Journal of Neuroradiology 46 (2019) 299–306

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original Article

The added prognostic value of magnetic resonance imaging in traumatic brain injury: The importance of traumatic axonal injury when performing ordinal logistic regression

Marta Cicuendez [a,*], Ana Castaño-León [b], Ana Ramos [c], Amaya Hilario [c], Pedro A. Gómez [b], Alfonso Lagares [b]

[a] Department of Neurosurgery, Vall d'Hebron University Hospital Research Institute (VHIR), Barcelona, Spain
[b] Department of Neurosurgery, Instituto de Investigación i+12, 12 de Octubre University Hospital, Universidad Complutense de Madrid, Madrid, Spain
[c] Department of Neuroradiology, 12 de Octubre University Hospital, Universidad Complutense de Madrid, Madrid, Spain

ARTICLE INFO

Article history:
Available online 1 September 2018

Keywords:
Traumatic axonal injury
Traumatic brain injury
Severe head trauma
Magnetic resonance imaging
Prognostic model

ABSTRACT

Background and purpose. – This study was performed to investigate the prognostic value of traumatic axonal injury (TAI) in severe head trauma.
Methods. – We attempted to determine whether any MR imaging findings of TAI could be related to prognosis in 264 patients with severe head trauma. We performed an ordinal logistic regression, adjusted for the prognostic factors according to the IMPACT studies, adding each MR feature related to prognosis one at a time. A new prognostic model was described by adding these MR features to the classic prognostic factors. The model was externally validated in a prospective series. Harrel's c-statistic and ordinal c-index (ORC) were calculated to measure its predictive accuracy.
Results. – We found 178 patients with TAI lesions. Lesions in the basal ganglia/thalamus, corpus callosum (CC) and brain stem were associated with poor outcome ($P<0.01$). The highest OR was for TAI lesions in the splenium (OR: 2.6) and brain stem dorsal lesions (OR: 3.1). We only found significant differences in outcome between haemorrhagic and non-haemorrhagic TAI lesions in the subgroup of patients with white matter and basal ganglia/thalamus lesions ($P=0.01$). We obtained a superior discriminatory capacity by adding these MR findings to the previous prognostic model (Harrel's c-statistic 0.72 and ORC 0.7) in a prospective series of 93 patients.
Conclusions. – The prognostic model including MR findings maintained a superior discriminatory capacity than that obtained for the model with the classic prognostic factors alone.

Introduction

Traumatic brain injury (TBI) is a major economic and social problem in all countries [1]. Although TBI is a leading cause of death and disability, none of the clinical trials performed on these patients have shown an overall significant treatment effect. Many authors have recently published recommendations in order to improve the statistical analysis and design of these trials, such as an adequate prognostic model and the use of ordinal rather than dichotomous outcome analysis [2].

Prognostic models are essential to identify patients with a high risk of poor outcome at admission and to help physicians in clinical decision-making. The IMPACT model provides an adequate outcome prediction, adding CT characteristics and laboratory findings to traditional predictors (age, motor score and pupillary reactivity) [3]. There are many studies on the importance of MR in the diagnosis of traumatic axonal injury (TAI) and its relationship to outcome prediction in TBI. However, magnetic resonance (MR) findings have not been included probably due to its lack of availability at hospital admission and the increased time and cost of the imaging studies [4–8]. Furthermore, there has not been sufficient exploration of the relationship between quantitative measures of TAI lesions in different brain locations and outcome.

Besides improving the prognostic model, dichotomous analysis of the ordinal outcome Scale in clinical trials and research studies

Abbreviations: TBI, traumatic brain injury; MR, magnetic resonance; TAI, traumatic axonal injury; CC, corpus callosum; PO, proportional odds; GCS, Glasgow Coma Scale Score; GOS-E, Extended Glasgow Outcome Score; ROI, regions of interest; ANOVA, analysis of variance; OR, odds ratios; ORC, ordinal c-index; TCDB, traumatic coma data bank.

* Corresponding author. Department of Neurosurgery, Vall d'Hebron University Hospital, Paseo Vall d'Hebron 119–129, 08035 Barcelona, Spain.
E-mail address: marta.cicuendez@gmail.com (M. Cicuendez).

https://doi.org/10.1016/j.neurad.2018.08.001
0150-9861/

results in a loss of information and reduces statistical power for the analysis of treatment effects or other covariates of interest [2]. An alternative to this approach is the use of ordinal outcome analysis, such as an ordinal logistic regression or proportional odds (PO) model [2,9]. The aim of this study is to investigate the added prognostic value of MR findings in addition to the traditional prognostic model, using an ordinal analysis.

Methods

Patients and data collection

We retrospectively investigated data from 288 patients with severe head trauma who underwent conventional MR imaging. They were selected from a prospectively registered cohort of 1048 consecutive patients with severe head injury admitted to our hospital from 1 January 2000 to 1 December 2014. Then, a prospective series of 93 patients consecutively admitted TBI patients were collected from December 2014 to November 2016 in order to assess the external validity of the proposed prognostic model (Fig. 3).

All of the patients fulfilled the inclusion criteria, which were:

- patient aged 15 or over;
- Glasgow Coma Scale Score (GCS) of 8 or less after non-surgical resuscitation at admission or GCS deterioration to 8 or less within 48 h after trauma;
- survival beyond 48 h after trauma;
- performance of an MR procedure during the first 60 days after TBI;
- no signs of brain death at admission.

The exclusion criteria included paediatric population, penetrating gunshot wounds, death prior to the performance of a CT scan and intubated patients whose level of awareness improved to the point of responding to orders after sedation withdrawal or after the effect of intoxication waned.

The collected variables included age, sex, mechanism of injury, presence of severe extracranial injury, pupil examination, post-resuscitation level of consciousness expressed by GCS and its motor subscale and presence of hypotension/hypoxia. Findings from the admission CT scan were recorded according to the Traumatic Coma Data Bank [10]. Neurological impairment was assessed at one year after injury by means of the Extended Glasgow Outcome Score (GOS-E) [11].

Imaging protocol

MR imaging was performed in the subacute phase of head injury. A total of 207 studies were performed during the first 30 days and 57 during the first 60 days after TBI (mean 21 ± 12 days). We excluded 24 studies from the analysis because they were performed more than 60 days after brain trauma.

Imaging was performed on a 1.5T scanner (Signa Excite; GE Healthcare, Milwaukee, Wisconsin). The MR imaging protocol consisted of a 3-plane localizer sequence, sagittal T1-weighted with an inversion recovery technique (TR = 2000, minimum TE = 8–48, inversion recovery = 750, NEX = 2, 320×256 matrix), axial T2-weighted fast spin-echo (TR = 4000, TE = 85, echo-train length = 12, NEX_2, 320×256 matrix), axial and coronal FLAIR (TR = 10,000, TE = 145, TI = 2200, NEX = 1, variable bandwidth = 20, 256×224 matrix) and gradient-echo T2 images in the axial and sagittal planes (TR = 550, TE = 18, flip angle = 28, NEX = 2, variable bandwidth = 15, 256×192 matrix). All data were obtained by using 4-mm-thick sections with a 1-mm skip, and a FOV of 24×24 cm.

Image analysis

The first author (MC), in cooperation with an experienced neuroradiologist (AR), characterised traumatic axonal injuries (TAI) based on visual inspection. All were blinded to patient identification, clinical information and time of examination. Both observers checked images for the presence of TAI lesions and determined their location. Inter-observer reliability was checked by means of kappa coefficient. Those cases in which there were discrepancies were resolved by consensus after joint review.

TAI lesions were classified as:

- haemorrhagic or non-haemorrhagic;
- location: subcortical white matter, basal ganglia and thalamus, corpus callosum (genu, splenium or body involvement) and brain stem (anterior or dorsal and uni or bilateral lesions);
- total number of lesions in each location;
- total volume of the lesions.

Based on MR signal characteristics on conventional imaging sequences, TAI lesions were classified as haemorrhagic or non-haemorrhagic. Non-haemorrhagic lesions were defined as areas of increased signal intensity on T2 and FLAIR, and haemorrhagic injuries were described as foci of decreased signal on gradient-echo T2. Periventricular signal hyper-intensities on T2 and FLAIR were considered a normal phenomenon [7,12] and they were excluded from the analysis. TAI lesions were counted separately in the different locations on T2, FLAIR, and T2*GRE sequences. Illustrations of the different TAI injuries are shown in Fig. 1.

The volume of the lesions was calculated using an OsiriX v.5.8.2 DICOM viewer. The axial FLAIR and T2 sequences were loaded in the system and the lesions were segmented manually by drawing contours around them in order to define the different regions of interest (ROI). The system computes the area of the ROI and the total volume of this group of ROIs in cubic centimetres (Fig. 2). The volume of the lesions on gradient-echo T2 sequences was not measured because of the magnetic susceptibility of haemoglobin degradation products [13]. For further information on the measurement of TAI lesions, we refer the reader to our earlier study on the prognosis value of CC lesions [14].

Statistical analysis

A descriptive analysis of the epidemiologic characteristics of patients presenting with TAI at MR imaging was performed. For the purpose of statistical analysis, the outcome was divided into three groups according to GOS-E: good recovery (GOS-E 7, 8), moderate disability (GOS-E 5, 6) and severe disability/persistent vegetative state or death (GOS-E 1, 2, 3, 4).

For the multivariable analysis, we used an ordinal logistic regression or proportional odds model (PO). The PO model is adequate for studying ordinal dependent variables, such as outcome, and it produces a common odds ratio (OR). It has a greater power to detect risk factors than binary logistic regression models, but it is performed under the assumption of proportionality of the odds. This assumption is equivalent to saying that any cut-point on the outcome scale would lead to the same binary logistic regression coefficient [9,15,16]. In order to assess the accuracy of our PO model, the outcome variable was dichotomised in 1 vs. 23 (bad prognosis vs. intermediate and good prognosis) and 12 vs. 3 (bad and intermediate prognosis vs good prognosis), and we applied binary logistic regression to develop models for these dichotomised responses. We observed that the estimated odds ratios remained constant, which assess the adequacy of the proportional odds model [17]. Furthermore, we also inspected the validity of the PO model by performing the Brant test to test the parallel regression

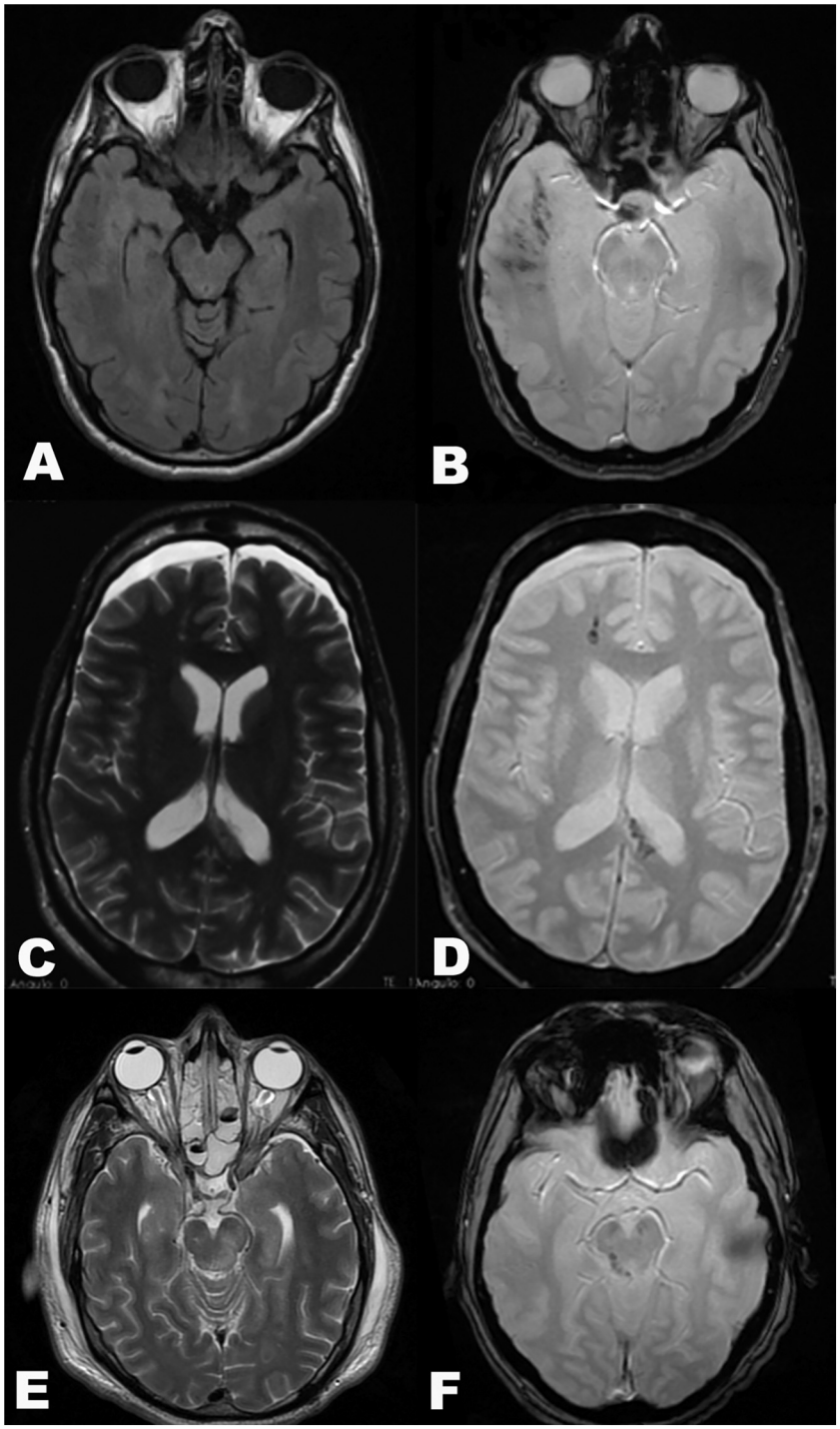

Fig. 1. Illustrations depicting the different types of TAI injury observed with subacute MR imaging in severe traumatic brain injury. Axial FLAIR (A) and T2*GRE (B) images of subcortical white matter haemorrhagic lesions visible on T2*GRE. Axial T2 (C) and T2*GRE (D) demonstrating haemorrhagic CC lesion. Axial T2 (E) image of non-haemorrhagic mesencephalic lesion and axial T2*GRE (F) showing an example of brain stem haemorrhagic lesion.

assumption in the IMPACT model and the rest of the MR variables [16].

An ordinal regression analysis was performed using the MR findings and the variables included in the IMPACT studies: the Core model (age, motor score at admission and pupillary reactivity) and the Extended model (including CT information and second insults) [18]. The association between MR findings and outcome was expressed as odds ratios by adding each MR feature related to prognosis one at a time. Finally, we defined a new prognostic model including the MR features with the highest OR.

Afterwards we calculated the c-statistic in order to determine if our new prognostic model improved outcome prediction. Harrel's c-statistic was used to compare the discriminatory capacity obtained by a model using clinical features and CT information to that of a model adding MR features with more relevance to prognosis. The c-statistic was obtained using two strategies. The first strategy was similar to that proposed by Newson [19] for comparing the predictive power of survival models, whereby Harrel's c is calculated from the linear predictors for each case obtained when computing the model. The second strategy was to compute

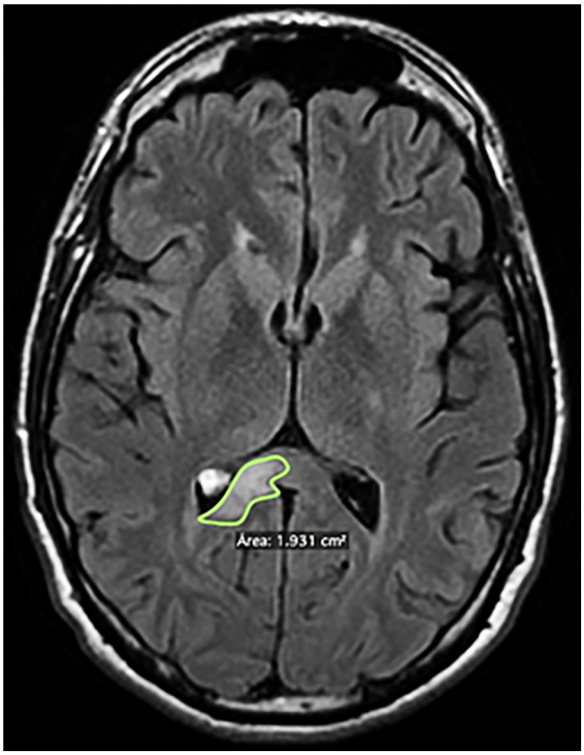

Fig. 2. The figure shows how the different regions of interest (ROI) were drawn manually. The system calculates the area of each ROI and the total volume of the lesion.

the ordinal c-index (ORC) as the average of all pairwise c-indexes among the different outcome categories for each model [20]. In this way, the ORC can be interpreted as the probability of correctly ranking two cases from two randomly selected outcome categories. The prognostic model was then validated in the prospective cohort of TBI patients. Harrel's c-statistic and ordinal c-index were calculated to assess the discriminatory capacity in this new sample.

Statistical analyses were performed using the SPSS program (IBM SPSS Statistics v20.0.0) and STATA (StataCorp, Texas, USA, v12.1). *P*-values < 0.05 were considered statistically significant.

Results

All the descriptive and multivariable analyses were performed in the retrospective series of TBI patients. We included a total of 264 patients with MR studies done in the early subacute phase (less than 60 days after brain trauma). In this group, 78% of these studies were done in the first 4 weeks after trauma (mean 21 ± 12 days). Inter-observer agreement was on average good (average kappa 0.7, $P < 0.01$) for all locations studied (subcortical white matter, corpus callosum and brainstem).

We found that 178 (65%) patients presented with traumatic axonal injury. We saw that 93% (165 patients) showed subcortical white matter lesions, 54% (97 patients) had lesions in the corpus callosum and 40% (70 patients) in the brain stem. In the group of 165 patients with subcortical white matter injuries, 94 patients also had lesions in the basal ganglia and thalamus (53%). In this group of hemispheric TAI lesions, 50 cases were only supratentorial lesions, whereas 50 patients had lesions in the cerebral hemispheric and CC, and 29 in the brain stem and cerebral hemispheric. Only 9 patients had lesions exclusively in the CC, 3 patients had isolated brain stem injury and 2 patients had both lesions in the CC and brain stem without subcortical white matter injury. Finally, a total of 36 cases presented with lesions in the three locations [14] (Fig. 3).

Table 1
Demographic and injury-related characteristics and outcomes of the two series of severe TBI patients included in our study.

Demographic Characteristics	Retrospective series $n = 288$	Prospective series $n = 93$	*P* value
Age	36,1 ± 14 years	40 ± 15,7years	< 0.03
Sex			
Male	229 (79%)	78 (84%)	NS
Female	59 (21%)	15 (16%)	
Mechanism of injury			
Traffic	188 (65%)	70(75%)	
Fall	71 (25%)	23 (25%)	0.004
Impact/Others	29 (10%)	0	
Pupillary Abnormality	45 (16%)	12 (13%)	NS
GCS at admission			
3	47 (16%)	17 (18%)	
4	30 (11%)	7(8%)	
5	32 (11%)	5(6%)	NS
6	36 (12%)	7(8%)	
7	30 (11%)	9 (9%)	
8	18 (6%)	3 (3%)	
> 8	95 (33%)	45 (48%)	
Hypotension/Hypoxia	66 (23%)	25 (26%)	NS
TCDB CT classification			
Type I–II	192 (67%)	59 (63%)	
Type III–IV	17 (6%)	14 (15%)	NS
Type V–VI	79 (27%)	20 (22%)	
Mortality	12 (4%)	4 (4%)	NS
Outcome 1 year			
Good outcome	192 (66%)	67 (71%)	NS
Poor outcome	96 (34%)	27 (29%)	

NS: non statistically significant difference.

The predominant mechanism of injury in our retrospective series of severe TBI and MR was high-energy impact trauma (65%), followed by falls (24%) and direct impact (11%). The patient population was young (mean age 36 years; interquartile range 26–45) and they were predominantly male (79%). An analysis of the different types of lesions visualised by CT at admission according to the Traumatic Coma Data Bank (TCDB) classification was performed. The most frequent lesion in the whole series of TBI patients was diffuse injury (TCDB type II). Demographic and injury-related characteristics are shown in Table 1.

For both the corpus callosum and brain stem, most lesions were found on T2 and FLAIR sequences. In contrast, for the subcortical white matter most TAI lesions were detected on T2*GRE sequence. A total of 77% presented with haemorrhagic lesions in the subcortical white matter, whereas only 35% of CC lesions and 44% of brain stem lesions were haemorrhagic. FLAIR and T2 lesion volumes in the corpus callosum and brain stem contributed to more than 50% of the whole brain lesion volumes. There was no statistically significant relationship between patients' age and volume lesions ($P = 0.7$).

Multivariable analysis

We performed a multivariable analysis adjusted for prognostic factors according to the IMPACT studies in the 264 TBI patients. To simplify the analyses, we chose the number and the volume measurements on T2 sequences. The PO assumption was violated only for brain stem lesions: dorsal and pons lesions (Table 2). The estimated odds ratios remained constant for all MR findings except for these lesions, probably due to the small number of patients included in group 2 [dorsal: 3 and pons: 10 patients, and group 3 (dorsal: 6 and pons: 7 patients), compared to group 1 (17 and 20 patients respectively)]. For the sake of interpretability and clinical usefulness, we chose to accept the violation of the PO assumption in the final PO model. Splenium and brain stem injury were the most important predictors in our multivariable PO model. This was also supported by the fact that when adding up, the whole model sta-

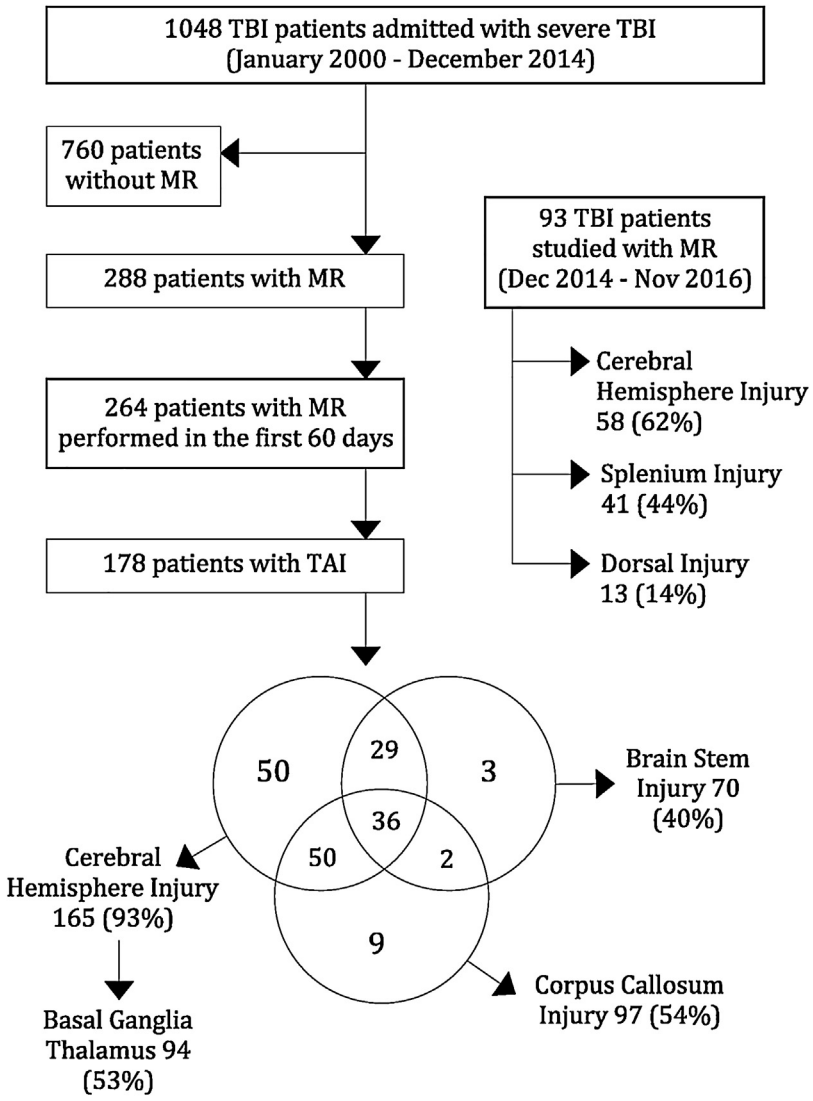

Fig. 3. Severe TBI patients admitted to the department of neurosurgery, hospital 12 de Octubre (Madrid, Spain) during the study period. Flow chart of the inclusion criteria as well as the final number of patients with traumatic axonal injury (TAI).

Table 2
The outcome variable was dichotomize in three groups: 1 vs. 23 and 12 vs. 3. We applied binary logistic regression to develop models for these dichotomized responses and check for systematic trends in the estimated odds ratio.

Categorization	GOS 1 vs. 2&3	GOS 1&2 vs. 3	Proportional OR
White matter			
Haemorrhagic	3.19	2.22	1.9 (1–3.58)
Number lesions	0.91	0.91	0.97 (0.89–1)
Volume lesion	0.34	0.41	0.36 (0.15–0.87)
Basal Ganglia &Thalamus	1.52	1.87	1.75 (1–2.89)
CC	2.24	1.47	1.77 (1.06–2.98)
Splenium	3.03	2.06	2.6 (1.5–4.5)
Number lesions	1	0.69	0.91 (0.49–1.02)
Volume lesion	0.61	0.79	0.66 (1–2.89)
Brain stem	1.83	1.89	1.96 (1.4–3.36)
Dorsal	4.18	1.64	3.1 (1.33–7.22)
Pons	6	3.13	2.69 (1.34–5.39)
Number	0.63	0.5	0.58 (0.41–0.81)
Volume	0.42	0.22	0.33 (0.12–0.91)

tistical tests corroborated the assumption of the PO model (Brand test *P*-value = 0.83).

The number of TAI lesions detected at all brain locations on T2*GRE sequences did not dependently predict outcome ($P > 0.5$). We only found significant differences in outcome between haemorrhagic and non-haemorrhagic TAI lesions in the subcortical white matter and basal ganglia/thalamus ($P < 0.05$, OR: 1.9, 95% CI: 1–3.58, Wald: 3.96).

We observed that the mere presence of TAI lesions at white matter level did not reach statistical significance ($P = 0.14$), but TAI lesions at basal ganglia and thalamus level were associated with poor outcome ($P < 0.001$, OR: 1.75, 95% CI: 1–2.89). The number and the volume of these TAI lesions on T2 sequence were also related to worse outcome (number: $P = 0.02$, OR: 0.94, 95% CI: 0.89–1, Wald: 5.19; volume T2: $P = 0.02$, OR: 0.36, 95% CI: 0.15–0.87, Wald: 5.19).

Corpus callosum lesions were associated with poor outcome ($P = 0.015$, OR 1.77 95% CI: 1.06–2.98, Wald 5.89). The presence of lesions in the splenium was also related to worse outcome, as described in our previous work about CC lesions in TBI ($P = 0.014$, OR: 2.6, 95% CI: 1.5–4.5, Wald: 11.7) [14]. The number of these lesions ($P > 0.05$, OR: 0.91, 95% CI: 0.59–1.42, Wald: 3.36) and their volume ($P = 0.09$, OR: 0.63, 95% CI: 0.44–0.89, Wald: 6.74) reached statistical significance after adjustment for prognostic factors.

At brain stem level, the presence of TAI lesions ($P = 0.015$, OR: 1.96, 95% CI: 1.14–3.36, Wald: 5.94) was associated with worse prognosis but not all patients with these injuries experienced poor outcome (44% patients had bad outcome, 30% presented moder-

Table 3
Multivariate analysis: the model predicts prognosis using PO with the indicated variable as a covariate together with core prognostic factors (age, motor score, and pupil dilation) and extended prognosis factors (CT information and second insults). The GOS E scale was divided in three groups and analyzed as a dependent variable, thus predicting the worse outcome category. Values are given in odds ratios (ORs) and 95% confidence intervals (CIs).

MR findings	OR (95% CI)	Wald statistic	*P* value	Nagelkerke R2
Hemorrhagic Subcortical/GGBBGG	1.9 (1–3.58)	3.96	<0.05	0.19
BB lesion	1.75 (1–2.89)	4.73	<0.01	0.18
Splenium lesion	2.6 (1.5–4.5)	11.7	<0.001	0.19
Volume CC lesion	0.66 (1–2.89)	4	0.04	0.19
Dorsal BS lesion	3.1 (1.33–7.22)	7.29	<0.001	0.18
Volume BS lesion	0.34 (0.12–0.91)	4.53	0.03	0.18
Pons lesion	2.69 (1.34–5.39)	7.49	<0.001	0.22

ate disability and 26% had good outcome). Dorsal lesions were also associated with poor outcome ($P = 0.007$, OR: 3.21, 95% CI: 1.37–7.48, Wald: 7.29), as were pons lesions ($P = 0.006$, OR: 2.69, 95% CI: 1.34–5.39, Wald: 7.49). Bilateral lesions did not reach statistical significance after adjustment for prognostic factors ($P = 0.1$). This result was probably due to the small number of patients in our series with bilateral involvement, only 26 patients presented with bilateral lesions and 23% (6 patients) had good prognosis. We also found that in this location, the number (number $P = 0.02$, OR: 0.58, 95% CI: 0.41–0.81, Wald: 9.96) and the volume ($P = 0.03$, OR: 0.34, 95% CI: 0.12–0.91, Wald: 4.53) of TAI lesions were associated with worse prognosis (Table 3).

We found no association between CT findings and TAI lesions in our series. We only saw that intraventricular haemorrhage in the first CT at admission was related to TAI lesions detected in MR studies ($P < 0.01$). We observed that it was also associated with moderate and severe disability at one year after TBI in our series ($P = 0.02$, OR: 1.84, 95% CI: 1.1–3.08, Wald: 5.41).

Prognostic model

We developed a prognostic model adding the following MR findings to the prognostic factors described in the IMPACT study: haemorrhagic subcortical/basal ganglia TAI lesions, splenium lesions and dorsal brain stem lesions. Each MR variable was an independent prognostic factor after performing the ordinal regression analysis in our series. Harrel's c-statistic for this model with MR findings (0.72, 95% CI: 0.67–0.77) was higher than for the IMPACT model alone (0.68, 95% CI: 0.63–0.73). Also, ORC was higher for the model including MR information (ORC = 0.71, 95% CI: 0.63–0.79) than that of the IMPACT model alone (0.64, 95% CI: 0.53–0.76). This modest improvement is based mainly on a better prognostication of patients in moderate outcome (c-statistic for moderate outcome using only IMPACT 0.53, for data including MR features 0.63).

We applied our suggested prognostic model to a prospective cohort of 93 TBI patients (validation sample). In this subset of patients, a total of 62 patients presented TAI lesions in the MR studies. We found 58 patients (62%) with subcortical white matter and basal ganglia/thalamus lesions, 41 patients (44%) with splenium lesions and 13 patients (14%) with dorsal brain stem lesions (Fig. 3).

Comparisons were made between the retrospective series and the prospective cohort of TBI patients. We saw that the mean age was 5 years younger in the retrospective series (36.1 ± 14 years vs. 40 ± 15.7 years, $P < 0.03$). There were also statistical differences in the mechanism of injury: traffic accidents were predominant in the prospective series ($P < 0.001$). However, despite these findings, there were no statistical differences between groups in mortality and the final outcome. Neither were there statistical differences in sex distribution, initial GCS, pupillary abnormality and second insults (Table 1).

Finally, we found that the model including MR findings maintained a superior discriminatory capacity than that obtained for the IMPACT model in our prospective series (Harrel's c statistic with MR 0.72 and IMPACT model alone 0.67; ORC with MR 0.7 and IMPACT model alone 0.66). These results support our hypothesis that MR findings added prognostic information in TBI patients.

Discussion

Traumatic axonal injury is commonly found in TBI patients and it is associated with their prognosis and quality of life [4,5,7]. Over the last few years, MR has become an essential tool for diagnosing TAI in order to identify patients at high risk of poor outcome. In our study, we observed that this risk was associated to the location and the extent of TAI lesions visible on conventional MR imaging after adjustment for prognostic factors.

For the multivariable analysis, we used an ordinal logistic regression to avoid the loss of information in predicting outcome, especially in those cases of moderate disability. In the IMPACT model, the patients were divided according to GOS in three groups: mortality, unfavourable or good outcome. However, in our series we divided the outcome according to GOS E to emphasise the prognosis of this group of patients with moderate disability.

According to the location of the lesions, we found that TAI lesions in the basal c, corpus callosum and brain stem were independent prognostic factors for poor outcome. The prognostic significance of thalamus and basal ganglia TAI lesions after brain trauma has been studied in previous studies. Thalamic injury is related to patients with disorders of consciousness and cognitive outcome [6,21]. Moen et al. [7,13] described the association between thalamus TAI lesions and poor outcome in 211 patients with severe and moderate brain trauma. In line with these studies, in our series, we observed that the presence of TAI lesions in the thalamus and basal ganglia was associated with worse outcome. We also found that patients with haemorrhagic TAI lesions in the subcortical white matter and basal ganglia/thalamus had worse outcome, but the number of T2*GRE lesions counted did not reach statistical significance. We did not find statistical differences in outcome between haemorrhagic and non-haemorrhagic lesions in the CC or brain stem lesions, as other authors have previously reported [14].

We also observed the importance of TAI lesions at CC and brain stem. The presence of TAI lesions in the corpus callosum and brain stem were associated with poor outcome [7,14]. As our group previously reported, we observed that the splenium involvement, and the number and volume of TAI lesions in the CC negatively correlates with the outcome after brain trauma [7,13,14,22].

Earlier studies showed that the presence of TAI lesions in the brain stem was associated with worse outcome [23–25]. However, not all patients with brain stem injury showed a dismal prognosis. We observed that dorsal lesions and TAI lesions at pons level independently predict outcome after performing ordinal logistic regression. As far as we are aware, this is one of the largest studies to highlight the importance of pons involvement in brain stem injury after TBI. In contrast to previous published studies, [5,6,23] bilateral involvement did not reach statistical significance after multivariable analyses. In our series, only 26 patients presented with bilateral lesions and 6 had good outcome.

Furthermore, this study also highlights not only the importance of the lesions location, but also the prognostic value of the extent of the injuries. The number and the volume of TAI lesions were related to worse prognosis in all locations, especially in the brain stem and corpus callosum. Our findings are consistent with previous results from Moen et al. [7,13], who found that both lesion measurements improved outcome prediction in a series of 64 patients with severe TBI after adjustment for age, GCS Score, and pupil dilation. There are

not many studies that examine the prognostic value of TAI lesion volume measurement in MR. Pierallini et al. [22] observed that the volume of CC lesion correlated significantly with disability and cognition disorders. In our previous work, we concluded that prognosis worsens in direct relationship to the extent of CC injury and the volume of corpus callosum lesion was significantly related to outcome. Chew et al. [24] and Chastain et al. [25] showed that the volume of brain stem injury predicted outcome, but they did not perform multivariable analyses adjusted for prognostic factors. However, the highest OR was for the anatomical TAI location: splenium (OR: 2.6) and brain stem dorsal lesions (OR: 3.1). These results support the Ommaya–Gennarelli model, in which the depth of brain injury correlates with TBI morbidity and mortality [26].

Thanks to the results of our study, we could develop a new prognostic model for TBI patients by adding MR information to the prognostic factors described in the IMPACT model. For this purpose, we chose the MR features with the highest OR: presence of haemorrhagic subcortical/basal ganglia TAI lesions, splenium lesions and/or dorsal brain stem lesions. We applied this model to a prospective cohort of 93 patients and we found an ORC and Harrel's c statistic slighter higher when MR features were added to the model. Therefore, we obtained a superior discriminatory capacity for outcome prediction in severe head trauma, especially in the moderate disability patient group.

There are some limitations to our study. Firstly, the major limitation of our series is that it was performed on a selected group of patients, as our study mainly included patients surviving the injury with a low mortality rate (12%). In addition, the median time between trauma and MR imaging was 21 days, which meant that some patients had relatively lengthy gaps between trauma and MR imaging (maximum of 60 days) and parenchymal changes may occur during this time-period. It has been reported that TAI lesions disappear during the first 3 months, especially non-haemorrhagic lesions [13]. Recently Toht et al. [27] described how haemorrhagic TAI lesions visualised on susceptibility-weighted imaging (SWI) grow in the first week after brain trauma. SWI is more sensitive in detecting micro-haemorrhages compared to T2*GRE, but our study was performed with conventional MR sequences. Nor was the diffusion weighted imaging (DWI) sequence included in our analysis. DWI is very important for demonstrating cytotoxic edema associated with diffuse axonal injury [28]. Unfortunately, this sequence was introduced later in our MR protocol and only half of the patients had DWI performed.

The timing of MR acquisition is relevant in determining the prognostic value of imaging findings. It is important to perform MR studies in the first 4 weeks after brain trauma in order to avoid attenuation of TAI lesions and improve outcome prediction. It would have been better if there had been more similarity in the time from injury to MR study, however that was not possible due to medical and logistical reasons. Lastly, we also consider as a study limitation the fact that imaging techniques are susceptible to evolve during the study period. Although we maintained the same protocol in 1.5T MR scanners, later sequences were more sensitive to TAI injuries than earlier ones. This should be taken into account when adapting our prognostic model to nowadays MR studies. Future studies performed on 3T MR scanners in TBI patients are therefore recommended.

Conclusion

This study confirms the prognostic value of the location and the extent of TAI visible lesions on conventional MR studies in TBI patients. As our results suggest, prognosis worsens in direct relationship to the number and the volume of these lesions. In our multivariable analysis, we found that haemorrhagic subcortical/basal ganglia TAI lesions, splenium lesions and dorsal brain stem lesions were independent prognostic factors for poor outcome. We developed a new prognostic model by adding these MR findings to the classic prognostic factors. With the use of MR information, better predictions regarding final outcome can be made in severe head trauma, especially in the moderate disability patient group.

Funding sources

This research was jointly funded by the ISCIII and FEDER European institutions; with FIS project number PI14/0157. The sponsor had no role in the design or conduct of this research.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Gomez PA, Castano-Leon AM, de-la-Cruz J, Lora D, Lagares A. Trends in epidemiological and clinical characteristics in severe traumatic brain injury: analysis of the past 25 years of a single centre data base. Neurocirugia 2014;25(5):199–210.
[2] Roozenbeek B, Lingsma HF, Perel P, et al. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. Crit Care 2011;15(3):R127.
[3] Panczykowski DM, Puccio AM, Scruggs BJ, et al. Prospective independent validation of IMPACT modeling as a prognostic tool in severe traumatic brain injury. J Neurotrauma 2012;29(1):47–52.
[4] Gentry LR, Godersky JC, Thompson B. MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. AJR Am J Roentgenol 1988;150(3):663–72.
[5] Firsching R, Woischneck D, Klein S, Reissberg S, Dohring W, Peters B. Classification of severe head injury based on magnetic resonance imaging. Acta Neurochir (Wien) 2001;143(3):263–71.
[6] Abu Hamdeh S, Marklund N, Lannsjo M, et al. Extended anatomical grading in diffuse axonal injury using MRI: hemorrhagic lesions in the substantia nigra and mesencephalic tegmentum indicate poor long-term outcome. J Neurotrauma 2017;34(2):341–52.
[7] Moen KG, Brezova V, Skandsen T, Haberg AK, Folvik M, Vik A. Traumatic axonal injury: the prognostic value of lesion load in corpus callosum, brain stem, and thalamus in different magnetic resonance imaging sequences. J Neurotrauma 2014;31(17):1486–96.
[8] Brown M, Baradaran H, Christos PJ, Wright D, Gupta A, Tsiouris AJ. Magnetic resonance spectroscopy abnormalities in traumatic brain injury: a meta-analysis. J Neuroradiol 2018;45(2):123–9.
[9] Risselada R, Lingsma HF, Molyneux AJ, et al. Prediction of two month modified Rankin Scale with an ordinal prediction model in patients with aneurysmal subarachnoid haemorrhage. BMC Med Res Methodol 2010;10:86.
[10] Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma 1992;9(Suppl. 1):S287–92.
[11] Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15(8):573–85.
[12] de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam scan study. J Neurolog Neurosurg Psychiatr 2001;70(1):9–14.
[13] Moen KG, Skandsen T, Folvik M, et al. A longitudinal MRI study of traumatic axonal injury in patients with moderate and severe traumatic brain injury. J Neurolog Neurosurg Psychiatr 2012;83(12):1193–200.
[14] Cicuendez M, Castaño-León A, Ramos A, Hilario A, Gómez PA, Lagares A. Prognostic value of corpus callosum injuries in severe head trauma. Acta Neurochir (Wien) 2016;59(1):25–32.
[15] Peterson B. Re: "Ordinal regression models for epidemiologic data". Am J Epidemiol 1990;131(4):745–8.
[16] Bender R, Grouven U. Ordinal logistic regression in medical research. J R Coll Physicians Lond 1997;31(5):546–51.
[17] Brant R. Assessing proportionality in the proportional odds model for ordinal logistic regression. Biometrics 1990;46(4):1171–8.
[18] Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic

scores based on admission characteristics. PLoS Med 2008;5(8):e165 [discussion e].
[19] Newson R. Comparing the predictive power of survival models using Harrell's c or Somers'D. Stata Journal 2010;10(3):339–58.
[20] Van Calster B, Van Belle V, Vergouwe Y, Steyerberg EW. Discrimination ability of prediction models for ordinal outcomes: relationships between existing measures and a new measure. Biometrics 2012;54(5):674–85.
[21] Laouchedi M, Galanaud D, Delmaire C, et al. Deafferentation in thalamic and pontine areas in severe traumatic brain injury. J Neuroradiol 2015;42(4):202–11.
[22] Pierallini A, Pantano P, Fantozzi LM, et al. Correlation between MRI findings and long-term outcome in patients with severe brain trauma. Neuroradiology 2000;42(12):860–7.
[23] Hilario A, Ramos A, Millan JM, et al. Severe traumatic head injury: prognostic value of brain stem injuries detected at MRI. AJNR Am J Neuroradiol 2012;33(10):1925–31.
[24] Chew BG, Spearman CM, Quigley MR, Wilberger JE. The prognostic significance of traumatic brainstem injury detected on T2-weighted MRI. J Neurosurg 2012;117:722–8.
[25] Chastain CA, Oyoyo U, Zipperman M, Joo E, Ashwal S, Shutter L, et al. Predicting outcomes of traumatic brain injury by imaging modality and injury distribution. J Neurotrauma 2009;26:1183–96.
[26] Ommaya AK, Gennarelli TA. Cerebral concussion and traumatic unconsciousness. Correlation of experimental and clinical observations of blunt head injuries. Brain 1974;97(4):633–54.
[27] Toth AKN, Tamas V, Kornyei B, Nagy M, Horvath A, Rostas T, et al. Microbleeds may expand acutely after traumatic brain injury. Neurosci Lett 2016;23(617):207–12.
[28] Zheng WB, Liu GR, Li LP, Wu RH. Prediction of recovery from a post-traumatic coma state by diffusion-weighted imaging (DWI) in patients with diffuse axonal injury. Neuroradiology 2007;49(3):271–9.