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REVIEW ARTICLE

Biofluid Biomarkers in Traumatic Brain Injury: A Systematic Scoping Review

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Abstract

Emerging evidence suggests that biofluid-based biomarkers have diagnostic and prognostic potential in traumatic brain injuries (TBI). However, owing to the lack of a conceptual framework or comprehensive review, it is difficult to visualize the breadth of materials that might be available. We conducted a systematic scoping review to map and categorize the evidence regarding biofluid-based biochemical markers of TBI. A comprehensive search was undertaken in January 2019. Of 25,354 records identified through the literature search, 1036 original human studies were included. Five hundred forty biofluid biomarkers were extracted from included studies and classified into 19 distinct categories. Three categories of biomarkers including cytokines, coagulation tests, and nerve tissue proteins were investigated more than others and assessed in almost half of the studies (560, 515, and 502 from 1036 studies, respectively). S100 beta as the most common biomarker for TBI was tested in 21.2% of studies (220 articles). Cortisol was the only biomarker measured in blood, cerebrospinal fluid, urine, and saliva. The most common sampling time was at admission and within 24 h of injury. The included studies focused mainly on biomarkers from blood and central nervous system sources, the adult population, and severe and blunt injuries. The most common outcome measures used in studies were changes in biomarker concentration level, Glasgow coma scale, Glasgow outcome scale, brain computed tomography scan, and mortality rate. Biofluid biomarkers could be clinically helpful in the diagnosis and prognosis of TBI. However, there was no single definitive biomarker with accurate characteristics. The present categorization would be a road map to investigate the biomarkers of the brain injury cascade separately and detect the most representative biomarker of each category. Also, this comprehensive categorization could provide a guiding framework to design combined panels of multiple biomarkers.

Keywords: Traumatic brain injuries, Biomarkers, Diagnosis, Prognosis

Introduction

Traumatic brain injury (TBI) is a major health concern globally [1]. In 2016, 55 million patients suffered from TBI worldwide with an estimated 8.1 years of life lived with disabilities [2]. TBI is a dynamic condition initiated by primary tissue damage followed by a complex secondary cascade of pathophysiological events mainly comprising excitotoxicity, ionic dysregulation, metabolic crisis, and neuroinflammation [3–5]. The complexity and inherent heterogeneity of TBI make it difficult to characterize

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by common techniques [6]. Glasgow coma scale (GCS) as the most common clinical index for TBI severity is a crude tool influenced by multiple confounding factors including baseline cognitive function, pharmacologic agents, ventilatory support, alcohol or drug intoxication, and circadian rhythm [7, 8]. Alternatively, clinical guidelines have recommended brain computed tomography (CT) scan as the imaging modality of choice for triage of TBI patients and for identifying the possible progression of injury. However, this technique has been criticized for being overused in up to 35% of mild TBI, and for the inadequacy of repeated brain CT scan in neurosurgical decision making, particularly in patients without neurological deterioration [9–11]. Besides, the low diagnostic and prognostic yields of the brain CT scan in subtle brain injuries such as diffuse axonal injuries have also raised additional concerns about the precision of this modality, particularly in mild TBI [12–16].

Biofluid biomarkers are quantitative biochemical and/or chemical measurements that could serve translatable metrics as clinical management tools for TBI [17]. Biofluid biomarkers aid to provide insight into the underlying cellular and molecular pathophysiology of TBI and to improve the classification of TBI severity in clinical applications [18]. In terms of diagnostic performance, rapid and readily accessible diagnostic biofluid biomarker testing could optimize clinical resource use by reducing the use of unnecessary brain CT and/or MRI scanning. Notably, they could work as surrogates where access to a brain CT scan is limited and the timely diagnosis is of critical importance [19]. Alternatively, in terms of prognosis, the integration of information from biofluid biomarker measurements to clinical parameters and brain CT scan findings may improve the precision of prognostic models. Monitoring of disease progression and guidance of clinical management are further clinically meaningful endpoints for biomarkers assessments [20, 21].

It is deemed that an ample amount of diversified evidence of biofluid biomarkers of TBI exists. However, owing to the lack of a conceptual framework or comprehensive review, it is difficult to visualize the breadth of materials that might be available. In this article, we systematically review the literature to identify all biochemical markers that have been assessed in prior clinical and animal experimental studies in the TBI field. This study would take the process of exploration of biomarkers relevant to TBI a step forward by providing a detailed overview of the current state of research.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA-P) statement [22]. MEDLINE and EMBASE were searched for English articles without date restriction in January 2019. The keywords were chosen based on the MeSH and Emtree thesaurus. The search strategy is presented in Online Appendix 1. We also performed a manual search of the reference lists of all relevant systematic and narrative reviews for additional potentially pertinent papers. We included randomized clinical trial, cohort, case–control, and case series studies assessing all kinds of TBI biomarkers. The screening of the titles/abstracts and data extraction were performed by two independent reviewer groups (MMM & MSM, SM & AH, ZK & MK, AA & MG, EJ & MMR). Any disagreements were discussed and resolved by a third reviewer (MSN, MSA). As the main objective, all human studies regarding TBI and biochemical markers were included. Duplicate, post-mortem, neuroimaging, experimental, review, and non-original articles were excluded. The purpose of data extraction was to obtain the type, categorization, source, and final meaningfulness or usability of the biomarkers, in addition to the properties of the study, the type and severity of TBI, and all of the outcome measures (Online Appendix 2). As a complementary objective, data extraction from relevant animal studies which were excluded in the screening phase was performed in terms of tested biomarker, animal species, and biofluids. Descriptive, comparative, and correlational summaries were conducted using SPSS 22 (IBM Corp., Endicott, NY, USA).

Results

A PRISMA flow diagram outlining the current search strategy at each step is presented in Fig. 1.

Initial records identified through literature searching included 25,317 articles. Thirty-seven additional articles were added from the reference lists of relevant reviews. Accordingly, 1036 met the eligibility criteria and were included for data extraction.

In total, 540 biochemical markers were extracted from 1036 included studies (Online Appendix 3, Part 1). One hundred and thirty-four biomarkers were studied in 423 individual papers (Online Appendix 3, Part 2). To measure biomarkers, a diverse range of biofluid and tissue samples collected and investigated including blood, cerebrospinal fluid (CSF), cerebral microdialysis (CMD), brain tissue, urine, saliva, bronchoalveolar lavage (BAL) fluid, buccal swabs, and gastric mucosa (Fig. 2).

Simultaneous sampling from blood and brain was done in 104 studies, of which 94 investigated blood and CSF. We classified the biomarkers based on the MeSH categories, mainly the “Chemicals and Drugs Category” [23]. Table 1 shows 19 categories of biomarkers sorted by frequency and biofluids in the included studies. Three categories of biomarkers including cytokines, coagulation

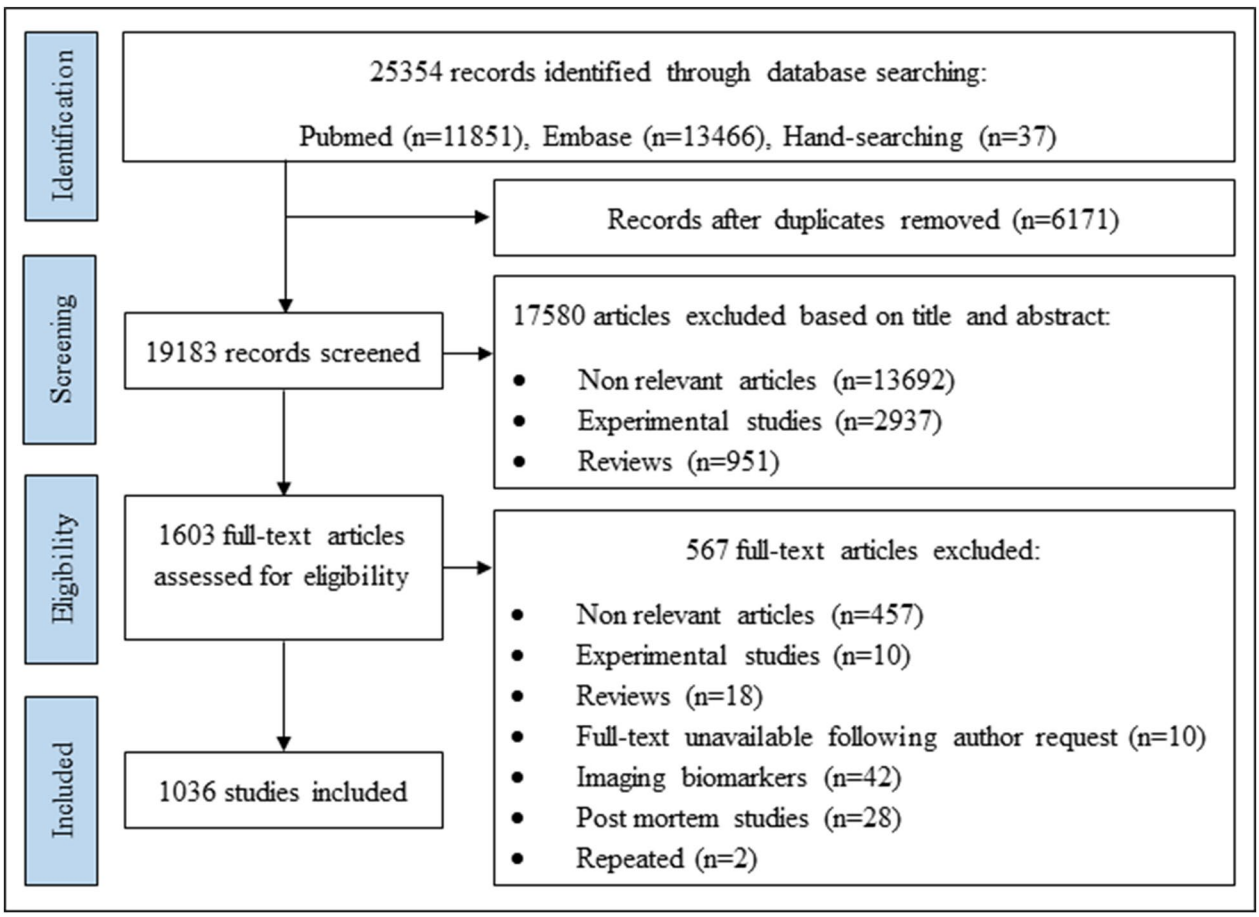

Fig. 1 Flow diagram of the summarized search procedure

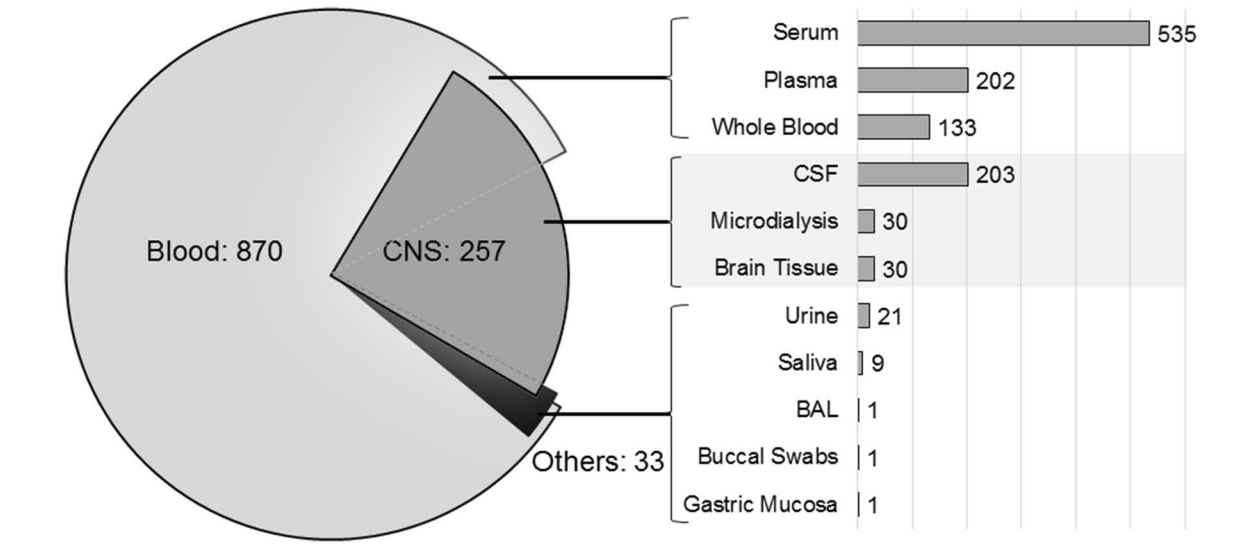

Fig. 2 Biofluids and tissues based on the number of 1036 studies. **CNS* Central Nervous System; *CSF* Cerebrospinal Fluid; *BAL* Bronchoalveolar Lavage Fluid

Table 1 Categories of biomarkers of TBI based on the biofluids

Categories of Biomarkers	Biofluid				Total (540 Biomarkers) 1036 studies
	Blood (435 Biomarkers) 870 studies	CNS (182 Biomarkers) 257 studies	Saliva (48 Biomarkers) 9 studies	Urine (10 Biomarkers) 21 studies	
Cytokines	(32) 477	(28) 195	–	–	(34) 560
Coagulation tests	(43) 514	(4) 5	–	–	(45) 515
Nerve tissue proteins	(29) 416	(26) 123	–	(1) 3	(34) 502
Proteins (except cytokines)	(92) 285	(47) 123	(1) 1	–	(105) 381
Pituitary function tests	(7) 265	(1) 1	–	–	(11) 265
Enzymes	(28) 193	(12) 54	(1) 1	–	(31) 225
Comprehensive Metabolic panel	(21) 146	(8) 40	–	–	(21) 169
Other hormones	(10) 140	(2) 5	(1) 5	(1) 5	(10) 155
Thyroid function tests	(3) 140	–	–	–	(3) 140
Sex hormones	(6) 74	(3) 3	–	–	(6) 75
Parameters of glycolysis (Cerebral energy metabolism)	(4) 20	(5) 71	–	–	(5) 75
Hematologic test	(5) 46	(2) 3	–	–	(6) 48
Lipids	(14) 26	(4) 10	–	(1) 1	(15) 29
Oxidative stress markers	(14) 26	(4) 5	–	–	(15) 27
Amino acids	(5) 18	(4) 6	–	–	(5) 20
Catecholamines	(4) 17	(1) 1	–	(3) 3	(4) 18
RNAs	(99) 12	(25) 3	(45) 3	–	(169) 16
Metals	(5) 7	–	–	–	(5) 7
Miscellaneous	(14) 35	(6) 12	–	(4) 13	(20) 59

tests, and nerve tissue proteins were investigated more than others and assessed in almost half of the studies (560, 515, and 502 from 1036 studies, respectively).

Cortisol was the only biomarker measured in blood, CSF, urine, and saliva. MicroRNAs and Apo-Lipoprotein E have assessed in blood, CSF, and saliva. S100 beta and norepinephrine were tested in blood, CSF, and urine. The ten most common biomarkers used in studies are shown in Fig. 3a.

The most common sampling times are at admission and within 24 h of the injury for these ten biomarkers which are consistent with Table 2 for all biomarkers. Table 2 shows the patient's age, characteristics of TBIs, and sampling time. Serial (>2) sampling of biofluids was performed in 48.4% of studies.

Assessing the relationship between the change of biomarker concentration and TBI prognosis was the most frequent goal among 1036 included studies (42.6%). The most common outcome measures were the change of biomarker concentration (60.1%), GCS (31.6%), Glasgow outcome scale (29.2%), brain CT scan (25.9%), and mortality (18.9%). The methods used to detect or measure concentrations of specific molecules were mentioned in 581 papers (Fig. 4).

In 548 studies (52.3%), more than one outcome measure was used. Table 3 shows post-injury assessments, sorted by frequency, based on the main goals of the included studies.

Within the 2947 excluded animal studies, 2228 studies were related to TBI and biomarkers (Online Appendix 4). Figure 5 shows species, biofluids, and tested biomarkers in relevant animal studies.

Discussion

We retrieved 540 biochemical markers from biofluid sources that are relevant to TBI from 1036 original human studies and systematically classified them into 19 distinct categories. This large body of evidence highlights the growing research and clinical interest in TBI biomarkers, particularly over the past two decades. Almost half of the studies focused on 3 out of the 19 classified categories of biomarkers including nerve tissue proteins, cytokines, and coagulation tests (Table 1).

Nerve tissue proteins were the most extensively assessed biomarkers in the TBI studies. They encompass a wide array of proteins that originate from neuronal and neuroglia cells and play diverse biological roles ranging from the structure, synaptic activity, myelination, to CNS development [24, 25]. These brain-derived proteins were elevated immediately in biofluids as a result of damage to the nerve cells and neuroglia cells [17, 26]. Therefore, these proteins were measured in studies mostly on

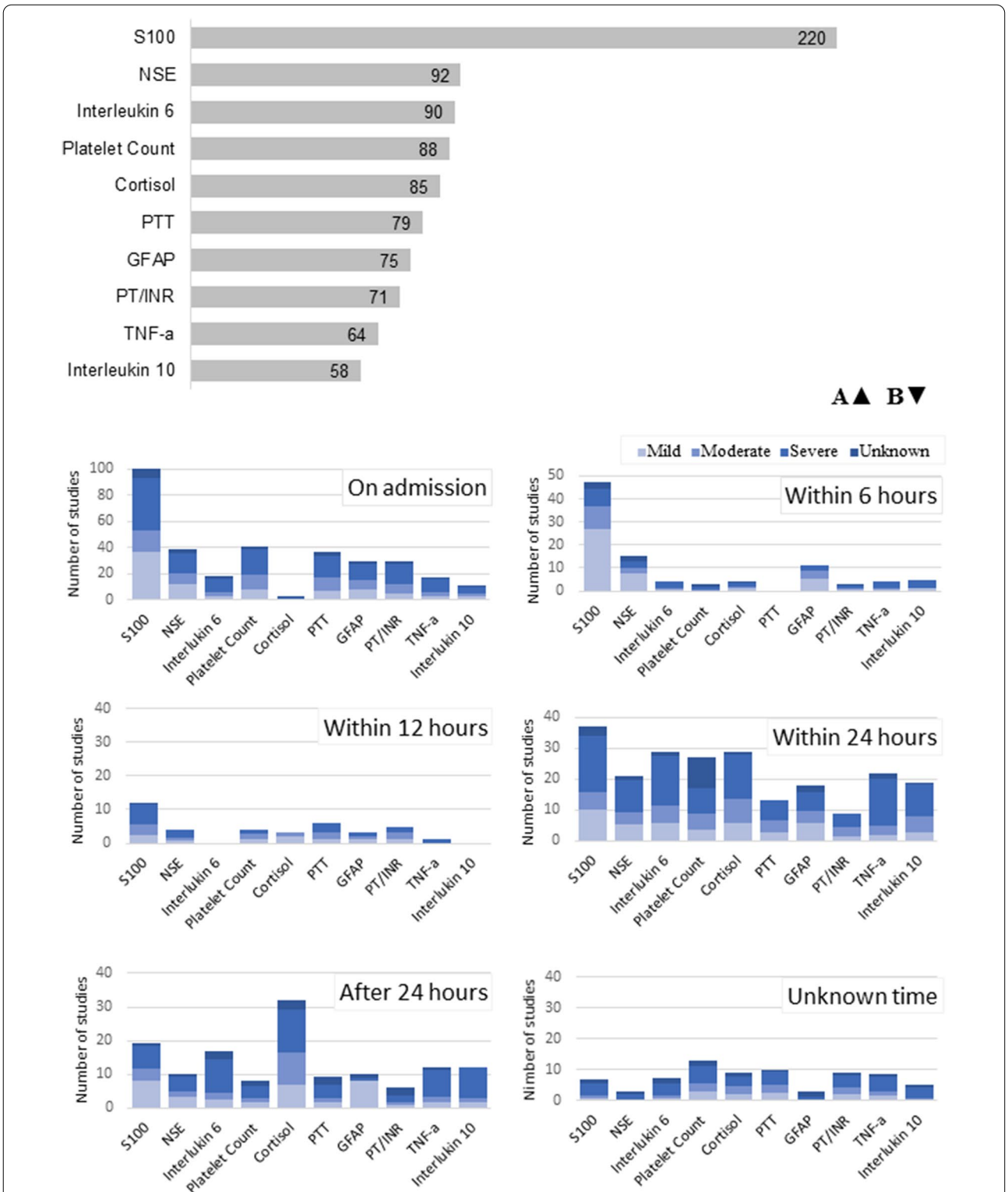

Fig. 3 Ten most common biomarkers in 540 included studies (**a**), based on sampling time and TBI severity (**b**). *GFAP* Glial Fibrillary Acidic Protein; *INR* International Normalized Ratio; *NSE* Neuron-Specific Enolase; *PT* Prothrombin Time; *PTT* Partial Thromboplastin Time; *TNF-α* Tumor Necrosis Factor-α

Table 2 Some characteristics of 1036 included studies

Patients age	< 1 year	33 (3.2%)
	1–15 years	123 (11.9%)
	> 15 years	832 (79.4%)
	Unknown	48 (4.6%)
Injury severity (based on GCS)	Mild	392 (37.8%)
	Moderate	316 (30.1%)
	Severe	720 (69.5%)
	Unknown	101 (9.7%)
Injury type	Blunt	369 (35.6%)
	Penetrating	4 (0.4%)
	Blunt and penetrating	55 (5.3%)
	Unknown	608 (58.7%)
Sampling time	On admission	315 (30.4%)
	Within 6 h	105 (10.1%)
	Within 12 h	42 (4.1%)
	Within 24 h	297 (28.7%)
	After 24 h	172 (16.6%)
	Unknown	105 (10.1%)

admission time and within 24 h of injury (Fig. 3b). In this category, numerous biomarkers with promising clinical utility identified including S100B, glial fibrillary acidic protein, microtubule-associated proteins, neurofilament proteins, and myelin basic proteins.

Cytokines were the second main category of biomarkers of TBI owing to their central pleiotropic roles in the initiation and regulation of local and systemic inflammatory response. Simultaneous to the post-traumatic inflammatory reaction, cytokines are synthesized by resident glial and neuronal cells of the CNS and by peripheral blood-borne immune cells and upregulated in biofluids [27]. They express pro-inflammatory and anti-inflammatory properties in a time- and concentration-dependent manner, which competes with each other to produce a balanced inflammatory response [28, 29]. Rapid expression, high peak concentration, and short half-lives are ideal attributes of cytokines as biomarkers, although their shortcomings, including a lack of specificity, should be considered [30]. According to our results, cytokines were assessed predominantly within 24 h of injury and in more severe types of TBI (Fig. 3b). In this category, several biomarkers such as interleukins, tumor necrosis factors, and chemokines have shown some promise as diagnostic and prognostic tools.

Coagulation tests comprised the third most widely evaluated biomarkers in TBI studies, plausibly due to the high prevalence of coagulopathy in brain injuries

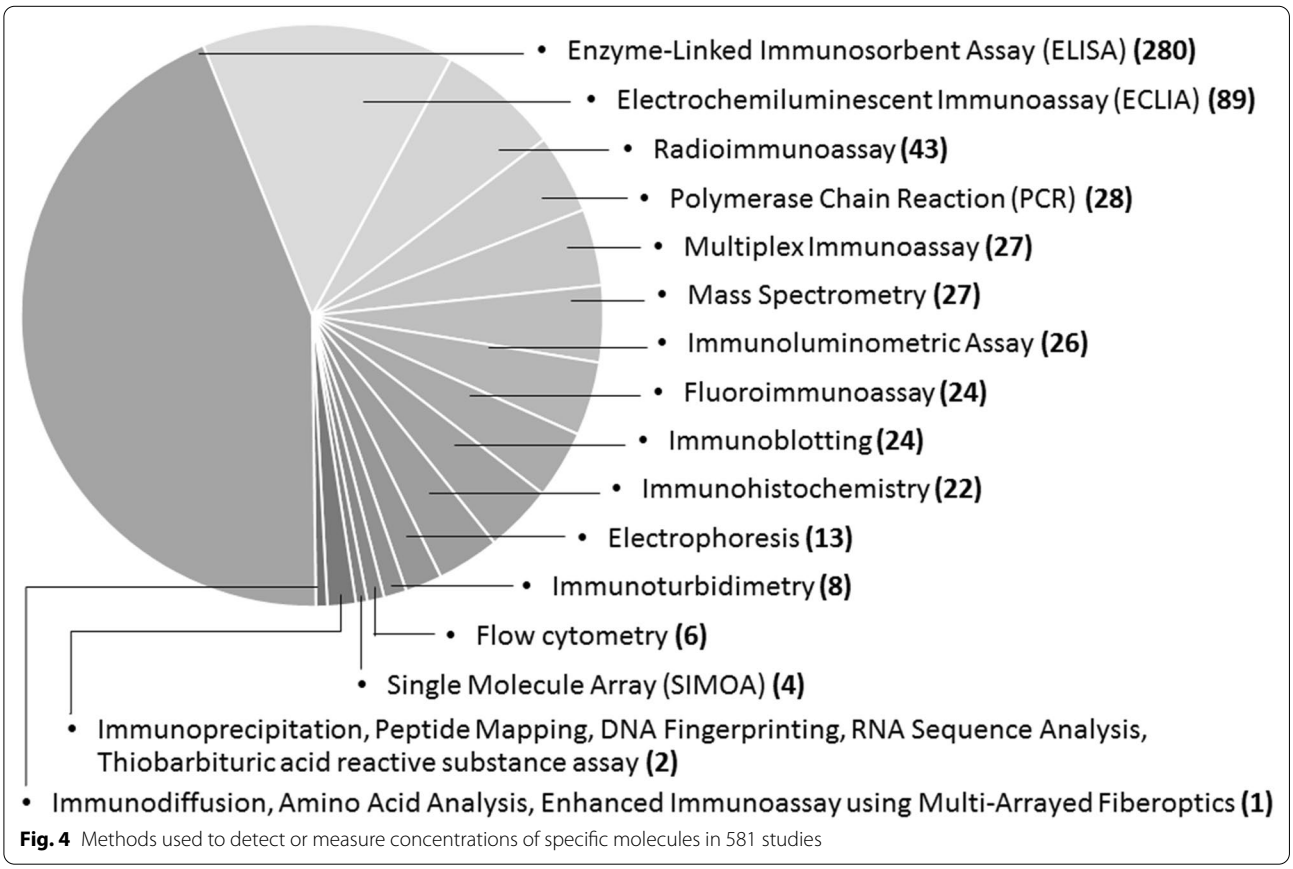

Fig. 4 Methods used to detect or measure concentrations of specific molecules in 581 studies

Table 3 Post-injury assessments and main goals of 1036 included studies

Post-injury assessment, *N* (%)*	Main goals, *N* (%)*				
	Prognosis, 441 (42.6)	Pathophysiologic changes, 361 (34.8)	Diagnosis/ Screening, 284 (27.4)	Monitoring recovery, 120 (11.6)	Effects of an intervention, 66 (6.4)
Examination of biomarkers, 623 (60.1)	204 (19.7)	204 (19.7)	197 (19)	72 (6.9)	43 (4.1)
GCS, 327 (31.6)	159 (15.3)	56 (5.4)	114 (11)	39 (3.8)	19 (1.8)
GOS, 302 (29.2)	188 (18.1)	82 (7.9)	59 (5.7)	29 (2.8)	22 (2.1)
Brain CT scan, 268 (25.9)	119 (11.5)	56 (5.4)	101 (9.7)	34 (3.3)	14 (1.4)
Mortality, 196 (18.9)	152 (14.7)	50 (4.8)	17 (1.6)	15 (1.4)	16 (1.5)
Neuropsychological status, 86 (8.3)	42 (4.1)	26 (24.5)	21 (2)	11 (1.1)	4 (3.9)
ICP/CPP, 83 (8)	25 (2.4)	30 (2.9)	19 (1.8)	15 (1.4)	10 (1)
Injury scores**, 49 (4.7)	31 (3)	9 (0.9)	12 (1.2)	3 (0.3)	5 (0.5)
Brain MRI, 39 (3.8)	11 (1.1)	14 (1.4)	17 (1.6)	11 (1.1)	1 (0.1)
Post-concussion syndrome, 29 (2.8)	14 (1.4)	8 (0.8)	11 (1.1)	4 (3.9)	0
Major adverse events, 27 (2.6)	14 (1.4)	7 (0.7)	3 (0.3)	5 (0.5)	2 (0.2)
Hospital LOS, 27 (2.6)	16 (1.5)	5 (0.5)	4 (3.9)	3 (0.3)	4 (3.9)
ICU LOS, 24 (2.3)	17 (1.6)	5 (0.5)	2 (0.2)	3 (0.3)	1 (0.1)
Functional assessment***, 24 (2.3)	16 (1.5)	5 (0.5)	5 (0.5)	1 (0.1)	2 (0.2)
Neurological examination, 17 (1.6)	10 (1)	4 (3.9)	4 (3.9)	1 (0.1)	3 (0.3)
Surgical interventions, 14 (1.4)	8 (0.8)	2 (0.2)	4 (3.9)	0	0
Mechanical ventilation, 5 (0.5)	4 (3.9)	1 (0.1)	1 (0.1)	0	1 (0.1)
ECG, 3 (0.3)	1 (0.1)	0	1 (0.1)	2 (0.2)	0
PET/SPECT, 3 (0.3)	4 (3.9)	2 (0.2)	0	0	0
SSEP, 2 (0.2)	1 (0.1)	0	0	0	0

CT computerized tomography scan; *ECG* electrocardiography; *GCS* glasgow coma scale; *GOS* glasgow outcome scale; *ICU* intensive care unit; *ICP/CPP* intracranial pressure monitoring/cerebral perfusion pressure; *LOS* length of stay; *MRI* magnetic resonance imaging; *PET/SPECT* positron emission tomography/Single-photon emission computerized tomography; *SSEP* somatosensory-evoked potentials

*Some studies had more than one main goal or outcome measure. The percentage was calculated based on 1036 included studies

**e.g.: Injury severity score (ISS), Revised trauma score (RTS), Trauma injury severity score (TRISS)

***e.g.: Level of cognitive functioning scale (LCFS), Disability rating scale (DRS), Functional independence measure (FIM), Rankin score, Barthel index, Quality of life after brain injury (QOLIBRI)

compared to injury to other organs [31]. Multiple mechanisms have been noted to trigger TBI-associated coagulopathy, although the implications of each one still need to be elucidated [32, 33]. Hemostatic disturbances following TBI may lead to hyper- or hypo-coagulable states that in turn can predispose patients to microvascular thrombosis or progressive hemorrhagic injuries [31, 34]. Numerous publications have illustrated a strong diagnostic and prognostic value of the standard coagulation tests in identifying post-TBI coagulopathy and guidance for timely therapy [31, 35–38].

In the sections below, we review the high-level evidence concerning the top ten biomarkers explored principally in prior TBI studies. These include nerve tissue proteins, enzymes, cytokines, coagulation tests, and cortisol levels (Fig. 3).

S100

Based on our findings, S100 proteins were by far the most often investigated biomarker in the context of TBI. These calcium-binding proteins are expressed predominantly in glial cells but in lower concentrations found in other cells such as adipocytes, chondrocytes, and melanocytes [39]. The S100B isoform (ββ homodimer) exists mainly in astrocytes, and has diverse neurotrophic and neuroprotective functions at physiologic nanomolar concentration, with a CSF to serum ratio of 18:1. Following TBI, S100B surges in biofluids to a pathologically high concentration (i.e., micromolar) due to release from damaged glial cells and/or disruption of the blood–brain barrier [39, 40]. Its serum half-life is frequently reported to be 4–6 h in mild TBI and 24 h in severe TBI [41]. Several systematic reviews and meta-analyses on the diagnostic value of S100B across all TBI severities established a significant association of serum S100B level with the presence of intracranial lesions on CT scan, TBI severity, and intracranial hypertension. Also, they revealed that S100B concentration > 0.16 μg/L provided the best sensitivity and specificity for predicting a positive brain CT scan in mild TBI [39, 40, 42–46]. However, two reviews showed

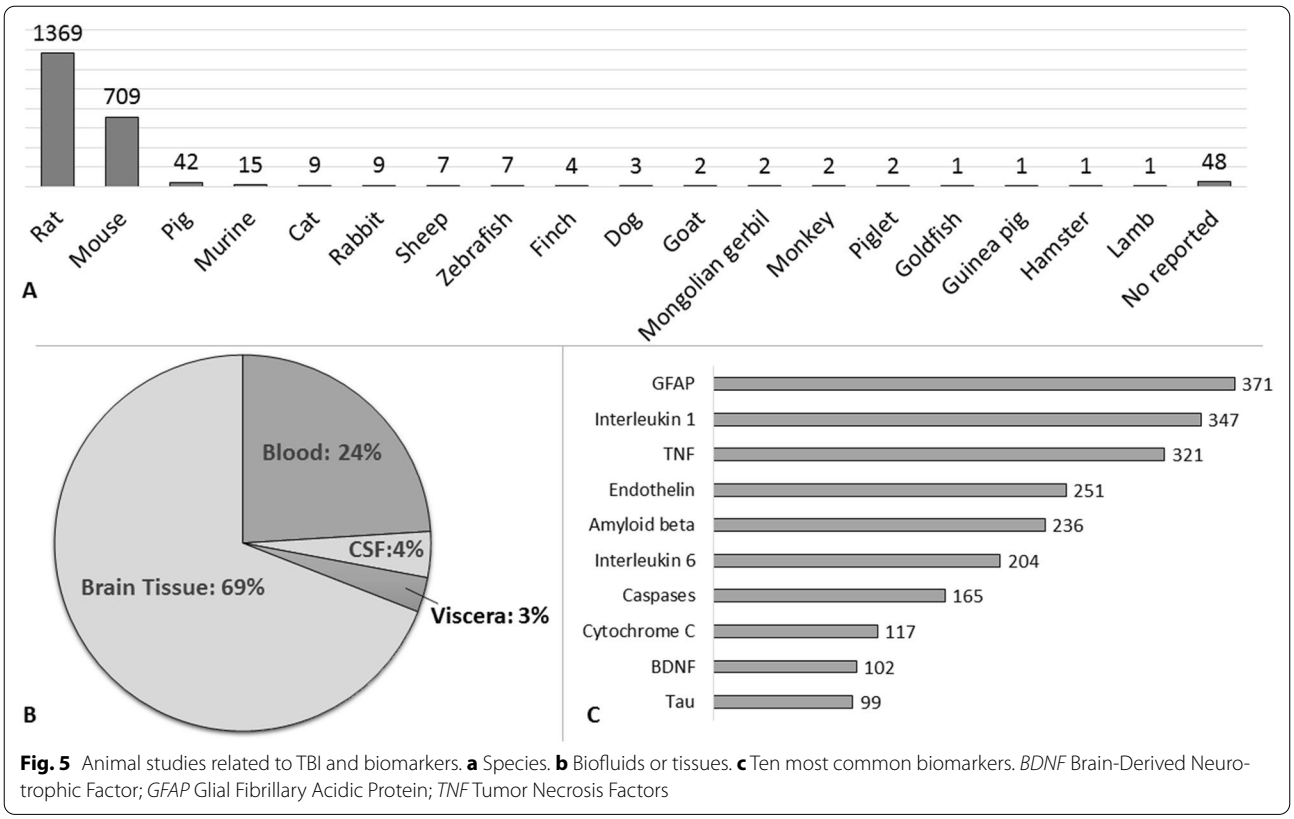

Fig. 5 Animal studies related to TBI and biomarkers. **a** Species. **b** Biofluids or tissues. **c** Ten most common biomarkers. *BDNF* Brain-Derived Neurotrophic Factor; *GFAP* Glial Fibrillary Acidic Protein; *TNF* Tumor Necrosis Factors

contradictory results about the diagnostic role of S100B [47, 48]. In mild TBI, the predictive role of serum S100B for early (7 days to 3 months) and persistent (≥ 3 months) post-concussion syndrome was weak in both adults and pediatrics [47, 49, 50]. Conversely, in patients with moderate and severe TBI, S100B had the potential to predict mortality and poor outcome, mainly if assessed within 24–48 h after admission [51–53].

Neuron-Specific Enolase (NSE)

The second most frequently assessed biomarker in TBI was NSE, a glycolytic enzyme predominantly originating from neurons. This protein is not normally detectable in extracellular fluids but is upregulated in biofluids during neuronal cell destruction [40, 54]. The presence of hemolysis, hemorrhagic shock, and renal failure tend to decrease the specificity of NSE for TBI diagnosis [55]. Besides, the high degree of stability of NSE, with a half-life beyond 20 h, limits its value for disease progression monitoring [41, 56]. However, NSE offers promising characteristics including high brain specificity, rapid release in serum, and age and sex-independent properties [41]. Some studies reported that in mild TBI, serum thresholds ≥ 9 µg/L for adults and ≥ 15 µg/L for children within 24 h of injury were associated with a positive brain CT scan [44, 48]. As a clinical tool for prognosis, the discriminatory capacity of serum NSE for unfavorable neurological prognosis and mortality across all severities was fair (with an area under the receiver operating curve (AUC): 0.73 and 0.76, respectively). Serum sampling within 12 to 24 h after trauma improved NSE prognostic power due to reflecting the impact of secondary injuries on fatal outcomes [40, 52, 57–60].

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a small glycoprotein and prototypical cytokine expressed by both resident glial and neuronal cells within the CNS, and by many peripheral immune cells [61]. IL-6 is upregulated markedly in the acute phase of TBI [62]. Rodney et al. reported a significant association of IL-6 with mortality, poor health outcome, and elevated ICP [63]. Two other reviews proved similar results regarding IL-6 in both peripheral blood and CSF samples [29, 53]. In parallel, a systematic review of CMD in severe TBI concluded that IL-6 was indicative of ongoing secondary damage, and was associated with functional and psychiatric outcomes [64]. Hence, IL-6 has been considered as a significant contributor to the inflammatory process after TBI. However, the lack of brain specificity was a drawback, since IL-6 could be produced by extracranial injuries. Also, variation in permeability of blood–brain barrier and glymphatic (glial-lymphatic) system

impairment after TBI would confound its accurate measurement. Albeit, the limitations noted for IL-6 are representative for almost all cytokines following TBIs [65].

Platelet Count

Damage to microvasculature following TBI and exposure of the subendothelial matrix activates coagulation pathways which eventually result in platelet consumption. This process is aggravated by platelet hyperactivation via the release of platelet-activating factor and other brain-derived procoagulant molecules [34]. Platelet count might serve clinically as a significant negative prognostic marker for TBI. Several investigations have found that reduced platelet count significantly increases the risk of mortality and detrimental outcomes. In particular, they have concluded that low platelet count is associated with progressive hemorrhagic injuries on repeated brain CT scan and a higher rate of neurosurgical intervention [66–68]. The optimal platelet count cut-off points for poor outcomes and a need for platelet transfusion remains ambiguous, although a platelet count less than 100,000 μL has been most commonly proposed [68, 69]. However, it seems that this test oversimplifies the post-TBI coagulopathy mechanism which is a sequential, complex series of events. For instance, platelet dysfunction after TBI is the earliest abnormality that increases the risk of intracranial bleeding even in the presence of normal platelet count [70, 71].

Cortisol

The extensive focus on cortisol may be due to its importance in early identification and treatment of post-TBI adrenal crisis and its chronic serious consequences such as chronic hypopituitarism [72, 73]. Therefore, rendering criteria for effective hormone replacement therapy and predicting chronic hypopituitarism have been the pivotal purposes of previous research on cortisol in the context of TBI. Correlation of cortisol concentration changes in the acute phase (within 7 days of injury) following TBI with mortality and unfavorable outcomes remains uncertain owing to conflicting results obtained [74–78]. Also, several studies mentioned a higher risk of adrenal insufficiency in more severe TBI; however, there were others with contrary findings [77]. Despite the growing body of evidence, there was not a systematic assessment of cortisol as a biomarker. This could be a result of the heterogeneity of previous studies in time elapsed since trauma, type and severity of brain injury, and disparities in definition and diagnosis of hypoadrenalism [79]. To avoid the interfering effects of acute critical illness on serum cortisol concentrations and to obtain samples readily, salivary and 24-h urinary cortisol have been frequently used to measure cortisol levels, successfully reflecting biologically active components of cortisol in serum [80].

Partial Thromboplastin Time (PTT)

PTT together with PT/INR is a frequently used parameter for detecting coagulopathy after TBI. Rigorous evidence supports that a prolonged PTT is not a significant prognostic indicator for adverse outcomes [66, 67]. Also, Maegele et al. reported that the routine screening tests of coagulopathy have repeatedly rendered results inconsistent with each other. This discrepancy could support the assumption that these tests are insensitive and occasionally may appear normal despite the presence of an abnormal coagulopathic state [34]. Haas et al. reported that PTT could not accurately portray the complex underlying mechanisms of post-TBI coagulopathy [81]. Since PTT measures the required time until initiating the formation of a clot, this static test would not provide complete information on the whole process of thrombin formation [82].

Glial Fibrillary Acidic Protein (GFAP)

GFAP is another nerve tissue protein that has been extensively studied in both human and animal studies in the TBI context. This protein is an intermediate filament protein serving as an integral structural unit in the cytoskeleton of astroglial cells. Importantly, the exclusive expression of this protein from the brain has resulted in its wide adoption as a TBI biomarker in the literature [83]. Blood GFAP levels increase within hours of TBI and remain elevated for days in more severe injury [84]. The long half-life (24–48 h) may hinder accurate interpretation of disease progression and secondary insults following TBI [41]. As a diagnostic test, acute (< 24 h post-TBI) GFAP level correlated with a positive brain CT scan and TBI severity which may be clinically useful for distinguishing dispersion of intracranial lesions (diffuse versus local mass lesions) [30, 39, 41, 46]. In terms of prognostic utility, several studies support GFAP as a promising predictive marker for mortality and unfavorable outcome in head trauma, including mild TBI in both adults and pediatrics [40, 46, 52, 53]. However, a systematic review of children with mild TBI showed contradictory results for early (< 1 month) post-concussion symptoms [47]. In light of the methodological limitations of prior studies, it was difficult to draw any solid conclusion concerning cut-off values [83, 84].

Prothrombin Time (PT)/International Normalized Ratio (INR)

PT and, interchangeably, INR in addition to PTT are standard tests that are conventionally used to monitor coagulation state in the clinical setting. Several

high-quality studies have shown that these tests have high predictive value for the detection of coagulopathy and can guide transfusion therapy [38, 66]. This concept, however, has been challenged by Yuan et al. [67]. Thus, the utility of PT/INR for earlier prediction of altered hemostasis before the development of deleterious neurologic outcomes is still under debate. The shortcomings of routine coagulation tests, e.g., clot-based endpoints being incapable of depicting the entire coagulation cascade could offer a plausible explanation for the failure of PT/INR tests for diagnosis of coagulopathy [34, 81, 82].

Tumor Necrosis Factor-alpha (TNF-α)

TNF-α is a proinflammatory cytokine released shortly after TBI from microglia and astrocytes and mediates neuronal cell death, excitotoxicity, and an increase in permeability of endothelial barrier [85, 86]. To our knowledge, post-TBI neuroinflammation has paradoxical impacts on the brain: neurorestorative effects via clearance of debris and neurotoxic effects by inducing neuronal cell death. TNF-α as a key cytokine participating in the neuroinflammatory process has also both these beneficial and detrimental effects in a concentration-dependent manner. Thus, the regulation of TNF-α production is essential for returning to the non-inflammatory state and clinical recovery [30]. The prognostic utility of TNF-α remains unclear according to contradictory findings. This discrepancy might be due to the lack of brain specificity of TNF-α [30].

Interleukin-10 (IL-10)

IL-10 is another well-established cytokine that suppresses the expression of pro-inflammatory cytokines, or their receptors. This cytokine is produced in high concentrations early after TBI by CNS resident cells or peripherally recruited immune cells [87]. As with IL-6, several systematic reviews found a significant linkage between IL-10 concentration and mortality, TBI severity, and unfavorable outcomes [63]. Additionally, Zeiler et al. showed that CMD-based IL-10 as more reliable metrics remain continuously elevated up to a week after a severe TBI [64]. This chronically elevated level of IL-10 would be of great importance for predicting the presence of intracranial lesions as an adjunct to brain CT, especially in mild TBI [88]. Considering the lack of evidence available on the diagnostic utility of IL-10, this topic merits further investigation.

There was no single definitive biomarker with accurate characteristics. But, combining multiple independent biomarkers may increase sensitivity and specificity [89]. Future studies should be conducted to investigate the biomarkers from the 19 categories separately to detect the most representative biomarker of each category. Thereby, a list of the most clinically useful biomarkers will be achieved from different categories and can be compared based on the rapidness, sensitivity, specificity, easiness, and cost-effectiveness. Exploratory studies assessed clinical specimens obtained from CNS, blood, urine, saliva, BAL fluid, and other sources to quantify biochemicals that might serve as relevant biomarkers in TBI. According to our comprehensive analysis of the literature, blood-based biomarkers in TBIs have been investigated more widely (Fig. 2). Low brain specificity of the blood-based biomarkers and their metabolism may reduce their accurate measurement. These, in turn, could illustrate the cause of the poor diagnostic and prognostic value of blood biomarkers more particularly in mild TBI [90]. Conversely, CNS-derived biomarkers including brain tissue, CSF, and CMD offer a more direct pathophysiological assay of the brain state but come at the cost of being more invasive given the current state of technology. A notable point is the potential confounding effect of the disruption of the blood–brain barrier integrity in the interpretation of elevated CSF biomolecules [91]. CMD as a technique for monitoring the extracellular metabolic state of the cerebral parenchyma could have a wide capability to indicate time-dependent pathophysiologic changes following TBI in the neuro-intensive care unit [92]. Despite some practical caveats of CMD such as limited temporal samplings and presumed complications after CMD catheter placement, some studies have shown the utility of CMD-based assays as surrogate markers for predicting functional and physiologic outcomes [93–95]. Besides, a relatively small body of evidence on other body biofluids such as saliva, urine, and lacrimal fluid indicate the uncertainty about the utility of these sources to reflect biochemical changes within the injured brain, despite their easy accessibility and relatively safe sampling approach. This issue could be addressed in future studies, especially for biomarkers with promising clinical utilities [96].

Biomarkers could be used in point of care applications in the wake of their early expression after TBI. Measuring biomarkers in the acute primary phase of TBI contributes to triaging patients for brain CT scans, hospitalization in the emergency room, and determining prognostics. Based on our systematic review, biofluid samples were obtained mainly within the first 24 h (>81% sampling time points) following injury. To track the time-course changes in concentrations of biochemicals in the later phases following TBI, only a handful of studies described the collection of biofluid samples after 24 h (Table 2 and Fig. 3b). This would be particularly important for identifying chronic effects of TBI, monitoring patients in the intensive care unit, and developing targeted therapies [17].

A wide range of standardized outcome determinants were used whereby one could assess multiple domains including functional outcomes, neuroimaging findings, psychological and cognitive outcomes, quality of life, TBI signs and symptoms, and adverse events (Table 3). The wide-ranging TBI consequences, from physical to cognitive and behavioral, could lead to a multidimensional approach in the assessment of TBI outcomes in more than half (52.3%) of studies [97]. Glasgow outcome scale is one of the most commonly used functional outcome measures due to its simple administration and validity, although it has been criticized for poor sensitivity to subtle functional changes and inter-rater variability [98].

In terms of injury type, the smaller number of studies exclusively focused on penetrating TBI as opposed to blunt injury (0.4% versus 35.6%) may be ascribed to its global lower incidence rate reaching only 12% of all types of TBI [99]. Furthermore, the disparate and complex mechanism of penetrating TBIs results in multiple subtypes of structural damage making it more difficult to study [100].

A large number of publications relevant to our study topic showed the importance of animal models in this context (Fig. 5; Online Appendix 4). Our study affirmed that the most commonly used animal model for TBI studies was rodents. This may be a result of low cost and the availability of histopathological and functional tests in these species. Regardless of the considerable contributions of rodent models to discovering molecular changes following TBI, many researchers speculate that non-human mammals replicate human TBI conditions better due to the greater degree of homology of brain morphology, structure, biomechanics, and cerebrovascular physiology. However, ethical issues, higher technical demands, and cost could always be prohibitive to their extensive use [101, 102]. Our review also found that brain tissue was the predominant source tissue in animal models of TBI (Fig. 5). In both human and animal studies, the top ten investigated biofluid biomarkers were from the same following categories: nerve-tissue proteins, cytokines, and proteins, except for coagulation tests incomparably being more assessed in human studies.

Conclusions

In this review, 540 TBI biomarkers were identified from 1036 existing studies and categorized into 19 categories using a valid categorizing approach. Biofluid biomarkers could be clinically helpful in the diagnosis and prognosis of TBI. The focus of more than half of the studies was on three categories of biomarkers, namely nerve tissue proteins, cytokines, and coagulation tests. However, there was no single definitive biomarker with accurate characteristics. The present categorization would be a road map to investigate the biomarkers of the brain injury cascade separately and detect the most representative biomarker of each category. Also, this comprehensive categorization could provide a guiding framework to design combined panels of multiple TBI biomarkers. This review revealed the inadequate attention to pediatric TBI, mild TBI, and other biofluids like saliva, urine and lacrimal fluid, which could serve as a diagnostic tool in early detection of TBI.

Supplementary Information
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Author Contributions
MS designed the study, developed the search strategy, and performed the statistical analysis. ME and MS wrote the manuscript. MS, MSN, and AB were involved in critical revision of the manuscript. Other authors performed data screening, acquisition, and appraising the quality of studies. All authors reviewed and approved the final draft.

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Conflict of interest
The authors declare that they have no conflict of interest.

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