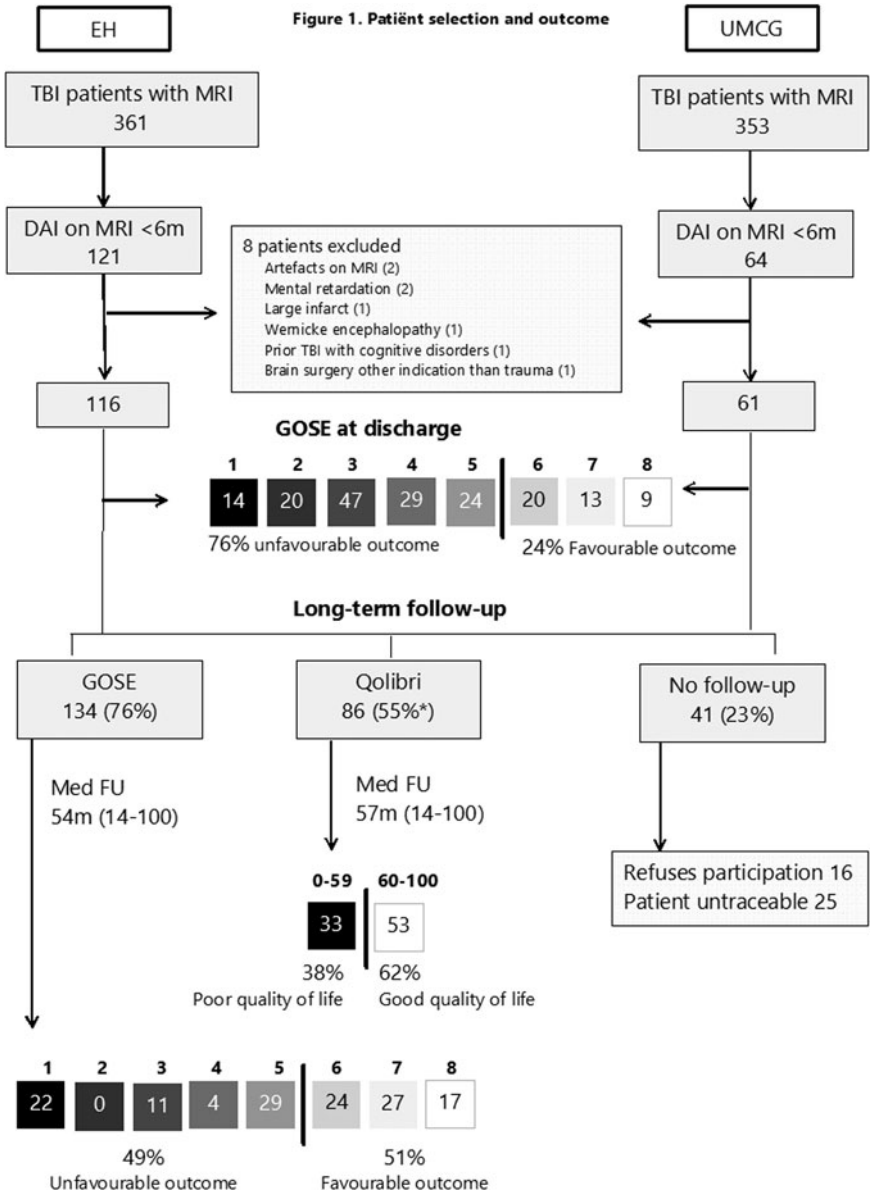

FIG. 1. Patient selection and outcome. The patient selection process and follow-up are presented. QOLIBRI collection possible in 155 patients (22 deceased). EH, Elisabeth Hospital; UMCG, University Medical Centre Groningen; TBI, traumatic brain injury; DAI, diffuse axonal injury; GOSE, Glasgow Outcome Score Extended; QOLIBRI, Quality of Life After Brain Injury; Med FU, median follow-up.

was performed in 21 patients (decompression [$n=11$], evacuation of an epidural [$n=4$] and/or a subdural [$n=7$] hematoma, depressed skull fracture [$n=2$], and extraventricular drainage [$n=1$]); 158 patients (89%) were admitted to the ICU, and the duration of ICU admission was median 11.0 days (0–100 days). The median duration of the hospital admission was 25 days (range 1–179), a higher DAI grading resulted in a longer hospital stay (DAI 1: median 17 days (range 1–77), DAI 2 median 29 days (range 4–94), and DAI 3 median 31 days (range 2–179]). The patient characteristics are summarized in Table 1.

Imaging data

For six patients, no CT brain scan at hospital admission was available, five patients were initially admitted in another country, and for one patient, no CT scan was performed. In the remaining 171 patients CT scans 82% had a Marshall score of 1 or 2. Microbleeds were found in 63% (111) of the CT scans, a subdural hematoma was found in 23%, and an epidural hematoma was found in 10%.

DAI was confirmed on MRI in all included patients. The MRI was performed a median of 22 days after trauma (range 1–250), in 57 patients (32%) the MRI was performed within the first 14 days and 58% of the MRI scans were performed on a 1.5 T MRI (34% were performed on a 3 T MRI, and 8% were performed on a 1 T MRI). All three grades of DAI were diagnosed in patients with mild, moderate, and severe TBI (Fig. 2).

Long-term follow-up: Functional outcome

The GOSE was assessed in 134 patients, a median of 54 months (range 14–100 months) after trauma, with a median score of 6.0

Table 1. Characteristics of Included DAI Patients

	n = *177*
Median age years (range)	33 (16–80)
Male gender *n* (%)	126 (71)
Medical history *n* (%)	
Blank	79 (45)
Mild TBI	3 (2)
DM	8 (5)
Hypertension	16 (9)
Cardiac	13 (7)
Malignancy	2 (1)
Medication *n* (%)	
None	123 (70)
Oral anticoagulants	2 (1)
Antiplatelet therapy	9 (5)
Other	35 (20)
Unknown	14 (8)
Trauma location *n* (%)	
Traffic	139 (79)
Home	16 (9)
Work	8 (5)
Sports	11 (6)
GCS median (range)	8.0 (3–15)
Alcohol intoxication *n* (%)	34 (19)
ISS score mean (SD)	27.9 (12.1)
Admission CT Marshall score median (range)	2.0 (1–6)
DAI grading on MRI *n* (%)	
DAI 1	65 (37)
DAI 2	45 (26)
DAI 3	67 (38)
Hospital admission days median (range)	25.0 (1–179)
Discharged to: *n* (%)	
Rehabilitation center	66 (37)
Home	34 (19)
Other hospital	32 (18)
Home with rehabilitation care	17 (10)
Deceased	14 (8)
Nursing home	12 (7)
Psychiatry ward	2 (1)

TBI, traumatic brain injury; DM, diabetes mellitus, GCS, Glasgow Coma Score; ISS, Injury Severity Scale; DAI, diffuse axonal injury.

(range 1–8). Fifty-one percent of the patients had a favorable long-term outcome; both the dichotomized and complete GOSE results are presented in Figure 1. The long-term outcome per DAI grade is described in Table 2.

Univariable analysis risk factors. In the univariable analysis, age, motor score ≥5, pupillary reaction, complications pre-hospital admission, Injury Severity Score (ISS), Hb, Marshall score, DAI grading, autonomic dysregulation ≤7 days, and return of consciousness ≤7 days were significantly associated with the GOSE at long-term follow up (Table 3).

Multivariable analysis risk factors. In the multivariable analysis, motor score ≥5, complications pre-hospital admission, ISS, Marshall score, and autonomic dysregulation ≤7 days were not independent risk factors. A higher Hb value, lower age, presence of pupillary reactions, DAI grade 1, and return to consciousness ≤7 days were significantly associated with a more favorable outcome. Results of the multivariable ordinal analysis are described in Table 3.

Long-term follow-up: HRQL

The QOLIBRI questionnaire was returned by 55% ($n = 86$) of the living patients at long-term follow-up (median 57 months, range 14–100). The median age at injury was 34.0 years (range 16–78); 75% of the respondents filled out the questionnaire completely, 24% of the questionnaires were incomplete but still valid. Questions regarding decision making, the ability to navigate, and the ability to express oneself in a conversation were completed by all participants. Patients scored highest on the domain concerning emotional well-being and lowest on cognition (Table 4). Younger patients scored lower on all domains, and 62% of the respondents scored a good quality of life (Fig. 1). The outcome of the QOLIBRI per DAI grade is presented in Table 2.

Univariable analysis risk factors. In the univariable analysis, age, the presence or absence of pupillary light reaction, Marshall score, and DAI grade 3 were significantly associated with the outcome score of the QOLIBRI at long-term follow up (Table 5). The length of the follow-up was not significantly correlated ($\beta = 0.1$ 95% CI 0.04–0.3) with HRQL.

Multivariable analysis risk factors. In the multivariable analysis, the presence or absence of pupillary light reaction, Marshall score, and DAI grade 3 were not independent risk factors. Only age was an independent risk factor; a higher age resulted in a better quality of life (Table 5).

The relationship between the GOSE and the QOLIBRI in surviving patients

One hundred and fifty-five patients had survived at long-term follow-up. Both the GOSE and the QOLIBRI were obtained from 84 patients (54%). Twenty-four (29%) of these patients showed an unfavorable outcome on the GOSE (scores 1–5), with a covariance

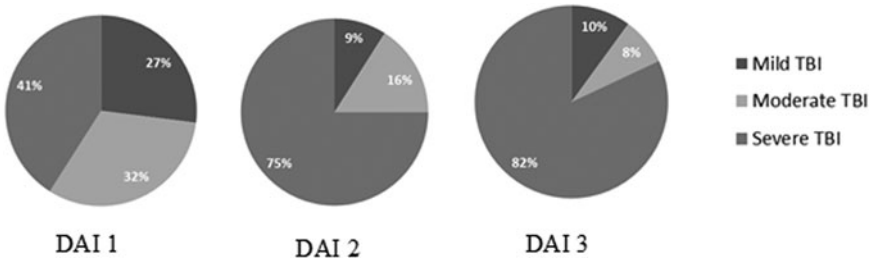

FIG. 2. DAI grading and TBI severity. In all three DAI grades patients with mild, moderate, or severe traumatic brain injury were represented. DAI, diffuse axonal injury, TBI, traumatic brain injury.

Table 2. Long-Term Outcome per DAI Grading

	GOSE										QOLIBRI		
	n	*D*	*VS*	*SD-*	*SD+*	*MD-*	*MD+*	*GR-*	*GR+*	*Unfav %*	n	*Median (range)*	*Unfav %*
DAI 1	49	7	0	2	1	7	8	14	10	35	35	69.4 (23.6–100)	34
DAI 2	34	4	0	2	1	11	7	7	2	53	21	71.0 (34.7–94)	24
DAI 3	51	11	0	7	2	11	9	6	5	61	30	58.7 (16–99)	53

The long-term functional outcome (GOSE) and quality of life outcome (QOLIBRI) per DAI grade.

GOSE, Glasgow Outcome Scale Extended; DAI, Diffuse Axonal Injury; QOLIBRI: Quality of Life After Brain Injury; D, death; VS, vegetative state; SD-, lower severe disability; SD+, upper severe disability; MD-, lower moderate disability; MD+, upper moderate disability; GR-, lower good recovery; GR+, upper good recovery; Unfav, unfavorable.

of 0.09 ($p < 0.001$). The majority (71%) of the patients with an unfavorable outcome on the GOSE also scored low on the QOLIBRI, indicating a poor HRQL. On the other hand, 44 (73%) of the patients with a favorable outcome on the GOSE had scores on the QOLIBRI indicating a good quality of life. The OR for a poor quality of life related to the GOSE was OR 6.7 (95% CI 2.3–19.1, $p < 0.001$).

Discussion

This study was performed to assess long-term outcome in patients with DAI and to identify prognostic factors for long-term functional outcome and HRQL. To the best of our knowledge, this is the largest report on prognosis and prognostic factors in DAI patients. Further, no other studies report HRQL in patients with proven DAI on MRI. We found that clinical data regarding hospital admission were important specifically for the functional outcome, whereas age was related to HRQL.

In this cohort of a total of 177 DAI patients, a favorable functional outcome (GOSE 6–8) at discharge was found in one out of four patients. At long-term follow-up, performed in 134 patients, a favorable functional outcome was present in half of the patients with DAI. Independent predictors for the functional outcome were mainly factors obtained early after admission, comprising: pupillary reaction, Hb, DAI grade, return of consciousness ≤7 days, and age. Long-term HRQL was obtained in 86 patients with DAI. The QOLIBRI could not be obtained when patients had died or were unable to fill out the questionnaire. This resulted in a possible overestimation of the HRQL. At long-term follow-up, a good quality of life was reported by 62% of the patients, and only age was an independent predictor for the HRQL. Younger patients scored lower on all domains of the QOLIBRI. This is in line with the results published by Finnanger and coworkers, who found that a younger age is related to more self-reported emotional and behavioral problems.[19] Possibly, young patients scored lower on the HRQL because they suffer more from higher social expectations

Table 3. Proportional Odds Analysis for the Long-Term Functional Outcome (GOSE)

	Univariable analysis			*Multivariable analysis*		
	OR	*95% CI*	p *value*	*OR*	*95% CI*	p *value*
Age (years)	1.0	0.97–1.0	0.14	0.97	0.95–0.99	0.002
Male sex	0.7	0.4–1.4	0.37	-		
High energy trauma	0.6	0.2–1.5	0.27	-		
M score ≥5	4.4	2.3–8.4	<0.001	*		
Pupillary reaction						
No light reaction both sides	0.3	0.1–0.8	0.013	0.2	0.1–1.0	0.05
Unilateral light reaction	0.2	0.04–0.6	0.009	0.3	0.1–0.7	0.01
RR diastolic	1.0	1.0–1.0	0.29	-		
Complications prehospital	0.6	0.3–1.2	0.14	*		
ISS	1.0	0.9–0.98	<0.001	*		
Glucose	1.0	0.8–1.1	0.52	-		
Hb	1.7	1.2–2.3	0.002	1.5	1.1–2.1	0.03
Marshall score						
Score 1 vs. 2–6	0.5	0.2–1.3	0.10	*		
Score 1–2 vs. 3–6	0.4	0.1–1.1	0.09	*		
DAI grade (1–3)						
Grade 3 vs. 1	3.0	1.5–6.0	0.003	2.3	1.01–5.0	0.05
Grade 3 vs. 2	1.5	0.7–3.3	0.29	*		
DAI 3	0.5	0.3–0.9	0.02	-		
Neurosurgical intervention	0.8	0.3–1.8	0.54	-		
Return of consciousness ≤7 days	7.4	3.7–15.0	<0.001	6.3	2.9–13.7	<0.001

Univariable and multivariable proportional odds analysis of potential prognostic variables in predicting a favorable long-term functional outcome (GOSE).

GOSE, Glasgow Outcome Scale Extended; OR, odds ratio; CI, confidence interval; M score, Motor score; BP, blood pressure; ISS, Injury Severity Score; DAI, diffuse axonal injury; -, not included in the model; *,eliminated in the step backward procedure.

Table 4. QOLIBRI Domain Scores

QOLIBRI	*Median scores*	*(range)*
Cognition	64.3	(14.3–100.0)
Self	67.9	(10.7–100.0)
Daily life/Autonomy	71.4	(3.6–100.0)
Social relationships	70.8	(12.5–100.0)
Emotion	80.0	(15.0–100.0)
Physical problems	75.0	(10.0–100.0)
Total	68.5	(16.0–100.0)

The QOLIBRI (Quality of Life After Brain Injury) domain scores and total scores at the long-term follow-up. The QOLIBRI was obtained in 86 patients.

and changed future perspectives. The QOLIBRI was previously assessed in older patients by Lin and coworkers, and it was found appropriate to use the QOLIBRI in elderly patients.[20] With the results of this report, we have no reason to assume that a bias in the QOLIBRI questionnaire is responsible for our result of age being related to HRQL. In the univariable analysis, DAI grade 3 was identified as a prognostic factor, and a higher DAI grade was often found in younger patients.

Age, pupillary reaction, Hb, and DAI grading are known prognostic factors in patients with DAI.[6,21–23] In this study, these factors were also identified for the functional outcome, and the relationship with HRQL was assessed. The duration of coma, autonomic dysregulation, the Marshall classification, and the ISS were also identified as independent prognostic factors in prior publications.[6,21,24,25] Instead of the coma duration, the regaining of consciousness in ≤7 days was assessed, because secondary complications are mostly treated at this stage and it provides the opportunity to assess the prognosis at a distinct time interval after trauma.

The median score on the QOLIBRI was 68.5, representing a good HRQL. In previous research on HRQL in TBI patients, the mean QOLIBRI score was 64.6 irrespective of the presence of DAI.[26] These results are comparable; therefore, HRQL in patients with TBI in general can be regarded as similar to HRQL in patients with TBI and DAI.

A good quality of life was found in a higher percentage than was a favorable functional outcome (62% vs. 51%).

In the analysis regarding variables predicting the functional outcome, all patients, including the deceased patients, were included. The analysis for HRQL could only be performed in patients who returned the QOLIBRI. Therefore, the patients who had died (22) were not included in this analysis. Of the surviving patients, 55% returned the QOLIBRI. In the subgroup of surviving patients who filled out the QOLIBRI, the functional outcome (GOSE) was strongly related to the score on the QOLIBRI, with a significant OR of 6.7. This indicates that patients with a higher, more favorable score regarding functional outcome, also scored higher on HRQL. This is in line with prior research.[26] The length of follow-up was not significantly correlated to HRQL; therefore, improved acceptance over time by the patients regarding their functional outcome did not influence the results.

Axonal injury was defined as microbleeds identified on T2*GRE or FFE MRI.[27–29] Grading of DAI in three grades (as proposed by Gentry and coworkers) is currently the most used MRI grading.[4] Therefore, this grading system was used in our study to define and grade the axonal injury. MRI sequences used by others to diagnose

Table 5. Linear Regression Analysis of Potential Prognostic Variables in Predicting Health Related Quality of Life (QOLIBRI)

	Univariable analysis			*Multivariable analysis*		
	B-coefficient	*(95% CI)*	p *value*	*B-coefficient*	*95% CI*	p *value*
Age (years)	0.2	–0.0–0.5	0.07	0.2	0.0–0.5	0.07
Male sex	–4.7	–13.5–4.0	0.29	-		
High energy trauma	–2.6	–14.6–9.4	0.67	-		
M score ≥5	3.4	–5.4–12.1	0.45	-		
Pupillary reaction						
LR intact	10.6	–5.3–26.6	0.19	*		
Unilateral LR	–0.9	–25.6–23.9	0.95	-		
No LR	–16.6	–36.6–3.3	0.10	*		
RR diastolic	0.1	–0.1–0.4	0.37	-		
Complications pre-hospital	4.2	–6.4–14.8	0.43	-		
ISS	–0.2	–0.6–0.1	0.22	-		
Glucose	0.1	–2.1–2.4	0.91	-		
Hb	–1.0	–5.6–3.6	0.66	-		
Marshall score						
Score 1	–8.1	–15.3–2.1	0.12	*		
Score 2	1.5	–7.5–10.4	0.32	-		
Score 3–6	10.7	–2.7–24.1	0.12	*		
DAI grade (1–3)						
Grade 1	3.0	–5.4–11.5	0.48	-		
Grade 2	4.8	–4.8–14.4	0.33	-		
Grade 3	–7.1	–15.7–1.5	0.10	*		
Neurosurgical intervention	4.3	–8.7–17.2	0.52	-		
Return of consciousness ≤7 days	2.3	–6.9–11.5	0.63	-		

Univariate and multivariate linear regression analysis of potential prognostic variables in predicting health related quality of life (QOLIBRI).

QOLIBRI: Quality of Life After Brain Injury; CI, confidence interval; M score, Motor score; LR, light reaction; BP, blood pressure; ISS: Injury Severity Score; DAI, diffuse axonal injury; -, not included in the model *,eliminated in the step backward procedure.

DAI are susceptibility weighed imaging (SWI), fluid-attenuation inversion recovery (FLAIR), and diffusion weighed imaging.[6,25,30] Although SWI is more sensitive in detecting microbleeds than T2*GRE and FFE, the prognostic value of SWI is still uncertain.[31,32] More recently, diffusion tensor imaging (DTI) has also been recognized to visualize axonal injury, but is not yet used regularly in clinical practice.[33,34] All included patients had an MRI with T2*GRE/FFE sequence imaging. Other sequences were either performed on a small number of patients or not at all, and were, therefore, not included in the analysis.

Functional outcome after TBI is often studied, whereas HRQL has barely received attention so far. Validated disease-specific questionnaires are available and provide the opportunity to reliably assess HRQL. Outcome measured as quality of life in combination with functional outcome provides valuable information for the clinician. Prospective longitudinal research to further explore and validate the prognostic factors for functional outcome and HRQL in patients with DAI is necessary. These prognostic factors will support caregivers in providing patient information not only on functional prognosis, but also concerning patient-perceived outcome. Therefore, we advocate for more awareness of HRQL of patients, and the inclusion of quality of life in prognostic models.

In addition to the size of the study, other strengths are the long-term follow-up addressing functional outcome and HRQL, with an especially high response rate on the functional outcome follow-up. The study results are applicable in everyday clinical practice; often TBI patients present not only with DAI but also have other lesions; patients with DAI were included even when additional TBI was present. Also, imaging was mostly performed on a 1.5 T MRI, such as is often available in everyday practice. Further, the outcome variables were exploited to their full potential by the use of proportional odds logistical regression and linear regression techniques, because dichotomization of outcome measures results in the loss of information.[15]

However, we also want to address some limitations. First, it is possible that not all patients were identified, because an MRI was not performed in all patients within 6 months after injury. Also, the collected clinical and imaging data were not always complete. To provide the most reliable results, multiple imputation was performed to impute the putative prognostic variables.

Second, increase in knowledge and the availability of MRI in everyday practice over the years has probably influenced the frequency in which DAI was diagnosed (i.e., in the EH in 2008, 11 patients were diagnosed with DAI, whereas in 2014, 24 patients were). Possibly, patients with more severe DAI were more often clinically identified, resulting in the performing of an MRI to confirm this diagnosis. As a result, the diagnosis in patients with a mild DAI was potentially missed. However, all grades of DAI were almost evenly represented in the study population, and, therefore, conclusions are applicable to all three grades of DAI.

Third, one third of the included patients were derived from the UMCG, and two thirds were derived from the EH. In both centers, the number of TBI patients with an MRI of the brain was similar (361 vs. 353). The lower number of included patients from the UMCG could indicate different patient management, as MRI assessment in the UMCG was more often performed ≥6 months after trauma.

Fourth, the MRI field strength differed among patients. The majority (58%) of the MRI scans was performed on a 1.5 T MRI and 35% were performed on a 3 T MRI. A higher field strength is more sensitive in diagnosing DAI. A scan on a 3 T MRI is almost twice as sensitive as that on a 1.5T MRI, showing a higher total number of lesions, and a higher number of lesions in the corpus callosum.[35] Possibly, DAI was classified in a lower grade or was missed in patients receiving an MRI on a 1 T or a 1.5 T scanner. However, the study results reflect clinical practice, because a 3 T MRI is not always available. Also, the DAI grading could have been underestimated because of the time interval between trauma and MRI. Non-hemorrhagic lesions on FLAIR are known to reduce considerably in the first 3 months after trauma.[36] However, non-hemorrhagic lesions were not included in our definition or our grading of DAI. Microbleeds on T2*GRE can also attenuate or even disappear over time, but appear to be stable in the first 6 months after trauma.[36,37] The MRI in this cohort was performed within the first 6 months after trauma.

Fifth and last, not all patients could be contacted or consented for participation in the long-term follow-up, although the response rate for the GOSE (76%) exceeded response rate expectations.[38] Possible explanations for the higher than expected response rate for the GOSE are the minimal time investment for the telephone interview and the fact that a caregiver could answer the questions. The inclusion number of patients for the QOLIBRI is lower than that for the GOSE, which could be explained by the fact that the QOLIBRI could only be obtained for surviving patients and was not always completely filled out.

Conclusion

In conclusion, more than half of the patients with DAI had a favorable functional outcome and a good HRQL at long-term follow-up. Also in patients with a DAI grade 3, a favorable outcome was seen; therefore, these patients should also receive a rehabilitation program similar to that provided for patients with a lower DAI grade. HRQL reflects perceived outcome by patients themselves and is, therefore, a clinically relevant outcome measure. Independent prognostic variables for functional outcome were factors obtained in the acute phase after injury, whereas age was an independent prognostic factor for HRQL. We propose the inclusion of quality of life predictors in prognostic models.

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