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Review

Exosome-Based Liquid Biopsy for Real-Time Diagnosis and Assessment in Acute Stroke and Its Subtypes

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Abstract

Acute stroke remained a leading cause of death and disability worldwide, emphasizing the need for rapid and accurate diagnostic tools to enable timely intervention. Conventional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) provided structural insights but lacked real-time molecular-level information and were often time-consuming and resource-intensive. Despite advances in neuroimaging, rapid differentiation between the ischemic and hemorrhagic stroke in real time diagnosis remained a significant clinical challenge, mainly in resource-limited settings. Exosome-based liquid biopsy presented a minimally invasive alternative with the potential for rapid stroke subtype identification using molecular biomarkers. The present review explored the emerging role of exosome-based diagnostics in stroke differentiation, highlighting the modern technological advancements, clinical findings, key challenges, and future directions for integration into precision neurovascular care.

Keywords

Acute stroke subtypes, Ischemic stroke, Hemorrhagic stroke, Exosome, Liquid biopsy, Molecular biomarkers

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1. Introduction

Globally, stroke is the second leading cause of death and the commonest cause of long-term disability [1]. The acute stroke could be broadly classified into ischemic and hemorrhagic subtypes. The ischemic stroke constitutes around 85% of all the stroke cases and it occurs due to obstruction in the cerebral blood flow, which is caused by thrombosis or embolism [2]. However, the hemorrhagic stroke results from the rupturing of blood vessels that leads to bleeding in the brain tissue and its surrounding areas caused by hypertension or aneurysmal rupture [1]. Rapid and accurate differentiation between these two subtypes is critical, as therapeutic approaches differ significantly, where thrombolytic therapy such as tissue plasminogen activator (tPA) is effective only for ischemic stroke but could be contraindicated in case of the hemorrhagic stroke, which aggravates the bleeding [3]. Neuroimaging techniques are standard diagnostic tests in acute stroke care. Non-contrast head Computed Tomography (CT) is the gold standard for the first diagnostic test in acute stroke. It is readily available in most emergency rooms. It can accurately and readily diagnose the presence of intracerebral hemorrhage. However, it is not sensitive in imaging early ischemic strokes. Magnetic Resonance Imaging (MRI) is sensitive and specific in acute ischemic strokes yet it is expensive and time-consuming. It is not available in resource-limited setting [4]. These diagnostic delays can narrow the therapeutic window, reinforcing the urgent need for rapid accessibility, and molecular-level diagnostic tools, which could differentiate the stroke subtypes in real time [2]. Therefore, the development of rapid, accessible, and molecular-level diagnostic tools is very crucial for early detection of stroke subtypes in differentiating and guiding the personalized, time-sensitive therapeutic decisions.

Liquid biopsy has emerged as a transformative, minimally invasive diagnostic approach that enables the analysis of circulating biomarkers in biological fluids such as blood, cerebrospinal fluid (CSF), and urine [5,6]. Although the liquid biopsy sources being widely used in oncology, recently it is gaining attention in stroke research due to its potential to detect the dynamic molecular alterations in real time [7]. Among the components of liquid biopsy, the exosomes are nanoscale extracellular vesicles (30-150 nm) secreted by nearly all cell types have attracted considerable attention [8]. These vesicles encapsulate a rich cargo of proteins, lipids, DNA, messenger RNA (mRNA), and microRNAs (miRNAs) that reflect the physiological or pathological state of origin of cells [7].

Exosome-based liquid biopsy offers a promising avenue for non-invasive and dynamic monitoring of stroke subtypes. It has the potential to complement the traditional imaging by providing the molecular-level insights into stroke onset, progression, therapeutic response, and most importantly, immediate diagnosis to distinguish the stroke subtypes. This innovative approach could revolutionize the stroke diagnostics and prognosis, paving the way for precision medicine in neurovascular care [9]. Exosomes act as dynamic molecular messengers in stroke pathology, reflecting the key processes including neuroinflammation, ischemic injury, and neuronal repair [10]. Moreover, exosomes could readily be accessed from the body fluids like plasma, thereby enabling systemic, real-time insights of cerebrovascular events and potentially overcoming the limitations of the conventional imaging [11]. Thus, the present review provides a comprehensive overview of exosome-based liquid biopsy for real-time stroke monitoring, emphasizing its role as a minimally invasive tool in the immediate diagnosis and differentiation of ischemic and hemorrhagic stroke. It also highlights the current technologies, clinical relevance, recent research advances, implementation challenges, and future perspectives.

2. Methodology

This review adopted a narrative approach to examine the diagnostic potential of exosome-based liquid biopsy in stroke subtype differentiation. Literature published till April 2025 was collected from PubMed, Scopus, Web of Science, and Google Scholar databases using the keywords “exosome AND stroke,” “exosomal biomarkers,” and “stroke diagnosis.” Only English-language studies focusing on exosome-based diagnostics for ischemic and hemorrhagic stroke were included. Blood, CSF, saliva, and urine were analyzed as biofluid sources, with blood being preferred for its accessibility, high exosome yield, and suitability for molecular profiling. The efficiency, speed, and point-of-care potential of exosome isolation and analysis on microfluidic platforms were also discussed in this review.

2.1 Diagnostic Potential of Exosome-Based Liquid Biopsy in Stroke Subtypes

Stroke presented a major global health burden, requiring rapid and accurate subtype differentiation for timely intervention. While CT and MRI remained standard for structural imaging, they often failed to capture the early molecular changes, which remained critical in acute settings. This narrative review consolidated the current evidence on exosome-based liquid biopsy as a promising diagnostic alternative. It highlighted the use of various biofluids, isolation and validation methods, and the profiling of exosomal miRNAs and proteins that enabled sensitive, minimally invasive, and early differentiation of ischemic and hemorrhagic stroke.

Exosomes, being nanosized vesicles secreted by most cell types facilitated intercellular communication by delivering bioactive molecules such as miRNAs, proteins, and lipids [12,13]. In the context of stroke, exosomes derived from neurons, astrocytes, and endothelial cells could specifically carry the molecular cargo reflecting the pathophysiological processes. Exosomal miRNAs, proteins and lipids served as stroke relevant biomarkers and were linked to membrane remodeling caused by neuroinflammation, neuronal injury, and blood-brain barrier disruption [14,15]. Therefore, the exosomes were speculated to be valuable candidates for early and precise stroke subtype differentiation.

2.2 Biofluid Sources for Exosome Isolation

Liquid biopsy emerged as a revolutionary and widely used minimally invasive diagnostic approach with profound implications in acute stroke care [16]. Unlike traditional neuroimaging or tissue biopsy, liquid biopsy analyzed the biofluids including plasma, serum, CSF, saliva, and urine to identify the circulating exosomes and other molecular markers such as cfDNA/cfRNA, microRNAs, and proteins [17]. Each biofluid had distinct diagnostic advantages based on its composition, proximity to the CNS, and exosome origin, as represented in Table 1.

Table 1. Overview of biofluids used in liquid biopsy for stroke diagnosis: Exosomal origins, biomarkers, and diagnostic relevance.

Biofluid	Exosomal Origin	Key Internal Exosomal Biomarkers	Advantages
Plasma	Endothelial cells, platelets, peripheral immune cells	miR-124, miR-9, Heat Shock Protein 70 (HSP70), Neuron-Specific Enolase (NSE), IL-6, TNF-α	Widely available, high exosome yield
Serum	Similar to plasma; more coagulation-derived vesicles	Glial Fibrillary Acidic Protein (GFAP), S100 calcium-binding protein, beta chain (S100β), miR-21, miR-223	Stable and accessible in clinical labs
CSF	Neurons, astrocytes, oligodendrocytes	Neurofilament light chain (NfL), α-synuclein, miR-132	High CNS specificity, ideal for brain injury markers
Urine	Kidney cells, filtered vesicles from circulation	Aquaporin-1, podocin, miR-200a	Non-invasive, lower CNS specificity
Saliva	Epithelial cells, peripheral nerve endings	miR-21, Interleukin-8 (IL-8), Tumor Necrosis Factor α (TNF-α)	Easy collection, low invasiveness

Note: Overview of key biofluids in stroke liquid biopsy, highlighting exosomal origin, internal biomarkers, and diagnostic relevance. Adapted from [12,18-24].

When assessing the biofluids for stroke diagnostics, plasma and serum served as accessible and sensitive sources that reflected the brain pathology, while urine and saliva showed lower CNS specificity. CSF remained the most specific but was limited by its invasive collection methods [25]. This balance of accessibility and specificity across biofluids was further illustrated in the overview depicted in Figure 1, which highlighted their exosomal origins, key biomarkers, and clinical roles in stroke diagnosis and monitoring.

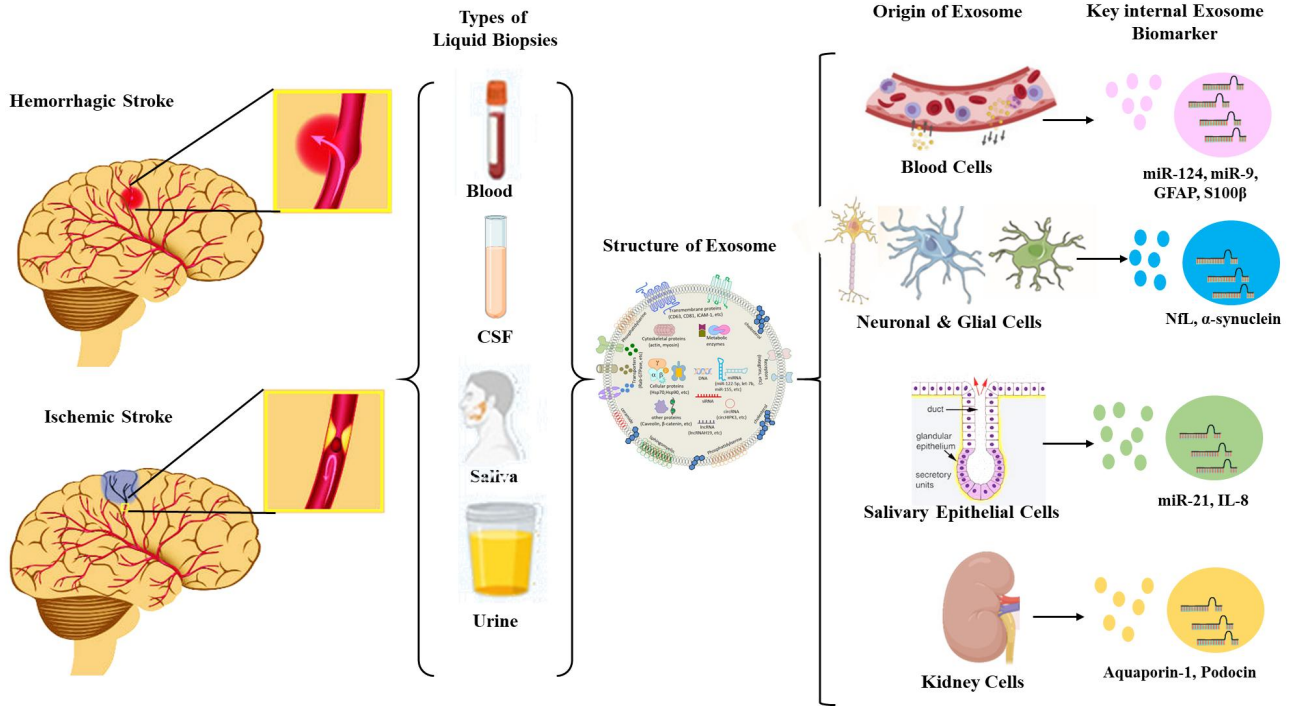

Figure 1. Exosome origins and biomarkers across biological fluids. Overview of biofluids utilized in stroke diagnostics *via* exosome analysis, illustrating their origins, key internal biomarkers (miRNAs, proteins, lipids), and clinical relevance for subtype differentiation and monitoring.

The plasma and serum were the most clinically accessible and rich in exosomal content when compared to the other types of biofluids, making them ideal candidates for high-throughput stroke diagnostics [12,14]. Although the CSF provided highly specific information about the CNS, its collection *via* lumbar puncture limited its routine clinical use [26]. Alternatively, saliva and urine represented highly non-invasive sources, but they were less specific to CNS pathology [27,28]. The exosomal cargo within these biofluids reflected their cellular origin and pathophysiological relevance [29]. The neuronal-derived exosomes (NDEs) were reported to be enriched in miR-124 and neurofilament proteins, which served as biomarkers for neuronal injury [30]. Similarly, studies reported that astrocyte-derived

exosomes contained glial fibrillary acidic protein (GFAP) and S100 calcium-binding protein, beta chain (S100β), while endothelial-derived exosomes carried adhesion molecules such as Intercellular Adhesion Molecule 1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1), which were linked to blood-brain barrier disruption [31,32]. Therefore, accurate interpretation of exosomal biomarkers based on the fluid type and cellular origin proved critical for precise stroke subtype classification, prognosis determination, and therapeutic response monitoring [32].

2.3 Exosome Isolation and Characterization Techniques

Blood (plasma or serum) proved to be the most clinically reliable biofluid for exosomal analysis in stroke diagnostics because of its accessibility, high vesicle yield, and suitability for high-throughput molecular assays. Once blood samples were collected, standardized pre-analytical handling including prevention of hemolysis, appropriate anticoagulant use, timely processing, and controlled storage played a critical role in preserving the exosomal integrity and ensuring the downstream analytical reliability [33-35].

Exosome isolation techniques varied in complexity, yield, and purity, each with unique advantages and limitations. Ultracentrifugation remained the gold standard due to its effectiveness in size- and density-based separation but was reported to be highly labor-intensive and could also co-isolate protein aggregates [36]. Size-exclusion chromatography (SEC) offered high purity while preserving vesicle integrity, making it widely suitable for translational applications [37]. Polymer-based precipitation methods were reported to be fast and user-friendly but often resulted in protein contamination [38]. Immunoaffinity capture using antibodies against exosomal markers like CD63, CD81, or CD9 (Cluster of Differentiation) provided high specificity but was reported to have lower yield and higher costs [39]. Recently, microfluidic platforms emerged as promising alternatives, offering rapid, label-free, and scalable isolation suitable for point-of-care diagnostics [40,41]. Table 2 summarized the comparative performance and limitations of these isolation strategies.

Table 2. Comparison of exosome isolation techniques.

Technique	Principle	Advantages	Limitations	Effectiveness
Differential Ultracentrifugation	Sequential centrifugation to separate by size/density	Widely used; high yield; gold standard for basic research	Time-consuming; labor-intensive; co-isolation of contaminants	Moderate: Good for basic research; less ideal for pure diagnostics
Size-Exclusion Chromatography (SEC)	Separation based on size using porous matrix	High purity; preserves exosome integrity; reproducible	Lower yield; may miss smaller vesicles	High: Preferred in clinical and translational settings
Polymer-Based Precipitation (e.g., PEG)	Polymer-induced aggregation and precipitation	Fast; easy; scalable	High protein contamination; less suitable for downstream analysis	Low to Moderate: Suitable for preliminary or high-throughput use
Immunoaffinity Capture	Antibody-based capture of exosome-specific surface markers	High specificity; suitable for targeting subpopulations	Low yield; expensive; limited scalability	High: Best for targeted biomarker studies; limited by cost
Microfluidic Platforms	Miniaturized devices using size, immunoaffinity, or acoustic/electrophoretic separation	Rapid; low sample volume; high precision; integrates isolation and detection; suitable for point-of-care	Limited availability; requires specialized devices; scalability still evolving	High: Promising for clinical translation, especially for rapid diagnostics and bedside use

Note: Comparison of exosome isolation techniques highlighting their complexity, yield, purity, and specific advantages and limitations. Methods include ultracentrifugation, size-exclusion chromatography (SEC), polymer-based precipitation, immunoaffinity capture, and emerging microfluidic platforms, each characterized by distinct performance profiles relevant to stroke diagnostics and translational applications. Adapted from [12,18,41-44].

2.4 Microfluidic Platforms for Exosome Isolation

Ultracentrifugation remained the most widely used traditional technique, but limited to labor-intensive, time-consuming technique, which required large sample volumes with a risk of co-isolating contaminants such as proteins and lipoproteins [36]. In contrast, the microfluidic systems integrated multiple steps including filtration, separation, and detection into a miniaturized, automated device, making them highly suitable for clinical diagnostics [41]. Microfluidic platforms operated based on various principles, including size-based filtration, immunoaffinity capture, and acoustic or electrophoretic separation. These methods facilitated label-free, non-invasive, and rapid isolation of exosomes from biological fluids like plasma, CSF, and urine, while preserving exosomal structure and molecular integrity [45]. Furthermore, some microfluidic chips incorporated nanostructured surfaces or antibody-coated microchannels to enhance specificity and yield by targeting exosomal surface markers such as CD63, CD81, CD9, L1 cell adhesion molecule (L1CAM), and GFAP, significantly increasing their diagnostic utility [18,46].

Microfluidic platforms offered a significant advantage in cost-effectiveness when compared to the conventional imaging modalities like CT and MRI, which were the established gold standards for stroke diagnosis. While CT and MRI provided essential anatomical and structural information, they involved high infrastructure costs, required trained personnel, and were not accessible in all healthcare settings. Microfluidic devices, by contrast, presented low-cost, portable, and capable of delivering the diagnostic results within 30–60 minutes, making them ideal for rapid bedside stroke diagnostics even in prehospital or resource-limited environments [40,41]. The table 3 represented a comparison of modern microfluidic platforms of exosome-based liquid biopsy diagnosis and traditional imaging techniques in stroke diagnosis.

Table 3. Comparative overview of modern microfluidic exosome-based liquid biopsy vs traditional MRI/CT imaging in stroke diagnosis

Parameter	Modern Diagnostics (Microfluidic Exosome-Based Liquid Biopsy)	Traditional Diagnostics (MRI/CT Imaging)
Sample Type	Blood, CSF, saliva, urine (minimally invasive)	No sample required (non-invasive imaging)
Turnaround Time	30–60 minutes (potential for real-time analysis)	Typically several hours depending on imaging availability
Detection Targets	Exosomes (CD9, CD63, CD81), miRNAs, proteins, lipids	Structural brain changes (e.g., infarct, edema, hemorrhage)
Invasiveness	Minimally invasive	Non-invasive
Timing of Detection	Detects early molecular changes before structural damage [47]	Detects changes after structural damage occurs [48]
Sensitivity	High molecular sensitivity (miR-124, GFAP, NSE)	High sensitivity to anatomical changes, but limited for early molecular events
Specificity	High–exosomal cargo is disease-specific	Moderate–anatomical findings may not reveal etiology or subtype
Repeatability	High–allows serial sampling for longitudinal monitoring	Limited–constrained by cost, access, and radiation exposure [48]
Diagnostic Utility	Enables subtype classification, prognosis, and monitoring	Primarily detects location/extent of damage; limited prognostic insight
Integration with Precision Medicine	Strong–aligns with genomic, proteomic, and AI decision-making	Limited–lacks molecular data
Technological Requirements	Requires microfluidic chip fabrication, molecular assays, and detection platforms	Requires CT/MRI imaging infrastructure
Point-of-Care Potential	High–portable, chip-based lab-on-a-chip devices under development	Low–confined to hospital-based imaging units
Cost-effectiveness	Potentially low-cost and scalable once standardized	High setup and maintenance costs
Volume Requirement	Low sample volume (10–100 μL)	Not applicable
Multiplexing Capability	High–simultaneous profiling of multiple biomarkers	Low–single-parameter structural analysis
Early Detection Potential	Yes–detects pre-symptomatic or pre-lesion molecular signals	Limited–detects established lesions only
Automation & Integration	Fully automatable lab-on-chip systems	Semi-automated or manual interpretation required
Clinical Validation	Emerging–promising preclinical and early clinical studies	Established–standard of care in stroke diagnosis
Limitations	Requires regulatory approval, standardization, and large-scale validation	Insensitive to early molecular or functional changes; high operational burden
Biological Insight	High–provides insights into inflammation, ischemia, repair pathways	Structural only–lacks molecular or cellular information

Note: Comparison of microfluidic exosome-based liquid biopsy and traditional stroke diagnostics (CT/MRI). Microfluidic platforms enabled rapid, minimally invasive detection of exosomal biomarkers (e.g., miRNAs, proteins) from small sample volumes, offering high molecular sensitivity, multiplexing, and potential for point-of-care use. In contrast, CT and MRI provided structural imaging with established diagnostic value but were limited in early detection, molecular specificity, and portability. Adapted from [9,15,40,42,45,47-49].

Blood-derived exosomes emerged as reliable indicators in distinguishing the stroke subtypes due to their abundance, accessibility, and stroke-relevant molecular cargo. Among the isolation methods, microfluidic platforms offered faster, more sensitive processing with minimal sample requirements, enabling integrated analysis and superior exosome preservation [41,42]. When compared to the traditional techniques like ultracentrifugation or polymer-based precipitation, the microfluidics was better suited for point-of-care use and real-time clinical decisions [40,45]. Its compatibility with routinely collected serum and plasma further supported rapid and scalable screening [18]. For

characterization, techniques including Nanoparticle Tracking Analysis (NTA), Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM) and immunoblotting or flow cytometry targeting CD9, CD63, and CD81 ensured analytical rigor. Collectively, these advances positioned the microfluidic isolation of blood-derived exosomes as a promising, minimally invasive approach for timely stroke diagnosis.

2.5 Molecular Profiling and Exosomal Biomarkers in Stroke Subtypes

Exosomes exhibited critical molecular messengers, transporting disease-specific cargo such as microRNAs and proteins that reflected the underlying pathophysiology of stroke [50]. These exosomal biomarkers presented molecular precision in differentiating the ischemic and hemorrhagic stroke subtypes. Key miRNAs such as miR-124, miR-9, and miR-210 were found to be significantly increased in ischemic stroke, while proteins like GFAP, S100β, and miR-223 were more prominent in hemorrhagic stroke [51,52]. These markers not only reflected the neuroinflammation, neuronal injury, oxidative stress, and blood-brain barrier disruption, but also revealed distinct exosomal molecular profiles that enabled early, minimally invasive stroke subtype identification [53].

Recent advances highlighted the use of exosome-based liquid biopsy in identifying the stroke subtype-specific biomarkers, aiding early and accurate differentiation between ischemic and hemorrhagic events [10]. For example, GFAP, a protein expressed in astrocytes and indicative of astrocyte injury, was elevated in hemorrhagic stroke, whereas NSE, a marker of neuronal injury, was significantly detectable in circulating exosomes predominantly in ischemic stroke patients [54-56]. The plasma GFAP levels were shown to be significantly higher in intracerebral hemorrhage when compared to the acute ischemic stroke, highlighting its diagnostic potential for hemorrhagic stroke [57]. Conversely, increased NSE levels correlated with neuronal damage and infarct severity in ischemic stroke, supporting its role as a biomarker for ischemic neuronal injury [58]. These findings emphasized the diagnostic importance of exosome-derived biomarkers in differentiating the stroke subtypes and paved the way for exploring their roles in underlying mechanisms such as neuroinflammation and blood-brain barrier disruption.

2.6 Neuroinflammation and Blood-Brain Barrier Disruption

Reports on exosomal cargo analysis suggested that the molecular diagnostics might have surpassed the conventional imaging in effectiveness during the hyperacute stroke phase, when the therapeutic window was critically narrow. Exosomes carried different neuroinflammatory biomarkers including cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), chemokines, and specific microRNAs that were strongly related to stroke severity and inflammatory responses [59-61]. Notably, miR-124 and miR-9 were found to be linked to the microglial activation and significantly increased in stroke patient exosomes [52]. Hypoxia-responsive miR-210 was also significantly upregulated, reflecting oxygen deprivation in affected brain tissue. Additional markers like miR-223 and miR-134 were associated with stroke severity and early inflammatory responses, while reduced levels of miR-152-3p were related to more severe atherosclerosis and higher NIH Stroke Scale (NIHSS) scores [10]. Elevated exosomal IL-6 and TNF-α levels in ischemic stroke correlated with larger infarct volumes and worse the neurological outcomes, reflecting systemic and central nervous system inflammation [62]. Hemorrhagic stroke, in contrast, involved distinct astrocytic and microglial activation with differing kinetics and magnitude of exosomal inflammatory markers [63]. These differential inflammatory profiles aided in stroke subtype differentiation and assessment in the levels of neuroinflammatory damage.

2.7 Markers of Neuronal and Glial Injury

The neuron and glial derived exosomes isolated from plasma or CSF carry proteins indicative of the nature and extent of brain injury [64]. In ischemic stroke, several miRNAs such as miR-124 and miR-9, proteins such as NSE, ICAM-1, VCAM-1 originating primarily from neurons were found to be elevated and correlated with infarct size, neuronal injury, and NIHSS scores, indicating neuronal damage [54]. However, hemorrhagic stroke was characterized by the presence of astrocyte-derived proteins such as GFAP and S100β, both of which were elevated due to glial activation and blood-brain barrier disruption [10, 65]. Exosomal miR-21, commonly upregulated in glial inflammation, and miR-144-5p, found in hematoma-derived exosomes, were also prominent in hemorrhagic conditions. MiR-144-5p was shown to inhibit angiogenesis and affect endothelial cell function, making it particularly relevant in chronic subdural hematoma [65]. Furthermore, increased levels of exosomes carrying surface markers such as CD45, CD146, and CD61 reflected activation of leukocytes, endothelial cells, and platelets during hemorrhagic events [66]. These exosomal miRNAs and proteins facilitated early diagnosis and accurate differentiation between ischemic and hemorrhagic stroke, supporting the prognosis and guided targeted clinical management.

2.8 Exosomal miRNAs as Early Diagnostic and Prognostic Biomarkers

In stroke, the exosomal biomarkers held strong diagnostic and prognostic potential by enabling early detection, subtype differentiation, and monitoring of disease progression. These vesicles carried the bioactive molecules that regulated gene expression, inflammation, angiogenesis, and apoptosis which played crucial role in determining the stroke pathophysiology. For example, neuronal miR-124 was elevated in ischemic stroke and reflected neuronal injury, while GFAP, derived from astrocytes, indicated glial damage and was elevated in hemorrhagic stroke [67,68]. The functional relevance of these biomarkers enhanced their clinical utility for subtype-specific diagnosis.

The circulating exosomal miRNAs provided non-invasive insights into stroke onset and progression. miR-124 and the hypoxia-responsive miR-210 were upregulated in ischemic stroke and correlated with infarct size and tissue hypoxia [68,69]. In contrast, miR-21 was typically increased in hemorrhagic stroke, reflecting inflammatory and glial responses [70]. These miRNAs often appeared before the imaging changes, reinforcing their role in early diagnosis. Combining the exosomal profiles with NIHSS clinical scales improved the outcome prediction, with decreased miR-124 and elevated miR-21 levels linked to poorer prognosis [71,72]. Additional markers like NSE and endothelial proteins (ICAM-1, VCAM-1) further stratified ischemic severity, while GFAP, S100β, and miR-155 identified hemorrhagic injury and blood-brain barrier disruption [73]. A summary of key exosomal biomarkers, their sources, and relevance to stroke subtypes was provided in Table 4.

Table 4. Summary of key exosomal biomarkers and their diagnostic role in stroke subtypes.

Biomarker	Type	Source	Stroke Subtype	Role	Clinical Relevance
miR-124	Circulating miRNA	Neuronal exosomes	Ischemic ↑	Neuronal injury, neuroinflammation, microglial activation	Early detection, subtype classification; downregulation = poor prognosis
GFAP	Protein/Glial injury protein	Astrocyte-derived exosomes	Predominantly Hemorrhagic	Astrocyte activation, astrogliosis	Differentiation from ischemia; indicates secondary injury
NSE	Protein/Neuronal injury	Neuron-derived exosomes	Predominantly Ischemic	Neuronal damage	Severity index; elevated in infarct severity
miR-155	miRNA	Not specified	Hemorrhagic	Inflammation	Predicts inflammatory status
S100β	Protein	Not specified	Hemorrhagic	BBB (blood-brain barrier) disruption	Prognosis and triage
ICAM-1	Protein	Not specified	Ischemic	Endothelial response	Marker of vascular inflammation
miR-210	miRNA/Hypoxia-responsive	Hypoxia-inducible exosomes	Ischemic (also in Both)	Hypoxia regulation	Early ischemic hypoxia marker; correlates with infarct size and oxygenation
CD63, CD81	Surface proteins	Exosomes	Both	Exosome identity, intercellular signaling	Included in diagnostic panels
IL-6, TNF-α	Neuroinflammatory markers	Plasma exosomes	Ischemic > Hemorrhagic	Systemic and central inflammation	Correlate with infarct volume in ischemic stroke
miR-9	Circulating miRNA	Neuronal exosomes	Ischemic	Neuroinflammation	Linked to microglial activity
miR-21	Prognostic miRNA	Multifactorial sources	Both (↑ in Hemorrhagic)	Inflammatory response	Associated with poor outcomes; elevated in hemorrhagic stroke

Note: Exosomal biomarkers, including surface tetraspanins (CD63, CD81, CD9) and stroke-specific miRNAs/proteins, enable precise subtype differentiation, early diagnosis, and outcome prediction in ischemic and hemorrhagic strokes. Adapted from: [15,47-49].

Although ischemic and hemorrhagic strokes were the most common, expanding exosomal biomarker analysis to include less prevalent stroke types played important role in understanding the comprehensive diagnosis and to avoid misclassification. Subtypes such as transient ischemic attack (TIA), cerebral venous sinus thrombosis (CVST), subarachnoid hemorrhage (SAH), and embolic stroke of undetermined source (ESUS) exhibited distinct exosomal signatures ranging from miR-16, miR-124, and Annexin A2 to CD63 and GFAP reflecting neurovascular dysfunction, thrombotic injury, or astroglial damage respectively [47,49,74]. The shared exosomal markers (CD63, CD81, CD9) confirmed vesicle identity, while others like miR-92a and HSP70 provided prognostic insight. Collectively, these molecular profiles highlighted the clinical relevance of exosome-based liquid biopsy in stroke diagnostics.

2.9 Clinical Applications and Diagnostic Impact

When integrated with microfluidic technologies, the exosomal biomarker profiling offered a rapid, sensitive, and accessible approach to stroke diagnosis critical during the narrow therapeutic window of acute events. Microfluidic platforms enabled efficient isolation and detection of subtype-specific biomarkers such as miR-210 and NSE for ischemic stroke, and GFAP and miR-21 for hemorrhagic stroke, using minimal blood volumes [69,75]. This integration not only improved the diagnostic precision but also supported personalized treatment decisions by permitting early molecular detection often before the structural changes were significantly visible in conventional imaging modalities like CT or MRI [49]. When compared to these traditional methods, microfluidic-based liquid biopsy provided greater sensitivity and specificity by capturing the dynamic pathophysiological changes in real time. Its portability and rapid

turnaround make it ideal for point-of-care testing, particularly in emergency and resource-limited settings, where timely intervention remains critical [7]. As illustrated in Figure 2, this technology bridged the molecular diagnostics with frontline stroke care, representing a significant advancement towards accessible, stratified, and outcome-driven management.

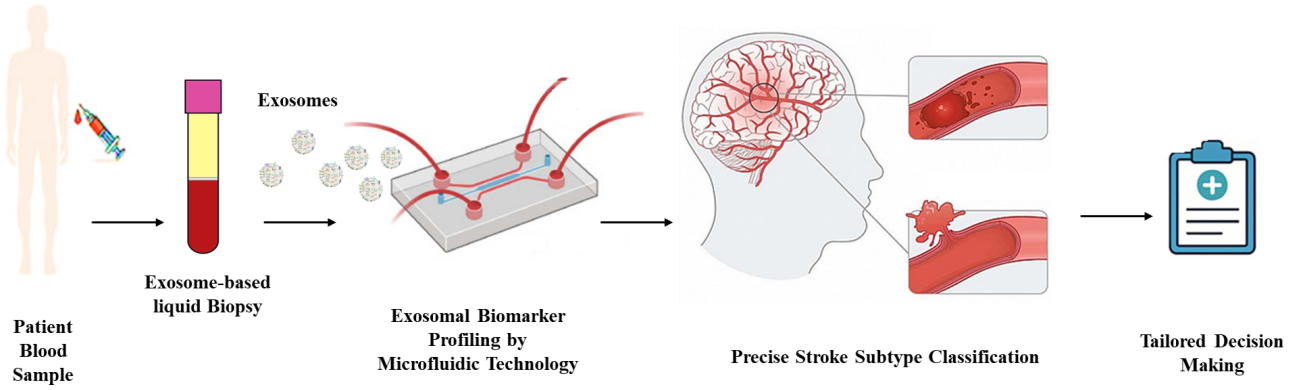

Figure 2. Microfluidic exosome profiling for stroke subtype differentiation: from blood draw to clinical decision-making. A visual workflow depicting the use of blood-derived exosomes isolated *via* microfluidic platforms in distinguishing ischemic and hemorrhagic stroke. The process involved blood collection, exosome extraction through lab-on-a-chip technology, biomarker profiling, and clinical classification for tailored stroke management.

2.10 Current Challenges and Future Directions

Microfluidic platforms enabled rapid, sensitive, and low-sample exosome isolation, making them ideal for stroke subtype diagnosis. However, lack of standardized protocols and patient-specific exosome variability limited the reproducibility and clinical adoption. Most findings were from small studies, so large, multicenter trials is very important in validating their reliability in distinguishing between ischemic from hemorrhagic stroke.

Future work should focus in establishing universal, standardized methods for microfluidic exosome isolation and analysis to ensure consistency across settings. Combining the microfluidic profiling with neuroimaging, genomics, and AI could significantly increase in identifying the early stroke classification and personalized treatment. Development of portable, affordable point-of-care microfluidic devices will enable rapid, bedside stroke diagnosis and monitoring. Addressing regulatory hurdles is also crucial for clinical translation. Advances in microfluidics and AI promise to improve the speed, sensitivity, and accuracy of exosome-based diagnostics, ushering in a new era of precise, rapid, and personalized stroke care.

3. Conclusion

Exosome-based liquid biopsy represented a transformative, non-invasive approach in distinguishing ischemic and hemorrhagic stroke diagnosis, enabling rapid, molecular-level insights into brain pathology that surpassed the traditional imaging techniques. By profiling specific exosomal miRNAs and protein markers, this technique could help in real-time differentiation between ischemic and hemorrhagic stroke subtypes where hypoxia-responsive miRNAs and neuronal injury proteins characterized ischemic stroke, and astrocyte-derived markers along with inflammation-related proteins were prominent in hemorrhagic stroke. Rapid isolation methods, particularly emerging microfluidic platforms, improved the feasibility of bedside or point-of-care application, supporting timely clinical decision-making. Despite the current challenges in standardization and clinical validation, integrating the exosome-based diagnostics within precision medicine frameworks promises to improve early subtype classification, monitor therapeutic response dynamically, and guide personalized treatment, ultimately elevating stroke care outcomes and potentially becoming an essential complement to conventional diagnostic modalities.

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Ethics Statement

This review paper has been prepared in accordance with the ethical standards expected in academic research and publication. The authors confirm that all the sources have been properly cited and acknowledged, and there is no fabrication, falsification or manipulation of information.

Informed Consent

This work does not involve any new human or animal research data. Instead, it synthesizes and analyzes previously published studies, respecting the intellectual property rights and academic integrity.

Author Contributions

The author conducted the literature review, synthesized the findings, and prepared the manuscript.

Conflict of interest

The authors declare no competing interests. The authors declare that the manuscript has not been submitted or published elsewhere for publication.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Abbreviations

AI: Artificial Intelligence

BBB: Blood-Brain Barrier

CD: Cluster of Differentiation

cfDNA/cfRNA: Cell-free DNA/RNA

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

CT: Computed Tomography

CVST: Cerebral Venous Sinus Thrombosis

DLS: Dynamic Light Scattering

ESUS: Embolic Stroke of Undetermined Source

GFAP: Glial Fibrillary Acidic Protein

HSP70: Heat Shock Protein 70

ICAM-1: Intercellular Adhesion Molecule 1

IL-8: Interleukin-8

L1CAM: L1 Cell Adhesion Molecule

miRNAs: microRNAs

MRI: Magnetic Resonance Imaging

mRNA: Messenger RNA

NDEs: Neuronal-Derived Exosomes

NfL: Neurofilament Light Chain

NIHSS: NIH Stroke Scale

NSE: Neuron-Specific Enolase

NTA: Nanoparticle Tracking Analysis

TEM: Transmission Electron Microscopy

TIA: Transient Ischemic Attack

TNF-α: Tumor Necrosis Factor α

tPA: Tissue Plasminogen Activator

SAH: Subarachnoid Hemorrhage

SEC: Size-Exclusion Chromatography

VCAM-1: Vascular Cell Adhesion Molecule-1

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