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REVIEW ARTICLE

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Biochemical, biomechanical and imaging biomarkers of ischemic stroke: Time for integrative thinking

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Abstract

Stroke is one of the leading causes of adult disability affecting millions of people worldwide. Post-stroke cognitive and motor impairments diminish quality of life and functional independence. There is an increased risk of having a second stroke and developing secondary conditions with long-term social and economic impacts. With increasing number of stroke incidents, shortage of medical professionals and limited budgets, health services are struggling to provide a care that can break the vicious cycle of stroke. Effective post-stroke recovery hinges on holistic, integrative and personalized care starting from improved diagnosis and treatment in clinics to continuous rehabilitation and support in the community. To improve stroke care pathways, there have been growing efforts in discovering biomarkers that can provide valuable insights into the neural, physiological and biomechanical consequences of stroke and how patients respond to new interventions. In this review paper, we aim to summarize recent biomarker discovery research focusing on three modalities

Abbreviations: ADC, apparent diffusion coefficient; ASL, arterial spin labeling; ATP, adenosine triphosphate; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BI, Barthel Index; CBF, cerebral blood flow; CNS, Canadian Neurological Scale; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CT, computerized tomography; DWI, diffusion-weighted imaging; EEG, electroencephalography; ELISA, enzyme-linked immunosorbent assay; EMG, electromyography; ESWT, extracorporeal shock wave therapy; FES, functional electrical stimulation; FIM, Functional Independence Measure; FLAIR, fluid-attenuated inverse recovery; GRE, gradient-recalled echo; HPLC, high-performance liquid chromatography, IL-6, interleukin 6; MEP, Motor Evoked Potential; MMP-9, metalloproteinase-9; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PLIC, posterior limb of the internal capsule; PWI, perfusion-weighted imaging; rTMS, repetitive transcranial magnetic stimulation; SS-QOL, Stroke Specific Quality of Life Scale; ST2, suppression of tumorigenicity 2; SWI, susceptibility-weighted imaging; T1W, T1-weighted; T2W, T2-weighted; TIA, transient ischemic attack; TMS, transcranial magnetic stimulation; TNF-alpha, tumour necrosis factor-alpha; TrkB, tropomyosin receptor kinase B; VLSM, voxel-based lesion-symptom mapping; WBC, white blood cell; WMI, white matter injury.

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(brain imaging, blood sampling and gait assessments), look at some established and forthcoming biomarkers, and discuss their usefulness and complementarity within the context of comprehensive stroke care. We also emphasize the importance of biomarker guided personalized interventions to enhance stroke treatment and post-stroke recovery.

KEYWORDS
blood biomarkers, clinical outcome, gait analysis, ischemic stroke, magnetic resonance imaging

1 | INTRODUCTION

Stroke is defined as 'an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction' that leads to brain injury (Sacco et al., 2013). It affects more than 13 million people each year, globally (Lindsay et al., 2019). Up to 30% of stroke patients die, whilst many survivors live with disabilities (Mansfield et al., 2018). Even though the post-stroke disability-adjusted life-years (years lost due to disability) have been decreasing since 2000s, the number of first stroke incidents has been increasing likely due to improved health care and increased life expectancy (Hankey, 2017).

Stroke is a complex neurological condition and its impact on the patient depends on a multitude of factors including the severity of stroke, affected brain region, brain neuroplasticity, treatment options, timely interventions (e.g., physiotherapy and rehabilitation programs), available community support (e.g., from family and friends), comorbidities as well as self-efficacy, motivation and physical status of the patient. As a result of this complexity, it is difficult to predict the long-term effects of stroke, and it is not uncommon that two patients with similar strokes would end up having different clinical and functional outcomes.

There is growing evidence that, compared to 'one-size-fits-all' stroke care, personalized and adaptive stroke care tailored to the individual's needs (which continuously change over time) combined with intensive rehabilitation programs may improve clinical outcomes (Ha et al., 2010; Teasell et al., 2005). However, maximizing the recovery potential of stroke patients requires large investments in health and social care services which are already under immense pressure due to limited resources and manpower. In addition to resource management, there is a need for discovering new cost-effective biomarkers, signs indicating the medical state of the patient accurately and objectively, that allow continuous monitoring of the patient. There is also a need for integrative approaches that enables multi-modal biomarker analysis to provide a more comprehensive picture about the patient's status and make meaningful clinical decisions in every step of the way.

Stroke biomarkers have already started revolutionizing stroke care from diagnosis to clinical outcome prediction and recovery monitoring. Notably, many of these biomarkers come from three modalities: brain imaging, analysis of blood samples and gait measurement. Brain imaging biomarkers are used for early diagnostics, confirming stroke and determining whether it is ischemic or hemorrhagic (Manwani et al., 2019). They are also useful for prognosis and studying neuroplasticity. Blood biomarkers, although not utilized for diagnostic purposes yet, can be useful for detection of comorbidities and evaluating the risk of post-stroke treatment complications and secondary conditions (Jickling & Sharp, 2011). Gait and mobility biomarkers, offering valuable information about patients' independence and quality of life, can be used for estimating fall risk, evaluating the effectiveness of rehabilitation programs and detecting undesired behaviors (e.g., prolonged sitting).

Here, we aim to provide a comprehensive, up-to-date review of post-stroke brain imaging (mainly focusing on magnetic resonance imaging), blood and gait biomarkers with an emphasis on their complementarity and potential integration for improving stroke care pathways. In this review, we focus on (i) ischemic stroke, (caused by restricted or blocked blood flow) which constitutes 70% of all stroke incidents (Lindsay et al., 2019), and (ii) post-stroke gait and balance disorders which affects almost 80% of patients (Lawrence et al., 2001).

We used PubMed to search through the scientific literature for English, full-text, peer-reviewed articles on ischemic stroke and three biomarker modalities. In recent years, there have been a couple of review papers discussing the progress for each modality separately, however, to the best of our knowledge, this is the first one focusing on all three of these modalities and their integration. Throughout the text, the term 'stroke' is used interchangeably with 'ischemic stroke' unless stated otherwise.

The organization of the paper is as follows: First section, describes stroke pathogenesis and timeline, then

points out key challenges within stroke care pathways including negative impact caused by the Coronavirus disease 2019 (COVID-19) pandemic. The following three sections summarize recent findings in biomarker discovery research: magnetic resonance imaging, blood and gait biomarkers. Next section advocates for integrative thinking and its potential use for future applications, and the last section concludes the paper with a short summary. Please note that this review mainly focuses on three biomarker modalities (magnetic resonance imaging, blood, and gait biomarkers). For more information about other biomarkers as well as gait rehabilitation methods, the reader is referred to excellent review papers elsewhere (Berger et al., 2019; Potter et al., 2019; Teasell et al., 2003).

2 | ISCHEMIC STROKE

2.1 | Pathogenesis

In ischemic stroke, brain cells die because of restricted blood flow which is caused by blood clots (Kuriakose & Xiao, 2020). The extent of brain damage largely depends on the location of the stroke and the duration of restricted blood flow. During stroke, the oxygen and glucose supply to the affected brain tissue (lesion) is disrupted exhausting adenosine triphosphate (ATP) stores within minutes. Without ATP, ion homeostasis cannot be restored, thus, causing inflammation and neuronal death (Sontheimer, 2015). The area with irreversible neuronal loss is called the ischemic core. Neurons around the ischemic core are hypoperfused, receiving limited blood supply, and they are under the risk of dying. This hypoperfused region is called the ischemic penumbra (S. Lindsay, 1980) and salvaging this tissue by reperfusion is one of main goals of early stroke treatment.

2.2 | Treatment and care

The timeline of standard stroke care can be divided into three general categories: (i) hospitalization to treat acute stroke and stabilize patients, (ii) rehabilitation to promote recovery and (e.g., physiotherapy, occupational therapy and speech therapy) and (iii) discharge when patients return to daily life with periodic clinical follow-ups. The stage of a stroke is generally defined according to the onset time after first symptoms appear; early hyperacute (0–6 h), late hyperacute (6–24 h), acute (24 h to 7 days), subacute (1–3 weeks) and chronic (more than 3 weeks).

During hyperacute stage, the main objective is to remove the blood clot through recanalization and reperfusion which can reverse the neurological symptoms by reducing the ischemic lesion, especially in cases with extensive penumbra. Intravenous thrombolysis (i.e., clot-busting) via tissue plasminogen activator or endovascular mechanical thrombectomy were both proven to provide reperfusion. However, not all patients are eligible for reperfusion therapies due to high risk of complications including haemorrhage (bleeding) and edema (swelling), both of which can result in neurological decline. In particular, patients with stroke onset more than 4.5 to 6 h, patients with larger ischemic core and patients with comorbidities are considered high-risk for reperfusion therapies (Herpich et al., 2020; Rabinstein, 2020). Therefore, establishing an accurate time for stroke onset, defining ischemic core and penumbra, and screening for comorbidities are vital prior to acute stroke treatment.

Once patients are stabilized, during acute and subacute stages, clinical assessments are performed to assess the degree of motor and cognitive impairments and their implications on functional independence. These evaluations are based on observer-rated scales that have standardized tests and outcome measures. One of the most utilized tools for the assessment of stroke severity is National Institutes of Health Stroke Scale (NIHSS). The Canadian Neurological Scale (CNS) can be used to provide a more focused assessment of neurological function. In the post-acute phase and for the evaluation of disabilities clinicians widely utilize modified Rankin Scale (mRS) to measure patient independence post-stroke. Another questionnaire, Functional Independence Measure (FIM), evaluates both motor and cognitive skills. Similarly, The Stroke Specific Quality of Life Scale (SS-QOL) questionnaire and The Barthel Index (BI) are used to evaluate functional independence in the activities of daily life. Additionally, Mini-Mental State Examination (MMSE) can be used to assess cognitive function and mental state. Montreal Cognitive Assessment (MoCA) scale can be used to evaluate cognitive function. Some examples of how these tests are utilized for research are listed in Table 1.

Six months after stroke, walking and balance disorders persist in more than 20% of patients (Wade & Hewer, 1987). Although the cause of these disorders is the brain injury, it is difficult to predict the exact functional outcome from the lesion (location, shape, size etc.) (Beyaert et al., 2015). This is due to the fact that multiple overlapping regions in the brain play roles in controlling gait and balance. In healthy subjects, voluntary movement commands are generated in the motor cortex and sent to the brain stem and spinal cord. Automatic movement commands such as those controlling fight-or-flight behaviors are generated in the limbic system and sent to the brain stem. Thalamocortical projections of the cerebellum regulate cognitive gait control, whereas brain

TABLE 1 Summary of blood biomarker candidates for the evaluation of clinical outcome post-stroke. BI, Barthel Index; CNS, Canadian Neurological Scale; ELISA, Enzyme-linked immunosorbent assay; FIM, Functional Independence Measure; HPLC, High-performance liquid chromatography; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SS-QOL, Stroke Specific Quality of Life Scale.

Blood biomarker	# of healthy controls	# of patients	Stroke Stage	Sample Type	Technique	Clinical assessment[a]	Results	Source
Amyloid-beta	30	30	Acute	Serum	ELISA	MoCA, MMSE	- Amyloid-beta levels in stroke patients were higher than in controls. - Increased amyloid-beta levels were correlated with cognitive decline in stroke patients.	(H. G. Chen et al., 2018)
Brain-derived neurotrophic factor	513	491	Acute	Serum	ELISA	mRS	- Decreased BDNF is seen in stroke patients compared to controls. - Poor outcome group had decreased BDNF compared to the good outcome group.	(Stanne et al., 2016)
Brain-derived neurotrophic factor	17	17	Chronic	Serum	ELISA	SS-QOL	- Chronic stroke patients have lower serum BDNF concentrations than healthy patients. - There was no correlation between BDNF levels and SS-QOL scores.	(Santos et al., 2016)
Brain-derived neurotrophic factor	30	30	Acute	Serum	ELISA	MoCA, MMSE	- Serum BDNF levels were significantly decreased in stroke patients. - Decreased BDNF was associated with cognitive impairment in stroke patients.	(H. G. Chen et al., 2018)
C-reactive protein	-	120	Acute	Serum	Immunoturbidimetric method	mRS, NIHSS, MMSE	Higher CRP was associated with stroke severity on admission, worse functional and cognitive outcome.	(Irimie et al., 2018)

TABLE 1 (Continued)

Blood biomarker	# of healthy controls	# of patients	Stroke Stage	Sample Type	Technique	Clinical assessment[a]	Results	Source
CD40L	28	54	Acute	Plasma	Flow cytometry	BI, mRS	- Good outcome: BI > 60. Poor outcome: BI < 60, or, mRS > 3, or, recurrent stroke, or, death. - CD40L levels of patients in the poor outcome group were significantly higher compared to the good outcome group.	(Tsai et al., 2009)
D-dimer	-	130	Acute, subacute	Not specified	Not specified	mRS	- Increased D-dimer levels were associated with worse outcomes.	(Sato et al., 2020)
Endostatin	-	613	Acute	Plasma	ELISA	NIHSS, MoCA	- Increased levels of endostatin were associated with an increased risk of post-stroke cognitive impairment.	(Qian et al., 2020)
Fibrinogen	-	266	Acute, subacute	Plasma	Modified Clauss method	mRS	- Sustained increase of fibrinogen post-stroke is associated with unfavorable outcome at 1-month follow-up. - Low fibrinogen level on day 1 was associated with increased fibrinogen levels in the following days, and with unfavorable outcome.	(Swarowska et al., 2014)
Glutamate	43	128	Acute	Plasma	Cation-exchange chromatography	CNS	Increased glutamate is correlated with higher neurological deficits compared to controls.	(Castillo et al., 1996)

(Continues)

TABLE 1 (Continued)

Blood biomarker	# of healthy controls	# of patients	Stroke Stage	Sample Type	Technique	Clinical assessment[a]	Results	Source
Glutamate	100	242	Acute	Plasma	HPLC	mRS, NIHSS	- Glutamate levels were higher in stroke patients as compared to controls - Glutamate levels were higher in patients with unfavorable functional outcome compared with patients with a favorable outcome	(Meng et al., 2015)
Glycine	43	128	Acute	Cerebrospinal fluid	Cation-exchange chromatography	CNS	- Increased glycine is correlated with higher neurological deficit compared to controls.	(Castillo et al., 1996)
Interleukin-6	-	26	Acute	Plasma	ELISA	mRS	- High peak plasma Interleukin-6 concentrations correlated with worse outcome at 3 months.	(Smith et al., 2004)
Neurofilament light chain	30	144	Subacute	Serum	Single-molecule array assay	FIM cognitive scores	- Serum NfL levels were 9-fold higher in patients compared to healthy controls. - Serum neurofilament light chain levels can predict cognitive outcome at discharge. - Nfl levels combined with MRI biomarkers show improved predictive value for cognition post-stroke.	(Peng et al., 2021)

TABLE 1 (Continued)

Blood biomarker	# of healthy controls	# of patients	Stroke Stage	Sample Type	Technique	Clinical assessment[a]	Results	Source
Neuropeptide Y	-	164 (78 with post-ischemic stroke epilepsy)	Acute	Serum	ELISA	NIHSS	- High NIHSS scores were associated with an increased risk of post-ischemic stroke epilepsy. - Increased neuropeptide Y was associated with decreased risk of post-ischemic stroke epilepsy.	(Wang, Wang, et al., 2021)
Occludin	-	171	Acute	Serum	ELISA	NIHSS	- Higher serum occludin levels are associated with worse prognosis and increased risk of hemorrhagic transformation.	(W. Li et al., 2020)
ST2	-	646	Acute	Plasma	ELISA	mRS	- Increased levels of plasma ST2 levels are associated with worse functional outcome and an increased risk of hemorrhagic transformation.	(Wolcott et al., 2017)
Thrombin-antithrombin complex	90	236	Acute	Plasma	Chemiluminescence enzyme immunoassay	NIHSS, mRS	- Levels of thrombin-antithrombin complex were higher in stroke patients compared to healthy controls. - Increased thrombin-antithrombin complex levels were good predictors for severe stroke and worse outcome at 1-month follow-up.	(Ye et al., 2020)

(Continues)

TABLE 1 (Continued)

Blood biomarker	# of healthy controls	# of patients	Stroke Stage	Sample Type	Technique	Clinical assessment[a]	Results	Source
Trimethylamine-N-oxide	100	256 (86 with post-stroke cognitive impairment)	Acute	Plasma	HPLC	NIHSS, MMSE	- Post-stroke cognitive impairment risk was associated with stroke severity and increased plasma trimethylamine-N-oxide levels.	(Zhu et al., 2020)
Uric acid	-	274 (188 with post-stroke cognitive impairment)	Acute	Serum	Not specified	MoCA	- Serum uric acid levels were significantly higher in patients with post-stroke cognitive impairment compared to patients with normal cognition.	(J. Sun, Lv, et al., 2020)
von Willebrand factor	-	108	Acute	Plasma	Immunoturbidimetric method	NIHSS	- Increased levels of von Willebrand factor were associated with worse clinical outcome.	(Menih et al., 2017)
White blood cell count & blood glucose	-	3124	Acute	Not specified	Automated cell counter, automatic biochemical analyzer	mRS	- Patients with normal white blood cell counts and blood glucose levels had better functional outcomes at discharge.	(You et al., 2019)

[a]See Section 1 for a brief description of clinical assessment tests.

stem projections regulate automatic gait control (Takakusaki, 2017). Following a stroke, hemiparesis (i.e., weakness of one side of the body) or hemiplegia (i.e., paralysis of one side of the body) may occur due to disruption of descending neurons. Strokes affecting the middle cerebral artery can result in problems with gait, speech or vision. In cases where sensory loss accompanies motor impairments, internal capsule is expected to be affected. On the other hand, strokes affecting anterior cerebral artery can cause weakness in the contralateral limbs (Paciaroni et al., 2012). The regions responsible for automatic control of gait i.e., brainstem and cerebellum are intact in most cases of stroke.

2.3 | Challenges in stroke care pathways

The symptoms of stroke vary greatly making it difficult to diagnose, treat, monitor, study and rehabilitate effectively and rapidly. In the clinics, differentiating various stroke subtypes and stroke mimicking cases (such as migraines and epilepsy) is extremely important for early and accurate stroke care (Makris et al., 2018). Offering patients individualized care is also key to achieve optimal treatment and recovery (Simpkins et al., 2020). Following diagnosis and treatment, monitoring patients effectively to estimate risk of falls, second strokes and other highly prevalent secondary conditions is essential, especially within the first-month post-stroke (Baylor et al., 2014; Vodencarevic et al., 2022). Also, the prediction of short-term and long-term functional outcomes is extremely valuable for the patients, their families, and medical professionals and allowing for better planning and resource allocation (König et al., 2008). Remote monitoring using telemedicine and wearable and home sensors can provide real-time, real-world data informing rehabilitation outcomes, quality of life and independence of patients (Eng & Pastva, 2022). However, the implementation of technology-enabled remote monitoring approaches is still in progress due to several bottlenecks such as technology readiness levels, infrastructure problems, ergonomics, accessibility and safety issues, as well as technology literacy and access of both the patient and the medical professionals to said technology (Merid et al., 2021). Nonetheless, accessible, easy-to-use, and affordable remote monitoring technologies are being investigated widely, expecting unique insights into the clinical decision-making processes (De Simone et al., 2019; D. Y. Kim et al., 2020).

To advance stroke research, there has been efforts to develop new techniques for objective and quantitative patient assessment and monitoring, treating adverse clinical outcomes, and demonstrating the benefits of cost-effective therapy and rehabilitation techniques. The outcome of these investigations should inform efforts aiming to improve stroke risk factor education, and lifestyle modifications for high risk groups are becoming increasingly important given the narrow of time window for effective treatment (Grossman & Broderick, 2013). One factor that is established to be critical is defining exactly when a stroke occurred, especially for patients who had a stroke during their sleep (L. M. Allen et al., 2012). Other aspects to consider are stroke care pathways in rural areas, low and middle-income countries where access to effective treatment may be comparatively restricted compared to more urban areas and high-income countries ascribed to the limited resources, the inadequacy of available medical doctors and dedicated stroke centers (Pandian et al., 2020; S. Wu et al., 2019). Moreover, the shortage of stroke radiologists and neurologists makes quick and reliable diagnosis a major challenge currently and in the near future (Wiborg & Widder, 2003).

COVID-19 created significant hardships and challenges to clinics and patients in almost every aspect of stroke care from diagnosis to management, and long-term rehabilitation. While there is evidence that COVID-19 might have increased the ischemic stroke risk by 3.6 times (Katsanos et al., 2021), the number of hospital admissions due to ischemic stroke decreased by 15% during the first 3 months of COVID-19 (Nogueira et al., 2021). This is thought to be a result of the unwillingness of patients to go to a hospital due to the fear of contracting the virus (Zhao et al., 2020). Due to extremely time-sensitive nature of ischemic strokes, the value of remote monitoring and telemedicine has become clear to medical professionals. Remote technologies utilizing accessible tools like smartphones can be helpful in monitoring recovery of the patients more effectively and avoiding complications by enabling expert medical attention to patients (Iodice et al., 2021; Sher et al., 2022). Incorporating objective and quantitative biomarkers for remote monitoring systems will introduce immense medical information for medical professionals.

Biomarkers obtained from imaging, biochemical and biomechanical measurements combined with clinical assessments can allow for objective and reproducible evaluation and monitoring of the patient. Yet, there is still no established integrative approach to specific biomarkers that is commonly utilized in the clinics.

3 | MAGNETIC RESONANCE IMAGING

Neuroimaging plays a critical role in the diagnosis of stroke by ruling out other neurological conditions that

mimic stroke-like symptoms (migraine headache, hypoglycemia, seizures), differentiating acute ischemic stroke from hemorrhagic stroke, and estimating the affected area, helping selection of optimal treatment and prediction of the outcome (Kamalian & Lev, 2019). The phrase 'time is brain' in stroke management emphasizes the irretrievable loss of brain tissues as the stroke progress and consequently, the outcome is time-dependent (Saver, 2006). With the advancements in radiology, multiple imaging modalities are available for the detection and management of stroke. Evaluations of a series of examinations gathered from a combination of available imaging modalities may support clinical decision-making. A non-contrast computerized tomography (CT) examination is frequently employed and is capable of rapidly excluding haemorrhage as a cause of the stroke (Vymazal et al., 2012). On the other hand, magnetic resonance imaging (MRI) is considered an outstanding modality and is increasingly used in stroke imaging (Kleindorfer et al., 2015). When CT and MRI were compared in terms of the diagnostic sensitivity for ischemic stroke, pooled sensitivity estimates from seven studies were found to be .39 for CT and .99 for diffusion-weighted imaging (DWI) (Brazzelli et al., 2009). MRI detects hyperacute ischemic stroke (González et al., 1999) and microhemorrhages with high sensitivity (Fiebach et al., 2004), visualizes vascular variations and lesions (Amoli & Turski, 1999) and provides non-invasive quantification of tissue-level perfusion (Verclytte et al., 2017). Moreover, recently developed vessel wall MRI and 4D MR angiography (MRA) can clarify the characteristics of stroke lesions and improve the management of ischemic stroke (Kilburg et al., 2017). Thus, MRI alone gathers a significant amount of information about the characterization of stroke type and timing of the stroke.

In the following sections we summarize the MRI biomarkers for stroke which have the potential to assess the characteristics of stroke lesions non-invasively and therefore employed for diagnosis, prognosis, and treatment guidance in clinics. While technical details of different MRI modalities are outside the scope of the present review, we mainly focus on (i) the structural changes in the brain both at micro and macro levels, (ii) the dating of stroke, (iii) the diagnosis and the prediction of secondary conditions and (iv) the prediction of clinical outcome.

3.1 | Identification of structural changes after stroke

MRI assessments identify the complete necrotic tissue (ischemic core) and salvageable brain tissue (penumbra) for planning appropriate therapeutic interventions. Penumbra is a hypoperfused region but still viable if adequate reperfusion occurs. Without reperfusion therapies, the penumbra would become necrotic and be part of the ischemic core by the propagation of infarction. To differentiate penumbra from ischemic core, several multiparametric MRI approaches have been proposed. Perfusion-weighted imaging (PWI) DWI mismatch (subtraction of DWI from PWI) is known as a simple clinical tool that separates the region of reduced cerebral blood flow (CBF) from reduced cellular depolarization (Heiss, 2011; Schlaug et al., 1999). However, it has been shown that PWI-DWI mismatch overestimates the penumbra by including the benign oligemia (CBF below normal range but tissue not at risk), and at the early stage of infarction (within 2–3 h), the diffusion lesions may include both reversible and irreversible tissues (Kidwell et al., 2003). Additionally, PWI needs gadolinium-based contrast agent delivery that is associated with rare and fatal conditions found in patients with acute kidney injury or stage 4 or 5 chronic kidney disease (Agarwal et al., 2008). Alternatively, MR-based noninvasive and free of contrast agent administration stroke imaging protocols are being developed including susceptibility-weighted imaging (SWI) and arterial spin labeling (ASL). SWI-DWI mismatch (Bhattacharjee et al., 2021; Luo et al., 2015) and ASL-DWI mismatch (Bhattacharjee et al., 2021; Huang et al., 2013; Zaharchuk et al., 2012) have been used as a marker for evaluating penumbra. Advanced methods such as pH-weighted and diffusion-kurtosis MRI can better detect the edges of the ischemic core, penumbra, and benign oligemia to prompt more effective reperfusion therapies (Cheung et al., 2021; Sun et al., 2007). MRA and DWI mismatch pattern were proposed as an alternative to PWI-DWI mismatch to select patients for reperfusion in a 3–6 h period (Lansberg et al., 2008). Manual segmentation of the ischemic regions usually suffers from interobserver variability. Additionally, the process is time-consuming for a clinician since the combination of MRI modalities has been used to determine imaging biomarkers of stroke evolution. The automated methods employ recent image processing and deep learning architectures for the segmentation of core and penumbra using different MRI modalities (Gupta et al., 2019; Sathish et al., 2019). Recently, Lee et al. proposed an automated and real-time algorithm to compute volumes of ischemic core and ischemic penumbra in 15 acute ischemic stroke patients (Lee, Jung, et al., 2020). The ischemic core was defined on DWI using adaptive thresholding and Tmax > 6 s was segmented as the penumbra. Over the years, a variety of methods for quantification of ischemic penumbra and core have been proposed but more integrative multimodal MRI techniques would better assist the therapeutic decision-making.

It is well established that signal abnormalities observed in DWI are the best predictor of ischemic core and are easily observable at the earliest stage of ischemia (Fung et al., 2011). Larger infarct volumes are associated with poor prognosis and increased risk of intracranial haemorrhage (Olivot et al., 2013; Šaňák et al., 2006). Multiparametric MRI including PWI and DWI are used for criteria of 'malignant profile', which is based on lesion volume and associated with severe intracranial haemorrhage and poor outcome (Albers et al., 2006). The criteria are defined as larger DWI or PWI lesion (>100 ml) or increased time-to-maximum (Tmax) delay (>8 seconds). Additionally, Tmax>6 seconds is commonly identified as irreversibly injured ischemic tissue if reperfusion does not occur. Final lesion volume can be approximated at 30 days after stroke since lesion volumes on 30 and 90 days are highly correlated. Even though lesion volume at 30 days is 5% larger than at 90 days, this difference was found to be in the range of inter-reader variability (Gaudinski et al., 2008). Lesion volume is the most utilized MRI biomarker for stroke patients. However, due to the heterogeneity of stroke symptoms, it falls short of becoming a comprehensive biomarker, especially for motor impairments (Schiemanck et al., 2005). Also, recently deep learning architectures like U-net have been employed to estimate subacute infarct volume without reperfusion information using PWI and DWI modalities (Yu et al., 2020).

In the ischemic brain, both grey and white matter is affected. Even though the role of white matter injury (WMI) in ischemic brain is not entirely clear, WMI is being investigated as either a stroke predictor or as a result of a stroke (Wang et al., 2016). Microstructural changes like white matter hyperintensities and grey matter integrity deformations following stroke have been evaluated with diffusion tensor imaging via measuring fractional anisotropy and diffusivity measures. Changes in these features have been were associated with cognitive impairments and functional outcome after stroke (Kliper et al., 2014; Sagnier et al., 2020, 2022).

3.2 | Dating of stroke

Early hyperacute infarcts are usually conspicuously visible on apparent diffusion coefficient (ADC) and DWI as hypointense and hyperintense regions respectively. In T1-weighted (T1W) and T2-weighted (T2W) MR images stroke is mostly invisible in the acute stage. After at least 6–8 h, the infarct appears as a hyperintense region in T2W MRI and fluid-attenuated inverse recovery (FLAIR) MR images. In chronic stages, T1W MRI shows low signal intensity, while T2W MRI shows high signal intensity and DWI shows variable intensities (L. M. Allen et al., 2012).

When considered together of ADC maps, DWI, and T2W images can be used to identify acute lesions from subacute or chronic stages. When the ischemic region appears hyperintense on both DWI and ADC map and hypointense on the exponential image, this phenomenon is called 'T2 shine-through' and may be observed in late subacute or chronic ischemic regions (Lin & Liebeskind, 2016). Around subacute stages, infarcts may become nearly invisible on some MRI modalities and this is known as fogging effect (De Cocker et al., 2017). It may be observed on T2W images around 50% of the patients are in the subacute stage (O'Brien et al., 2004). When combined, signal intensity characteristics on DWI, ADC and FLAIR images can give information about infarct lesion age. For instance, hyperintensity on DWI and no signal enhancement on FLAIR could reflect that infarct occurred less than the time window of 3 h (early hyperacute stage) (Aoki et al., 2010; Thomalla et al., 2009). On the other hand, hyperintense FLAIR images characterize the subacute infarctions because of existing vasogenic edema (Wouters et al., 2016). In a retrospective study, quantification of DWI and FLAIR signals of 194 stroke patients provided a helpful tool for stroke lesion age (Emeriau et al., 2016). Lee et al. showed that applying machine learning algorithms to DWI and FLAIR images could identify stroke lesions within 4.5-h window for acute thrombolysis even more sensitive than human readings (Lee, Lee, et al., 2020).

3.3 | Secondary conditions following stroke and stroke recurrence

It has been shown that cerebral microbleeds are indicators of early hemorrhagic transformations (Kidwell et al., 2002; Nighoghossian et al., 2002). Hemorrhagic transformation is the leakage of the blood from the vessels following ischemic stroke and it is seen in 10%–40% of people with ischemic stroke (Lu et al., 2018). Kim et al. reported that silent microbleeds that occurred at the ischemic stroke site showed hemorrhagic transformation (Kim & Lee, 2007). The cerebral microbleeds can be detected using T2*-weighted (T2*W), or gradient-recalled echo (GRE) sequence, which is sensitive to susceptibility effects of iron atoms (Kidwell, 2004; Makkat et al., 2002). On the other hand, some recent studies indicated that SWI provided more reliable and sensitive intracranial microbleed detection compared to GRE sequence and T2*W MRI via increased contrast and resolution (Cheng et al., 2013; Wycliffe et al., 2004).

Evaluation of associations between imaging markers and stroke recurrence could be critical because 12.8% of first onset stroke patients experienced a second stroke within the next year (Buenaflor, 2017). Therefore, surveillance of stroke patients and preventive strategies are critical for improving prognosis. Several studies have shown that multiplicity of stroke lesions and larger infarct volumes were associated with stroke recurrence (Nezu et al., 2016; Pan, Meng, et al., 2017). Additionally, a prospective study investigated the association between lesion locations and stroke recurrence (Yan et al., 2020). Their results indicated that first-ever stroke patients were prone to higher recurrence than those with pre-existing right-side lesions.

Transient ischemic attack (TIA) is a transient period of focal cerebral or retinal dysfunction. More than 10% of recurrent stroke lesions occur after a TIA and it has been reported that about 80% of stroke recurrence can be prevented with appropriate treatment strategies (Coutts, 2017). Thus, identifying TIA-associated lesions from chronic stroke lesions is critical, since a small but significant percentage of them will have a stroke within the following 90 days (Giles & Rothwell, 2007) with the highest risk at the first 24 h (Chandratheva et al., 2009). Outstanding features of DWI enable differentiation between TIA and chronic lesions (Ay et al., 2002; Kidwell et al., 1999; Winbeck et al., 2004). However, TIA can be invisible on DWI due to the smaller duration of the symptoms. PWI can increase the efficiency of DWI in the detection of TIA by providing objective focal perfusion abnormality (Lee, Nah, et al., 2017). An automated identification of TIA lesions study showed that perfusion TMax (the time when the residue function reaches its maximum) can reveal TIA lesions that are subtle on DWI (Kleinman et al., 2012).

3.4 | Prediction of clinical outcome using radiomics

A variety of mathematical approaches including thresholding (Wu et al., 2001), regression (Rajashekar et al., 2021), machine learning (Benzakoun et al., 2021) and deep learning (Pinto et al., 2018) methods are commonly utilized to predict clinical outcome using MRI. Radiomics analysis extracts a large set of data from images that can be examined by some of these methodologies to deduce clinically relevant information. Radiomics converts medical images into high dimensional mineable data (Gillies et al., 2016), by extracting the high-throughput quantitative imaging features including first-order intensity statistics, shape, and texture from standard imaging modalities (van Timmeren et al., 2020). Although radiomics was initially proposed for oncology studies (Aerts et al., 2014), it has the potential to be applied to various diseases (Gillies et al., 2016). As radiomics can objectively reflect the pathophysiologic characteristics of a lesion, it has been successfully employed in stroke studies. Recent studies showed promising results by using radiomics features for the determination of stroke onset time which has great importance in guiding stroke treatment (Regenhardt et al., 2022; Zhang et al., 2022). In other studies, radiomics features were extracted from FLAIR, T1W, T2W, and ADC maps. It has been shown that radiomics is can identify the presence of stroke lesions in post-acute stroke patients (Ortiz-Ramón et al., 2019) and penumbra in 241 acute ischemic stroke patients (Zhang, Zhu, et al., 2020). Moreover, several studies have investigated the potential of radiomics as a clinical biomarker for predicting the prognosis of stroke patients. It has been found that radiomics features extracted from ADC, FLAIR, and DWI images are associated with worse clinical outcomes (mRS > 2) in acute ischemic stroke patients (Quan et al., 2021; Şahin et al., 2021; Wang et al., 2020; Wang, Sun, et al., 2021). Another study found that penumbra-based radiomics could predict clinical outcomes of acute ischemic stroke patients for thrombolysis (Tang et al., 2020).

4 | BLOOD BIOMARKERS

Blood biomarkers can be used for a variety of applications following stroke, including diagnosis and identification of stroke subtypes, predicting clinical outcomes, selecting personalized treatments for patients, and monitoring recovery. However, as the search for finding a specific blood biomarker continues, it is becoming clearer that a single marker will probably not be adequate in capturing the heterogeneity of stroke and its systemic effects. Hence, integrating various techniques and approaches will be necessary to define a comprehensive and global biomarker system for stroke. Some of the promising cutting-edge blood biomarker candidates for predicting clinical outcomes post-ischemic stroke are listed in Table 1.

4.1 | Outcome and severity prediction following stroke

Acute stroke causes systemic inflammatory response as evidenced by the increased body and brain temperature and inflammatory markers in peripheral blood such as White Blood Cell count (WBC), complete blood count (Emsley, 2003), electrolyte levels (El-Fawal et al., 2019), von Willebrand factor (Hanson et al., 2011), C-reactive

protein (CRP), tumour necrosis factor-alpha (TNF-alpha) (Ferrarese et al., 1999), homocysteine (Shi et al., 2018), catalase (Milanlioglu et al., 2016) and superoxide dismutase (Milanlioglu et al., 2016). Post-stroke inflammation takes place due to the necrotic tissue in the brain post-stroke, and the larger the lesion size, the higher the inflammatory response (Audebert et al., 2004). Fibrinogen is an acute-phase protein whose concentration increase as a response to inflammation. Sustained increase in fibrinogen levels over 2 weeks were found to be associated with worse functional outcome at 1-month post-stroke (Swarowska et al., 2014). In a small study, peak levels of interleukin-6 (IL-6) post-stroke were significantly associated with CT infarct volume and mRS at 3 months (Smith et al., 2004). Interleukin-17 was also found to be an important dose-dependent contributor to neuronal injury following oxygen deprivation (Swardfager et al., 2013).

Von Willebrand factor is an important glycoprotein for coagulation. It was found that increased levels of von Willebrand factor are associated with increased stroke severity as measured by NIHSS and worse functional outcome as measured by mRS scores (Menih et al., 2017). Levels of platelet activation markers CD62P, CD63 and CD40L which are cluster of differentiation proteins, were higher in patients with stroke compared to controls and increased levels of CD40L were associated with worse functional outcome (Tsai et al., 2009). Thrombin-antithrombin complex was found to be an independent predictor of more severe stroke and poor prognosis at 1-month post-stroke (Ye et al., 2020). D-dimer is a protein fragment produced by activation of coagulation and fibrinolysis. An increased level of D-dimer on admission was associated with worse functional outcome at 3-month follow-up (Sato et al., 2020).

Increased CRP levels post-stroke are related to increased stroke severity (Irimie et al., 2018) and increased risk of mortality (Yu et al., 2019) post-stroke. However, the causal effect of the CRP levels on the risk of stroke is not exactly clear. Previously, elevated CRP levels were thought to be a risk factor for ischemic stroke (Nambi et al., 2009). In a 2019 Mendelian randomization study was unable to provide evidence for such an effect and concluded that increased levels of CRP are not related to increased risk of stroke (Zhang, Wang, et al., 2020).

Glutamate excitotoxicity is observed following stroke, as evidenced by up to 80 times more intercellular glutamate in the ischemic core (Hillered et al., 1989). This increase is also evident in blood and cerebrospinal fluid of humans post-stroke (Castillo et al., 1996). Increased plasma levels of glutamate were found to be an accurate predictor of worse functional outcome as evaluated by mRS scores (Meng et al., 2015). The targeting of small metabolites as biomarkers, highlights the potential of metabolomic approaches to investigate wide-ranging changes in the concentrations of small molecules post-stroke. Various analytical techniques allow for better differentiation and quantification of metabolites in bodily fluids which may be good candidates for diagnosing and monitoring stroke. A proton nuclear magnetic resonance metabolomics study in rats showed that the levels of 23 metabolites are altered significantly including amino acids and neurometabolites such as N-acetyl aspartate, glutamate, glutamine, myo-inositol, and adenosine diphosphate (S. Gupta et al., 2020).

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor, synthesized in its precursor form, proBDNF, in endoplasmic reticulum. The cleavage of the prodomain from the mature BDNF takes place in the Golgi apparatus. Mature BDNF acts on tropomyosin receptor kinase B (TrkB) receptor to modulate cell survival, differentiation, and synaptic function. Uncleaved proBDNF, on the other hand, acts on p75 receptors which can initiate apoptosis. This can result in retracted growth cones and long-term depression (Hempstead, 2015). Numerous studies are showing decreased acute (Stanne et al., 2016) and chronic (Santos et al., 2016) levels of BDNF in the peripheral blood post-stroke may indicate worse functional outcome.

4.2 | Predicting secondary conditions

Pathological mechanisms for hemorrhagic transformation are mostly attributed to blood–brain barrier (BBB) disruption. There are some predictors for spontaneous hemorrhagic transformation including increased levels of metalloproteinase-9 (MMP-9) (Krishnamoorthy et al., 2021; Turner & Sharp, 2016) which causes BBB disruption following ischemia, low platelet count (Wang et al., 2019) and hyperglycemia (Zhang et al., 2018). Suppression of tumorigenicity 2 (ST2), which is a protein belonging to toll-like receptor superfamily can alter inflammatory signalling. Soluble ST2 in the plasma of stroke patients up to 48 h post-stroke was collected and analysed to investigate whether this receptor can predict clinical outcome and hemorrhagic transformation (Wolcott et al., 2017). It was concluded that increased soluble ST2 can be used as a predictor for worse clinical outcome and hemorrhagic transformation even after adjusting for confounding factors. Occludin proteins can be found on tight junctions in the BBB. In the animal models of stroke, these proteins are cleaved from cerebral microvessels and released into the blood circulation (Pan, Yu, et al., 2017). Based on this finding, occludin levels of stroke patients within 72 h of stroke onset were investigated. It was found that higher serum occludin levels

predicted poor prognosis and hemorrhagic transformation (Li et al., 2020).

Post-stroke epilepsy is seen in 2–20% of patients with stroke (Abraira et al., 2020). Following an ischemic stroke, hypoxia, hypoperfusion, glutamate excitotoxicity and BBB disruption may lead to seizures, with cortical lesions carrying a higher risk (Tanaka & Ihara, 2017). Most common post-stroke epilepsy predictors are related to ischemic lesion size and location (Sarecka-Hujar & Kopyta, 2018). In more recent studies, researchers are trying to pinpoint some blood biomarkers to better understand and diagnose post-stroke seizures and epilepsy. In a study including 14 blood biomarkers and 895 acute stroke patients, decreased S100B and heat shock 70 kDa protein-8 (Hsc70) and increased endostatin levels were found to be associated with increased risk of developing post-stroke epilepsy. Hsc70 is involved in the synthesis of proteins important in BBB structure and functioning, whereas endostatin acts as an angiogenesis inhibitor that may damage cellular repair at higher levels (Abraira et al., 2020). Neuropeptide Y is an important antiepileptic factor that is being researched as a therapeutic agent for epilepsy (Wickham et al., 2019). Decreased neuropeptide Y levels were also predictive of post-stroke epilepsy in 164 patients with acute ischemic stroke whereas there was no correlation between hemorrhagic transformation and the levels of neuropeptide Y (Wang, Wang, et al., 2021).

Post-stroke cognitive impairment is another complication that can be experienced following stroke. 64% of people post-stroke suffer from some type of cognitive impairment including dementia, depression, and memory impairment (Jin et al., 2006). CRP was found to be an important predictor of long-term cognitive decline in a study of 5257 subjects (Zheng & Xie, 2018). Additionally, higher levels of CRP were associated with an increased risk of post-stroke depression (Yang et al., 2022). In a smaller study, lower serum BDNF levels, and higher serum amyloid-beta levels were indicative of increased cognitive impairment risk post-stroke (Chen et al., 2018). Increasing levels of plasma trimethylamine-N-oxide were also found to be correlated with the risk of cognitive impairment (Zhu et al., 2020). Increased plasma endostatin levels (Qian et al., 2020) and serum uric acid levels (J. Sun, Lv, et al., 2020) are also able to suggest an increased cognitive impairment.

5 | GAIT ANALYSIS

Gait is a poorly understood and complex process reinforced by various systems throughout the body. Strokes can result in impaired motor function and gait. This impairment occurs when the patient loses their normal function for executing daily activities (Frenkel-Toledo et al., 2021). Establishing specific regions and functions of the brain in terms of gait can lead to better understanding of gait impairments and offering diagnosis and treatment options to patients. Patients with stroke exhibit a wide array of gait impairments and recovery of normal gait is an important milestone in stroke recovery (Wilson et al., 2019).

5.1 | Gait in stroke

During the cyclic movement of gait, the two basic phases of stance and swing (with and without the foot in contact with the ground, respectively) follow each other. One gait cycle (i.e., one stride) describes the movement corresponding to one step with each foot, and in a healthy gait, there is a natural symmetry between the left and right sides (Vaughan et al., 1992). The hemiparetic gait after stroke is generally asymmetrical (Balasubramanian et al., 2007; Hsu et al., 2003) and affects stride and step lengths, and lateral foot placement (Chen et al., 2005; Nadeau et al., 2013). In spatiotemporal parameters this reflects as greater step length variability (Balasubramanian et al., 2009), implying reduced step length and rhythmicity, reduced preferred walking speed (Goldie et al., 1996; Perry et al., 1995), and related increase in gait cycle duration involving longer double-limb support and shorter single-limb support times (Chen et al., 2005; Wall & Turnbull, 1986).

The paretic stance phase shows some characteristic deviations in patients which play a role in the decreased gait speed. In the push-off phase for the patients, adverse effects on the joint kinematics include, for example, reduced paretic hip extension, knee flexion and ankle plantarflexion angles (Olney & Richards, 1996). Additionally, joint kinetics deteriorate, for example, due to a reduced calf muscle activity (Burridge et al., 2001), which yields a decreased plantarflexion moment and therefore a decreased push-off power (Kerrigan et al., 2001; Olney et al., 1994). These factors contribute to the slower walking speed of the patients compared to that of healthy individuals. The lower push-off power on the other hand also limits flexion angles during the early swing (Weerdesteyn et al., 2008). Consequently, the patients' kinematics in the swing phase show a decrease in knee flexion (Chen et al., 2005) and ankle dorsiflexion (Chen, 2003) angles, ascribable to a diminished activation of, for example, the tibialis anterior muscle (Otter et al., 2007). Overall, patients with hemiparesis are characterized by lower peak moments and powers (Allen et al., 2011; Nadeau et al., 2013), and higher energy expenditure (Kim & Eng, 2003) during gait. Such gait

impairments contribute to a worsening of the self-image perception (Hsu et al., 2003) and more importantly to a much-increased risk of falling and possible fractures (Ramnemark et al., 2000). Walking is a key activity for healthy daily living (Hamacher et al., 2011), yet ascribed to pathologies, it is also the most frequent cause of falls (Weerdesteyn et al., 2008). Following a stroke, 14% of the patients are estimated to experience a fall in the first month (Wagner et al., 2009), and the risk of falling increases up to 73% in the first 6 months, at least twice in about half of post-stroke patients (Forster & Young, 1995). Because stroke is associated with up to 4 times higher risk of hip and femur fractures than in the reference population (Pouwels, 2009; Ramnemark et al., 1998), quantifications of developing gait abnormalities and the risk of a fall are indicated as the key achievement that can support clinical stroke rehabilitation immensely.

5.2 | Brain lesions affecting gait patterns in stroke

Spasticity can be defined as the increase in the tonic stretch reflex (Lee et al., 2019). Following stroke, up to 42.6% of the patients may experience spasticity which can complicate daily activities for them (Wissel et al., 2010). Lee et al., have analysed brain lesions using voxel-based lesion-symptom mapping (VLSM) to investigate the effects of specific lesions in stroke patients and showed that spasticity developed in the first three months post-stroke (Lee et al., 2019; Lee, Kim, Hong, & Lim, 2017; Lee, Kim, Hong, Sul, et al., 2017). According to their results, superior corona radiate, internal capsule posterior limb, caudate nucleus, posterior corona radiate, thalamus, putamen and external capsule were all implicated in post-stroke spasticity.

Striatum was found to act as a pattern generator for gait. Posterolateral putamen is found to be associated with temporal gait symmetry. Walking speed is affected by chronic stroke lesions in corona radiata, caudate nucleus, and putamen (Lee et al., 2019). In an investigation of the relationship between lesion topography and motor impairment of affected lower limbs and gait, Frenkel-Toledo reported that lesions in the left and right hemispheres result in different impairments. When the damage is in the left hemisphere, lower limb impairment stems from damage to the posterior limb of the internal capsule (PLIC). When lesion is in the right hemisphere, lower limb impairment was affected by both the PLIC, and corona radiata, superior longitudinal fasciculus, and insula (Frenkel-Toledo et al., 2021).

Damage to the corticospinal tract due to stroke is known to be associated with motor impairment (Puig, 2010; Werring, 2000). A diffusion tensor imaging study of the brainstem and cervical spinal cord showed that the white matter integrity in corticospinal and bulbospinal tracts on the ipsilesional hemisphere was reduced in patients with stroke compared to controls (Karbasforoushan et al., 2019). Additionally, it was noted that reduced corticospinal tract integrity and increased medial reticulospinal tract integrity on the contralesional hemisphere correlated with increased motor impairment.

5.3 | Muscle level effects of stroke

For individuals with post-stroke spasticity, common clinical indicators are exaggerated stretch reflexes and muscle hypertonia, such that too much muscle tone causes difficulty in movement. They typically experience muscle weakness, enhanced intrinsic muscle stiffness and dynamic joint stiffness, sustained muscle contraction, increased antagonistic co-contraction, and reduced range of joint motion (Gracies, 2005a, 2005b; Mirbagheri et al., 2005, 2008). Understanding the post-lesion time-course of development of such muscle adaptations is highly relevant. Although the neuronal components of spasticity peak in 3 months, a permanent loss of range of joint motion has been reported to occur 3 to 6 weeks after stroke (Kuo & Hu, 2018). The prevalence during that period of post-stroke spasticity is around 25% (Lundström et al., 2010; Welmer et al., 2010; Wissel et al., 2010). Muscle structural and functional adaptations also in the subacute period are crucial. Post-stroke patients show decreased muscle mass, reduction of muscle cross-sectional area, and increased fat deposition in their paretic limbs compared with their nonparetic limbs (Carin-Levy, 2006; English et al., 2010; Ryan et al., 2002). Remarkably, those changes occur rapidly, and not only in the paretic limbs. In the first week after acute hemiplegic stroke, loss of quadriceps muscle weakness develops also in the unaffected limb (Harris et al., 2001). Muscle abnormalities occur due to a combination of denervation, disuse, remodeling, and spasticity effects, and structural adaptive changes in muscles have been observed to start as early as 4 h after cerebral infarction (Scherbakov & Doehner, 2011). Therefore, an objective and innovative monitoring of muscle structural and functional changes during the time course of their development can allow the design of new interventions to limit the progression of muscle pathologies, which can reflect positively on improving patients' functional capabilities.

5.4 | Clinical assessments and rehabilitation

To evaluate gait stability and risk of a fall, techniques such as the Berg Balance Scale score, Tinetti Performance Oriented Mobility Assessment, and the Timed Up and Go are popular, and gait speed measurement over a short distance is also utilized. Observational gait analysis typically done with the clinicians' naked eye, and occasionally supported by a video recording remains the most common approach to estimating the state of a patient's gait. This approach has its advantages, primarily the low cost, owing to a lack of need for specialized equipment and expertise. However, subjectivity is a problem (Toro et al., 2003), and more importantly, characterizing gait impairments by the observed movements of body segments rated against certain scales may easily fail to distinguish fallers from non-fallers, for example, in active elderly population (Laessoe et al., 2007), but certainly in post-stroke patients (Belgen et al., 2006; Harris et al., 2005; Hyndman et al., 2006). To eliminate such inadequacy in clinical diagnosis and to avoid incompetency in the selection of appropriate rehabilitation strategies, instrumented gait analysis is the gold standard. In practice, however, its usage gets restricted for obvious reasons including the need for a dedicated laboratory environment equipped with expensive devices and specifically trained staff (Cimolin & Galli, 2014; Nadeau et al., 2013). This indicates the need for reliable, but practical and affordable means of monitoring the patients' gait, particularly for an effective assessment of the risk of falling.

Various clinical instrumented assessment and rehabilitation techniques have been used in post-stroke patients. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that can be used in post-stroke rehabilitation as part of recovery focused on re-learning lost skills and regaining independence as much as possible. When this technique is applied superficially to the primary motor cortex, it stimulates the corticospinal pathway, generates a motor-evoked potential (MEP) at the contralateral limb, and elicits an MEP in muscles of the contralateral limb (Barker et al., 1985). The presence or absence of MEPs provides information about the functional integrity of the corticospinal tract (Stinear et al., 2006; Talelli et al., 2006). The amplitude and latency of the MEPs are considered as measures of the corticomotor system excitability.

In recent years, the use of TMS in stroke research has increased dramatically to treat motor function, depression, and aphasia in post-stroke patients. While single pulse TMS can predict the post-stroke recovery of motor function, repetitive TMS (rTMS) can be used to modify the excitability of the motor cortex to complement standard rehabilitation techniques (Stinear et al., 2015). Motor training, together with rTMS, optimizes plastic changes in the brain and strengthens the benefits of physical exercise (Yang et al., 2020). Following stroke, the high incidence of depression is known. Patients may benefit from rTMS because this procedure significantly improves the mood and depression symptoms (Hordacre et al., 2021).

Functional electrical stimulation (FES) is a non-invasive technique which is used to stimulate muscles during rehabilitation. The FES was shown to improve gait function when implemented along with a gait training protocol (Daly, 2011; Howlett et al., 2015). The FES can be combined with electromyography (EMG) to evaluate improvements in muscle activation and provide real time feedback to patients and clinicians. It has been previously shown that the EMG based acoustic feedback can aid in increasing peak ankle power, gait velocity and stride length in chronic stroke (Jonsdottir et al., 2010). A vibrotactile biofeedback system consisting of an insole, a plantar force acquisition unit, and a vibration feedback unit was also helpful in reducing the foot inversion on the affected side and knee flexion and hip abduction on the unaffected side (Ma et al., 2018). Electroencephalography (EEG) is used in clinics to record brain activity during various conditions, including epileptic seizures, but it has not yet been widely utilized for gait rehabilitation or clinical assessments following stroke (Vatinno et al., 2022). Few research studies show that gait kinematics and intent can be decoded from EEG signals, informing robot-assisted gait training (Contreras-Vidal et al., 2018). Extracorporeal shock wave therapy (ESWT) uses a probe to deliver high-energy shock waves to the selected tissue. A study investigating the effects of ESWT found that lower limb spasticity in subacute stroke patients was improved after ESWT, but the improvement was not long-lasting and diminished after four weeks (Moon, 2013). Lastly, virtual reality can provide a safe, controlled and fun environment for rehabilitation (Laver, 2017).

Home-based individual post-stroke rehabilitation techniques with portative devices gain popularity due to their low cost and ease of accessibility. These devices rely on novel balance and motion-sensing technologies and wearable devices developed utilizing either inertial measurement units such as accelerometers (Iosa, 2012), force sensors (Forner Cordero et al., 2004; Savelberg & Lange, 1999), goniometers (Ng & Chizeck, 1997), inclinometers (Luinge & Veltink, 2004), gyro sensors, strain gauges or plantar pressure sensors. Such devices can be worn over or attached to the various parts of the patient's body, like pressure sensors located inside footwear or body-weight accelerometers installed (Tao et al., 2012).

5.5 | Prospects for the use of wearable technology in patients with stroke

Measurements of upper-body accelerations are of growing interest by means of evaluating the ability of a person to maintain balance during walking such as in healthy elderly individuals (Kavanagh et al., 2004; Marigold & Patla, 2008; Mazzà et al., 2008, 2009; Senden et al., 2012). This technique has been used in post-stroke patients (Iosa, 2012, 2016; Mizuike et al., 2009) and studies indicate a correlation between decreased gait symmetry and gait stability with elevated acceleration amplitudes (Iosa, 2012; Isho et al., 2015; Mizuike et al., 2009). Inertial sensors integrated into mobile devices such as smartphones are actively in use (Nishiguchi et al., 2012; Yamada, 2012), and have an increasing potential to provide a self-analysis tool for health management. With a smartphone mounted to the participants' torso and utilizing the embedded tri-axial acceleration sensor, Isho et al (Isho et al., 2015). recorded trunk accelerations during walking post-stroke and reported a greater inter-stride variability of medio-lateral trunk acceleration for participants with a history of falling compared to non-fallers. Similarly, with a tri-axial accelerometer bearing wearable motion sensor system (Bruin et al., 2007; Najafi, 2003) Taylor-Piliae (Taylor-Piliae et al., 2016) assessed and confirmed in-home usage feasibility for fall risk and gait monitoring in post-stroke patients. Relying on the patients' cooperation for continuous use of such in-home wearable devices, the study was able to characterize specific fall risk indicators including postural transitions (duration in seconds, and the number of unsuccessful attempts) and gait parameters (e.g., step count, seed speed and duration), which showed significant differences between the patients and healthy individuals.

The need of using multi-sensors for a comprehensive assessment of dynamic balance has been addressed: although trunk accelerations are relevant because of a strong correlation between trunk movements and patient mobility both in subacute and chronic stroke (Isho & Usuda, 2016; Verheyden et al., 2006), such single inertial measurement is not representative of the entire pelvis-to-head accelerations (Bergamini et al., 2017). Additional to those of the trunk (Doi, 2013), head (Allum et al., 1997; Menz et al., 2003), shoulder (Mazzà et al., 2008) or the whole upper body accelerations (Marigold & Patla, 2008) can be associated with an increased risk of walking instability and falling, since they all allow for the stabilization of the optic flow, for more effective processing of the vestibular system signals, and for the consequent control of equilibrium (Berthoz & Pozzo, 1994; Cappozzo, 1981; Holt et al., 1999). Menz et al. (Menz et al., 2003) reported elevated accelerations at the head but lower accelerations at pelvis level in active elderly subjects. In concert with these issues, for post-stroke patients, the use of multi-sensor systems for simultaneous measurement of accelerations at different body levels shows major promise for diagnostic and therapeutic applicability capacity. A multi-sensor gait stability assessment by Bergamini et al. (Bergamini et al., 2017), subacute phase (1-to-6 months) post-stroke patients coupled with a clinical instrumented assessment of gait showed the plausibility of a multi-sensor protocol to be used as a useful tool to quantify gait stability. This, if related as a metric to the patient's risk of falls, can support clinicians to assess the effectiveness of rehabilitation protocols used in the clinical routine. Therefore, the potential of wearable sensor devices in the post-stroke assessment of the risk of falls is high.

However, the use of such devices can be very demanding regarding economic costs, weight, and energy requirements. As any added sensor actually elevate such device and operational costs, minimizing the sensor number is highly relevant, and biosignal-based applications can be used for this purpose. For example, owing to its relative simplicity, surface electromyography (sEMG) appears to bear a high potential to be used in more practical multi-sensor systems to analyse muscular functions (Au et al., 2008). A recently developed neural-network approach allowed the prediction of ankle angle and moment during level walking of a healthy population with high accuracy, while eliminating the use of force sensors and using a minimum number of sEMG sensors (Keleş & Yucesoy, 2020). The usability of such an approach to detect the risk of falls, particularly in post-stroke patients, requires further testing. However, although the electrophysiological activation of a muscle observed with sEMG reflects the degree of mechanical force production, it should also be noted that this may not directly represent it. Intraoperative, direct measurements of muscle forces in patients with cerebral palsy indicated that the force characteristics of spastic muscles quantified as functions of joint angles, may not be in concert with the clinically observed pathological condition in the joint (Ates et al., 2014, 2016; Kaya, 2019; Kaya et al., 2020). This suggests that the pathological condition is ascribable to a more complex mechanism than independent actions of muscles, which is conceivable also for the spastic muscles of post-stroke patients. In light of the available body of knowledge, the design of a lightweight, low-cost, portable and/or wearable multi-sensor system is promising but continues to involve major challenges that need to be tackled.

6 | INTEGRATION OF DIFFERENT MODALITIES AND FUTURE DIRECTIONS

Recently, blood biomarker investigations have shifted towards a more integrative approach, where instead of individual markers, researchers are starting to focus more on combined effects of various analytes. A study with more than 3000 acute and subacute stroke patients, reported the prognostic value of a combined analysis of WBC and blood glucose levels (You et al., 2019). According to the study, co-existing high WBC and high blood glucose levels may be utilized as a predictor of mortality and pneumonia in stroke patients. In acute and subacute stroke patients, higher neutrophil to lymphocyte ratios was found to be independently predictive of hemorrhagic transformation (Sun, Meng, et al., 2020). Another study including 937 acute ischemic stroke patients investigated the levels of 14 blood biomarkers and found that combined evaluation of increased endostatin, tumour necrosis factor receptor-1, and IL-6 levels was able to predict increased risk of death post-stroke. Mortality risk increased up to 70% when these three biomarkers were elevated, compared to 10% when the levels of the aforementioned biomarkers were normal (Ramiro et al., 2021).

Nonetheless, the literature is lacking integrative studies that utilize various modalities. At the time of writing this review, we have searched the PubMed database for the last 5 years where the species is selected as 'Human' on the PubMed website. In our search, 'stroke "blood biomarkers" "magnetic resonance imaging"' resulted in 13 studies; 'stroke "gait analysis" "magnetic resonance imaging"' resulted in six studies; and lastly, 'stroke "blood biomarkers" "gait analysis"' resulted in 0 studies. Even when the time and species filters are cleared, the search for 'stroke "blood biomarkers" "gait analysis"' did not return any articles. Such a lack of published studies indicates that objective evaluations of these modalities in conjunction go in baby steps.

When these 19 studies were investigated more closely, we found that only five of them relate to establishing biomarkers of stroke from different modalities. One study investigating the relationship between gait impairments and brain lesions using MRI showed that the lesions in the posterior limb of the internal capsule, the hippocampus, frontal lobe, paracentral lobule, thalamus and lentiform nucleus are all significantly associated with gait parameters including speed, knee extension, cadence, and stride length (Kim et al., 2018). The remaining four studies focused on blood biomarkers and magnetic resonance imaging. A study showed that the growth differentiation factor-15 level is associated with the severity of cerebral damage and can be used as a prognostic marker for patients who underwent intraarterial thrombectomy following an ischemic stroke (Jeong et al., 2020). Another study utilizing gradient echo T2*W imaging found that susceptibility vessel sign and admission MMP-9 levels can be used to differentiate between subtypes of stroke (Alhazmi et al., 2021). In a 3D MR vessel wall imaging study, type 2 diabetes mellitus was found to be associated with an increased number of intracranial plaques (Li et al., 2021). Lastly, a study utilizing genetic and imaging traits did not report any independent associations between cardiac traits and stroke other than the already established confounders; atrial fibrillation, atherosclerosis, and hypertension (Frerich et al., 2022). Another study that did not come up in our PubMed search, reported a biomarker panel containing levels of neurofilament light chain (NfL) in blood serum and T2 FLAIR image biomarkers for predicting post-stroke cognitive impairments. NfL which is leaked into peripheral blood following axonal damage, combined with lesion volume and white matter hyperintensity volume was found to be predictive of cognitive impairment (Peng et al., 2021).

Clinical decision making using multimodal data has a great potential to improve stroke care pathways (Figure 1). However, integration of multimodal data with varying temporal and spatial resolution is not straightforward, and the traditional statistical methods may not be sufficient to capture the relationship between these modalities and patient outcomes. We believe that artificial intelligence can play a significant role in mining this multimodal data enhancing evidence-based practice.

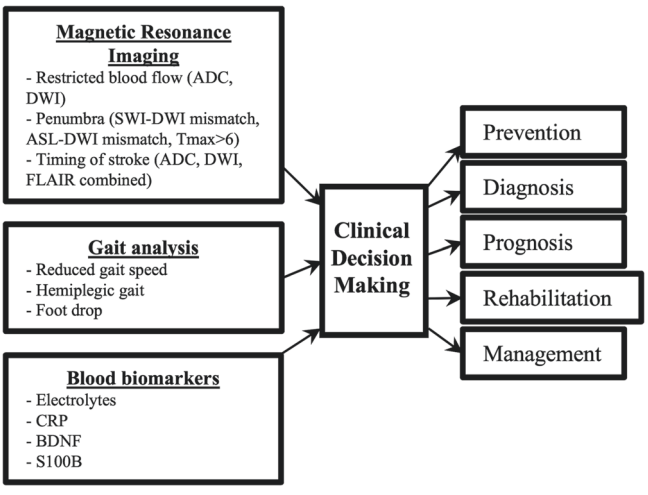

FIGURE 1 Various modalities can provide biomarkers that can guide clinical decision making to help with prevention, diagnosis, prognosis, rehabilitation and management of ischemic stroke.

7 | CONCLUSIONS

Stroke can be experienced as ischemia and haemorrhage, and the effect of stroke depends largely on the duration of abnormal blood flow, and the location of the stroke in the brain. The structure of the lesion, levels of blood biomarkers, gait impairments, and psychological and social well-being of the patient before and after stroke, all have implications for the clinical outcome of the patients. When the heterogeneity of strokes in terms of symptoms and severity is considered, the necessity to implement an interdisciplinary approach to investigate the disease becomes clearer. In the future, developing smart systems supported with artificial intelligence enhanced by inputs from various modalities to assist medical professionals is promising for better patient care, and will be very valuable in clinical settings. Here, we attempted to offer a general overview of the functions of various modalities for stroke diagnosis, treatment, and management. We wish to highlight the integrative perspectives for the amelioration of the diagnosis and prognosis of patients with stroke.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16245.

DATA AVAILABILITY STATEMENT

The papers that are reviewed in this study are available in standard research databases such as PubMed, Science Direct or Google Scholar and/or on public domains that can be searched with either key words or DOI numbers.

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