



REVIEW

Head injury outcome prediction: A role for protein S-100B?

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Summary

Introduction: Prediction of the likely outcome of head injury from the outset would allow early rehabilitation to be targeted at those with most to gain. Clinical evaluation of a head injured patient may be confounded by intoxicants such as alcohol. Imaging modalities are insensitive (CT) or impractical (MR) for screening populations of such patients. A peripheral marker that reflected the extent of brain injury might offer an objective indication of likely adverse sequelae. This review evaluates the evidence for Protein S-100B as such a marker.

Methods: A search of published literature revealed 18 studies designed to evaluate the relation between serum S-100B and measures of outcome after head injury.

Results: A cut-off point of 2.5 µg/L is related to dependent disability in those presenting with low conscious level, and may be a specific test for this. There appears to be a relation between initial serum S-100B concentration and measures of disability as well as post-concussion symptoms for those with seemingly mild injuries. There does not appear to be a relation between S-100B and measures of neuropsychological performance.

Conclusion: Patients with high levels of S-100B at initial assessment (>2.5 µg/L) may represent a high risk group for disability after head trauma.

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Introduction

Head injury severity affects prognosis. A prompt and full recovery should be more likely following a mild head injury, than an injury classified moderate, and, in turn, one classified as severe. Classification of head injury severity has been based on conscious level, enumerated by the Glasgow Coma Scale (GCS).³⁵ This approach has been validated by large scale studies showing a higher risk of intracranial haematoma requiring evacuation with low GCS scores recorded at initial assessment.^{22,23} This complication, however, is experienced by only 0.5% of head injured patients presenting to health care services.^{22,36} It is much more likely that a patient experiences disabling symptoms without the need for surgery, although estimates of incidence vary.^{38,41} The highest possible score on the Glasgow Coma Scale accounts for around 88% of head injured patients presenting to hospital.³⁹ The reported rate of disability, up to 47%,³⁸ implies that disabling late sequelae cannot be confined to those with impaired conscious level at initial assessment. A taxonomy of severity, and thereby prognosis, based on GCS score is therefore limited.

Identifying a high-risk group for adverse outcome after head trauma would allow after care to be targeted at those with most to gain. One approach has been to search for objective indicators of brain tissue damage, as the clinical assessment of a head injured patient can be confounded by intoxication by alcohol or street drugs.³ A comparison of the rate of scan abnormality, around 6% in unselected head injury patients^{11,33} and estimates of the incidence of head injury sequelae [23–47%]^{38,41} suggest that CT would not be sensitive enough for this purpose. Magnetic resonance imaging has practical and cost limitations as a first line test for the extent of brain injury after trauma. A blood test that reflects the degree of disruption to brain architecture might be such an indicator. The aim of this review is to evaluate the use of protein S-100B, the potential marker most studied thus far, for clinical use in the assessment of the head injured patient.

Methods

A review of published literature evaluating relations between S-100B and outcome of head injury was performed as follows:

- Medline from 1966 to December 2005 and Embase from 1980 to December 2005 were searched using the Ovid web-based interface using the following search terms: {Exp S-100\$ OR S100\$ OR exp biological markers OR serum markers m.p.} AND {Exp craniocerebral trauma OR head injury m.p. OR exp brain injury or brain injury m.p. or brain trauma m.p.} LIMIT {human}.
- Cochrane database.
- Bibliographic search of relevant papers from the reference section of those papers identified by initial database searches.

The abstracts were evaluated, and those papers directly relevant to this review, i.e. those designed to evaluate relations between serum S-100B level and any measures of outcome after head injury, were appraised in more detail.

The studies identified are summarised in Tables 1–3.

Results

This search yielded 18 studies. These are sub-classified into three groups to rationalise comparisons:

- Pilot studies.^{13,44} (Table 1).
- “Minor” head injury studies^{14,29,15,12,39,9,30,34,8,31,32} (Table 2).
- “Severe” head injury studies^{46,28,16,6,21} (Table 3)

Pilot studies

The first study of protein S-100B as a potential serum marker for head trauma, by Ingebrigtsen and co-workers, showed that patients with detectable serum levels after mild injury were hospitalised 2 days longer than those without.¹³ This outcome

Table 1 S-100B and head injury outcome: pilot studies

Study	Inclusion criteria	Outcome measures (follow-up rate)	S-100B cut-off used (how defined)	Findings	Main study weaknesses
Ingebrigtsen et al. ¹³ Tromsø, Norway (N = 50)	Adults GCS 13–15; LOC < 20 min; normal CT scan; admitted to neurosurgical unit	Length of hospital stay	0.2 µg/L (detection limit of assay)	Average length of stay 2 days longer for those with elevated S-100B levels	Not a validated measure of outcome
Waterloo et al. ⁴⁴ Tromsø, Norway (N = 7)	Adults GCS 14–15; LOC; normal CT scan; admitted to neurosurgical unit. Neuropsychological tests	Neuropsychological tests at 12 months (100%)	0.2 µg/L (detection limit of assay)	Comparisons made with age and sex-matched controls No significant differences found	Pilot study

measure has potential confounders, although the authors stated that these patients had no other injury to cause a prolonged stay. The same team, however, was unable to demonstrate a worse performance in a battery of neuropsychological tests performed at 12 months for those with initially raised S-100B levels in a second study of seven mildly injured patients with raised S-100B levels and age and sex-matched head injured patients without a measured rise in circulating S100B.⁴⁴

Minor injury

Eleven studies included patients with minimal impairment of conscious level (GCS 13–15).

Inclusion criteria

Most studies in this group used conscious level as the primary inclusion criterion. A range of further criteria for some studies are based on the presence and duration of loss of consciousness and amnesia coincident with injury. Most have aimed for a seemingly low risk cohort, whilst excluding the most trivial injuries. Four studies included hospitalised patients only.

Method and timing of S-100B sampling

Early studies used a radio immunoassay technique to estimate S-100B concentration in blood,^{14,15} with a detection limit of 0.2 µg/L. Subsequent studies used a luminescence immunoassay with a lower detection limit (0.02 µg/L). The later assay has enabled more sensitive cut-off points to be derived in minor head injury patients.

All studies included patients presenting within 12 h of injury, and describe a rapid release and clearance of S-100B as the reason for this. Five studies include those presenting within 6 h only. The purpose of recruiting patients in the early aftermath of injury is to reduce the confounding of S-100B concentrations by time elapsed. Savola and Hillbom went a step further and adjusted their data for this by attempting to “normalise” the serum S-100B levels for the time between injury and sampling.³⁰ They used a half-life of 120 min for this purpose (not referenced). Repeating ROC curve analysis with normalised levels, they found that the AUC was increased from 0.702 (95% CI 0.60–0.81) to 0.752 (95% CI 0.66–0.84) and the cut-off point 0.2 µg/L gave a sensitivity of 92% and specificity 41% (sensitivity 68% and specificity of 67% for unadjusted data using this cut-off point).

Outcome measures

Methods used to assess outcome can be broadly grouped as functional scores, symptom inventories and measures of neuropsychological impairment.

Table 2 S-100B and head injury outcome: mild head injury

Study	Inclusion criteria	Outcome measures (follow-up rate)	S-100B cut-off used (how defined)	Findings	Main study weaknesses
Rothoerl et al. ²⁹ ; Regensburg, Germany (N = 41)	Adults GCS 3–15; admitted to neurosurgical unit	Glasgow outcome score (GOS) at hospital discharge; 1–2 unfavourable, 3–5 good (100%)	No cut-offs used	Lower mean S-100B level for those with favourable outcome 1.2 vs. 4.9 µg/L $p < 0.0025$	Small numbers; findings of limited clinical value
Ingebrigtsen et al. ¹⁴ ; Tromsø, Norway (N = 50)	Adults GCS 13–15; LOC < 20 min; normal CT scan	Neuropsychological tests; at 3 months (72%)	0.2 µg/L (detection limit of assay)	Impaired information processing, attention and memory in those S-100B “positive”	Small numbers; clinical value of findings not clear
Ingebrigtsen et al. ¹⁵ Tromsø, Norway (multi-centre) (N = 182)	Adults admitted to neurosurgical unit GCS 13–15	Rivermead post-concussion questionnaire PCS defined as presence of three or more symptoms persisting (87%)	0.2 µg/L (detection limit of assay)	Mean number of persistent symptoms compared. S-100B +ve 4.5 S-100B –ve 3.0 ($p = 0.07$) No difference in numbers with PCS in each group	Diagnostic characteristics not given. subjective outcome measure
Herrmann et al. ¹² (N = 69)	Adults admitted to neurosurgical unit	Neuropsychological tests assessed at 6 months (42%)	Cut-off 0.14 µg/L (ROC curve)	Area under ROC curve = 0.77; sens = 65%, spec = 88%	Median sample time 27 h after trauma
Townend et al. ³⁹ (N = 148) Manchester, UK	Adults GCS 4–15; (88%GCS 15); no necessity for LOC or PTA; presentation within 6 h of injury; no exclusion for alcohol intoxication or extra-cranial injury	GOSE at 1 month (80%)	Favourable outcome GOSE 7–8 cut-off 0.27 µg/L; favourable outcome GOSE 5–8 cut-off 0.32 µg/L (ROC curve)	Cut-off 0.32 µg/L sensitivity 93% (68–100%); specificity 72% (62–90%); area under ROC curve 0.77 (0.67–0.87) for moderate and 0.89 (0.79–0.99) for severe disability	Cut-off not validated in a second cohort
De Kruijk et al. ⁹ ; (N = 107) Maastricht, The Netherlands	15 years and above GCS 14–15 with LOC or PTA presentation within 6 h of injury	Presence of symptoms at 6 months (74%)	Cut-off 0.3 µg/L. From authors' earlier study on levels in head injured patients and healthy controls	Full recovery (100%) if no symptoms at initial assessment and S-100B below cut-off	Exclusion for multi-trauma or alcohol ingestion

Table 2 (Continued)

Study	Inclusion criteria	Outcome measures (follow-up rate)	S-100B cut-off used (how defined)	Findings	Main study weaknesses
Savola and Hillbom ³⁰ (N = 199) Oulu, Finland	GCS 13–15 adults; no necessity for LOC or PTA presentation within 6 h of injury	Presence of symptoms lasting more than 1 month (86%)	Cut-off 0.2 µg/L (ROC curve)	AUC for “normalised” S-100B levels = 0.75 (0.66–0.84); sens = 92% spec = 41%	Follow-up at 8–30 months to evaluate whether symptoms lasted more than 1 month
Stranjalis et al. ³⁴ (N = 100) Athens, Greece	GCS 15 LOC or PTA < 15 min; negative CT scan; age 16–65 No extra-cranial injury	Return to work or activities within 1 week (93%)	Cut-off 0.15 µg/L (from reference range of uninjured patients in published literature)	S-100B level only predictor of outcome; sensitivity 74%; specificity 80%	99% of patients back to usual activities by 1 month
De Boussard et al. ⁸ (N = 122) Stockholm, Sweden	GCS 14–15 Adults LOC < 30 min PTA < 24 h Presentation within 24 h	Cognitive deficit on computerised neuropsychological tests at 3 months (80%)	Cut-offs 0.15 µg/L S100B; 0.085 µg/L S100A1B; (97.5 percentile of non-injured controls)	No relation found between S-100B or S-100A1B and cognitive impairment	Median time to sampling not recorded
Stålnacke et al. ³¹ (N = 88) Umeå, Sweden	GCS 13–15; adults LOC < 30 min; hospitalised patients; first blood samples taken 3 h (±2.2) Second at 10.3 (±3.3)	Post-Concussion symptoms, disability (RHFUQ), Life satisfaction (LiSat-11) at 1 year (78%)	Not used	S100 (OR 10 CI 1.46-69) for each 1 µg rise, nausea and dizziness on admission significant predictors of disability in logistic regression model	Included intoxicated patients
Stapert et al. ³² (N = 50) (with 56 controls) Maastricht, The Netherlands	GCS14–15 PTA < 1 h LOC < 15 min presentation within 6 h of injury	Cognitive function and memory deficit on neuropsychological screening at 13 days, range 7–21 days (100%)	Cut-off 0.22 µg/L; median split	No significant difference in memory performance OR 0.3–10.1) and cognitive speed (OR 0.1–3.2) in those with higher S-100B levels	No significant difference between memory and cognitive performance in injured and non-injured controls (OR 0.7–19.2 and 0.7–54, respectively)

Table 3 S-100B and head injury outcome: severe head injury

Study	Inclusion criteria	Outcome measures (follow-up rate)	S-100B cut-off used (how defined)	Findings	Main study weaknesses
Raabe et al. ²⁸ Leipzig, Germany (N = 82)	Adults initial GCS \leq 8; admitted to neurosurgical unit.	GOS at 6 months; 1–3 unfavourable, 4–5 good (100%)	2.5 μ g/L (ROC curve analysis)	Sensitivity for detecting GOS < 4 = 44%, specificity 97%, PPV = 94%, NPV = 72%	Small study. No confidence intervals given. Cut-off requires validation in a second cohort
Woertgen et al. ⁴⁶ ; Regensburg, Germany (N = 44)	Adults initial GCS \leq 8; admitted to neurosurgical unit.	GOS at 11 months; 1–3 unfavourable, 4–5 good (100%)	2.0 μ g/L (not defined)	Sensitivity for detecting GOS < 4 = 82%, specificity = 84%, PPV = 87%, NPV = 77%	Small study. No confidence intervals given. Cut-off requires validation in a second cohort
Jackson et al. ¹⁵ London, UK, (N = 30)	Severe multi-trauma with head injury; all anaesthetised adult patients	(GOS) at 6 months; 1–3 unfavourable, 4–5 good (87%)	No cut-offs used	Correlation between outcome and S-100B level at admission $p = 0.0155$	Small numbers; correlation of limited clinical use. Biased sample
Chatfield et al. ⁶ ; (N = 20); Cambridge, UK	Adults sedated patients on critical care unit	Glasgow outcome score at 6 months (favourable outcome GOS 4–5) (100%)	Not used	Significant difference in day 1 S-100B level between those with favourable and unfavourable outcome. All those with S-100B >2.5 μ g/L had GOS 3 or less	Small numbers
Li Ning et al. ²¹ (N = 40) Shanghai, China	Age range not specified GCS 8 or less; no severe extracranial injury within 12 h of injury	GOS at 6 months 4–5 favourable 1–3 unfavourable (100%)	Cut-off 2 μ g/L (ROC curve)	Sensitivity 72%; specificity 91%; relative risk 4.33	Small numbers

1. Dead
2. Vegetative state
3. Severe disability
4. Moderate Disability
5. Good recovery

Figure 1 The Glasgow outcome scale.

Length of follow-up

The time point at which outcome was assessed varied between studies from hospital discharge and 1 week at the earliest to 1 year.

Findings

Ingebrigtsen and co-workers followed up their initial work with a study of the relation between serum S-100B level and neuropsychological function in a group of 50 patients with normal CT scan after injury.¹⁴ They found a trend towards impaired performance on a battery of neuropsychological tests, with significant differences in results of subtests measuring visual memory and information processing speed.

Rothoerl and co-workers used the Glasgow Outcome Score (GOS) to assess outcome (see Fig. 1). They found a significant difference between the mean S-100B levels of those with favourable and adverse outcomes.²⁹ They did not, however, describe whether any patients with an adverse outcome were S-100B “negative”. These data are important if S-100B is to be considered as a “rule out brain injury” modality.

A Scandinavian multi-centre collaboration used the Rivermead Post-concussion Questionnaire

(RPQ),¹⁵ and concluded that the Post-concussion Syndrome (PCS) was present if three or more symptoms persisted. They found no overall statistically significant difference between the S-100B levels of patients with PCS compared to those without.

A study from Herrmann and others included patients admitted to a neurosurgical unit after head injury.¹² The selection criteria for such admission were not given, but there was a predominance of those with higher conscious level (median GCS score 13). They assessed the accuracy of outcome prediction using Receiver Operator Characteristics (ROC) curve analysis.¹ They defined an unfavourable outcome as one characterised by a patient performing less well than one standard deviation below age-adjusted normal data for three of seven cognitive domains at 6 months. They did not state whether this end-point is validated. They found the area under the curve (AUC) to equal 0.77. They used a cut-off of 0.14 µg/L to divide their data, and at this level found S-100B to have a sensitivity of 65% and a specificity of 90%. Confidence intervals were not given.

Townend and others studied 148 predominantly mildly head injured adults (including intoxicated patients and those with extra-cranial injury) and showed a relation between initial S-100B concentration and neurological outcome using the Extended Glasgow Outcome Score (GOSE see Fig. 2).^{39,18} The AUC, with data dichotomised at GOSE four, was 0.89 (95% CI 0.79–0.99). They found S-100B to be the only predictor of outcome, in a regression model with age, gender, loss of consciousness, amnesia and GCS less than 15. A cut-off point of 0.32 µg/L detected 93% (95% CI 68–100%) of the most disabled after injury (GOSE < 5).

As with all studies that describe the diagnostic characteristics of a clinical variable in a cohort of

- | | |
|---|--|
| 1 | Dead |
| 2 | Vegetative state |
| 3 | Lower Severe Disability-completely dependent on others |
| 4 | Upper Severe Disability- dependent on others for some activities |
| 5 | Lower Moderate Disability- unable to return to work, or participate in social activities |
| 6 | Upper Moderate Disability- return to work at reduced capacity, reduced participation in social activities. |
| 7 | Lower Good Recovery- good recovery with minor social or mental deficits |
| 8 | Upper Good Recovery |

Figure 2 The extended Glasgow outcome score.

patients, based on cut-off points derived from the same cohort, caution in interpreting these results is required. The sensitivity will be the best possible for that group, and results will need validation in a second cohort if they are to be generalised.⁴² This effect applies to all the studies with diagnostic methodology in this review.

de Kruijk and co-workers studied a series of 103 patients attending the Emergency Department after head injury, excluding patients with multi-trauma and suspected alcohol intoxication.⁹ They found that if patients had no symptoms at initial presentation then 78% would have fully recovered at 6 months. Patients with no symptoms and S-100B level of less than 0.3 µg/L all recovered. The authors cautioned the reader about the possible confounding of their results by sample size.

Stranjalis and co-workers included only patients who were fully conscious at initial assessment and some without loss of consciousness or amnesia.³⁴ They used return to work or usual activities at 1 and 4 weeks as their outcome measure. They did not specify how this was ascertained for those not in work (32% of their sample). Only 1% of followed up patients had an adverse outcome at 4 weeks. They again found S-100B to be the only predictor of inability to return to full activity at 1 week, in a regression model with age, gender, loss of consciousness, amnesia and occupation.

A study of 122 Emergency Department patients in Stockholm by de Bousard and others revealed no significant relations between S-100B, or indeed the heterodimeric form S-100A1B, which they detected using an ELISA method, and cognitive function at 3 months.⁸ The results of neuropsychological tests were considered abnormal if one test was below 2S.D. or two or more tests were below 1S.D.

Stålnacke and co-workers described the incidence of disability, symptoms and life satisfaction at 1 year.³¹ They found no association between S-100B concentration and symptoms or life satisfaction, but a significant relation between S-100B concentration and disability. They used the Rivermead Head Injury Follow-up Questionnaire (RHFUQ) to classify disability.⁷ They used any disability highlighted using this 10 item self-reporting tool as an adverse outcome (48% of patients).

Stapert and colleagues studied the sub-acute neuropsychological sequelae of mild injury.³² Impaired cognitive speed was found in 21% of patients and 2% of controls. Memory problems were found in 23% of patients and 4% of controls. They found no difference in the proportion of these patients above and the below the median split of S-100B values. They suggest that the concentration

of S-100B in peripheral blood does not reflect cognitive dysfunction after mild TBI.

“Severe” head injury

Five papers describe the relation between outcome and S-100B level following injuries associated with low GCS scores (GCS < 8).

The study by Woertgen and others found S-100B level to be a sensitive predictor of an unfavourable outcome after severe head injury.⁴⁶ It was also shown to be more sensitive than a very low initial GCS (3–5) or Marshall CT classification (sensitivity 82%, 59%, 69%, respectively). They did not mention, however, how their cut-off point was derived.

Raabe and co-workers prioritised a low false positive rate (specificity 97%, sensitivity 44%) when choosing their cut-off point using (ROC) curve analysis.²⁸ In a clinical setting where a raised level might lead one to instigate more invasive treatment, or the transfer of a potentially unstable patient for further imaging, this would be an important consideration.

The study by Jackson and co-workers included anaesthetised patients following multi-trauma. In this sub-group of head injured patients, they found a statistically significant correlation between S-100B level at initial attendance in the Emergency Department and disability scores at 6 months.¹⁶

Chatfield and co-workers found that, for 20 patients on their neuro-intensive care unit, an arterial S-100B concentration of 2.46 µg/L (± 0.32 µg/L) was associated with an unfavourable outcome, a GOS of three or less in all cases (specificity 100%). They did not report the proportion of their patients with high S-100B concentrations or the number disabled with lower S-100B estimates.⁶

Li Ning and colleagues used a cut-off of 2 µg/L, from ROC curve analysis, to divide their data set. They also found this cut-off point to be specific for disability (91%). As with all the studies of severe injury, confidence intervals were not given.²¹

Discussion

This review identified 18 papers designed to investigate the prognostic significance of circulating S-100B concentration after head trauma. Studies were variable in conduct and findings. The studies of patients with low conscious level at presentation were more similar in design than those of the mildly injured. The Glasgow Outcome Scale has been recommended for use in this population,⁵ and it was performed at 6 months in 3/5 of these studies.

This is the time point recommended by the scales originators.³⁷ Each of these studies demonstrated a significant relation between GOS scores of three or less (dependent disability) and initial S-100B concentration in blood.

The high specificity of a cut-off of 2.5 µg/L, used by Raabe and co-workers (97%), was also found by Chatfield and others and Li Ning and colleagues found a similar result (specificity 91%) for a cut-off of 2.0 µg/L. These studies included relatively small numbers, and no confidence intervals were given. The specificity at this level is despite contribution to circulating S-100B from extra-cranial sources, from damaged tissue and from hypovolaemic shock,^{2,24,25} and the variations in secondary brain injury that might befall such a patient. No study yet published in this patient group have demonstrated what initial S-100B level adds to the array of clinical information that has been accumulated during the patient's stay on intensive care and beyond. However, a patient with S-100B concentration of 2 µg/L could reasonably be considered high risk for subsequent disability.

The mildly injured sub-group have more heterogeneous study designs and findings. The variation in outcome measures used probably reflects uncertainty as to how an adverse outcome after head injury should be defined. A mixture of symptom inventories, disability scales and neuropsychological measures have been used. A range of problems, from inability to work at 1 week to a single symptom at 1 year has been used to betoken an adverse outcome. Significant relationships have been reported between S-100B estimates and measures of disability and symptoms in all but one study, but in only one of four studies of neuropsychological performance. As neither the mechanism of S-100B expression in the circulation after injury, nor indeed the pathobiology of mild brain injury complications, are fully understood it is not possible to extrapolate the implications of this.

A number of authors mentioned the rapid elimination of S-100B, and later studies include patients presenting within 6 h of injury to minimise the potential loss of sensitivity a S-100B is cleared. The biological half-life has recently been estimated at 97 min for those with GCS 15 at initial presentation.⁴⁰ The kinetics of a rapidly cleared protein would be expected to have an impact on the comparison of blood test results taken from patients presenting at varying times after injury. Loss of sensitivity of the test with time elapsed would be expected. Savola and Hillbom investigated whether adjusting for time elapsed between injury and sampling would improve the discrimination of S-100B as a test for post-head injury symptoms. They found a

small increase in the area under the ROC curve. One limitation of this technique is that by extrapolating all measured concentrations to time "zero" an assumption of S-100B rise for all patients is made. Some patients do not have a rise in S-100B as a consequence of injury.⁴⁰ "Correction" of such readings could reduce the specificity of a positive test for brain injury sequelae.

Protein S-100B is known to lack specificity for neural injury. The suggestion that it is released after extra-cranial trauma in humans has been confirmed in animal models of long bone fracture and hypovolaemic shock.^{24,26} The search for a specific marker of brain damage, therefore, goes on. Glial fibrillary acidic protein (GFAP) may have such properties.²⁷

The aim of the research presented in this review is ultimately to enable planning of head injury after-care by defining a high-risk population, thereby optimising available resources. For diagnostic style studies, where the characteristics of a test can be used to perform Bayesian analysis and yield a post-test probability of an adverse outcome, a reference standard is required. The use of such methodology gives readily understandable numerical expressions of diagnostic performance. The diagnosis of a head injury at its most basic level is straightforward, and indeed has been described thus—"any blow to the head causing a clinical diagnosis of head injury to be made".⁴³ Consequences of such a blow can be expected. There is no consensus in the biomarker literature for mild head injury as to when these become pathological in terms of severity or prolongation.

The reporting of future studies of S-100B as a diagnostic test for use in head injury, and indeed markers that may follow, should adhere to the Standards for Reporting of Diagnostic Accuracy (STARD) statement,⁴ and be adequately powered. Researchers must decide whether the limitation of S-100B in terms of specificity render such efforts worthwhile, or whether large scale studies should be reserved for novel markers that may be more specific. New markers should go through the early work presented here for S-100B before comprehensive studies could be justified.

The mechanism by which protein S-100B enters the circulation and indeed how its expression in circulating blood reflects brain parenchymal damage or blood brain barrier dysfunction is not known. This does not obviate a pragmatic approach, with adequately rigorous clinical trials allowing conclusions to be made about what an initial S-100B result means to the prognosis of the patient. At present the amassed data do not allow this.

Head injury outcome prediction has proved enigmatic.¹⁰ Protein S-100B, or indeed future putative

markers of brain damage, should be considered in studies of head injury outcome prediction if this is not to remain the case.

References

- Altman, D, *Statistics with confidence*. 2nd ed.: BMJ books. p. 110–116.
- Anderson RE, Hansson LO, Nilsson O, et al. High serum S100B levels for trauma patients without head injuries. *Neurosurgery* 2001;48(6):1255–8. discussion 12.
- Bakay RA, Ward Jr AA. Enzymatic changes in serum and cerebrospinal fluid in neurological injury. *J Neurosurg* 1983;58(1):27–37.
- Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326(7379):41–4.
- Bullock MR, Merchant RE, Choi SC, et al. Outcome measures for clinical trials in neurotrauma. *Neurosurg Focus* 2002;13(1):ECP1.
- Chatfield DA, Zemlan FP, Day DJ, Menon DK. Discordant temporal patterns of S100beta and cleaved tau protein elevation after head injury: a pilot study. *Br J Neurosurg* 2002;16(5):471–6.
- Crawford S, Wenden FJ, Wade DT. The Rivermead head injury follow-up questionnaire: a study of a new rating scale and other measures to evaluate outcome after head injury. *J Neurol Neurosurg Psychiatry* 1996;60(5):510–4. 1.
- de Boussard CN, Lundin A, Karlstedt D, et al. S100 and cognitive impairment after mild traumatic brain injury. *J Rehabil Med* 2005;37(1):53–7.
- de Kruijk JR, Leffers P, Menheere PP, et al. S-100B and neuron-specific enolase in serum of mild traumatic brain injury patients. A comparison with health controls. *Acta Neurol Scand* 2001;103(3):175–9.
- Fabbri A, Servadei F, Marchesini G, et al. Prospective validation of a proposal for diagnosis and management of patients attending the emergency department for mild head injury. *J Neurol Neurosurg Psychiatry* 2004;75(3):410–6.
- Haydel MJ, Preston CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. *N Engl J Med* 2000;343(2):100–5.
- Herrmann M, Curio N, Jost. et al. Release of biochemical markers of damage to neuronal and glial brain tissue is associated with short and long term neuropsychological outcome after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2001;70(1):95–100.
- Ingebrigtsen T, Romner B, Kongstad P, Langbakk B. Increased serum concentrations of protein S-100 after minor head injury: a biochemical serum marker with prognostic value? *J Neurol Neurosurg Psychiatry* 1995;59(1):103–4.
- Ingebrigtsen T, Waterloo K, Jacobsen EA, et al. Traumatic brain damage in minor head injury: relation of serum S-100 protein measurements to magnetic resonance imaging and neurobehavioral outcome. *Neurosurgery* 1999;45(3):468–75. discussion 475–6.
- Ingebrigtsen T, Romner B, Marup-Jensen S, et al. The clinical value of serum S-100 protein measurements in minor head injury: a Scandinavian multicentre study. *Brain Inj* 2000;14(12):1047–55.
- Jackson RG, Samra GS, Radcliffe J, et al. The early fall in levels of S-100 beta in traumatic brain injury. *Clin Chem Lab Med* 2000;38(11):1165–7.
- Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry* 1981;44(4):285–93.
- Li N, Shen JK, Zhao WG, et al. S-100B and neuron specific enolase in outcome prediction of severe head injury. *Chin J Traumatol* 2004;7(3):156–8.
- Mendelow AD, Teasdale G, Jennett B, et al. Risks of intracranial haematoma in head injured adults. *Br Med J (Clin Res Ed)* 1983;287(6400):1173–6.
- Mendelow AD, Teasdale GM, Jennett B. Avoidable factors contributing to death of children with head injury. *BMJ* 1990;300(6721):398–440.
- Pelinka LE, Toegel E, Mauritz W, Redl H. Serum S 100 B: a marker of brain damage in traumatic brain injury with and without multiple trauma. *Shock* 2003;19(3):195–200.
- Pelinka LE, Bahrami S, Szalay L, et al. Hemorrhagic shock induces an S 100 B increase associated with shock severity. *Shock* 2003;19(5):422–6.
- Pelinka LE, Szalay L, Jafarmadar M, et al. Circulating S100B is increased after bilateral femur fracture without brain injury in the rat. *Br J Anaesth* 2003;91(4):595–7. 43.
- Pelinka LE, Kroepfl A, Schmidhammer R, et al. Glial fibrillary acidic protein in serum after traumatic brain injury and multiple trauma. *J Trauma* 2004;57(5):1006–12.
- Raabe A, Grolms C, Seifert V. Serum markers of brain damage and outcome prediction in patients after severe head injury. *Br J Neurosurg* 1999;13(1):56–9.
- Rothoerl RD, Woertgen C, Holzschuh M, et al. S-100 serum levels after minor and major head injury. *J Trauma* 1998;45(4):765–7.
- Savola O, Hillbom M. Early predictors of post-concussion symptoms in patients with mild head injury. *Eur J Neurol* 2003;10(2):175–81.
- Stalnacke BM, Bjornstig U, Karlsson K, Sojka P. One-year follow-up of mild traumatic brain injury: post-concussion symptoms, disabilities and life satisfaction in relation to serum levels of S-100B and neurone-specific enolase in acute phase. *J Rehabil Med* 2005;37(5):300–5.
- Stapert S, de Kruijk J, Houx P, et al. S-100B concentration is not related to neurocognitive performance in the first month after mild traumatic brain injury. *Eur Neurol* 2005;53(1):22–6.
- Stiell IG, Lesiuk H, Wells GA, et al. Canadian CT head rule study for patients with minor head injury: methodology for phase II (validation and economic analysis). *Ann Emerg Med* 2001;38(3):317.
- Stranjalis G, Korfiatis S, Papapetrou C, et al. Elevated serum S-100B protein as a predictor of failure to short-term return to work or activities after mild head injury. *J Neurotrauma* 2004;21(8):1070–5.
- Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2(7872):81–4.
- Teasdale GM, Murray G, Anderson E, et al. Risks of acute traumatic intracranial haematoma in children and adults: implications for managing head injuries. *BMJ* 1990;300(6721):363–7.
- Teasdale GM, Pettigrew LE, Wilson JTL, et al. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. *J Neurotrauma* 1998;15(8):587–97.
- Thornhill S, Teasdale GM, Murray GD, et al. Disability in young people and adults one year after head injury: prospective cohort study. *BMJ* 2000;320(7250):1631–5.
- Townend WJ, Guy MJ, Pani MA, et al. Head injury outcome prediction in the emergency department: a role for protein S-100B? *J Neurol Neurosurg Psychiatry* 2002;73(5):542–6.

40. Townend WJ, Dibble C, Abid K, et al. Rapid elimination of protein S-100B from serum after minor head trauma. *J Neurotrauma* 2006;23(2):149–55.
41. van der Naalt J, van Zomeren AH, Sluiter WJ, Minderhoud JM. One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. *J Neurol Neurosurg Psychiatry* 1999;66(2):207–13.
42. Wade A. Derivation versus validation. *Arch Dis Child* 2000;83(6):459–60.
43. Wade DT, Crawford S, Wenden FJ, et al. Does routine follow-up after head injury help? A randomised controlled trial. *J Neurol Neurosurg Psychiatry* 1997;62(5):478–84.
44. Waterloo K, Ingebrigtsen T, Romner B. Neuropsychological function in patients with increased serum levels of protein S-100 after minor head injury. *Acta Neurochir (Wien)* 1997;139(1):26–31. discussion 31-2.
46. Woertgen C, Rothoerl RD, Metz C, Brawanski A. Comparison of clinical, radiologic, and serum marker as prognostic factors after severe head injury. *J Trauma* 1999;47(6):1126–30.