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Circulating MicroRNA as a Non-Invasive Prognostic Biomarker in Traumatic Brain Injury: A Narrative Review of Current Evidence and Translational Considerations for Resource-Limited Settings

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ABSTRACT

Introduction: Traumatic brain injury (TBI) remains a major cause of neurological morbidity and mortality, particularly in low- and middle-income countries such as Indonesia. Conventional prognostic tools, including the Glasgow Coma Scale (GCS) and computed tomography, have limitations in resource-limited settings. Circulating microRNAs (miRNAs) have emerged as potential non-invasive prognostic biomarkers due to their stability in blood and detectability using RT-qPCR.

Methods: A structured literature search was conducted in PubMed, Scopus, Google Scholar, and Cochrane for English-language human studies published between 2015 and 2024 using the terms *microRNA*, *traumatic brain injury*, *prognosis*, and *biomarker*. Following PRISMA-based screening, 32 studies were included for narrative synthesis.

Results: Multiple circulating miRNAs, particularly miR-21, miR-146a, miR-155, and miR-124, were consistently associated with TBI severity and neurological outcomes measured by GCS, GOS, and GOSE. Additional candidates included miR-16, miR-92a, miR-93, miR-191, miR-499, miR-206, and miR-549a-3p. Multi-miRNA panels demonstrated superior prognostic performance compared with single biomarkers, especially when combined with clinical variables. The most informative sampling period was within 24–72 hours post-injury. Key barriers include methodological variability and lack of standardized protocols.

Conclusion: Circulating miRNAs show strong potential as non-invasive prognostic biomarkers for TBI. Further multicenter validation and standardized implementation strategies are needed, particularly in resource-limited settings.

Keywords: Traumatic brain injury; circulating microRNA; prognostic biomarker; neurological outcome; translational potential; low-resource setting

1. Introduction

Traumatic brain injury (TBI) is a major global public health problem and a leading contributor to disability-adjusted life years among non-communicable neurological conditions. The Lancet Neurology Commissions on TBI estimate that 50 to 60 million people sustain a TBI each year, at an approximate global economic cost of US$400 billion annually [1,2], while modelling studies extrapolating from road traffic injury data suggest that the true global incidence may be as high as 69 million per year [3]. Standardised analyses from the Global Burden of Disease 2016 study estimated 27.08 million new cases of TBI in 2016 alone, with a substantial proportion of the burden concentrated in low- and middle-income countries where road traffic injuries, falls, and interpersonal violence are the dominant mechanisms of injury [4]. The Lancet Neurology Commission on TBI has repeatedly emphasized that progress in clinical care has been slower than for other acute neurological conditions, in part because TBI is a heterogeneous disease process with variable trajectories that are difficult to stratify using current clinical tools alone [1,2]

Indonesia, as a large archipelagic middle-income country with a high density of two-wheeled vehicle use, bears a particularly high burden of TBI related to road traffic injuries. Access to advanced neuroimaging, neurocritical care, and neurosurgical expertise is unevenly distributed, with tertiary centres concentrated in major urban areas, while peripheral and rural facilities often rely on basic clinical assessment. These structural realities amplify the consequences of diagnostic and prognostic uncertainty during the acute phase of care and strengthen the case for objective biomarkers that can be deployed with laboratory infrastructure already available at secondary and tertiary hospitals.

Prognostic assessment in TBI currently relies predominantly on the Glasgow Coma Scale [5], pupillary examination, mechanism of injury, and findings on computed tomography, often integrated with age and physiological variables. Although these elements remain essential, they exhibit well-recognized limitations. The GCS can be confounded by intoxication, sedation, intubation, and periorbital trauma, while early neuroimaging may not fully capture evolving secondary injury such as diffuse axonal injury or delayed cerebral oedema [1,2]. Outcomes assessed by GOS or GOSE [6,7] therefore correlate only moderately with early clinical and imaging features, motivating the search for molecular markers that reflect the underlying pathobiology.

Protein biomarkers of neuronal and glial injury, including S100B, glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH-L1), and neuron-specific enolase (NSE), have been investigated extensively, and a combined GFAP-UCH-L1 assay has received regulatory clearance to assist in ruling out intracranial injury after mild TBI on the basis of the ALERT-TBI study and related work [8,9]. However, these protein biomarkers have variable performance for prognostication of longer-term functional outcomes, short half-lives in circulation, and, in the case of S100B, limited specificity for the central nervous system [10]. Complementary to these protein-based candidates, simple haematological indices derived from the routine complete blood count, most notably the platelet-to-lymphocyte ratio (PLR) have also been examined as accessible prognostic markers in adult TBI, with systematic-review-level evidence suggesting that an elevated admission PLR may independently predict short-term mortality and unfavourable functional outcomes assessed by GOS, an avenue that is particularly attractive for rural and resource-limited settings where more complex assays are unavailable [11].

Circulating microRNAs (miRNAs) have attracted growing interest as an alternative or complementary class of biomarker. MiRNAs are short non-coding RNAs of approximately 22 nucleotides that regulate post-transcriptional gene expression [12,13]. Their detection in cell-free form in plasma and serum, where they are protected from ribonuclease degradation by association with argonaute proteins, high-density lipoproteins, and extracellular vesicles, was a pivotal observation that established their feasibility as blood-based biomarkers [14]. Altered plasma miRNA levels in humans after TBI were first documented in a seminal study by Redell

et al. (2010) [15], which demonstrated injury-associated changes in a defined subset of miRNAs and opened a still-active line of investigation [16,17].

Subsequent translational studies have reported associations between specific circulating miRNAs and TBI severity, early neurological deterioration, neuroinflammation, and longer-term functional outcomes, often with greater discriminative performance when miRNAs are combined into panels or integrated with conventional clinical variables[18,19,20,21]. Nevertheless, most published investigations are single-centre, employ heterogeneous pre-analytical and analytical protocols, and lack harmonized outcome definitions, which has constrained meta-analytic synthesis and delayed clinical implementation [22,23].

The gap between promising biomarker discovery and routine clinical utility is particularly consequential for health systems in countries such as Indonesia. Molecular laboratory capacity, including RT-qPCR infrastructure, expanded markedly during the COVID-19 response and remains under-utilised in many settings; this represents an opportunity to test and deploy miRNA-based prognostic tools if methodological issues can be resolved. The present review therefore aims to critically synthesize current evidence on circulating miRNAs as prognostic biomarkers in TBI, evaluate their position relative to established protein biomarkers, and examine the opportunities and barriers for implementation within the Indonesian and broader low-resource neurosurgical context.

2. Pathophysiological Rationale For microRNA Release After TBI

TBI produces a sequence of primary mechanical injury followed by evolving secondary injury mechanisms, including excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, apoptosis, and disruption of the blood-brain barrier (BBB) [1,10]. These processes unfold over hours to weeks, and their relative contributions differ by injury severity and phenotype. Molecular mediators released during secondary injury have plausible access to the systemic circulation through a disrupted BBB, cerebrospinal fluid-blood exchange, and glymphatic clearance pathways, providing a mechanistic basis for central nervous system-derived markers to be detectable in peripheral blood.

MiRNAs are generated from longer primary transcripts through sequential processing by Drosha and Dicer, producing mature 20-24-nucleotide guide strands that associate with Argonaute proteins within the RNA-induced silencing complex to repress translation or destabilize target messenger RNAs [12,13]. Specific miRNAs are enriched in the central nervous system or in particular neural cell types, and their expression is dynamically modulated by injury, inflammation, and repair processes [16,17]. Consequently, altered patterns of miRNA release after TBI reflect underlying cellular responses rather than non-specific tissue disruption alone.

In peripheral blood, miRNAs circulate in several compartments: bound to Argonaute-2 protein, complexed with high-density lipoprotein particles, and packaged within extracellular vesicles, including exosomes and microvesicles [14]. Vesicular packaging is of particular interest in TBI, because exosomes can cross the BBB bidirectionally and may carry signatures that more closely reflect brain-derived cellular states, as illustrated by recent studies of serum exosomal miR-206 and miR-549a-3p in relation to TBI [24]. This stability and compartmentalization explain why miRNAs remain detectable in plasma and serum samples subjected to standard clinical handling, including freeze-thaw cycles, although pre-analytical variability is not negligible [9].

Mechanistically, several miRNAs implicated in TBI regulate neuroinflammatory, apoptotic, and neuroregenerative pathways that are directly relevant to secondary injury. For example, miR-155 is a recognised positive regulator of pro-inflammatory signalling in myeloid cells, whereas miR-146a acts as a feedback inhibitor of NF-κB-driven innate immune responses. MiR-21 modulates cell survival and apoptosis, and miR-124 is a highly abundant neuronal miRNA that contributes to neuronal identity and plasticity [16,17,23]. The behaviour of these miRNAs in circulation after TBI therefore offers a molecular window onto ongoing pathological processes, rather than merely a static index of tissue disruption.

3. Circulating microRNA as Prognostic Biomarkers in TBI

Prognostication in TBI encompasses multiple linked questions: acute triage and severity stratification; prediction of early neurological deterioration or need for neurosurgical intervention; prediction of mortality; and prediction of longer-term functional outcome, typically indexed by GOS or GOSE at three or six months [7]. Circulating miRNAs have been evaluated across several of these domains, although with uneven depth of evidence.

Multiple primary studies and syntheses have reported associations between circulating miRNA profiles and TBI severity defined by admission GCS, with distinct differences described between mild, moderate, and severe TBI groups, as well as between TBI patients and uninjured or orthopaedic trauma controls [18,19,21]. Systematic review and meta-analytic work suggests that several miRNAs show reproducible directional changes across independent cohorts, with pooled estimates indicating high diagnostic accuracy for blood-based miRNAs in distinguishing TBI from controls, although heterogeneity in sampling times, control groups, and normalization strategies tempers interpretation [21].

For prognostication of functional outcome, a consistent observation is that panels of miRNAs outperform individual miRNAs, and that integration of miRNA signatures with established clinical variables further improves discriminative performance [16,15,21] This pattern mirrors the broader evolution of prognostic modelling in TBI, in which multimodal integration, combining clinical, imaging, and molecular data, appears more fruitful than reliance on any single marker. However, reported effect sizes vary across studies, and the generalizability of any given panel to external cohorts, different severity mixes, and different health system contexts requires further external validation [9,22].

Beyond dichotomous outcome prediction, circulating miRNAs have also been examined in relation to the trajectory of recovery, including markers of ongoing neuroinflammation and markers of neuroregenerative capacity. Although such work is still at an early stage in TBI, it is conceptually important because biomarkers that track a modifiable biological process have greater potential as surrogate endpoints for interventional trials than static markers of tissue disruption [16]. The translational value of miRNA profiling may therefore extend beyond prognostication in isolation, into patient selection and treatment monitoring in future therapeutic studies.

4. Key Candidate microRNA and Their Clinical Relevance

Although more than a hundred miRNAs have been reported as altered in at least one TBI study, a smaller core set recurs with sufficient consistency across independent cohorts to merit specific discussion. The following subsections summarize current understanding of miR-21, miR-146a, miR-155, and miR-124, with brief comment on additional candidates. Conceptual illustration of circulating microRNAs is visualised in Figure 1.

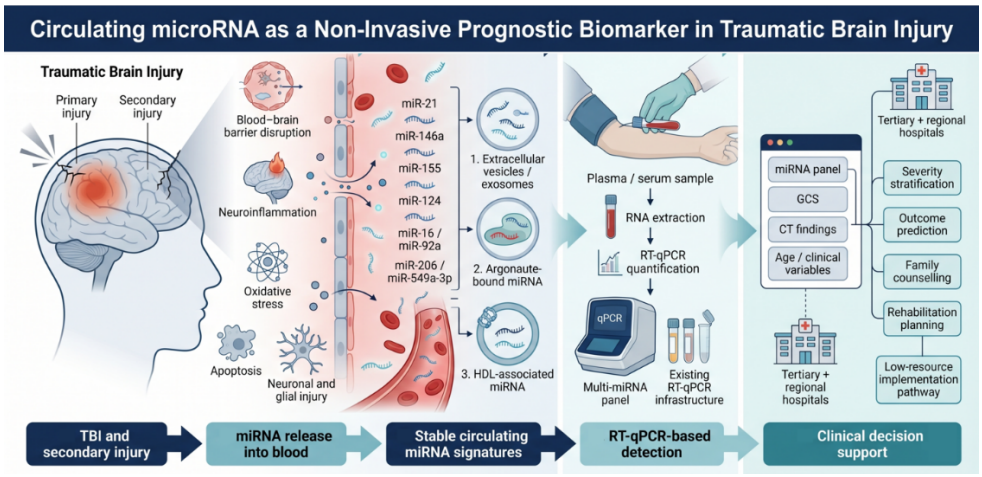

Figure 1. Conceptual illustration of circulating microRNAs as non-invasive prognostic biomarkers after traumatic brain injury. Secondary injury mechanisms and blood–brain barrier disruption promote the release of stable miRNA signatures into the circulation, where they can be quantified using RT-qPCR. Integration of miRNA panels with clinical variables, GCS, and CT findings may support severity stratification, outcome prediction, and clinical decision making in resource-limited settings.

4.1 miR-21

miR-21 is among the most frequently cited miRNAs across human and experimental TBI studies. It is widely expressed and has well-characterized roles in regulating apoptosis, cell proliferation, and inflammatory signalling through targets including PTEN and PDCD4. Altered circulating levels of miR-21 have been reported in patients with TBI in multiple cohorts, and miR-21 modulation has been explored experimentally as a candidate therapeutic strategy, supporting the interpretation that circulating miR-21 reflects a biologically relevant process rather than a non-specific injury signal [16,17,23].

4.2 miR-146a

miR-146a is a key negative-feedback regulator of innate immune signalling, targeting TRAF6 and IRAK1 within the toll-like receptor / NF-κB pathway. Its expression is induced during acute inflammation and serves to attenuate pro-inflammatory responses. In the context of TBI, altered circulating miR-146a has been associated with neuroinflammatory dynamics and, in some reports, with clinical severity and outcome [15,16]. Its biological profile makes miR-146a an attractive candidate not only for prognostication but also as a marker of ongoing neuroimmune activation relevant to secondary injury.

4.3 miR-155

miR-155 is a pro-inflammatory miRNA enriched in activated macrophages and microglia, where it promotes M1-like polarization and amplifies cytokine responses. Elevated miR-155 signals have been reported in several TBI cohorts and experimental models, including the recent work of Consalvo et al. (2024) which identified miR-155 among a panel of miRNAs associated with severity and survival after fatal TBI. In circulation, miR-155 has been explored both as a marker of injury severity and as a candidate therapeutic target, although clinical prognostic thresholds have yet to be established.

4.4 miR-124

miR-124 is one of the most abundant neuronal miRNAs and contributes to the establishment and maintenance of neuronal identity, as well as to the dampening of microglial activation. Its presence in circulating form after TBI is of particular interest because alterations may reflect neuronal injury and ongoing neurogenesis or repair processes [15,16]. Reported associations with clinical severity and outcome support its inclusion in candidate prognostic panels, although directionality and magnitude of change are influenced by sampling window and matrix.

4.5 Additional Candidates

Other miRNAs implicated in TBI research include miR-16 and miR-92a [14]; let-7 family members (Bhomia et al., 2016); and miR-93, miR-191, and miR-499, which Yang et al. (2016) reported as elevated in serum from a cohort of 76 TBI patients compared with 38 healthy controls, with miR-93 in particular showing strong discriminative performance (AUC 1.000 for distinguishing TBI from healthy controls in their dataset, including in mild TBI). More recently, Yang et al. (2024) reported serum exosomal miR-206 and miR-549a-3p as potential biomarkers of TBI, illustrating the growing interest in vesicle-enriched fractions to improve specificity. Plasma miRNA signatures have also been explored for multi-organ injury prediction in polytrauma populations, where TBI frequently co-occurs with thoracic, abdominal, or musculoskeletal injury [27]. These broader signatures may complement CNS-focused panels in complex clinical scenarios. The exceptionally high AUC reported by Yang et al. (2016) for miR-93 should, however, be interpreted with caution: such ceiling-level discrimination is uncommon for circulating biomarkers in heterogeneous TBI cohorts and warrants independent replication in larger and more diverse populations before clinical claims are made.

5. Temporal Profile and Sampling Considerations

Because miRNA release, degradation, and redistribution are dynamic processes, the timing of sample collection is a critical determinant of biomarker performance. Current literature converges on the view that the first 24 to 72 hours post-injury represent the most informative sampling window for prognostication in moderate-to-severe TBI, while sampling windows in mild TBI and sport-related concussion may differ [15,16]. In many acute TBI studies, the very early window (<6-24 hours) can capture peak release of certain miRNAs [14], whereas the 24-72-hour window integrates ongoing secondary injury signals that are more closely linked to functional outcome.

Choice of biological matrix is a further determinant of signal quality. Plasma and serum yield broadly comparable results for many miRNAs, but for several candidates the two matrices are not interchangeable because of differential contributions from platelet-derived RNA during clotting [25]. Whole blood captures cellular miRNAs that may dilute CNS-derived signals, whereas exosome-enriched fractions can improve specificity for CNS-originating miRNAs at the cost of additional processing complexity [24]. For low-resource settings, plasma using EDTA anticoagulation with prompt processing and freezing at -80°C remains a pragmatic default, provided that pre-analytical conditions are standardised.

Pre-analytical variability, including time to processing, haemolysis, platelet contamination, and freeze-thaw cycles, can substantially affect measured miRNA concentrations. Several reviews have highlighted that standardization of sample handling and the use of validated endogenous or exogenous normalization controls are prerequisites for reliable multi-centre studies [9,25]. The lack of a single universally accepted normalization strategy, with candidates including miR-16, miR-191, RNU6B, or spike-in synthetic controls, remains a barrier to cross-study comparability.

6. Comparison With Conventional TBI Biomarkers

Established protein biomarkers of TBI have different biological origins and kinetics that condition their clinical applications. S100B, an astrocytic calcium-binding protein, rises rapidly after injury but has limited CNS specificity because it is also expressed in adipocytes, chondrocytes, and melanocytes, which restricts its usefulness in polytrauma [9]. GFAP, also derived from astrocytes, and UCH-L1, a neuronal enzyme, are more CNS-specific and together form the basis of an FDA-authorized assay for rule-out of intracranial injury on head CT after mild TBI, grounded in the ALERT-TBI study and subsequent work [8,9]. NSE is detectable in neurons and neuroendocrine cells and has been used as a prognostic marker in severe TBI and cardiac arrest, though its interpretation is complicated by haemolysis [9].

Relative to these protein biomarkers, circulating miRNAs offer several theoretical advantages: high stability in blood through extracellular vesicle packaging and protein binding, the possibility of multiplex quantification to capture different biological processes simultaneously, and the use of RT-qPCR platforms that are increasingly available in middle-income countries [13,15,16]. Reported head-to-head or integrated analyses suggest that miRNA panels, particularly when combined with clinical variables, can achieve discriminative performance at least comparable to single protein biomarkers for diagnostic and prognostic endpoints, although the strength of evidence varies by outcome and study design [9,20].

Importantly, miRNAs and protein biomarkers reflect partly overlapping and partly distinct biological processes. Protein markers indicate cellular disruption and release, while miRNAs additionally reflect transcriptional and post-transcriptional regulatory responses. A combined molecular panel that integrates both classes, rather than selecting between them, is likely to be the most biologically informative and clinically robust approach. This perspective aligns with broader trends in precision neurocritical care [2].

7. Clinical and Translational Utility

Potential clinical applications for circulating miRNA biomarkers in TBI span several points along the care pathway. In acute triage, rapid miRNA or combined miRNA-protein assays could support decisions about imaging, admission, and level of care in settings where CT availability is limited or delayed. In the intensive care unit, serial miRNA measurements could contribute to monitoring the evolution of secondary injury, complementing intracranial pressure, cerebral perfusion pressure, and imaging data. At a slightly longer horizon, miRNA profiles could inform prognostic conversations with families, supporting shared decision-making about goals of care and rehabilitation planning [15,16].

From a translational standpoint, the path from candidate biomarker to clinical tool requires analytical validation, clinical validation in prospective multicentre cohorts, demonstration of incremental value over existing clinical and imaging risk models, assessment of clinical utility (that is, improvement in patient-relevant outcomes or resource use), and regulatory review [9]. Few miRNA studies in TBI have yet progressed beyond the first two stages, and none has the level of evidence underpinning established protein markers such as GFAP and UCH-L1. The field would benefit from explicit adoption of biomarker development frameworks and reporting standards.

MiRNAs have additional translational relevance as therapeutic targets, because miRNAs and their antagonists are amenable to pharmacological modulation through oligonucleotide-based strategies. Although TBI-specific miRNA therapeutics remain pre-clinical, the dual role of miRNAs as biomarkers and as candidate therapeutic targets creates an opportunity for integrated development of companion diagnostics for future trials [16]. This integrated vision is particularly attractive for conditions such as TBI, in which clinical heterogeneity has historically frustrated one-size-fits-all therapeutic strategies.

8. Opportunities and Challenges in the Indonesian and Resource-Limited Context

The implementation landscape for miRNA-based prognostic biomarkers in Indonesia is shaped by several favourable factors. RT-qPCR capacity expanded markedly during the COVID-19 response and is now distributed across district and provincial hospitals, research institutes, and private laboratories. National reference centres, including the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono and its academic partners, provide a natural base for early-phase validation studies with strong neurosurgical case volume. The large national burden of TBI, driven substantially by road traffic injuries, ensures that well-characterized prospective cohorts can be assembled in reasonable timeframes.

At the same time, several barriers require explicit strategy. Reagent supply chains for specialized miRNA assays, including primers and master mixes optimised for low-abundance targets, can be vulnerable to import delays and cost pressures. Quality management systems for molecular laboratories are uneven, and laboratory

personnel trained specifically in miRNA workflows are relatively few. Data infrastructure for linking biobanked samples to longitudinal clinical outcomes, including GOSE at three and six months, is not yet standard in all Indonesian centres. Ethical and regulatory frameworks for biomarker studies, biobanking, and data sharing continue to evolve [2,9].

A pragmatic phased approach is therefore appropriate. An initial phase focused on analytical validation and feasibility, using a small set of high-priority candidate miRNAs in a limited number of tertiary centres, could establish local reference intervals and confirm assay robustness under real-world conditions. A second phase of multicentre prospective clinical validation, aligned with international reporting standards and outcome definitions, would clarify the incremental prognostic value over existing clinical models. A third phase of implementation and health-technology assessment would examine cost-effectiveness and clinical utility in Indonesian practice. Embedding this programme within existing national neurosurgical networks and academic partnerships would leverage available infrastructure while building sustainable local capacity.

9. Limitations of Current Evidence

Despite encouraging signals, several important limitations qualify the current evidence base. Most human studies of circulating miRNAs in TBI are single-centre investigations with modest sample sizes, heterogeneous inclusion criteria, and variable outcome definitions. Meta-analytic work, although increasingly available, is constrained by the small number of studies reporting compatible effect measures for the same miRNA-outcome-timepoint combinations [20,22]

Technical heterogeneity is a second major limitation. Variability in pre-analytical handling (time to processing, presence of haemolysis, matrix choice, freeze-thaw cycles), RNA extraction methods, quantification platforms (RT-qPCR, small RNA sequencing, digital droplet PCR, microarray), and normalization strategies all contribute to between-study variation that is often not fully reported or controlled. This limits the ability to pool data and to translate findings across cohorts [9,25].

A third limitation is the relative paucity of studies that explicitly compare miRNAs head-to-head with established protein biomarkers, or that integrate both classes into combined prognostic models with pre-specified analyses and external validation. As a result, the true incremental value of miRNAs over current biomarker-clinical combinations remains uncertain for most prognostic endpoints [15,16]. Finally, representation of low- and middle-income country populations in the existing literature is limited, which raises questions about the generalizability of findings derived predominantly from high-income settings to contexts such as Indonesia.

10. Future Directions

Several priorities emerge for advancing the field. First, the TBI biomarker community would benefit from consensus pre-analytical and analytical standards specifically for circulating miRNA measurement, analogous to those developed for established protein biomarkers. Key elements include recommended matrix, processing timeframes, normalization strategies, reporting of haemolysis indices, and minimal dataset requirements for publication [9,25]. Second, multicentre prospective cohort studies with harmonized sampling windows, endpoints, and biobanking protocols are needed to confirm candidate panels and estimate their incremental value over existing clinical and protein biomarker-based models. International collaborative infrastructures, and their regional extensions into Southeast Asia, offer a plausible scaffold for such studies [2].

Third, integration of miRNA data with clinical variables, imaging features, and other molecular biomarkers using modern statistical learning approaches is likely to yield more robust and generalizable prognostic tools than miRNA data in isolation. Care should be taken to address overfitting, to pre-specify analyses, and to externally validate models before clinical deployment [15,16]. Fourth, implementation-oriented research is essential, particularly in low- and middle-income countries. Beyond analytical and clinical

validation, studies should examine cost, turnaround time, feasibility in existing laboratory workflows, and impact on clinician decision-making. Finally, the mechanistic insight offered by miRNAs into secondary injury pathways provides a natural bridge to interventional studies, in which miRNA panels may serve as integrated companion diagnostics and treatment-response markers [15,27].

11. Tables

Table 1. Summary of Key Studies and Reviews on Circulating microRNA and TBI Prognosis The following table summarises representative verified studies and reviews informing this synthesis. References listed have been individually checked against PubMed/PMC. Numerical performance metrics are summarised qualitatively; readers are referred to original publications for quantitative detail.

Author (Year)	Country / Region	Study design	Sample type	microRNA (s) studied	Timing of sampling	Comparator / outcome	Main finding
Redell et al. (2010)	USA	Human cohort (microarray + qRT-PCR validation)	Plasma	108 miRNAs profiled; miR-16, miR-92a, miR-765 validated	<24 h post-injury (severe TBI); <10 h (mild TBI)	Healthy volunteers; orthopaedic injury controls	Established that human TBI alters plasma miRNA levels; miR-16 and miR-92a discriminated severe TBI from controls.
Bhomia et al. (2016)	USA	Human observational	Serum and CSF	Panel of serum miRNAs	Within 48 h	Mild-moderate TBI vs severe TBI vs orthopaedic injury controls	Identified a panel of serum miRNAs distinguishing TBI severity categories from controls.
Yang et al. (2016)	China	Human observational (n=76 TBI vs 38 controls)	Serum	miR-93, miR-191, miR-499	Multiple time points post-injury	TBI severity (GCS); outcome (GOS)	All three miRNAs elevated in TBI vs controls; AUC 1.000 reported for miR-93 distinguishing TBI from healthy controls; levels correlated with severity and outcome (single-centre; requires independent replication).
Mitra et al. (2017)	Australia	Human pilot study	Plasma	Selected miRNAs	Acute post-injury	Diagnosis and prognosis of TBI	Pilot evidence supporting diagnostic and prognostic potential of plasma miRNAs in TBI.

Di Pietro et al. (2017)	UK / Italy	Human cohort (TaqMan Array)	Serum	754 miRNAs screened; candidates including miR-425-5p, let-7i	Acute TBI	Mild and severe TBI vs healthy and extracranial-injury controls	Identified novel miRNAs as diagnostic and prognostic biomarkers for mild and severe TBI.
Di Pietro et al. (2018)	UK	Comprehensive review	Various biofluids	Multiple candidates	Variable	Diagnostic / prognostic synthesis	Reviewed miRNA signature of TBI and proposed point-of-care development.
Atif and Hicks (2019)	USA (Penn State)	Comprehensive review	Plasma, serum, saliva, CSF	Synthesis of 14 human studies; 17 candidate biomarkers	Acute and subacute	Diagnostic and prognostic value	Distilled ≥291 miRNAs to 17 candidate biomarkers overlapping across multiple studies and biofluids.
Toffolo et al. (2019)	USA	Critical review (preclinical and clinical)	Plasma, serum	Multiple miRNAs	Variable	Diagnostic, prognostic, pharmacodynamic biomarkers	Synthesised circulating miRNA evidence and emphasised influence of pre-analytical and analytical variables.
Zhou et al. (2021)	China	Systematic review and meta-analysis (8 studies)	Blood, brain tissue, saliva	Multiple miRNAs	Acute to subacute	Diagnostic accuracy in TBI	Pooled sensitivity 89%, specificity 92%, AUC 0.95 for blood-based miRNAs in TBI diagnosis; multi-miRNA panels outperformed single miRNAs.
Ghaith et al. (2022)	Multinational	Comprehensive literature review	Multiple	Protein biomarkers and miRNAs	Acute and longitudinal	Diagnostic and prognostic overview	Synthesised TBI biomarker landscape including miRNAs, GFAP, UCH-L1, S100B, NSE, and emerging exosomal markers.
Cente et al. (2023)	Slovakia	Bioinformatics analysis of	Blood-derived signature	Previously reported	Variable	Pathway and protein-protein	Linked peripheral miRNAs to neurodegenerativ

		severe TBI miRNAs	s (re-analysis)	peripheral miRNAs		interaction enrichment	e cascades after severe TBI.
Consalvo et al. (2024)	Italy	Forensic case-control profiling	Post-mortem blood	miR-16, miR-19a, miR-21, miR-23a, miR-130a, miR-155	By survival time strata and AIS severity	TBI fatalities vs controls	Differential miRNA expression correlated with survival time and severity of injury.
Yang et al. (2024)	China	Human observational	Serum exosomes (n=45)	miR-206 and miR-549a-3p	Acute post-injury	Severity of TBI; correlation with BDNF, NSE, S100β	Serum exosomal miR-206 and miR-549a-3p associated with TBI severity and correlated with established protein markers.
Pryzmont, Kosciuczuk and Maciejczyk (2025)	Poland	Narrative review	Serum, CSF	Protein biomarkers; miRNAs as emerging class	Acute and longitudinal	Mortality and neurological prognosis in neurointensive care	Combined biomarker panels outperform single markers; miRNA studies emerging as a key trend.
Wang et al. (2025)	China	Comprehensive review	Multiple matrices	Multiple candidates including miR-21, miR-124, miR-146a, miR-155	Variable	Mechanism elucidation and clinical translation	Synthesised mechanistic and translational evidence on miRNAs in TBI.
Ren et al. (2025; preprint)	USA	Human cohort (n=48 blunt trauma)	Plasma	12-miRNA panel selected via RNA-seq + machine learning	Admission post-trauma	Multi-organ injury including TBI; severity and outcome	Plasma miRNA panel associated with multi-organ injury markers and inflammation in trauma; preprint, not yet peer reviewed.

Table 2. Key Circulating microRNAs and Proposed Biological/Clinical Significance in TBI

microRNA	Main biological role	Association with TBI severity/outcome	Potential clinical relevance
miR-21	Regulation of apoptosis, cell proliferation, and inflammatory signalling via PTEN, PDCD4 and related targets	Altered in multiple TBI cohorts; associated with severity and pathophysiological processes	Candidate core marker for severity- and outcome-oriented panels; potential therapeutic target

		(Atif and Hicks, 2019; Consalvo et al., 2024)	
miR-146a	Negative-feedback regulator of innate immune signalling (targets TRAF6, IRAK1); attenuates NF-κB-driven inflammation	Altered levels associated with neuroinflammatory dynamics in TBI	Marker of neuroimmune activation; complementary to severity/outcome panels
miR-155	Pro-inflammatory; drives M1-like polarization of macrophages/microglia and amplifies cytokine responses	Identified in panels associated with TBI severity and survival in fatal TBI (Consalvo et al., 2024)	Candidate severity marker; candidate therapeutic target
miR-124	Highly abundant neuronal miRNA; supports neuronal identity, plasticity, and dampening of microglial activation	Altered circulating levels reported in TBI; relevance to neuronal injury and repair [16]	Candidate marker of neuronal injury and recovery trajectory
miR-16, miR-92a, miR-765	Broad regulatory roles; miR-16 in apoptosis (BCL2); miR-92a in cell cycle	Validated as diagnostic candidates by Redell et al. (2010); discriminate TBI from controls and orthopaedic injury	Foundational candidates for diagnostic and prognostic panels
miR-206, miR-549a-3p (exosomal)	Emerging roles in neural injury signalling; vesicle-enriched fractions may improve CNS specificity	Serum exosomal levels associated with TBI severity [24]	Illustrates value of vesicle-enriched sampling for improved specificity
miR-93, miR-191, miR-499	Broad cell-cycle and inflammatory regulators; miR-499 implicated in cardiac and CNS stress responses	Elevated serum levels reported across multiple post-injury time points and associated with TBI severity (GCS) and outcome (GOS); high reported AUC for miR-93 in distinguishing TBI from controls (Yang et al., 2016)	Candidates for diagnostic and severity-stratification panels; require independent multi-centre validation given single-centre origin of strongest evidence
Additional miRNAs (let-7 family, miR-130a, miR-23a, miR-19a, miR-425-5p)	Broad roles in cell cycle, inflammation, and translational regulation	Variable associations reported across cohorts; require external validation	May contribute to extended panels or serve as normalization references

Table 3. Practical Opportunities and Barriers for Implementation in Indonesia and Resource-Limited Settings

Domain	Opportunity	Barrier	Potential solution
Laboratory infrastructure	Expansion of RT-qPCR capacity following COVID-19; reference laboratories in major tertiary centres	Uneven distribution; limited experience with low-abundance miRNA assays; reagent supply variability	Designate regional miRNA reference laboratories; national procurement frameworks for reagents; structured training programmes
Clinical infrastructure	High TBI case volume driven by road traffic injuries; established neurosurgical networks; national reference hospitals	Variable outcome documentation; inconsistent GOSE follow-up at 3 and 6 months	Embed structured outcome assessment in national TBI registries; align with international reporting standards
Workforce	Growing cohort of clinician-scientists with interest in translational neuroscience; academic partnerships	Limited personnel formally trained in miRNA workflows and bioinformatics	Fellowship programmes, cross-institutional training, and partnerships with international centres
Research governance	Strengthening ethics infrastructure and biobanking regulations	Evolving frameworks for data sharing, biobanking, and multicentre collaboration	Harmonised multicentre protocols, ethics committee coordination, and national biobank governance
Health economics	Generic RT-qPCR platforms comparatively affordable; potential for cost savings through earlier and more accurate triage	Out-of-pocket expenditure model; uncertain reimbursement pathways; cost-effectiveness evidence lacking	Prospective health-technology assessment aligned with implementation studies; stakeholder engagement with national insurance
Clinical integration	Growing demand for objective prognostic tools to support family counselling and triage in decentralised systems	Risk of premature adoption without analytical and clinical validation	Phased implementation anchored in national guidelines; stepwise expansion from reference centres to secondary hospitals

12. Conclusion

Circulating microRNAs represent a biologically grounded and logistically feasible candidate class of non-invasive prognostic biomarkers for TBI. A small core of miRNAs, including miR-21, miR-146a, miR-155, and miR-124, together with additional candidates such as miR-16, miR-92a, miR-206, and miR-549a-3p, reappears across independent studies as associated with injury severity and neurological outcome, and multi-miRNA panels generally outperform single markers. Current evidence nonetheless remains preliminary: most studies are single-centre, technical standards are not yet harmonized, and head-to-head comparisons with established protein biomarkers are limited. For Indonesia and similar resource-constrained settings, existing RT-qPCR infrastructure offers an important opportunity to undertake analytically rigorous, clinically anchored

validation studies. A phased programme of analytical validation, multicentre clinical validation, and implementation research, developed within national and regional collaborative networks, could realistically position circulating miRNAs as an adjunct to current prognostic tools in the coming years, while helping to close the persistent gap between biomarker discovery and routine clinical care

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Conflict of Interest

The authors declare that there is no competing interest in this research.

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