Research Article

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Clinical & Radiological Prognostication of Diffuse Axonal Injury

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Abstract

Introduction: Traumatic Brain Injuries (TBI) are a leading cause of morbidity and mortality. Considering the vast number of individuals in the economically productive age group who are afflicted by this entity, it is important to realise the epidemiology, risk factors and other essential data to effectively prognosticate the outcome in these patients so that the limited resources are put to optimal use. We have endeavoured to study the efficacy of the admission neurological status (Glasgow Coma Score - GCS) and the radiological findings (Marshall, Rotterdam and MRI scoring systems) in prognostication of Diffuse Axonal Injury (DAI) using the Glasgow Outcome Score (GOS) to quantify the clinical outcome.

Material & Methods: This is a prospective observational study of 158 consecutive Diffuse Axonal Injury (DAI) patients conducted at Madras Medical College. GCS at admission was taken as the clinical data. Marshall's, Rotterdam and MRI scores were taken as radiological data. The patients' GOS at 1 month was taken as clinical outcome. Statistical analyses were then made to correlate the clinical and radiological data with the one-month outcome of the patients. Statistical analysis was done using the SPSS software – version 16, using statistical tests like Pearson's coefficient and ANOVA. A p-value of less than 0.05 was considered statistically significant.

Results: The admission GCS and MRI grade of DAI showed a statistically significant correlation with the clinical outcome, but the Marshall and Rotterdam scores did not.

Conclusion: Proper neurological evaluation of the patient with GCS score on admission and MRI brain when feasible, with both having a statistically significant correlation with clinical outcome, provide reliable prediction models for prognosticating outcome in DAI patients.

Keywords: Traumatic Brain Injury, Diffuse Axonal Injury, Glasgow Coma Score, Marshall's score, Rotterdam score, MRI grading of DAI, Glasgow Outcome Score.

Introduction

Traumatic Brain Injuries (TBI) are a leading cause of morbidity and mortality. In a country like India, with its rapid urbanization and industrialization and with a huge growing population, TBI has emerged as one of the major causes of preventable morbidity and disability1,2 and the burden is only going to become higher considering the increasing vehicular density, unregulated transportation, poor road infrastructure, inadequate traffic management and laxity in the implementation of traffic rules and penalties by the authorities and apathy on the part of the common man. Also, considering the vast number of individuals in the economically productive age group who are afflicted by this entity, it is important to realise the epidemiology, risk factors and other essential data to effectively prognosticate the outcome in these patients so that the limited resources are put to optimal use.

Diffuse Axonal Injuries (DAI) are the most common form of TBI and the least understood. They occur either independently or superimposed on other forms of traumatic brain injuries like SDH, EDH or contusions.

There are very few studies concerning diffuse axonal injuries and their prognostication based on clinical and radiological criteria from this part of the world. This lacuna needs to be rectified. Various factors are associated with the prognosis in DAI. Of significance are the initial neurological status (Glasgow Coma Score - GCS) of the patient on admission and the findings in the initial radiological investigation. In our study, we have tried to analyse the efficacy of GCS, CT brain and MRI brain findings in prognostication of the outcome in DAI.

REVIEW OF THE LITERATURE

The main determinant of the outcome of diffuse axonal injuries is the amount and distribution of the axonal damage and the associated 'diffuse vascular injury'3.The differential movement of the brain matter in relation to space not only causes shearing of the axons, but also leads to the tearing of many small blood

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vessels resulting in multiple petechial haemorrhages. A Brazilian prospective cohort study in 78 diffuse axonal injury patients showed 44.9% of the patients to have mild grade and 35.8% to have severe grade injury4. Majority of the patients with mild to moderate grades of injuries return to living an independent life, albeit with some minor cognitive impairments like altered sleep patterns, mild cognitive changes, mood swings etc. In contrast, most of the severe grade injury patients do not reach the stage of independent living and they are disabled needing the help of other persons for their activities of daily living. Prolonged hospital stay or ICU stay can have adverse effects on outcome of these patients(4). Hence, it is important not only to treat the severe diffuse axonal injury patients but also rehabilitate them so that the length of hospital or ICU stay is minimized.

As with any traumatic brain injury, the first investigation is usually the CT scan. But in DAI there is a relative paucity of findings in CT scan. Severe DAI patients may show findings in CT scan compatible with the pathology, but moderate and mild diffuse axonal injury patients may not have many findings to aid in their diagnosis and only by correlating with the clinical features, the patient can be diagnosed as having DAI.

The National Institute of Health (NIH)5 found out that patients with CT scans showing features of herniation (particularly effacement of cisterns and midline shift) had higher mortality rates. Conversely, when there were no features like effacement of cisterns, mass effect and midline shift, the risk for mortality was lower. Mass lesions with normal cisterns had a better prognosis compared to mass lesions with absent or compressed cisterns and extracerebral mass lesions were worse compared to intracerebral mass lesions. The degree of midline shift was also an independent predictor for worse outcome. They also concluded that subarachnoid blood was an independent predictor for increased risk of mortality.

Marshall et al elaborated the 'MARSHALL CT SCORING SYSTEM' (Table 1) based on the initial CT scan findings.

It must be emphasised that Marshall scoring system does not substitute other established scoring system like Glasgow Coma Score, but is merely complementary to other scoring systems, and can be specifically used to identify patients who are at risk for deterioration in traumatic brain injuries. A striking correlation was noticed between the initial CT scan findings and the clinical outcome in traumatic brain injury patients, a fact that has also been confirmed by many other studies.[6]

This classification helps to find patients with moderate grade head injuries who are at risk for developing raised intracranial pressure and thereby, enabling early therapeutic intervention, and resulting in improved outcome.Though Marshall score proved a reliable prognosticating model, the non-inclusion of traumatic SAH, IVH and brainstem lesions which have been found to be significant predictors of adverse outcomes in DAI.[7,8,9] was a main drawback (Figure 1)

Table 1: Marshall ct scoring system

	DEFINITION
DIFFUSE INJURY I (No visible pathology)	No visible intracranial pathology seen on CT scan
DIFFUSE INJURY II	Cisterns are present with midline shift 0-5mm and/or: Lesion densities present No high or mixed density lesion > 25cc May include bone fragments and foreign bodies
DIFFUSE INJURY III (swelling)	Cisterns compressed or absent with midline shift 0-5mm, no mixed or high-density lesion > 25cc
DIFFUSE INJURY IV (Shift)	Midline shift > 5mm, no mixed or high-density lesion > 25cc
EVACUATED MASS LESION	Any lesion surgically evacuated
NONEVACUATED MASS LESION	Mixed or high-density lesion > 25cc, not surgically evacuated

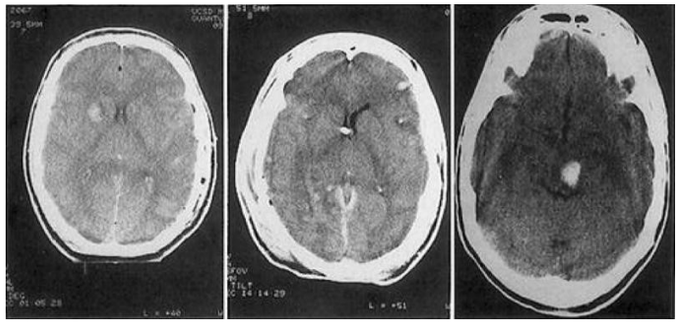

Figure 1: CT Brain images showing various Marshall's Grade II injuries

Maas et al enumerated the 'ROTTERDAM CT SCORING SYSTEM' 10 (Table 2). Significant predictors of mortality named in this study were:

i. Midline shift
ii. Basal cisterns
iii. Traumatic Subarachnoid haemorrhage
iv. Intraventricular haemorrhage

The prognostic value of Marshall system was confirmed in their study. They showed that the addition of traumatic subarachnoid haemorrhage and intraventricular haemorrhage increased the prognostic value. The presence of epidural hematoma was considered favourable, when compared to other types of intradural lesions.

There are certain limitations in Rotterdam scoring. First, their study included only moderate and severe head injuries but not mild head injuries. Second, the outcome parameter considered was mortality, which is an arbitrary endpoint, rather than the standard Glasgow Outcome Score (GOS) dichotomised into a favourable and an unfavourable outcome. Third, the CT scan findings that they considered were within 4 hours of injury, a time when many injuries might be evolving. Many studies have showed that the CT taken with "maximal findings" during the

clinical course has a greater prognostic predictive value than one taken at 4 hours.

Despite its limitations, the Rotterdam CT score is one of the most favoured prognostic scoring -systems because of its ease and simplicity of use and low intra- and inter-observer variability and a good predicting value.[11,12]

Table 2: Rotterdam scoring system

PARAMETER		SCORE
BASAL CISTERNS	**Normal**	**0**
	Compressed	**1**
	Absent	**2**
MIDLINE SHIFT	No shift or shift < 5mm	**0**
	Shift > 5 mm	**1**
EPIDURAL MASS LESION	**Present**	**0**
	Absent	**1**
INTRAVENTRICULAR BLOOD or tSAH	Absent	**0**
	Present	**1**
SUM SCORE		**+1**

Various other scores have also been evaluated like the 'HELSINKI SCORE' model and the 'STOCKHOLM SCORE' model. These newer prediction models involve more parameters that are known to independently influence outcome like pupil reactivity etc. The results of these studies need more validation by further research.[13]

With its widespread availability, MRI is being increasingly used to detect lesions of DAI. Adams et al proposed three grades of diffuse axonal injuries.[14,15] We have extrapolated Adam's microscopic grading to MRI grading of DAI, wherein Grade I has lesions in hemispheric white matter, Grade II has lesions in the midline structures like corpus callosum and Grade III has lesions in the brainstem and cerebellum (Figure 2). Chelly et reported that increasing grades of lesions in MRI studies resulted in worse outcomes and six or more locations of lesions also resulted in poor outcomes in these patients.[16]

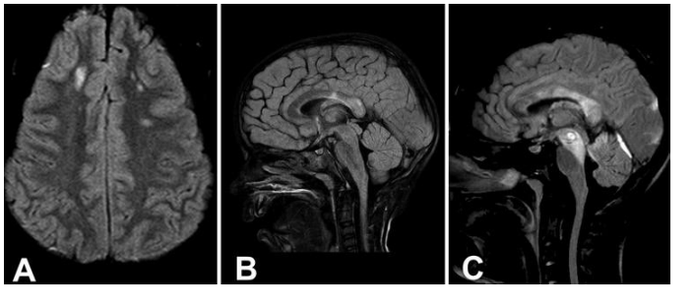

Figure 2: FLAIR MR images. A: Axial image demonstrating signal intensity changes in the lobar white matter (Grade 1). B: Sagittal image demonstrating signal intensity changes in the splenium of the corpus callosum (Grade 2). C: Sagittal image demonstrating signal intensity changes in the rostral brainstem (Grade 3).

Among the various MRI sequences, Gradient Echo images (Figure 3 B) are the most sensitive to microbleeds and haemorrhages.[17]

They also have a positive correlation to the GCS. For lesions that are non-haemorrhagic, T2-weighted images, particularly the FLAIR sequence, provides good visualisation, more so in patients with normal CT brain and clinically suspicious DAI (Figure 3 A). FLAIR also helps to identify other associated small contusions, subarachnoid haemorrhage and subdural hematomas.

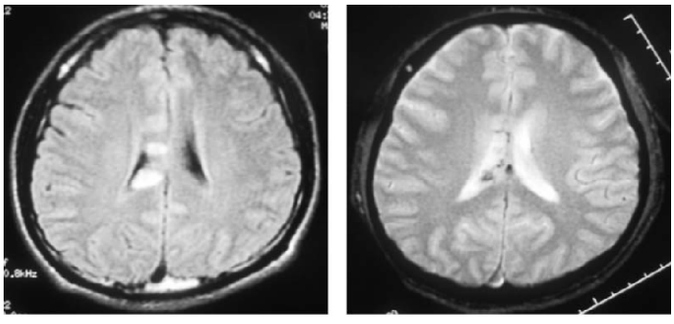

Figure 3: 35-year-old man who was a passenger in a road traffic accident. MRI was performed 5 days after the accident. A: FLAIR image showing Hyperintensities and B: T2-GRE showing hypointensities in the corpus callosum

Newer MRI techniques result in better visualisation of the structural changes that take place following DAI and dynamically check the metabolic changes that take place following head injury. Diffusion Weighted Imaging (DWI) sequences are better than FLAIR sequences in identifying diffuse injury lesions and had better prognosticating values with ADC values positively correlating with the duration of coma in diffuse injury patients.[18,19] To date, Diffusion Tensor Imaging (DTI) has emerged as the most sensitive MRI technique for the evaluation of DAI, and it also has a high negative predictive value. Fractional Anisotropy (FA) values are calculated and they have a positive correlation to the clinicaloutcome.[20,21]

A modification of GRE is Susceptibility weighted Imaging (SWI). It has higher specificity and sensitivity in identifying microbleeds and haemorrhages. MR Spectroscopy (MRS) identifies metabolic changes in the brain following injuries. Studies have shown a decreased NAA/Cr ratio and decreased NAA/Choline ratio and an increase in Cho/Cr ratio in DAI patients. Though these newer techniques can't be routinely done in all patients, they can be useful in specific circumstances.

In MRI, lesions in the brainstem, dorsal brainstem and bilateral brainstem lesions were associated with worse outcomes compared to lesions in the corpus callosum.[22,23,24,25,26] Age ≥ 30 years, lesions in Substantia Nigra, mesencephalic tegmentum, genu of the corpus callosum, multiple and larger lesions are significant factors predicting long-term poor outcome.[27,28]

Even though MRI prognostic models are gaining widespread use and relevance currently, CT brain still remains the gold standard in the evaluation of acute trauma worldwide.[29]The most common outcome predictor used in traumatic brain injury literature is the GLASGOW OUTCOME SCALE (Table 3).[30], which we have used to assess clinical outcome at the end of 1 month.

Table 3: glasgow outcome scale

5	GOOD RECOVERY	Resumption of normal life, though there may be minor neurological or psychological deficits
4	MODERATE DISABILITY	***DISABLED BUT INDEPENDENT*** Such patients can travel by public transport and can work in a sheltered environment, and are therefore independent as far as daily life is concerned, but may have varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory and personality change
3	SEVERE DISABILITY	***CONSCIOUS BUT DISABLED*** These patients are dependent for daily support by reason of mental or physical disability, usually a combination of both
2	PERSISTENT VEGETATIVE STATE	hey stay unresponsive and speechless for weeks or months after acute brain damage until death. Eye-opening may be present with cycles of sleeping and waking
1	DEATH	

Material & Methods

This is a prospective observational study of 158 consecutive Diffuse Axonal Injury (DAI) patients conducted at Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, for a period of one year. All the patients who were admitted with suspected head injuries were evaluated with CT brain scans. Patients who had Diffuse Brain Injury as per Marshall's CT grading criteria (Grades I – IV) were only included in this study. The Glasgow Coma Score (GCS) at the time of admission and the Rotterdam score of their initial CT brain were recorded. Their neurological status (GOS) at the end of one month was recorded.

Head injury patients who presented within 24 hours of injury with loss of consciousness for more than 6 hours, whose CT brain with either normal or abnormal with mass lesion of size less than 25ml were included in the study.

Patients who had loss of consciousness less than 6 hours, patients who presented more than 24 hours after injury, CT brain with any mass lesion above 25ml, mass lesions that were surgically evacuated, associated major long bone fractures and major organ injuries, any abnormal metabolic parameters, previously existing systemic co-morbid illness, psychiatric patients, and patients with seizure disorders were excluded from the study.

The GCS at the time of admission was taken as the clinical data. The patients were classified into three categories based on their admission GCS as mild (GCS 14-15), moderate (GCS 9-13) and severe (GCS 3-8) injuries.

Rotterdam and Marshall scores calculated from the CT Brain and MRI brain findings were considered as the radiological data.

The patients were followed up for a period of one month from the time of injury, and neurological status at the end of 1 month was observed using the Glasgow Outcome Scale (GOS). The patients who survived were dichotomised into favourable outcome (GOS 4&5) who were independent and unfavourable outcome (GOS 2&3) who were dependent groups.

Statistical analyses were then made to correlate the clinical and radiological data with the one-month outcome of the patients. Statistical analysis was done using the SPSS software – version 16, and the outcome was analysed using statistical tests like Pearson's coefficient and ANOVA. A p-value of less than 0.05 was considered statistically significant.

Results

172 diffuse axonal injury patients were enrolled in our study. 14 patients were lost from follow-up and hence, 158 patients were finally included in the study and analysis.

Among the total number of patients (n=158), 129 were males and 29 were females. Most of the patients admitted fell under the age groups 21-40 (n=103) with males comprising 88 and females comprising 15. The next age group to be affected most was 41-60 (n=31), where males comprised 21 and females comprised 8. Road traffic accidents accounted for most injuries (n=146). Most of the patients presented between 6-12 hours of injury.

GCS vs GOS

There were 6 patients with mild injury (3.8%), 63 patients with moderate injury (38.9%) and 89 patients with severe injury (56%). Statistical analysis made to compare the clinical severity (GCS) with the GOS via the test of homogeneity of variances, Levene statistical analysis and sum of squares / ANOVA tests yielded a p-value was 0.000 ($p < 0.05$), implying a statistically significant correlation between the clinical severity (GCS) and the clinical outcome (GOS). The more the initial GCS, the better was the clinical outcome and vice-versa. (Table 4).

Table 4: ANOVA correlation between admission GCS and GOS

Total GOS	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	688.701	3	229.567	84.126	.000
Within Groups	420.242	154	2.729		
Total	1108.943	157			

ROTTERDAM SCORE vs GOS

Patients' Rotterdam score were calculated from the CT scans and then their correlation to the clinical outcome (GOS) was analysed. Most of the patients had a Rotterdam score of 3 (n=55), followed by 4 (n=44), 2 (n=26), 5 (n=24), 6 (n=5) and 1 (n=4). Among the variables in the Rotterdam score, subarachnoid haemorrhage was seen most commonly (n=109, 69%), followed by cisternal effacement (n=89, 56%) with partial effacement 68 and complete effacement 21, midline shift (n=16, 10.12%). These variables were found in variable combinations.

Statistical analysis revealed a p value of 0.23. So, there was no significant statistical correlation between Rotterdam score and the clinical outcome (GOS).

MARSHALL SCORE vs GOS

Marshall score was also calculated from the patients CT scans and its correlation to clinical outcome was analysed. Most of the patients had score of 3 (n=71), followed by 2 (n=52), 4 (n=19) and 1 (n=16). Statistical analysis yielded a p value of 0.281. So, there was no significant statistical correlation between Marshall score and the clinical outcome (GOS).

MRI GRADES vs GOS (Clinical outcome)

MRI data was then analysed and compared the patient's clinical outcome. Because of economic and logistical reasons, MRI was done for only 35 patients. There were 11 patients with Grade I MRI findings, 14 with grade II and 10 with grade III. The Pearson's Coefficient showed a p value of 0.001 ($p < 0.005$) which was statistically significant. Hence it can be seen that the grades of MRI correlated with the clinical outcome of the patient, and they had an inverse correlation, the more the MRI grade, the worse was the outcome and clinical severity, and vice-versa (Table 5).

Table 5: Statistical analysis for correlation between MRI grades & GOS

		GOS Score	MRI
GOS Score	Pearson Correlation	1	-.527**
	Sig. (2-tailed)		.001
	N	35	35
MRI	Pearson Correlation	-.527**	1
	Sig. (2-tailed)	.001	
	N	35	35

**Correlation is significant at the 0.01 level (2-tailed).

OUTCOME ANALYSIS

We measured the clinical outcome as the Glasgow Outcome Score at one month after trauma. Patients were also dichotomised into dependent and independent status at one-month follow-up, with 86 (54.43%) patients being independent (GOS 4&5) and 72 (45.57%) patients being dependent (GOS 1,2&3).

Discussion

Clinical outcomes (GOS) in our study showed that 44 (28%) patients died, and the rest of the patients survived (n=114, 72%). The patients who survived were dichotomised into favourable outcome group (GOS 4&5; n=86, 75%) who were independent and unfavourable outcome group (GOS 2&3; n=28, 25%) who were dependent. In the surviving group, almost 3/4th of the patients were independent by the end one month post-trauma. This is more than what we can find in other similar studies.[7]

Statistical analysis revealed a significant correlation between the clinical severity (GCS) and the one-month outcome (GOS) with $p < 0.05$ which is comparable to other studies in the literature.

In our study, most patients had a Rotterdam score of 3 (n=55, 35%) and 4 (n=44, 28%). Only 5 patients had a score of 6 and none of them survived. 4 patients had a Rotterdam score of 1 and all of them survived. Most of our patients had a Marshall score of 3 (n=71, 45%) and 2 (n=52, 33%). We could not find a significant correlation and statistical association of either the Rotterdam score or the Marshall score to the clinical outcome (p – 0.23 and p – 0.281).

In our study, MRI brain could be taken for only 35 patients due to and logistical reasons. There were 11 patients with Grade I, 14 with Grade II and 10 with Grade III MRI findings. This grading also correlated with the admission GCS of the patients where most of the Grade I and II patients recovered earlier than the Grade III patients. We were able to establish a statistically significant negative association between the MRI grades and outcome at one month, with higher MRI grades leading to poor outcomes.

Though our study had certain limitations like a relatively small sample size and a short follow-up period, we were able to establish a statistically significant association of both admission GCS scores and MRI brain findings with one-month clinical outcome (GOS).

Conclusion

Diffuse Axonal Injuries have always been a challenge for the clinician to diagnose and treat. Despite various advances in imaging and treatment, there is no appreciable improvement in the clinical outcome in DAI. Though CT brain does have a role in diagnosis, its role as a prognosticating tool by way of the Marshall and Rotterdam Scores has been found unreliable in this study. Proper neurological evaluation of the patient with GCS score on admission and evaluation with MRI brain when feasible, with both having a statistically significant correlation with clinical outcome, provide reliable prediction models for prognosticating outcome in these patients.

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