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FRAILTY SYNDROME IN CLINICAL NEUROLOGY: A COMPREHENSIVE REVIEW OF NERVOUS SYSTEM PATHOPHYSIOLOGY, PROGNOSIS IN SELECTED CONDITIONS, AND SOCIO-TECHNOLOGICAL PERSPECTIVES

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ABSTRACT

Background: Neurological conditions are now the leading cause of disability worldwide. Frailty syndrome, defined as a multisystemic state of physiological impairment, often predicts clinical outcomes more accurately than chronological age.
Objective: This review examines the molecular pathophysiology of neuro-frailty, its prognostic significance in acute ischemic stroke, multiple sclerosis (MS), and Parkinson's disease (PD), as well as the integration of emerging diagnostic technologies.
Methodology: A comprehensive review of English-language articles published from 2001 to 2026 in PubMed, Scopus, and Cochrane was conducted. Grey literature and animal studies were excluded from the analysis. The synthesis focused on meta-analyses and human-based research connecting artificial intelligence diagnostics, fluid biomarkers, and clinical neurology.
Results: Neuro-frailty is associated with the phenomenon of inflammaging, the secretory ageing-associating phenotype (SASP), and progressive mitochondrial dysfunction. The presence of pre-existing frailty also elevates the risk of unfavorable functional recovery (mRS > 2) in acute phase of ischaemic stroke by 3.11 times. In MS, ongoing neurodegeneration accelerates biological ageing, often resulting in premature frailty. The sarcopenia-frailty axis in Parkinson's disease affects over 35% of patients and significantly increases the risk of recurrent falls. Modern diagnostic methods now enable objective and precise quantification of this impairment.
Conclusions: Frailty is a dynamic clinical condition that is possible to reverse. The transition from age-based metrics to AI-powered biological screening enables a personalized approach to care by clinicians. These targeted strategies are essential for maintaining neurological functions and reducing socio-economic consequences of ageing.

KEYWORDS

Frailty Syndrome, Clinical Neurology, Neurodegeneration, Inflammaging, Ageing Society, Digital Health

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1. Introduction

The ageing of the population is one of the most significant public health challenges of the 21st century. We have been observing an increase in life expectancy and simultaneously a rise in the prevalence of neurological conditions. According to the Global Burden of Disease Study 2021, diseases of the nervous system are now the main reason for disability-adjusted life years (DALYs) worldwide, affecting approximately 3.4 billion individuals (GBD 2021 Nervous System Disorders Collaborators, 2024). Although mortality from certain conditions has declined, numerous people living with or dying from non-communicable neurological disorders have increased over the past three decades (Feigin et al., 2020). Frailty syndrome, a clinical condition that extends beyond chronological age, has emerged as a key factor in determining health outcomes in geriatric and neurological patients.

Frailty syndrome is characterized by a reduced physiological reserve and increased susceptibility to low-intensity stressors (Evans et al., 2021). It is a state of homeostatic instability in which even minor injuries can provoke a disproportionate decline in functional capacity (Borges et al., 2019). In the past, this concept was defined in terms of two dominant models. The first is the frailty phenotype, which emphasizes physical manifestations (e.g. weakness, slowness) (Fried et al., 2001) the second is the frailty index, which is based on the accumulation of successive health deficits (Rockwood & Mitnitski, 2007). Neurologists currently believe that this syndrome results from 'brain frailty,' a condition in which the nervous system's resilience is weakened by subclinical neuropathological changes, thereby increasing the risk of cognitive and motor impairment (Evans et al., 2021).

Several scientific studies demonstrate that frailty is independently associated with poorer outcomes in various diseases, particularly in cerebrovascular conditions. As an example, pre-stroke frailty is a strong predictor of stroke severity measured by the National Institutes of Heath Stroke Scale (NIHSS) and correlates with a lower likelihood of successful recovery following reperfusion therapies, such as thrombolysis or mechanical thrombectomy (Evans et al., 2021). Recent data from longitudinal studies show that higher levels of frailty are associated with an overall decline in cognitive function, independent of the burden of cerebral small vessel disease (cSVD) and brain atrophy (Siejka et al., 2022). These studies imply that frailty may act as a latent factor that lowers the threshold for the clinical expression of neurodegenerative diseases, such as Alzheimer's disease and vascular dementia (Borges et al., 2019; Robinson et al., 2021).

According to researchers, the phenomenon of 'inflammation' is responsible for the onset of neurofrailty – a state of chronic, low-grade, systemic inflammation. Pro-inflammatory cytokines are released, mitochondrial disfunction and oxidative stress occur, impairing the integrity of the blood-brain barrier and promoting neurodegeneration (Bozi-Soares et al., 2025; Evans et al., 2021). Neuropathological studies have indicated that cerebrovascular changes are associated with increased frailty levels even in individuals with normal cognitive function, pointing to the early and direct role of vascular health in the progression of frailty (Bozi-Soares et al., 2025).

From a socio-technological perspective, the management of physical frailty exerts a considerable systemic and economic burden on society. This results in ever-increasing healthcare costs. A study by Pradana et al., (2025) demonstrates that seniors with weakened health generate additional annual expenditure ranging from 2,000 to over 4,600 US dollars compared to those in good physical condition. The use of artificial intelligence (AI) and machine learning (ML) models to routinely collected data from everyday life may enable automated and, above all, large-scale screening for frailty syndrome (Yang et al., 2025). Natural language processing (NLP) techniques applied to electronic health records and digital biomarkers from wearable sensors are paving the way for a more personalized and objective assessment of frailty (Bai & Mardini, 2024; Yang et al., 2025).

Despite the increasing awareness of physical frailty, its incorporation into routine neurological decision-making remains underdeveloped. The present review synthesizes recent research on frailty syndrome in clinical neurology, emphasizing its molecular basis, prognostic significance in different neurological conditions, and the potential of advanced diagnostic technologies. Prioritizing biological frailty over chronological age enables more effective interventions, better recovery, and enhanced quality of life for the ageing population.

2. Methodology

This review is the result of a comprehensive literature review that integrates clinical data with recent technological advancements in the field of neurology.

2.1. Search Strategy

A comprehensive search was performed across major biomedical databases, including PubMed, Scopus, Google Scholar, and the Cochrane Library. The analysis included peer-reviewed publications from 2001 to early 2026, integrating both foundational pathophysiology and recent scientific and technological developments. The search strategy employed specific MeSH terms and Boolean operators including:

- ("frailty syndrome" AND "neurology"),
- ("brain ageing" AND "pathophysiology"),
- ("stroke prognosis" AND "frailty")
- ("multiple sclerosis" AND "frailty")
- ("neuroimaging" AND "artificial intelligence").

2.2. Criteria of Inclusion and Exclusion

To ensure high data quality, strict inclusion criteria were established. Original research studies, meta-analyses, systematic reviews, and longitudinal cohort studies published in English were included. Priority was given to studies focusing on modern diagnostic tools, such as biomarkers in body fluids and AI-assisted neuroimaging.

Exclusion criteria consisted of:

- Studies conducted exclusively on animal models.
- 'Grey literature', including conference abstracts, editorial articles, and unpublished manuscripts.
- Publications demonstrating low methodological rigor, insufficient sample size or a clear conflict of interest.

2.3. Data Selection and Synthesis

The literature selection process was comprised of two distinct stages: initial screening of titles and abstracts, followed by a detailed analysis of the full texts of eligible articles. Due to the clinical and technological diversity of the topics, which range from molecular pathophysiology to socio-economic implications, a narrative synthesis approach was adopted.

3. Results

3.1. Pathophysiology of Ageing in the Nervous System

The transition from physiological brain ageing to the clinical manifestations of neuro-frailty results from complex interactions among molecular and cellular disorders. Unlike healthy ageing, which preserves some homeostatic resilience, the pathophysiology of neuro-frailty involves a systemic breakdown of biological reserves at multiple levels, including genomic instability and structural atrophy. The following section discussed the primary factors driving this transition: cellular ageing, mitochondrial dysfunction, and neuroendocrine dysregulation.

3.1.1. Cellular Ageing and the Senescence-associated Secretory Phenotype (SASP)

Neural ageing is caused by cellular ageing, a state of definitive growth cessation caused by chronic DNA damage, oxidative stress and telomere shortening. Though cellular ageing evolved as a protective mechanism against the development of tumors, the abnormal accumulation of ageing cells in the ageing brain is a major driver of neuroinflammation and tissue dysfunction (Birch & Gil, 2020; Wang et al., 2024).

Ageing cells in the central nervous system (CNS) – including neurons, astrocytes and microglia – undergo profound metabolic and genetic reprogramming (Wang et al. 2019). These cells, however, remain metabolically active and develop a profile of excessive secretion known as the senescence-associated secretory phenotype (SASP). SASP consists of a potent mix of pro-inflammatory cytokines (IL-6, IL-8), chemokines (CCL2, CCL20), growth factors (VEGF, AREG), and matrix metalloproteinases (MMPs) (Birch & Gil, 2020; Lopes-Paciencia et al., 2019). SASP regulation is a multiphase process involving the activation of key transcription factors, in particular nuclear factor kappa B (NF-kappa B) and CCAAT/enhancer-binding protein beta (C/EFP/beta) (Lopes-Paciencia et al., 2019). Chronic activation of these pathways drives a self-amplifying feedback loop in which SASP components propagate ageing to neighboring healthy cells via paracrine signaling a phenomenon termed ‘bystander ageing’ (Birch & Gil, 2020). In the context of the body’s vulnerability, this ‘toxic’ microenvironment promotes chronic, low-grade systemic inflammation (Birch & Gil, 2020; Wang et al., 2018).

3.1.2. Mitochondrial Dysfunction and Abnormal Mitophagy: The Energy Crisis

Because of its enormous metabolic demands, the nervous system is particularly vulnerable to mitochondrial dysfunction. In a weakened brain, cellular ‘powerhouses’ suffer a double disadvantage: increased macromolecular damage and limited efficiency of mitochondrial quality control (Cai & Jeong, 2020; Doblado et al., 2021).

Effective mitochondrial replacement is reliant on mitophagy, a selective form of macroautophagy that directs damaged mitochondria towards lysosomal degradation. This process is primarily regulated by the PINK1-Parkin pathway. Physiologically, PINK1 is imported into healthy mitochondria and undergoes degradation. During the ageing process, PINK1 stabilizes on the outer mitochondrial membrane (OMM) and recruits Parking, an E3 ubiquitin ligase (Cai & Jeong, 2020; Doblado et al., 2021).

This mechanism is severely disrupted when the body is weakened or in cases of neurodegenerative diseases. Studies show that lower cytosolic Parkin concentrations and accumulation of uncut PINK1 lead to abnormal retention of dysfunctional mitochondria (Cai & Jeong, 2020). These organelles then produce excessive amounts of reactive oxygen species (ROS). They are unable to sequester intracellular Ca 2+, resulting in a catastrophic loop of oxidative damage to proteins, lipids, and mitochondrial DNA (mtDNA) (Doblado et al., 202; Wang et al., 2018).

The energy deficit caused by this impairs synaptic plasticity and axonal transport, directly causing the physical and cognitive components of frailty syndrome (Evans et al., 2021; Wang et al., 2018). The failure of mitophagy and further promotes the “fire” of inflammaging (Cai & Jeong, 2020; Doblado et al., 2021).

3.1.3. Neuroendocrine Dysregulation and HPA Axis

Progressive dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis worsens pathophysiological manifestations of physical weakness. This axis maintains homeostasis in response to stressors; however, in physically weakened individuals, it exhibits signs of chronic overactivity and loss of control through negative feedback (Gupta & Morley, 2014; Wang et al., 2018).

As we age, levels of adrenocorticotropic hormone (ACTH) and cortisol rise. In elderly adults in a state of frailty, flattening of the daily cortisol rhythm is frequently observed, preventing the achievement of a normal nocturnal low point (Gupta & Morley, 2014). Chronic hypercortisolemia exerts a neurotoxic effect on the hypothalamus and prefrontal cortex. Researchers indicate in their studies that chronic activation of the HPA axis reduces synaptic density and impair neurogenesis, providing the biological basis for the cognitive impairment in states of frailty (Gupta & Morley, 2014). Other neuroendocrine changes, like a decrease in dehydroepiandrosterone (DHEA) and insulin-like growth factor-1 (IGF-1) levels, promote sarcopenia (muscle wasting) and further reduce the physiopathological reserve of the nervous system (Wang et al., 2018).

3.1.4. Structural and Vascular Correlates of Neuro-frailty

The molecular mechanisms explained above manifest themselves as visible changes in the brain. Arteriolar sclerosis – a marker of small vessel disease – and the accumulation of neurofibrillary tangles (NFTs) are highly associated with increased frailty, even in the absence of clinical dementia (Bozi-Soares et al., 2025).

They contribute to brain atrophy, characterized by a reduction in grey matter volume and loss of white matter integrity (Siejka et al., 2022). Data from longitudinal studies suggest that frailty acts as a latent factor that accelerates cognitive impairment regardless of the total burden of cerebral small vessel disease (cSVD) (Siejka et al., 2022).

3.2. Frailty Syndrome in Selected Neurological Conditions

3.2.1. Frailty in Cerebrovascular Diseases: The Case of Acue Ischaemic Stroke

As was mentioned earlier, the latest scientific reports indicate that frailty is an independent prognostic factor for stroke risk, symptom severity, and subsequent recovery (Burton et al., 2022; Evans et al., 2021).

3.2.1.1. Prevalence and Risk of Stroke in the Frail Population

The frequence of frailty syndrome among patients with acute stroke is extremely high. Systematic reviews indicate that at least one in four people (24.6%) experiencing an acute stroke suffer from frailty, and this number rises to almost two-thirds (66.8%) when pre-frailty is also taken into account (Burton et al., 2022; Chen et al., 2024).

A study by Chen et al. (2024) demonstrates that pre-stroke frailty is significantly associated with an increased risk of stroke. A meta-analysis involving over 1.6 million participants showed that people with pre-stroke frailty have a 1.72-fold higher risk of stroke compared to those in good physical condition (Chen et al., 2024).

3.2.1.2. Impact on Stroke Severity and Functional Outcomes

Studies also show that pre-stroke frailty is associated with higher scores on the National Institutes of Health Stroke Scale (NIHSS). It is believed that a weakened brain has a reduced capacity to maintain viability within the penumbra and to withstand the metabolic cascade induced by ischaemic injury (Evans et al., 2021).

The impact of frailty on long-term prognosis is even more pronounced. Meta-analytic data indicate that pre-stroke frailty is associated with a 3.11-fold increase in the risk of poor functional outcomes, defined as a modified Rankin Scale (mRS) score >2 or >3 at follow-up (Chen et al., 2024). Similarly, frailty is a strong predictor of mortality. Burton et al. (2022) found that frailty increases the likelihood of mortality in the long term by a factor of 3.75, whilst Chen et al. (2024) established a combined risk ratio of 1.68 for stroke-related deaths in the frail population.

3.2.1.3. Modulation of Reperfusion Therapy Efficacy

A key finding in contemporary neurology is the impact of frailty syndrome on outcomes following reperfusion therapy in patients with ischaemic stroke. Frailty is associated with poorer treatment outcomes as measured by the NIHSS scale (Evans et al., 2021).

Studies indicate that for every one-point increase on the Clinical Frailty Scale (CFS), the degree of neurological improvement following reperfusion decreases. Frail patients undergoing mechanical thrombectomy show lower rates of functional independence with patience of the same age who are not frail (Evans et al., 2021; Burton et al., 2022).

3.2.2. Multiple Sclerosis – A Model of Accelerated Biological Ageing

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease; however, recent research suggests that it is associated with accelerated ageing of the nervous system. The incorporation of the concept of ‘brain fragility’ into MS research highlights a state of heightened vulnerability, in which the clinical phenotype of fragility, typically associated with geriatric populations, manifests prematurely in young and middle-aged adults (Evans et al., 2021).

3.2.2.1. Premature Frailty and the Depletion of Brain Reserved

The classic model of fragility in response to stressors is especially relevant in the case of multiple sclerosis. In this context, the disease itself acts as a chronic stressor that gradually depletes the body and neurological reserve of the patient. Patients with multiple sclerosis may exhibit a frailty phenotype as early as their 40s, with a significant proportion meeting criteria for physical frailty, including slow walking speed and decreased grip strength (Evans et al., 2021).

3.2.2.2. Cognitive Frailty and Neuropathological Substrates

Cognitive impairment is a characteristic symptom of frailty associated with multiple sclerosis, often preceding significant physical disability. Systematic review indicates a strong association between frailty and cognitive function across multiple domains (Robinson et al., 2021).

The pathophysiology of this decline is multifaced. Recent studies reveal that physical frailty is associated with an overall impairment in cognitive function, independent of traditional markers such as brain atrophy or small-vessel disease (Siejka et al., 2022).

These findings suggest that physical frailty functions as a latent factor, reducing the threshold for the clinical manifestation of neurological impairment.

Neuropathological data further indicate that specific changes, including tangles and microvascular alterations such as hyaline arteriosclerosis, are crucially associated with greater frailty (Bozi-Soares et al., 2025).

3.2.2.3. Socioeconomic Impact and the Role of Modern Diagnostics

Premature frailty in people with MS has serious socio-economic consequences. Those affected by frailty generate significantly higher healthcare costs and are at increased risk of hospitalization and long-term disability (Pradana et al., 2025). Because of that, the earliest possible detection of such symptoms is of great importance, and machine learning models appear promising in this area (Yang et al., 2024). The use of digital biomarkers and natural language processing to analyze clinical notes may also provide a more detailed understanding of the progression of a patient's weakness than traditional functional scales (Bai & Mardini, 2024; Yang et al., 2024).

3.2.3.1. Parkinson's Disease: The Sarcopenia-Frailty Axis

In Parkinson's disease, the latest cross-sectional data indicate that frailty affects approximately 35.6 of patients receiving specialist care, compared with just 5.2% in the control group without the condition (Peball et al., 2019). These statistics correlate strongly with sarcopenia – the loss of skeletal muscle mass, strength, and function – which affects 55% of patients with Parkinson's disease (Peball et al., 2019; Lima et al., 2025).

The motor features of the disease, such as rigidity, bradykinesia, and postural instability, accelerate the progression of physical frailty. On the other hand, the presence of sarcopenia is a major determinant of poor outcomes. According to Lima et al. (2025), longer disease duration and greater motor symptom severity, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS-III), are independent prognostic factors for recurrent falls.

Furthermore, non-motor symptoms, such as dysautonomia (e.g. orthostatic hypotension, constipation) and comorbidities, such as type 2 diabetes, significantly exacerbate the weakness phenotype in PD. In particular, researchers emphasize diabetes accelerates the decline in neurocognitive function, further depleting the patient's homeostatic reserve (Lima et al., 2025).

3.3.3.2. Alzheimer's Disease and Cognitive Frailty: The Neuropathological Substrate

Research by Bozi-Soares et al., (2025) indicates that Lewy body diseases (LBD) are significantly associated with higher frailty scores. It is important to note that the neuropathological co-occurrence sore (NPC) - which accounts for the presence of multiple lesions – is a robust predictor of frailty status (Bozi-Soares et al., 2025; Borges et al., 2019).

3.2.3.3. Clinical Implications and Modern Diagnostic Perspectives

Integrating digital biomarkers, such as gait analysis using wearable sensors, into routine care enables clinicians to predict the risk of falls and disability more accurately. This approach supports early interventions to preserve remaining brain and muscle reserves (Lima et al., 2025; Yang et al., 2024).

Ultimately, because physical frailty is a major determinant of elevated healthcare expenditures (Pradana et al., 2025), addressing the sarcopenia-neurodegeneration axis is both a clinical necessity and socio-economic priority in rapidly ageing societies (GBD 2021 Nervous System Disorders Collaborators, 2024).

3.3 Assessment and Modern Diagnostic Perspectives

Manual scales remain the gold standard in clinical practice for assessing the severity and symptoms of frailty syndrome, although they are inherently subjective and time-consuming. To address these limitations, clinicians increasingly employ assessments based on instrumental measurements. For example, fitting a patient with a discreet trunk sensor during the 5-repetition sit-to-stand test (5xSTS) captures microkinematic variables, such as hip velocity and force consistence, which are often missed by human observation.

This approach distinguishes frail individuals from fit ones with over 85% accuracy, providing a precise biological assessment of physical reserves (Park et al., 2021). Diagnostic capabilities now extend into the home environment, where remote monitoring of spontaneous daily activity enables tracking of actual homeostatic resilience (Park et al., 2021). Furthermore, combining wearable devices with dual-task walking paradigms, such as walking while counting backwards, reveals the neurological cost of divided attention. Patients exhibiting significant gait deterioration during these cognitive load tests are at an increased risk of developing dementia (Zhou et al., 2022)

Beyond physical kinematics, quantifying brain frailty relies on advanced neuroimaging and fluid analysis. Structural changes, specifically cerebral small vessel disease (cSVD) manifested by white matter hyperintensities, physically signal neurological vulnerability (Siejka et al., 2022; Bozi-Soares et al., 2025). Rather than relying on visual assessments of atrophy, artificial intelligence (AI) models now compare individual MRI scans with vast datasets to calculate the brain's biological age (Velazquez-Diaz et al., 2023). A brain age that significantly exceeds chronological age is a clear warning sign of impending cognitive decline (Bashkirtsev & Doskaliuk, 2025). These imaging techniques are complemented by liquid biomarkers, which offer a compelling liquid biopsy approach for latent neurodegeneration. The neurofilament light chain (NfL) in plasma reliably enters the bloodstream following neuronal damage. Elevated NfL levels in older adults without dementia are directly associated with increasing frailty scores and impending loss of independence (Li et al., 2023). Therefore, a routine blood test can detect a systemic decline in physical function long before the onset of apparent clinical symptoms.

3.4. Social and Ethical Consequences

The rapidly growing number of older people is a major challenge for modern neurology (GBD 2021 Nervous System Disorders Collaborators, 2024; Feigin et al., 2020). Adults with frailty syndrome generate up to $4,653 in additional annual healthcare expenditure, resulting from prolonged hospitalizations and long-term care in care facilities, which significantly aggravates existing health inequalities in resource-constrained regions (Pradana et al., 2025; Huang et al., 2023). At the same time, the integration of digital solutions into healthcare poses clear ethical risks. Although wearable sensors enable people to age in their own homes, they require a difficult trade-off between constant supervision and carry the risk of widening the digital divide among marginalized populations (Predel et al., 2022; Chen et al., 2023). What is more, AI models, trained primarily on large cohorts, often misdiagnose vulnerable minorities due to inherent algorithmic bias (Bashkirtsev & Doskaliuk, 2025). Ultimately, technology cannot replicate the holistic empathy required in high-stakes geriatric care. The greatest hidden cost of neuro-frailty remains the enormous physical and emotional burden on family carers. Moving forward in this environment requires implementing objective digital tools to maintain autonomy whilst strongly protecting transparent, non-discriminatory clinical assessment (Freitas & Costa, 2023; Predel et al., 2022).

4. Discussion

Frailty is increasingly recognized as a dynamic and potentially reversible state of multisystemic depletion, rather than an inevitable consequence of ageing. Targeted clinical protocols and emerging digital interventions show significant potential to alter this pathological trajectory.

4.1. Multimodal Interventions and Phenotypic Reversibility

Once the clinical reversibility of the frailty phenotype has been established, it has become a major focus of contemporary geriatric neurology. Systematic reviews indicate that physical exercise is the most effective intervention for delaying or reversing this process (de Labra et al., 2015).

Researchers emphasize the exceptional importance of programs that combine resistance aerobics and balance training and provide measurable benefits in terms of walking speed, muscle strength and overall functional independence (de Labra et al., 2015).

Lower-limb resistance training directly counteracts the sarcopenia-frailty axis (Lima et al., 2025; de Lebra et al., 2015).

Physical activity, combined with targeted nutritional support, particularly adequate intake of protein and vitamin D, can maximize the reversal of frailty (de Labra et al., 2015).

4.2. Cognitive Reserve as a Biological Buffer

Educational level, the complexity of one's occupation and regular leisure-time activity are powerful biological buffers that protect against the clinical manifestation and progression of cognitive decline (Sardella et al., 2020). A high baseline level of cognitive reserve modulates the overall path of frailty, extending its protective effect far beyond standard dementia prevention (Sardella et al., 2020). From a neurological perspective, this solid reserve allows the central nervous system to effectively overcome the toxic microenvironment generated by the secretory phenotype associated with ageing (SASP), as well as the accompanying deficits in mitochondrial energy (Wang et al., 2024; Sardella et al., 2020). Non-pharmacological interventions requiring continuous social and cognitive engagement provide fundamental protection by strengthening the brain's resilience to the constant physiological stressors associated with ageing (Sardella et al., 2020).

4.3. Technological Integration: Promises and Barriers in Practice

The combination of clinical neurology with digital biomarkers and artificial intelligence enables highly personalized diagnostics. Machine learning models that process kinematic sensor data currently achieve diagnostic accuracy exceeding 90% (Velazquez-Diaz et al., 2023; Park et al., 2021). These tools detect subtle movement anomalies, such as micro-fluctuations in gait stability and physical exhaustion, which signal a breakdown in homeostasis long before manual identification is possible (Zhou et al., 2022; Park et al., 2021). However, translating this high accuracy into routine geriatric care presents significant challenges. Such as logistical and ethical difficulties. The literature contains numerous retrospective proof-of-concept models that lack prospective external validation across diverse demographic cohorts (Bashkirtsev & Doskaliuk, 2025). Additionally, the inherent black box architecture of deep learning algorithms complicates medical-legal liability and clinical transparency (Bashkirtsev & Doskaliuk, 2025; Presel et al., 2022)

4.4. The Economic Necessity of Early Screening

The absence of a systematic approach to neuro-fragility guarantees an unsustainable economic burden. Generating up to $4,653 in excess annual costs per patient, uncontrolled frailty threatens to overwhelm regional healthcare budgets (Pradana et al., 2025). Neuropathological evidence confirms that silent cerebral vascular damage accelerates the decline in physical fitness, even in adults with intact cognitive function, suggesting that aggressive management of cardiovascular risk directly serves as a preventive measure against structural frailty (Bozi-Soares et al., 2025). Shifting the focus of clinical protocols to the vulnerable period before the onset of frailty enables the implementation of highly effective, cost-effective dietary and exercise interventions (Huang et al., 2023; de Labra et al., 2015).

5. Conclusions

The frailty syndrome emerges as a distinct biological phenomenon rather than merely a by-product of ageing. It constitutes a significant, independent prognostic factor for serious adverse outcomes in cases of acute ischaemic stroke, multiple sclerosis, and neurodegenerative diseases (Evans et al., 2021; Chen et al., 2024). The physical progression to this vulnerable state results from a measurable deterioration in neuropathological status, specifically hyaline arteriosclerosis and neurofibrillary tangles, which independently deplete physiological reserves (Bozi-Soares et al., 2025; Siejka et al., 2022). Fortunately, a high cognitive reserve built up through continuous educational and social engagement acts as a key biological buffer. It enables the central nervous system to maintain functional stability despite the relentless accumulation of age-related structural damage (Sardella et al., 2020). Navigating this complex landscape requires a complete break from traditional age-centered clinical models.

Subjective bedside examinations are increasingly being replaced by advanced diagnostic systems that include wearable device kinematics and plasma NfL biomarkers, enabling clinicians to objectively assess the degree of neurological decline (Park et al. 2021; Li et al., 2023; Yang et al.,2025). Early diagnosis of these deficits provides a critical opportunity to alter disease progression. Multicomponent exercise programs and targeted nutritional protocols consistently demonstrate efficacy in reversing the frailty phenotype, preserving biological reserves, and reducing the substantial socio-economic burden associated with this syndrome (de Labra et al., 2015; Pradana et al., 2025). Ultimately, addressing logistical barriers to digital health innovations and ensuring ethical and equitable access will be essential for the future success of neurogeriatric care (Bashkirtsev & Doskaliuk, 2025; Predel et al., 2022).

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