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Review

Biomarkers for Post-Traumatic Epilepsy: Advances in Imaging, Molecular Signatures, and AI-Assisted Prediction

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Abstract

Early diagnosis of post-traumatic epilepsy (PTE) is crucial for timely intervention. However, it is hampered by the lack of reliable biomarkers. In this review, we provide a comprehensive summary of current advances in PTE biomarker research covering (i) neuroimaging, including CT, MRI, and EEG/qEEG, which reveal structural and functional alterations associated with epileptogenesis; (ii) molecular biomarkers, including RNAs, proteins, metabolites, and extracellular vesicle (EV)–derived molecules that reflect neuroinflammation, blood–brain barrier dysfunction, neuronal injury, and synaptic remodeling; and (iii) artificial intelligence (AI)–assisted approaches, which integrate multimodal datasets to identify complex predictive patterns. While individual modalities offer valuable but incomplete prognostic information, AI-driven analytics hold the greatest promise for early predictive power when combining multimodal data. Future progress will depend on the combination of high-resolution imaging, multi-omics profiling, and rigorous validation to deliver clinically actionable biomarker panels and ultimately reduce the burden of PTE.

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1. Introduction

Epilepsy is a common neurological disorder characterized by recurrent, unprovoked seizures. Epilepsy affects 65-70 million individuals worldwide, imposing substantial social and economic burdens [1,2]. Approximately 50% of epilepsy cases are attributed to structural brain abnormalities, primarily caused by traumatic brain injury (TBI) [1]. Post-traumatic epilepsy (PTE), a form of epilepsy that results from TBI, accounts for ~5% of all epilepsy cases and up to 20% of symptomatic epilepsy cases [1,3–6]. Of the seizures that occur within 4 weeks after TBI, approximately 90% occur in the first week [7]. Recent studies have revealed several molecular mechanisms associated with the epileptogenesis of PTE, including neuroinflammation, blood-brain barrier (BBB) dysfunction, cell-signaling pathway perturbations, astrocyte dysregulation, and epigenetic dysregulation [8,9].

Although progress has been made in understanding molecular mechanisms underlying PTE, accurately predicting an individual's risk of developing PTE remains a major clinical challenge [10]. This challenge is largely due to the heterogeneous nature of TBI and the long latency period between the initial trauma and seizure onset [3]. To overcome this, researchers attempted to explore early diagnostic strategies for PTE over the past two decades [11]. These efforts included the identification of neuroimaging biomarkers, molecular indicators detectable in biofluids, and the development of advanced computational tools, such as artificial intelligence (AI)-driven predictive models.

In this review, we first provide a comprehensive overview of current progress in PTE biomarker studies, focusing on: (1) neuroimaging biomarkers such as magnetic resonance imaging (MRI) and computed tomography (CT), which aim to identify structural brain alterations linked to epileptogenesis; (2) molecular biomarkers, including RNA and protein signatures that elucidate

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underlying mechanisms and identify therapeutic targets; and (3) AI-assisted models, which leverage neuroimaging and molecular data to improve predictive accuracy. We also discuss future directions of PTE biomarker research.

2. Neuroimaging Biomarkers

Neuroimaging is a non-invasive tool for the detection and diagnosis of PTE, providing insights into structural changes in the brains of affected patients. In this section, we review the major neuroimaging technologies used in PTE, including CT, MRI, and electrophysiology (EEG). **Table 1** summarizes the comparison between these modalities, highlighting their respective strengths and weaknesses.

Table 1. Comparison of Neuroimaging Modalities for PTE.

Modality	Strengths	Limitations	Predictive Utility	Example Biomarkers
CT	Fast, widely available, detects acute hemorrhages and contusions	Low sensitivity for subtle changes, limited prognostic power alone	Moderate (AUC ~0.61); improved with qEEG	Temporal/frontal lesions [12]
MRI	High spatial resolution detects microstructural and volumetric changes	Expensive, limited use in acute/unstable settings	Higher when combined with clinical data; up to 89% accuracy	Hippocampal atrophy, cortical thinning [13,14]
EEG/qEEG	Real-time functional monitoring; captures subclinical epileptiform activity	Short monitoring windows, limited by skull conductivity	Stronger when used early and quantitatively	Epileptiform discharges, suppression burden [15]

2.1. CT

CT is a foundational neuroimaging modality for the detection of acute lesions in patients who have sustained a traumatic brain injury (TBI) [16]. CT head scans play a significant role in predicting the risk of post-traumatic epilepsy (PTE). Focal brain damage seen on early CT scans, particularly temporal lobe lesions, are strongly associated with the later development of PTE [17,18]. One study found that in patients with TBI and early seizures, CT scan with single temporal or frontal lesions in the acute phase was associated with a PTE risk 8.58 and 3.43 times higher respectively than for those without [19]. Higher CT Marshall scores, which indicate more severe injury, are also associated with increased PTE risk in pediatric patients [20]. Other CT findings linked to increased PTE risk include depressed skull fracture, epidural hemorrhage, subarachnoid hemorrhages, and subdural hemorrhages [21,22].

While CT is the mainstay of imaging for acute traumatic brain injury—as it is fast, cost-effective, and accurate in detecting primary and secondary injuries [16]—it has notable limitations. CT findings alone do not capture all patients at risk for PTE, and some with normal CTs may still develop epilepsy. CT, unlike MRI, cannot detect diffuse axonal injury and gliosis, both of which are associated with increased risk of PTE [23]. Incorporating electroencephalography (EEG) and clinical data alongside CT findings improves prediction of PTE, as EEG abnormalities and clinical features provide additional risk stratification [24]. This underscores the need for multimodal assessment.

2.2. Magnetic Resonance Imaging (MRI)

MRI is another valuable tool in predicting PTE. In a study using animal models, Pitkänen and Immonens found that the highest predictive value for seizure development at 12 months post-TBI could be achieved by jointly assessing diffusion in the perilesional cortex and the thalamus at 2 months after TBI. Evaluating specific MRI parameters in the perilesional cortex or the thalamus 9

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days following TBI also provided high sensitivity and specificity for predicting increased seizure susceptibility at 12 months after TBI. However, the differences between animals with and without epilepsy were not examined [25].

In a small cohort of human subjects with TBI, applying a novel technique of lesion normalization to diffusion MRI (dMRI) had PTE predictive performance with a mean area under the curve of 0.785. dMRI alterations of certain white matter tract can be used as potential biomarkers [26]. However, some histopathological changes associated with PTE cannot be detected by standard MRI [27].

More recent studies utilizing fMRI for PTE prediction in rats have shown that the perilesional cortex exhibits sensitivity to hyperexcitability induced by pentylenetetrazol (PTZ) following TBI, suggesting the development of a perilesional epileptogenic zone [28]. fMRI in patients with PTE has shown networks that are abnormally hyper-connected, hyper-integrated, and hypo-integrated compared to those without [29]. When used in combination with structural MRI, fMRI has more significant predictive value for PTE. Machine learning has been used as a predictive model which employed imaging features including lesion volumes, resting-state fMRI-based measures of functional connectivity, and amplitude of low-frequency fluctuation (ALFF). Of the machine learning methods applied, the Kernel support vector machine (KSVM) classifier achieved the highest accuracy with an area under the curve (AUC) of 0.78. The analysis also revealed significant differences in the bilateral temporal lobes and cerebellum between patients with and without PTE [30].

While MRI techniques that investigate the structural and functional changes after TBI hold promise for biomarker detection, the physical deformations that occur following moderate to severe TBI create challenges for the standard processing of neuroimaging data, complicating the search for biomarkers [26].

2.3. Electrophysiology (EEG/qEEG)

Electroencephalography (EEG) is a widely used clinical tool in TBI populations both for diagnosis and PTE prediction. Earlier work from the 1970s did not establish EEG as a reliable predictor of PTE [31], but more recent studies have demonstrated its value. Epileptiform abnormalities as early as within five days after TBI can independently predict PTE within one year with an odds ratio (OR) of 3.16 [32]. Focal EEG abnormalities over a month after TBI are also associated with three-fold increase in risk of PTE one year after TBI [19]. EEG findings that predict PTE include non-seizure epileptiform activities defined as one or a combination of interictal discharges, generalized and lateralized periodic discharges as well as lateralized rhythmic delta activity [33].

Quantitative EEG has shown that in addition to epileptiform discharges, altered EEG background can also be of prognostic value. Greater epileptiform burden, suppression burden, and beta variability are associated with PTE risk 4.6 times higher in the first year after TBI [24]. A more recent study which accounted for lateralization of post traumatic lesions and breach artifacts on qEEG found that more pronounced and variable delta activity were predictive of PTE [34]. Although commercially available software can facilitate analysis, creating a dedicated index specifically optimized for predicting PTE could potentially provide better diagnostic accuracy and predictive value [35].

Despite these advancements, the use of EEG as a biomarker still faces several challenges including limited EEG monitoring periods, a primary focus on early post-injury monitoring, and a complete lack of data on sleep abnormalities [35].

3. Molecular Biomarkers

Molecular biomarkers are measurable molecules, such as RNAs, proteins, lipids, or metabolites, that reflect biological processes, disease states, or responses to therapy. Table 2 summarizes representative molecular biomarkers used in PTE studies, highlighting their sample sources, accessibility, stability, disease stage, and relevance across different stages of PTE development. These biomarkers can be detected in various body fluids and compartments, including blood cells, plasma,

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and extracellular vesicles (EVs). Some of these biomarkers are also linked to key pathological mechanisms, including neuroinflammation, blood-brain barrier disruption, oxidative stress, and aberrant synaptic remodeling. In the following section, we discuss these molecular biomarkers across different molecular levels, from RNAs to metabolites.

3.1. RNA Biomarkers

RNAs, particularly microRNAs (miRNAs), have emerged as promising PTE biomarker candidates because of their regulatory roles in gene expression pathways implicated in epileptogenesis. miRNAs are short (approximately 22 nucleotides), non-coding RNA molecules that modulate gene expression post-transcriptionally. Changes in miRNA expression have been detected in both brain tissue and peripheral blood of individuals with PTE (PMID: 37895044). A recent review summarized miRNAs as potential biomarkers for epilepsy, traumatic brain injury, and ischemic stroke [36]. The present review focuses on the role of miRNAs in PTE prediction.

Table 2 summarizes 11 miRNAs investigated as biomarkers for PTE, detailing their biological roles, detectability, relevance to PTE, and associated publications. These miRNAs have been detected in accessible biofluids such as plasma, serum, and cerebrospinal fluid (CSF), making them minimally invasive candidates for biomarker development. The human miRNAs included were identified by overlapping findings from both TBI and epilepsy studies [37]. For those miRNA biomarkers identified in experimental animal study, the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) performed a small RNA sequencing of plasma samples collected from rats, identifying six potential miRNA biomarkers for PTE (miR-212-3p, miR-124-3p, miR-434-3p, miR-136-5p, miR-323-3p, and miR-9a-3p). Functionally, these m0iRNAs can be categorized based on their involvement in key epileptogenic mechanisms (Figure 1). A detailed summary of their roles is provided below.

3.1.1. miRNAs Associated with Neuroinflammation, Blood-Brain Barrier (BBB) Dysfunction, and Astrocyte Dysregulation

Several miRNA biomarkers are implicated in inflammatory, BBB, and glial dysregulation. These biomarkers include miR-21-5p, miR-155, miR-124-3p, and miR-136-3p. miR-21-5p promotes neuroinflammation by enhancing cytokine production and contributes to BBB disruption through effects on endothelial cells and astrocytes [38]. miR-155 acts as a proinflammatory regulator, activating microglia and sustaining inflammatory signaling that further compromises BBB integrity [39,40]. In contrast, miR-124-3p generally suppresses neuroinflammation by inhibiting microglial activation and modulating astrocyte responses [41]. miR-136-3p modulates inflammatory cytokine signaling and cell survival pathways, thereby impacting neuroinflammatory balance [42]. As their dysregulation reflects key neuroinflammatory and BBB changes that precede the development of PTE, these miRNAs have potential as early indicators following TBI (Figure 1).

3.1.2. miRNAs Associated with Cell Signaling

miRNAs such as miR-181a, miR-335-5p, and miR-434-3p predominantly influence neuronal signaling and inflammatory pathways. Altered expression of these miRNAs has been detected in human serum and rat plasma, correlating with disrupted neuronal excitability and increased seizure susceptibility [37,43]. For example, miR-335-5p has been associated with AKT/GSK3β signaling, where it reduces inflammation by negatively regulating TPX2-mediated activation [44]. In addition, miR-335-5p can modulate the TGF-β signaling pathway by targeting SMAD7, an inhibitory SMAD, thereby enhancing downstream TGF-β–mediated effects on cell differentiation [45]. It also participates in regulating the NF-κB pathway in inflammatory contexts such as osteoarthritis, where it downregulates pro-inflammatory cytokines and attenuates NF-κB activation [46].

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Table 2. Summary of microRNAs associated with PTE.

miRNA	Biological Role	Biofluid/Model	PTE Relevance	Source
miR-21-5p	Neuroinflammation, BBB Dysfunction, Astrocyte Dysregulation	CSF (human)	Shared dysregulation in TBI and epilepsy	Kumar et al., 2023
miR-155	Neuroinflammation, BBB Dysfunction	Serum (human)	Shared dysregulation in TBI and epilepsy	Vasilieva et al., 2023
miR-181a	Cell Signaling Perturbation, Neuroinflammation	Serum (human)	Shared dysregulation in TBI and epilepsy	Vasilieva et al., 2023
miR-30b-5p	Cell Signaling	CSF (human)	Shared dysregulation in TBI and epilepsy	Vasilieva et al., 2023
miR-328-3p	Cell Signaling	Serum (human)	Shared dysregulation in TBI and epilepsy	Vasilieva et al., 2023
miR-335-5p	Cell Signaling Perturbation	Serum (human)	Shared dysregulation in TBI and epilepsy	Vasilieva et al., 2023
miR-212-3p	Epigenetic Dysregulation, Cell Signaling Perturbation	Plasma (rat)	The EPITARGET Cohort	Heiskanen et al., 2024
miR-124-3p	Neuroinflammation, Astrocyte Dysregulation, Epigenetic Dysregulation	Plasma (rat)	The EPITARGET Cohort	Heiskanen et al., 2024
miR-434-3p	Cell Signaling Perturbation	Plasma (rat)	The EPITARGET Cohort	Heiskanen et al., 2023
miR-136-3p	Neuroinflammation, Cell Signaling Perturbation	Plasma (rat)	The EPITARGET Cohort	Heiskanen et al., 2024
miR-323-3p	Epigenetic Dysregulation	Plasma (rat)	The EPITARGET Cohort	Heiskanen et al., 2023
miR-9a-3p	Epigenetic Dysregulation, Cell Signaling Perturbation	Plasma (rat)	The EPITARGET Cohort	Heiskanen et al., 2024

3.1.3. miRNAs Associated with Epigenetic Dysregulation

miRNAs, such as miR-323-3p and miR-9a-3p, are linked to epigenetic mechanisms that modify gene expression implicated in epileptogenesis. Both miR-323-3p and miR-9a-3p act as regulators and targets of modifications like DNA methylation and histone acetylation. For example, miR-9a-3p

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regulates the activity of polycomb repressive complex 2 (PRC2) by interacting with the EED mRNA (a component of PRC2), leading to reduced EED protein levels and decreased H3K27me3 levels, a histone modification associated with PRC2 activity [47] (PMID: 23821546). Their dysregulation has been associated with alterations in neuronal excitability, synaptic remodeling, and inflammatory pathways, contributing to the development of epilepsy [48].

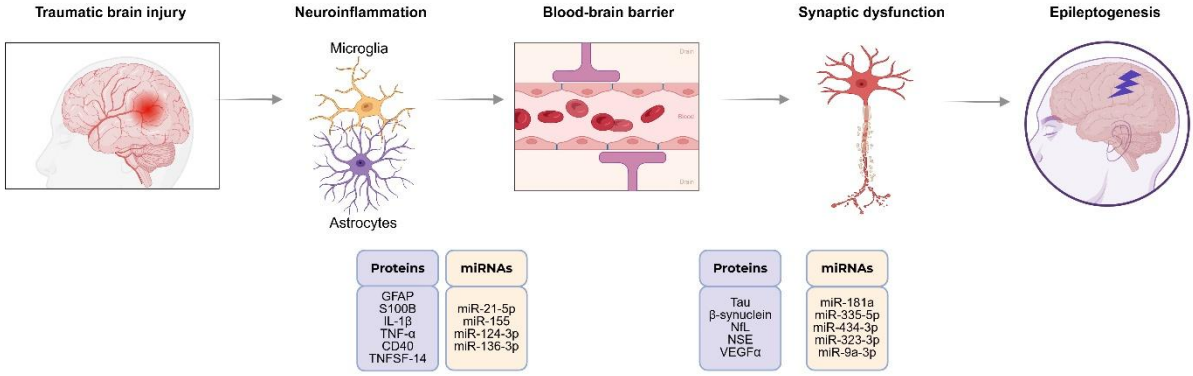

Figure 1. Schematic representation of molecular mechanisms underlying PTE and associated biomarker candidates.

3.2. Protein Biomarkers

Protein biomarkers detectable in biofluids have recently gained attention for their potential to assess injury severity and predict PTE. Table 3 summarizes protein biomarkers associated with PTE. Compared with miRNAs, they are generally more stable in circulation, more supported by well-established detection platforms, and more accurately reflect acute pathophysiological changes. In this section, we summarize several key protein biomarkers implicated in PTE, highlighting their biological roles and relevance to PTE (Figure 1).

Table 3. Summary of protein biomarkers associated with PTE.

Biomarker	Biological Role(s)	Biofluid/Model	PTE Relevance	Original Reports
GFAP	Neuroinflammation, BBB Dysfunction, Astrocyte Dysregulation	Blood, CSF, Brain tissue	Early marker correlating with astroglial injury	Saberi, 2024
S100B	Cell Signaling	Blood, CSF	Elevated in epilepsy; overlaps with NSE	Hanif et al., 2024
IL-1β	Neuroinflammation, Cell Signaling Perturbation	CSF, Brain tissue	Key inflammatory mediator in epileptogenesis	Hanif et al., 2024
TNF-α	Epigenetic Dysregulation, Cell Signaling Perturbation	CSF, Brain tissue	Promotes neuronal hyperexcitability and seizure risk	Hanif et al., 2024
CD40	Neuroinflammation, Cell Signaling Perturbation	Blood, Brain tissue	Altered in post-stroke epilepsy; may overlap with PTE	Hanif et al., 2024
TNFSF-14	Neuroinflammation	Blood	Downregulated in PSE; predictive value (AUC 0.73)	Hanif et al., 2024

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Tau	Neuronal damage and synaptic function	CSF, Blood, Brain tissue	Linked to epileptogenesis and tauopathies	Ferreira et al., 2024
Beta-synuclein	Neuronal damage and synaptic function	Brain tissue	Correlates with early synaptic injury	Ferreira et al., 2024
NfL	Neuronal damage and synaptic function	Blood, CSF	Reflects chronic axonal damage in PTE	Saberi, 2024
NSE	Neuronal damage and synaptic function	Blood, CSF	Injury severity marker; limited seizure specificity	Saberi, 2024
VEGFα	Neurovascular function	Blood, Brain tissue	Linked to neurovascular changes; seizure risk factor	Saberi, 2024

3.2.1. Proteins Associated with Astrocyte Dysregulation and Neuroinflammation

Protein biomarkers are involved in astrocyte dysregulation (GFAP and S100B) and neuroinflammation (IL-1β and TNF-α). GFAP and S100B are well-established astrocytic markers that serve as indicators of astrocyte activation and BBB compromise. Following TBI, astrocytic injury leads to their release into CSF and peripheral blood. In a recent study [49], plasma GFAP concentrations were markedly elevated in polytrauma patients compared with healthy controls, underscoring its utility as an early biomarker of central nervous system (CNS) injury. Neuroinflammatory cytokines, such as IL-1β and TNF-α, play crucial roles in the pathophysiology of epileptogenesis. Both proteins can alter synaptic transmission, enhance neuronal excitability, and lower seizure thresholds by modulating ion channel activity and neurotransmitter release. Their sustained elevation after TBI promotes a pro-epileptogenic milieu characterized by microglial activation, astrocyte reactivity, and disruption of neuronal network homeostasis.

3.2.2. Proteins Associated with Neuronal Damage, Synaptic Function, and Neurovascular Function

Several protein biomarkers implicated in PTE are directly associated with neuronal injury, synaptic dysfunction, and neurovascular disruption. Tau is a microtubule-associated protein primarily expressed in neurons. Hyperphosphorylated tau is one of the hallmarks of Alzheimer's disease (AD) as it disrupts microtubule stability and axonal transport, contributing to the accumulation of neurofibrillary tangles. An early study indicated that the total tau and phosphorylated tau levels in human serum increased during the acute phase and decreased during the chronic stage but was still detectable beyond six months post TBI [50]. Beta-synuclein modulates synaptic vesicle dynamics and maintains synaptic integrity. While less studied than alpha-synuclein, beta-synuclein is thought to play a neuroprotective role and may regulate excitatory neurotransmission. Alterations in its expression following TBI may indicate synaptic dysfunction and are under investigation for their relevance to epileptogenesis.

3.3. Metabolite Biomarkers

Metabolites are increasingly recognized as potential molecular biomarkers for PTE. Although direct metabolite biomarkers specific to PTE remain under investigation, altered amino acid and lipid metabolism after TBI—especially in the acute to subacute phase—may serve as early markers of brain vulnerability. These metabolic shifts could complement protein and RNA biomarkers in a multimodal prediction strategy for epileptogenesis. For example, a recent study [51] explored the glucose-to-potassium ratio (GPR) as a biomarker for early prognostication in PTE. GPR reflects acute metabolic stress, integrating hyperglycemia and hypokalemia—two hallmarks of the systemic response to brain injury. The study reported a significant nonlinear association between GPR and early PTE risk, identifying a critical threshold of GPR 2.835. Patients with values above this threshold demonstrated a markedly higher incidence of epilepsy.

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4. Molecules from Extracellular Vesicles as Biomarkers

Extracellular vesicle (EV)-derived molecules, including proteins, RNAs, and metabolites, are promising candidates as biomarkers for PTE due to their ability to cross the BBB into accessible biofluids (e.g., CSF and blood). EVs are nano- to microscale, membrane-bound particles secreted by virtually all cell types, including neurons and glial cells. They include different subtypes, including exosomes (30–150 nm) and microvesicles (100–1,000 nm). Compared with other molecules directly derived from biofluids, EVs offer the unique advantage of protecting their cargo from degradation, making them particularly suited for early, minimally invasive detection of PTE-related molecular changes [52]. Although no EV-derived biomarkers have yet been identified specifically in PTE patients, multiple studies have investigated EV cargo in TBI [53,54]. A recent study analyzed data from 18 animal and 19 human studies and found that miRNAs were the most frequently reported EV components [53]. Among these, miR-124-3p was the most consistently upregulated and was associated with neuroprotective effects, particularly through the modulation of neuroinflammation via neuronal and microglial EVs. miR-21 was also commonly elevated. Frequently identified EV proteins included GFAP, UCH-L1, and tau, as described above.

5. AI-Assisted Predictive Biomarker Discovery for PTE

Despite the identification of diverse molecular biomarkers in blood and CSF, their predictive power for PTE remains limited due to the heterogeneity of TBI and the multifactorial nature of epileptogenesis. Recently, AI has introduced a paradigm shift in biomarker discovery by enabling the integration of multimodal datasets to identify hidden patterns, stratify risk, and develop more accurate predictive models for the prognosis of PTE.

5.1. AI in Neuroimaging-Based Biomarker Discovery

The richness and spatial complexity of neuroimaging data make them particularly well suited to AI-based analysis, which can uncover predictive biomarkers that are difficult to detect through conventional methods. For example, one study used tensor-based morphometry combined with machine learning to detect brain shape changes in TBI patients, revealing imaging biomarkers predictive of future seizure development [54]. Another study applied traditional machine learning methods, including random forest (RF) and support vector machine (SVM), to multimodal MRI data, identifying key anatomical regions such as the left hippocampus, right putamen, and cingulate gyrus as critical discriminators of PTE risk [55].

5.2. AI for Molecular Biomarker Discovery

AI is particularly powerful when used in high-dimensional molecular datasets (e.g., large-scale transcriptomics, epigenomics, and proteomics) to identify predictive biomarkers. For instance, integrating data from EV proteomics, inflammatory cytokine profiles, and time-resolved gene expression could enable the development of multiplexed biomarker panels optimized for early prediction of PTE. By extracting meaningful patterns from these heterogenous datasets, AI offers a compelling approach to overcoming signal-to-noise challenges in complex disorders like epilepsy.

6. Conclusions

Early diagnosis of PTE remains a significant clinical challenge. While advances in neuroimaging, molecular biomarker discovery, and computational approaches have deepened our understanding of epileptogenesis, no single approach yet provides sufficient predictive power across diverse PTE cases. Neuroimaging modalities such as CT, MRI, and EEG offer critical structural and functional insights, whereas molecular biomarkers capture dynamic biological changes during disease progression. Integrating these complementary approaches holds the greatest promise for accurate, early risk stratification. AI further enhances predictive capacity by identifying complex, non-linear

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patterns across multimodal datasets. Future progress will depend on access to high-resolution neuroimaging, large-scale omics datasets, and rigorous validation of biomarker panels. Ultimately, reliable biomarkers will enable preventive interventions and reduce the long-term burden of PTE.

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