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## **Global mean diffusivity: a radiomarker discriminating good outcome long term after traumatic brain injury**

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## **Global mean diffusivity: a radiomarker discriminating good outcome long term after traumatic brain injury**

### **Abstract**

**Background.** Traumatic brain injury (TBI) is a chronic pathology responsible for cognitive disorders impacting outcome. Global clinical outcome several years after TBI may be associated with anatomical sequelae. Anatomical lesions are not well described because characterizing diffuse axonal injury and brain atrophy require using specific MRI sequences with quantitative measures. The best radiologic parameter to describe the lesions long term after TBI is not known.

**Objective.** We aimed to first, assess the global volumetric and diffusion parameters related to long-term outcome after TBI and second, define the most discriminating parameter.

**Methods.** In this observational study, we included 96 patients with severe TBI and 22 healthy volunteers. The mean delay after TBI was 63.2 months [range 31-119]. The Glasgow Outcome Scale Extended (GOS-E) was used to assess the global long-term clinical outcome. All patients underwent multimodal MRI with measures of brain volume, ventricle volume, global fractional anisotropy (FA) and global mean diffusivity (MD).

**Results.** All 96 participants had significant impairment in global FA, global MD, brain volume and ventricle volume as compared with the 22 controls ( $p < 0.01$ ). Only global MD significantly differed between the “good recovery” group (GOS-E score 7-8) and the other two groups: GOS-E scores 3-4 and 5-6. Brain volume significantly differed between the GOS-E 7-8 and 3-4 groups. Global MD was the most discriminating radiological parameter for the “good recovery” group versus other patients, long term after TBI. FA appeared less relevant at this time. Global atrophy was higher in patients than controls but lacked reliability to discriminate groups of patients.

**Conclusion.** Global mean diffusivity seems a more promising radiomarker than global FA for discriminating good outcome long term after TBI. Further work is needed to understand the evolution of these long-term radiological parameters after TBI.

**Keywords:** traumatic brain injury, long-term. diffusion tensor imaging, brain atrophy, GOS-E, mean diffusivity.

## **Introduction**

Traumatic brain injury (TBI) is a leading cause of persistent disability, including cognitive or neurobehavioral disorders (1). The impact on daily life activity and therefore on the global outcome depends on many factors (2) including environmental and socio-cultural factors (3,4). Nevertheless, anatomical lesions such as diffuse axonal injury have been associated with global outcome in the first year (5,6) and seem to contribute importantly to long-term disability. However, no relevant radiological parameter associated with long-term global outcome exists.

Diffuse axonal injuries (DAIs) (7–11) and brain atrophy (12–16) are the most common post-TBI anatomical lesions. Standard MRI fails to accurately describe DAI (7,17,18) because this technique does not allow for visualizing and measuring them. Recently, quantitative MRI tools, such as diffusion tensor imaging (DTI) (19–21) and 3DT1 volumetric MR sequences (22,23), have offered new opportunities to assess and quantify post-TBI anatomical lesions (7,12). These tools provide 2 different ways of analyzing brain sequelae: 1) evaluation of microstructural alterations by DTI, which evaluates DAI via global fractional anisotropy (FA) and global mean diffusivity (MD), and 2) evaluation of brain atrophy by 3DT1 sequences, which assesses neuro-degeneration based on the quantification of the global brain volume and

the global volume of the ventricles. The question remains as to their association with clinical outcome more than 3 years after head injury.

We hypothesized that long-term clinical outcome after TBI is associated with global quantitative MRI endpoints. In this prospective observational study, our objectives were to associate global volumetric and global diffusion parameters (brain volume, ventricular volume, global FA and global MD) with long-term outcome as assessed by the Glasgow Outcome Scale-Extended (GOS-E) and to compare these quantitative endpoints to determine the most discriminating parameter.

## **Patients and methods**

### *Cohort and design study*

This monocentric prospective observational study examined the long-term outcome of a cohort of severe TBI patients assessed more than 2.5 years after head injury. The inclusion period extended from November 2012 to December 2016. We included alive patients who were hospitalized for at least 48 hr in the Surgical Neuro-Intensive Care Unit (NICU) of our institution, which defined them as having severe TBI according to the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER TBI) classification (<https://www.center-tbi.eu/project/overview>), and who were able to come to the hospital for a 1-day assessment. Long-term follow-up with clinical and imaging evaluation was proposed as routine for all TBI patients and was maintained after the study. For this prospective study, we excluded patients unable to come in our institution on their own, to participate in the evaluation or to undergo MRI without any medication; with a history of previous neurological disease, with psychotic disease, or drug abuse interfering with neuropsychological assessment; and unable to understand or speak French or undergo medical evaluation because of blindness or deafness.

We included 22 healthy volunteers without any history of TBI or other neurologic disease to calibrate the measurements on the machine for the protocol used in this study. Volunteers were matched to patients by age but not sex or educational level.

This descriptive study is part of a large data collection project on the long-term follow-up of patients with severe TBI. Patient management was not modified. In accordance to French law, this non-interventional study was approved by ethical research committee and covered by the national committee for individual data protection CNIL organization (no.: 1934708v0). Written information was given and all patients gave their oral consent for participating in this study and for collecting and processing data.

#### *Initial characterization of the TBI cohort*

Demographic data such as sex, age at the time of TBI, cause of injury and time since TBI were recorded. Initial severity criteria were collected from medical records and included the initial Glasgow Coma Score (GCS) and the duration of coma in days. Lesions visible on the initial CT scan were recorded from the radiological record according to the Marshall score. The duration of stay in the NICU and intracranial hypertension were recorded, and the initial prognostic score developed by the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) was calculated for each patient, measuring the risk of unfavorable outcome at 6 months (24). Post-traumatic amnesia (PTA) was defined as the time from TBI to the recovery of memory capacity according to a scale of 6 periods ranging from < 24 hr to > 2 months (25–27).

#### *Quantitative MRI assessment*

MRI acquisition was performed for all patients with the 3-Tesla System (GE or Siemens) available for routine care on medical prescription in our University Hospital Center. The MRI acquisition protocol included 3DT1 sequences [IR-FSPGR (GE) or MPRAGE (Siemens)]

sequences, voxel size 1.2 mm, isotropic] and DTI (50 directions, strict axial acquisition, B=1000 s/mm<sup>2</sup>, TR=14000 ms, TE=85 ms, 2.5 mm thickness, fat-sat activated, matrix 128x128, field-of-view 28 cm). As in Velly et al. (28), calibration and standardization of MRI measures involved using a group of 22 healthy volunteers.

This MRI acquisition protocol was performed by independent operators, and MRI analyses were performed with blinding to clinical results.

Four quantitative endpoints (2 volumetric endpoints and 2 structural endpoints) were recorded for this study.

Volumetric segmentation was achieved from the T1-weighted volume by using the Freesurfer 5.3 pipeline (<http://surfer.nmr.mgh.harvard.edu/>) (29–31). To take into account brain size inter-subject variability, all volumes were normalized by dividing them by the total intracranial volume. Only whole-brain and ventricular volumes were considered for further analysis.

Diffusion-weighted data were processed by using the FDT pipeline implemented in FSL 5.0 (<http://www.fmrib.ox.ac.uk/fsl>) (32) to fit a diffusion tensor model to each voxel and compute FA and MD maps. These maps were then non-linearly co-registered to the FSL FA template in the stereotaxic space of the Montreal Neurological Institute (MNI space). The mean FA (and MD) values were calculated across all voxels within the CATANI atlas (33) to produce global FA (and MD) metrics quantifying global white-matter alterations.

Raw global FA, global MD, brain volume and ventricular volume measures were further normalized by dividing each individual data by the mean value of controls, thus assigning the value 1 as a reference for the mean value of the control group. Radiological data are presented as mean (SD) [range].

### *GOS-E assessment*

Clinical evaluations were conducted in the Physical Medicine and Rehabilitation (PMR) Department by a medical doctor used to following TBI patients, with blinding to MRI assessments. Long-term outcome was assessed by the GOS-E (34) validated for our local language (35), which is the gold standard for determining the clinical outcome of patients with TBI. If necessary, relatives were consulted to clarify the global disability. During a structured interview, all patients were classified into 6 levels ranging from “severe disability: lower level” (GOS-E score 3) to “good recovery: upper level” (GOS-E score 8), considered to be without any sequelae. In this post-TBI survivor cohort, no patient had GOS-E 1-2 (deceased and vegetative state). GOS-E scores were then merged in 3 groups for statistical analysis: GOS-E 3-4 for “severe disability”, GOS-E 5-6 for “moderate disability” and GOS-E 7-8 for “good recovery”, given the small number of patients in each GOS-E category and according to clinical relevance, in particular similarities in daily life activities. Indeed, patients in the GOS-E 3-4 group need help in daily living activities. Patients in the GOS-E 5-6 group can live alone but cannot work in a standard professional environment. By contrast, patients in the GOS-E 7-8 group are able to return to work but may present some cognitive complaints or behavioral disorders.

### *Statistical analysis*

All data are presented as mean (SD) [range] when available, mean (SD) for continuous data or number (%) for categorical data. All statistical analyses were performed with Stata/IC v11.2 (Stata Corp, College Station, TX, USA). The radiological values for patients, especially volumetric data, were non-normal data according to the Kolmogorov-Smirnov test. Therefore, we used the Wilcoxon-Mann-Whitney test to compare the raw values of radiological parameters (global FA, global MD, brain volume and ventricular volume) between patients and controls. Differences were considered statistically significant at  $p < 0.05$ .



To identify the radiological parameter that best discriminated the 3 GOS-E groups (GOS-E 3-4 for severe disability, GOS-E 5-6 for moderate disability and GOS-E 7-8 for good recovery), we tested whether each radiological parameter that significantly differed between the 3 groups by Kruskal-Wallis test. Each pair of categories was further compared by Dunn's method for multiple tests. Differences were considered statistically significant at  $p < 0.015$  ( $p < 0.05$  Bonferroni-corrected for multiple tests).

We tried to highlight the radiological parameter that best distinguished the good recovery group (GOS-E 7-8) from the others (GOS-E 3-6). After a logistic regression for each parameter, we compared the area under the receiver operating characteristic (ROC) curve (AUC) for each radiological parameter by using the method proposed by DeLong et al. (roccomp function in Stata)(36). Results are presented as a ROC curves for global FA, global MD, brain volume and ventricular volume.

We report this study according to the STROBE guidelines for observational study, with the checklist added as supplementary material (suppl 1). We also paid attention to the COBIDAS recommendations when reviewing the paper.

## **Results**

We included 101 patients with severe TBI from November 2012 to December 2016, at least 2.5 years after TBI. Five patients were excluded after MRI data quality check owing to large movements (>6 mm) or diffusion signal losses. Thus, 96 patients participated in this study (82 men). The mean (SD) age at injury was 33.5 (5.4) years [range 15-69] and at evaluation was 38.6 (15.9) years [range 19-73]. The mean delay between injury and assessment was 63.2 (22.0) months [31-119]. The mean (SD) age of the control group was 36.7 (14.4) years [range 37-80] and did not significantly differ from the age of patients (Wilcoxon-Mann-Whitney test).

Demographic and clinical characteristics of patients are presented in the Table. Six patients were classified as GOS-E 3, 7 as GOS-E 4, 23 as GOS-E 5, 28 as GOS-E 6, 22 as GOS-E 7 and 10 as GOS-E 8 (suppl 2). The initial severity criteria are described for each GOS-E category in supplementary data (suppl 3).

For all 4 radiological endpoints, the raw values significantly differed between patient and control groups. Patients had significantly lower global FA ( $p < 0.01$ ), significantly higher global MD ( $p < 0.001$ ), significantly lower brain volume ( $p < 0.001$ ) and significantly higher ventricular volume ( $p < 0.001$ ) than controls (Fig. 1; suppl 4 for numerical data).

As detailed in Methods, patients were classified into 3 groups: GOS-E 3-4, GOS-E 5-6, and GOS-E 7-8. The GOS-E 7-8 group had a significantly lower MD than the other 2 groups ( $p < 0.015$ ) (Fig. 2). This group also had a higher brain volume than the GOS-E 3-4 group ( $p < 0.015$ ). Global FA and ventricular volume did not significantly differ between the 3 groups.

Then we focused on the differences between the “good recovery” group (i.e., the GOS-E 7-8 group) and the other groups. Using simple logistic regression, we tested which parameter among global FA, global MD, brain volume and ventricular volume could discriminate the groups. Global MD appeared to be the most discriminant of the 4 endpoints at 5 years after a severe TBI in comparing the “good recovery” group with other groups (Fig. 3b). The AUC comparison confirmed that global MD was significantly more discriminating than global FA in isolating the “good recovery” group from the other groups (AUC 0.68 [95% CI 0.57-0.80] for global MD; 0.56 [0.44-0.68] for global FA,  $p = 0.005$ ) (Fig. 3a).

## **Discussion**

At 5 years after a severe TBI, all radiological parameters significantly differed between patients and controls. Global MD was the only parameter able to discriminate between the good recovery group characterized by a GOS-E score 7 or 8 and the other patients with lower

GOS-E scores. Although FA is generally used to compare outcomes in the first few years after TBI (8), this parameter seems less relevant in the long term after TBI. Accordingly, long-term studies of this parameter are rare. Global atrophy, as measured by the brain volume, was more severe in patients than controls but lacked reliability in discriminating between patients with “good recovery” (GOS-E 7-8) and “moderate disability” (GOS-E 5-6).

Because TBI is considered a chronic disease affecting all regions of the brain (37–39), we chose to study global radiological parameters that explore the entire brain, to assess their ability to describe global levels of disability. Many studies have correlated DTI abnormalities in the corpus callosum with outcome, and others have focused on the association between specific white-matter pathways and some cognitive impairments (40). However, the results are not always consistent across studies and it seems impossible to establish a valid meta-analysis (39,41).

Furthermore, we lack consensus on the most relevant measures to reflect diffuse axonal injury (DAI) at  $\geq 2$  years after TBI (7,12). FA appears to return to normal after 2 years, which suggests partial and localized recovery (42), whereas MD may be more sensitive in describing the clinical status of patients and appears to be associated with long-term functional network activity (43). In the present study, global FA was not a good indicator of long-term global functional outcome after TBI because the confidence interval of the ROC curve of the model included the value 0.5. Nevertheless, global FA is still impaired in “good recovery” patients, long term after TBI. Global MD tends to return to normal values in patients with good recovery but remains altered in patients with more severe condition. This parameter appears to be the most related to long-term clinical status. These results suggest that quantitative DTI approaches to assess TBI in the long term should involve the combination of different global measures, at least global FA and global MD.

Unfortunately, few post-mortem studies have compared DTI MRI findings with histological lesions after TBI (44). In a mouse model of closed head injury, DTI metrics agreed well with

histology (45). In humans, lower FA in white matter was associated with increased axon disruption, whereas other diffusion MRI parameters such as apparent diffusion coefficient, radial diffusivity or axial diffusivity were not associated with white-matter histological abnormalities (46). The relation between DTI measurements and long-term anatomical lesions needs to be further explored.

Regardless, volumetric measures are used to characterize brain atrophy after TBI. Atrophy of different brain structures has been associated with cognitive impairment, even for mild TBI (13,14,39). However, the degree of atrophy is not associated with level of disability, several years after TBI. Here we show that brain volume significantly differed between patients with good recovery and those with severe disability. Regardless, we also show that brain atrophy was significant in the “good recovery” group as compared with controls. Similarly, ventricular volume significantly differed between the “good recovery” group and controls. Unfortunately, we were unable to show significant differences in volumetry among the 3 GOS-E groups.

The analysis of long-term anatomical lesions after severe TBI should include several radiological parameters because the “good recovery” group considered as a whole showed global anatomical impairments (white-matter bundle alteration or global brain atrophy). In this group, volumetric parameters seemed sensitive to detect anatomical abnormality, although they did not allow us to detect the good recovery group from the others, in contrast to global MD.

As discussed above, TBI disease is the long-term consequence of initial trauma with anatomical lesions evolving on their own and the contribution of additional parameters. Here we tried to relate the global outcome of patients with the degree of anatomical lesions, knowing that the environmental condition or ways of compensating for the disability would smooth the impact of anatomical sequelae when assessing the global outcome by the GOS-E.

For this reason at least, the generalization of the results of this study requires exploring further cohorts with severe TBI.

The “good recovery” group presented a higher initial GCS score than the other groups but with a median value of 8.5 [range 3-15], and the mean coma duration for these patients was 13 days. The initial Marshall score did not differ between the 3 groups. Although this group had fewer complaints, they still showed anatomical impairments 5 years after TBI.

Our study has several limitations. First, it was an observational study of patients with severe TBI followed in a PMR unit with routine care. Unfortunately, one of the difficulties after TBI is to limit the number of patients lost to follow-up (48), thereby implying selection bias. We cannot be sure that our population is accurately representative of all severe cases of TBI admitted in an NICU. Second, if all patients were in chronic phase after TBI, we had a relatively heterogeneous population in that some were assessed 3 years after TBI and others more than 9 years after. We are not sure that the radiological parameters of the white-matter lesions evolve in the same way throughout this period. Finally, the control group was matched for age but not sex and education. We do not know how this might affect white-matter measures.

## **Conclusion**

Five years after severe TBI, all radiological parameters differed between patients and controls. Global MD was the only parameter able to discriminate the good recovery group from the other patients. Global FA was not as informative as what could be reported in the early years after TBI. The total brain volume showed cerebral atrophy in patients but did not allow for discriminating them according to the severity of their clinical impairment. A better understanding of the evolution of diffusion and volumetric MRI parameters long term after TBI is needed to relate anatomical sequelae to clinical outcome. Individual clinical status depends on many factors and for now, cannot be explained by only one radiological

parameter, even a global one. The analysis of anatomical lesions at the global level should probably include a combination of several radiological parameters.

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### Legends

Figure 1. Comparison of mean raw data between individuals with traumatic brain injury (TBI) and controls. FA, fractional anisotropy; MD, mean diffusivity. \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  by Wilcoxon-Mann-Whitney test

Figure 2. Comparison of Glasgow Outcome Scale Extended (GOS-E) groups for each normalized radiological value. \*  $p < 0.015$  corrected by Dunn's test for multiple comparison for non-normal data (following Kruskal-Wallis analysis). MD, mean diffusivity; FA, fractional anisotropy. Mean value for each group is represented with confidence interval. Dashed line represents mean value for controls.

Figure 3. Receiver operating characteristic curve comparing the ability of the 4 global radiological parameters to discriminate the GOS-E 7-8 group from the other groups. a) Comparing global MD and global FA. b) ROC curves for the 4 global radiologic parameters. AUC, area under the curve; MD, mean diffusivity; FA, fractional anisotropy

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Fig 1.

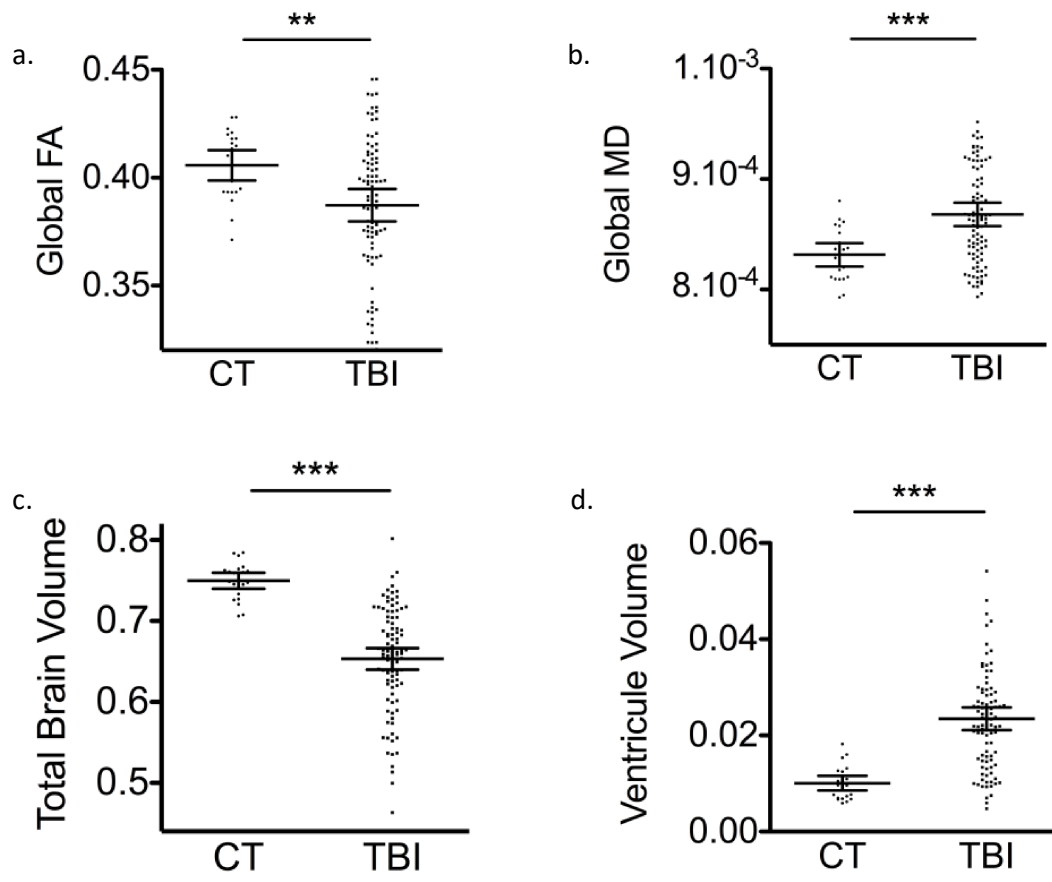


Fig 2.

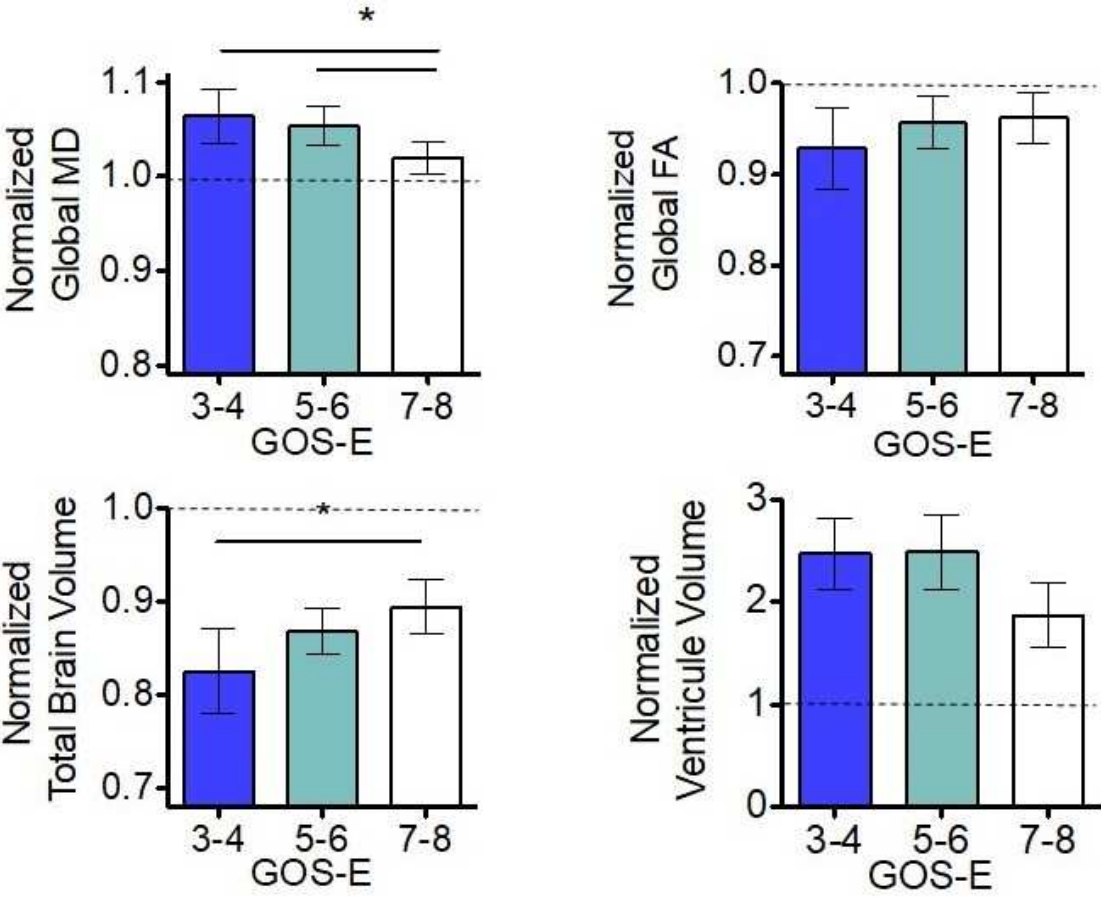
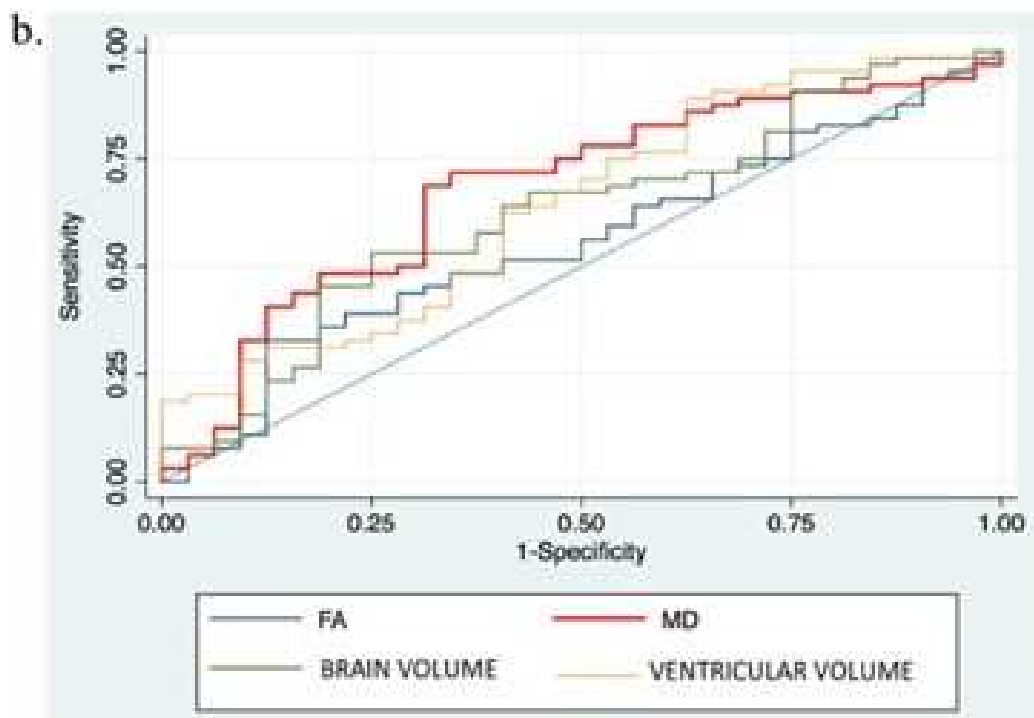
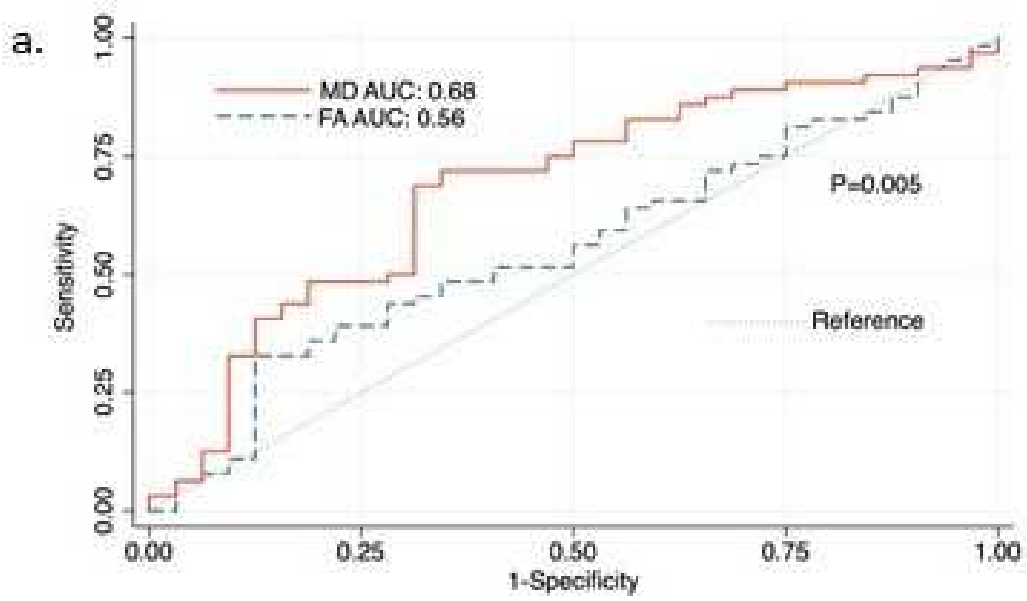


Fig 3.



**Table I.** Demographic and clinical characteristics of the population (n=96).

<b>Demographics</b>	
Age at TBI, mean (SD) [range]	33.5 (5.4) [15-69]
Sex: male/female, n (%)	82/14 (85/15)
<b>Cause of injury, n (%)</b>	
Road accidents	59 (61)
Assaults	13 (14)
Falls	16 (17)
Throwing through window	2 (2)
Other	6 (6)
Delay post-injury (months), mean (SD) [range]	63.2 (22) [31-119]
<b>Initial criteria of TBI severity</b>	
<b>Initial GCS (n=95), n (%)</b>	
≤ 8	70 (74)
9-12	12 (13)
13-15	13 (13)
Coma duration (days) (n=89), mean (SD) [range]	15 (10) [0-41]
<b>Initial CT-scan lesions (n=94), n (%)</b>	
<b>Marshall score</b>	
Grade I	3 (31)
Grade II	54 (57)
Grade III	3 (31)
Grade IV	1 (1)
Grade V	18 (19)
Grade VI	15 (16)
<b>ICU data</b>	
ICU stay (days) (n=91), mean (SD) [range]	35 (18) [3-81]
Intracranial hypertension (n=91)	55 (60)
Initial prognostic score (IMPACT%) (n=88)	33.6 (18.7) [3-82]
<b>PTA duration (n=86), n (%)</b>	
< 24 hr	2 (2)
1-7 days	11 (13)
7-29 days	21 (25)
30-60 days	29 (34)
>60 days	23 (27)
<b>Long-term outcome</b>	
GOS-E score (n=96), mean (SD) [range]	5.9 (1.3) [3-8]
GOS-E 3-4, n (%)	13 (14)
GOS-E 5-6, n (%)	51 (53)
GOS-E 7-8, n (%)	32 (33)

TBI, traumatic brain injury; GCS, Glasgow Outcome Scale; PTA, post-traumatic amnesia; ICU, intensive care unit; GOS-E, Glasgow Outcome Scale-Extended.