**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 typeScoring 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 typeLesion number/volumeScoring 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 typeLesion 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 typeLesion number/volumeScoring 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 typeScoring 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 typeLesion 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 typeScoring system/Image Classification |
| Zurek J, *2010* (g)58  | S100B | Paediatric | 43 | 3-8 | CT | 90.7 | Lesion typeScoring 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 tauNF-H; Serum Amyloid A1; CRP; YKL-40 | S100B: LIAISON-mat S100 system; Sangtec Medical GFAP: Glial Fibrillary Acidic Protein Human ELISA; BioVendorNSE: Elecsys NSE immunoassay; Roche DiagnosticsT-tau: KHB0041; InvitrogenNF-H: Human Phosphorylated Neurofilament H ELISA; BioVendorSerum Amyloid A1: EL10015L; AnogenCRP: Cobas CRP; Roche DiagnosticsYKL- 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 | S100BNSE | Sangtec 100; Sangtec Medical  | Median: 30 hrs | 66 | Increased S100B and NSE with increased contusion volumeNo 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 | S100BNSE | S100B: Sangtec 100; SangtecNSE: 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 hrsGroup 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 DiagnosticsS100B: 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 MedicalNSE: 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; BioVendorS100B: YK151S-100B Elisa; Yanaihara InstituteNSE: 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 MedicalNSE: Roche Diagnostics | <24 hours | Continuous | 45 | Significant positive correlation |
| Pelinka LE, *2004* (d)36 | GFAP; S100B | GFAP: LIAISON GFAP; DiaSorinS100B: 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 | S100BNSE | 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: SangtecGFAP, 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 MedicalS100B: Sangtec 100; AB Sangtec MedicalGFAP: 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 DiagnosticsS100B: 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: SangtecGFAP, 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 DiagnosticsS100B: 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: SangtecGFAP, 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 ResearchIL-8: IL-8 ELISA Kit; Diaclone Research IL-10: IL-10 ELISA Kit; Diaclone ResearchL-selectin: Human sL-Selectin Immunoassay; R&D SystemsSIACAM: 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 DiagnosticsS100B: 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 ICH24 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; BiovendorS100B: 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 assayGFAP: 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 MedicalNSE: 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.

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