**Supplemental Digital Content 3.** **Results**

**Supplemental Digital Content 3, Table 1**. Basic demographics, imaging modality and review question for all included studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (first) and year** | **Biomarker** | **Patient Cohort** | **TBI case numbers** | **GCS range** | **Imaging modality** | **Positive imaging in cases (%)** | **Review question investigated** |
| Abbasi M, *2004*1 | S100B | Adult | 90 | 9-15 | CT | 51.1 | Lesion type |
| Al Nimer F, *2015* (e)2 | NF-L, S100B, NSE | Adult | 182 | 3-15 | CT, MRI | 100 | Lesion type Scoring system/Image Classification |
| Bogoslovsky T, *2017*3 | GFAP, Tau, AB42 | Adult | 34 | 3-15 | CT | 100 | Scoring system/Image Classification |
| Carabias CS, 20204 | S100B, GFAP, NSE, T tau, NF-H, Serum Amyloid A1 (SAA1), CRP, procalcitonin, chitinase-3-like protein 1 (YKL-40) | Adult | 115 | 3-15 | CT | 57.4 | Lesion number/volume |
| Castello LM, *2018*5 | copeptin | Adult | 105 | 13-15 | CT | 20 | Lesion type |
| De Oliveira CO, *2007*6 | vWF | Adult | 44 | 3-8 | CT | NA | Scoring system/Image Classification |
| Dickens AM, *2018*7 | GFAP, UCH-L1, d- galactose,  unknown sugar derivative,  A203003, 3-Deoxyhexitol,  phenolic compound,  unknown sugar (saccharide),  2 Aminobutyric acid,  glutamic acid, amino acid,  3-deoxyhexonic acid,  3-oxobutanoic acid,  acetoacetic acid,  glycerol 3 phosphate,  arabinofuranose,  A190025,  amino acid, 3-Hydroxybutyric acid,  Phosphoric acid monomethyl ester, Aminomalonic acid,  2-Monopalmitoylglycerol,  Octanoic acid,  Unknown amino acid,  Pentitol 3-desoxy,  Amino Acid,Phenolic compound,  H-Indole-3-acetic acid,  1-hydroxy,Tartronic acid,  Unknown sugar (deoxyaldose),  Serotonin,  A249004 (sugar, saccharide),  Decanoic acid,  Diethylene glycol, Inositol,  Ribonic acid,  Glucuronic acid,  Unknown carboxylic acid | Adult | 210 | 3-15 | CT | 54.8 | Scoring system/Image Classification |
| Egea-Guerrero JJ, *2012*8 | S100B | Adult | 143 | 13-15 | CT | 10.5 | Lesion number/volume |
| Egea-Guerrero JJ, *2018*9 | S100B | Adult | 260 | 13-15 | CT | 8.5 | Lesion number/volume |
| Faulkinberry S, *2019*10 | Tau | Paediatric | 36 | 3-12 | CT | NA | Lesion type |
| Ghonemi MO, *2013*11 | NF-H | Adult | 30 | 3-15 | CT | NA | Scoring system/Image Classification |
| Guzel A, *2008*12 | NSE | Adult, Paediatric | 169 | 3-15 | CT | 100 | Lesion type |
| Hatefi M, *2016*13 | Uric acid | Adult | 725 | 3-8 | CT | 58.21 | Scoring system/Image Classification |
| Heidari K, *2015*14 | S100B | Adult | 165 | 13-15 | CT | NA | Lesion type |
| Herrmann M, *2000*15 | S100B, NSE | Adult | 66 | 3-15 | CT | 60.6 | Lesion type Lesion number/volume Scoring system/Image Classification |
| Honda M, *2010*16 | S100B, GFAP, NSE | Adult | 18 | 3-15 | CT | 100 | Scoring system/Image Classification |
| Ingebrigtsen T, *1999* (b)17 | S100B | Adult, Paediatric | 50 | 13-15 | CT, MRI | 10 | Lesion type |
| Kelmendi FM, *2018*18 | S100B | Paediatric | 80 | 13-15 | CT | 66.25 | Lesion number/volume |
| Korfias S, *2007*19 | S100B | Adult | 112 | 3-8 | CT | 99 | Scoring system/Image Classification |
| Kou Z, 201320 | GFAP, UCH-L1 | Adult | 9 | 15 | CT, MRI | 33.3 | Lesion type  Lesion number/volume |
| Langness S, *2018*21 | D-Dimer | Paediatric | 663 | 3-15 | CT | 38.3 | Lesion type |
| Li Q, *2017*22 | GFAP, NSE, S100B | Adult | 80 | NA | CT | NA | Scoring system/Image Classification |
| Ljungqvist J, *2017*23 | NF-L and S100B | Adult | 9 | 3-15 | MRI | 100 | Lesion type |
| Lo TY, *2009*24 | S100B, NSE, IL-6, Il-8, IL-10, SICAM, L-selectin, endothelin | Paediatric | 28 | 3-15 | CT | 100 | Injury Pattern |
| McMahon PJ, *2015*  (a)25 | GFAP-BDP | Adult | 215 | 3-15 | CT, MRI | 51.5 | Scoring system/Image Classification |
| Metting Z, *2012*26 | GFAP, S100B | Adult | 94 | 13-15 | CT, MRI | 20 | Lesion type |
| Mondello S, *2012* (c)27 | GFAP, UCH-L1 | Adult | 59 | 3-8 | CT | 98 | Scoring system/Image Classification |
| Mondello S, *2016*28 | GFAP, UCH-L1 | Paediatric | 45 | 3-15 | CT | 78 | Lesion type |
| Mondello S, *2011* (c)29 | GFAP, UCH-L1 | Adult | 81 | 3-8 | CT | 98 | Scoring system/Image Classification |
| Muller K, *2007*30 | S100B | Adult | 226 | 13-15 | CT | 9 | Lesion type |
| Naeimi ZS, *2006*31 | S100B NSE | Adult | 45 | 3-15 | CT | 71.1 | Scoring system/Image Classification |
| Okonkwo DO, *2013* (a)32 | GFAP-BDP | Adult | 215 | 3-15 | CT | NA | Lesion number/volume |
| Pandey S, *2017*33 | C Tau | Adult | 40 | 3-8 | CT | 87.5 | Lesion type |
| Papa L, *2017*34 | UCH-L1 | Adult, Paediatric | 148 | 13-15 | CT | 11 | Lesion type |
| Papa L, *2014*35 | GFAP, S100B | Adult | 209 | 3-15 | CT | 26 | Lesion type |
| Pelinka LE, *2004* (d)36 | GFAP, S100B | Adult | 92 | 3-8 | CT | 100 | Scoring system/Image Classification |
| Pelinka LE, *2004* (d)37 | GFAP | Adult | 101 | 3-8 | CT | 100 | Scoring system/Image Classification |
| Pleines, UE *2001*38 | S100B, NSE | Adult | 13 | 3-8 | CT | 100 | Lesion number/volume |
| Posti JP, *2016*39 | GFAP, UCH-L1 | Adult | 389 | 3-15 | CT | 72.8 | Scoring system/Image Classification |
| Raabe A, *1998*40 | S100B, NSE | Adult | 44 | 3-8 | CT | NA | Lesion type Lesion number/volume Scoring system/Image Classification |
| Radwan W, *2013*41 | NF-H | Adult | 30 | 13-15 | CT | NA | Scoring system/Image Classification |
| Romner B, *2000* (b)42 | S100B | Adult | 278 | 3-15 | CT | 92 | Lesion type |
| Rubenstein R, *2017* (a)43 | P Tau, T Tau | Adult | 196 | 3-15 | CT | 44.9 | Scoring system/Image Classification |
| Sandsmark DK, *2019*44 | vWF, Cellular Fibronectin, NF-H | Adult | 76 | 3-15 | MRI | 39.5 | Lesion type |
| Shakeri M, *2014*45 | S100B | Adult | 72 | 3-8 | CT | NA | Scoring system/Image Classification |
| Skandsen T, *2018*46 | GFAP, NF-L | Adult | 93 | 13-15 | MRI | 10 | Lesion type |
| Skogseid IM, 199247 | Creatine Kinase BB, NSE | Adult | 60 | 3-15 | CT | 61.6 | Lesion number/volume |
| Thelin EP, *2019* (e,f)48 | S100B, NSE, GFAP, UCH-L1, Tau, NF-L | Adult | 172 | 3-15 | CT | NA | Scoring system/Image Classification |
| Thelin EP, *2016* (e,f)49 | NSE, S100B | Adult | 417 | 3-15 | CT | 99.8 | Scoring system/Image Classification |
| Thelin EP, *2013* (e)50 | S100B | Adult | 265 | 3-15 | CT | NA | Lesion type |
| Thelin EP, *2016* (f)51 | S100B | Adult | 127 | 3-15 | CT | 30 | Lesion type Scoring system/Image Classification |
| Tomita K, *2019*52 | Tau | Adult | 40 | 3-15 | MRI | 32.5 | Lesion type |
| Vervliet B, *2012*53 | B-FABP | Adult | 20 | 3-15 | CT | NA | Scoring system/Image Classification |
| Vos PE, *2004*54 | S100B, GFAP, NSE | Adult | 85 | 3-8 | CT | 95 | Scoring system/Image Classification |
| Wolf H, *2015*55 | S100B | Adult | 1696 | 3-15 | CT | 8 | Lesion type  Lesion number/volume |
| Yue JK, *2019* (a)56 | GFAP | Adult | 450 | 13-15 | MRI | 26.7 | Lesion type |
| Zurek J, *2011* (g)57 | NF-H | Paediatric | 49 | 3-15 | CT | 87.8 | Lesion type Scoring system/Image Classification |
| Zurek J, *2010* (g)58 | S100B | Paediatric | 43 | 3-8 | CT | 90.7 | Lesion type Scoring system/Image Classification |
| Zurek J, *2011* (g)59 | GFAP | Paediatric | 59 | 3-8 | CT | NA | Scoring system/Image Classification |

(a)-(g) indicates papers with potentially shared populations. Lesion Type = Biomarker concentration and specific intracranial lesion type or types, Scoring system/Image Classification = Biomarker concentration and imaging classifications, Lesion number/volume = Biomarker concentration and volume or number of intracranial lesions, Injury Pattern = Biomarker concentration and specific intracranial lesion types injury pattern (diffuse or focal injury). GCS = Glasgow Coma Score, GFAP = Glial Fibrillary acidic protein, GFAP-BDP= Glial fibrillary acidic protein Breakdown Products, S100B = S100 B calcium-binding protein, NSE = neuron specific enolase, CRP=C-reactive Protein, UCH-L1 = Ubiquitin carboxy-terminal hydrolase L1, NF-H = Neurofilament heavy, NF-L = Neurofilament heavy, vWF = von willebrand factor, IL= Interleukin, SICAM = soluble intracellular adhesion molecule, CT = Computed Tomography, MRI = Magnetic Resonance Imaging. The lettering a-g indicate studies with potentially shared or overlapping patient cohort

**Demographics descriptive summary**

A total of 9667 TBI patients were included (median patients per paper 90, range 920,23-169655), the majority male (median 69.7%, range 30.2%12 – 89%20), with a median prevalence of traumatic imaging findings of 59.4% (range 855-100%). Forty-nine studies assessed CT imaging, five assessed MRI and five assessing both imaging modalities (Supplemental Digital Content 3, Table 1). Fifty-eight unique compounds were assessed as potential biomarkers of TBI (Supplemental Digital Content 3, Table 2). Thirty papers assessed imaging classifications or injury patterns, 28 assessed lesion type, and 11 assessed lesion volume or number. Paper numbers, demographics, and imaging characteristics for the most commonly occurring biomarkers are presented in Table 1.

**Supplemental Digital Content 3, Table 2 –** Biomarkers of traumatic brain injury (TBI) highlighted in this review

|  |  |
| --- | --- |
| **Biomarkers** | **Number of papers** |
| S100B (S100 calcium-binding protein B) | 30 |
| GFAP (Glial Fibrillary Acidic Protein) | 19 |
| NSE (Neuron Specific Enolase) | 14 |
| UCH-L1 (Ubiquitin carboxy-terminal hydrolase L1) | 8 |
| Tau proteins (including c-tau, t-tau and p-tau) | 7 |
| NF-H (Neurofilament heavy) | 5 |
| NF-L (Neurofilament light) | 4 |
| Amino acid | 4 |
| GFAP-BDP (Glial Fibrillary Acidic Protein Breakdown Products) | 2 |
| Phenolic compound | 2 |
| vWF (Von Willebrand factor) | 2 |
| 2 Aminobutyric acid | 1 |
| 2-Monopalmitoylglycerol | 1 |
| 3-Deoxyhexitol | 1 |
| 3-deoxyhexonic acid | 1 |
| 3-Hydroxybutyric acid | 1 |
| 3-oxobutanoic acid | 1 |
| A190025 | 1 |
| A203003 | 1 |
| A249004 (sugar, saccharide) | 1 |
| AB42 | 1 |
| acetoacetic acid | 1 |
| Aminomalonic acid | 1 |
| arabinofuranose | 1 |
| B-FABP (Brain fatty acid binding protein) | 1 |
| Cellular Fibronectin | 1 |
| chitinase-3-like protein 1 (YKL-40) | 1 |
| Copeptin | 1 |
| CRP | 1 |
| Creatine Kinase BB | 1 |
| d- Galactose | 1 |
| D-Dimer | 1 |
| Decanoic acid | 1 |
| Diethylene glycol | 1 |
| endothelin | 1 |
| Glucuronic acid | 1 |
| glutamic acid | 1 |
| glycerol 3 phosphate | 1 |
| H-Indole-3-acetic acid, 1-hydroxy | 1 |
| IL-10 | 1 |
| IL-6 | 1 |
| Il-8 | 1 |
| Inositol | 1 |
| L-selectin | 1 |
| Octanoic acid | 1 |
| Pentitol 3-desoxy | 1 |
| Phosphoric acid monomethyl ester | 1 |
| Procalcitonin | 1 |
| Ribonic acid | 1 |
| Serotonin | 1 |
| Serum Amyloid A1 | 1 |
| SICAM (soluble intercellular adhesion molecule) | 1 |
| Tartronic acid | 1 |
| Unknown carboxylic acid | 1 |
| Unknown sugar (deoxyaldose) | 1 |
| Unknown sugar (saccharide) | 1 |
| Unknown sugar derivative | 1 |
| Uric acid | 1 |

**Supplemental Digital Content 3, Table 3 -** Biomarker, Assay, time to biomarker and key findings of each included study assessing biomarker concentration and volume or number of intracranial lesions.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (first) and year** | **Biomarker** | **Biomarker Assay** | **Time to first biomarker sample** | **Number of patients** | **Significant associations of biomarker to lesion volume or number** |
| Carabias CS, 20204 | S100B; GFAP; NSE; T tau  NF-H; Serum Amyloid A1; CRP; YKL-40 | S100B: LIAISON-mat S100 system; Sangtec Medical  GFAP: Glial Fibrillary Acidic Protein Human ELISA; BioVendor  NSE: Elecsys NSE immunoassay; Roche Diagnostics  T-tau: KHB0041; Invitrogen  NF-H: Human Phosphorylated Neurofilament H ELISA; BioVendor  Serum Amyloid A1: EL10015L; Anogen  CRP: Cobas CRP; Roche Diagnostics  YKL- YKL-40 EIA kit; Quidel | Median: 9.15 hrs | 115 | S100B - Correlation with ICH, IVH, tSAH and total haemorrhage volume. Weak correlation to EDH. No correlation to SDH. GFAP - Correlation with ICH, IVH, tSAH and total haemorrhage volume. No correlation to EDH or SDH.  T tau - Correlation with ICH, IVH, tSAH and total haemorrhage volume. Weak correlation to EDH. No correlation to SDH. NSE - Correlation with IVH, tSAH and total haemorrhage volume. No correlation to ICH, EDH or SDH. NFH - Correlation with ICH, SDH and total haemorrhage volume. Weak correlation to tSAH. No correlation to IVH or EDH. SAA1 - Correlation with ICH, IVH, tSAH, SDH and total haemorrhage volume. No correlation to EDH.  CRP - Correlation with ICH, IVH, tSAH, SDH and total haemorrhage volume. No correlation to EDH. PCT - Correlation with ICH, IVH, tSAH, EDH and total haemorrhage volume. Weak correlation to SDH.  YKL-40 - Correlation with ICH, IVH, tSAH, SDH and total haemorrhage volume. No correlation to EDH. |
| Egea-Guerrero JJ, *2012*8 | S100B | Elecsys 2010; Roche Diagnostics | <6 hrs post injury | 143 | Increased S100B with increased lesion numbers |
| Egea-Guerrero JJ, *2018*9 | S100B | Elecsys 2010; Roche Diagnostics | <6 hrs post injury | 260 | Increased S100B with increased lesion numbers |
| Herrmann M, *2000*15 | S100B  NSE | Sangtec 100; Sangtec Medical | Median: 30 hrs | 66 | Increased S100B and NSE with increased contusion volume  No correlation between NSE or S100B and SDH, EDH volume |
| Kelmendi FM, *2018*18 | S100B | Elecsys S100; Roche Diagnostics | <3 hrs post injury | 80 | Increased S100B with increased lesion numbers |
| Kou Z, 201320 | GFAP, UCH-L1 | MesoScale Discovery Platform, Banyan Biomarkers | <6 hrs post injury | 9 | No correlation found between UCH-L1 or GFAP concentrations and structural MRI grading or DTI lesion load |
| Okonkwo DO, *2013* (a)32 | GFAP-BDP | GFAP-BDP ELISA; Banyan Biomarkers | <24 hrs post injury | 215 | Increased GFAP-BDP with increased lesion numbers |
| Pleines, UE *2001*38 | S100B  NSE | S100B: Sangtec 100; Sangtec NSE: Wallac Sverige AB | Admission | 13 | Increased S100B with contusion volume. No correlation between NSE and contusion volume |
| Raabe A, *1998*40 | S100B  NSE | S100B: Sangtec 100; Sangtec Medical  NSE: NSE assay; Sangtec Medical | Median (range) - 12 hrs (6-24) | 44 | Increased S100B and contusion volume. No correlation between NSE and contusion volume |
| Skogseid IM, 199247 | Creatine Kinase BB, NSE | Own Assay | Group 1 Median: 1 hrs  Group 2 Median: 2.5 hrs | 60 | Correlation between CK and NSE with volume of contusion |
| Wolf H, *2015*55 | S100B | Elecsys S100; Roche Diagnostics | <3 hrs of injury | 1696 | Increased S100B with increased lesion numbers |

GFAP-BDP = Glial fibrillary acidic protein break down products, GFAP= Glial fibrillary acidic protein, S100B = S100 B calcium-binding protein, NSE = neuron specific enolase, UCH-L1 = Ubiquitin carboxy-terminal hydrolase L1, NF-H = Neurofilament heavy, NFL = Neurofilament heavy, T tau = Total tau, YKL-40 = Procalcitonin chitinase-3-like protein 1, SAA1 = Serum Amyloid A1, DTI = Diffusion Tensor Imaging, CT = Computed Tomography, CRP= C Reactive Protein, ICH= Intracerebral haemorrhage, IVH= interventricular haemorrhage, tSAH= traumatic subarachnoid haemorrhage, EDH = Extradural haematoma, SDH= Subdural haematoma

**Supplemental Digital Content 3, Table 4 -** Biomarker, Assay, time to biomarker, analysis technique and key findings of each included study assessing biomarker concentration and imaging classification systems

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author (first) and year** | **Biomarker** | **Biomarker Assay** | **Time to first biomarker sample** | **Score used as categorical or continuous variable** | **Number of patients** | **Association with named score** |
| **Marshall Score** | | | | | | |
| Al Nimer F, *2015* (e)2 | NF-L; S100B;  NSE | NF-L: Uman Diagnostics NF-light® assay; Uman Diagnostics  S100B: LIAISON-mat S100 system, Sangtec, until September 2008 followed by Elecsys S100B; Roche Diagnostics.  NSE: Liaison, DiaSorin | Admission | Continuous | 182 | No significant association |
| Bogoslovsky T, *2017*3 | GFAP; Tau; AB42 | Digital array; Quanterix Corporation | <24 hours of injury | Continuous | 34 | Significant positive correlation – Tau only |
| De Oliveira CO, *2007*6 | vWF | Own Assay | Admission | Continuous | 44 | Significant positive correlation |
| Dickens AM, *2018*7 | Serum metabolites | Own Assay | <12 hours of admission | Categorical | 210 | Significantly higher in Grade V–VI |
| Ghonemi MO, *2013*11 | NF-H | Human Phosphorylated Neurofilament H ELISA; BioVendor | <24 hours of admission | Continuous | 30 | Significant positive correlation |
| Hatefi M, *2016*13 | Uric acid | Not provided | < 24 hours of admission | Continuous | 725 | Significant negative correlation |
| Herrmann M, *2000*15 | S100B; NSE | S100B: Sangtec 100; AB Sangtec Medical  NSE: LIA-mat® system | Median: 30 hrs | Categorical | 66 | Significantly higher in Grade IV-VI |
| Honda M, *2010*16 | S100B; GFAP; NSE | GFAP: Glial Fibrillary Acidic Protein Human ELISA; BioVendor S100B: YK151S-100B Elisa; Yanaihara Institute  NSE: NSE kit; Alpha Diagnostic | <3 hrs post admission | Categorical | 18 | No significant result |
| Korfias S, *2007*19 | S100B | Lia-mat Sangtec 100, | Admission | Categorical | 112 | Significantly higher in Grade V vs VI, and VI vs I-II |
| Mondello S, *2011* (c)27 | GFAP; UCH-L1 | GFAP: BioVendor  UCH-L1: Own Assay | Median: 7 hrs | Categorical | 59 | GFAP significantly higher in mass lesions. UCH-L1 significantly higher in diffuse injury. |
| Naeimi ZS, *2006*31 | S100B; NSE | S100B: Sangtec 100; AB Sangtec Medical NSE: Roche Diagnostics | <24 hours | Continuous | 45 | Significant positive correlation |
| Pelinka LE, *2004* (d)36 | GFAP; S100B | GFAP: LIAISON GFAP; DiaSorin S100B: Sangtec 100; AB Sangtec Medical | Admission | Categorical | 101 | Higher in abnormal scans |
| Pelinka LE, *2004* (d)37 | GFAP | LIAISON GFAP; DiaSorin | Admission | Categorical | 92 | Higher in abnormal scans |
| Posti JP, *2016*39 | GFAP; UCH-L1 | Randox biochip; Randox Laboratories | <24 hours after Admission | Categorical | 389 | Higher in abnormal scans |
| Raabe A, *1998*40 | S100B  NSE | Sangtec 100; AB Sangtec Medical | Median (range): 12 (6-24) hrs | Continuous | 44 | Significant positive correlation -S100B only |
| Radwan W, *2013*41 | NF-H | Not stayed | Admission | Continuous | 30 | Significant positive correlation |
| Rubenstein R, *2017* (a)43 | P Tau; T Tau | a-EIMAF | Mean (SD): 10.6 (6.4) hrs | Categorical | 196 | Higher in abnormal scans |
| Shakeri M, *2014*45 | S100B | Not stated | Mean (SD): 2 (0.5) hrs after admission | Continuous | 72 | Significant positive correlation |
| Thelin EP, *2019* (e,f)48 | S100B; NSE; GFAP; UCH-L1; Tau; NF-L | S100B LIAISON-mat S100 system, Sangtec, and Elecsys S100B; Roche Diagnostics.  NSE: LIAISON NSE: Sangtec  GFAP, UCH-L1, Tau and NFL: Neurology 4-plex assay, Quanterix | Admission | Continuous | 172 | Significant positive correlations except for Tau and NF-L. |
| Thelin EP, *2016* (e,f)49 | NSE; S100B | NSE: LIAISON NSE; Sangtec Medical  S100B: LIAISON-mat S100 system, Sangtec Medical and Elecsys S100B; Roche Diagnostics. | Admission | Continuous | 417 | No significant associations |
| Vervliet B, *2012*53 | B-FABP | Not stated | Admission | Categorical | 20 | Higher in abnormal scans |
| Vos PE, *2004*54 | S100B; GFAP; NSE | NSE: Prolifigen NSE IRMA; AB Sangtec Medical  S100B: Sangtec 100; AB Sangtec Medical GFAP: in-house ELISA | Median (range): 2.5 (0.25–30.0) hrs | Continuous | 85 | Significant positive correlations |
| Zurek J, *2011* (g)57 | NF-H | Phosphorylated Neurofilament H Human ELISA; BioVendor | Admission | NA | 49 | Higher in diffuse injury |
| Zurek J, *2010* (g)58 | S100B | Elecsys S100B; Roche Diagnostics | Admission | Categorical | 43 | No significant associations |
| Zurek J, *2011* (g)59 | GFAP | Glial Fibrillary Acidic Protein Human ELISA; BioVendor | <3 hours of injury | Categorical | 59 | No significant associations |
| **Rotterdam** | | | | | | |
| Al Nimer F, *2015* (e)2 | NF-L; S100B; NSE | NF-L: Uman Diagnostics NF-light® assay; Uman Diagnostics  S100B: LIAISON-mat S100 system, Sangtec, until September 2008 followed by Elecsys S100B; Roche Diagnostics.  NSE: Liaison, DiaSorin | Admission | Continuous | 182 | No significant associations |
| McMahon PJ, *2015*  (a)25 | GFAP-BDP | Banyan Biomarkers | <24 hours | Categorical | 215 | Significant correlation with worse scan |
| Thelin EP, *2019* (e,f)48 | S100B; NSE; GFAP; UCH-L1; Tau; NF-L | S100B LIAISON-mat S100 system, Sangtec, and Elecsys S100B; Roche Diagnostics.  NSE: LIAISON NSE: Sangtec  GFAP, UCH-L1, Tau and NFL: Neurology 4-plex assay, Quanterix | Admission | Continuous | 172 | Significant positive correlations except for NF-L. |
| Thelin EP, *2016* (e,f)49 | NSE; S100B | NSE: LIAISON NSE; Sangtec Medical  S100B: LIAISON-mat S100 system, Sangtec Medical and Elecsys S100B; Roche Diagnostics. | Admission | Continuous | 417 | Significant positive correlations |
| **Stockholm** | | | | | | |
| Al Nimer F, *2015* (e)2 | NF-L; S100B; NSE | NF-L: Uman Diagnostics NF-light® assay; Uman Diagnostics  S100B: LIAISON-mat S100 system, Sangtec, until September 2008 followed by Elecsys S100B; Roche Diagnostics.  NSE: Liaison, DiaSorin | Admission | Continuous | 182 | Significant positive correlation for S100B. |
| Thelin EP, *2019* (e,f)48 | S100B; NSE; GFAP; UCH-L1; Tau; NF-L | S100B LIAISON-mat S100 system, Sangtec, and Elecsys S100B; Roche Diagnostics.  NSE: LIAISON NSE: Sangtec  GFAP, UCH-L1, Tau and NFL: Neurology 4-plex assay, Quanterix | Admission | Continuous | 172 | Significant positive correlations for all. |
| Thelin EP, *2016* (e,f)49 | NSE; S100B | NSE: LIAISON NSE; Sangtec Medical  S100B: LIAISON-mat S100 system, Sangtec Medical and Elecsys S100B; Roche Diagnostics. | Admission | Continuous | 417 | Significant positive correlations for all. |
| Thelin EP, *2016* (f)51 | S100B | Elecsys S100B; Roche Diagnostics | Median (range): 48 (40– 57) hrs | Continuous | 127 | Significant positive correlation. |
| **Self-created scoring system** | | | | | | |
| Li Q, *2017*22 | GFAP; NSE; S100B | Elecsys S100B; Roche Diagnostics | <24 hours from admission | Continuous | 80 | Significant correlation with worsening score. |
| **Biomarker concentration and specific intracranial lesion types injury pattern (diffuse or focal injury)** | | | | | | |
| Lo TY, *2009*24 | S100B; NSE; IL-6; IL-8; IL-10; L-selectin;  SICAM;  Endothelin | S100B, NSE: Nexus Dx S-100 Test Kit; Synx Pharma Inc.  IL-6: IL-6 ELISA Kit; Diaclone Research  IL-8: IL-8 ELISA Kit; Diaclone Research  IL-10: IL-10 ELISA Kit; Diaclone Research  L-selectin: Human sL-Selectin Immunoassay; R&D Systems  SIACAM: sICAM-1 ELISA Kit; Diaclone Research  Endothelin: Endothelin 1-21 Test Kit; Biomedica) | 24 hours post injury | N/A | 28 | NSE levels significantly higher in diffuse rather than focal injury. |

GFAP-BDP = Glial fibrillary acidic protein break down products, GFAP= Glial fibrillary acidic protein, S100B = S100 B calcium-binding protein, NSE = neuron specific enolase, UCH-L1 = Ubiquitin carboxy-terminal hydrolase L1, NFH = Neurofilament heavy, NFL = Neurofilament heavy, T tau = Total tau, YKL-40 = Procalcitonin chitinase-3-like protein 1, CT = Computed Tomography, CRP= C Reactive Protein, ICH= Intracerebral haemorrhage, IVH= interventricular haemorrhage, tSAH= traumatic subarachnoid haemorrhage, EDH = Extradural haematoma, SDH= Subdural haematoma, IL= Interleukin, UCH-L1 = Ubiquitin carboxy-terminal hydrolase L1, B-FABP= Brain fatty acid binding protein, vWF= von Willebrand factor, AB42= Amyloid beta 42, DAI= Diffuse axonal injury

**Supplemental Digital Content 3, Table 5 -** Biomarker, Assay, time to biomarker and key findings of each included study assessing biomarker concentration and intracranial lesion type as demonstrated on neuroimaging

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (first) and year** | **Biomarker** | **Biomarker Assay** | **Time to first biomarker sample** | **Number of patients** | **Results** |
| Abbasi M, *2004*1 | S100B | S100B Human ELISA; BioVendor | < 6 hrs | 90 | S100B elevated in DAI |
| Al Nimer F, *2015* (e)2 | NF-L; S100B; NSE | NF-L: Uman Diagnostics NF-light® assay; Uman Diagnostics  S100B: LIAISON-mat S100 system, Sangtec, until September 2008 followed by Elecsys S100B; Roche Diagnostics.  NSE: Liaison, DiaSorin | NA | 182 | Association with MLS on MRI but not CT.  No significant association with DAI. |
| Castello LM, *2018*5 | Copeptin | BRAHMS Copeptin proAVP assay; Thermo Fisher Scientific | < 8 hrs | 105 | No association found. |
| Faulkinberry S, *2019*10 | Tau | Not provided | Admission to ICU | 36 | Elevated in DAI |
| Guzel A, *2008*12 | NSE | Modular analytics E170; Roche Diagnostics | < 2 hrs | 169 | 2- hours post injury elevated in cerebral oedema and ICH  24 hours post injury elevated in cerebral oedema with or without other lesions.  At 48 hours lower in EDH, elevated in cerebral oedema and cerebral oedema with ICH |
| Heidari K, *2015*14 | S100B | Elecsys S100, Roche Diagnostics | 3 and 6 hrs | 165 | The presence of tSAH or ICH independently increased serum S100B concentrations at 3 and 6 hours in patients with MTBI. |
| Herrmann M, *2000*15 | S100B; NSE | S100B: Sangtec 100; AB Sangtec Medical NSE: LIA-mat system; Sangetc Medical | Median: 30 hrs | 66 | In cerebral contusion NSE and S100B concentrations peaked earlier following injury (NSE: 0-24 hrs, S100B:25-48 hrs) as compared to diffuse axonal injury (NSE and S100B 49-72 hrs). |
| Ingebrigtsen T, *1999* (b)17 | S100B | Sangtec 100; AB Sangtec Medical | Mean (range): 3.6 (1.0–7.5) hrs | 50 | The proportion of S100-B positive patients was higher in MRI confirmed contusion compared to those without. |
| Kou Z, 201320 | GFAP, UCH-L1 | MesoScale Discovery Platform, Banyan Biomarkers | < 6 hrs | 9 | GFAP levels significantly higher in patients with haemorrhages on structural MRI as compared with the non-haemorrhagic group |
| Langness S, *2018*21 | D-Dimer | Alere Triage MeterPro D-Dimer; Quidel | < 6 hrs | 663 | D Dimer significantly higher with isolated skull fracture, TBI and ciTBI as compared to CT negative.  No significant difference between TBI and isolated skull fracture.  Significant difference between ciTBI and TBI. |
| Ljungqvist J, *2017*23 | NF-L; S100B | NF-L: Simoa NF-light assay; Quanterix  S100B: Elecsys S100, Roche Diagnostics | < 6 days | 9 | NF-L association with DAI on MRI |
| Metting Z, *2012*26 | GFAP; S100B | GFAP: Glial Fibrillary Acidic Protein Human ELISA; Biovendor S100B: Human S100B ELISA; Biovendor and LIAISON-mat S100 system, Diasorin | Mean (SD): 2.4 (2.1) hrs | 94 | GFAP was increased in those with contusion. No significant difference in serum S100B levels.  On MRI GFAP significantly raised as compared to patients without diffuse axonal injury. No significant difference in serum S100B levels. |
| Mondello S, *2016*28 | UCH-L1; GFAP | UCH-L1: Own assay GFAP: R-PLEX Human GFAP Antibody Set; MesoScale Discovery | Median (range): 4.7 (0.5 –20.6) hrs | 45 | UCH-L1 significantly higher in intracranial haemorrhage vs skull fracture. |
| Muller K, *2007*30 | S100B | LIAISON-mat S100 system, Diasorin | < 12 hrs | 226 | No association found to lesion type |
| Pandey S, *2017*33 | C-Tau | C-MAPT/C-TAU ELISA Kit (CUSABIO-CSB-ECL013481H) | <12 hrs | 40 | Significant difference between those with extradural haematoma, contusion/intraparenchymal haematoma, negative CT, subarachnoid haemorrhage, subdural haemorrhage and skull bone fracture. |
| Papa L, *2017*34 | UCH-L1 | Banyan UCH-L1; Banyan Biomakers Inc. | <6 hrs | 148 | UCH-L1 significantly lower in patients who did not meet study criteria for CT head than those with intracranial lesions, scalp injury or skull fracture |
| Papa L, *2014*35 | GFAP; S100B | GFAP: Banyan GFAP; Banyan Biomarkers Inc.  S100B: own assay | < 4 hrs | 209 | GFAP significantly higher in intracranial lesions compared with extracranial lesions.  No significant difference in S100B levels between intracranial and extracranial lesions. |
| Raabe A, *1998*40 | S100B; NSE | S100B: Sangtec 100; AB Sangtec Medical  NSE: NSE assay; Sangtec Medical | Median (range): 12 hrs (6 -24) hrs | 44 | S100B and NSE levels higher in subdural haematoma and contusions compared to extradural haematomas.  Serum S100B and NSE was higher in tSAH compared to those without. |
| Romner B, *2000* (b)42 | S100B | Sangtec 100; AB Sangtec Medical | Mean (range): 3.8 (0.5 – 24.0) hrs | 278 | Raised S100 in isolated skull fracture and no findings on acute CT but contusions present on MRI compared to no acute CT abnormalities. |
| Sandsmark DK, *2019*44 | NF-H; vWF;  Cellular Fibronectin | NF-H: Phosphorylated Neurofilament H Human ELISA; BioVendor  vWF: vWF ELISA;Life Technologies  Cellular Fibronectin: Cellular Fibronectin ELISA; ThermoFisher | < 48 hrs | 76 | <48 hrs vWF highest in the traumatic haemorrhage group compared to traumatic vascular injury. No significant difference between MRI negative and the traumatic haemorrhage group.  No significant difference in Cellular Fibronectin levels between lesions.  NF-H significantly raised in the traumatic vascular <48 hrs following injury, as compared to the traumatic haemorrhage group and MRI negative patients. Levels of serum NF-H were also significantly raised in the traumatic haemorrhage group as compared to MRI negative patients. |
| Skandsen T, *2018*46 | GFAP, NF-L | Neurology 4-plex assay, Quanterix | < 72 hrs for GFAP, 2 weeks for NF-L | 93 | NF-L was not raised in traumatic axonal injury compared other lesions. |
| Thelin EP, *2013* (e)50 | S100B | LIAISON-mat S100 system, Diasorin, and Elecsys S100B, Roche Diagnostics | < 48 hrs | 265 | S100B levels correlated with tSah, the absence of EDH, the presence of a contusion and the presence of a hypodense lesion on CT. SDH was non-significant. |
| Thelin EP, *2016* (f)51 | S100B | Elecsys S100, Roche Diagnostics | Median (range): 48 (40– 57) hrs | 127 | Presence of contusions, SDH, and skull fractures were significantly correlated with S100B levels. No correlation between S100B and the presence of EDH and tSAH. |
| Tomita K, *2019*52 | Tau | Not provided | < 6 hrs | 40 | Tau levels significantly higher in MRI proven DAI than those without.  No significant difference in serum tau levels found between patients with and without tSAH. |
| Wolf H, *2015*55 | S100B | Elecsys S100; Roche Diagnostics | < 3 hrs | 1696 | S100B significantly higher in cerebral oedema than extradural haematoma, subdural haematoma, subarachnoid haemorrhage and contusion. |
| Yue JK, *2019* (a)56 | GFAP | i-STAT; Abbott point-of-care | < 24 hrs | 450 | DAI significantly higher plasma GFAP concentrations than traumatic axonal injury. |
| Zurek J, *2011* (g)57 | NF-H | Phosphorylated Neurofilament H Human ELISA; BioVendor | Admission | 59 | Phosphorylated NF-H significantly higher in those with DAI compared to those with other injuries. |
| Zurek J, *2010*58 | S100B | Elecsys S100; Roche Diagnostics | Admission | 43 | S100B significantly higher in intracranial bleeding, subdural haematoma, and intracerebral oedema compared to those without. |

GFAP-BDP = Glial fibrillary acidic protein break down products, GFAP= Glial fibrillary acidic protein, S100B = S100 B calcium-binding protein, NSE = neuron specific enolase, UCH-L1 = Ubiquitin carboxy-terminal hydrolase L1, NFH = Neurofilament heavy, NFL = Neurofilament heavy, T tau = Total tau, YKL-40 = Procalcitonin chitinase-3-like protein 1, CT = Computed Tomography, CRP= C Reactive Protein, ICH= Intracerebral haemorrhage, IVH= interventricular haemorrhage, tSAH= traumatic subarachnoid haemorrhage, EDH = Extradural haematoma, SDH= Subdural haematoma, IL= Interleukin, UCH-L1 = Ubiquitin carboxy-terminal hydrolase L1, B-FABP= Brain fatty acid binding protein, vWF= von Willebrand factor, AB42= Amyloid beta 42, DAI= Diffuse axonal injury.

**Supplemental Digital Content 3 References**

1. Abbasi M, Sajjadi M, Fathi M, Maghsoudi M. Serum S100B protein as an outcome prediction tool in emergency department patients with traumatic brain injury. *Turkiye Acil Tip Derg*. 2014;14(4):147-152. doi:10.5505/1304.7361.2014.74317

2. Al Nimer F, Thelin E, Nyström H, et al. Comparative assessment of the prognostic value of biomarkers in traumatic brain injury reveals an independent role for serum levels of neurofilament light. *PLoS One*. 2015;10(7):e0132177. doi:10.1371/journal.pone.0132177

3. Bogoslovsky T, Wilson D, Chen Y, et al. Increases of plasma levels of glial fibrillary acidic protein, tau, and amyloid β up to 90 days after traumatic brain injury. *J Neurotrauma*. 2017;34(1):66-73. doi:10.1089/neu.2015.4333

4. Carabias CS, Gomez PA, Panero I, et al. Chitinase-3-Like Protein 1, Serum Amyloid A1, C-Reactive Protein, and Procalcitonin Are Promising Biomarkers for Intracranial Severity Assessment of Traumatic Brain Injury: Relationship with Glasgow Coma Scale and Computed Tomography Volumetry. *World Neurosurg*. 2020;134:e120-e143. doi:10.1016/j.wneu.2019.09.143

5. Castello LM, Salmi L, Zanotti I, et al. The increase in copeptin levels in mild head trauma does not predict the severity and the outcome of brain damage. *Biomark Med*. 2018;12(6):555-563. doi:10.2217/bmm-2018-0041

6. De Oliveira CO, Reimer AG, Da Rocha AB, et al. Plasma von Willebrand factor levels correlate with clinical outcome of severe traumatic brain injury. *J Neurotrauma*. 2007;24(8):1331-1338. doi:10.1089/neu.2006.0159

7. Dickens AM, Posti JP, Takala RSK, et al. Serum Metabolites Associated with Computed Tomography Findings after Traumatic Brain Injury. *J Neurotrauma*. 2018;35(22):2673-2683. doi:10.1089/neu.2017.5272

8. Egea-Guerrero JJ, Revuelto-Rey J, Murillo-Cabezas F, et al. Accuracy of the S100β protein as a marker of brain damage in traumatic brain injury. *Brain Inj*. 2012;26(1):76-82. doi:10.3109/02699052.2011.635360

9. Egea-Guerrero JJ, Rodríguez-Rodríguez A, Quintana-Díaz M, et al. Validation of S100B use in a cohort of Spanish patients with mild traumatic brain injury: a multicentre study. *Brain Inj*. 2018;32(4):459-463. doi:10.1080/02699052.2018.1429019

10. Faulkinberry S, Wang K., Yang Z, Li X, Kerrigan M, Ghosh S. Tau as a potential biomarker for prognosis and diagnosis of pediatric traumatic brain injury. *J Neurotrauma*. 2019;36(13):A139-A139.

11. Ghonemi MO, Rabah AA, Saber HM, Radwan W. Role of Phosphorylated Neurofilament H as a diagnostic and prognostic marker in traumatic brain injury. *Egypt J Crit Care Med*. 2013;1(3):139-144. doi:10.1016/j.ejccm.2013.03.002

12. Guzel A, Er U, Tatli M, et al. Serum neuron-specific enolase as a predictor of short-term outcome and its correlation with Glasgow Coma Scale in traumatic brain injury. *Neurosurg Rev*. 2008;31(4):439-445. doi:10.1007/s10143-008-0148-2

13. Hatefi M, Dastjerdi MM, Ghiasi B, Rahmani A. Association of Serum Uric Acid Level with the Severity of Brain Injury and Patient’s Outcome in Severe Traumatic Brain Injury. *J Clin Diagn Res*. 2016;10(12):OC20-OC24. doi:10.7860/JCDR/2016/21918.8993

14. Heidari K, Asadollahi S, Jamshidian M, Abrishamchi SN, Nouroozi M. Prediction of neuropsychological outcome after mild traumatic brain injury using clinical parameters, serum S100B protein and findings on computed tomography. *Brain Inj*. 2015;29(1):33-40. doi:10.3109/02699052.2014.948068

15. Herrmann M, Jost S, Kutz S, et al. Temporal profile of release of neurobiochemical markers of brain damage after traumatic brain injury is associated with intracranial pathology as demonstrated in cranial computerized tomography. *J Neurotrauma*. 2000;17(2):113-122. doi:10.1089/neu.2000.17.113

16. Honda M, Tsuruta R, Kaneko T, et al. Serum glial fibrillary acidic protein is a highly specific biomarker for traumatic brain injury in humans compared with S-100B and neuron-specific enolase. *J Trauma - Inj Infect Crit Care*. 2010;69(1):104-109. doi:10.1097/TA.0b013e3181bbd485

17. Ingebrigtsen T, Waterloo K, Jacobsen EA, Langbakk B, Romner B. 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):468-476. doi:10.1097/00006123-199909000-00010

18. Kelmendi FM, Morina AA, Mekaj AY, et al. Serum S100B Levels Can Predict Computed Tomography Findings in Paediatric Patients with Mild Head Injury. *Biomed Res Int*. 2018;2018:6954045. doi:10.1155/2018/6954045

19. Korfias S, Stranjalis G, Boviatsis E, et al. Serum S-100B protein monitoring in patients with severe traumatic brain injury. *Intensive Care Med*. 2007;33(2):255-260. doi:10.1007/s00134-006-0463-4

20. Kou Z, Gattu R, Kobeissy F, et al. Combining biochemical and imaging markers to improve diagnosis and characterization of mild traumatic brain injury in the acute setting: Results from a pilot study. *PLoS One*. 2013;8(11). doi:10.1371/journal.pone.0080296

21. Langness S, Ward E, Halbach J, et al. Plasma D-dimer safely reduces unnecessary CT scans obtained in the evaluation of pediatric head trauma. *J Pediatr Surg*. 2018;53(4):752-757. doi:10.1016/j.jpedsurg.2017.08.017

22. Li Q, Zhou Q. Relationship between CT features and serum gfAP, NSE and S100B protein in patients with severe traumatic brain injury. *Biomed Res*. 2017;28(22):9926-9929.

23. Ljungqvist J, Zetterberg H, Mitsis M, Blennow K, Skoglund T. Serum Neurofilament Light Protein as a Marker for Diffuse Axonal Injury: Results from a Case Series Study. *J Neurotrauma*. 2017;34(5):1124-1127. doi:10.1089/neu.2016.4496

24. Lo TYM, Jones PA, Minns RA. Pediatric brain trauma outcome prediction using paired serum levels of inflammatory mediators and brain-specific proteins. *J Neurotrauma*. 2009;26(9):1479-1487. doi:10.1089/neu.2008.0753

25. McMahon PJ, Panczykowski DM, Yue JK, et al. Measurement of the glial fibrillary acidic protein and its breakdown products GFAP-BDP biomarker for the detection of traumatic brain injury compared to computed tomography and magnetic resonance imaging. *J Neurotrauma*. 2015;32(8):527-533. doi:10.1089/neu.2014.3635

26. Metting Z, Wilczak N, Rodiger LA, Schaaf JM, Van Der Naalt J. GFAP and S100B in the acute phase of mild traumatic brain injury. *Neurology*. 2012;78(18):1428-1433. doi:10.1212/WNL.0b013e318253d5c7

27. Mondello S, Jeromin A, Buki A, et al. Glial neuronal ratio: A novel index for differentiating injury type in patients with severe traumatic brain injury. *J Neurotrauma*. 2012;29(6):1096-1104. doi:10.1089/neu.2011.2092

28. Mondello S, Kobeissy F, Vestri A, Hayes RL, Kochanek PM, Berger RP. Serum Concentrations of Ubiquitin C-Terminal Hydrolase-L1 and Glial Fibrillary Acidic Protein after Pediatric Traumatic Brain Injury. *Sci Rep*. 2016;6:28203. doi:10.1038/srep28203

29. Mondello S, Papa L, Buki A, et al. Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: A case control study. *Crit Care*. 2011;15(3):R156. doi:10.1186/cc10286

30. Müller K, Townend W, Biasca N, et al. S100B serum level predicts computed tomography findings after minor head injury. *J Trauma - Inj Infect Crit Care*. 2007;62(6):1452-1456. doi:10.1097/TA.0b013e318047bfaa

31. Naeimi ZS, Weinhofer A, Sarahrudi K, Heinz T, Vécsei V. Predictive value of S-100B protein and neuron specific-enolase as markers of traumatic brain damage in clinical use. *Brain Inj*. 2006;20(5):463-468. doi:10.1080/02699050600664418

32. Okonkwo DO, Yue JK, Puccio AM, et al. GFAP-BDP as an acute diagnostic marker in traumatic brain injury: Results from the prospective transforming research and clinical knowledge in traumatic brain injury study. *J Neurotrauma*. 2013;30(17):1490-1497. doi:10.1089/neu.2013.2883

33. Pandey S, Singh K, Sharma V, et al. A prospective pilot study on serum cleaved tau protein as a neurological marker in severe traumatic brain injury. *Br J Neurosurg*. 2017;31(3):356-363. doi:10.1080/02688697.2017.1297378

34. Papa L, Mittal MK, Ramirez J, et al. Neuronal Biomarker Ubiquitin C-Terminal Hydrolase Detects Traumatic Intracranial Lesions on Computed Tomography in Children and Youth with Mild Traumatic Brain Injury. *J Neurotrauma*. 2017;34(13):2132-2140. doi:10.1089/neu.2016.4806

35. Papa L, Silvestri S, Brophy GM, et al. GFAP out-performs S100β in detecting traumatic intracranial lesions on computed tomography in trauma patients with mild traumatic brain injury and those with extracranial lesions. *J Neurotrauma*. 2014;31(22):1815-1822. doi:10.1089/neu.2013.3245

36. Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: Relationship to brain damage and outcome. *J Neurotrauma*. 2004;21(11):1553-1561. doi:10.1089/neu.2004.21.1553

37. 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):1006-1012. doi:10.1097/01.ta.0000108998.48026.c3

38. Pleines UE, Morganti-Kossmann MC, Rancan M, Joller H, Trentz O, Kossmann T. S-100β reflects the extent of injury and outcome, whereas neuronal specific enolase is a better indicator of neuroinflammation in patients with severe traumatic brain injury. *J Neurotrauma*. 2001;18(5):491-498. doi:10.1089/089771501300227297

39. Posti JP, Takala RSK, Runtti H, et al. The Levels of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 during the First Week after a Traumatic Brain Injury: Correlations with Clinical and Imaging Findings. *Neurosurgery*. 2016;79(3):456-463. doi:10.1227/NEU.0000000000001226

40. Raabe A, Grolms C, Keller M, Döhnert J, Sorge O, Seifert V. Correlation of computed tomography findings and serum brain damage markers following severe head injury. *Acta Neurochir (Wien)*. 1998;140(8):787-792. doi:10.1007/s007010050180

41. Radwan W, Rabah A, Saber H. Phosphorylated neurofilament heavy subunit (PNF-H) in blood as a potential diagnostic and prognostic biomarker in traumatic brain injury. ESICM 2013 - Abstracts of Oral Presentations and Poster. *Intensive Care Med*. 2013;39:201–539. doi:http://dx.doi.org/10.1007/s00134-013-3095-5

42. Romner B, Ingebrigtsen T, Kongstad P, BoØrgesen SE. Traumatic brain damage: Serum S-100 protein measurements related to neuroradiological findings. *J Neurotrauma*. 2000;17(8):641-647. doi:10.1089/089771500415391

43. Rubenstein R, Chang B, Yue JK, et al. Comparing plasma phospho tau, total tau, and phospho tau–total tau ratio as acute and chronic traumatic brain injury biomarkers. *JAMA Neurol*. 2017;74(9):1063-1072. doi:10.1001/jamaneurol.2017.0655

44. Sandsmark DK, Bogoslovsky T, Qu B-X, et al. Changes in Plasma von Willebrand Factor and Cellular Fibronectin in MRI-Defined Traumatic Microvascular Injury. *Front Neurol*. 2019;10:246. doi:10.3389/fneur.2019.00246

45. Shakeri M, Dokht YGM, Panahi F, Mahdkhah A, Foladi P. S100B protein value in predicting brain death after head trauma. *Neurosurg Q*. 2014;24(4):291-296. doi:10.1097/wnq.0b013e3182a2fc6e

46. Skandsen T, Clarke G., Einarsen C., et al. Levels of blood biomarkers in patients with mtbi were related to injury severity, but not to the post-concussive symptoms. *J Neurotrauma*. 2018;35(16):A209-A209.

47. Skogseid IM, Nordby HK, Urdal P, Paus E, Lilleaas F. Increased serum creatine kinase BB and neuron specific enolase following head injury indicates brain damage. *Acta Neurochir (Wien)*. 1992;115(3-4):106-111. doi:10.1007/BF01406367

48. Thelin E, Al Nimer F, Frostell A, et al. A Serum protein biomarker panel improves outcome prediction in human traumatic brain injury. *J Neurotrauma*. 2019;36(20):2850-2862. doi:10.1089/neu.2019.6375

49. Thelin EP, Jeppsson E, Frostell A, et al. Utility of neuron-specific enolase in traumatic brain injury; relations to S100B levels, outcome, and extracranial injury severity. *Crit Care*. 2016;20(1). doi:10.1186/s13054-016-1450-y

50. Thelin EP, Johannesson L, Nelson D, Bellander B-M. S100B Is an Important Outcome Predictor in Traumatic Brain Injury. *J Neurotrauma*. 2013;30(7):519-528. doi:10.1089/neu.2012.2553

51. Thelin EP, Zibung E, Riddez L, Nordenvall C. Assessing bicycle-related trauma using the biomarker S100B reveals a correlation with total injury severity. *Eur J Trauma Emerg Surg*. 2016;42(5):617-625. doi:10.1007/s00068-015-0583-z

52. Tomita K, Nakada T aki, Oshima T, Motoshima T, Kawaguchi R, Oda S. Tau protein as a diagnostic marker for diffuse axonal injury. *PLoS One*. 2019;14(3):e0214381. doi:10.1371/journal.pone.0214381

53. Vervliet B, Hulscher J, Van Der Naalt J, Ten Duis H., Nijsten M, Wilczak N. The diagnostic value of brain fatty acid binding protein in traumatic brain injury. *Brain Inj*. 2012;26(4):678-678. doi:http://dx.doi.org/10.3109/026990...- opens in a new window

54. Vos PE, Lamers KJB, Hendriks JCM, et al. Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. *Neurology*. 2004;62(8):1303-1310. doi:10.1212/01.wnl.0000120550.00643.dc

55. Wolf H, Frantal S, Pajenda G, Leitgeb J, Sarahrudi K, Hajdu S. Analysis of s100 calcium binding protein b serum levels in different types of traumatic intracranial lesions. *J Neurotrauma*. 2015;32(1):23-27. doi:10.1089/neu.2013.3202

56. Yue JK, Yuh EL, Korley FK, et al. Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study. *Lancet Neurol*. 2019;18(10):953-961. doi:10.1016/S1474-4422(19)30282-0

57. Žurek J, Bartlová L, Fedora M. Hyperphosphorylated neurofilament NF-H as a predictor of mortality after brain injury in children. *Brain Inj*. 2011;25(2):221-226. doi:10.3109/02699052.2010.541895

58. Žurek J, Bartlová L, Marek L, Fedora M. Serum S100B Protein as a Molecular Marker of Severity in Traumatic Brain Injury in Children. *Czech Slovak Neurol Neurosurg*. 2010;73(1):37-44.

59. Žurek J, Fedora M. Dynamics of glial fibrillary acidic protein during traumatic brain injury in children. *J Trauma - Inj Infect Crit Care*. 2011;71(4):854-859. doi:10.1097/TA.0b013e3182140c8c