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RESEARCH

Predictive value of S-100β protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis

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Abstract

Objectives To determine the ability and accuracy of the S-100β protein in predicting prognosis after a moderate or severe traumatic brain injury.

Design Systematic review and meta-analysis of randomised controlled trials and observational studies.

Data sources Medline, Embase, Cochrane Central Register of Controlled Trials, BIOSIS (from their inception to April 2012), conference abstracts, bibliographies of eligible articles, and relevant narrative reviews.

Study selection Two reviewers independently reviewed citations and selected eligible studies, defined as cohort studies or randomised control trials including patients with moderate or severe traumatic brain injury and evaluating the prognostic value of S-100β protein. Outcomes evaluated were mortality, score on the Glasgow outcome scale, or brain death.

Data extraction Two independent reviewers extracted data using a standardised form and evaluated the methodological quality of included studies. Pooled results were presented with geometric means ratios and analysed with random effect models. Prespecified sensitivity analyses were performed to explain heterogeneity.

Results The search strategy yielded 9228 citations. Two randomised controlled trials and 39 cohort studies were considered eligible (1862 patients). Most studies (n=23) considered Glasgow outcome score ≤3 as an unfavourable outcome. All studies reported at least one measurement of S-100β within 24 hours after traumatic brain injury. There was a significant positive association between S-100β protein concentrations and mortality (12 studies: geometric mean ratio 2.55, 95% confidence interval 2.02 to 3.21, I^2=56%) and score ≤3 (18 studies: 2.62, 2.01 to 3.42, I^2=79%). Sensitivity analysis based on sampling time,

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Appendix 1: Medline search strategy
Appendix 2: Instrument used for evaluation of risk of bias of included studies (adapted from QUADAS-2)
Appendix 3: Methodological quality of included studies (STROBE criteria)
Appendix 4: Sensitivity and specificity
Appendix 5: Funnel plots

sampling type, blinding of outcome assessors, and timing of outcome assessment yielded similar results. Thresholds for serum S-100β protein values with 100% specificity ranged from 1.38 to 10.50 µg/L for mortality (six studies) and from 2.16 to 14.00 µg/L for unfavourable neurological prognosis as defined by the Glasgow outcome score.

Conclusions After moderate or severe traumatic brain injury, serum S-100β protein concentrations are significantly associated with unfavourable prognosis in the short, mid, or long term. Optimal thresholds for discrimination remain unclear. Measuring the S-100β protein could be useful in evaluating the severity of traumatic brain injury and in the determination of long term prognosis in patients with moderate and severe injury.

Introduction

Early determination of prognosis after traumatic brain injury is a priority for relatives and physicians involved in the care of these patients.[1 2] Despite recent improvement in management of patients with traumatic brain injury in intensive care and the development of guidelines to standardise care,[3 4] mortality and morbidity in these patients remain high.[5-7] About 30% of patients admitted after severe traumatic brain injury will die, and 50% will be moderately disabled.[7 8] In a recent multicentre cohort study, we observed variable mortality rates across Canadian trauma centres, despite comparable severity of injury, and considerable variation in the incidence of withdrawal of life sustaining treatments.[9] As many of these patients are young with no previous comorbidity, the decision to withdraw life sustaining treatments is based mainly on prognostic evaluation. Current prognostic indicators and models, however, are limited by their lack of sufficient discriminative capacity to inform clinical decision making.[10-12] 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.[13]

Over the past 20 years, biochemical markers of brain damage have been increasingly studied as potential tools for prognostic evaluation.[13-17] Concentrations of S-100β protein, the β subunit of a calcium binding protein present mainly in glial and Schwann cells,[18] increase in human blood and cerebrospinal fluid after a wide range of diseases or conditions leading to brain damage.[19-28] Increased concentrations in blood and cerebrospinal fluid have been reported in patients with traumatic brain injury.[29] Despite growing evidence suggesting a potential clinical role for S-100β as a biomarker, its association with short, mid, and long term prognosis remains unclear in patients with traumatic brain injury. There are also concerns that extracerebral injuries could contribute to increases in concentrations. Measurements of S-100β protein, or other biomarkers, are not widely used in clinical practice and are not considered standard of care.[14 15] We therefore conducted a systematic review to evaluate the prognostic value of the S-100β protein after moderate or severe traumatic brain injury.

Materials and methods

Search strategy

We searched Medline, Embase, Cochrane Central Register of Controlled Trials (Central), and BIOSIS from their inception to April 2012 for relevant studies. For Medline and Embase, we used validated combinations of terms for prognostic studies to achieve optimal search sensitivity and specificity.[30 31] Broad text and MeSH or EMTREE terms for biomarkers were used to maximise sensitivity. Our search strategy was designed to identify a wide range of biomarkers to increase sensitivity. The full search strategy for Medline is provided in appendix 1. We screened abstracts from relevant meetings (American Association of Neurological Surgeons, European Association of Neurosurgical Societies, Société de Neurochirurgie de Langue Française, Congress of Neurological Surgeons, Critical Care Canada Forum, International Trauma Anesthesia and Critical Care Society, World Federation of Societies of Intensive and Critical Care Medicine, Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium on Intensive Care Medicine, American association for the surgeons of trauma) and reference lists of selected articles and relevant narrative reviews.

Study selection

Search results were combined and duplicates were excluded with EndNote (version X5, Thomson Reuters, 2011). Two reviewers (EM and JFS or AB) independently reviewed all citations and selected eligible studies. A third author (AFT) was consulted in case of disagreement.

We included cohort studies and randomised controlled trials that determined S-100β protein concentrations in patients with moderate and/or severe traumatic brain injury as defined by a Glasgow coma score <13.[32] Included studies had to report at least one outcome of interest (mortality, Glasgow outcome score,[33] or brain stem death) and had to report S-100β protein concentrations in cerebrospinal fluid, venous blood, arterial blood, and/or urine. One quantitative measurement of S-100β protein in the emergency room or the intensive care unit, along with at least one follow-up outcome measure after discharge from intensive care, was also required for inclusion. Studies with one or no patient having a favourable or an unfavourable outcome were excluded as no standard deviation could be computed. We included prospective and retrospective outcome assessments and avoided language based study exclusions. We excluded studies limited exclusively to children (aged <18) and studies in which less than half of included patients had moderate or severe traumatic brain injury, unless we could extract the data related to patients with moderate or severe traumatic brain injury.

Data abstraction

Two reviewers (EM and JFS or AB) independently collected data using a standardised data abstraction form. We abstracted information related to study design, patient characteristics (age, sex, severity of injury, blunt or penetrating injury, type of lesions, mechanism of injury, Marshall score for computed tomography, clinical pupillary reaction, hypotension, hypoxaemia, intracranial pressure, and mechanical ventilation), treatments (operative and pharmacological), laboratory aspects of S-100β protein testing (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 of S-100β 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. When the Glasgow outcome scale was dichotomised by the authors, we retained their definition of unfavourable outcome. When the entire spectrum of the Glasgow outcome score was provided, we defined an unfavourable outcome as a score ≤3.

Methodological quality and risk of bias of included studies

We developed a modified version of the QUADAS-2 assessment tool[34] (appendix 2) to evaluate the risk of bias in prognostic studies. We also used the criteria for reporting observational studies proposed in the STROBE statement[35] to complete the methodological evaluation of the included studies (appendix 3).

Statistical analysis

The distribution of S-100β concentrations were right skewed and we therefore log transformed them to yield a normal distribution, assessed with Shapiro-Wilk and Kolmogorov-Smirnov normality tests. A log normal distribution facilitated the analysis and presentation of outcomes between groups with geometric means ratios, for which the null value is one.[36] Therefore, a ratio greater than one indicates that mean concentrations are higher in the group with an unfavourable prognosis compared with the group with a favourable prognosis.[36]

Analyses were performed with random effects models. The presence of potential heterogeneity was assessed with the I^2 statistic.[37] Sensitivity analyses based on a priori hypotheses (time period of evaluation, sampling time, sampling type, severity of traumatic brain injury, isolated traumatic brain injury, biochemical technique, blinding of outcome assessment) were performed to investigate expected or measured heterogeneity. When individual patient data were available, we computed receiver operating characteristics curves for each study and used a bivariate random effects regression model[38] to pool the sensitivity and specificity of intervals of S-100β threshold values for mortality and Glasgow outcome score. We also computed discrimination threshold values for 100% specificity for each of these studies.

In some studies, it was unclear whether the authors presented standard deviations or standard errors. In these cases, to prevent an incorrect rejection of the null hypothesis (type I error), we assumed the reported statistics to be standard errors. Analyses were conducted with Review Manager version 5.0 (Cochrane Collaboration, Copenhagen, Denmark) and SAS version 9.2 (SAS Institute, Cary, NC). For all tests and confidence intervals we used a two tailed type I error rate of 5%. The reporting of this systematic review complies with the PRISMA statement.[39] Publication bias was evaluated through visual inspection of funnel plots.

Quality of the evidence

The quality of the evidence for the three main outcomes was determined with the GRADE approach[40] with the GRADEpro software (version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008).

Results

Study identification and selection

Our search strategy retrieved 9228 citations after removal of duplicates. After screening and the application of our inclusion and exclusion criteria, we included 41 studies[41-81] published between 1987 and April 2012 (1862 patients) (fig 1⇓). With the exception of one conference proceeding[44] and one pilot study reported as a table in the final study publication,[75] all included studies were published peer reviewed manuscripts.

Study characteristics

Thirty nine studies were observational cohort studies and two were randomised controlled trials[68 72] (table 1⇓). Three studies were published in languages other than English: Chinese,[61] Japanese,[65] and Czech.[70] Each study evaluated between four and 149 patients with moderate and severe traumatic brain injury. Only one study reported including penetrating trauma, which represented 6.7% of its sample.[53] The main outcome measures presented were the Glasgow outcome score (30 studies), mortality (18 studies), and brain stem death (two studies). Site of S-100β protein sampling was venous (31 studies), arterial (10 studies), or cerebrospinal fluid (five studies). Eighteen studies presented data from two or more samples at different time points after traumatic brain injury. Ten studies presented individual patient data.[42 45 49 51 53 57 66 73-75] Individual data for three studies by the same group[42 49 57] were combined in the meta-analysis as they presented data from the same patients. All analyses were performed with serum (arterial or venous) S-100β protein concentrations.

Fifteen of the 41 included studies could not be incorporated in the meta-analysis: nine presented the peak concentrations of serial samples of S-100β protein plasma or cerebrospinal fluid[43 47 48 50 60 71 72] or the mean value[52 79]; two did not report measures of dispersion[44 61]; two presented data on four or five patients, with one patient having a favourable outcome in each case[41 56]; and one reported only the threshold value for a 100% specificity for unfavourable prognosis.[55] Finally, two studies reported brain stem deaths,[58 79] but one reported the mean value of serial samples, which precluded the application of meta-analysis for this specific outcome.

Methodological quality of included studies

Seventeen studies examined the risk of bias, six studies presented a flow diagram of participants, 14 studies adequately described their study population (including missing data and patients lost during follow-up), and 13 studies presented their funding sources. Figure 2 and appendix 3 present a more complete evaluation of the methodological quality and risk of bias⇓.

Outcome measures

We observed significant positive associations between serum concentrations of S-100β protein and outcome. Increased concentrations correlated with increased mortality (12 studies: geometric mean ratio 2.55, 95% confidence interval 2.02 to 3.21; I^2 56%; fig 3⇓), a Glasgow outcome score ≤3 (18 studies: 2.62, 2.01 to 3.42; I^2 79%; fig 4⇓), and brain stem death (one study: 2.9, 2.3 to 3.5). The results were consistent in all sensitivity analyses and were not influenced by the presence of associated traumatic injuries in other parts of the body (tables 2⇓ and 3⇓). In mortality subgroup analyses, heterogeneity was lowered according to testing method and timing of outcome assessment. In the studies that we excluded because of lack of information on measures of dispersion,[44 61 80] we observed a significant and consistently positive association between serum concentrations of S-100β protein and mortality. In eight studies excluded from the meta-analysis because they reported only the peak or the mean values over serial samples, authors reported a significant association (P<0.05) between serum concentrations and mortality,[48 72] Glasgow outcome score ≤3,[43 47 48 50 60 71] and brain stem death.[79] Three studies reported a significant association between S-100β protein concentrations in cerebrospinal fluid and a Glasgow outcome score ≤3.[51 59 62] We also analysed the data using the Taylor series method,[82 83] and

this did not substantially change the results (data available from authors). These analyses, however, yielded to a quasi-absence of statistical heterogeneity in all analyses.

Discrimination threshold

For mortality (six studies), serum threshold values of 2.5-3.0 µg/L yielded a mean specificity of 91% (95% confidence interval 84% to 95%) and a sensitivity of 39% (24% to 57%), while concentrations >3.0 µg/L yielded a mean specificity of 97% (95% to 98%) (see appendix 4). When we considered each study individually, the respective serum thresholds to attain 100% specificity for prognosis of death, meaning that all surviving patients are correctly identified by the test (no false positive overdetection of prognosis of death), ranged from 1.38 µg/L to 10.50 µg/L, with an associated sensitivity ranging from 14% to 60% (fig 5⇓).

Similarly, for unfavourable neurological prognosis (Glasgow outcome score ≤3) (five studies), threshold values of 2.5 µg/L to 3.0 yielded a specificity of 94% (95% confidence interval 85% to 98%) and a sensitivity of 38% (15% to 67%) and values >3.0 µg/L yielded a specificity of 96% (91% to 98%) (appendix 4). Again, when we considered each study individually, threshold values for 100% specificity for unfavourable neurological prognosis ranged from 2.16 µg/L to 14.0 µg/L, with an associated sensitivity ranging from 9% to 50% (fig 6⇓).

Publication bias and quality of evidence

Visual evaluation of funnel plots did not indicate any publication bias (see appendix 5). The quality of the evidence for mortality and for unfavourable neurological outcome (Glasgow outcome score ≤3) was moderate (table 4⇓).

Discussion

This meta-analysis identified a significant association between S-100β protein serum concentrations and short (less than three months), mid (three to six months) or long term (six months and above) prognosis in patients with moderate or severe traumatic brain injury. The concentrations were significantly correlated with unfavourable prognosis, as defined by mortality or Glasgow outcome score ≤3, irrespective of concomitant traumatic injuries. Serum thresholds values ranging from 1.38 µg/L to 10.5 µg/L and from 2.16 µg/L to 14.0 µg/L were associated with 100% specificity for mortality and a Glasgow outcome score ≤3, respectively. Our findings are highly relevant to the care of critically ill patients with traumatic brain injury, especially as to help informed decision with respect to the determination of prognosis.

Strengths and weakness of study

There are limitations of our systematic review. Firstly, there was considerable heterogeneity for all outcomes of interest. Heterogeneity among studies that assessed mortality was explained by the testing method used and by the time period over which outcome was evaluated. Sensitivity analyses including the type of assay used, the timing of sampling, the sampling type, isolated versus multiple trauma, and the timing of outcome evaluation after traumatic brain injury, however, did not fully explain the observed heterogeneity for the Glasgow outcome score. Secondly, the use of the first measurement of S-100β in our meta-analysis when more than one sample was collected could have generated more conservative estimates as samples obtained between 12 and 24 hours after admission showed a stronger association with outcome measures, which could reflect the impact of secondary neurological injuries like hypoxaemia, hypotension, and increased intracranial pressure. Thirdly, though we carried out our systematic review according to high methodological standards,[39] the results of the meta-analysis are limited by the quality of studies included. For example, only 16 studies reported outcome assessment that was blinded from S-100β protein concentrations, which implies a high risk of bias. Moreover, we cannot exclude potential publication bias.

Fourthly, we could not perform sensitivity analyses related to age, pupillary reactivity, or the motor component of the Glasgow coma score, which are known indicators of prognosis in such patients, because of the variable presentations or absence of these data in included studies. Finally, the different chemical assays used could have affected the accuracy and precision of the measured thresholds of S-100β protein concentrations. Although the sensitivity analyses did not show any major impact on the results, some of the assays were used in only a few studies, thus precluding a robust interpretation of their impact. Finally, the S-100β protein concentrations could potentially be affected by previous neurological diseases[84] or high serum alcohol concentrations.[85] Data on those variables were rarely available and precluded any sensitivity analysis. While these variables could potentially have an impact in mild traumatic brain injury, however, this is unlikely to be considerable for moderate and severe injuries considering the importance of the traumatic brain injury.

Our systematic review had important strengths. We conducted a thorough systematic search, including different databases, and used a comprehensive analytical approach that allowed the inclusion of studies presenting not only means and standard deviations, but also centiles such as medians, thus improving the exhaustiveness of the results. Our rigorous methods were based on guidelines for conducting and reporting systematic reviews.

Comparison with previous knowledge

Previous narrative reviews published to date have outlined the potential of S-100β protein concentrations for predicting outcome after moderate or severe traumatic brain injury, but none of these used systematic review methods or incorporated meta-analyses.[14 15 17 86-95] The results of our study are consistent with those from two previous systematic reviews conducted in patients with stroke or cardiac arrest.[96 97] The first review found an association between S-100β protein concentrations and prognostic features (infarct volume and stroke severity),[97] while the second review showed that S-100β protein might be a better outcome predictor than the neurone specific enolase after cardiac arrest.[96] Our results are also consistent with a large observational study performed in unselected neurocritically ill patients that found that S-100β was associated with neurological deterioration or complications.[98]

The presence of extracerebral sources of S-100β protein could lead to an overestimation of the severity of the brain lesion in the early phase after traumatic brain injury in patients with multiple injuries.[16 99-102] Only four studies included in our meta-analysis[62 68 70 81] specified not enrolling patients with associated multiple trauma. The association between S-100β protein concentrations and prognosis, however, was consistent irrespective of other injuries. This result is concordant with the observations that S-100β protein concentrations are more specific to the brain than to any other organ. Given that 80-90% of the total amount of S-100β is found in cerebral tissue,[93] and that serum concentrations of S-100β protein have been correlated

with the extent of brain damage in traumatic brain injury on computed tomography[46] and in patients with ischaemic stroke,[103] the attributable concentrations and influence of extracerebral sources of S-100β is thus likely to be minimal.[100] One excluded study previously proposed such an approach,[104] but we could not evaluate this hypothesis as no study that included isolated head trauma reported individual patient data. Furthermore, we could not explore potential confounding from severity of extracerebral injuries as data were not reported by outcome groups.

The discriminative capacity of the S-100β protein in the prediction of mortality and neurological outcome in patients with moderate and severe traumatic brain injury provides a glimpse at its potential usefulness as part of a shared decision making process. Indeed, medical teams and relatives faced with decisions about level of care are often left with little information on probabilistic expectations regarding the prognosis in these patients. The high specificity observed at thresholds over 2.5 µg/L makes the S-100β protein a candidate variable to include—in combination with other prognostic indicators such as data from the clinical examination, imaging, and electrophysiological tests—in a prognostic model to help in a shared decision making process. Such a model could better inform clinical teams and relatives on expected clinically important outcomes and optimise the provision of healthcare. On the other hand, the high sensitivity of the S-100β protein to rule out a clinically important brain injury could be useful to provide guidance for the decision whether to perform additional diagnostic assessment such as imaging in patients with traumatic brain injury. As part of a decision aid, the S-100β protein concentration could serve to rule out important traumatic brain injury and avoid exposing patients to unnecessary radiation from imaging, allow better triage and use of resources, and thus be a potentially cost effective measure.

Many questions remain unanswered, such as the optimal biochemical method, timing of sampling, and prognostic threshold. Different assays and timing of sampling might call for different thresholds. With the current level of evidence, we cannot comment on the optimal parameters for prognostic evaluation. Further research is needed to explore combination of variables known to be associated with clinical outcomes of traumatic brain injuries to develop a prognostic model with a high discriminative capacity.

Conclusion

We observed a significant association between serum concentrations of S-100β protein and unfavourable prognosis as defined by mortality, Glasgow outcome score ≤3, and brain stem death. The optimal discrimination threshold values for S-100β protein and the optimal sampling time remain uncertain as there were important variations between studies. The measure of S-100β protein concentrations could potentially play a role as part of a decision aid in the prognostic evaluation of patients with traumatic brain injury as well as to potentially rule out important traumatic brain injury. Further efforts should focus on standardising testing methods and further research on identifying optimal threshold values and sampling time for prognosis determination and on combining S-100β protein concentrations with other prognostic indicators to improve the accuracy of prognostic models and help guiding level of care decisions in a shared decision making process.

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Ethical approval: Not required.

Data sharing: No additional data available.

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What is already known on this topic

Many indicators have been independently associated with prognosis after traumatic brain injury, but they are of limited clinical use when considered separately and current prognostic models do not have sufficient discriminative capacity to inform clinical decision making

S-100β protein concentrations have been shown to increase in blood and cerebrospinal fluid after a wide range of diseases or conditions leading to brain damage

What this study adds

S-100β protein serum concentrations correlate significantly with unfavourable prognosis in patients with moderate or severe traumatic brain injury, as defined by mortality, Glasgow outcome score ≤3, or brain stem death, with or without concomitant traumatic injuries

The association between serum concentrations of S-100β protein and prognosis was observed at discharge from intensive care and at one, three, and six months.

Serum threshold values ranging from 1.38 µg/L to 10.50 µg/L and from 2.16 µg/L to 14.00 µg/L were associated with 100% specificity for mortality and a Glasgow outcome score ≤3, respectively

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Tables

Table 1| Characteristics of studies included in review of role of S-100β protein concentrations in prognosis in patients with moderate and severe traumatic brain injury

Studies	No patients	Inclusion criteria	Age (years)*	Female/male	Severity scales	Assay	Main outcome
Persson et al[41]	4	NR	NR	NR	NR	Custom	GOS at hospital discharge: 1-3 unfavourable, 4-5 favourable
McKeating et al[43]	21	Traumatic brain injury, admitted to ICU	35 (17-69)	4/17	Median (range) GCS 6 (3-13), ISS 25 (9-38)	RIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Meissner et al[44]	20	NR	NR	NR	NR	NR	Mortality
Raabe et al[45]	15	GCS ≤8. Retrograde jugular venous catheter inserted	39 (17-61)	5/10	Median (range) GCS 5 (3-8), APACHE II 15 (14-17)	LIA, DiaSorin Diagnostic	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Raabe et al[46]	44	Severe head injury	41 (16-83)	11/33	Median (range) GCS 5 (3-8)	RIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Raabe et al[47]	82	GCS ≤8 after resuscitation. Admitted to neurosurgical ICU	38 (16-85)	16/66	NR	RIA and LIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Raabe et al[48]	84	GCS ≤ 8 post-resuscitation Closed TBI	39 (16-85)	17/67	15 (18%) with extracranial injuries	RIA and LIA, DiaSorin Diagnostica	Mortality at 6 months
Elting et al[50]	10	No epidural haematoma requiring surgery. No previous head injury, stroke or CNS infection within past 3 months	Mean (SD) 43 (21)	4/6	Mean (SD) GCS 10.3 (4.3), range 3-13	LIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favorable
Jackson et al[51]	30	History suggestive of severe traumatic brain injury	NR	20/10	NR	LIA, DiaSorin Diagnostica	GOS at hospital discharge and at 6 months: 1-3 unfavourable, 4-5 favourable
Pleines et al[52]	13	GCS ≤8 admission. Isolated traumatic brain injury	Mean (range) 36 (16-67)	NR	NR	ELISA, DiaSorin Diagnostica	GOS between 3 and 6 months
Regner et al[53]	15	Clinical condition equivalent to GCS ≤8 at admission and 12 and 48 h. Signs of intracranial lesions on computed tomography. Admitted to trauma ICU	Mean (range) 33 (18-50)	2/13	Mean GCS 5	RIA, DiaSorin Diagnostica	Mortality at ICU discharge
Chatfield et al[54]	20	Traumatic brain injury. Admission into neurosciences ICU required	Mean (SD) 29 (15), range 16-60	NR	Median (range) GCS 6 (3-9), APACHE II 14 (7-19), ISS 25 (9-50)	LIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Mussack et al.[55]	20	GCS ≤8 on admission. Isolated traumatic brain injury. No traumatic circulatory arrest. Surviving at least 12 h after admission	Mean (95% CI) 45 (24.1 to 81.9)	4/16	NR	LIA, DiaSorin Diagnostica	GOS at 12 months: 1-3 unfavourable, 4-5 favourable
Townend et al[56]	5	Traumatic brain injury and presentation to emergency department within 6 h after injury	Mean (range) 47.4 (18-94)	50/93	130 with GCS 15, 5 with GCS ≤8	LIA, DiaSorin Diagnostica	GOSE at 1 month
Woertgen et al[42] [49] [57]	54	GCS ≤8. Admitted between 1-6 h after injury. No spinal cord injury. No history of neurological disease. No resuscitation or shock	Mean (range) 34.5 (16-79)	15/42	NR	RIA, DiaSorin Diagnostica	Mortality and GOS at 12 months: 1-3 unfavourable, 4-5 favourable
Dimopoulou et al[58]	47	GCS ≤8. Admitted to ICU. No brain stem death at admission	34 (17-75)	6/41	Median (range) GCS 6 (3-8)	LIA, DiaSorin Diagnostica	Brain stem death at 6 days
Pelinka et al[59]	92	Traumatic brain injury with or without multiple trauma <12 h after admission.	Median (IQR) 39 (28-55)	25/67	Median (IQR) GCS 6 (3-8), ISS 25 (18-34)	LIA, DiaSorin Diagnostica	Mortality and GOS at 3 months

Table 1 (continued)

Studies	No patients	Inclusion criteria	Age (years)*	Female/male	Severity scales	Assay	Main outcome
Hayakata et al[60]	23	GCS ≤8. Age >9. No severe life threatening injury to vital organs other than brain	Mean (range) 40 (14-68)	6/17	NR	RIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Hu et al[61]	66	GCS ≤8	Mean (range) 37.5 (16-75)	14/52	Mean (range) GCS 5 (3-8)	ELISA, Roche Diagnostica	Mortality at 6 months
Li et al[62]	40	GCS ≤8. No severe systemic injury. No heart or renal failure. No severe infection of central nervous system	NR	NR	NR	LIA, DiaSorin Diagnostica	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Ucar et al[63]	48	GCS ≤8. Admitted to emergency department soon after traumatic brain injury	NR	15/33	NR	RIA, DiaSorin Diagnostica	GOS at 6-9 months after hospital discharge: 1-3 unfavourable, 4-5 favourable
Vos et al[64]	84	GCS ≤8 after resuscitation. Admitted within 36 h after injury. Closed head injury. Blood sample taken. Informed consent. Possibility of long term follow-up	32 (15-81)	24/61	Median (range) GCS 4 (3-8), ISS 29 (9-75)	LIA, DiaSorin Diagnostica	Mortality at 6 months
Sawauchi et al[65]	41	Consecutive traumatic brain injury	NR	NR	30 with GCS >8, 11 with GCS ≤9	NR	GOS at 3 months: 1-3 unfavourable, 4-5 favourable
daRocha et al[66]	23	GCS ≤8 at emergency admission. Age 18-65. No history of neurological or psychiatric disorder. Transferred to ICU ≤24 h after traumatic brain injury. Male	34 (19-64)	0/23	Mean (SD) GCS 6.0 (2.5), APACHE II 16.9 (6.2)	LIA, DiaSorin Diagnostica	Mortality at ICU discharge
Wang et al[67]	34	Admitted to department of neurosurgery <24 h after injury	Range 15- 73	15/19	NR	ECLIA	GOS at 3 months: 1-3 unfavourable, 4-5 favourable
Ghori et al[68]	28	GCS ≤8. Age 18-65. Isolated head injury. Requirement for mechanical ventilation. No previous organic brain disease or brain surgery or spinal cord injury. No renal or hepatic failure. BMI ≤32. No pregnancy. No substance abuse at ICU admission	NR	1/27	Median (range) GCS 4,73 (3-7) with midazolam, 5.07 (3-7) with propofol	RIA, DiaSorin Diagnostica	GOS at 3 months: 1-3 unfavourable, 4-5 favourable
Korfias et al[69]	102	GCS ≤8 at admission. Age >14. Admitted to neurological ICU	35 (16-86)	21/81	GCS: 36 with score 3-4; 24 with score 5-6; 42 with score 7-8	LIA, DiaSorin Diagnostica	Mortality at 1 month
Lavicka et al[70]	98	Isolated traumatic brain injury admitted	NR	NR	GCS	LIA, DiaSorin Diagnostica	GOS at hospital discharge: 1-3 unfavourable, 4-5 favourable
Nylen et al[71]	59	GCS ≤8 admitted to neurosurgical ICU. Therapeutic indication for monitoring ICP. Therapeutic indication for ventilator treatment. Start of sampling on day 2 at latest. No life threatening trauma to other organs	37 (8-81)	15/44	NR	ELISA, Fujirebio Diagnostics	GOS at 12 months: 1-3 unfavourable, 4-5 favourable
Baker et al[72]	64	GCS ≤8. Coma or loss of consciousness from isolated blunt traumatic brain injury	Mean (range) 41.4 (18.3-87.9)	23/41	Mean (SD) GCS 5.7 (2.7)	ELISA, Nexus DX	Mortality and GOS at hospital discharge (or 30 days): 1-3 unfavourable, 4-5 favourable
Olivecrona et al[73]	48	GCS ≤8. Age 15-70. First recorded CPP >10 mm Hg. Arrival <24 h after traumatic brain injury	31 (15-63)	17/31	Median (range) ISS 29 (9-50), APACHE II 21 (12-32)	LIA, DiaSorin Diagnostica	Mortality and GOS at 3 and 12 months: 1 deceased, 2-3 unfavourable, 4-5 favourable

Table 1 (continued)

Studies	No patients	Inclusion criteria	Age (years)*	Female/male	Severity scales	Assay	Main outcome
Rainey et al[74]	100	GCS ≤8. Age >15. Admitted to ICU < 24 h after traumatic brain injury	31 (16-86)	19/81	Median (range) ISS 25 (9-50), multiple trauma 47%	ELISA, DiaSorin Diagnostica	Mortality and GOS at 3 months: 1-3 unfavourable, 4-5 favourable
Rainey-pilot study[75]	9	GCS ≤8	NR	NR	NR	ELISA, DiaSorin Diagnostica	Mortality
Murillo-Cabezas et al[76]	87	GCS ≤8. Age >14. Serum sampling ≤24 hours after traumatic brain injury. Haemodynamically stable	30 (15.0-76.0)	14/73	GCS at admission: 20 with score 3-4; 23 with score 5-6; 44 with score 7-8	ECLIA, Elecsys	Mortality and GOS at 12 months: 1-3 unfavourable, 4-5 favourable
Vos et al[77]	79	GCS ≤13. Age >17. Hospital admission ≤24 hours after traumatic brain injury	47.0 (18.0-91.0)	22/57	Median (range) GCS 3 (3-12)	LIA, IntraOperative platform, Future Diagnostics	Mortality and GOSE at 6 months: 1 deceased, 1-4 unfavourable, 5-8 favourable
Weismann et al[78]	60	Admitted <24 h after traumatic brain injury. No known neurological disease. No spinal cord injury	Mean (SD) 44 (21)	15/45	Mean (SD) GCS 8 (4)	NR	GOS at 6 months: 1-3 unfavourable, 4-5 favourable
Böhmer et al[79]	20	GCS ≤8 with abnormal result on computed tomography on admission	Mean (SD) 29 (13)	2/18	NR	ELISA, DiaSorin Diagnostica	Brain stem death
Gonzalez-Mao et al[80]	149	Admission within 6 h of injury. Main diagnosis of traumatic brain injury. Evaluation of history of psychiatric and neurological disease. Computed tomography within 24 h of lesion	Mean (95% CI) 42.85 (39.5 to 46.1), range 15-84	30/119	Mean GCS 9.3. 77 with score <9; 32 with score 9-13; 40 with score 14-15	LIA, DiaSorin Diagnostica	Mortality at hospital discharge
Stein et al[81]	24	Age >17. Admission within first 6 h after injury. GCS score <9 on admission. Placement of clinically indicated ICP monitor	Mean (SD) 30.7 (12.3), range 19-64	3/21	Mean admission (SD) GCS 5.8 (3.4)	ELISA, Biovendor Candor	GOSE at 3 months, 6 months and 1 year: 1-4 unfavourable, 5-8 favourable

APACHE II=acute physiology and chronic health evaluation II; CPP=cerebral perfusion pressure; ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbant assay; GCS=Glasgow coma scale; GOS=Glasgow outcome scale; GOSE=extended Glasgow outcome scale; ICP=intracranial pressure; ICU=intensive care unit; IQR=interquartile range; ISS=injury severity score; LIA=luminescence immunoassay; NR=not reported; RIA=radioimmunoassay.
*Median (range) unless stated otherwise.

Table 2| Sensitivity analyses for association of S-100β protein concentrations with mortality in patients with traumatic brain injury. Figures are geometric mean ratios (95% confidence interval)

	No of studies	GMR (95% CI)	I^2 (%)
Evaluation time:			
Intensive care unit	1	2.83 (1.38 to 5.81)	—
Hospital	1	3.82 (2.39 to 6.05)	—
1 month	1	2.01 (1.20 to 3.35)	—
3 months	4	2.64 (1.97 to 3.49)	0
6 months	3	2.25 (1.63 to 3.13)	0
12 months	2	2.46 (0.79 to 7.77)	94
Sampling time (hours):			
<12	9	2.59 (1.92 to 3.49)	68
<24	16	2.75 (2.27 to 3.29)	56
48	4	4.10 (3.03 to 5.47)	28
72	4	3.03 (2.36 to 3.86)	0
Sample type:			
Arterial	2	2.44 (1.73 to 3.46)	0
Venous	10	2.59 (1.95 to 3.42)	64
Biochemical method:			
RIA	2	3.94 (2.53 to 6.05)	11
LIA	7	2.61 (2.12 to 3.22)	0
ELISA	2	2.44 (1.73 to 3.46)	0
ECLIA	1	1.39 (1.03 to 1.90)	—
Other	0	—	
Minimal severity of traumatic brain injury:			
Mild	2	3.49 (2.41 to 5.10)	—
Moderate	1	2.08 (1.34 to 3.22)	—
Severe	9	2.46 (1.84 to 3.25)	60
Isolated traumatic brain injury:			
Isolated	0	—	—
Multiple trauma or unspecified	12	2.53 (2.01 to 3.19)	56
Blinding:			
Blinded	6	2.03 (1.57 to 2.66)	39
Unspecified	6	3.16 (2.53 to 3.94)	4

ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbent assay; LIA=enzyme linked immunoluminometric assay; RIA=immunoradiometric assay; TBI: traumatic brain injury.

Table 3| Sensitivity analyses for association of S-100β protein concentrations with Glasgow outcome score ≤3 in patients with traumatic brain injury. Figures are geometric mean ratios (95% confidence interval)

	No of studies	GMR (95% CI)	I^2 (%)
Evaluation time (months):			
3	5	2.92 (1.41 to 6.06)	89
6	10	2.53 (2.00 to 3.19)	48
12	3	2.74 (1.01 to 7.44)	90
Sampling time (hours):			
<12	14	2.52 (1.89 to 3.36)	81
<24	24	2.65 (2.16 to 3.26)	78
48	5	2.37 (1.51 to 3.73)	67
72	7	2.68 (1.58 to 4.56)	82
Sample type:			
Arterial	4	2.99 (2.09 to 4.30)	54
Venous	13	2.43 (1.73 to 3.40)	82
Biochemical method:			
RIA	5	2.20 (1.45 to 3.32)	61
LIA	7	2.42 (1.72 to 3.40)	67
ELISA	2	3.10 (1.99 to 4.81)	11
ECLIA	2	1.60 (0.76 to 3.35)	64
Other	2	6.64 (1.54 to 28.71)	93
Minimal severity of traumatic brain injury:			
Mild	4	4.29 (2.24 to 8.24)	84
Moderate	1	2.13 (1.50 to 3.02)	—
Severe	13	2.27 (1.68 to 3.06)	74
Isolated traumatic brain injury:			
Isolated	4	2.41 (1.67 to 3.48)	43
Multiple trauma or unspecified	14	2.68 (1.92 to 3.73)	83
Blinding:			
Blinded	10	1.83 (1.41 to 2.37)	50
Unspecified	8	3.56 (2.57 to 4.92)	73

ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbent assay; LIA=enzyme linked immunoluminometric assay; RIA=immunoradiometric assay.

Table 4| **Summary of evidence for association of S-100β protein concentrations with mortality and unfavourable neurological outcomes in patients with traumatic brain injury**

Outcome	No of participants (studies)	Quality of evidence (GRADE)	GMR (95% CI)
Mortality	770 (12)	Moderate	2.55 (2.02 to 3.21)
GOS ≤3	933 (18)	Moderate	2.62 (2.01 to 3.42)

GMR=geometric mean ratio; GOS=Glasgow outcome score.

Figures

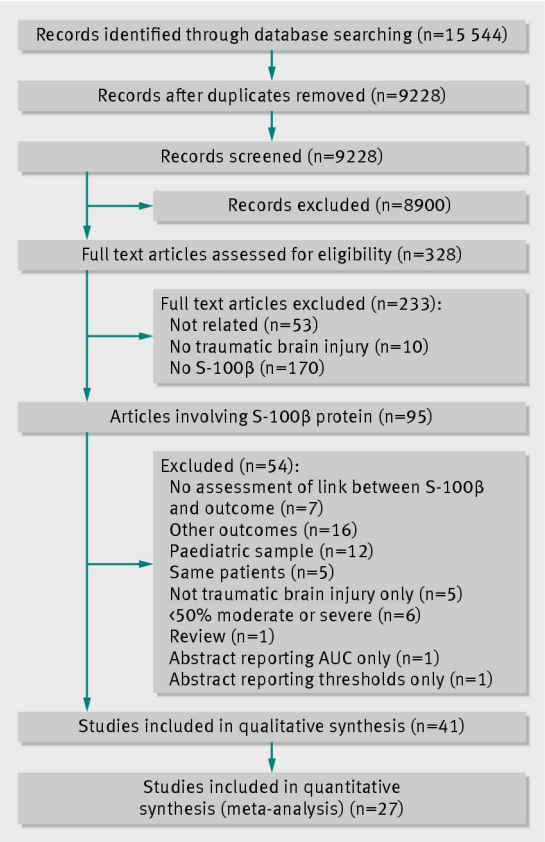

Fig 1 Identification of studies for inclusion in review of role of S-100β protein concentrations in prognosis in patients with moderate and severe traumatic brain injury

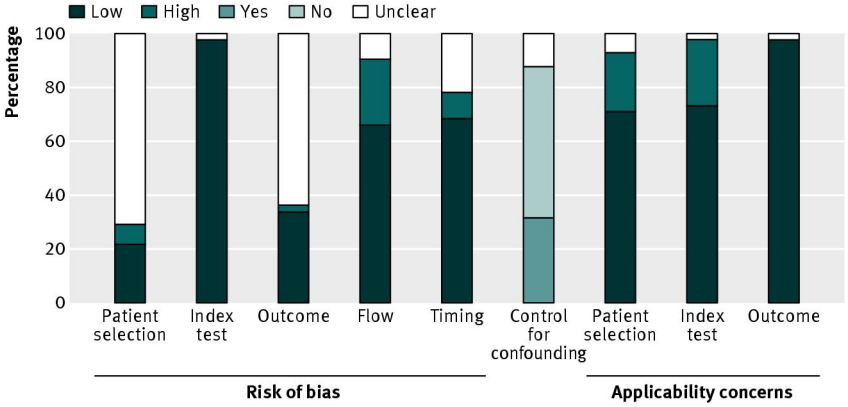

Fig 2 Risk of bias and applicability concerns of included studies examining role of S-100β protein concentrations in prognosis in patients with moderate and severe traumatic brain injury

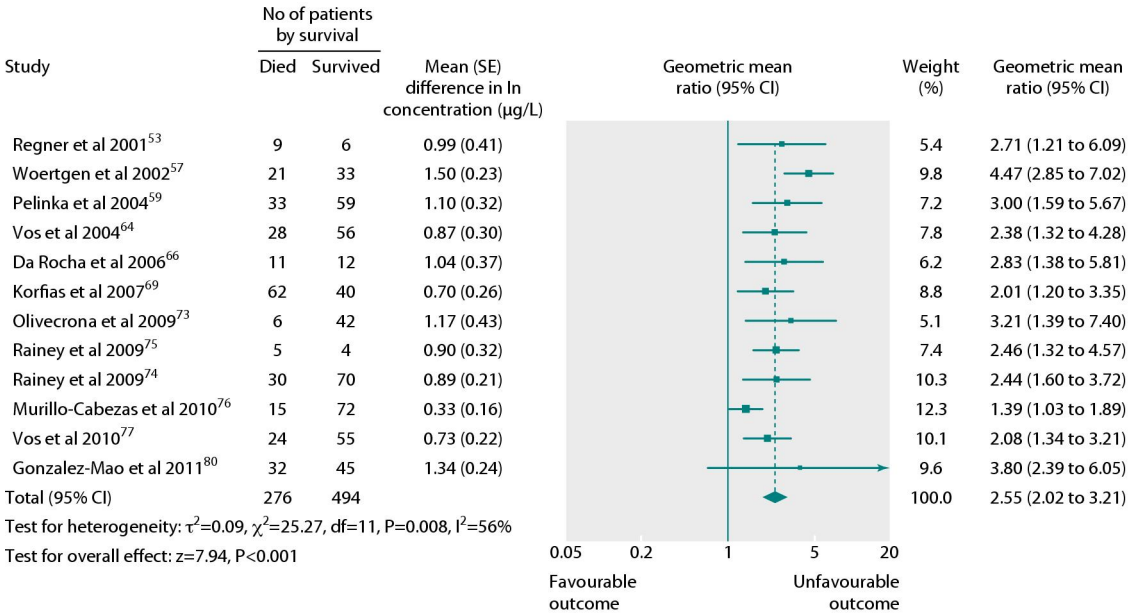

Fig 3 Association between S-100β protein (shown as mean (SE) ln transformed concentration) and mortality in patients with moderate and severe traumatic brain injury

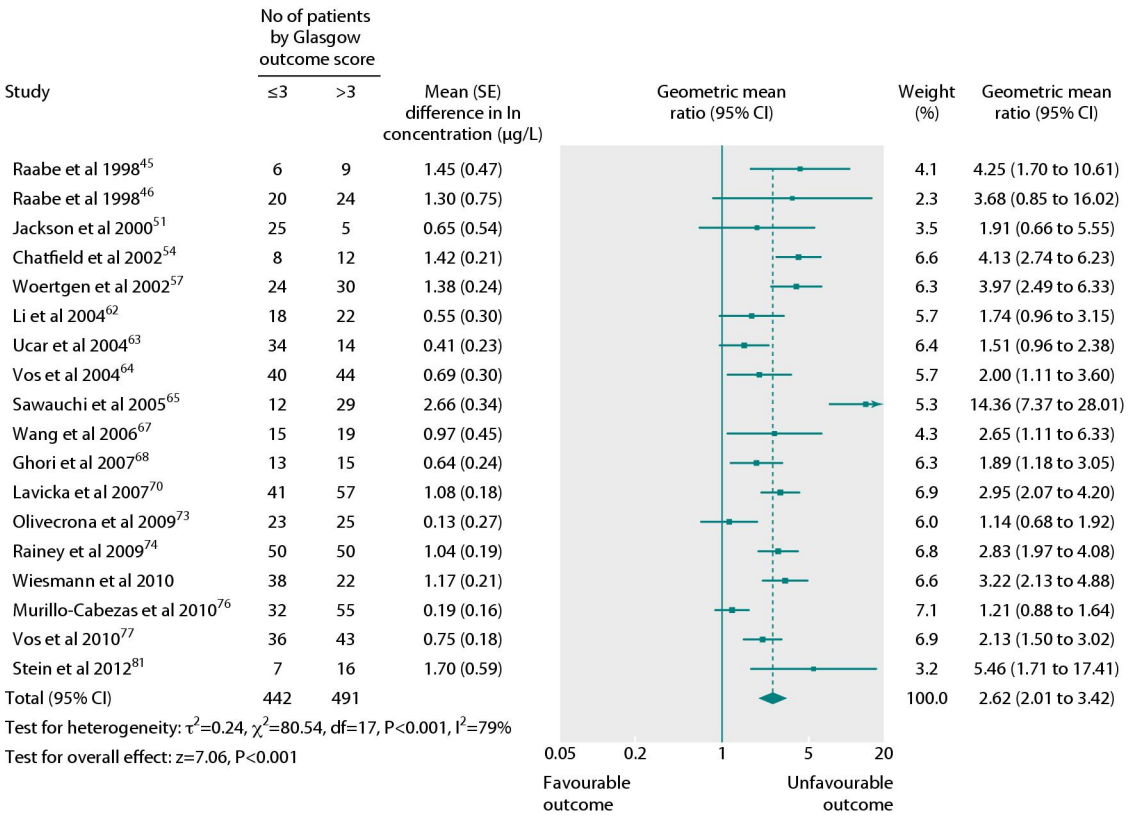

Fig 4 Association between S-100β protein (shown as mean (SE) ln transformed concentration) and Glasgow outcome score ≤3 in patients with moderate and severe traumatic brain injury

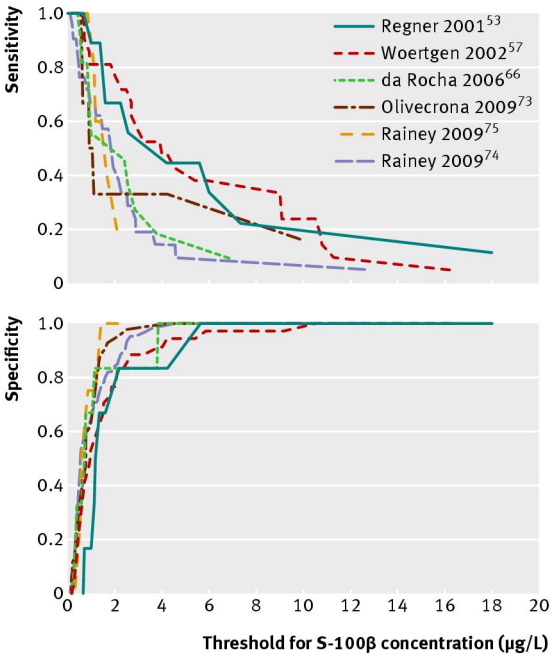

Fig 5 Sensitivity and specificity of prediction of mortality according to S-100β protein concentrations (µg/L) in patients with moderate and severe traumatic brain injury

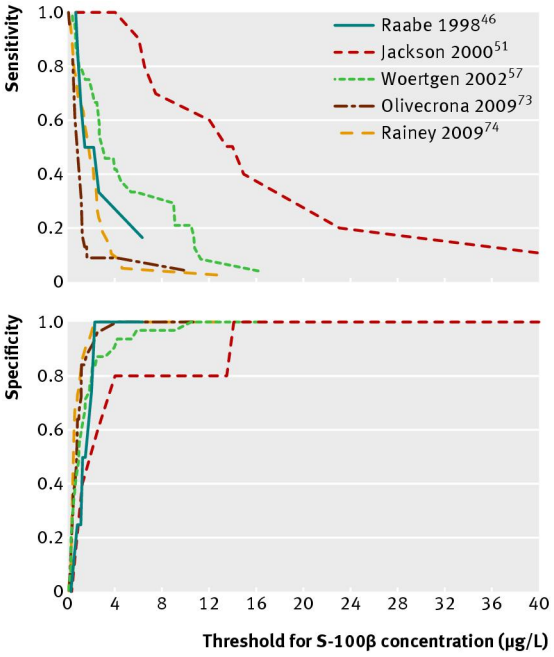

Fig 6 Sensitivity and specificity of prediction of Glasgow outcome score ≤3 according to S-100β protein concentrations (µg/L) in patients with moderate and severe traumatic brain injury