Predictors of recovery in moderate to severe traumatic brain injury

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I HAVE NO DISCLOSURES

- Study was carried out at the Nelson Mandela Academic Hospital and WSU for a doctorate of philosophy study in neurosciences between 2014 March-2017 March
- ETHICAL AND SCIENTIFIC APPROVAL
- **(WSU Protocol number 019/2013**

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CLINICAL ARTICLE

Predictors of recovery in moderate to severe traumatic brain injury

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OBJECTIVE Traumatic brain injury (TBI) is a significant cause of morbidity and mortality worldwide. Clinical outcomes in TBI are determined by the severity of injury, which is dependent on the primary and secondary brain injury processes. Whereas primary brain injury lesions are related to the site of impact, secondary brain injury results from physiological changes caused by oxidative stress and inflammatory responses that occur after the primary insult. The aim of this study was to identify important clinical and biomarker profiles that were predictive of recovery after moderate to severe TBI. A good functional outcome was defined as a Glasgow Outcome Scale (GOS) score of ≥ 4.

METHODS This was a prospective study of patients with moderate to severe TBI managed at the Nelson Mandela Academic Hospital during the period between March 2014 and March 2016. Following admission and initial management, the patient demographic data (sex, age) and admission Glasgow Coma Scale score were recorded. Oxidative stress and inflammatory biomarkers in blood and CSF were sampled on days 1–7. On day 14, only blood was sampled for the same biomarkers. The primary outcome was the GOS score—due to its simplicity, the GOS was used to assess clinical outcomes at day 90. Because of difficulty in performing regular follow-up due to the vastness of the region, difficult terrain, and long travel distances, a 3-month follow-up period was used to avoid default.

RESULTS Sixty-four patients with Glasgow Coma Scale scores of ≤ 12 were seen and managed. Among the 56 patients who survived, 42 showed significant recovery (GOS score ≥ 4) at 3 months. Important predictors of recovery included antioxidant activity in the CSF (superoxide dismutase and total antioxidant capacity).

CONCLUSIONS Recovery after TBI was dependent on the resolution of oxidative stress imbalance.

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KEYWORDS trauma; traumatic brain injury; oxidative stress; inflammatory changes; recovery

TRAUMATIC brain injury (TBI) is a significant cause of death and disabling neurological deficits.[2,32] Although the Glasgow Coma Scale (GCS) score is important in assessing the state of consciousness,[48] it has been noted to have great limitations and inconsistencies when used in assessing survival and functional outcomes among patients with TBI.[23,31] Clinical outcomes in patients with TBI can be assessed using the Glasgow Outcome Scale (GOS) score.[22] Although current management strategies take into account factors such as the admission GCS score, pupillary reactivity, age of the patient, mechanism of injury,[20] CT scan findings,[30] intracranial pressure (ICP), and brain tissue oxygen tension (PBO_2), little or no information regarding the degree of ischemic cell damage, the level of oxidative stress imbalance, and inflammatory changes can be deduced from these parameters.

Oxidative stress is a disturbance in the equilibrium status of prooxidant/antioxidant systems and accounts for most of the negative consequences of secondary brain injury. The process of oxidative stress involves enhancement in the production of free radicals and strong oxidants as well as depletion of body stores of antioxidants following

ABBREVIATIONS AUC = area under the curve; BBB = blood-brain barrier; CI = confidence interval; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HR = hazard ratio; ICP = intracranial pressure; IL = interleukin; MDA = malondialdehyde; PBO_2 = brain tissue oxygen tension; ROC = receiver operating characteristic; SOD = superoxide dismutase; TAC = total antioxidant capacity; TBARS = thiobarbituric acid reactive substances; TBI = traumatic brain injury; TNF-α = tumor necrosis factor-α.

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INCLUSION CRITERIA

patients with moderate to severe TBI (GCS ≤ 12) in whom neuromonitoring and surgical intervention were indicated.

patients whose relatives gave a clear informed consent to participate in the study.

Patients with intracranial pathology requiring surgical intervention and or temporary CSF drainage to lower intracranial pressure

EXCLUSION CRITERIA

- Patients whose relatives refused to participate in the study
- Patients with severe ballistic injuries with GCS=3, fixed and dilated pupils.
- Patients for whom neuromonitoring was not carried out due to logistical problems
- Patients not admitted to the neurosurgical service
- Patients who died while still in the A/E or before admission

In OR: EVD inserted, craniotomy or craniectomy;burr hole done for Licox/ICP done

Daily ICP/PBO2 assessed

In ICU: daily blood and CSF analysed for CSF SOD, TAC, Malondialdehyde; serum IL-1β, IL-6 and IL-10;;Sedation protocol with morphine/ dormicum or Propofol and fentanyl

: on day 14 blood samples taken

On day 14 and 90; GOS assessed

Statistical analysis=SPSS 23

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RESULTS

- 64 Patients with GCS ≤ 12
- After week 2 and before 3rd week ; 8 pts (12.5%) died, GOS 5=66%, GOS 4=11%, GOS 3=14%, GOS 2=9%

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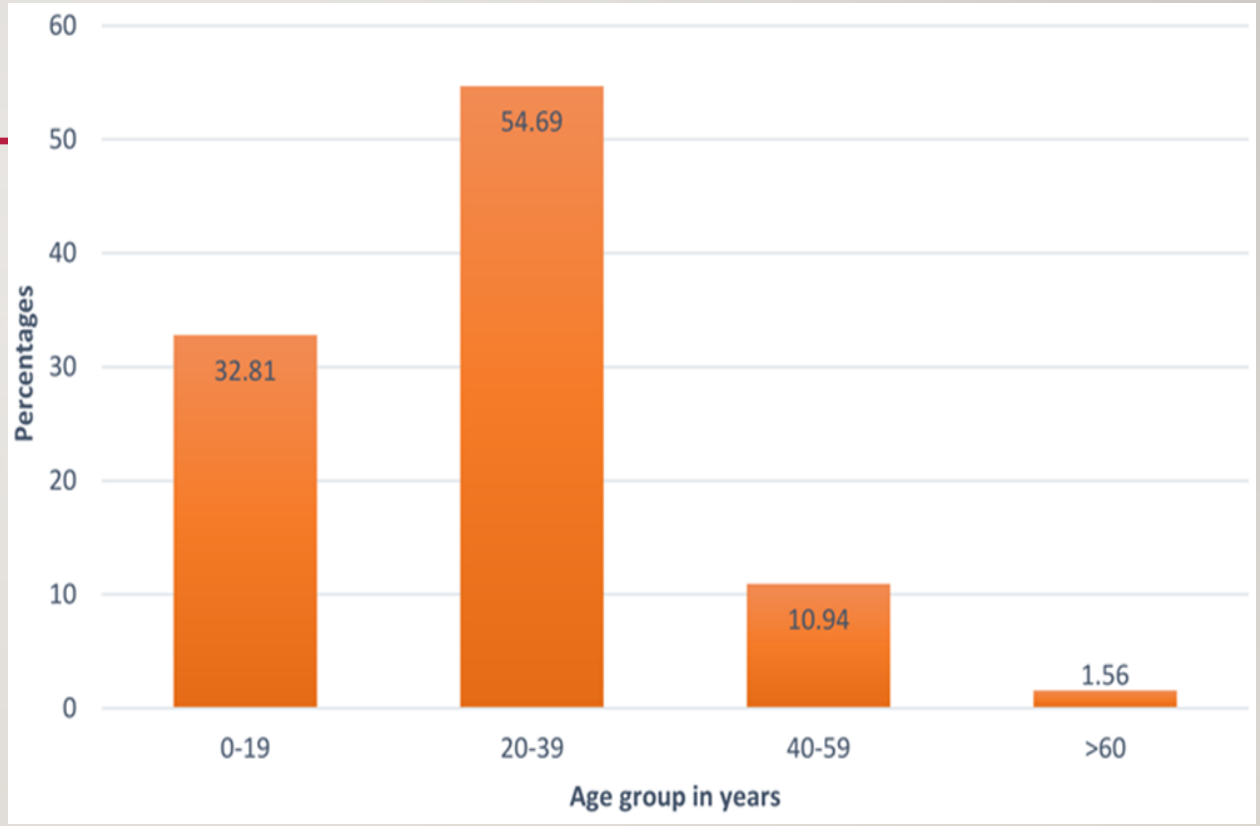
Mechanism	Frequency	Percent
Assault	42	65.6
Motor Vehicle accident	14	21.9
Falls from heights	6	9.4
Others	2	3.1
Total	64	100.0

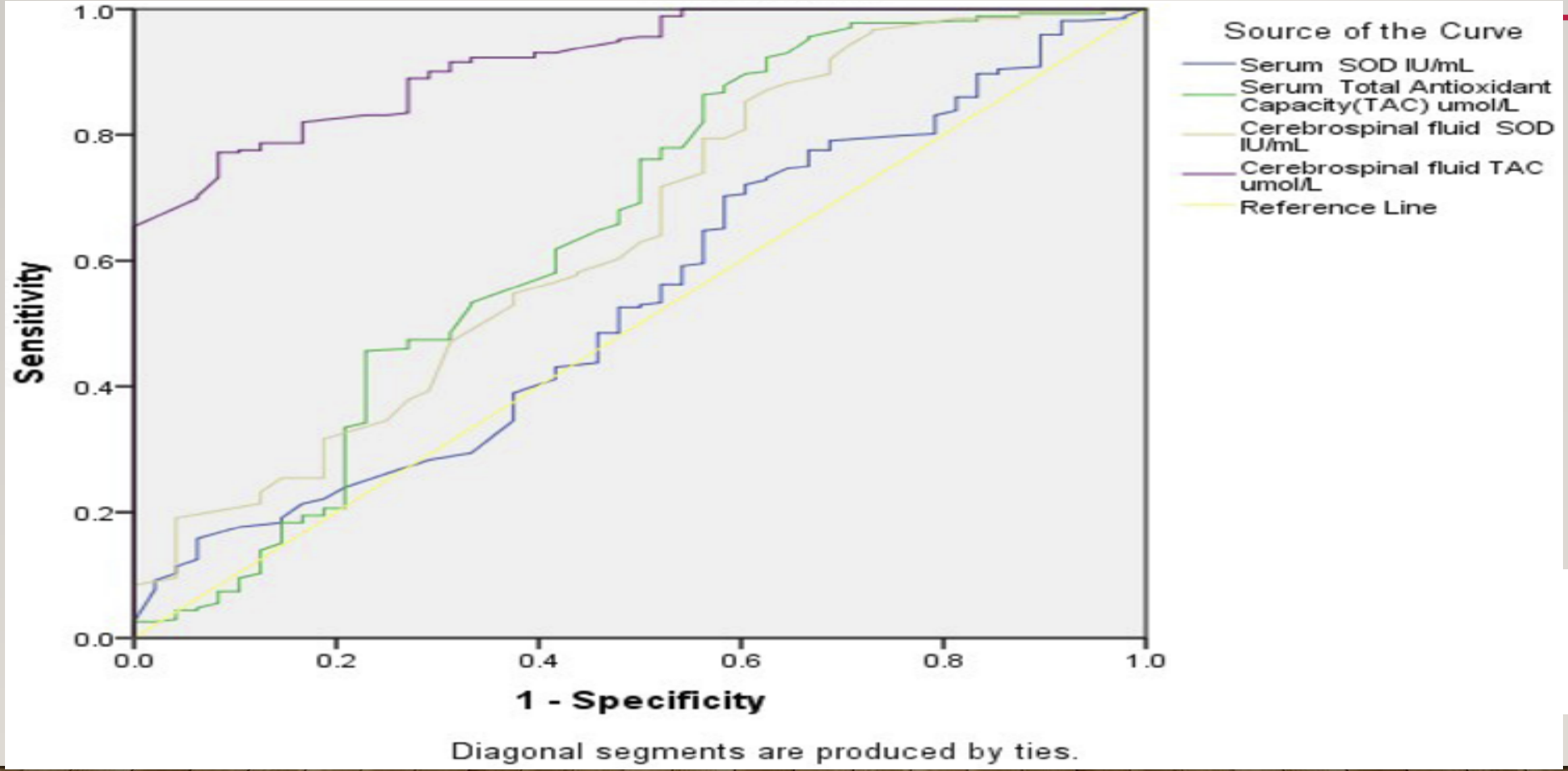


Significant univariate correlates of recovery of good function (GOS ≥ 4) were identified using optimal cutoffs to discriminate unchanged neurological status from recovery of good functional status by using ROC methods. Indeed, serum IL-1b, serum MDA, serum SOD, serum TAC, CSF SOD, and CSF TAC were confirmed as either significant or important

OPTIMAL CUT OFF BY ROC CURVE ANALYSIS

Marker	Cut-off	AUC	95%CI	SE	%Sensitivity	%Specificity	P-Value
Serum IL-1β	≤35 pg/ml	0.619	0.533-0.704	0.043	66	57	0.08
Serum MDA	≤1.4µmol/L	0.653	0.567-0.738	0.044	70	52	<0.001
Serum SOD	≥ 0.3 IU/mL	0.573	0.475-0.671	0.050	60	60	0.08
Serum TAC	≥ 450IU/mL	0.662	0.566-0.757	0.049	72.2	52	P<0.0001
CSF SOD	≥ 0.3 IU/mL	0.635	0.547-0.734	0.045	63	52	0.002
CSF TAC	≥ 300IU/mL	0.577	0.488-0.666	0.045	70	50	0.083

ROC CURVES SHOWING CORRELATES OF RECOVERY PREDICTORS



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MULTIVARIATE ANALYSIS

- Multivariate analysis was done to identify the most significant independent predictors of recovery by using:
- Cox regression analysis and stratified Kaplan-Meier curves
- In Cox regression; after adjusting for serum SOD, TAC, IL-1b, IL-10, and MDA, only CSF SOD and CSF TAC were the most significant independent predictors of recovery of good functional status

INDEPENDENT PREDICTORS OF RECOVERY OF GOOD FUNCTIONAL STATUS BY COX REGRESSION ANALYSIS

	B	Std.Error SE	Wald	HR(95%) CI	P-Value
CSF-TAC **≥ 300µmol/L** **≤ 300µmol/L**	0.363	0.180	4.085 referent	1.4(1.01-2.1) 1	0.043
CSF-SOD **≥ 0.3 IU/ML** **≤ 0.3 IU/ML**	0.471	0.189	6.224 referent	1.6(1.1-2.3) 1	< 0.01

- Indeed, the likelihood of recovery of good functional status—defined as GOS ≥ 4—was multiplied in excess of 90% by both CSF SOD ≥ 0.3 IU/ml and CSF TAC ≥ 300 μmol/L (as shown below).

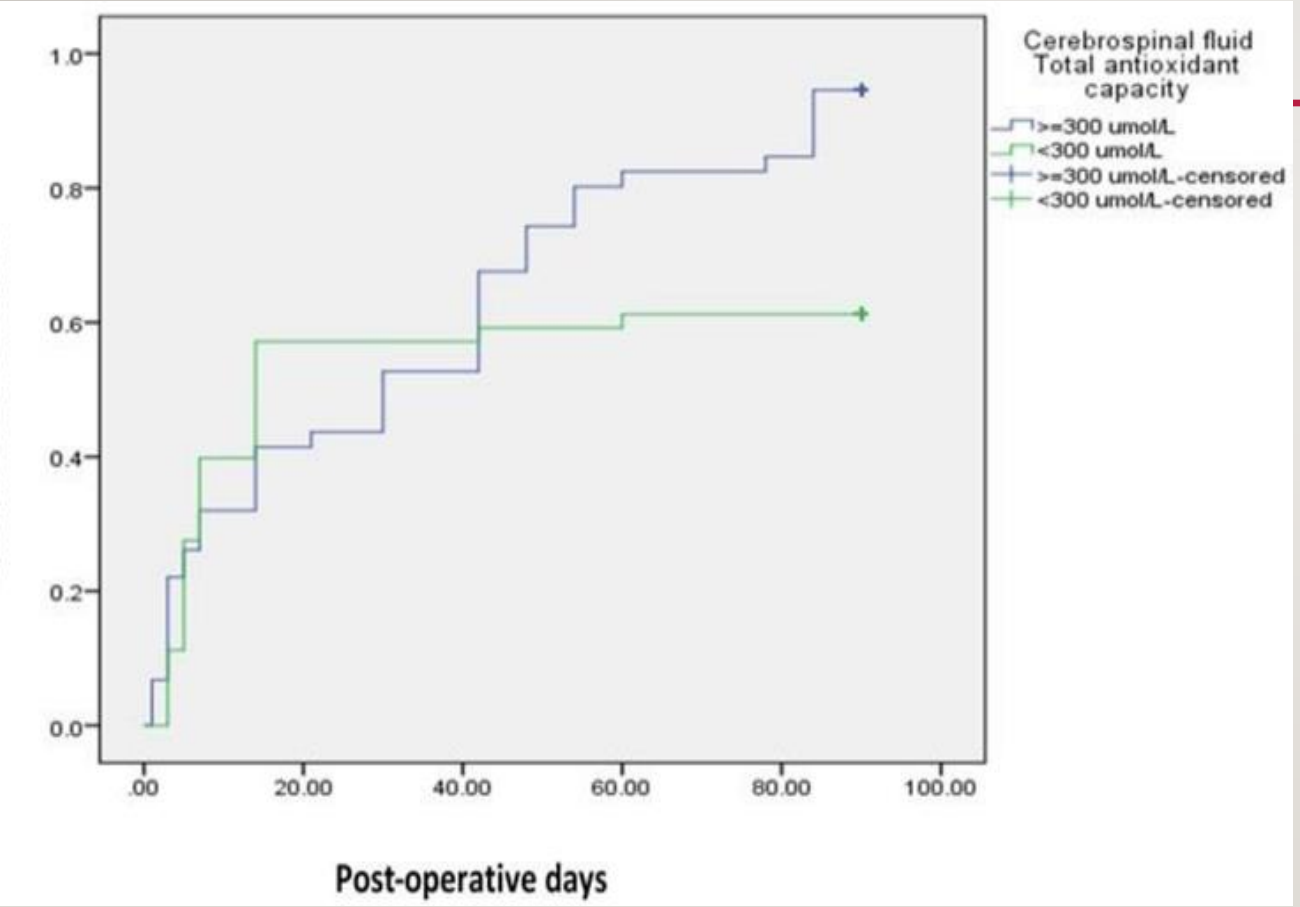
KAPLAN-MEIER ANALYSIS OF CSF SOD AS AN INDICATOR OF RECOVERY

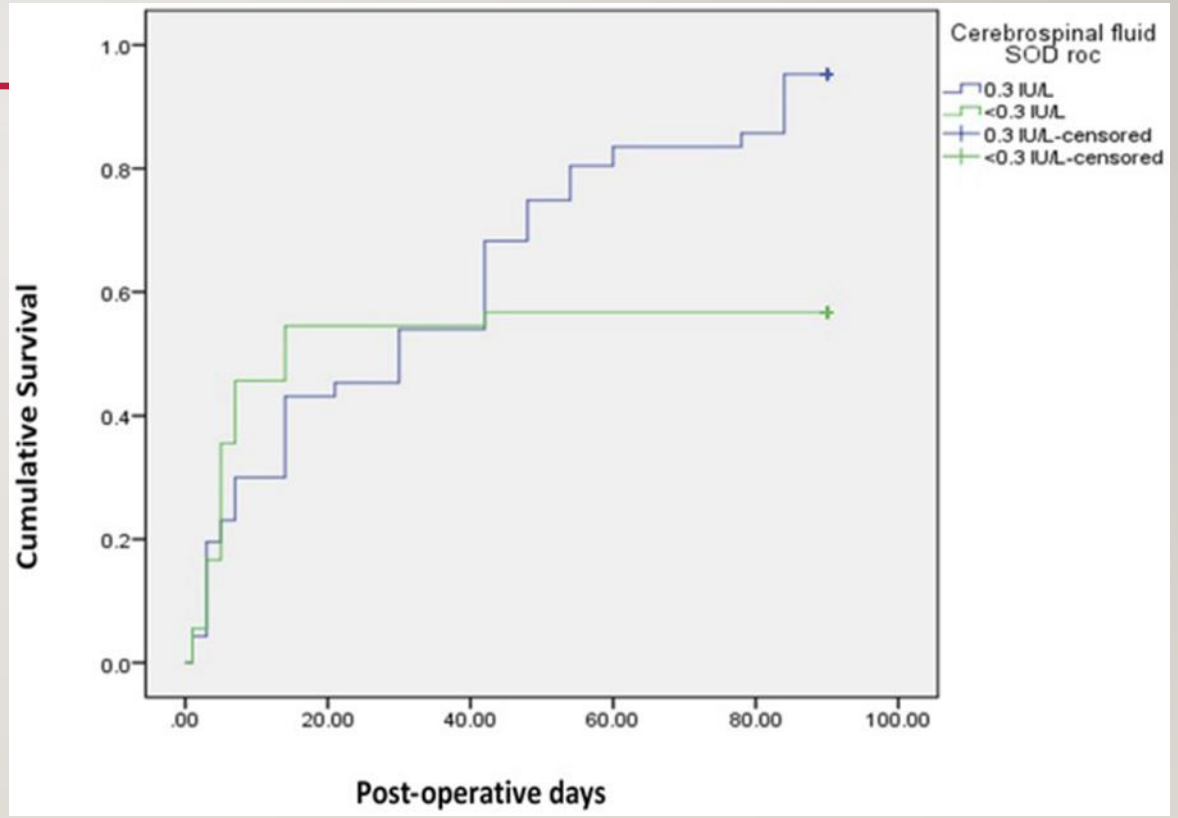
Based on Kaplan-Meier analysis the cumulative proportion of patients with CSF SOD activity ≥ 0.3 IU/ml who recovered good functional status= was 95.7%, with a mean time to recovery of 34 ± 1.9 days.

This was statistically significant ($p < 0.0001$ by the logrank Mantel-Cox test) when compared with the proportion of patients with CSF SOD activity < 0.3 IU/ml who recovered to GOS = 4 (55.6%, with mean time to recovery = of 43 ± 4.4 days). Values for continuous variables are expressed as the mean ± SD throughout.

- Kaplan-Meier analysis was used to estimate the survival of patients based on the biomarkers.
- The cumulative proportion of patients with CSF TAC = 300 µmol/L surviving and recovering to GOS ≥ 4 was 95.5%, with a meantime to recovery of 34.6 ± 1.97 days. This is significant when compared (log-rank Mantel-Cox test, $p < 0.001$) with the cumulative proportion of patients with CSF TAC < 300 µmol/L who would recover (60%, mean time to recovery 41.4 ± 4.03 days).

KAPLAN MEIER CURVES FOR CSF SOD AND CSF TAC





The prognostic information was mainly obtained from CSF TAC and SOD activity.

- None of the previous models including the IMPACT model (International Mission for Prognosis and Clinical Trials in TBI) and CRASH (corticosteroid randomization after significant bead injury) ever reviewed the profiles as seen in this study.

IN CONCLUSION

- CSF SOD AND CSF TAC are strong independent predictors of recovery in patients with moderate to severe TBI.
- An elevation in the antioxidant levels in the CSF was associated with better clinical outcomes.

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