Elecsys® S100 assay
A promising marker to aid in the management of traumatic brain injury
In the USA alone, an estimated 1.7 million people sustain a traumatic brain injury (TBI) each year. Of these, 275,000 are hospitalized (16.3%), 1,365,000 are treated and released from emergency departments (80.7%) and 52,000 (3%) die.1

Patients with a severe TBI are at high risk of post-traumatic events, such as intracranial bleeding or brain edema, which lead to a rise in intracranial pressure and secondary brain damage. In such cases, rapid intervention is essential in order to relieve the intracranial pressure through medication and/or surgery (craniotomy).

Patients with severe TBI are typically treated under analgo-sedation in an intensive care unit. Although sedation provides an optimal environment for physical recovery, it limits the clinician’s options to examine the patient’s cognitive state. It is therefore common practice to monitor the stability of the patient’s neurological state using computer tomography (CT) imaging. While CT serves as a gold standard to monitor structural changes of TBI patients, two limitations restrict its usage to daily intervals or longer:

1. The need to transport a patient for CT
2. Exposure to high-dose radiation

This brochure describes the accumulating evidence that supports the value of successive S100 serum measurements in monitoring the cerebral status of patients with severe TBI. The role of S100B in the triage of adults and children with minor head injury is also reviewed. As the majority of these individuals do not have clinically significant intracerebral lesions on CT scan,2,3 a negative S100B value is a valuable tool for ruling out pathological findings and preventing unnecessary radiation exposure after minor head injury.
Role of S100

S100 proteins are a family of small, dimeric multigenic calcium-binding proteins comprising various combinations of α and β subunits. S100 proteins most commonly occur as S100A (α - α) or S100B (α - β [S100A1B] and β - β [S100BB]) subtypes. S100B is predominately confined to glial and Schwann cells and is the most well-studied subtype in TBI. Both S100A1B and S100BB have been implicated in severe TBI.

Severe TBI invariably results in neuronal destruction and destabilization of the blood–brain barrier (BBB). These phenomena are accompanied by a release of S100B protein into the blood. S100B is measurable within minutes of a TBI, and can be detected for an extended period in the bloodstream. S100B is removed from the serum by the renal clearance pathway, with a half-life of 20 to 25 minutes.

A schematic representation of the blood-brain barrier (BBB) (adapted from Deetjen/Specmann: Physiologie; München 1992; S100 added).

*Lower concentrations of S100 have been observed in chondrocytes, melanocytes, muscle tissue, and adipocytes.
Monitoring TBI progression

Monitoring progression of severe TBI with S100 assays

S100B protein is a marker that displays high clinical sensitivity for severe TBI, and the extent of S100B elevation has been found to be useful in predicting clinical outcome after brain injury.7,8

Serial daily measurements of serum S100B were found to be a useful non-invasive means for identifying brain damage and could be used for prediction of mortality.7,9* Furthermore, some studies have reported that S100B levels above certain thresholds might have predictive value on trauma-induced brain death.4,9,10

In patients with severe TBI, S100B levels in the first week post-trauma are higher in patients who died within a month, compared with those who survived for one month (Mean ± SEM).10

*Values from polytraumatic patients should only be interpreted 24 hours post-trauma owing to possible release of S100B from peripheral tissues.
Assessing severity of brain damage

**S100B levels correlate with the severity of brain damage**

S100B concentrations in serum have been shown to be representative of the extent of primary brain damage, as corroborated by clinical scales of neurological status, subsequent CT examination, and neurological outcome.

For example, in 60 patients with S100B measured within 24 hours of trauma, levels correlated with neurological outcome as assessed by the Glasgow Outcome Scale (GOS). Another study of 102 adult patients with severe TBI, demonstrated that initial serum S100B concentrations correlated with the severity of brain injury on CT imaging as determined by the Marshall classification.

Mean (±SD) S100B levels measured 24 h after trauma were highest in patients who died or were in a persistent vegetative state (GOS 1/2) than in those with severe disability (GOS 3; p < 0.001) or those with moderate/low disability (GOS 4/5; p < 0.0001).

**Dark green bars:** S100B measured on admission; **light green bars:** S100B measured 24 h after trauma. GOS, Glasgow Outcome Scale.
Warning of secondary deteriorations

**S100 levels may indicate secondary neurological deterioration in patients with severe TBI**

Secondary neurological events are accompanied by an elevation in the serum levels of S100B, often visible earlier than when detected with diagnostic imaging.\(^4\,15\,16\) S100B levels have been shown to rise hours to days before changes in intracranial pressure or onset of cerebral hypoxia.\(^4\,17\) S100B levels may be used to monitor comatose intensive care patients for neurological complications such as a new infarction, new hemorrhage, or a newly developed progressive disease.\(^16\)

Serial measurements using the S100 assay may therefore help a clinician to recognize the onset of a neurological complication and enable early therapeutic intervention.\(^16\) The same study has shown that this information affected patient management in 21% of severe TBI cases.\(^16\)

![Change in serum S100B concentrations in a patient with severe craniocerebral trauma classified as 8 on Glasgow Coma Scale (GCS) coupled with subarachnoid hemorrhage. The patient was under analgo-sedation and intubated.\(^16\)](image)

**S100B value at admission was 0.88 μg/L. Value decreased steadily over 12 days, then rose sharply to 1.99 μg/L at day 13, coinciding with a neurological complication. Emergency CT revealed a cerebral infarction of medium size, which was possibly caused by a secondary cerebral vasospasm.**\(^16\)
### Predicting outcome

**S100 levels predict short-, medium-, and long-term patient outcome**

S100B is related to outcome prognosis. Serial measurement of S100B accurately predicts short-term mortality, with the strongest correlation with clinical outcome seen >84 hours after trauma. Comparison of time courses of S100B levels in patients with favorable and unfavorable outcomes also indicate that S100B values by day 2 after admission independently predict 12-month mortality.

In a meta-analysis of 41 studies, serum S100B concentrations measured after moderate or severe TBI were significantly associated with prognosis in the short (<3 months), medium (3–6 months) or long term (6 months), as defined by mortality or a Glasgow Outcome Score ≤3. Furthermore, this association was unaffected by concomitant traumatic injuries.

#### Table: Associations between S100B and mortality in patients with moderate and severe TBI

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients by survival</th>
<th>Mean (SE) difference in ln concentration (μg/L)</th>
<th>Geometric mean ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Geometric mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regner et al, 2001</td>
<td>9</td>
<td>0.99 (0.41)</td>
<td></td>
<td>5.4</td>
<td>2.71 (1.12–6.09)</td>
</tr>
<tr>
<td>Woertgen et al, 2002</td>
<td>21</td>
<td>1.50 (0.23)</td>
<td></td>
<td>9.8</td>
<td>4.47 (2.85–7.02)</td>
</tr>
<tr>
<td>Pelinka et al, 2004</td>
<td>33</td>
<td>1.10 (0.32)</td>
<td></td>
<td>7.2</td>
<td>3.00 (1.59–5.67)</td>
</tr>
<tr>
<td>Vos et al, 2004</td>
<td>28</td>
<td>0.87 (0.30)</td>
<td></td>
<td>7.8</td>
<td>2.38 (1.32–4.28)</td>
</tr>
<tr>
<td>Da Rocha et al, 2006</td>
<td>11</td>
<td>1.04 (0.37)</td>
<td></td>
<td>6.2</td>
<td>2.83 (1.38–5.81)</td>
</tr>
<tr>
<td>Korfas et al, 2007</td>
<td>62</td>
<td>0.70 (0.26)</td>
<td></td>
<td>8.8</td>
<td>2.01 (1.20–3.35)</td>
</tr>
<tr>
<td>Olivecrona et al, 2009</td>
<td>6</td>
<td>1.17 (0.43)</td>
<td></td>
<td>5.1</td>
<td>3.21 (1.39–7.40)</td>
</tr>
<tr>
<td>Rainey et al, 2009a</td>
<td>5</td>
<td>0.90 (0.32)</td>
<td></td>
<td>7.4</td>
<td>2.46 (1.32–4.57)</td>
</tr>
<tr>
<td>Rainey et al, 2009b</td>
<td>30</td>
<td>0.89 (0.21)</td>
<td></td>
<td>10.3</td>
<td>2.44 (1.60–3.72)</td>
</tr>
<tr>
<td>Murrillo-Cabezas et al, 2010</td>
<td>15</td>
<td>0.33 (0.16)</td>
<td></td>
<td>12.3</td>
<td>1.38 (1.03–1.89)</td>
</tr>
<tr>
<td>Vos et al, 2010</td>
<td>24</td>
<td>0.73 (0.22)</td>
<td></td>
<td>10.1</td>
<td>2.08 (1.34–3.21)</td>
</tr>
<tr>
<td>Gonzalez-Mao et al, 2011</td>
<td>32</td>
<td>1.34 (0.24)</td>
<td></td>
<td>9.6</td>
<td>3.80 (2.39–6.05)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>276</td>
<td>0.95 (0.2)</td>
<td>1</td>
<td>100</td>
<td>2.55 (2.02–3.21)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2 = 0.009$, $\chi^2 = 25.27$, df = 11, $P= 0.008$, $I^2 = 56$

Test for overall effect: $z = 7.94$, $P<0.001$

Associations between S100B (shown as mean ±SEM ln transformed concentration) and mortality in patients with moderate and severe TBI.
Reducing CT use in low-risk head injury patients

S100B testing can help determine which low-risk patients with minor head injury do not need a CT

A CT scan has high sensitivity for detecting intracranial injuries in patients with head injury. However, the technique is costly, exposes the patient to high doses of radiation, and clinically relevant lesions are found in less than 10% of cases of minor head injury. Several studies have demonstrated that a normal S100B level reliably predicts normal CT findings after minor head injury in adults.

In a prospective multicenter study of 1,309 patients with minor head injury, an S100B cutoff of 0.10 μg/L (the 95th percentile of healthy volunteers) identified those patients with trauma-relevant CT findings with a sensitivity of 99% and a negative predictive value of 99.68%.

A meta-analysis of 12 studies of adults with minor head injury reported a pooled sensitivity for S100B for the prediction of CT findings of 97% (95% CI, 91–99%) and pooled specificity of 40% (95% CI, 30–51%). This equated to a negative predictive value of >99% (95% CI, 98–100%) at an average prevalence for intracranial findings after minor head injury of 8%. Omitting CT in adults with minor head injury and an S100B concentration of <0.10 μg/L would reduce the number of CTs by approximately one-third.

International guidelines advise that adult patients with mild head injury and no risk factors who have a serum S100B level <0.10 μg/L measured within 6 hours of injury may be discharged without the need for CT.

<table>
<thead>
<tr>
<th>S100B</th>
<th>CCT+</th>
<th>CCT-</th>
<th>Positive predictive value, 10% (95% CI, 7–13%)</th>
<th>Negative predictive value 99.68% (95% CI, 99–100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.10 μg/L</td>
<td>92</td>
<td>855</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.10 μg/L</td>
<td>1</td>
<td>361</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>1,216</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contingency table for serum S100B according to cranial CT (CCT) findings in 1,309 patients with minor head injury. CCT-, patients without any sign of trauma-relevant intracerebral lesions on CT; CCT+, patients with at least one trauma-relevant CT finding.

The specificity of only 30% at this cutoff value indicates that elevated S100B levels may also indicate head injuries that are not reflected by the initial CT scan.
S100B is a valuable tool to rule out pathological findings in children with mild TBI

Diagnosis of TBI in children with head injury can be more challenging than in adults, as obtaining a reliable patient history may be difficult and physical examination can be uncomfortable for the child.

Similar to studies in adult populations, S100B levels measured following TBI in pediatric populations predict CT findings\(^{24,25}\) and outcomes.\(^{26,27}\) In a study of 446 children who presented within 3 hours of mild TBI, S100B levels correlated with severity of TBI and predicted a poor clinical evolution with 100% sensitivity (95% CI, 84–100%).\(^{24}\) Furthermore, S100B levels had a 100% negative predictive value for ruling out trauma-relevant intracerebral lesions on CT. Hence, S100B determination during the first 3 hours after TBI can potentially reduce the number of CT scans in children.

\[\text{Median (IQR) concentration of S100B increased with increasing Masters Score group (*p <0.05 across all three groups)}\]^\(^{23}\) IQR, interquartile range; GCS, Glasgow Coma Scale.

The proportion of patients with a positive S100B value for each Masters Score group was 60%, 70%, and 100% for Masters Score 1, 2 and 3 respectively (age-specific cutoffs were used to determined positivity: 0.3 μg/L for age 0–9 months; 0.23 μg/L for age 10–24 months; 0.18 μg/L for age >24 months).