

SUPPLEMENT

BIOMARKERS TO RULE OUT INTRACRANIAL INJURIES IN MILD TRAUMATIC BRAIN INJURY



LORENA SAN MIGUEL, DOMINIQUE ROBERFROID, VICKY JESPERS



Title:	Biomarkers to rule out intracranial injuries in mild traumatic brain injury – Supplement
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Reported interests KCE members:	KCE is a federal institution funded by INAMI/RIZIV, by the Federal Public Service of Health, Food chain Safety and Environment, and by the Federal Public Service of Social Security. KCE's mission is to advise policymakers on decisions relating to health care and health insurance on the basis of scientific and objective research. It is expected to identify and shed light on the best possible solutions, in the context of an accessible, high-quality health care system with due regard for growing demand and budgetary constraints. KCE has no interest in companies (commercial or non-commercial, i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of the recommendations. All experts involved in the writing of the report or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.
Reported interests:	All experts and stakeholders consulted within this report were selected because of their involvement in the topic of this study. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report
Layout:	Ine Verhulst

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- The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.
- Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.
- Finally, this report has been approved by common assent by the Executive Board.
- Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.

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1 SEARCH STRATEGIES

1.1 Search strategies – Clinical Effectiveness Review

1.1.1 Medline (OVID)

Database(s): Ovid MEDLINE(R) ALL May 22, 2025

Search Strategy:

#	Searches	Results
1	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/	142845
2	((skull or cranial) adj3 fracture*).ti,ab.	5230
3	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.	156208
4	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.	6826
5	or/1-4	221888
6	letter/	1295818
7	editorial/	726370
8	news/	230341
9	exp historical article/	415945
10	Anecdotes as Topic/	4747
11	comment/	1051116
12	case report/	0
13	(letter or comment*).ti.	213055
14	or/6-13	3011420
15	randomized controlled trial/ or random*.ti,ab.	1761907
16	14 not 15	2984004
17	animals/ not humans/	5305452
18	exp Animals, Laboratory/	998193
19	exp Animal Experimentation/	10709
20	exp Models, Animal/	682428
21	exp Rodentia/	3713855
22	(rat or rats or mouse or mice or rodent*).ti.	1529359
23	or/16-22	9326430
24	5 not 23	170987
25	Biomarkers/	385191
26	exp S100 Proteins/	26824



- 27 Glial Fibrillary Acidic Protein/ 17518
- 28 Phosphopyruvate Hydratase/ 8758
- 29 Ubiquitin Thiolesterase/ 5957
- 30 MicroRNAs/ 141599
- 31 Brain-Derived Neurotrophic Factor/ 21419
- 32 Neurofilament Proteins/ 6813
- 33 Spectrin/ 3646
- 34 Myelin Basic Protein/ 7576
- 35 Extracellular Vesicles/ 15509
- 36 tau Proteins/ 21844
- 37 (Ubiquitin Thiolesterase* or "Ubiquitin C-terminal hydrolase*" or "Ubiquitin C-Terminal Esterase*" or "Ubiquitin Carboxy-Terminal Hydrolase*" or "Ubiquitin Carboxy-Terminal Esterase*" or uch-l1 or UCHL1).ti,ab. 2103
- 38 (S100* or GFAP or "glial fibrillary acid* protein*" or "brain-derived neurotrophic factor*" or "brain-derived nerve growth factor*" or BDNF or spectrin* or tau or proteomic* or microRNA* or miRNA* or micro-rna*).ti,ab. 429927
- 39 ((muscle or nervous or neuron* or alpha or beta or gamma) adj3 enolase*).ti,ab. 10244
- 40 (Phosphopyruvate Hydratase* or 2-phosphoglycerate* or 2-phospho-D-glycerate* or NSE).ti,ab. 8029
- 41 ((neurofilament* adj3 (protein* or chain* or polypeptide*)) or NF-L or NF-H).ti,ab. 8103
- 42 ((myelin basic or nerve tissue* or golli* or hog* or mbp*) adj2 protein*).ti,ab. 12397
- 43 (((extracellular or secretory) adj vesicle*) or exovesicle* or apoptotic bod* or exosome* or endosome* or ectosome* or microvesicle* or ((membrane or cell-derived) adj microparticle*)).ti,ab. 84463
- 44 biomarker*.ti,ab,kf. 514775
- 45 marker*.ti,ab. 1020958
- 46 or/25-45 2026425
- 47 randomized controlled trial.pt. 638639
- 48 controlled clinical trial.pt. 95680
- 49 randomi#ed.ti,ab. 897827
- 50 placebo.ab. 258800
- 51 randomly.ti,ab. 461552
- 52 Clinical Trials as topic.sh. 205049
- 53 trial.ti. 336804
- 54 or/47-53 1750178
- 55 Meta-Analysis/ 216034
- 56 Meta-Analysis as Topic/26263
- 57 (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. 347834



- 58 ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. 466405
- 59 (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. 60647
- 60 (search strategy or search criteria or systematic search or study selection or data extraction).ab. 104285
- 61 (search* adj4 literature).ab. 120848
- 62 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. 457502
- 63 cochrane.jw. 17122
- 64 ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. 4424
- 65 or/55-64 847172
- 66 Epidemiologic studies/ 9674
- 67 Observational study/ 175771
- 68 Cohort studies/ 357897
- 69 (cohort adj (study or studies or analys* or data)).ti,ab. 411900
- 70 ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. 430471
- 71 ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. 2363183
- 72 Controlled Before-After Studies/782
- 73 Historically Controlled Study/ 238
- 74 Interrupted Time Series Analysis/ 2489
- 75 (before adj2 after adj2 (study or studies or data)).ti,ab. 11076
- 76 case control study/ 347919
- 77 case control*.ti,ab. 176331
- 78 Cross-sectional studies/544369
- 79 (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. 598121
- 80 or/66-79 3368906
- 81 Sensitivity.mp. and Specificity/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 379582
- 82 (sensitivity or specificity).ti,ab. 1388938
- 83 ((pre test or pretest or post test) adj probability).ti,ab. 3683
- 84 (predictive value* or PPV or NPV).ti,ab. 166359
- 85 likelihood ratio*.ti,ab. 21815
- 86 Likelihood Functions/ 24328



- 87 ((area under adj4 curve) or AUC).ti,ab. 222454
- 88 (receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab. 187149
- 89 gold standard.ab. 100907
- 90 exp Diagnostic Errors/ 124912
- 91 (false positiv* or false negativ*).ti,ab. 97932
- 92 Diagnosis, Differential/ 476806
- 93 (diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab. 379751
- 94 or/81-93 2705034
- 95 46 and (54 or 65 or 80 or 94) 617988
- 96 craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/ 142845
- 97 ((skull or cranial) adj3 fracture*).ti,ab. 5230
- 98 ((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab. 156208
- 99 (trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab. 6826
- 100 or/96-99 221888
- 101 letter/ 1295818
- 102 editorial/ 726370
- 103 news/ 230341
- 104 exp historical article/ 415945
- 105 Anecdotes as Topic/ 4747
- 106 comment/ 1051116
- 107 case report/ 0
- 108 (letter or comment*).ti. 213055
- 109 or/101-108 3011420
- 110 randomized controlled trial/ or random*.ti,ab. 1761907
- 111 109 not 110 2984004
- 112 animals/ not humans/ 5305452
- 113 exp Animals, Laboratory/ 998193
- 114 exp Animal Experimentation/ 10709
- 115 exp Models, Animal/ 682428
- 116 exp Rodentia/ 3713855
- 117 (rat or rats or mouse or mice or rodent*).ti. 1529359
- 118 or/111-117 9326430
- 119 100 not 118 170987



- 120 Biomarkers/ 385191
- 121 exp S100 Proteins/ 26824
- 122 Glial Fibrillary Acidic Protein/ 17518
- 123 Phosphopyruvate Hydratase/ 8758
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- 133 (S100* or GFAP or "glial fibrillary acid* protein*" or "brain-derived neurotrophic factor*" or "brain-derived nerve growth factor*" or BDNF or spectrin* or tau or proteomic* or microRNA* or miRNA* or micro-rna*).ti,ab. 429927
- 134 ((muscle or nervous or neuron* or alpha or beta or gamma) adj3 enolase*).ti,ab. 10244
- 135 (Phosphopyruvate Hydratase* or 2-phosphoglycerate* or 2-phospho-D-glycerate* or NSE).ti,ab. 8029
- 136 ((neurofilament* adj3 (protein* or chain* or polypeptide*)) or NF-L or NF-H).ti,ab. 8103
- 137 ((myelin basic or nerve tissue* or golli* or hog* or mbp*) adj2 protein*).ti,ab. 12397
- 138 (((extracellular or secretory) adj vesicle*) or exovesicle* or apoptotic bod* or exosome* or endosome* or ectosome* or microvesicle* or ((membrane or cell-derived) adj microparticle*).ti,ab. 84463
- 139 biomarker*.ti,ab,kf. 514775
- 140 marker*.ti,ab. 1020958
- 141 or/120-140 2026425
- 142 randomized controlled trial.pt. 638639
- 143 controlled clinical trial.pt. 95680
- 144 randomi#ed.ti,ab. 897827
- 145 randomly.ti,ab. 461552
- 146 trial.ti. 336804
- 147 Meta-Analysis/ 216034
- 148 (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. 347834
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- 150 ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. 4424



- 151 Epidemiologic studies/ 9674
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- 156 ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. 2363183
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- 158 Historically Controlled Study/ 238
- 159 Interrupted Time Series Analysis/ 2489
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- 161 case control study/ 347919
- 162 case control*.ti,ab. 176331
- 163 Cross-sectional studies/544369
- 164 (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. 598121
- 165 or/142-164 4991303
- 166 Sensitivity.mp. and Specificity/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 379582
- 167 (sensitivity or specificity).ti,ab. 1388938
- 168 ((pre test or pretest or post test) adj probability).ti,ab. 3683
- 169 (predictive value* or PPV or NPV).ti,ab. 166359
- 170 likelihood ratio*.ti,ab. 21815
- 171 Likelihood Functions/ 24328
- 172 ((area under adj4 curve) or AUC).ti,ab. 222454
- 173 (receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab. 187149
- 174 gold standard.ab. 100907
- 175 exp Diagnostic Errors/ 124912
- 176 (false positiv* or false negativ*).ti,ab. 97932
- 177 Diagnosis, Differential/ 476806
- 178 (diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab. 379751
- 179 or/166-178 2705034
- 180 119 and 141 and 165 and 179 965
- 181 limit 180 to yr="2025" 69



- 182 craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries,
closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
142845
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156208
- 185 (trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
6826
- 186 or/182-185 221888
- 187 letter/ 1295818
- 188 editorial/ 726370
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- 192 comment/ 1051116
- 193 case report/ 0
- 194 (letter or comment*).ti. 213055
- 195 or/187-194 3011420
- 196 randomized controlled trial/ or random*.ti,ab. 1761907
- 197 195 not 196 2984004
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- 200 exp Animal Experimentation/ 10709
- 201 exp Models, Animal/ 682428
- 202 exp Rodentia/ 3713855
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- 204 or/197-203 9326430
- 205 186 not 204 170987
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- 224 (((extracellular or secretory) adj vesicle*) or exovesicle* or apoptotic bod* or exosome* or endosome* or ectosome* or microvesicle* or ((membrane or cell-derived) adj microparticle*).ti,ab. 84463
- 225 biomarker*.ti,ab,kf. 514775
- 226 marker*.ti,ab. 1020958
- 227 or/206-226 2026425
- 228 randomized controlled trial.pt. 638639
- 229 controlled clinical trial.pt. 95680
- 230 randomi#ed.ti,ab. 897827
- 231 randomly.ti,ab. 461552
- 232 trial.ti. 336804
- 233 Meta-Analysis/ 216034
- 234 (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. 347834
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- 242 ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. 2363183
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 246 (before adj2 after adj2 (study or studies or data)).ti,ab. 11076
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 248 case control*.ti,ab. 176331
 249 Cross-sectional studies/544369
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 598121
 251 or/228-250 4991303
 252 Sensitivity.mp. and Specificity/ [mp=title, book title, abstract, original title, name of substance
 word, subject heading word, floating sub-heading word, keyword heading word, organism
 supplementary concept word, protocol supplementary concept word, rare disease supplementary
 concept word, unique identifier, synonyms, population supplementary concept word, anatomy
 supplementary concept word] 379582
 253 (sensitivity or specificity).ti,ab. 1388938
 254 ((pre test or pretest or post test) adj probability).ti,ab. 3683
 255 (predictive value* or PPV or NPV).ti,ab. 166359
 256 likelihood ratio*.ti,ab. 21815
 257 Likelihood Functions/ 24328
 258 ((area under adj4 curve) or AUC).ti,ab. 222454
 259 (receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab. 187149
 260 gold standard.ab. 100907
 261 exp Diagnostic Errors/ 124912
 262 (false positiv* or false negativ*).ti,ab. 97932
 263 Diagnosis, Differential/ 476806
 264 (diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or
 precision or validat* or validity or differential or error*)).ti,ab. 379751
 265 or/252-264 2705034
 266 205 and 227 and 251 and 265 965

1.1.2 Cochrane

Date: 26 May 2025

#1 MeSH Brain injuries, Traumatic	1798
#2 (brain OR head OR cerebral OR cortical) AND (concussion OR injury OR trauma)	18750
#3 #1 OR #2	18826
#4 #3 OR TBI	19643
#5 Biomarker OR marker	40918
#6 GFAP OR UCH	374
#7 Glial fibrillary acidic protein	228



#8 Ubiquitin	302
#9 #5 OR #6 OR #7 OR #8	41447
#10 minor OR mild OR minimal OR severity	264260
#11 sensitivity OR specificity OR "predictive value" OR predict*OR prognos*OR likelihood OR classification OR stratification OR diagnosis	341658
#12 #4 AND #9 AND #10 AND #11	208

1.1.3 Embase

Session Results 20 January 2025

No. Query Results	Results
#34. #5 AND #30 AND #31 AND #32 AND [humans]/lim AND [embase]/lim AND [2022-2025]/py	624
#33. #5 AND #30 AND #31 AND #32	2,089
#32. #26 OR #27 OR #28 OR #29	2,629,213
#31. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	7,267,954
#30. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2,706,950
#29. diagnos*:ti,ab AND (performance*:ti,ab OR accurac*:ti,ab OR utilit*:ti,ab OR value*:ti,ab OR efficien*:ti,ab OR effectiveness:ti,ab OR precision:ti,ab OR validat*:ti,ab OR validity:ti,ab OR differential:ti,ab OR error*:ti,ab)	1,568,428
#28. 'diagnostic accuracy' OR 'diagnostic test accuracy study' OR 'diagnostic error' OR ((false:ti,ab AND positiv*:ti,ab OR false:ti,ab) AND negativ*:ti,ab) OR 'differential diagnosis'	1,143,555
#27. ((receive*:ti,ab AND operat*:ti,ab AND characteristic*:ti,ab OR receive*:ti,ab) AND operat*:ti,ab AND curve*:ti,ab OR roc:ti,ab) AND curve*:ti,ab	237,056
#26. ('sensitivity' AND 'specificity' OR sensitivity:ti,ab OR specificity:ti,ab OR ((pre:ti,ab AND test:ti,ab OR pretest:ti,ab OR post:ti,ab) AND test:ti,ab AND probability:ti,ab) OR (predictive:ti,ab AND value*:ti,ab) OR ppv:ti,ab OR npv:ti,ab OR likelihood) AND	523,406



ratio*:ti,ab OR (area:ti,ab AND under:ti,ab AND adj4:ti,ab AND curve:ti,ab) OR auc:ti,ab	
#25. cross:ti,ab AND sectional:ti,ab AND (study:ti,ab OR studies:ti,ab OR review:ti,ab OR analys*:ti,ab OR cohort*:ti,ab OR data:ti,ab)	745,159
#24. 'cross-sectional study'	732,213
#23. case AND control*:ti,ab 689,392	
#22. (longitudinal:ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR cross:ti,ab) AND sectional:ti,ab AND (study:ti,ab OR studies:ti,ab OR review:ti,ab OR analys*:ti,ab OR cohort*:ti,ab OR data:ti,ab)	745,465
#21. ((follow:ti,ab AND up:ti,ab OR observational:ti,ab OR uncontrolled:ti,ab OR non:ti,ab) AND randomized:ti,ab OR epidemiologic*:ti,ab) AND (study:ti,ab OR studies:ti,ab OR data:ti,ab)	623,264
#20. cohort:ti,ab AND (study:ti,ab OR studies:ti,ab OR analys*:ti,ab OR data:ti,ab)	1,433,978
#19. cohort*:ti,ab 1,673,879	
#18. (multiple:ti,ab AND treatment*:ti,ab OR indirect:ti,ab OR mixed:ti,ab) AND comparison*:ti,ab	103,116
#17. (systematic*:ti,ab OR evidence*:ti,ab) AND (review*:ti,ab OR overview*:ti,ab)	1,040,164
#16. (meta:ti,ab AND analy*:ti,ab OR metanaly*:ti,ab OR metaanaly*:ti,ab OR meta:ti,ab) AND regression:ti,ab	35,881
#15. random*:ti,ab OR factorial*:ti,ab OR ((crossover*:ti,ab OR cross:ti,ab) AND over*:ti,ab) OR ((doubl*:ti,ab OR singl*:ti,ab) AND blind*:ti,ab) OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab OR placebo*:ti,ab OR 'crossover procedure' OR 'single blind procedure' OR 'randomized	4,097,043



controlled trial' OR 'randomised controlled trial' OR 'double blind procedure' OR 'systematic review' OR 'meta-analysis'	
#14. biomarker*:ti,ab,kw OR marker*:ti,ab	2,009,528
#13. ((extracellular:ti,ab OR secretory:ti,ab) AND vesicle*:ti,ab OR exovesicle*:ti,ab OR apoptotic:ti,ab) AND bod*:ti,ab OR exosome*:ti,ab OR endosome*:ti,ab OR ectosome*:ti,ab OR microvesicle*:ti,ab OR ((membrane:ti,ab OR 'cell derived':ti,ab) AND microparticle*:ti,ab)	90,341
#12. ((myelin:ti,ab AND basic:ti,ab OR nerve:ti,ab) AND tissue*:ti,ab OR golli*:ti,ab OR hog*:ti,ab OR mbp*:ti,ab) AND protein*:ti,ab	27,296
#11. neurofilament*:ti,ab AND adj3:ti,ab AND (protein*:ti,ab OR chain*:ti,ab OR polypeptide*:ti,ab) OR 'nf l':ti,ab OR 'nf h':ti,ab	1,680
#10. phosphopyruvate:ti,ab AND hydratase*:ti,ab OR '2 phosphoglycerate*':ti,ab OR '2 phospho d glycerate*':ti,ab OR nse:ti,ab	10,969
#9. (muscle:ti,ab OR nervous:ti,ab OR neuron*:ti,ab OR alpha:ti,ab OR beta:ti,ab OR gamma:ti,ab) AND enolase*:ti,ab	12,381
#8. s100*:ti,ab OR gfap:ti,ab OR 'glial fibrillary acid* protein*':ti,ab OR 'brain-derived neurotrophic factor*':ti,ab OR 'brain-derived nerve growth factor*':ti,ab OR bdnf:ti,ab OR spectrin*:ti,ab OR tau:ti,ab OR proteomic*:ti,ab OR microrna*:ti,ab OR mirna*:ti,ab OR 'micro rna*':ti,ab	547,295
#7. ubiquitin:ti,ab AND thiolesterase*:ti,ab OR 'ubiquitin c-terminal hydrolase*':ti,ab OR 'ubiquitin c-terminal esterase*':ti,ab OR 'ubiquitin carboxy-terminal hydrolase*':ti,ab OR 'ubiquitin carboxy-terminal esterase*':ti,ab OR 'uch l1':ti,ab OR uchl1:ti,ab	3,089



#6. 'biological marker'/exp OR 'protein s 100' OR 'glial fibrillary acidic protein' OR 'enolase' OR 'ubiquitin thiolesterase' OR 'microna' OR 'brain derived neurotrophic factor' OR 'neurofilament protein' OR 'spectrin' OR 'myelin basic protein' OR 'exosome' OR 'tau protein'	996,359
#5. #1 OR #2 OR #3 OR #4 544,345	
#4. 'head injury'/exp OR 'brain injury'/exp OR 'skull injury'/exp OR 'skull fracture'/exp	389,356
#3. trauma*:ti,ab AND (subdural:ti,ab OR intracranial:ti,ab) AND (h?ematoma*:ti,ab OR h?emorrhage*:ti,ab OR bleed*:ti,ab)	4,637
#2. (skull:ti,ab OR cranial:ti,ab) AND fracture*:ti,ab	11,484
#1. (head:ti,ab OR brain:ti,ab OR craniocerebral:ti,ab OR cranial:ti,ab OR cerebral:ti,ab OR skull:ti,ab) AND (injur*:ti,ab OR trauma*:ti,ab)	318,023

1.1.4 Embase Update May 2025

Session Results

No. Query Results	Results
#41. #38 AND #39 AND [2025-2025]/py	437
#40. #38 AND #39	3,850
#39. #20 AND #21 AND #22	8,599
#38. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	8,354,823
#37. cross:ti,ab AND sectional:ti,ab AND (study:ti,ab OR studies:ti,ab OR review:ti,ab OR analys*:ti,ab OR cohort*:ti,ab OR data:ti,ab)	745,445
#36. 'cross-sectional study'	732,524
#35. case AND control*:ti,ab 689,498	

#34. (longitudinal:ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR cross:ti,ab) AND sectional:ti,ab AND (study:ti,ab OR studies:ti,ab OR review:ti,ab OR analys*:ti,ab OR cohort*:ti,ab OR data:ti,ab)	745,751
#33. (follow:ti,ab AND up:ti,ab OR observational:ti,ab OR uncontrolled:ti,ab OR ((non:ti,ab AND randomized:ti,ab OR non:ti,ab) AND randomized:ti,ab) OR epidemiologic*:ti,ab) AND (study:ti,ab OR studies:ti,ab OR data:ti,ab)	2,409,440
#32. cohort:ti,ab AND (study:ti,ab OR studies:ti,ab OR analys*:ti,ab OR data:ti,ab)	1,434,348
#31. cohort*:ti,ab 1,674,304	
#30. (multiple:ti,ab AND treatment*:ti,ab OR indirect:ti,ab OR mixed:ti,ab) AND comparison*:ti,ab	103,137
#29. (systematic*:ti,ab OR evidence*:ti,ab) AND (review*:ti,ab OR overview*:ti,ab)	1,040,507
#28. (meta:ti,ab AND analy*:ti,ab OR metanaly*:ti,ab OR metaanaly*:ti,ab OR meta:ti,ab) AND regression:ti,ab	35,895
#27. 'crossover procedure' OR 'single blind procedure' OR 'randomized controlled trial' OR 'randomised controlled trial' OR 'double blind procedure' OR 'systematic review' OR 'meta-analysis'	1,882,700
#26. assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab OR placebo*:ti,ab	1,360,230
#25. (doubl*:ti,ab OR singl*:ti,ab) AND blind*:ti,ab	324,873
#24. (crossover*:ti,ab OR cross:ti,ab) AND over*:ti,ab	428,387
#23. random*:ti,ab OR factorial*:ti,ab	2,196,411
#22. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	4,199,301
#21. #5 OR #6 OR #7 OR #8 2,275,897	
#20. #1 OR #2 OR #3 OR #4 568,019	



#19. diagnos*:ti,ab AND (performance*:ti,ab OR accurac*:ti,ab OR utilit*:ti,ab OR value*:ti,ab OR efficien*:ti,ab OR effectiveness:ti,ab OR precision:ti,ab OR validat*:ti,ab OR validity:ti,ab OR differential:ti,ab OR error*:ti,ab)	1,568,794
#18. 'differential diagnosis'	513,952
#17. (false:ti,ab AND positiv*:ti,ab OR false:ti,ab) AND negativ*:ti,ab	82,227
#16. 'diagnostic accuracy' OR 'diagnostic test accuracy study' OR 'diagnostic error'	609,710
#15. ((receive*:ti,ab AND operat*:ti,ab AND characteristic*:ti,ab OR receive*:ti,ab) AND operat*:ti,ab AND curve*:ti,ab OR roc:ti,ab) AND curve*:ti,ab	237,147
#14. area:ti,ab AND under:ti,ab AND adj4:ti,ab AND curve:ti,ab OR auc:ti,ab	239,910
#13. likelihood AND ratio*:ti,ab	69,953
#12. predictive:ti,ab AND value*:ti,ab OR ppv:ti,ab OR npv:ti,ab	338,574
#11. (pre:ti,ab AND test:ti,ab OR pretest:ti,ab OR post:ti,ab) AND test:ti,ab AND probability:ti,ab	10,780
#10. sensitivity:ti,ab OR specificity:ti,ab	1,744,349
#9. 'sensitivity' AND 'specificity'	713,392
#8. gfap:ti,ab OR 'glial fibrillary acid* protein*:ti,ab	40,538
#7. ubiquitin:ti,ab AND thiolesterase*:ti,ab OR 'ubiquitin c-terminal hydrolase*:ti,ab OR 'ubiquitin c-terminal esterase*:ti,ab OR 'ubiquitin carboxy-terminal hydrolase*:ti,ab OR 'ubiquitin carboxy-terminal esterase*:ti,ab OR 'uch l1':ti,ab OR uchl1:ti,ab	3,089
#6. 'glial fibrillary acidic protein' OR 'ubiquitin thiolesterase'	45,916
#5. 'biological marker'/exp OR biomarker*:ti,ab,kw OR marker*:ti,ab	2,093,739



#4. 'head injury'/exp OR 'brain injury'/exp OR 'skull injury'/exp OR 'skull fracture'/exp	389,412
#3. trauma*:ti,ab AND (subdural:ti,ab OR intracranial:ti,ab) AND (h?ematoma*:ti,ab OR h?emorrhage*:ti,ab OR bleed*:ti,ab)	4,638
#2. (skull:ti,ab OR cranial:ti,ab) AND fracture*:ti,ab	11,485
#1. (head:ti,ab OR brain:ti,ab OR craniocerebral:ti,ab OR cranial:ti,ab OR cerebral:ti,ab OR skull:ti,ab) AND (injur*:ti,ab OR trauma*:ti,ab)To be added	318,069

1.2 Search strategies – Cost-Effectiveness Review

1.2.1 Medline

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 14, 2025

N.	Searches	Results
1	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/	143487
2	((skull or cranial) adj3 fracture*).ti,ab.	5271
3	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.	157679
4	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.	6896
5	Biomarkers/	389031
6	Glial Fibrillary Acidic Protein/	17586
7	Ubiquitin Thiolesterase/	6031
8	(Ubiquitin Thiolesterase* or "Ubiquitin C-terminal hydrolase*" or "Ubiquitin C-Terminal Esterase*" or "Ubiquitin Carboxy-Terminal Hydrolase*" or "Ubiquitin Carboxy-Terminal Esterase*" or uch-l1 or UCHL1).ti,ab.	2132
9	(S100* or GFAP or "glial fibrillary acid* protein*" or "brain-derived neurotrophic factor*" or "brain-derived nerve growth factor*" or BDNF or spectrin* or tau or proteomic* or microRNA* or miRNA* or micro-rna*).ti,ab.	435429
10	biomarker*.ti,ab,kf.	526107
11	marker*.ti,ab.	1031967
12	Sensitivity.mp. and Specificity/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	380944



13	(sensitivity or specificity).ti,ab.	1403814
14	((pre test or pretest or post test) adj probability).ti,ab.	3712
15	(predictive value* or PPV or NPV).ti,ab.	168378
16	likelihood ratio*.ti,ab.	22045
17	Likelihood Functions/	24381
18	((area under adj4 curve) or AUC).ti,ab.	227838
19	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.	191159
20	exp Diagnostic Errors/	125180
21	(false positiv* or false negativ*).ti,ab.	98766
22	Diagnosis, Differential/	477764
23	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.	385622
24	1 or 2 or 3 or 4	223541
25	5 or 6 or 7 or 8 or 9 or 10 or 11	1935304
26	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	2665452
27	24 and 25 and 26	2309
28	exp Economics/	758061
29	exp Health Care Costs/	75337
30	(cost and cost analysis).mp.	60847
31	exp Economics, Pharmaceutical/ or exp Economics, Medical/ or exp Economics, Hospital/ or exp Economics, Nursing/	47160
32	exp "Value of Life"/	5838
33	exp Cost-Benefit Analysis/	98340
34	(cost effectiveness or cost-effectiveness).mp.	89715
35	(cost utility or cost-utility).mp.	7371
36	exp Quality-Adjusted Life Years/	18101
37	exp Health Expenditures/	27723
38	budget*.mp.	47078
39	(price or prices or pricing).mp.	59399
40	exp "Costs and Cost Analysis"/	280426
41	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	870285
42	27 and 41	10

1.2.2 EMBASE

Embase session results (15 Jul 2025)

No. Query Results

#38	#20 AND #21 AND #22 AND #37	100
#37	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	1002561
#36	budget* AND [embase]/lim	53664
#35	'budget impact analysis' AND [embase]/lim	2861
#34	(price OR prices OR pricing) AND [embase]/lim	105052
#33	'cost minimization analysis'/exp AND [embase]/lim	4225
#32	'cost utility analysis'/exp AND [embase]/lim	13768
#31	'hospital cost'/exp AND [embase]/lim	40746
#30	'cost control'/exp AND [embase]/lim	60098
#29	'cost of illness'/exp AND [embase]/lim	12586
#28	'cost effectiveness analysis'/exp AND [embase]/lim	203055
#27	'cost benefit analysis'/exp AND [embase]/lim	71392
#26	'health care financing'/exp AND [embase]/lim	13556
#25	'health economics'/exp AND [embase]/lim	886912
#24	'health care cost'/exp AND [embase]/lim	326777
#23	'economics'/exp AND [embase]/lim	18876
#22	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	4199301
#21	#5 OR #6 OR #7 OR #8	2275897
#20	#1 OR #2 OR #3 OR #4	568019
#19	diagnos*:ti,ab AND (performance*:ti,ab OR accurac*:ti,ab OR utilit*:ti,ab OR value*:ti,ab OR efficien*:ti,ab OR effectiveness:ti,ab OR precision:ti,ab OR validat*:ti,ab OR validity:ti,ab OR differential:ti,ab OR error*:ti,ab)	1568794
#18	'differential diagnosis'	513952
#17	(false:ti,ab AND positiv*:ti,ab OR false:ti,ab) AND negativ*:ti,ab	82227
#16	'diagnostic accuracy' OR 'diagnostic test accuracy study' OR 'diagnostic error'	609710
#15	((receive*:ti,ab AND operat*:ti,ab AND characteristic*:ti,ab OR receive*:ti,ab) AND operat*:ti,ab AND curve*:ti,ab OR roc:ti,ab) AND curve*:ti,ab	237147
#14	area:ti,ab AND under:ti,ab AND adj4:ti,ab AND curve:ti,ab OR auc:ti,ab	239910
#13	likelihood AND ratio*:ti,ab	69953
#12	predictive:ti,ab AND value*:ti,ab OR ppv:ti,ab OR npv:ti,ab	338574
#11	(pre:ti,ab AND test:ti,ab OR pretest:ti,ab OR post:ti,ab) AND test:ti,ab AND probability:ti,ab	10780
#10	sensitivity:ti,ab OR specificity:ti,ab	1744349



- #9 'sensitivity' AND 'specificity' 713392
- #8 gfap:ti,ab OR 'glial fibrillary acid* protein*:ti,ab 40538
- #7 ubiquitin:ti,ab AND thiolesterase*:ti,ab OR 'ubiquitin c-terminal hydrolase*:ti,ab OR 'ubiquitin c-terminal esterase*:ti,ab OR 'ubiquitin carboxy-terminal hydrolase*:ti,ab OR 'ubiquitin carboxy-terminal esterase*:ti,ab OR 'uch l1':ti,ab OR uchl1:ti,ab 3089
- #6 'glial fibrillary acidic protein' OR 'ubiquitin thiolesterase' 45916
- #5 'biological marker'/exp OR biomarker*:ti,ab,kw OR marker*:ti,ab 2093739
- #4 'head injury'/exp OR 'brain injury'/exp OR 'skull injury'/exp OR 'skull fracture'/exp 389412
- #3 trauma*:ti,ab AND (subdural:ti,ab OR intracranial:ti,ab) AND (h?ematoma*:ti,ab OR h?emorrhage*:ti,ab OR bleed*:ti,ab) 4638
- #2 (skull:ti,ab OR cranial:ti,ab) AND fracture*:ti,ab 11485
- #1 (head:ti,ab OR brain:ti,ab OR craniocerebral:ti,ab OR cranial:ti,ab OR cerebral:ti,ab OR skull:ti,ab) AND (injur*:ti,ab OR trauma*:ti,ab) 318069

1.2.3 EconLit

19	5 and 10 and 18	0
18	11 or 12 or 13 or 14 or 15 or 16 or 17	511
17	UCH-L1.mp.	0
16	Ubiquitine carboxyl-terminal hydrolase L1.mp.0	
15	GFAP.mp.	0
14	Glial Fibrillary Acidic Protein.mp.	0
13	biomarker.mp.	107
12	marker.mp.	394
11	(biological adj marker*).mp.	19
10	6 or 7 or 8 or 9	2198
9	(brain adj concussion).mp.	0
8	traumatic.mp.	295
7	trauma.mp.	375
6	injury.mp.	1604
5	1 or 2 or 3 or 4	6250
4	cerebral.mp.	39
3	cortical.mp.	30
2	brain.mp.	1841
1	head.mp.	4387

2 AMSTAR NICE REVIEW

NICE Guideline NG232 - Head injury: assessment and early management (update)	May-23	
1. Research question and inclusion criteria include components of PICO	yes	Detailed PICO and explanations provided in an appendix A
2. Explicit statement on protocol prior to conduct of review	yes	Protocol provided in appendix A
3. Explain selection study design (RCT and/or observational)	yes	No studies were excluded apriori other than conference abstracts
4. Comprehensive literature search strategy	yes	Provided in Appendix B
5. Study selection in duplicate	partial yes	10% done in duplicate and discussions held.
6. Data extraction in duplicate	partial yes	10% done in duplicate and discussions held.
7. List of excluded studies	yes	Full list and reasons provided
8. Details included studies	yes	Detailed data extraction tables provided
9. Satisfactory technique to assess Risk of Bias included studies	yes	QUADAS performed by one researcher and checked by a second
10. Source of funding included studies	yes	Included in appendix
11. Appropriate methods for statistical combination of results (meta-analysis)	partial yes	Data on diagnostic accuracy synthesized in a quantitative data analysis. Meta-analysis performed only for a limited N. of studies for S100 β , given their equivalent/similar cut-offs. For the remaining, authors show data in detailed tables, including GRADE
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	yes	A dedicated section is offered in the report to this matter
13. Account for risk of bias individual studies when interpreting/discussing results of the review	yes	This is discussed in the report
14. Satisfactory explanation for heterogeneity observed	no	The protocol explains that heterogeneity will be looked into but no results are found in the report.
15. Adequate investigation of publication bias	no	No funnel plot provided, probably a consequence of the categorisation of studies per cut-off level (< 10 studies in all cases)
16. Report potential sources of conflict of interest including funding	yes	Statement provided



3 RESULTS

3.1 Overview of studies included in the systematic review of clinical literature

Study ID	Adults	Children	GFAP	UCH-L1	GFAP + UCH-L1	S100β	Incl. in Puravet 2025
Bazarian 2018{Bazarian, 2018 #27}	√		√	√	√		√
Bazarian 2021(Bazarian 2021)	√				√		
Chayoua 2024(Chayoua 2024)	√		√	√	√		√
Chiollaz 2024(Chiollaz 2024)		√	√			√	
Curran 2025(Curran 2025)	√				√		
Forouzan 2021(Forouzan 2021)	√		√				
Gardner 2018(Gardner 2018)	√		√				√
Harris 2024 (Harris 2025)	≥17		√	√	√		
Iverson 2022(Iverson 2022)	√ (>60y)		√	√	√		√
Keski-Pukkila2024(Keski-Pukkila 2024)	√		√				
Ladang 2024(Ladang 2025)	√		√	√	√		√
Lagares 2024(Lagares 2024)	√ separate analysis 65y cut-off large numbers	A limited N. of 15-17y included	√	√	√	√	√
Lagerstedt 2018(Lagerstedt 2018)	√	15-17y included; n=2	√			√	

Study ID	Adults	Children	GFAP	UCH-L1	GFAP + UCH-L1	S100 β	Incl. in Puravet 2025
<i>Lapić</i> 2024(<i>Lapić</i> 2024)	√		√	√	√		√
<i>Legramante</i> 2024(<i>Legramante</i> 2024)	√				√		√
<i>Li</i> 2023(<i>Li</i> 2023)	√		√	√	√	√	√
<i>Kopcinovic</i> 2025(<i>Kopcinovic Milevoy</i> 2025)	√		√	√	√		
<i>Okonkwo</i> 2020(<i>Okonkwo</i> 2020)	√		√				√
<i>Oris</i> 2023(<i>Oris</i> 2024)	√		√	√	√	√	√
<i>Oris</i> 2024(<i>Oris</i> 2024)	√				√		
<i>Papa</i> 2022(<i>Papa</i> 2022)	√		√	√	√		√
<i>Polat</i> 2022(<i>Polat</i> 2022)	√		√				
<i>Posti</i> 2019(<i>Posti</i> 2019)	√		√			√	√
<i>Puravet</i> 2025(<i>Puravet</i> 2025)		√	√	√	√	√	
<i>Trivedi</i> 2024(<i>Trivedi</i> 2024)	√		√	√	√	√	
<i>Welch</i> 2025(<i>Welch</i> 2025)	√				√		
<i>Whitehouse</i> 2025(<i>Whitehouse</i> 2025)	√		√	√		√	



3.2 Reasons for exclusion for primary studies

Study ID	Reason for exclusion
<i>Biberthaler 2021</i> (<i>Biberthaler 2021</i>)	Population: mild and moderate cases mixed
<i>Bielanin 2024</i> (<i>Bielanin 2024</i>)	Narrative review
<i>Cevik 2019</i> (<i>Çevik 2019</i>)	Sample mixing children and adults
<i>Chen 2022</i> (<i>Chen 2022</i>)	Population: mild and moderate cases mixed
<i>Czeiter 2020</i> (<i>Czeiter 2020</i>)	Population: mild and moderate cases mixed
(<i>Datwyler 2023</i>)	Abstract
<i>Diaz-Arrastia 2014</i> (<i>Diaz-Arrastia 2014</i>)	Population: mild and moderate cases mixed
(<i>Korley 2022</i>)	Population: mild and moderate cases mixed and outcome wrong
(<i>Ladang 2024</i>)	Abstract
<i>Mahan 2019</i> (<i>Mahan 2019</i>)	Population: mild and moderate cases mixed
(<i>Malhotra Armaan K 2022</i>)	Abstract
(<i>Mastandrea 2025</i>)	Abstract
<i>McMahon 2015</i> (<i>McMahon 2015</i>)	Population: mild and moderate cases mixed
(<i>Morell-Garcia D 2023</i>)	Abstract
(<i>Munoz Pareja 2024</i>)	Population children: mild and moderate cases mixed
<i>Okonkwo 2013</i> (<i>Okonkwo 2013</i>)	Population: mild and moderate cases mixed
<i>Papa 2012</i> (<i>Papa 2012</i>)	Population: mild and moderate cases mixed
<i>Papa 2012</i> (<i>Papa 2012</i>)	Population: mild and moderate cases mixed
<i>Papa 2014</i>	Only individuals presenting with extracranial fractures considered
<i>Papa 2022</i> (<i>Papa 2022</i>)	No data to calculate accuracy
<i>Papa 2023</i> (<i>Papa 2023</i>)	Population: mild and moderate cases mixed
(<i>Pecoraro 2024</i>)	Abstract
<i>Puccio 2022</i> (<i>Puccio A 2022</i>)	Abstract
<i>Puccio 2024</i> (<i>Puccio 2024</i>)	No data to calculate accuracy
(<i>Tsitsipanis 2023</i>)	Population: mild and moderate cases mixed
<i>Wang 2023</i> (<i>Wang 2023</i>)	Population: mild and moderate cases mixed
<i>Welch 2016</i> (<i>Welch 2016</i>)	Population: mild and moderate cases mixed



3.3 Characteristics of the included studies

Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
Bazarian 2018 (Bazarian 2018)	22 sites: 15 USA; Canada, 7 Europe Dec 2012- March 2014	Secondary analysis of banked samples (samples from the ALERT-TBI study)	Adults (mean age 49). LoC or amnesia not required for inclusion. Non-contrast head CT scanning within 12h of injury.	14-15 (14=92, 15=1828)	Time of injury could not be determined, head CT scanning not performed, venepuncture not feasible, or informed consent not obtainable.	CT-positive: acute epidural haematoma, acute subdural haematoma, indeterminate extraaxial haemorrhage, intraventricular haemorrhage, parenchymal haematoma, petechial haemorrhagic or bland sheer injury, subarachnoid haemorrhage, brain oedema, brain herniation, non-haemorrhagic contusion, ventricular compression, ventricular trapping, cranial fractures, depressed skull fractures, facial fractures, scalp injury, or skull base fractures



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
Bazarian 2021(Bazarian 2021)	22 sites: 15 USA; Canada, 7 Europe Dec 2012-March 2014	Secondary analysis of banked samples (samples from the ALERT-TBI study)	Adults (mean age 49) mTBI GCS 13–15. LoC or amnesia not required for inclusion. Non-contrast head CT scanning, <12h	13-15 (13 n=22, 14 n=90, 15 n=1789)	Time of injury could not be determined, head CT scanning not performed, venepuncture not feasible, or informed consent not obtainable.	CT-positive: acute epidural hematoma, acute subdural hematoma, intraventricular hemorrhage, parenchymal hemorrhage/contusion, petechial hemorrhage/bland shear injury, subarachnoid hemorrhage, brain edema/herniation, and ventricular compression/trapping.
Chayoua 2024(Chayoua 2024)	Netherlands: ED in two level 1 trauma centers Jan 2020-Dec 2022	Cross-sectional study with consecutive enrollment	Adults (median age 48) mTBI: GCSS 13-15 and LOC ≤30 min and/or amnesia ≤24 hrs. CT scan decided based on CHIP-decision rule{Foks, 2018 #132}	13-15	Significant neurologic or psychiatric comorbidity, prior hospital admission for TBI, drug abuse, mental disability, language barriers, or illiteracy	CT scans were scored according to the Marshall score. Scores were dichotomized as negative (Marshall score 1, no abnormalities) or positive (Marshall score >1, indicating lesions, compressed cisterns, or midline shifts).

Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
Chiollaz 2024 (<i>Chiollaz 2024</i>)	5 pediatric EDs Switzerland Oct 2020 and Feb 2023 and in 4 pediatric EDs Spain 2019 and 2021	Cross-sectional study with consecutive enrollment	Children ≤ 16 years (mean age 8). Head trauma < 24 h; GCS 14 or GCS 15 with min 1 of following: LOC for < 30 min with onset within the first 20 min post-trauma, post-traumatic amnesia of < 24 h duration with onset within 30 min post-trauma, persistent headaches, irritability, three or more episodes of vomiting, confusion, dizziness, or transient neurological abnormality such as seizure; OR signs for basal skull fracture; OR high-energy trauma. N=302 of which n=230 observation, n=72 for CT (< 6 h n=222 and CT n=43)	14-15	Patients already included in another clinical study with pharmacologic treatment, alcohol consumption or use of other substances, history of recent TBI, recent history of epileptic seizures, Down syndrome, acute encephalopathy, encephalitis, or meningitis.	CT positive with intracranial injury defined by the presence of any of these findings: intracranial hemorrhage or contusion, cerebral edema, traumatic infarction, diffuse axonal injury, shearing injury, sigmoid sinus thrombosis, midline shift of intracranial contents or signs of brain herniation, diastasis of the skull, pneumocephalus or skull fracture depressed by at least the width of the table of the skull (PECARN criteria)
Curran 2025 (<i>Curran 2025</i>)	Tertiary referral trauma centre in Scotland	Cross-sectional study of unclear design (not stated if consecutive enrollment was applied)	Adult patients ≥ 18 years (mean age 63, alcohol intox 34%), < 12 hours head injury, CT head scan was requested	13-15	Penetrating head injury; poly-trauma; blood sampling > 12 hours from injury; insufficient sample volume, and lack of test calibration materials	CT+ defined as: any traumatic intra or extra-axial haemorrhage or shear-type injury or traumatic brain oedema +/-



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
						associated herniation or ventriculomegaly
Forouzan 2021(Forouzan 2021)	Iran: 2 trauma hospitals 2019	Cross-sectional study of unclear design (not stated if consecutive enrollment was applied)	≥16 years of age (mean age 36, range 16-90), clinical diagnosis of TBI with indications CT scan NICE criteria; <6 hours event and examination	14-15 (13 n=0)	<16 years old; explosive or penetrating damage; chronic subdural hematoma; previous brain disorders; TBI requiring no CT; living in another province that made it difficult to follow-up	Positive CT scan: acute epidural or subdural hematoma, cortical contusion, ventricular compression, ventricular trapping, cerebral herniation, intraventricular hemorrhage, hydrocephalus, subarachnoid hemorrhage, cerebral edema, post-traumatic ischemia, intracranial hematoma, and Cerebral venous sinus thrombosis
Gardner 2018(Gardner 2018)	USA ED of one of the three participating centra TRACK-	Cross-sectional retrospective analysis on banked samples; no consecutive enrollment	≥16 years of age and able to provide informed consent <24h trauma CT needed: according to the American College of Emergency Physicians (ACEP)/Centers for Disease Control and Prevention	13-15 (n=169)	Non-English speaking, pregnant, in custody, undergoing psychiatric evaluation, contraindications to MRI, or pre-existing medical or neurological conditions that would interfere with evaluation of TBI (eg. pre-existing dementia or severe psychiatric illness)	CT+ was defined as presence of at least one of the following: epidural hemorrhage (EDH), subdural hemorrhage (SDH),



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
	TBI Level 1 trauma		(CDC) evidence-based joint practice guidelines.			subarachnoid hemorrhage (SAH), brain contusion, intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), traumatic or diffuse axonal injury (TAI/DAI), midline shift >5 mm, partial or complete effacement of basal cisterns, or cerebral edema. CT- was defined as having none of these aforementioned findings. Additionally, intra-parenchymal injury was defined as contusion, ICH, TAI/DAI, or edema; extra-parenchymal injury, as EDH, SDH, SAH, or IVH
<i>Harris 2024</i>	18 U.S. Level I	Cross-sectional retrospective analysis on banked	≥17, presented to ED, clinically-indicated non-contrast brain CT within 24 h of TBI.	Results in suppl for GCS 13-15 in	Prisoner or in police custody, pregnant, psychiatric hold, major debilitating baseline mental health	CT+ defined as the presence of any intracranial



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
	trauma ED Feb 2014 -Aug 2018	samples from the TRACK-TBI study (nonconsecutive enrollment)	Acute TBI as defined by the American Congress of Rehabilitation Medicine (ACRM) Criteria: sustained traumatically induced physiological disruption of brain function, as manifested by more than one of the following: any period of loss of consciousness, any loss of memory for events (e.g., amnesia) immediately before or after the accident, any alteration of mental state at the time of the accident (feeling dazed, disoriented, and/or confused), and any focal neurologic deficits that may or may not be permanent.	patients without blood alcohol level available (not obtained clinically)	disorders, or major debilitating neurological disease; participants in an interventional trial; penetrating head injury; or spinal cord injury with an American Spinal Injury Association (ASIA) score of C or worse	lesion as defined by the National Institute of Neurological Disorders and Stroke (NINDS) common data elements (CDEs) for neuroimaging.(Ha acke 2010) For a list of lesions see Iverson. (Iverson 2022)
Iverson 2022(Iverson 2022)	Finland 1 ED neurosurg ical referral centre Level 1 trauma Nov 2015 and Nov 2016	Cross-sectional retrospective analysis on banked samples	Older patients ≥60 (mean age 79), acute TBI within 24hrs. Either blunt injury to the head or acceleration/deceleration type injury resulting in witnessed LoC, disorientation, or amnesia	14-15	Seen after 24hrs from injury GCS<14	NINDS CDEs: skull fracture, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, vascular dissection, traumatic aneurysm, venous sinus injury midline shift, cisternal compression, fourth ventricle shift/effacement,



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
						contusion, intracerebral hemorrhage, intraventricular hemorrhage, diffuse axonal injury, penetrating injuries, craniocervical junction injury, brain swelling, ischemia/infarction /hypoxic-ischemic injury. Excluded: isolated skull fracture
Keski-Pukkila2024(Keski-Pukkila 2024)	Finland, ED neurosurgical referral centre; Level 1 trauma Nov 2015 to Nov 2016	Cross-sectional retrospective analysis on banked samples (except for S100β)	Adults (mean age 61); Blunt injury to the head or acceleration /deceleration-type injury resulting in a witnessed LoC, disorientation, or amnesia. CT after an evaluation by the on-call physician; Scandinavian Guidelines: Mild (Low risk) group, either 1) patients with GCS of 15 who have suspected/confirmed loss of consciousness, repeated vomiting, or both or 2) patients with GCS of 14	14-15 at 30min after injury	ED admission >24 hrs post-injury. GCS< >65 years on antiplatelet medication (Medium Risk=head CT), post-traumatic seizures, focal neurological deficits, clinical signs of depressed or basal skull fracture, shunt-treated hydrocephalus, therapeutic anticoagulation, or a coagulation disorder (i.e., patients with any of those features are referred for head CT).	Traumatic CT abnormalities systematically coded by a neuroradiologist based on the NINDS CDEs.(Haacke 2010) A list of abnormalities is not presented in the paper but is listed in the Iverson 2022 paper (see above)(Iverson 2022)



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
Kopcinovic 2025(Kopcinovic Milevoy 2025)	12 healthcare centers from 6 European countries (Croatia, Poland, Portugal, Romania, Slovak Republic, and Slovenia) Feb 2022-June 2024	Cross-sectional study; consecutive enrollment unclear	Adult patients ≥18 years (median age: 64; 49%>65y) with suspected mTBI caused by external mechanical force, attendance to the ED within 12 h from a head injury, a GCS 13–15 assessed at the time of admission, and a head CT performed within 12 h of head trauma. Suspected mTBI was assessed and clinically evaluated as per locally instituted routine protocols or guidelines	13-15	Unknown time of injury, head CT scan not performed, and inability to obtain a blood sample. Demographics, medical history, GCS, alcohol consumption, injury mechanism, and CT results were collected.	A positive head CT was defined as the presence of acute intracranial hemorrhage or hematoma
Ladang 2024(Ladang 2025)	Greece (corresponding author from BE) ED general hospital Athens 2022-2023	Cross-sectional study with consecutive enrollment	Adults (median age 63) with CT scan decided by neurosurgeon. Indication of brain CT scan: neurological focal deficit; anterograde amnesia; GCS <15 after 2 h post-TBI; suspicion of vault depression fracture; fracture of the basal skull; persisting nausea, vomiting or headache; post-TBI seizures; pre-injury treatment with antithrombotic drugs; loss of consciousness or amnesia with age >65 years, fall >1m or hit pedestrian. 68.8 % CT-; 31.2 % CT+.	13-15	Children; GCS 3–12; 1ary admission non-traumatic neurological disorder; diagnosed neurodegenerative disease or other neurological disorder; blood collection not feasible, undetermined time of injury; penetrating head trauma; on mechanical ventilation; 1ary diagnosis of ischemic or hemorrhagic stroke or transient ischemic attack last 6 months or history of neurosurgery procedure in last 90 days	Positive or negative result not defined. (Experienced radiologist with Philips ingenuity 5,000 CT scanner)

Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
Lagares 2024(Lagares 2024)	France: 11 trauma centres and 1 community hospital; Spain 3 trauma centres and 1 one community hospital August 2019-June 2021	Cross-sectional analysis of data at baseline from BRAINI study. Not clear if enrollment was consecutive. Total follow-up 3 months.	≥18 France, ≥15 Spain: (median age 63; range 16-100) TBI: alteration in brain function CT scan performed based on Canadian Head Rule and other risk factors i.e neurological focal deficit; anterograde amnesia; GCS <15 after 2h post TBI; suspicion of vault depression fracture; fracture of the basal skull; persisting nausea, vomiting or headache; post-TBI seizures; preinjury treatment with antithrombotic drugs; loss of consciousness or amnesia in patients over 65 years of age; fall more than 1m or hit pedestrian; and any other condition requiring a CT according to the in-charge physician	13-15 (13 n=9 or 1%)	GCS 3–12, unknown time of injury, time of CT scan or blood sampling unknown or >12h after TBI, admission for a non-traumatic neurological disorder, penetrating head injury, neuropsychiatric and neurological comorbidities that might interfere with the evaluation, venipuncture not feasible, brain CT scan not performed, pregnant or breastfeeding	A CT-positive: (1) epidural haematoma, (2) acute subdural haematoma, (3) subarachnoid haemorrhage, (4) intraventricular haemorrhage, (5) intraparenchymal contusion, (6) petechial haemorrhage or (7) any finding related to diffuse axonal injury and depressed skull fracture. Linear skull fractures were recorded but were not included in the definition of a CT-positive result.
Lagerstedt 2018(Lagerstedt 2018)	Patients recruited from 3 European sites (2 in Spain and 1 in Switzerland: Geneva,	Cross-sectional analysis with partial inclusion of a study (original study with consecutive enrollment)	Patients with mTBI and min 1 additional clinical symptom: vomiting or nausea, LoC, amnesia, equilibrium disorder or headache. Age >14 years (n=2 below 18y). Blood sample taken within 6hrs and CT scan needed and performed <24h.	15	No CT scan, no clinical symptoms, GCS score below 15, pregnancy and no signed informed consent form	Defined in Lagerstedt 2017: epidural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, intracerebral haemorrhage,



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
	Seville and Barcelona) Dates not given					contusion with haemorrhage, cerebral oedema or skull fracture was classified as CT-positive
Lapić 2024(Lapić 2024)	Croatia tertiary hospital ED – level 1 trauma centre May 2022-March 2023	Cross-sectional study; no consecutive enrollment	Adult were selected for mild neurological symptoms: headache, vertigo, nausea, vomiting, alterations in mental status such as confusion, amnesia, LoC <30 min, disorientation. CT decided by ED physician after examination Those with acute head trauma (median age: 62); <12h were then included. Patients with a neurological diagnosis excluded.	14-15	>12h after head trauma, neurological or psychiatric disorders, neurosurgical interventions, and/or previous traumatic brain lesions confirmed by CT Patients with presenting symptoms attributed to gastrointestinal disease, sepsis, pneumonia, non-neurological disorder were not included.	Intracranial abnormality (results section); not further specified
Legramante 2024(Legramante 2024)	Italy 1 centre Oct 2022-Jan 2023	Cross-sectional retrospective study on banked samples	>18 year (mean age: 54) with mild cranial trauma and head CT scan Within 12h	13-15 (0% 13)	GCS score < 13; CRP >5mg/L; anticoagulant therapy; venous sampling >12h after trauma	Positive result in the clinical notes; not further defined
Li 2023(Li 2023)	USA one centre with 24h neurosurgery facilities	Cross-sectional retrospective study of ED data and banked samples; non-consecutive (Monday – Friday)	Adults (mean age: 50.8) with suspected mTBI brought to the centre by ambulance or helicopter. All had a CT scan.	13-15 (72% 15)	Adults in which a CT scan or a blood sample was not performed. Non-English-speaking patients and patients without the capacity to consent	Presence/absence of closed head injuries including skull fracture, pneumocephalus, hemorrhage, mass effect, and brain parenchymal

Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
	specialised TBI Dec 2015-Apr 2017					injuries. The volumes of each type of hematoma or contusion, as well as the extent of midline shift, were quantified as continuous variables, while the extent of subarachnoid hemorrhage, intraventricular hemorrhage, brain edema/swelling, cisternal compression, and hydrocephalus was characterised on ordinal scales.
Okonkwo 2020 (Okonkwo 2020)	USA TRACK-TBI study. Level I trauma Feb 2014-July 2018.	Cross-sectional retrospective analysis on banked samples from the TRACK-TBI study; nonconsecutive enrollment	Adults, on whom a CT scan was performed based on the American College of Emergency Physicians/Centers for Disease Control (ACEP/CDC) guidelines for neuroimaging (2008)	Most mTBI GCS 13-15: (89%),	NR (get from Track TBI protocol)	Head CT scans classified as positive based on the presence of traumatic intracranial abnormalities such as subarachnoid hemorrhage, subdural hematoma or contusion
Oris 2023(Oris 2024)	France 1 ED	Cross-sectional retrospective analysis on banked	Adult (mean age 59.1); at least one associated risk factor: antiplatelet monotherapy, loss of consciousness	14-15	Children. Low or high risk within the mTBI according to the French guidelines: GCSS ≤ 13	CT scans were considered positive if any



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
	Jan 2023-June 2023	samples (except for S100 β); consecutive enrollment	or posttraumatic amnesia of facts 30 min before the injury. Patients with S100β levels above the decision threshold of 0.10 μg/L (<3h) underwent CT scanning. Sampling within 12h. For the other patients (blood sampling >3 h), a CT scan was systematically performed. Since 2022, the new French guidelines also recommend the blood determination of "GFAP and UCH-L1" for the management of mTBI patients with blood sampling <12h.			signs of cranial (skull fracture) or intracranial pathology (hematoma, air, or contusion) were present.
Oris 2024(Oris 2024)	France 1 ED Jan 2023-June 2023	Cross-sectional retrospective analysis on banked samples (except for S100 β); consecutive enrollment	Adult (mean age 66.2) mTBI patients intermediate risk as per the French guidelines: routine S100 β Cobas® system (Roche Diagnostics, Meylan, France) for patients who underwent blood sampling within 3h of mTBI. Patients with S100 β levels above the decision threshold of 0.10 μ g/L underwent CT scanning. Sampling within 12h. Patients>3h no S100 β	13-15 (95.7% 15)	mTBI patients defined as having a low or high risk as per the French guidelines.	CT scans were considered positive if any signs of cranial (skull fracture) or intracranial pathology (hematoma, air, or contusion) were present.
Papa 2022(Papa 2022)	USA ED level I trauma center March 2010-	Cross-sectional study based on a convenience sample	Adults (mean age 40); blunt head trauma followed by a change in sensorium such as LoC, amnesia, or disorientation. mTBI determined by physician; within 4h injury; most patients with blunt head injury and subsequent symptoms have a head	GCS 13-15 (90% 15).	<18years; no history of trauma as their 1ary event; known dementia, chronic psychosis, or active central nervous system pathology; pregnant; incarcerated; or systolic blood pressure < 100mmHg	Acute traumatic intracranial lesion CT scan, including extra-axial lesions (eg, epidural, subdural, and subarachnoid hemorrhage) or

Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
	March 2014		CT scan performed as part of usual care.			intra-axial lesions (eg, contusions, intraparenchymal hemorrhage, cerebral edema, traumatic axonal injury, and midline shift of intracranial contents), as well as any signs of brain herniation or pneumocephalus.
Polat 2022(Polat 2022)	Turkey1 ED centre	Cross-sectional study based on a convenience sample	Adults with mTBI <3h and indication for a CT scan (nausea-vomiting and trauma signs above the clavicle, contusion, abrasion, laceration , with symptoms of deformity, facial and skull fractures)	14-15 (60% 15)	Patients with known neurologic or psychiatric disease, patients with known spinal cord injury, patients with cancer, children, pregnant women, patients who presented after the 3rd hour post injury	CT fracture, subdural, and subarachnoid hemorrhage, contusions, epidural hemorrhage
Posti 2019(Posti 2019)	Finland 1 University hospital Nov 2011-Oct 2013	Cross-sectional study (TBIcare); consecutive enrollment (see Posti 2016)	≥18 (mean age 42.8); mTBI with or without other concomitant extracranial injuries using the Injury Severity Score (ISS), and indications for acute head CT according to NICE criteria.	13-15 (mean 14.7)	Blast-induced or penetrating injury, chronic subdural hematoma, inability to live independently as a result of pre-existing brain disease, TBI or suspected TBI not needing head CT, >2 weeks from the injury, not speaking the local language, no consent obtained	CT scans were classified according to the Marshall grading system. Diffuse injury/grade I (no visual pathology) was considered CT-, whereas the other grades (II-VI) were regarded as CT+. Neuroradiologists and senior neurosurgeon



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
						double-read the CT scans
Puravet 2025(Puravet 2025)	France; ED of 11 hospitals. Nov 2016-Oct 2021	Cross-sectional retrospective analysis on banked samples from a S100β stepped wedge cluster randomised trial	Children ≤16 (median age 4.7) GCS 15 requiring hospitalisation or CT scan according French Pediatric Society guidelines (PECARN-based). Within 3h of injury. < 2 GCS paediatric, inclusion if parietal or occipital scalp haematoma, a loss of consciousness for more than 5s, serious accident, atypical behaviour according to the parents. ≥2 inclusion if loss of consciousness for any length of time, vomiting, serious accident, severe headache	15	Enrolment in another therapeutic trial involving drug administration; having Down syndrome or melanoma; the trauma occurring more than 3 h before admission to hospital; being in the group at high risk as per the PECARN algorithm; having mTBI that did not require hospitalisation or a CT scan	Cranial CT result: Positive for intracranial brain injury e.g. Epidural haematoma, Haemorrhagic contusion, Subdural haematoma, Pneumocephalus, Subarachnoid haemorrhage, Othematoma
Trivedi 2024(Trivedi 2024)	65 sites (includes UZA) across 18 countries Dec 2014-Dec 2017; Trauma Level 1=60, Level 2=4, Level 3=1	Retrospective analysis CENTER-TBI study of banked samples; convenience sample	TBI adults with GCS 14-15 on admission. Clinical suspicion of TBI, indication for CT scanning as determined by physician in charge and presentation to a study center within 24h of injury.	14-15 (score 15 within 6h 88.7%)	Patients with severe pre-existing neurological disorders. Patients with GCS ≤13, with missing data on CT scanning, and/or aged under 18	Clinically significant traumatic CT abnormality (mass lesion, extra-axial hemorrhage, epidural hemorrhage [EDH], acute or chronic subdural hemorrhage [SDH], contusion, traumatic axonal injury, traumatic subarachnoid hemorrhage, intraventricular hemorrhage,



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
						midline shift, or cisternal compression). A skull fracture was included as a CT abnormality only if it was a depressed fracture or if the subject was taking antithrombotic medications, in accordance with NICE guidance.
Welch 2025(Welch 2025)	USA 15 sites, 7 in Europe Dec 2012 to March 2014	Retrospective analysis of data and banked blood samples ALERT-TBI trial; nonconsecutive enrollment	Adults (mean age 49); ED or other healthcare facility with a non-penetrating head injury; GSC 13-15; banked blood available CT scan as part of routine care, evaluation by the treating physician.	13-15 (94.1% score 15)	Patients for whom injury time could not be determined, blood samples could not be obtained within 6h, a CT scan was not deemed necessary, or appropriate consent was not obtained.	any sign of study-defined traumatic intracranial injury: acute epidural hematoma, acute subdural hematoma, intraventricular hemorrhage, parenchymal hemorrhage/contusion, petechial hemorrhage/bland sheer injury, subarachnoid hemorrhage, brain edema/herniation, or ventricular compression/trapping. Skull fractures without any of the above intracranial



Study ID	Country	Design	Population - Inclusion	Glasgow Coma Scale	Exclusion criteria	Outcome on CT
						findings were not considered positive
Whitehouse 2025(Whitehouse 2025)	65 sites (includes UZA) across 18 countries Dec 2014-Dec 2017	Retrospective analysis CENTER-TBI study of banked samples; convenience sample	Age 16+ (median age 59); non-penetrating brain injury; NG232 CDR criteria for CT scan within 8 h (some loss of consciousness or amnesia since injury AND either: aged >65, bleeding or clotting disorder, dangerous injury mechanism or over 30 min of retrograde amnesia), and (2) did not meet other NICE NG232 CDR criteria but had a record of anticoagulant or antiplatelet use (excluding those on aspirin monotherapy), in which case CT imaging is currently advised to be "considered" by NICE	15 (100%)	Subjects without an acute CT report or complete biomarker panel within 24h Polytrauma patients ISS≥15 NG232 CDR criteria for imaging within 1h of identifying risk factors (these subjects considered high-risk)	Clinically significant traumatic CT abnormality (mass lesion, extra-axial hemorrhage, epidural hemorrhage [EDH], acute or chronic subdural hemorrhage [SDH], contusion, traumatic axonal injury, traumatic subarachnoid hemorrhage, intraventricular hemorrhage, midline shift, or cisternal compression). A skull fracture was included as a CT abnormality only if it was a depressed fracture or if the subject was taking antithrombotic medications, in accordance with NICE guidance.



3.4 Results of studies on the S100 β to rule out a cerebral injury vs to GFAP and UCH-L1 (in combination or individually)

Study ID		Biomarker	Cut-off values	Measured within (hrs)	Analyser (provider)	N	CT+ %	Sensitivity (95% CI) %	Specificity (95% CI) %	LR-
Chiollaz 2024	Children. Aged ≤ 16 . Mean age: 8. GCS 14-15	S100 β	43 pg/mL	6	ELISA in serum (Meso Scale Diagnostics)	39	?	100	34.4 (18.6; 51.0)	0.0
		GFAP	204 AUC	6	ELISA in serum (Meso Scale Diagnostics)	43	16.3	100 ^a	38.9 (23.1; 56.5)	0.0
		GFAP	78 AUC	24	ELISA in serum (Meso Scale Diagnostics)	72		100 ^a	22.2 (12.0; 35.6)	0.0
Lagares 2024	Adults in FR and ≥ 15 in Sp. Median age 69. GCSS 13–15	S100 β	0.1 μ g/L	6	Electrochemiluminescence immunoassay (ECLIA) in serum (Cobas®, Roche)	846	11.7	87.8 (79.8; 93.6)	34.8 (31.4; 38.3)	0.35 (0.20; 0.60)
		GFAP	22pg/ml	12	VIDAS in serum (Biomérieux)	1436	12.2	98.3 (94.9; 99.7)	31.3 (28.8; 33.9)	0.05 (0.02; 0.17)
		UCH-L1	327pg/ml	12	VIDAS in serum (Biomérieux)	1437	12.2	57.0 (49.7; 64.0)	63.0 (60.3; 65.7)	0.68 (0.57; 0.81)
		GFAP+UCH-L1	GFA: 22 pg/ml + UCH-L1: 327 pg/ml		VIDAS in serum (Biomérieux)	1438	12.2	98.3 (95; 99.7)	24.9 (22.6; 27.4)	0.07 (0.02; 0.21)
Lagerstedt 2018	Aged > 14 years. Weighted mean	S100 β	0.06 μ g/L	6	Electrochemiluminescence immunoassay (ECLIA) in serum	132	15.9	100	10.8 (5.4; 17.1)	0

^a Sensitivity was set at 100% by the authors to determine the cut-off allowing the best specificity on the ROC curve

Study ID		Biomarker	Cut-off values	Measured within (hrs)	Analyser (provider)	N	CT+ %	Sensitivity (95% CI) %	Specificity (95% CI) %	LR-
	age (by CT result): 48.7 GCS 15 .				(Cobas®, Roche) EZHS100B-33K (Millipore)					
		GFAP	97 AUC	6	Electrochemiluminescence (F211M kit) in serum/plasma (Meso Scale Diagnosis)	132	15.9	100	30.6 (22.0; 39.6)	0
Li 2023	Adults. Mean age: 50.8. GCS 13-15. (72% GCS: 15)	S100β	105 pg/mL	6	Electrochemiluminescence immunoassay (ECLIA) in serum (Cobas®, Roche)	189	23.3	93.2 (81.3; 98.6)	17.2 (11.5; 24.4)	0.40 (0.13; 1.25)
		GFAP	22pg/ml	6	ELISA in plasma/serum ^b (Banyan)	440	27	96.6 (91.6; 99.1)	50.5 (44.9; 56.1)	0.07 (0.03; 0.18)
		UCH-L1	327pg/ml	6		440	26.9	95.0 (89.4; 98.1)	17.7 (13.7; 22.3)	0.29 (0.13; 0.65)
		GFAP+UCH-L1	22pg/ml (GFAP) and 327pg/ml (UCH-L1)	6		663	27	100 (98; 100)	13 (10; 16)	0
Oris 2023	Adults. Mean age: 59.1. Moderate risk within the mTBI according to French guidelines: GCS 14-15	S100β	0.1 µg/L	3	Electrochemiluminescence immunoassay (ECLIA) in serum (Cobas®, Roche)	192	9.8	100 (66.4; 100)	25.7 (19.5; 32.6)	0
		GFAP	30pg/ml	3		192	9.8	100 (66.4; 100)	39.3 (32.2; 46.8)	0

^b Results are available in the article for serum and plasma. As these results are highly correlated, we report here merged results.



Study ID		Biomarker	Cut-off values	Measured within (hrs)	Analyser (provider)	N	CT+ %	Sensitivity (95% CI) %	Specificity (95% CI) %	LR-
		UCH-L1	360pg/ml	3	i-STAT Alinity in plasma (Abbott)	192	9.8	33.3 (7.5; 70.1)	59.0 (51.5; 66.2)	1.13 (0.70; 1.8);
		GFAP+UCH-L1	30pg/ml (GFAP) and 360pg/ml (UCH-L1)	3		192	9.8	100 (66.4; 100).	29 (22.5; 36.1)	0
				12		239	4.6	100 (73.5; 100)	31.7 (25.7; 38.2)	0
Posti 2019	Adults. Mean age: 42.8. All severities (n=160) but here only GCS 13-15 (n=93). Mean GCS for the 13-15: 14.65	S100β	179 pg/mL AUC	24	EZHS100B-33K (Millipore)	93	39.8	91.9	12.5	0.65 (0.18; 2.35)
		GFAP	66.62 pg/mL	24	Neurology 4-Plex A assay (N4PA) in plasma (Quanterix)	93	39.8	100 (91; 100)	16.1 (8; 28)	0
Puravet 2025	Aged ≤16. Median age: 4.67. GCSS: 15 requiring hospitalisation or CT scan according to French guidelines	S100β	By age group ^c	3	Electrochemiluminescence immunoassay (ECLIA) in serum (Cobas®, Roche)	68	20.6	92 (64; 100)	51.9 (37.8; 65.7)	0.15 (0.02; 1.01)
		GFAP		3	Alinity i platform in serum (Abbott)	68	20.6	100 (75; 100)	27 (16; 41)	0
		UCH-L1		3		68	20.6	100 (75; 100)	27 (16; 41)	0
		GFAP+UCH-L1		3		68	20.6	100 (75; 100)	42 (29; 56)	0
Trivedi 2024	Adults. Median age 47 (ICI present), 58 (no ICI present)	S100β	AUC	6	Electrochemiluminescence immunoassay (ECLIA) in serum	531	24.9	78 (68; 83)	61 (56; 66)	0.36 (0.26; 0.50)

^c Cutt-off GFAP and UCH-L1 by age group <2y 180 pg/mL and 373 pg/mL; 2-4y 118 pg/mL and 272 pg/mL; >4y 73 pg/mL and 217 pg/mL based on the 95th percentile for the mean of a control group of children. For S100B 0–9 months, greater than 0.35 µg/L; 10–24 months, greater than 0.23 µg/L; and older than 24 months, greater than 0.18 µg/L. The result combines the ages groups together.

Study ID		Biomarker	Cut-off values	Measured within (hrs)	Analyser (provider)	N	CT+ %	Sensitivity (95% CI) %	Specificity (95% CI) %	LR-
	GCS 14-15 (88.7% GCS 15).				(Cobas®, Roche)					
		GFAP	AUC	6	Simoa digital immunoassay in serum (Quanterix)	531	24.9	71 (61; 78)	87 (76, 93)	0.33 (0.25; 0.43)
		UCH-L1	AUC	6		531	24.9	73 (64, 81)	77 (67, 84)	0.35 (0.27; 0.47)
		GFAP+UCH-L1	AUC	6		531	24.9	76 (66, 83)	83 (71, 90)	0.29 (0.22; 0.40)
Whitehouse 2025	Aged ≥16. Median age: 59. Overall sample larger. Here only results for GCS 13-15	S100β	0.1µg/L	6	Electrochemiluminescence immunoassay (ECLIA) in serum (Cobas®, Roche)	127	18.1	95.7 (78.1; 99.9)	31.7 (23; 41.6)	0.14 (0.02; 0.95)
		GFAP	145 AUC	6	Neurology 4-Plex A assay (N4PA) in serum (Quanterix)	127	18.1	95.7 (78.1; 99.9)	18.3 (11.4; 27.1)	0.24 (0.03; 1.69)
		UCH-L1	31.6 AUC	6		127	18.1	95.7 (78.1; 99.9)	32.7 (23.8; 42.6)	0.13 (0.02; 0.92)



4 SURVEY (ENGLISH VERSION) TO HEADS OF EMERGENCY DEPARTMENT

Section 1: DESCRIPTION OF FACILITIES

1. For what type of hospital do you work?

- ☐ University hospital
- ☐ General hospital
- ☐ General hospital with academic beds.

2. Do you have a CT scan at your ED?

- ☐ YES.
- ☐ NO.

3. For urgent matters is it generally possible to perform a CT scan at your premises within a short time (max. 2 hours from arrival at the ED)?

- ☐ YES, usually within 1 hour.
- ☐ YES usually within 2 hours.
- ☐ NO. It usually takes longer than 2 hours.

4. Is the staff (technicians and radiologists) necessary to perform CT scans available 24/24h?

- ☐ YES at the hospital
- ☐ YES on call
- ☐ NO.



Section 2: MILD HEAD TRAUMA PATIENT NUMBERS

5. Approximately how many patients with a head trauma (of any severity - mild, moderate or severe) have visited your ED in the last two years?

(If you do not have data on this, please give your best approximation).

Children (<18 years)

- ☐ In 2023: _____
- ☐ In 2024: _____
- ☐ I do not know

Please let us know if the figures provided come from registered data or if they are estimations

- ☐ Data
- ☐ Estimations

Adults (≥18 years)

- ☐ In 2023: _____
- ☐ In 2024: _____
- ☐ I do not know

6. Do you follow the definition by the WHO in your ED to classify head trauma cases as mild (moderate or severe)?

"Mild head trauma": A Glasgow Coma Scale score (GCSS) 13 -15 at 30 min. post-injury, and ≥ 1 of the following symptoms: <30min loss of consciousness; <24hours post-traumatic amnesia; impaired mental state at time of accident (confusion, disorientation, etc.); and/or transient neurological deficit."

- ☐ YES
- ☐ NO
- ☐ I don't know.

- If NO, how do you define mild head trauma cases in your ED?



7. Approximately how many (or what proportion of) head trauma patients visiting your ED were classified as MILD in 2023 and 2024?

(If you do not have data on this, please give your best approximation).

Please let us know if the figures provided come from registered data or if they are estimations

- ☐ Data
- ☐ Estimations

Number (or percentage) of head trauma children (<18 years) classified as mild.

- ☐ In 2023: _____
In 2024: _____
- ☐ I do not know

Number of head trauma adults (≥18 years) classified as mild.

- ☐ In 2023: _____
- ☐ In 2024: _____
- ☐ I do not know



Section 3. MANAGEMENT OF PATIENTS WITH SUSPECTED MILD HEAD INJURY IN YOUR EMERGENCY DEPARTMENT (ED)

8. What (standard) guidelines or recommendations do you use in your ED department for deciding when a CT scan should be performed in PAEDIATRIC patients (<18 years) with suspected mild traumatic brain injury?

- PECARN - Pediatric Head Injury Algorithm guidelines
- New Orleans Criteria
- Guidelines of the National Institute for Health and Care Excellence (NICE 2014)
- National Emergency X-Radiography Utilization Study II (NEXUS-II)
- Other (eg. Internal guidelines or protocols).
 - *If “Other”, Please specify which ones and (if possible), attach copy or provide reference*

- I don't know

- **NONE**

9. If “NONE”, What aspects do you consider in your ED to decide to perform a CT scan in suspected MILD head injury PAEDIATRIC patients (<18 years)?

- Palpable skull fracture
- AMS (agitation, somnolence, slow response, repetitive questioning)
- Scalp haematoma
- Not acting normally (judged by parents)
- Dangerous mechanism of injury (ie. ejection from a motor vehicle, a pedestrian struck, and a fall from a height of > 1 meter or 5 steps)
- Other



- *If “Other”, Please specify*

- I don't know

10. Approximately in what proportion of suspected MILD traumatic brain injury PAEDIATRIC patients (<18 years) visiting your ED are CT scans performed?

- Almost all ($\geq 90\%$ -100%)
- Most ($\geq 70\%$ but $< 90\%$)
- More than half ($\geq 60\%$ but $< 70\%$)
- Around half ($\geq 40\%$ but $< 60\%$)
- Around 1/3 ($\geq 30\%$ but $< 40\%$)
- Around 1/4 ($\geq 20\%$ but $< 30\%$)
- Few ($< 20\%$).
- I don't know.

11. What (standard) guidelines or recommendations do you use in your ED department specifically for deciding when CT scans should be performed in suspected MILD traumatic brain injury ADULT patients (≥ 18 years)?

- Canadian CT Head Rule
- Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate head trauma in Adults
- New Orleans Criteria
- Guidelines of the National Institute for Health and Care Excellence (NICE 2014)
- Neurotraumatology Committee of the World Federation of Neurosurgical Societies (NCWFS)
- Guidelines of the French Society for Emergency Medicine (SFMU)
- Other
 - *If “Other”, Please specify which ones and (if possible), attach copy or provide reference*



○ I don't know

• **NONE.**

If "NONE", what aspects do you consider in your ED to decide whether to perform a CT scan in suspected MILD traumatic brain injury ADULT cases (≥ 18 years)?

- GCS score < 15 at two hours after injury
- Suspected open or depressed skull fracture
- Vomiting more than once
- Age > 65 years
- Antiplatelet or anticoagulant medication
- Dangerous mechanism of injury
- Persistent amnesia (over 30 min or 60 min)
- Other
 - *If "Other", Please specify*

• I don't know

12. Approximately in what proportion of suspected MILD traumatic brain injury ADULT patients (≥ 18 years) visiting your ED are CT scans performed?

- Almost all (90%-100%)
- Most ($\geq 70\%$ but $< 90\%$)
- More than half ($\geq 60\%$ but $< 70\%$)
- Around half ($\geq 40\%$ but $< 60\%$)
- Around 1/3 ($\geq 30\%$ but $< 40\%$)
- Around 1/4 ($\geq 20\%$ but $< 30\%$)
- Few ($< 20\%$)



- I don't know.

13. Are there any suspected mild traumatic brain injury patient groups in which you would ALWAYS consider it necessary to perform a CT scan?

- YES
- NO.
- I don't know
 - If YES, in which ones?
 - Elderly
 - On antiplatelet or anticoagulant treatment
 - Age > 65 and on antiplatelet or anticoagulant medication
 - GCS of 13
 - Repeated vomiting
 - Suspected or confirmed LoC
 - Retrograde amnesia 30 min prior to injury
 - Other

If "Other", Please specify

14. On average, how long does it take between arrival to your ED and the clinical decision (immediate discharge, performing a CT scan or keeping a patient under observation)?

- Less than 1 hour
- 1-2 hours
- 2-3 hours
- 3-4 hours.
- More than 4 hours
- I don't know



15. In those suspected mild traumatic brain injury cases for which a CT scan is performed, how long do you have to wait on average for results, from the moment it is requested?

- Less than 1 hour
- 1-2 hours
- 2-3 hours
- 3-4 hours.
- More than 4 hours
- I don't know

16. From the suspected mild traumatic brain injury patients in which a CT scan is NOT performed: Approximately what proportion is immediately discharged home after triage or specialist consultation?

- Children (<18 years) _____
- Adults (≥18 years) _____
- I don't know

17. From the suspected mild traumatic brain injury patients in which a CT scan is NOT performed: Approximately what proportion is kept under observation for 6 hours after triage or specialist consultation?

- Children (<18 years) _____
- Adults (≥18 years) _____
- I don't know.

18. From the suspected mild traumatic brain injury patients in which a CT scan is NOT performed: Approximately what proportion is kept under observation for longer than 6 hours after triage or specialist consultation? (Mandatory)

- Children (<18 years) _____
- Adults (≥18 years) _____
- I don't know.



Section 4: USE OF BLOOD-BASED BIOMARKERS FOR MILD HEAD TRAUMA

19. Which of the existing blood-based biomarkers do you think could add value to the diagnosis of mild head trauma in your ED?

- ☐ Protein S100 β
- ☐ GFAP
- ☐ UCH-L1
- ☐ Combination of GFAP and UCH-L1
- ☐ Others (Please specify _____)
- ☐ None,
- ☐ I don't know.

if "None", please let us know the reason why?

20. Do you currently use any blood-based biomarkers in patients visiting your ED with mild head trauma to help you exclude a brain injury?

- ☐ YES.

If "YES", which ones and in what patients?

	We do not use this test in any mild head trauma patient	We use this test in ALL mild head trauma patients	We use this test in SOME mild head trauma patients	I do not know
Protein S100 β				
GFAP				
UCH-L1				
Combination GFAP+UCH-L1 (POC test)				



Combination
GFAP+UCH-L1
(Lab-based test)

Others (please
specify_____)

If YES and “we use this test in SOME mild head trauma patients” are selected, the following additional question should appear as many times as these answers have been chosen.

Please specify in which mild head trauma patients you use the biomarkers

- ☐ GCS 14-15
- ☐ GCS 13-15,
accompanied by one or more of the following symptoms:
 - ☐ Suspected or confirmed loss of consciousness
 - ☐ Vomiting episodes (≥ 2)
 - ☐ Retrograde amnesia 30 minutes before the injury
 - ☐ Antiplatelet or anticoagulant therapy
 - ☐ ≥ 65 years
 - ☐ Other (please specify)

- ☐ I don't know.

If “YES”, how does your use of these biomarkers in the ED affect your CT scan use?

We perform a CT scan ...

- ONLY if the result of the biomarker test is positive (or other symptoms of intracranial head injuries appear)
- Independently of the result of the biomarker test
 - If so, why?



- _____
 - _____
 - In some cases, independently of the results of the biomarker test.
 - If so, in what cases/types of patients or situations
 - _____
 - _____
 - _____
 - _____
 - _____
 - _____
 - I don't know
 - **NO.**
 - If "NO", why not?
 - Not reimbursed
 - Accuracy not high enough,
 - Short time window in which the biomarker test can effectively be used to identify intracranial injuries (*eg. S100 β is recommended to be used within 6 hrs from injury*)
 - Fear to miss some complications
 - Lack of training or knowledge
 - Long waiting times linked to CT scans
 - Other (specify) _____
 - I don't know

21. What do you consider the three most important factors for a biomarker to be adopted in your ED department for diagnosis of mild head injuries?

- Long diagnostic time window (i.e. the biomarker test can still be performed long after the injury eg. More than 6 hours after injury)
- High sensitivity
- High specificity
- Rapid results (specify maximum waiting time _____)
- Cost
- Compatible with existing laboratory instrumentation (*i.e. no need to invest in additional equipment*)



- ☐ No additional training needed for the staff
- ☐ Available required personnel
- ☐ Available as point of care
- ☐ Others
(specify _____).

22. Is there a minimum cut-off for the sensitivity of the test, below which you would NOT use a blood-based biomarker in your ED to exclude the presence of intracranial injuries on “suspected” mild traumatic brain injuries (mTBI) ?

- ☐ 95%
- ☐ 96%
- ☐ 97%
- ☐ 98%
- ☐ 99%
- ☐ 100%
- ☐ Other. Specify _____
- ☐ I don't know

23. Is there a minimum cut-off for the negative predictive value of the test, below which you would NOT use a blood-based biomarker in your ED to exclude the presence of intracranial injuries ?

- ☐ 95%
- ☐ 96%
- ☐ 97%
- ☐ 98%
- ☐ 99%
- ☐ 100%
- ☐ Other. Specify _____
- ☐ I don't know



24. If blood-based biomarker tests were (or are) available as point of care (POC) test in your ED, would (or do) you still ask for a confirmatory laboratory test for the same markers?

- ☐ YES
- ☐ NO
- ☐ I don't know

25. What would be the maximum acceptable waiting time for results for such biomarkers to be useful in your ED?

- ☐ Less than 30 min
- ☐ 30 min to 1 hour
- ☐ 1-2 hours
- ☐ 2-3 hours.
- ☐ More than 3 hours
- ☐ I don't know

26. Would this maximum acceptable time differ for a point of care (POC) biomarker tests versus laboratory-based tests?

- ☐ YES.
If "YES", how?

FOR POC tests

- Less than 30 min
- 30 min to 1 hour
- 1-2 hours
- 2-3 hours.
- More than 3 hours
- I don't know

FOR laboratory tests

- Less than 30 min
- 30 min to 1 hour
- 1-2 hours
- 2-3 hours.
- More than 3 hours



- I don't know
- NO
- I don't know.

27. If answer to question 20 was NO, ask questions 27 and 28. If not, move to question 29.

If you start using these biomarkers in your ED, in what mild head injury patients would you use them?

-
- GCS 14-15

OR

- GCS 13-15

accompanied by one or more of the following symptoms:

- Suspected or confirmed loss of consciousness
- Vomiting episodes (≥ 2)
- Retrograde amnesia 30 minutes before the injury
- Antiplatelet or anticoagulant therapy
- ≥ 65 years
- Other (please specify) Free text

- I don't know.

28. Why in those?

29. In your opinion, are there any MILD head injury patients in which the use of these blood-based biomarkers would have no added value?



- ☐ YES

If “YES”, which ones?

- ☐ NO
- ☐ I don't know.



5 PROTOCOL MTBI UZ LEUVEN

OBJECTIVE

To streamline the appropriate duration of neurological observation and the decision on the necessity and optimal timing of CT imaging of the skull and brain in patients with clinical signs of a concussion. A neurological examination and observation of at least 6 hours is recommended for every concussion.

CARE RESPONSIBILITY

Patients with blunt head trauma are cared for by the traumatology department, with or without the support of emergency medicine. These disciplines are also responsible for the patient, request examinations and consultations (if a CT scan is required, the traumatologist or emergency physician will request it; if an S100 β determination is indicated, this is also initiated by the traumatologist or emergency physician), and prepare discharge documents and follow-up appointments (if deemed necessary). The neurological examination is performed by the ASO neurology.

TARGET POPULATION

Adult patients (≥ 16 years old) with blunt head trauma who:

1. have either lost consciousness
2. have post-traumatic amnesia
3. have risk factors*
4. and have a GCS score of 13, 14, or 15 upon arrival at the ED.

Patients who have sustained blunt head trauma without any loss of consciousness or amnesia, thus consistently having a GCS of 15 and without any risk factors, generally do not require further screening or observation.

Patients who have sustained blunt head trauma and have a GCS score lower than 13 are classified as moderate to severe head trauma and are not discussed here. Head trauma of this severity (GCS < 13) must always be managed by the trauma team as a red or yellow code according to the polytrauma manual, due to the risk of associated injuries. These patients will then be managed by the neurosurgery department in the future (see sub-ZP head trauma with intracranial abnormalities). Cervical spine management and imaging in trauma are not discussed here.

ALGORITHM

Group 1

GCS = 14 or 15 upon admission to the ED, and LOC lasting no more than 15 minutes, and amnesia lasting no more than 60 minutes, and no risk factors present:

- neurological examination,
- S100 β determination within 6 hours of trauma if possible

- a. a. If the serum S100 β level is less than 0.10 $\mu\text{g/L}$, the patient is observed for 6 hours. If their neurological condition is normal by then, they can be discharged. A "commotio" letter (with information about the "commotio" and follow-up options) is provided upon discharge. Wake-up advice is not required.

Any abnormality of consciousness or any neurological function at the end of the observation period requires a neurosurgical consultation.

Caution: If, with an initial GCS score of 14, the score does not return to 15 within 2 hours, this is considered a risk factor. These patients belong in group 2, where observation lasts 24 hours and a CT scan of the skull is performed after 4-5 hours.

- b. b. If the serum S100 β level is greater than or equal to 0.10 $\mu\text{g/L}$, the patient is observed for 6 hours and a CT scan of the skull is performed after 4-5 hours. This also applies if an S100 β determination cannot be performed within 6 hours of the trauma. If the scan shows no abnormalities and the neurological condition is normal at the end of the observation, the patient can be discharged. Upon discharge, a "commotio" letter (with information about "commotio" and the possibility of follow-up) is provided. Wake-up advice is not required.

Any abnormality of consciousness or any neurological function at the end of the observation, or any abnormality on the scan, requires a neurosurgical consultation. Note: If an initial GCS score of 14 does not normalize to 15 within 2 hours, this is considered a risk factor. These patients belong in group 2, where observation lasts 24 hours and a CT scan of the skull is performed after 4-5 hours.

Group 2

GCS 13 upon admission to the ED, or LOC lasting longer than 15 minutes, or amnesia lasting longer than 60 minutes, or a risk factor is present:

- Neurological examination
- The patient is observed for 24 hours.
- After 4-5 hours, a CT scan of the skull is performed.

If the scan shows no abnormalities and the neurological status is normal at the end of the observation, the patient can be discharged. Upon discharge, a "commotio" letter (with information about the "commotio" and the possibility of follow-up) is provided. Wake-up advice is not required.

Any abnormality of consciousness or any neurological function at the end of the observation, and any abnormality on the scan, requires a neurosurgical consultation.

*RISK FACTORS

Trauma mechanism (high-energy trauma)

- Traffic accident involving pedestrian or cyclist hitting a vehicle
- Ejected from a vehicle
- Fall from a height of >1 meter or >5 flights of stairs

**Symptoms:**

- Vomiting ≥ 2 times
- GCS < 15 2 hours after the trauma
- Clinical signs of a skull fracture (cerebrospinal fluid leak, skull discontinuity, ear bleeding, periorbital ecchymosis)
- Observable serious external injury above the shoulder level
- Suspected intoxication with sedative, excitatory, or hallucinogenic drugs

Other:

- Use of blood-thinning medications
- Preexisting coagulation deficits
- Post-traumatic epileptic seizure
- Age >60 years
- Abnormal neurological examination
- GCS decline of 1 point or more during observation

S100 β ANALYSE

Only to be requested for patients in group 1 and within six hours of the trauma. Request as "S100," the request number is 177.

Important

- The sample must be accompanied by a pink (urgent) request slip (XXXX), currently with the handwritten request "S100 β ."
- During on-call hours (after 6 PM and before 8 AM during the week, as well as on weekends), the lab should be called at XXXX. The results of S100 β have not been validated for patients under the age of 16 or over the age of 65. Based on this UZ Leuven algorithm, S100 β is only requested for patients between the ages of 16 and 60.

OBSERVATION

In patients with an indication for observation, the nurses will check the level of consciousness every hour for 4 hours and then every 2 hours for the remainder of the observation.

EXPLANATION FOR PATIENT AND FAMILY

A letter with an explanation for the patient and their family is available. This letter also discusses the possibility of follow-up.