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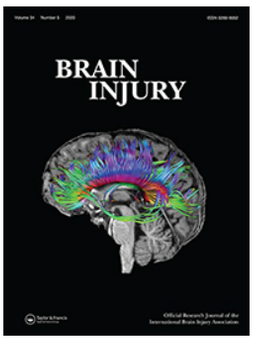

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Accuracy in prediction of long-term functional outcome in patients with traumatic axonal injury: a comparison of MRI scales

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ABSTRACT

Purpose: Functional outcome prediction for patients with traumatic axonal injury (TAI) is not highly related to the MRI classifications. The aim of this study was to assess the accuracy in predicting functional outcome in patients with TAI with several MRI scoring methods and to define the most accurate method.

Methods: Patients with TAI (2008–2014) confirmed on MRI <6 months after injury were included in this retrospective study. Long-term functional outcome was prospectively assessed using the Glasgow Outcome Score Extended. The Gentry classification is most used in clinical practice. This method was compared to methods that score lesion load, lesion locations, and to modified Gentry classifications. The area under the curve (AUC) was calculated for the scoring methods.

Results: A total of 124 patients with TAI were included, medium follow-up 52 months. The AUC for the Gentry classification was 0.64. All tested methods were poor predictors for functional outcome, except for the 6-location score (area under the curve: 0.71). No method was significantly better than the Gentry classification.

Conclusion: The Gentry classification for TAI correlates with functional outcome, but is a poor predictor for the long-term functional outcome. None of the other tested methods was significantly better.

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Traumatic axonal Injury; diffuse axonal injury; traumatic brain Injury; MRI; outcome prediction

Introduction

Acceleration deceleration forces during trauma can cause shear injury of cerebral axons, resulting in axonal injury. The axonal injury can be diagnosed as microbleeds on MRI (1–3). For these lesions, the terms traumatic axonal injury (TAI) and diffuse axonal injury (DAI) are both being used in clinical practice. According to the NINDS common data elements, DAI is defined as a widespread distribution of lesions in multiple lobes including the corpus callosum. When lesions are present in one to three lobes, the term TAI is being used. When both patients with TAI and DAI are included in one article, the term TAI is often used to describe all patients (3,4).

The most often used MRI grading for TAI is described by Gentry et al. in 1994 (5), this MRI classification is based on prior histopathological research (6). A higher grade represents deeper located lesions and is associated with increasing severity of trauma (5–7). The Gentry classification is widely known and easy to apply, and is, therefore, a useful scoring method in clinical practice (8–10). This classification is found to be correlated with functional outcome in patients with TAI (10–12). An unfavorable outcome is found in 48% of the patients with TAI and with each step increase in TAI grade the odds for an unfavorable outcome increase almost three times (13). However, the clinical applicability of the Gentry classification in predicting outcome in individual patients with TAI is limited. In the Gentry classification, three grades are assigned which represent the depth of the lesions (1. on the gray-white matter interface, 2. corpus callosum, and 3. brainstem). In clinical practice, cortical lesions are often attributed to grade I TAI. In this scoring method, a single lesion in the corpus callosum or brainstem results in a higher grading of TAI. The relation between the number of TAI lesions and outcome is still unclear. Several studies demonstrated a relation with the total number of lesions and outcome irrespective of location (3,11,14), but other studies did not find this relation (15–19).

Alternative scoring methods for TAI, with the use of a specific lesion location as predictor, have been proposed (11,19,20). However, none of these alternative scoring methods were compared to the Gentry classification in terms of accuracy of outcome prediction and studies are often not validated. Therefore, these alternative scoring methods currently have no role in clinical practice.

With this study, we aimed to evaluate the accuracy of several clinical applicable MRI scoring methods for TAI in predicting long-term functional outcome and to assess whether there is a better TAI classification method than the grade 1 to 3

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Supplemental data can be accessed on publisher's website.

classification. We hypothesized that extending this classification with a simple method would enhance the outcome prediction.

Methods

Study design

In this retrospective cohort study, clinical characteristics (age, sex, comorbidity, trauma mechanism, and duration of hospital admission) and MRI data were collected from the electronic patient records. TAI scoring methods were applied and the functional outcome was assessed prospectively. Patients or their representatives were contacted by telephone or mail to obtain long-term functional outcome. The functional outcome was assessed with the Glasgow Outcome Scale Extended (GOSE), with 8 grades (1 = death and 8 = full recovery). A score of ≥6 indicates participation in a working environment and was considered a favorable outcome (21).

Participants

The electronic patient records of the St. Elisabeth Hospital and University Medical Center Groningen, The Netherlands (both level I trauma centers) were searched for the terms trauma and MRI Brain (at any given time and for all indications). The inclusion criteria were trauma between January 1, 2008 and December 31, 2014, age ≥16 at trauma, and TAI confirmed on a 1.5 T or 3 T MRI within 6 months after trauma. TAI was defined as the presence of microbleeds on Fast Field Echo (FFE) or T2* Gradient Echo (T2*GRE) MRI. Exclusion criteria were intellectual development disorder, other (neurological) condition influencing outcome, artifacts on MRI impairing judgment, and no long-term follow-up.

Test/scoring methods

All scoring methods were applied to the FFE or T2* GRE MRI to assess microbleeds. Low-signal lesions in a lesion compatible with a contusion were considered as a hemorrhagic contusion and not rated as TAI lesions. A microbleed was defined as a black round or oval lesion (diameter 1–10 mm) on FFE or T2*GRE. All MRI scans were initially assessed by a neuroradiologist and reassessed for the TAI grading methods by a researcher (ME), in case of inconclusive assessment a neuroradiologist (JP) was consulted and consensus was reached. Twenty randomly selected MRIs were also assessed by a second assessor (MH). Both assessors were blinded for the clinical information and outcome. Assessor 2 was blinded for the rating of assessor 1.

The Gentry classification was defined as the reference scoring method. Three grades were scored according to the location of lesions: 1. cortical, 2. corpus callosum, and 3. brainstem (5). The scoring methods compared with the Gentry classification can be classified in three groups: 1. microbleed lesion load, 2. lesion location, and 3. modified Gentry classifications.

Microbleed lesion load

Throughout literature several scoring or counting methods for TAI are being used, clinically applicable and often described methods were selected. The first method concerned the total number of TAI lesions (3,14,15). Second, the number of lesions in the corpus callosum were assessed (20,22–24). Both the total number of lesions and the presence of multiple or single lesions in the corpus callosum were valuated. Third, the presence of multiple or single lesions in the brainstem was assessed (20).

Lesion location

The presence of a lesion in the corpus callosum in full and specified for genu, body, and splenium (22) was tested first. Second, the presence of bilateral thalamic lesions was assessed (4). Finally, a scoring method including several locations in the brain was constructed. The selected locations were the frontal lobe, the parietal-occipital lobe, the temporal lobe, the corpus callosum, the basal ganglia, and the brainstem. One point was awarded to the locations in the brain in which at least one microbleed (left or right) was present. Finally, the points were added up resulting in the 6-locations score with a range of 1–6 points.

Modified Gentry classifications

Small modifications to the Gentry classification were made and tested. These modifications were all conceived with clinical practice in mind, complex scoring methods were not considered.

Modified Gentry classification 1: a weighted score per grading location in the original Gentry classification. An OR for unfavorable outcome per grade was calculated using logistic regression analysis. Based on these ORs, points were awarded for the 3 regions (cortical, corpus callosum, and brainstem). The scores per region were added to result in the Modified Gentry classification 1.

Modified Gentry classification 2: Lesions in the basal ganglia or thalamus were included in Grade 2 instead of Grade 1, resulting in the following grading: 1 cortical lesion, 2 lesions in the corpus callosum, basal ganglia, and/or thalamus, and 3 lesions in the brainstem.

Modified Gentry classification 3: The presence of lesions in the basal ganglia and the thalamus were allocated a separate grade. Resulting in the following grading: 1 cortical lesion, 2 lesions in the corpus callosum, 3 lesions in the basal ganglia and/or thalamus, and 4 lesions in the brainstem.

Statistical analysis

The interobserver agreement was determined by Cohen's kappa, for the 20 MRIs rated by two assessors. Cohen's kappa was calculated for the Gentry classification, the total number and the location of microbleeds. Values of kappa from 0.40 to 0.59 were considered moderate, 0.60–0.79 substantial, and ≥0.80 outstanding (25).

A receiver operating curve (ROC) and area under the curve (AUC) with 95% confidence interval (CI) were calculated for all the methods. The state variable was functional outcome,

the various scoring methods were defined as the test variables. An AUC of 0.50–0.59 was considered a failing method, 0.60–-0.69 poor, 0.70–0.79 fair, 0.80–0.89 good, and 0.90–1.0 an excellent method. The AUC of the Gentry classification and the tested methods were compared with the Hanley method to test for statistical significance (26).

Only patients with complete functional follow-up were included. Statistical analyses were performed with IBM SPSS version 24.

Ethical considerations

This study was presented to the Medical Ethical Committee Brabant, The Netherlands. Patients and/or their representatives were asked for a written informed consent for participation in the long-term follow-up.

Results

Participants

A total of 714 patients with a trauma between January 1, 2008 and December 31, 2014 had an MRI of the brain, at any given time. Eventually, 124 patients with TAI were included for analysis (Flowchart 1 and Table 1). All three TAI Gentry grades were present; Grade 1 in 37%, Grade 2 in 27%, and Grade 3 in 36% of the patients. The MRI was performed median 20.5 days (range 2–192) after trauma. A favorable outcome was present in 66 (53%) patients, with a follow-up of median 52 months (range 14–100 months). There was no significant correlation relation between timing of the MRI and outcome (Pearson Correlation p 0.08), nor between timing of the MRI and TAI grading (Pearson Correlation p 0.08). An unfavorable outcome was present in 30% of the patients with Gentry Grade 1, in 52% of patients with Grade 2, and in 60% of patients with Grade 3.

Table 1. Patient characteristics of the included patients.

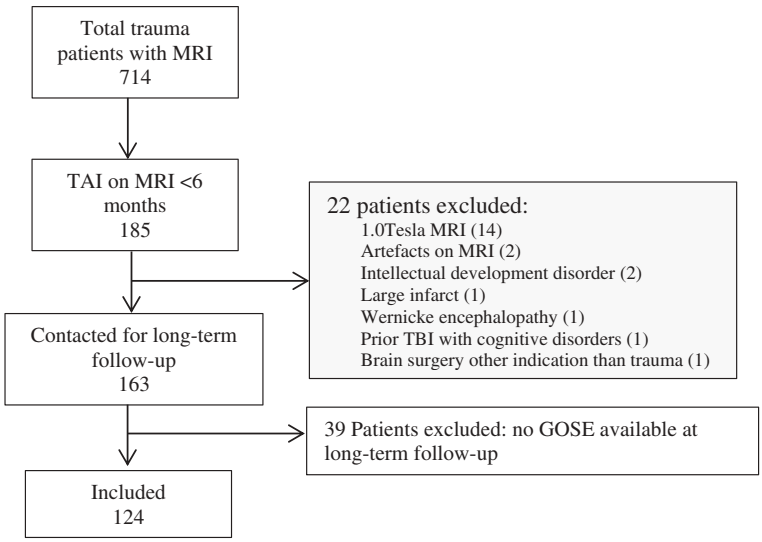
	Total n = 124
Male sex n (%)	88 (71)
Age median (range)	34 (16–80)
GCS n (%)	
3–8	74 (60)
9–12	23 (19)
13–15	21 (17)
unknown	6 (4)
Injury Severity Score mean (SD)	29 (13)
Timing MRI	
Days median (range)	20.5 (2–192)
≤7 days n (%)	19 (15)
≤3 months n (%)	86 (69)
Other lesions on MRI n(%)	
Contusion	50 (40)
Subdural hematoma	29 (23)
Epidural hematoma	2 (2)
Length of hospital stay in days median (range)	25 (1–179)
GOSE n (%)	
1	19 (15)
2	0 (0)
3	9 (7)
4	4 (3)
5	26 (21)
6	24 (19)
7	26 (21)
8	16 (13)

Abbreviations: n = number, GCS: Glasgow Coma Score, SD: standard deviation, MRI: Magnetic Resonance Imaging, GOSE: Glasgow Outcome Score Extended.

Scoring methods

The AUC of the reference test (the Gentry classification) was 0.64 (95%CI 0.54–0.74), indicating this to be a poor method for outcome prediction. Concerning the interobserver agreement, Cohen's kappa was k = 0.92, $p < .001$ regarding the Gentry classification, indicating an outstanding interobserver agreement. The interobserver agreement for the number of lesions (per 10 lesions or >100) was k = 0.66 $p < .001$, and for the number of locations k = 0.49, $p < .001$.

The ROC for the reference test and the tested methods is presented in Figure 1. Table 2 presents the results of the reference test and the tested methods.



Flowchart 1. Patient selection process.
Abbreviations: TAI: traumatic axonal injury, TBI: traumatic brain injury, GOSE: Glasgow Outcome Scale Extended

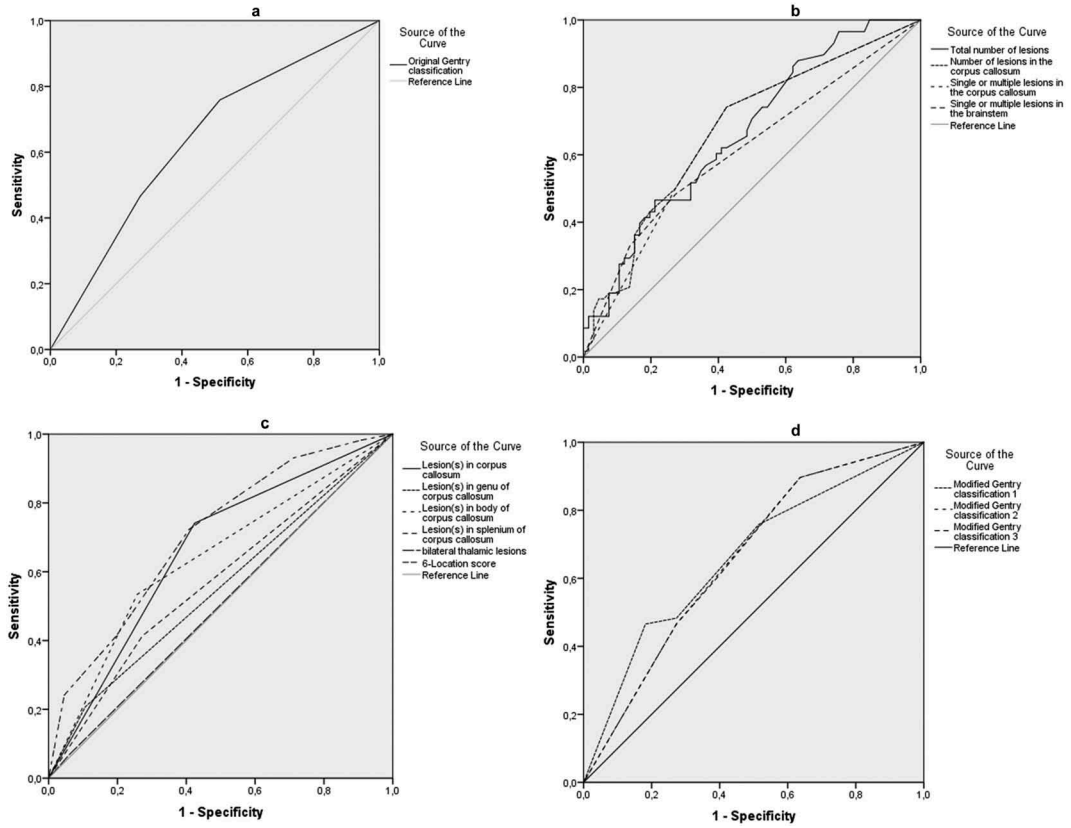


Figure 1. Receiver Operating Curves (ROC) of the scoring methods.
(a). ROC for the reference test, the Gentry classification. (b). ROC for the lesion load methods (number of TAI lesions, number of lesions in the corpus callosum, presence of single or multiple lesions in the corpus callosum, and the presence of single or multiple lesions in the brainstem). (c). ROC for the lesion location methods (corpus callosum, brainstem, 6-location score). (d). ROC of the modified Gentry classifications 1–3.

Microbleed lesion load

A higher AUC compared to the reference test was found for the total number of TAI lesions (AUC 0.67 (95%CI 0.57–0.76)), the number of lesions in the corpus callosum (AUC 0.67 (95%CI 0.58–0.77)), and the presence of a single lesion or multiple lesions in the corpus callosum (AUC 0.66 (95%CI 0.57–0.76)). A lower AUC compared to the reference test was found for the presence of single or multiple lesions in the brainstem (AUC 0.62 (95%CI 0.-52–0.72)). All tested methods indicated to be poor in predicting functional long-term outcome and none were statistically significant better than the original Gentry classification.

Lesion location

A higher AUC compared to the reference test was found for the location of lesions in the corpus callosum AUC 0.66 (95% CI 0.56–0.76) and for the 6-location score AUC 0.71 (95%CI 0.62–0.80). The 6-location score indicated to be fair in predicting long-term functional outcome. Both methods were not statistically significantly better than the Gentry classification. A lower AUC was found for lesions located in the genu, body, or splenium of the corpus callosum AUC 0.55 (95%CI 0.45–-0.65), AUC 0.64 (95%CI 0.54–0.74), and AUC 0.57 (95%CI 0.47–0.67), respectively. Also, bilateral thalamus lesions had a lower AUC of 0.50 (95%CI 0.40–0.61).

Modified Gentry classifications

First, the 'modified Gentry classification 1′ was composed. The OR for an unfavorable outcome for increase from Grade 1 to Grade 2 was 2.43 (95%CI 0.96–6.14), and the OR for Grade 2 to Grade 3 was 3.43 (95%CI 1.44–8.15). Based on these ORs cortical lesions were awarded one point, lesions in the corpus callosum two points, and lesions in the brainstem three points. Finally, scores were added, resulting in the modified Gentry classification 1 (scores 1–6).

All three modified Gentry classification methods scored a higher AUC, modified Gentry classification 1 AUC 0.66 (95%CI 0.57–0.76), modified Gentry classification 2 AUC 0.66 (95%CI 0.56–0.75), and modified Gentry classification 3 AUC 0.66 (95%CI 0.56–0.75). All the modified Gentry classifications were poor methods to determine long-term functional outcome. None of the tested methods were statistically significant better than the original Gentry classification.

Discussion

TAI is diagnosed and scored on MRI in everyday practice. A higher percentage of unfavorable outcome was found with an increasing TAI grade (Gentry classification). However, when a ROC was calculated for this commonly used grading system, the AUC indicates the long-term outcome prediction to be poor. Also, several other newly developed methods for

Table 2. TAI grading scores on the several tested methods. Results of the several tested grading methods for traumatic axonal injury. The reference test (the Gentry classification), test for microbleed lesion load, microbleed lesion location and modified Gentry classifications are presented.

	Method	Score
Reference test	Gentry classification n(%)	
	Grade 1	46 (37)
	Grade 2	33 (27)
	Grade 3	45 (36)
Microbleed lesion load	Total number of TAI lesions, median (range)	21 (1–169)
	Corpus callosum total number of TAI lesions, median (range)	1 (0–21)
	Corpus callosum	SL: 24 (19)
	single or multiple lesions	ML: 47 (38)
	Brainstem	SL: 18 (15)
	single or multiple lesions n (%)	ML: 28 (23)
Microbleed lesion location	Corpus callosum location	
	Genu n (%)	19 (15)
	Body n (%)	48 (39)
	Splenium n (%)	42 (34)
	Bilateral thalamus lesions	8 (7)
	6-locations, median (range)	4.0 (1–6)
Modified Gentry classifications	Modified Gentry 1, median (range)	3.0 (1–6)
	Modified Gentry 2 n (%)	
	Grade 1	30 (24)
	Grade 2	49 (40)
	Grade 3	45 (36)
	Modified Gentry 3 n (%)	
	Grade 1	30 (24)
	Grade 2	16 (13)
	Grade 3	33 (27)
	Grade 4	45 (36)

Abbreviations: n = number, TAI: traumatic axonal injury.

scoring TAI were poor. Only the 6-location score was found to be a fair method to predict outcome. Even though this method provides a slight improvement in outcome prediction, it is more complicated and not significantly better than the Gentry classification. Therefore, we do not advise the use of this grading method in clinical practice.

Prior research demonstrated a relation between the Gentry classification and functional outcome (10–13). In an attempt to optimize the outcome prediction, other scoring methods such as number of lesions (3,14), lesions in the corpus callosum (20,22), and lesion location (24) were studied. So far, several studies showed contradicting results (13). Also, adjustments to the Gentry classification were developed and related to outcome. However, scoring methods were not compared to the Gentry classification (27). In the present study, none of the tested methods was significantly better than the Gentry classification regarding long-term outcome prediction.

TAI is most often studied in patients with moderate to severe traumatic brain injury (11,19,28). However, axonal injury can also be present in patients with mild traumatic brain injury (12,15). In patients with mild traumatic brain injury and TAI, no relation was found with functional outcome (29), nor with neurocognitive function (15). Though in clinical practice, TAI grading methods are applied to all patients with TAI, irrespective of the severity of brain injury. In this study, a total of 21 patients (17%) with mild traumatic brain injury and TAI were included. Besides, not only patients with pure TAI after TBI but also patients with accompanying other types of brain injury, were included in this study. The inclusion of these patients resembles clinical practice, in which TAI grading is applied despite severity of trauma or accompanying lesions, but this possibly influenced the results.

The basal ganglia and thalamus are gray matter nuclei, strictly, lesions in these areas are not axonal injury. However, these areas are included in TAI grading (4,19,24). Bilateral thalamic lesions are related to an impaired consciousness in the acute phase but have no predictive value for the long-term prognosis (4). The depth of lesions is related to the severity of trauma (6,7). Lesions in the thalamus and/or basal ganglia occur in more severe trauma resulting in lesions in multiple locations. Perhaps the outcome is mostly influenced by the severity of trauma and the presence of multiple lesions, whereby bilateral thalamic lesions as part of a scoring method does not add to the predictive value.

The 6-location score, in which each region with lesions was awarded one point, scored the highest AUC regarding the long-term functional outcome prediction. In patients with mild traumatic brain injury, temporal microbleeds and outcome are related while frontal microbleeds were not (29). This might suggest that outcome prediction will be improved when regions are not all equally awarded with points.

Other clinical and MRI factors influence the outcome but were not included in the analysis of this study.

Functional outcome was the only used outcome measure, but cognitive function and quality of life can also be affected by TAI. Functional outcome and health-related quality of life (HRQL) are related in patients with TAI. However, a good functional outcome does not mean automatically a good HRQL. Prior research showed that 29% of patients with an unfavorable functional outcome had a good HRQL and 27% of patients with a favorable functional outcome had a poor HRQL (12). The aim of this study was not to identify all prognostic factors in patients with TAI but to evaluate MRI scoring methods for TAI. Currently, TAI scoring methods do not take into account other prognostic factors and are mainly reported in relation to the GOSE. Therefore, other factors or outcome measures were not included in this study. When assessing prognosis in patients with TAI, in future studies it is preferable to include outcome measures such as HRQL and cognitive functioning besides functional outcome, with the use of a continuous statistical analysis of outcome measures.

The scoring methods were applied on the FFE or T2*GRE sequence, these sequences are often described in research regarding TAI and outcome (4,19,22,30). However, TAI lesions can also be assessed on other MRI sequences. Though, lesions on T2*GRE have a better relation with outcome compared to FLAIR and DWI (4). SWI is a more sensitive sequence for the detection of microbleeds, but the relation with functional outcome is not clear yet (31–33).

In this study, multiple methods for assessing TAI were analyzed for their accuracy in outcome prediction. Some limitations regarding this retrospective study should be addressed. Patients who had no MRI within 6 months after trauma were not included, it is possible that patients with TAI were not included because of this time limitation. Also, 39 patients without a GOSE at long-term follow-up were excluded. With a higher number of patients, statistical differences between scoring methods might have been demonstrated.

MRI was performed on either a 1.5 T or a 3 T MRI, with varying scanning protocols. A 3 T MRI scan is almost twice as sensitive for microbleeds on T2*GRE (34). Therefore, the MRI field strength may influence the grading of TAI. However, in clinical practice, TAI grading is assessed on both 1.5 T and 3 T MR scanners and protocols differ between hospitals. The supplementary Table A.1. differences in scores on 1.5 T or 3 T MRI are presented. All scoring methods had a higher AUC on the 3 T scanner in comparison to the 1.5 T scanner, although not statistically significant.

The time interval between trauma and MRI varied from 2 to 191 days after trauma. Moen et al. found that non-hemorrhagic TAI lesions reduce in volume and number within the first 3 months and that microbleeds can attenuate or disappear between 3 and 12 months (3). In this study, there was no assessment of the microbleeds 6 months after trauma. Another study found no change in number of microbleeds 4–6 months after trauma (35). Therefore, microbleeds can attenuate or disappear over time, but appear stable in the first 3–6 months. However, it is unclear when exactly lesions decrease in number. Therefore, the timing of the MRI in our study might have resulted in an underestimation of the severity of TAI.

Conclusions

The widely used scoring method for TAI, the Gentry classification, is a poor predictor for the long-term functional outcome in patients with TAI. None of the other tested methods performed significantly better.

Although the 6-location MRI scoring method had the highest AUC, this was not statistically significantly different from the more simple Gentry classification, and therefore, we advise using the Gentry score. Clinicians should realize the limitations of long-term outcome prediction based on current MRI scoring methods for TAI. Other clinical and trauma-related factors might be important for prediction of outcome. Perhaps a scoring system combining MRI grading with clinical and trauma-related features will provide a more reliable outcome prediction.

Declaration of interest

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