

# Prognostic Serum Factors in Traumatic Brain Injury: A Systematic Review

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## Abstract

**Background & Aim:** Traumatic brain injury is one of the main causes of death and disability. The aim of this study is to systematically review the articles which assessed some serum factors of traumatic brain injury patients in relation to their outcomes.

**Methods & Materials/Patients:** Databases were searched for relevant publications from 2005 to 2014. Selection criteria were: Studies which evaluate the factors affecting the outcome after TBI, TBI defined as “acute changes in brain function resulting in a strong external force to the head”. Results were measured by Glasgow Outcome Score or a comparable measure. Factors were measured in first month after injury and the prognosis was addressed. All papers were checked and approved by a specialist and expert in that field. A systematic review was performed for prognostic factors.

**Results:** Sixty-three studies were included. Most studies used Glasgow Outcome Score at 6 months post-injury as outcome measure, sometimes in combination with other outcome measures. Strong evidence for predicting outcome was found for serum concentration of S100 protein, NSE, MBP, NF-H, GFAP, UCH-L1, blood glucose levels, serum levels of LDH, sodium level, prothrombin time, partial thromboplastin time, platelet count, D.dimer, HSP 70, serum levels of IL-8, number of circulating EPCs, and DNA levels in serum. Moderate evidence for predicting outcome was found for high serum MMP9. Strong evidence of no association was found for WBC count and serum cortisol levels. Moderate evidence of no association was found for serum total cholesterol for other determinants, inconclusive or no evidence or limited evidence was found.

**Conclusion:** S100 protein, NSE, MBP, NF-H, GFAP, UCH-L1, blood glucose levels, serum levels of LDH, sodium level, prothrombin time, Partial thromboplastin time, platelet count, D.dimer, HSP 70, serum levels of IL-8, number of circulating EPCs, and DNA levels in serum predicted outcome after traumatic brain injury. WBC count, serum cortisol levels, total cholesterol and MMP9 did not have predictive value.

**Keywords:** Prognostic; Serum Factors; Traumatic Brain Injury

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## Introduction

Traumatic brain injury still remains a serious concern and one of the leading causes of death and disability, particularly among young adults (1,2). Based on studies of prevention of diseases in United States, the most common causes of traumatic brain injury include factors like traffic accidents (20%), hit a barrier (19%) and assault (11%) (1). Traumatic brain injury can be classified into two types, primary and secondary. The primary injury occurs at the time of the accident causing direct damage to nerve tissue. Secondary damage is not seen at an early stage. Such harm is the natural and physiological response to the initial injury. Tissue hypoxia, which occurs within hours to months after the initial injury is this group (1). Early determination of prognosis after traumatic brain injury is a priority for relatives and physicians involved in the care of these patients (2,3). New prognostic information beyond the clinical examination, patient demographics and radiological

imaging from admission is needed to allow early prediction of short, mid, and long term outcome of patients with moderate and severe traumatic brain injury (1,2,3). One of the factors involved in secondary damage that may occur following head trauma is the changes in blood parameters and biomarkers. Assessment of brain damage using biochemical tests and cerebrospinal fluid (CSF) and serum enzymes during the past decade has been done (4). Biomarkers of structural damage such as S-100, tau, enolase Neuron Specific (NSE) and myelin basic protein (MBP) may be used as potential diagnostic tools, prognostic and therapeutic supplements (1). The purpose of this study was to systematically review articles that studied the changes in hematological parameters in patients with traumatic brain injury and its correlation with the final outcome of treatment of brain damage using biochemical tests, and cerebrospinal fluid (CSF) and serum enzymes during the past decade has been done (4). Biomarkers

of structural damage, such as S-100, tau, enolase Neuron Specific (NSE) and myelin basic protein (MBP), may be used as potential diagnostic tools, prognostic and therapeutic supplements (1). The purpose of this study was to systematically review articles that studied the changes in hematological parameters in patients with traumatic brain injury and its correlation with the final outcome of treatment.

## Methods and Materials/Patients

### Search strategy

Sampling based on the search of information resources PUBMED, COCHRANE, Embase, Google scholar. Databases were searched for relevant publications between 2005 and 2014. The following keywords were used: prognosis, prognostic model, predict, head trauma, brain trauma, head injury, brain injury, biochemistic tests, biomarkers, blood markers, blood glucose, and serum markers.

### Study selection

Two reviewers (FS and AM or AR) independently reviewed all publications and selected eligible studies. A third author (GS) was consulted in case of disagreement. We included cohort studies and determined serum factors concentrations in patients with moderate and/or severe traumatic brain injury as defined by a Glasgow coma score <13.

### Inclusion criteria were:

1. (Due to the dramatic change in measuring biomarker concentrations and the treatment of traumatic injuries in recent years), studies which were published from 2005 until 2014.
2. Studies in which, factors affecting the outcome after TBI were evaluated.
3. Studies that defined TBI as "acute changes in brain function resulting in a strong external force to the head.
4. Studies in which the result was measured by Glasgow Outcome Score or a comparable measure describing the activity limitation and neurological state.
5. Studies in which correlation between the measured factors in the first month after injury and the prognosis was addressed.
6. The studies population were patients with moderate and/or severe (GCS <13) TBI with or without patients with mild injury or a subgroup consisting of patients with moderate or severe TBI were analyzed separately.
7. The article was written in English or English form of it was available.

### Quality Assessment

Each paper was qualitatively evaluated according to criteria intended to establish study strength. These included:

1. Twenty-five or more patients in the series with complete follow-up.
2. Outcomes measured -Glasgow Outcome Scale or Mortality- at six months or more.
3. Data gathered prospectively, although retrospective examination from a database creating an ongoing cohort of patients could be used.
4. Glasgow Coma Scale score measured within 24 hours.
5. Appropriate statistics (e.g. multivariate analysis) was used to include adjustment for prognostic variables.

### Data Extraction

Two reviewers (FS and AM or AR) independently collected data using a standardised data abstraction form. We abstracted information related to study design, patient characteristics,

treatments (operative and pharmacological), laboratory aspects of the testing factor (type of assay used, time period of sampling, and sampling type) and clinical outcomes (outcome type and timing of assessment). In instances of duplicate reporting, we used data from the study that included the largest number of patients or, when available, individual patient data from each study. We contacted authors for clarification on study sample or for missing data. If multiple measurements were carried out, we used the first measurement after the injury for analysis. If outcomes were assessed at multiple time points, we used the measurement furthest from injury for analysis. Data of studies, inclusion and exclusion criteria, number of participants, time after injury, failure to continue follow-up, measurements of outcome, prognostic factors and results of their relationships with outcome were extracted using a standardized form.

### Analysis

Significant relative risk ratios (RR), odds ratios (OR) or significant correlations ( $P < 0.05$ ) which were introduced by studies, was used to determine levels of evidence. If multivariate analysis was performed in the study, the results of it were used to establish the level of evidence. Otherwise, the results of the univariate analysis were used (table 1).

## Results

### Study selection

In total, 1021 citations were identified and after elimination of duplicates and screening and after using the inclusion and exclusion criteria, agreement was initially reached in 82 of articles and consensus was sought and finally, 63 articles were selected.

### Study characteristics

The study characteristics are presented in Table 2. All articles were written in English. The number of patients studied was from 20 to 834 individuals with moderate to severe and sometimes mild traumatic brain injury. Penetrating trauma was not mentioned. The main measure used for prognosis was GOS (30 studies). Other measures include mortality, GCS, ASI, PCPC, GOSE, EDSS, and DRS (Table 2). Most of the investigated factors were: blood glucose, serum protein S100 and NSE, as follows: 16 study assessed the serum S100 protein (13 studied: S100B, 2 study: S100BB, 1 study: S100A1B), 22 study assessed the blood glucose levels and in 14 study, NSE levels were examined. 45 studies exclusively evaluated adults and 16 studies exclusively evaluated children. In other studies, age was not an entry criterion. Of all studies, in 20 studies, venous blood samples were taken. In 11 studies, arterial blood and in one study capillary blood (finger) was sampled. Other studies did not specify the sampling site.

### Neuronal markers:

#### 1. Protein S100:

According to the studies, serum concentration of S100 protein is a strong prognostic factor in adults and in children and there was strong evidence of relationship between serum levels of protein S100 and outcome. 19 studies were reviewed which assessed S100 protein in the blood as a prognostic factor in TBI. In all but two studies (6,7), high levels associated with poor prognosis. All of these studies assessed serum levels of S100B but a study conducted in 2012 by Yousefzadeh et al. (28) evaluated the S100BB levels and Nyle'n et al. (62) studied serum levels of 3 types of this protein (S100B, S100A1B and S100BB). In studies on children with TBI (6,9,10,11,12,13) in many of them significant

correlation with the prognosis of patients was achieved except a study performed by Beers et al. (2007) (6) in which a statistical correlation between serum protein and GOS at 3-4 and 6-8 months after trauma was not found. Of the studies on the adults with traumatic brain injury (7,8,15, 16,17,18,19,20) all except one study (7) showed significant correlation between prognosis and S100 levels in serum.

### 2. Neuron specific enolase:

The evidence for the predictive value of concentration of neuron specific enolase in adults and in children with TBI was strong. 12 studies which had evaluated NSE as a prognostic factor were reviewed; all but three studies (6,13) achieved significant associated between high levels of NSE and poor prognosis. Six studies were performed on children with traumatic brain injury (6,11,12) and seven studies on adults (13,15,16,17,20,22,23)

### 3. Hyperphosphorylated neurofilament:

According to the studies, serum concentration of NF-H is a strong prognostic factor in children. Two studies (10,24) evaluated serum NF-H levels as a prognostic factor in TBI; Both studies performed on children in both studies, high levels associated with poor prognosis.

### 4. Ubiquitin C-Terminal Hydrolase:

5 articles that studied (Table 2) serum levels of UCHL1 as a prognostic factor in TBI were reviewed. All of them studied the correlation between UCHL1 values and GOS except for a study conducted in 2012 by L.Papa et al. (25) in which outcome measures included the following:

- (1) GCS scores obtained at presentation to the ED,
- (2) the presence of intracranial lesions on initial CT scan; and
- (3) the need for neurosurgical intervention (NSI).

In this study, there was a significant relationship between all these three outcome measures, and levels of UCHL1 in adult patients with TBI. All of the other studies also found a significant correlation between high serum UCHL1 values and low GOS (unfavorable outcome).

### 5. TAU Protein

The evidence for the prognostic value of serum levels of TAU protein was Limited. Only one study (26) assessed serum levels of TAU protein as a prognostic factor in TBI. This study was conducted in 2008 by L. Nyle'n et al. (62) and reported high level of TAU protein levels as an independent risk factor for a poor outcome (GOS 1-3) (P=0.043). ROC evaluating the ability of serum t protein level to predict a poor outcome showed an area under the curve of 0.939 with 88% sensitivity and 94% specificity at a serum TAU protein level of 114.5 pg/mL.

### 6. Myelin basic protein

2 studies (6,11) evaluated the levels of myelin basic protein (MBP) in serum, as a TBI prognostic factor. In the study which was performed on children under 15 years of age with traumatic brain injury, a significant relation was found between levels of this protein and the GOS, 3-4 and 6-8 months after trauma (6). In another study on children under 3 years who suffered a traumatic brain injury of varying intensities, high serum levels of MBP correlated with bad 6-month outcome which was measured by (Glasgow Outcome Scale using (GOS), Vineland Adaptive Behavior Scale (VABS) and the Intelligence Coefficient (IQ)

### 7. Glial Fibrillary Acidic Protein

The evidence for the prognostic value of serum levels of GFAP was strong. Seven studies (7,10,27,28,29,30,31) investigated serum GFAP levels as a prognostic factor and all of them reported the high values of GFAP correlates with poor prognosis. Four studies evaluated prognosis of TBI in children and reminding were performed on adults. In a study performed by S. Mondello and coworkers (27) in 2011, multivariate logistic regression analysis showed that of all the variables assessed, only UCH-L1 was an independent predictor of mortality at discharge and also strongly predicted deaths in 6 months after the damage predicted. Highly significant correlation between UCH-L1 and GFAP were found. GFAP did not have an additional contribution when UCH-L1 was already entered in the model. Similar predictive value for GFAP and UCH-L1 ( $c=0.93$ ) was determined.

## - Biochemical test

### 1. Blood sugar:

In 22 studies, blood glucose levels were investigated as a prognostic factor. All but three studies (32,33,34) reported that high levels of BS is associated with poor prognosis. All of the studies performed on children with traumatic brain injury (35,36,37,38) achieved significant correlation between BS levels and patient prognosis. All of the studies on adults with traumatic brain injury (32,33,34,40,41,42,43,44,45,46,47,48,49,50,74) and studies without a age limit (51,52) reported a significant relationship between blood glucose levels and prognosis achieved except two studies (32,34). The evidence for the prognostic value of BS levels was strong both in adults and in children with traumatic brain injury.

### 2. Lactate Dehydrogenase:

One study (53) evaluated Lactate Dehydrogenase levels as a prognostic factor of TBI. In both studies high levels were associated with poor prognosis. The evidence for the prognostic value of serum levels of LDH was strong. In V. Jain et al. study (68) in 2010, a significant relationship between serum LDH outcome after traumatic brain injury was found in patients with isolated brain trauma. In this study, the average increase in serum LDH was found in patients with a poor outcome and LDH levels increased continuously during the study period in both disabled and dead groups.

### 3. Plasma Osmolarity:

Two studies (34,46) investigated plasma osmolarity as a prognostic factor. In a study by WhaSook Seo and HyunSoo Oh in 2009 (72) on patients with traumatic brain injury (and hemorrhagic stroke), 6 months after the trauma one of the physiologically significant predictors of cognitive abilities in patients with TBI was admission serum osmolarity ( $p= 0.01$ ), but there was no significant association between plasma osmolarity mortality and functional disability. In Nelson DW et al. study (49), poorer outcomes were observed with increasing osmolarity. According to these two studies, the evidence for the prognostic value plasma osmolarity was inconclusive.

### 4. Total cholesterol:

In WhaSook Seo and HyunSoo Oh study (72), 6 months after trauma, relationship between total cholesterol and mortality, cognitive abilities and functional disability in patients with TBI were not significant. In another study by Adel Helmy et al. (50), Total cholesterol only had a statistical relationship with traumatic brain injury outcome, via at least one other variable and was designated as 'level 2' of the hierarchy. According to these studies, serum total cholesterol probably is not a prognostic factor

in patients with traumatic brain injury with a moderate level of evidence.

#### 5. Albumin:

3 studies (34,46,50) investigated albumin level as a prognostic factor in TBI. In WhaSook Seo and HyunSoo Oh study (72) and in Adel Helmy et al. study (50), correlation of albumin levels with outcome was like total cholesterol level. In Nelson DW et al. study (49), low albumin relationship with poor outcome in patients with TBI was statistically significant. According to these studies, the evidence for the prognostic value of low albumin was also inconclusive.

#### 6. Other biochemical tests:

Nelson DW study in 2005 (61) reported blood creatinine as an independent predictor of outcome after TBI. In study by Helmy et al. (50), low magnesium only had a statistical relationship with outcome via at least two other variables and was designated as 'level 3' of the hierarchy. Hohl and colleagues in a study in 2012 (12) found that sodium in the blood of those who died after TBI was significantly higher. According to the above studies, the levels blood sodium was a strong prognostic factor of poor outcome in patients with traumatic brain injury, but the evidence for the prognostic value of the other variables was limited and uncertain.

#### Complete Blood Count (CBC):

##### 1. Hemoglobin

Five studies (34,43,46,48,50) were reviewed which assessed Hb levels as a prognostic factor in TBI. In 3 of them (43,48,50), low levels associated with poor prognosis. In two studies (34,46) there was no significant correlations between Hb levels and prognosis. According to the studies, there was inconclusive evidence of relationship between Hb level and outcome in traumatic brain injury.

##### 2. The leukocyte count

Three studies (38,50,55) were reviewed which assessed WBC count as a prognostic factor in TBI. None of them showed significant correlations between WBC levels and TBI prognosis. According to the studies, there was strong evidence of no relationship between WBC level and outcome in traumatic brain injury.

#### - Blood Gases and ABG Results:

3 studies (34,39,43) were reviewed which assessed ABG results as a prognostic factor in TBI. In study by WhaSook Seo & HyunSoo Oh (72), 6 months after trauma physiological predictors of mortality in patients with traumatic brain injury was arterial oxygen pressure ( $F=11.83$ ,  $p=0.00$ ) and arterial carbon dioxide pressure ( $F=4.40$ ,  $p=0.02$ ). In another study performed by Tude Melo et al. in 2010 (38), low blood oxygen saturation found to be a prognostic factor for mortality ( $OR=1.67$ ). According to the studies, there was a limited evidence of relationship between  $PaCO_2$ ,  $PaO_2$ ,  $aPH$ ,  $O_2sat$  and outcome of traumatic brain injury.

#### Coagulation Factors and Products:

8 studies (23,31,38,39,43,58,71) were reviewed which assessed coagulation factors and products as a prognostic factor in TBI: 5 studies (23,38,39,43,58) assessed prothrombin time (PT) as a prognostic factor in TBI and all of them found a significant correlation between increased PT and poor outcome and mortality. So the evidence about prognosis prediction of PT is strong.

3 studies (23,38,58) assessed partial thromboplastin time (PTT) as a prognostic factor in TBI and two studies (38,58) found a significant correlation between increased a PTT and poor outcome. So the evidence about prognosis prediction of PTT is strong.

3 studies (23,38,58) assessed platelet count as a prognostic factor in TBI and two studies (23,58) found a significant correlation between decreased platelet count and poor outcome. So the evidence about prognosis prediction of platelet count is strong.

2 studies (23,14) assessed D.dimer levels in serum as a prognostic factor in TBI and none of them found a significant correlation between its levels and outcome. Therefore, the evidence about that there is no relation between prognosis and levels of D.dimer is strong.

Only one study assessed each serum FDP levels (23) and serum VWF factor levels (31) found a significant correlation between them and outcome. Thus, the evidence about prognosis prediction of both of these is limited.

#### -Acute Phase Reactants:

##### 1. Heat Shock Protein 70 (HSP 70):

2 studies (58,59) assessed HSP 70 levels in serum as a prognostic factor in TBI and both of them found a significant correlation between its levels and outcome. So the evidence about prognosis prediction of HSP70 is strong.

##### 2. Pentraxin-PTX3

Only one study (54) investigated Pentraxin-PTX3 serum protein as a prognostic factor. In this study which was conducted in 2011 by Jackson da Silva Gullo et al., (20) increased PTX3 levels correlated with mortality ( $P<0.04$ ). Thus, the evidence about prognosis prediction of PTX3 levels is limited.

#### -Inflammatory Factors:

3 studies (60,61,62) assessed some of the cytokines and inflammatory factors as prognostic factor in TBI. In Gopcevic et al. study (8), plasma level of IL-8 was significantly lower in survivors ( $71.00 \pm 14.17$  pg/ml) than in non-survivors ( $111.26 \pm 16.9$  pg/ml). In Stein et al. study (60), median daily IL-8 levels associated with poor outcome, the median serum values of other Cytokine levels (IL-1B, IL-6, IL-8, IL-10, and TNF-alfa) were not different between 2 groups (GOSE 1-4 vs 5-8). In Soares et al. study (58), significant correlations of elevated serum levels of IL-10, but not TNF- $\alpha$ , with hospital mortality in patients with severe TBI were reported ( $p=0.01$ ). Considering all these studies suggest that increased serum levels of IL-8 may be a strong prognostic factor but uncertain and limited predictive power of other inflammatory factors was seen.

#### - Hormones

1. ACTH
2. Cortisol
3. Estradiol
4. Testosterone
5. Progesterone
6. LH & FSH

2 studies (63,64) were reviewed which assessed Cortisol (63,64), ACTH (63) and sex hormones (64) as prognostic factors in TBI. In K. Wagner et al. study (42), high estradiol and testosterone associated with mortality ( $p=0.026$  and  $p=0.033$ , respectively). Significant effect of LH, FSH, progesterone on mortality through their association with estradiol ( $p=0.049$ ). High estradiol was

associated with worse outcomes. Stradiol mediated progesterone associations with GOS ( $p=0.045$ ). Serum cortisol was not associated with mortality or GOS. In Llompart-Poué et al. study (37), patients with low ACTH values ( $<9$  pg/mL): statistically significant lower mortality (7% vs. 55%,  $p<0.0001$ ) and low plasma ACTH in patient who survived, correlated with increased ICU length of stay ( $p<0.03$ ). But no significant differences with baseline and stimulated serum cortisol after a high-dose corticotrophin stimulation test were seen. According to these studies, the serum cortisol strongly has no relation with outcome of patients with brain injury. And the evidence of the prognostic value of serum levels other hormones mentioned, was inclusive.

#### **Matrix metalloproteinase 9:**

In the study conducted by M. DeFazio et al. (17) a significant difference in the mean concentration of MMP-9 at admission ( $P=0.115$ ) or in 24 h ( $P=0.535$ ) was not found between the short term outcome groups. The study conducted by J. Copin et al. (11) a significant relationship between serum MMP-9 levels and three-month GOSE in patients with severe TBI was not seen. According to these studies, the serum MMP9 levels have no relation with outcome of patients with brain injury with moderate evidence.

#### ***α II-Spectrin Breakdown Product 145kDa:***

Only one study (6) investigated serum SBDP145 level as a prognostic factor in TBI.

In one study (6), unfavorable outcome was correlated with higher concentrations of SBDP145.

According to this study, the evidence for the prognostic value of low SBDP145 was limited.

#### **Circulating endothelial progenitor cells:**

2 studies (66,67) were reviewed which assessed circulating endothelial progenitor cells as prognostic factor in TBI.

In Li Liu et al. study (9), number of circulating EPCs was significantly lower in who died  $p<0.01$ .

In Gong D et al. study (69), number of circulating EPCs was significantly correlated with GOS scores 6 months after TBI. Thus, the evidence for the predictive value of circulating endothelial progenitor cells was strong.

#### **- Miscellaneous:**

The studies of other factors, including serum oxidative stress parameters: thiobarbituric acid reactive species (TBARS) and carbonyl group (48), serum leptin (68) serum fibronectin CFn (65) and troponin cTnI were also reviewed which due to the low number of these studies for each factor, they can be a potential prognostic factors with limited evidence for TBI.

### **Conclusion**

This systematic review summarized the results of 63 articles about the predictive value of various factors on prognosis after brain damage. Providing new information or explaining the findings in terms of pathophysiology is not the primary goal of a systematic review. Therefore, although relevant for clinicians, we were cautious not to speculate about underlying mechanisms or explanations for which no evidence was given in the included studies. Our study established strong evidence that serum concentration of S100 protein, neuron specific enolase, MBP, NF-H, GFAP, UCH-L1, blood glucose levels, serum levels of LDH, sodium level, prothrombin time, partial thromboplastin time,

platelet count, D-dimer, HSP 70, serum levels of IL-8, number of circulating EPCs, and DNA levels in serum were predictors of post-TBI outcome. This study found strong evidence that WBC count and serum cortisol levels do not predict outcome. Moreover, moderate evidence was found that serum total cholesterol count do not predict outcome. Moderate evidence showed that high serum MMP9 levels predict poor outcome. For all other determinants the evidence was limited or inconclusive. Although these profiles are best evidence for prognosis after TBI, they seem to be of limited value; hence still we are not able to correct or prevent or treat some of these factors. Overall, it can be concluded that much information is needed on long term outcome moderate and severe traumatic brain injury.

#### **Limitations of the review**

It was very difficult to reach a consensus on all epidemiological findings across the 63 published studies because of critical differences in methods employed across the reports. Firstly, we searched studies published between the 2005 and 2014. It is possible that relevant publications before or after that time were not included in this review. However, we think that it would be inappropriate to include older studies in a review on prognostic factors, because there have been dramatic changes in measuring biomarkers concentrations and the treatment of traumatic injuries over the last years.

Some of the included studies excluded penetrating head injury, other studies did not. Little information was given in the studies about how many patients had closed or open head injuries. It is not clear whether this has influenced our results. There was considerable heterogeneity for all outcomes of interest and in the time period over which outcome was evaluated. In the literature, different definitions for traumatic brain injury and the diagnostic methods are used. We decided to define brain injuries as the changes in brain function because of severe damage by an external force. We choose this fairly extensive definition is brain damage, so we would be able to enter many of the relevant studies. Furthermore, the populations studied were varied extensively in each literature from the other, in terms of gender, age, region and country in which they lived and were treated. Finally, we did not include studies published in languages other than English.

#### **Recommendations:**

Prediction of outcome after brain injury is not always straightforward, and there is always some uncertainty. Multiple factors may affect the outcome. Much of the literature available is written from an isolated neurological, neurosurgical or rehabilitation perspective. To improve outcome prediction, multidisciplinary research should take place, and knowledge should be integrated.

Although several biomarkers of brain injury have been identified, continued research is required. A single biomarker may not have desired sensitivity and specificity for predicting outcome. Biomarkers, in combination with other clinical data, such as GCS and head CT scan, would maximize the accuracy. Future studies will be required to not only identify these biomarkers prognostic ability together with other factors.

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None declared.

#### **Conflicts of Interest**

The authors declare that they have no competing interests.

Table 1. Levels of evidence (6)

<b>Strong</b>	Consistent findings ( $\geq 80\%$ ) in at least 2 high quality cohorts
<b>Modrate</b>	One high-quality cohort and consistent findings ( $\geq 80\%$ ) in one or more low-quality cohorts
<b>Limited</b>	Findings of one cohort or consistent findings ( $\geq 80\%$ ) in one or more low-quality cohorts
<b>Inconclusive</b>	Inconsistent findings irrespective of study quality

Table 2. Data Extraction in Prognosis Serum Factors in Traumatic Brain Injury

Author(s)	Patient Characteristics	Outcome	Factor	Result
DeFazio et al. 2013 (5)	United states, ? patients, 44 completing. Age 16–64 years. Inclusion: head injury, severe TBI GCS $\leq$ 8. admitted within 3 hours of injury	GCS 72h, mortality	S100b, MMP-9, D-dimer 1 <sup>^</sup> 24h Venous blood samples	Significant: correlations: serum S-100B 1 <sup>^</sup> , plasma D-dimer, serum S-100B 24 h
Lin et al. 2012 (31)	China ? patients, 142 completing, age below 15 years. Inclusion: head injury, severe TBI GCS $\leq$ 8. admitted within 6 hours of injury. Exclusion: disagreement of parents, recent infection, previous TBI or history of seizure	GOS 1–3 vs 4–5	plasma leptin level	Significant
Chabok et al. 2012 (28)	Iran, 414 patients, 28 patients completing. Age $\geq$ 16 years. Inclusion: head trauma (GCS $\leq$ 8), without hematoma in CT and any injury or with minor injuries such as lacerations in other anatomic regions. admitted within 3 hours after injury. Exclusion: acute alcohol intoxication, polytrauma, preexisting disease, focal lesion in their second CT scan at 48 hours, who died or were discharged before 72 hours of injury	GOS 1–3 vs 4–5	NSE and S100BB 6 h 24 h 48 h 72 h Venous blood samples	not significant : NSE 6 h, 24 h 48 h . S100BB6 h Significant :S100BB t 24 ,48 h 72 h. NSE72 h
Papa et al. 2012 (34)	United states, ? patients, 96 completing. Age 18–89 years. Inclusion: adult patients with blunt head trauma followed by either loss of consciousness, amnesia or disorientation and present within 4 hours of injury with a GCS score of 9-15. Exclusion: age $<$ 18 years; no history of trauma, dementia, chronic psychosis, active CNS pathology, pregnant or incarcerated	GCS13-15 vs 9-12 CT positive vs negative	UCH-L1	Significant for both (p $<$ 0.001)
Czeiter et al. 2012 (22)	Hungary, ? patients, 45 completing. Age $<$ 18 years years. Inclusion: GCS score $\geq$ 8 on admission caused by TBI less than 24 h. Exclusion: age $<$ 18 years, autoimmune disease and pregnancy	GOS 1 vs 2–5 6 months	UCH-L1 GFAP 1h,6h	Significant: correlations: lethal outcome: significant for GFAP_1H, UCH-L1_1H, GFAP_24H, UCHL1_24H unfavorable: significant AUCs for GFAP_1H, UCH-L1_1H, GFAP_24H, UCH-L1_24H
Gong et al. 2012 (69)	China. ? patients, 21 completing, age $>$ 16 years. Inclusion: head injury, severe TBI. GCS $\leq$ 8. admitted within 6 hours of injury	GOS scores 6 months	endothelial progenitor cells on days 1, 4, 7, 14 and	Significant: correlations;EPCs 7 days
Hohl et al. 2012 (17)	Brazil, ?patients, 79 completing, age 18-80 years. Inclusion: with severe TBI admitted to the intensive care unit, GCS 8 or lower after the ICU admission. Exclusion: Victims of gunshot injury and patients who evolved to brain death before 24 hours of admission	Hospital mortality	Oxidative stress parameters: thiobarbituric acid reactive species (TBARS) carbonyl groups 1st, 2nd, and 3rd day blood pH, glucose, sodium, Hct, Hb Venous blood samples	no statistical differences in plasma levels of TBARS and protein carbonyl groups between survivors and non-survivors who died had significantly higher pH (P= .01), glucose (P= .04) and Na & lower levels of Hct and Hb
Zurek et al. 2012 (64)	United states, ? patients, 49 completing. Age 8–204 months. Inclusion: head injury. admitted within 3 hours of injury	GOS 1vs 2–5	Serum pNF-H Venous blood samples admission and every 24 h for 6 days	The quantitative level of pNF-H remained significantly higher in GOS=1
Mondello et al. 2012 (56)	United states, ? patients, 95 completing. Age $<$ 18 years. Inclusion: TBI patients GCS of 8 and a ventricular intracranial pressure monitoring as part of their routine clinical care. Patients with multiple trauma were excluded (Injury Severity Score=15)	survival in first 7-day GOS=1 vs 2–5 3 months	blood UCH-L1 every 6 hours up to a maximum of 7 days	Significant: correlations: 7day mortality: (P= .01) 3 months mortality

Author(s)	Patient Characteristics	Outcome	Factor	Result
Copin et al. 2012 (11)	Switzerland. ? patients, 49 completing, age 25-55 years. Inclusion: Patients with TBI from blunt trauma were enrolled and included if severe TBI was confirmed by cerebral CT scan	1. ICU LOS of survivors 2. Death before 3 m 3. Consciousness at 14 days 4. GOSE at 3 months	MMP-9, c-Fn at 6, 12, 24 and 48 hours	Significant correlations; 1. early MMP-9 (+32%, p = 0.14, n = 34) or late c-Fn concentration (+127%, p = 0.06, n = 34)
Soares et al. 2012 (58)	Brazil, ? patients, 93 patients completing, age >16 years old. Inclusion: severe TBI (GCS 3-8) presented within 24 hours of the head injury	hospital mortality	serum levels of IL-10, and TNF- $\alpha$ 10 h, 30 h, 68 h	Significant correlations: Elevated serum levels of IL-10, but not TNF- $\alpha$ , with hospital mortality (p = 0.01)
Macher et al. 2012 (25)	Spain, ? patients, 65 patients completing, age <16 years. Inclusion: admitted at ICU suffering severe trauma brain injury (GCS <9). Exclusion: previous history of neurological or psychiatric disease	survival/non-survival	Circulating cell-free DNA levels At study entry and after 24, 48h	Increased DNA levels: correlations: non-survival
Gopcevicet al. 2012 (8)	Croatia, ? patients, 20 patients completing. Age >16 years. Inclusion: isolated severe TBI admitted to ICU, (GCS $\leq$ 8). Exclusion: injury of other organs, dementia, acute infection, stroke, using anti-inflammatory drugs, autoimmune disease	survival rates	Plasma interleukin-8 blood samples from central venous and jugular bulb catheter at admission	Central venous plasma level of IL-8 was significantly lower in survivors (71.00 +/- 14.17 pg/ml), than in non-survivors (111.26 +/- 16.9 pg/ml)
Smith et al. 2012(30)	United states, ? patients, 57 completing. Age 9-90 years. Inclusion: Head trauma GCS $\leq$ 8	GOS 1-2 vs 3-5	hyperglycemia serum Blood glucose >11.1 mmol/l (200 mg/dl). Early (first 48 hrs) and Late (49-168 hrs) arterial blood samples	Significant: In the Late period, an association between elevated mean serum BS and outcome was observed (133.5 +/- 5.6 mg/dL in unfavorable group vs. 115.4 +/- 4.1 mg/dL in favorable group, p=.02).
Goyal et al. 2012 (1)	United states, ? patients, 80 completing. Age >16 years. Inclusion: adult subjects with severe TBI. Exclusion: Brain injury due to other causes; associated with other tissue injury, liver disorders, renal diseases, hyperuricemias	acute mortality GOS Disability Rating Scale (DRS)	S100b in serum within 24 hours	higher S100b concentrations had higher acute mortality (p<0.001) and with worse GOS scores (p=0.002) and Disability Rating Scale (DRS) scores (p=0.039) 6 months post-injury.
Olivercrona et al. 2012 (64)	Sweden, ? patients, 21 completing. Inclusion: verified head injury, GCS $\leq$ 8, age 15-70 years, an initial CPP $\geq$ 10 mmHg. Arrived within 24 hours. Exclusion: penetrating head injuries, pregnant or breastfeeding women. initial CPP < 10 mmHg were regarded as dead on arrival	GOS 3 and 12 months 1-3 vs 4-5 1 vs 4-5	S-100B and NSE was sampled twice daily during the first five days	S-100B & NSE higher GOS 1 at 3 and 12 months compared with GOS 2-5 (p < 0.01). Nostatistically significant difference in S-100B & NSE when results were dichotomized into unfavorable (GOS 1-3) and favourable (GOS 4-5) outcome.
Saadat et al. 2012 (44)	Iran, 122 patients, 116 completing, all children and adolescents admitted to the emergency room and ICU with blunt trauma with severe traumatic brain injury (GCS $\leq$ 8), who were younger than 18 years of age, admitted to the emergency room within the first 12 hours of injury. Exclusion: died within 48 h of admission or had a history of diabetes mellitus	mortality rate, hospital length of stay (LOS)	Admission and daily BS, up to the end of the third day of ICU peripheral vein samples	Persistent high BS in first 2 and 3 days: 5, 10-fold increased risk of mortality, respectively (P < 0.001 for both) BS of survivals not correlated with LOS in, whereas BS of who died inversely correlated with LOS in days 1 and 2 (P = 0.014 and P = 0.039, respectively).
Prisco et al. 2012 (73)	United states, ? patients, 39 completing. Age <15 years. Inclusion: had a head CT, had blood collected for biomarker measurement within 24 hours	GOS score (1=good outcome, 5=death). 3-4 months 6-8 months	UCH-L1, SBDP145, NSE, S100B, MBP	Significant correlations: unfavorable: Higher concentrations of both UCH-L1 and SBDP no correlation between NSE, S100B, or MBP and outcome.
Matsushima et al. 2012 (40)	United states, 282 patients, 109 completing. Age 23-55 years; Inclusion: Abbreviated Injury Scale of head of 3 to 5, SICU length of stay >2 days) TGC protocol instituted during the entire ICU stay. Exclusion: age $\leq$ 13 years, brain tumor, previous brain injury, encephalitis/meningitis, brain abscess, vascular malformation, MS, Alzheimer, HIV, encephalitis, or stroke; difficult F/U including homeless or incarcerated patients; mortality during the initial hospital stay	GOS 6 months	Hourly glucose level was measured using finger capillary blood sampling	Higher mean glucose levels (OR: 1.28 for a 10-mg/dL increase; P = .05); significantly associated with lower GOSE score. (Mean glucose of 130 mg/dL has 1.28 times higher odds of a lower GOSE score compared with mean glucose 120 mg/dL.
Liu et al. 2011 (9)	China, ? patients, 84 completing. Age: 18-85 years. Inclusion: head injury, TBI. Exclusion criteria include patients with complex trauma in trunk and limbs, hematologic disorders, cancer and patients on sedation	deteriorated or improved outcomes (GCS) mortality	EPC, BS Morning fasting venous blood 1, 4, 7, 14, and 21 days	number of circulating EPCs was significantly lower in who died p < 0.01. BS was significantly higher in who died or deteriorated

Author(s)	Patient Characteristics	Outcome	Factor	Result
Maaty et al. 2011 (28)	Egypt, ? patients, 100 completing. Age: 22-71 years. Inclusion: all patients who had sustained TBI either alone or as a part of multiple trauma. Exclusion: brain death, penetrating injury, infection and possible diseases that alter the parameters.	Mortality	serum S100 protein, NSE, GFAP venous blood samples	Significant: correlations: Non-survivors higher admission serum S100 protein and GFAP levels; serum NSE was non-significantly higher in non-survivors
Salehpour et al. 2011 (59)	Iran, ? patients, 52 completing. Age >18 inclusion: 52 patients with severe head trauma (GCS ≤ 8). Patients with major accompanying trauma were excluded.	GOS mortality 6 months	platelet count, PT, PTT, INR	Significant negative correlations were found between PT, PTT, and INR with GOS scores and mortality Significant positive correlations were found between the platelet count and GOS scores and mortality
Žureket et al. 2011 (64)	Czech Republic, ? patients, 63 pediatric patients completing, age 0–19 years old. Inclusion: TBIs, maximum of 12 h before admission. TBIs were verified by computerized tomography (CT). Exclusion: whose parents (legal guardians)	GOS 1–3 vs 4–5	NSE, S100B, GFAP, pNF-H, secretagogin and Hsp70 Average within 6 days Venous blood	Significant: correlations: unfavorable: S100B, NSE and GFAP levels (p < 0.001) not significant: pNF-H, secretagogin and Hsp70
Stein et al. 2011 (60)	United states, ? patients, 24 patients completing. Age 18–83 years. Inclusion: admission within the first 6 h, GCS < 9, placement of a clinically indicated ICP monitor. TBI confirmed by CT. Exclusion: multisystem trauma, nonsurvivable injury	GOS 1–4 vs 5–8	Cytokine levels (IL-1B, IL-6, IL-8, IL-10, and TNF-alfa) admission + twice daily for 7 days arterial blood samples	median daily IL-8 levels: associated with poor outcome, the median serum values of others were not different between 2 groups
Fraser et al. 2011 (13)	United states, ? patients, 24 patients completing. Age 18–83 years. Inclusion: admission within the first 6 h, GCS < 9, placement of a clinically indicated ICP monitor. TBI confirmed by CT. Exclusion: multisystem trauma, nonsurvivable injury. Canada, ? patients, 27 pediatric patients completing, age 1–17 years old, Inclusion: age 1–17 y, TBI GCS ≤ 8, CT scan showing acute brain injury, need for mechanical ventilation. Exclusion: enrolled > 8 hrs post injury, refractory shock, suspected brain death, intentional injury, prolonged cardiac arrest, high cervical spinal cord injury, severe neurodevelopmental disability before the injury, brain injury secondary to a gunshot wound, acute isolated epidural hematoma, or pregnancy.	PCPC score at 6 months	GFAP daily arterial blood samples	Serum GFAP concentrations correlated with PCPC scores (p < .008) GFAP concentrations on PICU day 1 associated with a good outcome (PCPC score of = < 2 (normal to mild disability)
Mondello et al. 2011 (27)	United states, ? patients, 81 completing. Age ≥ 18 years; Inclusion: GCS eight or less. Exclusion: younger than 18 years; no history of trauma; known dementia, chronic psychosis, or active CNS pathology; pregnant; incarcerated	GOS 1 vs 2–5	UCH-L1 and GFAP Venous blood samples at admission (median seven hours) and every six hours thereafter	UCH-L1 was the only independent predictor of death at discharge [adjusted odds ratios 2.95;], but both UCH-L1 and GFAP levels strongly predicted death 6 months post-injury
Mc Gozales-Mao et al. 2011 (57)	Spain, ? patients, 149 completing. Age 15–84 years. Inclusion: 1) Arrival within 6 h of the injury. 2) Main diagnosis of TBI. 3) Evaluation of a history of psychiatric and neurological disease. 4) Completion of a CT scan within 24 h. Exclusion: Patients with some circumstance related to elevated serum levels of S100B such as Down's syndrome, Alzheimer's disease, schizophrenia, bipolar disorder, multiple sclerosis, melanoma, glioblastoma	GOS, mortality	S100B at 6, 24, 48 and 72 hours	Significant: correlations: between the GOS S100B: a negative and significant correlation for all the sampling times. The average levels of S100B at 6, 24, 48, and 72 h in all cases, significantly higher in the exitus group compared with the survivors (p < 0.05)
Greuters et al. 2011 (21)	Netherlands, 247 patients, 107 completing, age > 18 years. Inclusion: TBI, GCS of 8 or less who survived for 5 days or more. Exclusion: medical record lacked complete data, or if the GCS improved to 13 or higher over the initial 24 hours	hospital mortality	APTT, INR, PT, platelet count, within 72h (Coagulopathy defined as a PTT > 40 seconds and/or INR > 1.2 and/or a platelet count < 120 * 10 <sup>9</sup> per liter)	both coagulopathy upon ED arrival and during the first 24h: an independent prognostic factor for unfavorable outcome (P = 0.04) and (P = 0.003)
Aşıloğlu et al. 2011 (2)	Turkey, ? patients, 65 completing. Age < 18 years. Inclusion: under 18 years of age and were admitted to the PICU severe head trauma, defined by an initial GCS < 8. None of these children received intravenous infusion of glucose or steroid therapy and none had a previous history of diabetes mellitus or endocrine disease. Exclusion: patients without a documented blood glucose value at the time of admission	GOS at hospital discharge and 6 months	levels of blood glucose venous blood sample	mean glucose level of the patients in bad outcome group at hospital discharge and 6 months was found to be significantly higher p = 0.01, p = 0.04, respectively



Author(s)	Patient Characteristics	Outcome	Factor	Result
DeOliveira et al. 2011 (70)	Brazil, ? patients, 44 patients completing, age 18–64 years old. Inclusion: severe TBI (GCS 3–8 at emergency room admission), without previous history of neurological or psychiatric disease, transferred to the trauma ICU within 24 h of the head injury	GOS 1–3 vs 4–5 at the ICU discharge survivors/non-survivors Venous blood samples	Plasma VWF antigen (VWF:Ag) levels at admission, 24 h, 7 days total serum protein Venous blood samples	Significant: correlations: initial VWF, Ag; nonsurvivors ( $p < 0.001$ ) not significant 1. initial plasma VWF concentrations and outcome 2. total serum protein between survivors and Non-survivors
Wagner A.K et al. 2011 (42)	United states, ? patients, 117 completing. Age 16 - 75. Inclusion: severe TBI GCS $\leq$ 8 with positive findings on head CT, required an EVD, and had at least two serum samples available for analysis. Exclusion: penetrating brain injury or prolonged cardiac or respiratory arrest at injury previous history of pituitary or hypothalamic tumor, history of breast cancer requiring chemotherapy treatment/tamoxifen, history of prostate cancer requiring orchiectomy or LH suppression agents, or untreated thyroid disease	GOS 1 vs. 2/3 vs. 4/5	Serum cortisol, testosterone, progesterone, and estradiol at ~7:00 a.m. daily	High estradiol and testosterone associated with mortality ( $p=0.02$ and $p=0.03$ , respectively), and GOS. significant effect of LH FSH, progesterone on mortality through their association with estradiol ( $p=0.04$ ). Estradiol mediated progesterone associations with ( $p=0.04$ ). Serum cortisol was not associated with mortality or GOS
Jain et al. 2010 (67)	India. ? patients, 63 patients completing, age: no age exclusion. Inclusion: Isolated head injury patients with no extracerebral injury. Exclusion: Any patient revealing extracerebral injury, either at admission or at subsequent follow-up	Outcome specified as (1) dead (2) severely disabled (3) Moderately disabled (4) good	Serum LDH at admission and serially on 5 days arterial blood sample	significantly: high mean serum LDH in patients with poor outcome
Melo et al. 2010 (51)	France, 315 patients, 286 completing. Age 1 month to 17 years Inclusion: severe TBI GCS $\leq$ 8	Mortality & GOS 2–3 vs 4–5 6 months	hyperglycemia (blood glucose levels $\geq$ 200 mg/dl) Blood arterial samples	Significant: correlations: Mortality rate with high BS ( $p < 10^{-4}$ ) A good outcome in 71% Normoglycemic patients compared with 32% in other groups ( $p=0.03$ )
Samit et al. 2010 (53)	India; ? patients, 40 completing, age 15 -50 years. Inclusion GCS $>$ 9. admitted within 6 hours of injury, no gross systemic injury. Exclusion: gross systemic injury, compound head injury, comorbid illness, or cancer, psychiatric or other neurological illnesses, shock, post-resuscitation, patients outside the time frame	GOS 1–3 vs 4–5 3 months	serum S-100B and NSE days 0, 3, 5. Venous blood samples	Significant: correlations; A strong statistical significance exists between day 0 serum levels of biochemical markers and outcome assessment ( $P = .003$ between GOS and S-100B and $P < 0.001$ between GOS for NSE)
Melo et al. 2010 (38)	France, ? patients, 315 completing. Age 1 month to 17 years. Inclusion: children $<$ 17 years of age who presented with a severe TBI defined by an initial GCS $\leq$ 8. Exclusion: non-accidental injury or initial GCS $>$ 8	mortality	oxygen saturation, blood glucose levels, PT at admission & every 6 hours	1. inadequate SaO <sub>2</sub> increased the incidence of death 3-fold (odds ratio = 1.67) 2,3. hyperglycemia (odds ratio = 6.14) and severe coagulation disorders (odds ratio = 3.10) increased the risk of death 5 times
Jackson da Silva Gullo et al. 2010 (20)	Brazil, ? patients, 83 patients completing, age $>$ 16 years old, Inclusion: severe TBI in ICU GCS $\leq$ 8 gunshot injury and patients who evolved to brain death before 24 hour of admission were excluded	Hospital mortality	serum PTX3 level leukocytes count	Elevated PTX3 significantly associated with mortality ( $P < 0.04$ ) no differences in the leukocytes count
Kan et al. 2009 (14)	Malaysia, 167 patients, 146 completing, age 2 to 16 years. Inclusion: head injury, severe TBI GCS $\leq$ 8. Exclusion: lost upon follow up	PCPC scores 6 months	serum glucose, PT and a PTT ratio, INR, platelet counts and TWBC upon admission	Significant: correlations; serum glucose level ( $P = 0.001$ ), TWBC counts ( $P = 0.04$ ), aPTT ratio ( $P = 0.03$ ), PT ratio ( $P < 0.001$ ), INR ( $P = 0.009$ )
WhaSook et al. 2009 (72)	Republic of Korea, 190 patients, 82 TBI. Age $>$ 18 inclusion: adult $>$ 18 years, TBI or hemorrhagic stroke who were admitted within 24 hours of injury at the ICU	GOS mortality 6 months	Hct, PaO <sub>2</sub> , PaCO <sub>2</sub> , serum osmolality, pH, total cholesterol and glucose levels on admission	The identified predictors of mortality for patients with TBI: PaO <sub>2</sub> ( $F = 11.83$ , $p = 0.00$ ), PaCO <sub>2</sub> ( $F = 4.40$ , $p = 0.02$ ) on admission Others: non-significant
Seif El-Deenet al. 2009 (4)	Egypt, ? patients, 40 completing, age 26–61 years. Inclusion: head injury and presentation within 6h. Exclusion: history of Alzheimer's disease, Down's syndrome, multiple sclerosis, schizophrenia, depression, cerebral stroke, spinal cord injury were excluded	Expanded Disability Status Scale (EDSS) 6 months unfavorable :EDSS $\geq$ 5	Serum S100 B Protein venous blood sample	Significant correlation: Serum S100 B increased in non-survivors and in patients with unfavorable outcome

Author(s)	Patient Characteristics	Outcome	Factor	Result
Helmyet al. 2009 (50)	United Kingdom, 367 patients, 327 patients completing. Age $\geq 16$ years. Inclusion: head trauma	GOS 1-3 vs 4-5	Na, potassium, glucose, alb, corrected calcium, phosphate, serum osmolality, creatine kinase, magnesium, Hb, WBC,PT,APTT, CRP	Significant: raised serum glucose, low haemoglobin The remaining five variables only had a statistical relationship with outcome via at least one other variable.
Melo et al. 2009 (54)	France, 58 patients, age below 6 years. with severe head trauma defined by an initial GCS $\leq 8$	mortality	Elevated blood glucose & coagulation Disorders in first 48 h defined as a BS $\geq 200$ mg/dL & PT <50%	Significant correlation: glucose level $\geq 200$ mg/dL with mortality rate (p=0.02) and coagulation disorders with mortality rate (p=0.02).
Griesdale et al. 2009 (36)	Canada, 273 patients, 170 patients completing. Mean age, 38 years. Inclusion: admitted to the ICU severe TBI (GCS $\leq 8$ ). Exclusion: obeying within 12h, indicating a non-severe TBI, died within 12 hour, non-traumatic etiology of the neurologic injury or concomitant high cervical spine injury	hospital mortality	Hyperglycemia was defined as serum blood glucose >11.1 mmol/l (200 mg/dl). Venous blood samples	Significant correlation: Any episode of hyperglycemia (>200 mg/dl) with 3.6-fold increased risk of hospital mortality
Liu et al. 2009 (35)	United states, 429 patients, 380 completing, age >18 years. Inclusion: TBI, >18 years of age, admitted to the ICU within 24 h of injury, and required ICU care for more than 24 hour. Exclusion: a glucose level reading was not recorded within the first 24 h	hospital mortality	Blood Glucose During the first 5 consecutive ICU days Venous blood samples	Non-survivors had significantly higher glucose levels on admission and first day glucose cut-off values of 135 mg/dl for admission and 160 mg/dl for day-1 peak
Salehpoor et al. 2009 (15)	Iran, ? Patients, 96 completing. Age 3-75 years. Inclusion: severe head injuries admitted to our neurosurgical department and laid up in the trauma and ICU sections	GOS 1-3 vs 4-5 at discharge and 6 months	serum glucose levels	Significant: correlations: between good outcome (GOS=4,5) and poor outcome (GOS =1,2) and mean blood sugar amount (p=0.006)
Nyle'n et al. 2008 (52)	Sweden, 222 patients, 73 completing, age below 15 years. Inclusion: severe TBI admitted to NICU, Reaction Level Scale (RLS) $\geq 4$ , corresponding GCS $\leq 8$ , therapeutic indication to monitor ICP, Need for ventilator, living in Sweden, first blood sample obtained $\leq$ day 2	GOS 1-3 vs 4-5	Serum levels of S100B, S100A1B and S100BB Venous blood samples	Patients with an unfavorable outcome had significantly increased maximum levels of S100B (p<0.05), S100A1B (p<0.01) and S100BB (p<0.01)
Rainey et al. 2008 (63)	United kingdom, ? Patients, 100 completing. Age: 16-86 years. Inclusion : aged $\geq 16$ years with severe head trauma, admitted to ICU within 24 hours of injury. Exclusion: Late referrals to ICU ( $\geq 24$ h)	GOS 1-3 vs 4-5-3-months	S100b 24 harterial blood samples	Significant: correlations: S100b higher in unfavorable outcome (p=0.000) & in who died (p=0.003)
Meier et al. 2008 (16)	Switzerland, 320 patients, 228 patients completing, age 18-81 years Inclusion: severe TBI treated on ICU >24h. ICP probe placed in first 8 hours. Exclusion: died in first 24h, without ICP probe, incomplete data	Mortality and length of ICU stay	Arterial blood glucose levels during the first 2 weeks	Non-significant: correlations: Overall mortality rates and ICU stay with BS
Guzel et al. 2008 (24)	Turkey, ? Patients, 169 completing. Age 1 to 75 years. Inclusion: isolated head injury Exclusion: major health problems: DM, renal or cardiac failure, CNS diseases, and bleeding disorders, concomitant extracranial injury, spinal cord damages, alcohol intoxications, injury more than 24 h ago, Hx of neurological or neuropsychiatric disorders, alcohol, drug, substance abuse, previous TBI	outcome within the first 24-48 h after trauma (short-term outcome), and GCS and mortality 30 days after trauma	Serum NSE ,the first 2(NSE1), 24 (NSE2), 48 (NSE3)hours venous blood samples	The levels of NSE were significantly higher in who died in 30 days after trauma or GCS lower than or equal to 8 (p<0.001)
Lilianget al. 2008 (18)	Taiwan, ? Patients, 44 completing. Age >18 years. Inclusion: severe closed head injury admitted to NICU, within 6 h of injury Exclusion: age <18 y, unavailability of blood sample or informed consent or outcome data of 6-mo. neurologic disabilities prior to injury, brought more than 6 h after injury, prolonged cardiac arrest, high cervical spinal cord injury, died from controllable hemorrhage or multiple life-threatening injuries	GOS 1-3 vs 4-5 6months	tau protein level, Venous blood samples	Significant: correlations: high serum tlevels (P $\frac{1}{4}$ 0.043) were the independent prognostic factors for a poor outcome
Salim et al. 2008 (63)	United states, 1,221 patients, 420 completing, age >18 years. Inclusion: blunt trauma with severe TBI (head Abbreviated Injury Scale score [AIS] $\geq 3$ ) admitted to the Surgical Intensive Care Unit (SICU); with serial cTnI measurements. Exclusion: non-survivable head injuries (head AIS score >6), significant extracranial injury (AIS score >3), died within 24 hours.	hospital mortality	serial cTnI measurements during the first 24 to 48 hours	Significant correlation: Elevated peak troponin with mortality (p< 0.0001); Whereas admission troponin elevation was not (p=0.01).
Mowery et al. 2007 (2)	United states, 977 patients, 160 completing. Age: 38-73 years. Inclusion: All critically ill, mechanically ventilated patients with IV insulin administration for glucose above 110 mg/dL and repeating 2-hour glucose sampling and insulin adjustments.	hospital mortality	2-hour glucose sampling	The median blood glucose was statistically different but not clinically different among the patients who lived and died (114; interquartile range, 109-132 vs. 118; 111-136, p = 0.01).

Author(s)	Patient Characteristics	Outcome	Factor	Result
Beers et al. 2007 (6)	United states, ? patients, 30 completing. Age <3years. Inclusion: head injury, severe TBI GCS=< 8). admitted within 3 hours of injury	GOS IQ measure	NSE, S100B, and MBP	NSE, S100B, and MBP levels significantly correlated with poorer outcome. p<0.05
Llompert-Pouet al. 2007 (37)	Spain, ? patients, 50 completing. Age: 16–77 years Inclusion:isolated TBI admitted to ICU, intubated, mechanically ventilated, and had ICP monitoring. Exclusion: <16 years, lack of indication to measure ICP, injury of other organs, probability of survival <48 hours, previous use of drugs known to affect cortisol secretion (corticosteroids, etomidate), septic shock.	ICU survival rates	plasma ACTH levels, baseline and stimulated serum cortisol after a high-dose corticotrophin stimulation test	-low ACTH values (<9 pg/mL) : lower mortality (p<0.0001) -low plasma ACTH +higher survival: increased ICU length of stay (p<0.03). -No significant differences with other related variables
Yurgel et al. 2007 (3)	Brazil ? patients, 41 completing, age 18-64 years. Inclusion: 41 male victims of severe TBI (GCS 3–8 at the emergency room admission, without previous history of neurological or psychiatric Disease. who transferred to the ICU within 24 hours of the head injury	GOS 1 vs 2–5	Plasma DNA at study entry&24 h after	significant correlation: higherDNA concentrations and fatal outcome 24 h after study entry (p=0.03)
Bayir et al. 2006 (10)	Turkey, ? patients, 15 completing,age 2-73 years. Inclusion: isolated head injury, admitted within 3 hours of injury. Exclusion criteria were multisystem trauma, existing coagulation disorders and presentation after the first three hours	Mortality	platelet number (Plt), PT, PTT, fibrinogen, fibrin degradation products (FDP) and D-dimer levels venous blood samples	Significant: correlations; Mortality with PT, FDP and D-dimer (P<0.001, P<0.001 and P<0.001, respectively). And with Plt (p=0.007) Not Significant: PTT(p=0.1)
Naeimi et al. 2006 (45)	Austria, ? patients, 45 completing. Age >16 years. Inclusion: head injury, admitted within 3 hours of injury	1.minor and severe head injuries 2.a cerebral pathological finding in CT scans	Serum S-100B and NSE proteins Venous blood samples admission and every 24 h for 7days	a significant difference between the S-100B serum concentration and the two groups-minor head injuries and severe head injuries. A statistically significant correlation was observed between an increase of S-100B and NSE serum values and a cerebral pathological finding in CT scans
Nyle'n et al. 2006 (56)	Sweden, 222 patients, 73 completing, age below 15 years. Inclusion: severe TBI admitted to NICU, Reaction Level Scale (RLS)≥4, corresponding GCS≤8, therapeutic indication to monitor ICP, Need for ventilator. Only patients living in Sweden included. First blood sample had to be obtained on day 2 at the latest	GOS 1–3 vs 4–5 1 year	Venous blood samples for GFAP 0, 1, 2, 3, 4, 6, 8 and once in between days 11 and 14.	Significant: unfavorable outcome : (p<0.001) higher maximal s-GFAP
Salim et al. 2005 (7)	United states, 1221 patients, 834 completing, age>18 years. Inclusion: blunt trauma with severe traumatic brain injury (head Abbreviated Injury Score≥3) admitted to SICU. Exclusion: who died within 48h, non-survivable head injuries (head AIS=6), significant extracranial injury (AIS>3 for other anatomical regions)	mortality	Admission and daily blood glucose yp to 7 days	Persistent hyperglycemia significantly higher mortality (64% vi 21%, P<0.0001). Excluding deaths, relation with the hospital length of stay and intensive care unit length of stay: not significant
Jeremitsky et al. 2005 (29)	United states, 121 patients, 77 completing, age>18 years. Inclusion: TBI, GCS of 8 or less who survived for 5 days or more. Exclusion: medical record lacked complete data, or if the GCS improved to 13 or higher over the initial 24 hours	hospital mortality hospital LOS day 5 GCS	highest daily serum glucose (mg/dL) Hyperglycemia was defined as a serum glucose level of 170 mg/dL or higher	worse survival for the individuals with an HS (p < 0.03; HS were independent predictors of lower day 5 GCS, whereas HS 3–5 and day 4 GCS were related to prolonged hospital length of stay
Nelson et al 2005 (49)	Sweden, ? patients, 757 completing. Age<18. Inclusion: >18 years, evaluated within 24 hours of sustaining TBI, requiring a CT scan. Exclusion: penetrating TBIs, intentional head trauma,multisystem injuries, pelvic or lower extremity fractures, spinal cord injuries or bleeding disorders, cerebral palsy, mental retardation, developmental delay, or ventricular shunts	GOS	Serum Glucose, Creatinine, albumin, hemoglobin, and osmolality levels	Creatinine: an independent predictor of TBI outcome. Glucose, albumin, and osmolality levels were also identified as predictors, depending on analysis method. A worse outcome related to increasing osmolality. hemoglobin was not found significant when adjusted for post-resuscitation GCS
Pelinka et al. 2005 (29)	Germany. ? patiens, 92completing, age? Med 39 years. Inclusion: TBI with or without multiple trauma <12h before admission verified by CT	GOS 3 months 1 vs 4-5	Venous blood for GFAP and S100B daily	GFAP & S100B: lower in GOS 4–5 than in GOS 1 (p < 0.0005). GFAP, but not S100B, was low-er in GOS 4–5 than in GOS 2–3 (p < 0.05)
Salehpoor et al. 2005 (15)	Iran, ? patients, 30completing. Age 9-90 years; Inclusion: Head trauma GCS≤8. All of them were in intensive care unit Exclusion: Multiple trauma patients were omitted	GOS 1–3 vs 4–5	LDH level Venous blood samples	Significant: meaningful relation: change of LDH level (At = 4, P<0.01).

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## Comments

The authors of this study included 63 reports including patients with 'different levels of TBI' and their 'outcome measure has been GCS after 6 months'. Even though design of this systematic review can bring up some information for the readers but there are issues important to be stressed regarding further similar future reviews; a) The question about different humoral factors effective upon the outcome of TBIs is an old issue for neurosurgeons treating emergency cases. A systematic review evaluating these elements is better to include prior publications with similar power-level from the literature and not only the bank of 8 years duration. b) For a systematic review to be of good conclusive remark, the studies with higher level of evidence and not, only cohort studies should be included in the chart. If there has been no such reports available, the power of the review would be low regarding the biases and threats to the validities and interpretation of the results. These errors are the results of flaw in either the method of selection of the studies or the procedures undertaken in gathering, interpreting and including the measures and/or disease information. c) To obviate the concordance of interpretation of information, the first step would be drawing the flow chart (lacking in this report). To evaluate the possible inter-observer errors in a limited sample of cases, drawing the chart to measure the Kappa index (also lacking here) is helpful. Including a 'Prisma' model to coordinate between entry point, case management process and functional outcome is another way to empower a systematic review. d) A systematic review can be summarized in a 'funnel chart' till the readers could beware of the level of similarity/ concordance of the data extracted from all the references in a glance (lacking). e) Including all the levels of TBI in a systematic review includes quite a very large heterogeneous group of patients with all dissimilarities of the pathophysiological changes both in CNS and in the immune responses. Evaluating all the possible factors with or without independent and confounding impact upon a single outcome variable, can be very hard both for statistical analysis and for scientific interpretation of the results. f) For discussing a systematic review, it is not enough to select a single variable and highlight the points drawn from data extracted from a large table (as it is included) but the most empowered and proven variables are better to be discussed only, otherwise misclassification of the information (regarding exposure and outcome categories) would be a common error. Anyhow, the kind researchers have done a great job preparing this excellent review for our readers, even though it would be better to name it a 'narrative review of the literature'.

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Firooz Salehpoor and colleagues showed that based on a systematic review there is strong evidence for predicting poor prognosis for six-month outcome of moderate and severe traumatic brain injury (TBI) for the high serum concentration of S100/S100B protein (17 out of 19 studies), neuron specific enolase (NSE: 9 out of 12 studies), myelin basic protein (MBP: 2 out of 2 studies in childhood), Hyperphosphorylated neurofilament (NF-H: 2 out of 2 studies in childhood), Glial Fibrillary Acidic Protein (GFAP: 7 out of 7 studies), Ubiquitin C-Terminal Hydrolase (UCHL1: 4 out of 5 studies), blood glucose levels (19 out of 22 studies), Lactate Dehydrogenase (LDH: 2 out of 2 studies), admission/increasing serum osmolarity (high sodium: 2 out of 2 studies), prothrombin time (PT: 5 out of 5 studies), partial thromboplastin time (PTT: 2 out of 3 studies), Heat Shock Protein 70 (HSP 70: 2 out of 2 studies), serum levels of interleukin (IL)-8 (2 out of 2 studies), increased circulating cell-free DNA levels (DNA: 2 out of 2 studies) (1). They found two more strong evidence of decreased platelet count (2 out of 3 studies), and decreased number of circulating endothelial progenitor cells (EPCs: 2 out of 2 studies) in poor outcome of TBI patients. They stated moderate evidence for high serum MMP9 levels as a marker of poor outcome prediction for TBI. On the other hand, there was no relation between D-dimer level and poor outcome of moderate and severe TBI in the available two studies. I would acknowledge their extensive study and the importance of their study design. I believe the systematic reviews have high impact in promotion of science and literature. However, there are several important concerns in their study: Assessing quality and susceptibility to bias is essential when interpreting primary research and conducting systematic reviews for observational epidemiological studies such as cohort studies (2). The recommended tool is STROBE guidelines for reporting observational epidemiological studies (3). For each included study in the systematic review of cohort studies, we have to perform quality assessment which has to be done based on the STROBE guideline not based on the consensus. It is the main difference between systematic review and narrative review. In the systematic review, any researcher can use guideline and evaluate if any study has high or low quality. However, in narrative review, an expert or a few experts perform their judgement based on the experience not based on the evidence. There are 22 items (the STROBE Statement) that relate to the title, abstract, introduction, methods, results, and discussion sections of articles. 18 items are common to all three study designs and four are specific for cohort, case-control, or cross-sectional studies. Our readers need

to know if in each included cohort, did authors state the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up? For matched studies, did they give matching criteria and number of exposed and unexposed? If applicable, did they explain how loss to follow-up was addressed? Did authors summarize follow-up time (average and total amount)? Did they report numbers of outcome events or summary measures over time? Did they give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval)? Did they make clear which confounders were adjusted for and why they were included? Did they report category boundaries when continuous variables were categorized? If relevant, did they consider translating estimates of relative risk (RR) into absolute risk for a meaningful time period? Did they perform analyses of subgroups and interactions, and sensitivity analyses? Did they summarize key results with reference to study objectives? Did they discuss limitations of the study, taking into account sources of potential bias or imprecision? Did they discuss both direction and magnitude of any potential bias? Did authors give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence? Did they discuss the generalisability (external validity) of the study results? Did they give the source of funding and the role of the funders? Authors mentioned databases were searched from 2005 to 2014. There is no included paper in 2014 and the standard in systematic review is to write the exact date or month (not year) of systematic review (4). There is no flow diagram of studies based on the PRISMA statement; therefore we do not know how many papers selected from each database; and how many duplicates were removed; how many abstracts were screened; how many and why full papers were excluded. Finally, I would suggest the following title for this so called systematic review: A non quality assessed literature review of serum markers for moderate and severe traumatic brain injury based on the published papers from 2005 to 2013.

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