ORIGINAL RESEARCH PAPER

Physiotherapy & Rehabilitation

KEY WORDS: Biomarkers, Rehabilitation, Personalized Medicine, Precision Rehabilitation, Outcome prediction, Neurorehabilitation

BIO-MARKER GUIDED REHABILITATION STRATEGIES: A COMPREHENSIVE REVIEW

C. S. Prerana Associate Professor, Department of Physiotherapy, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka

Shilpashree Assistant Professor, Department of Physiotherapy, Garden City University, Bengaluru, Karnataka

Shilpi Pal Assistant Professor, Department of Physiotherapy, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka

ABSTRACT

This review synthesizes current research on biomarker-guided rehabilitation strategies, highlighting their potential to personalize interventions and improve patient outcomes. Biomarkers, measurable indicators of biological processes, offer objective insights into a patient's physiological state and recovery potential, enabling tailored rehabilitation programs [1]. The integration of laboratory diagnostics, including blood biomarkers, imaging, and metabolic evaluations, refines therapy plans and enhances recovery [2]. This approach marks a shift towards precision medicine in rehabilitation, moving away from generalized protocols. It also examines various biomarker types, including inflammatory markers, neurophysiological indicators derived from EEG, and muscle oxygen saturation (SmO2). In post-COVID syndrome, pro-inflammatory biomarkers and liver metabolism indicators guide targeted interventions, improving lipid metabolism and quality of life [3]. EEG biomarkers, such as delta waves, show promise in stroke rehabilitation, indicating neuronal dysfunction and predicting clinical recovery [4]. Muscle oxygen saturation (SmO2) serves as an important marker for internal physiological recovery of the quadriceps following ACL reconstruction [5]. Despite promising advances, challenges persist, including heterogeneity in biomarker assessment, limited understanding of biomarker-outcome relationships, and the technical complexity and cost of assessments. Future research should focus on large-scale longitudinal studies, integration of multiple biomarkers, point-of-care testing, and personalized strategies based on individual biomarker profiles. By addressing these gaps, biomarker-guided rehabilitation can optimize interventions, predict outcomes, and enhance recovery across diverse conditions.

INTRODUCTION

Rehabilitation strategies have evolved significantly in recent years, moving from standardized protocols toward more personalized approaches that consider individual patient characteristics and needs. One of the most promising developments in this field is the use of biomarkers to guide rehabilitation interventions. Objective of Biomarkers is to have an indicator for biological processes along with pathogenic processes and their responses to therapeutic intervention which can provide valuable insights into a patient's physiological state and potential for recovery, allowing clinicians to tailor rehabilitation strategies accordingly. This approach represents a paradigm shift from conventional rehabilitation methods toward precision medicine in rehabilitation.

The integration of biomarker assessment into rehabilitation practice has gained significant attention as it enables more personalized and effective rehabilitation strategies. The incorporation of laboratory diagnostics into physical therapy practices has been increasingly recognized for its potential to enable more personalized and effective rehabilitation strategies. Various types of laboratory tests, including blood biomarkers, imaging techniques, and metabolic evaluations, have demonstrated their value in tailoring therapy plans and enhancing recovery outcomes [1]. The concept of biomarker-guided rehabilitation is fundamentally based on the premise that objective biological indicators can inform clinical decision-making, optimize treatment approaches, and potentially improve rehabilitation outcomes.

The integration of biomarkers into rehabilitation practice, particularly in physiotherapy, represents a transformative shift toward personalized medicine, offering enhanced precision in treatment strategies. Traditionally reliant on clinical assessments and generalized protocols, rehabilitation practices are evolving with the advent of biomarkers giving measurable indicators of the biological processes and the disease states including therapeutic responses. Various types of biomarkers relevant to rehabilitation include inflammatory markers, muscle damage markers, oxidative stress markers, metabolic biomarkers, genetic biomarkers, and physical performance metrics. These biomarkers have applications in diagnosis, prognosis, treatment response monitoring, rehabilitation progress tracking, and risk stratification, underlining their transformative potential. By tailoring rehabilitation programs to individual patient profiles, biomarkers enable clinicians to optimize recovery, reduce complications, and improve overall outcomes. Despite challenges such as standardization, ethical considerations, and technological demands, the future of biomarker-driven rehabilitation is promising, fostering interdisciplinary collaboration and advancing precision medicine [2].

This review aims to provide a comprehensive and deep analysis of the current state of biomarker-guided rehabilitation strategies across various conditions and contexts. It examines the types of biomarkers being utilized with their methodological approaches, their clinical applications, limitations along with future directions in this rapidly progressing field.

Types of Biomarkers in Rehabilitation

Inflammatory Biomarkers

Inflammatory biomarkers have emerged as important indicators of disease severity, progression, and recovery potential in various conditions requiring rehabilitation. Research on COVID-19 has identified that the chemokine RANTES (CCL5) gets significantly elevated from an early stage of infection in patients who have mild disease but not in those with severe disease. Additionally, early production of inhibitory mediators such as IL-10 and IL-1RA has been associated to predominantly link with disease severity, and a combination of CCL5, IL-1Ra and IL-10 at week 1 may become a predictor for patient outcomes [3]. This suggests that inflammatory profiles could potentially guide rehabilitation strategies by identifying patients at risk of poor outcomes early in the disease course.

In osteoarthritis (OA), a condition often requiring extensive

rehabilitation, inflammatory markers have shown promise in monitoring treatment efficacy. A study evaluating the effects of a 21-dayf of individually adjusted generalized rehabilitation program in osteoarthritis patients 90 days after hip or knee replacement found significant changes in serum concentrations of several inflammatory markers. Almost all the anti/pro-inflammatory markers, including IL-1 receptor antagonist (IL-1RA), IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-15, and some of the chemokines like macrophage inflammatory protein-1 alpha (MIP-1 /CCL3), RANTES/CCL5, and the eotaxin-1/CCL11, as well as the vascular endothelial growth factor (VEGF), pointedly increased after rehabilitation. Meanwhile, basic fibroblast growth factor (FGF basic) significantly decreased [4].

Notably, there were no changes in pro-inflammatory cytokine levels such as tumor necrosis factor-alpha (TNF-α), interferon-γ (IFN-γ), and IL-12 (p70) after the 21-day general rehabilitation, indicating stable and controlled inflammatory status in osteoarthritis patients. The significantly higher levels of anti-inflammatory factors after 21 days of moderate physical activity confirm the beneficial outcome of the applied therapy. The increased level of IL-6 after rehabilitation may reflect its anti-inflammatory effect in osteoarthritis patients [4]. These findings indicate that inflammatory biomarkers can potentially serve as objective measures of rehabilitation efficacy in OA.

In the context of neurological rehabilitation, inflammatory markers have also shown utility. Previous studies suggest that the level of activation of inflammatory responses in the periphery correlates with the severity of cognitive impairment in patients with neurodegenerative diseases and can serve as an indicator of the activity of the current pathological process in the brain. Epigenetic factors are also suggested to influence the regulation of neuroinflammation and cognitive recovery in elderly patients, which opens up a wide spectrum of therapeutic strategies for the treatment of age-associated diseases [5].

Neurophysiological Biomarkers

Neurophysiological biomarkers, particularly those derived from electroencephalography (EEG), have emerged as valuable tools in guiding rehabilitation for neurological conditions. Recent advances in EEG signal processing and recording technology have demonstrated remarkable phenomena in humans previously only recorded invasively in animals, such as the electrical correlates of memory consolidation during sleep. EEG offers an advantage over fMRI in that it can explore real-time spontaneous electrical brain activity with excellent temporal resolution (milliseconds). When coupled with new forms of mathematical signal analysis (signal coherence, fractal dimension, small world and entropy analyses), EEG can be used to investigate functional connectivity and explore how neural networks are organized and interact [6].

Delta waves, in particular, have been identified as a potentially important biomarker of brain plasticity. Slow delta waves (DW) during non-rapid eye movement (NREM) sleep have been associated with memory consolidation. DW are the most prominent EEG feature of human NREM sleep, originating in cortical neurons and proposed as possible effectors of sleep-dependent synaptic plasticity [6]. High-density EEG studies have revealed an increase in parietal cortex DW after learning a visuo-motor task, while DW activity was reduced over sensorimotor cortex if the contralateral arm was immobilized during the day. In the latter case, synaptic depression was confirmed behaviorally by reduced motor performance and physiologically by reduced amplitude sensory evoked responses. The sensitivity of sleep DW to neural plasticity was also corroborated by demonstrating changes in DW after the induction of long-term potentiation (LTP) and depression-like phenomena in the brain following repetitive TMS [6].

In stroke rehabilitation, EEG biomarkers have shown particular promise. Clinical studies on acute stroke patients have demonstrated that delta waves of the affected hemisphere are a very sensitive indicator of neuronal dysfunction, related to both the lesion volume and the acute neurological deficit. The spread of delta waves from the affected to unaffected hemisphere is associated with poor prognosis. Indeed, EEG or magnetoencephalography measures of delta wave activity in acute stroke can provide additional predictive value of clinical recovery at 3 months over and above that given by clinical examination alone [6].

Another study has highlighted the potential of EEG biomarkers in spinal cord injury (SCI) rehabilitation. In SCI patients undergoing robotic-assisted gait training, high beta EEG activity in the central area had a negative correlation with gait and balance measured at baseline, in a way that greater high beta EEG power was related to worse clinical function. Moreover, improvement in gait and balance had negative correlations with the change in alpha/theta ratio in the parietal area. These findings suggest that EEG parameters may serve as potential surrogate markers of functional improvement during rehabilitation for SCI patients [7].

Gamma oscillations have also been identified as a potential biomarker for motor learning. A significant relation between motor performance and neural activity was found for Alpha ($p = 0.0149$) and Gamma (0.0005) oscillatory patterns. Specifically, gamma oscillations with frequencies between 41 and 49.75 Hz appear to be an adequate EEG marker for motor performance guided through the action observation network. This technology is easy to use, low-cost, and presents valid measurements for the recommended oscillatory frequencies, implying possible use in rehabilitation by collecting data in real-time during therapeutic interventions and assessments [8].

Other Physiological Biomarkers

Beyond inflammatory and neurophysiological markers, various other physiological biomarkers have demonstrated utility in guiding rehabilitation strategies. Heart rate variability (HRV) represents one such promising biomarker. High-intensity interval training (HIIT) has proven effective in cardiac rehabilitation programs, but due to inter-individual variability in physiological responses to training associated with cardiovascular diseases, exercise regimens should be closely controlled and individualized. Heart rate variability (HRV) is being used for this purpose, as it is closely linked to parasympathetic nervous system activation, with high HRV scores associated with good cardiovascular adaptation. Research has investigated the effect of HRV-guided training compared to standard HIIT in terms of cardiorespiratory fitness, heart rate variability, functional parameters, body composition, quality of life, inflammatory markers, and cognitive function in stroke patients [9].

Muscle oxygen saturation (SmO2) has emerged as a valuable biomarker in orthopedic rehabilitation. Clinical practice guidelines for rehabilitation following ACL reconstruction (ACLR) traditionally emphasize functional and strength testing, patient-reported outcomes, chronobiological age, and physician expertise. However, recent literature has suggested that muscle oxygen saturation (SmO2) may be an important marker to indicate the internal physiological recovery of the quadriceps following ACLR [10]. Research has found that at 6-months post-op, surgical limbs had significantly higher SmO2% during all exercises compared to the contralateral healthy limb, with this difference persisting at 9-months but beginning to normalize by 12-months for some exercises. While shorter exercises saw a return of normal physiology by 12 months, exercises of longer duration remained statistically different. This suggests that while athletes may reach external parameters for return to play by 9-months post-op, internal muscle physiology continues to

recover up to and potentially beyond the 12-month time point [10].

Oxidative stress markers have shown utility in monitoring rehabilitation progress in chronic obstructive pulmonary disease (COPD). COPD involves local and systemic factors such as inflammation, exacerbated immune response, and oxidative stress. The use of oxidative stress parameters as progression markers or even as a way to monitor the response to non-pharmacological interventions, like pulmonary rehabilitation (PR), is feasible [11]. Research has demonstrated that intracellular and extracellular capacity (GSH/GSSG and FRAP) in patients undergoing PR increased significantly after 10 sessions compared to baseline values. Blood lipid peroxidation showed significant reduction at both the 10th and 20th sessions, demonstrating improvements in oxidative parameters with long-term exercise [11].

Biomarker-Guided Rehabilitation in Different Conditions

Under Neurological Conditions- Stroke Rehabilitation

Stroke rehabilitation has been at the forefront of biomarker-guided approaches. Post-stroke cognitive impairment affects more than one-third of patients after an ischemic stroke (IS). Identifying markers of potential cognitive recovery after ischemic stroke can guide patient selection for treatments, enrollment in clinical trials, and cognitive rehabilitation methods to restore cognitive abilities in post-stroke patients [12]. Research utilizing structural Magnetic Resonance Imaging (MRI) has highlighted baseline markers of cerebral small vessel disease and cortical atrophy as predictors of cognitive recovery. Functional Magnetic Resonance Imaging (fMRI) using resting-state functional connectivity and Diffusion Imaging have emerged as potential biomarkers of cognitive recovery after IS, although more precise predictive tools are still needed [12].

The relationship between brain activity and limb motor function in stroke has been explored using various neuroimaging techniques. Limb motor dysfunction is a common complication of stroke and an important factor in disability, making the restoration of limb function a crucial task in rehabilitation. Accurate assessment of motor function in stroke patients forms the basis for formulating effective rehabilitation strategies. With the development of neuroimaging technology, researchers have begun to study objective evaluation methods for limb motor dysfunction in stroke to determine reliable neural biomarkers that can accurately identify brain functional activity and its relationship with limb motor function [13].

The prefrontal cortex (PFC) plays an important role in motor control and in response to motor state changes. Research has found that PFC network characteristics of stroke patients are related to their motor function status, and the topological properties of the PFC network under resting state can predict the motor function of stroke patients to some extent. Functional near-infrared spectroscopy (fNIRS) has been used to evaluate prefrontal neuroplasticity markers and their relationships with limb motor function in stroke patients with limb motor dysfunction, which could help clarify the relationship between brain neuroplasticity and cerebral hemodynamics [13].

Gene expression biomarkers have also shown potential in predicting stroke recovery outcomes. In ischemic stroke, the concentration of hemoglobin (Hb) is determined by genes expressed several hours earlier, creating a time gap between gene expression and protein concentration that could make these genes predictive biomarkers for IS outcome [14]. Research has identified several genes positively correlated with the recovery degree of IS patients, including ELANE, FGF23, HBB, PIEZO1, RASA4, and PRTN3, while CPM was negatively correlated with clinical outcomes. These genes could be considered as new predictors for the recovery of IS patients [14].

Graph theoretic measures of brain connectivity have also emerged as potential biomarkers for assessing rehabilitation efficacy. One of the challenges in stroke rehabilitation is identifying biomarkers that correlate with amelioratory changes in the recovery of brain function that can be verified by a clinician. For strokes related to the upper extremity, clinicians use the Fugl Meyer Assessment - Upper Extremity (FMA-UE) score for verification. Research has hypothesized that even before clinical measures of function recovery show facilitatory changes, structural and functional changes in the brain connectome may indicate early changes in stroke patients. Graph theoretic measures on structural and functional connectivity matrices have been proposed as early biomarkers of rehabilitation-related changes in brain plasticity [15].

Spinal Cord Injury Rehabilitation

Biomarkers have shown considerable promise in guiding rehabilitation for spinal cord injury (SCI) patients. Brain plasticity is an intrinsic property of the nervous system that is modified during its lifetime. This is one mechanism of recuperation after injuries with an important role in rehabilitation. Evidence suggests that injuries in the nervous system disturb the stability between inhibition and excitability essential for the recuperation process of neuroplasticity [16]. However, the mechanisms involved in this balance are not completely understood, and despite advancement in the field, the knowledge has had a low impact on the rehabilitation practice. Therefore, understanding the relationship between biomarkers and functional disability may help to optimize and individualize treatments and build consistent studies in the future [16].

EEG biomarkers have been particularly valuable in assessing functional recovery in SCI. Functional changes after spinal cord injury (SCI) are related to changes in cortical plasticity, which can be measured with electroencephalography (EEG) and has potential to be used as a clinical biomarker [7]. In a study where SCI patients underwent robotic-assisted gait training, all participants showed clinical improvement with the rehabilitation program. EEG data revealed that high beta EEG activity in the central area had a negative correlation with gait and balance measured at baseline, with greater high beta EEG power related to worse clinical function. Moreover, improvement in gait and balance had negative correlations with the change in alpha/theta ratio in the parietal area. These findings suggest that in SCI, functional impairment and subsequent improvement following rehabilitation therapy with robotic-assisted gait training correlated with changes in cortical activity measured by EEG, indicating that EEG alpha/theta ratio may be a potential surrogate marker of functional improvement during rehabilitation [7].

Recent research has further explored the role of EEG oscillations as neuroplastic markers in SCI rehabilitation. Spinal cord injury (SCI) affects approximately 250,000 to 500,000 individuals annually, with current therapeutic interventions predominantly focusing on mitigating the impact of physical and neurological impairments, yet showing limited functional recovery in many patients. Electroencephalogram (EEG) oscillations have been investigated in the context of rehabilitation to identify effective markers for optimizing rehabilitation treatments [17]. Research has demonstrated a positive correlation between frontal delta asymmetry and depression symptoms, while the frontal alpha asymmetry band and anxiety symptoms were negatively correlated in SCI patients. Theta oscillations were negatively associated with motor-evoked potential (MEP), whereas alpha oscillations were positively associated with MEP in all regions of interest and negatively correlated with conditioned pain modulation (CPM) response. Based on the potential role of lower-frequency oscillations in exerting a salutogenic compensatory effect, detrimental clinical and neurophysiological markers, such as

depression and lower MEP, likely induce slow oscillatory rhythms. Alpha oscillations may indicate a more salutogenic state, often associated with various cognitive functions, such as attention and memory processing. These results reveal an attempt by the central nervous system to reorganize and restore function despite the disruption caused by SCI, challenging the notion that low-frequency EEG rhythms are associated with cortical lesions [17].

Musculoskeletal Conditions

Osteoarthritis (OA) represents a significant focus area for biomarker-guided rehabilitation strategies. Within the UK Armed Forces, musculoskeletal injuries account for over half of all medical downgrades and discharges, with osteoarthritis being more common in military personnel and likely contributing to this burden, both in its primary form and following injury (post-traumatic OA, PTOA), which typically presents in the third or fourth decade. OA is not a progressive 'wear and tear' disease, as previously thought, but a heterogenous condition with multiple aetiologies and modulators, including joint damage, abnormal morphology, altered biomechanics, genetics, low-grade inflammation and dysregulated metabolism [18].

Current clinical diagnosis of OA, based on symptomatic or radiological criteria, is followed by supportive measures, including education, exercise, analgesia, potentially surgical intervention, with a particular focus on exercise rehabilitation within the UK military. Recent developments in OA have led to a new paradigm of organ failure, with an emphasis on early diagnosis and risk stratification, prevention strategies (primary, secondary and tertiary) and improved aetiological classification using genotypes and phenotypes to guide management, with the introduction of biological markers (biomarkers) potentially having a role in all these areas. In the UK Armed Forces, multiple research studies are focusing on OA risk factors, epidemiology, biomarkers, and the effectiveness of different interventions [18].

The role of inflammatory biomarkers in OA rehabilitation has been further elucidated. Osteoarthritis (OA) is the most common chronic disease of human joints, with pathologic changes involving all tissues forming the joint and having the nature of inflammation with varying degrees of severity from an early stage. Analysis of the complex relationships indicates that the processes taking place inside the joint are not merely catabolic effects but also include anti-inflammatory anabolic processes that occur continually. These phenomena are driven by various mediators, with a key role attributed to the interactions within the cytokine network [19]. The most important group controlling the disease appears to be inflammatory cytokines, including IL-1 , TNF , IL-6, IL-15, IL-17, and IL-18, balanced by anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. The role of these inflammatory and anti-inflammatory cytokines in the pathogenesis of OA with respect to inter- and intracellular signaling pathways continues to be investigated [19].

Post-COVID and Other Conditions

The COVID-19 pandemic has accelerated research into biomarker-guided rehabilitation strategies for post-COVID syndrome. The development of post-COVID syndrome is accompanied by an increase in markers of systemic inflammation and a violation of the detoxification function of the liver, caused by both direct viral damage to hepatocytes and an increased iatrogenic load on the hepatobiliary system due to polypharmacy [20]. Research has assessed patients with post-COVID syndrome aged 30 to 60 years, with steatosis and steatohepatitis (increased levels of liver transaminases), evaluating the clinical effectiveness of hepatoprotective treatments based on the dynamics of pro-inflammatory biomarkers, liver metabolism indicators, as well as functional tests and psychological questionnaires. Findings indicated that targeted rehabilitation interventions led to a more pronounced improvement in lipid metabolism parameters, correction of liver metabolism parameters, a decrease in the level of pro-inflammatory biomarkers, and an improvement in the quality of life compared to control groups [20].

Neurotherapy approaches guided by biomarkers have shown promise in managing long neuro-COVID Parkinson's-like syndrome. In a case study of a 51-year-old female artist who contracted COVID-19, four months after the acute phase, the patient weakened and presented a set of neurological symptoms resembling Parkinson's disease. Neurodiagnosis conducted by a multidisciplinary team (a neurologist, a neuropsychiatrist, and a neuropsychologist) led to the diagnosis of long neuro-COVID Parkinson's-like syndrome [21]. In the neurodiagnosis, the Human Brain Index (HBI) methodology was used, which provides diagnostics of various disease syndromes using quantitative qEEG and event-related potentials (ERPs) neuromarkers. Comparison of EEG spectra with normative data revealed excess Rolandic beta (a neuromarker of Parkinson's disease) and frontal alpha asymmetry with a strong alpha component generated in the left frontal-temporal areas (a neuromarker of depression) [21]. Based on these identified changes, the patient was referred to specialized care, dopaminergic treatment, and antidepressants were introduced. An individualized neurotherapy program using EEG-Neurofeedback and art therapy tailored to the patient's needs was also proposed. This case study highlights the complexity of diagnosing and treating long neuro-COVID Parkinson's-like syndrome and the use of advanced neurotechnologies in identifying specific neurological markers. The individualized neurotherapy program played a significant role in the patient's recovery and improvement in quality of life, underscoring the importance of personalized treatment plans and multidisciplinary care in managing long-term neurological effects of COVID-19 [21].

Biomarker-guided approaches have also been explored in psychosocial rehabilitation for schizophrenia. An important aspect of rehabilitation programs is assessment of their effectiveness, which is carried out mainly through clinical and psycho-pathological examinations, psychometric and psychological scales and questionnaires. The use of biological markers of the schizophrenic process to assess the effectiveness of rehabilitation assistance is of considerable interest [22]. Research has compared the clinical and socio-psychological characteristics of schizophrenia patients receiving psychosocial treatment in various forms of psychiatric care with the level of immune system activation reflecting the activity and severity of the pathological process in the brain. In a study of 77 schizophrenia patients in remission of varying quality, both patient groups showed a similar increase in the level of inflammatory and autoimmune markers compared to control [22]. The group that participated in a long-term comprehensive rehabilitation program compared to those receiving short-term assistance had significantly higher levels of social functioning, stress resistance, awareness of the disease, motivation, and comprehensiveness, as well as less severity of psycho-pathological symptoms. These results indicate the effectiveness of a long-term comprehensive rehabilitation program to stabilize clinical remission, improve social functioning and the quality of life in schizophrenia patients, despite the active pathological process in the brain [22].

Methodological Approaches and Technologies

A variety of methodological approaches and technologies have been employed to identify and utilize biomarkers in rehabilitation strategies. Neuroimaging techniques have been particularly valuable. Several neurophysiological assessment methods, including transcranial magnetic stimulation, electroencephalography, functional near-infrared spectroscopy, and magnetic resonance imaging, have been employed to assess plasticity in the motor cortex before and after rehabilitation [16].

Over the last decades, the availability of sophisticated neuroimaging techniques, particularly functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS), has made it possible to explore in vivo the on-line functioning of the brain and its plasticity. However, the impressive visual impact of fMRI and the quick and reliable measures obtained by TMS have tended to divert attention from one of the oldest neuroimaging techniques available in humans: electroencephalography (EEG) [6].

Functional near-infrared spectroscopy (fNIRS) has emerged as a valuable tool for assessing brain activity in rehabilitation contexts. In a study of stroke patients with limb motor dysfunction, fNIRS was used to collect 22 channels of cerebral blood oxygen signals in the prefrontal cortex (PFC) in the resting state. Differences in prefrontal oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) concentrations were analyzed between stroke patients and healthy subjects, and the lateralization index (LI) of HbO in stroke patients was calculated. Pearson's correlation analysis was performed between the LI and the scores of the Fugl-Meyer Assessment Scale (FMA) of motor function in stroke patients [13]. Results found that the prefrontal HbO concentration was significantly decreased in stroke patients with limb motor dysfunction compared with healthy subjects, and there was a significant, positive correlation between the LI of the PFC and FMA scores in stroke patients. These findings show that stroke can cause cerebral hemodynamic changes in the PFC, and the functional imbalance of the left and right PFC in the resting state is correlated with the severity of limb motor dysfunction, emphasizing that cerebral hemodynamic activity reflected by fNIRS could be used as a reliable neural biomarker for assessing limb motor dysfunction in stroke [13].

Advanced computational approaches have been developed to analyze biomarker data and guide rehabilitation strategies. The past decade has witnessed an explosive proliferation of data analytics modalities seeking to unravel insight into large-scale data sets. Machine learning and AI methodologies now occupy a central role in analyses of data sets ranging from genomics, "omics", clinical, real-world evidence, and demographic data. Despite advances in data analytics/machine learning and access to complex population-level clinical and related datasets, translating information into actionable guidance in human health and disease remains a challenge. The Interrogative Biology platform, a systems biology/AI approach, generates an unbiased, data-informed network for identifying targets (disease drivers) and biomarkers for disease interception at the point of transition to dysregulation, preceding clinical phenotype [23].

Recent advances in automated pattern identification of neuroimaging data can provide empirical support for developing training programs for rehabilitation. For example, in a study focusing on cochlear implant (CI) users, a machine-learning approach was used to identify emotion-processing bio-markers in high-density electroencephalograms. Participants' brain responses elicited by short musical and vocal emotional (happy, sad, and neutral) stimuli were used to train an algorithm to help identify, in each group, the pattern of brain responses that can best predict the presented emotion. Using this approach, researchers were able to confirm the presence of emotion-specific patterns of brain activity in CI users despite their reported emotion perception deficit, bringing forward support for implementing a rehabilitation program for emotion perception for this population [24].

Wearable sensors represent an emerging technology for biomarker monitoring in rehabilitation. In a study involving athletes following ACL reconstruction, a non-invasive and fully wireless Moxy™ muscle oxygen sensor was placed over the athletes' vastus medialis (VMO) muscles bilaterally to monitor muscle oxygen saturation during various exercises, allowing for continuous data collection throughout rehabilitation [10]. Similarly, in human-robot interaction for rehabilitation, real-time kinematics or electromyography (EMG) feedback has been shown to improve rehabilitation using assist-as-needed strategies. Muscle forces are expected to provide even more comprehensive information than EMG to control assistive rehabilitation devices, though measuring in vivo muscle force is challenging. Moving horizon estimator (MHE) algorithms have been employed to track experimental biosignals in real-time, providing consistent estimates of muscle forces and kinematics with visual feedback [25].

Clinical Applications and Outcomes

The clinical application of biomarker-guided rehabilitation strategies has demonstrated promising outcomes across various conditions. In stroke rehabilitation, biomarkers have been used to predict recovery and guide intervention intensity. A narrative review summarizing the current literature on the use and utility of neuroimaging as a predictive biomarker of cognitive recovery after ischemic stroke found that most studies utilized structural Magnetic Resonance Imaging (MRI) to predict cognitive recovery, highlighting baseline markers of cerebral small vessel disease and cortical atrophy as predictors. Functional Magnetic Resonance Imaging (fMRI) using resting-state functional connectivity and Diffusion Imaging emerged as potential biomarkers of cognitive recovery, although more precise predictive tools are needed. Comparison of these studies is limited by heterogeneity in cognitive assessments, and for all modalities, current findings need replication in larger samples. Although no neuroimaging tool is ready for use as a biomarker at this stage, these studies suggest a clinically meaningful role for neuroimaging in predicting post-stroke cognitive recovery [12].

In the context of COVID-19 rehabilitation, biomarker-guided approaches have shown efficacy. The inclusion of targeted interventions in the rehabilitation program for patients with post-COVID syndrome leads to a more pronounced improvement in lipid metabolism parameters, correction of liver metabolism parameters, a decrease in the level of pro-inflammatory biomarkers, and an improvement in the quality of life than in control groups. Significantly positive dynamics in the severity of complaints of general weakness and sleep disturbance, as well as indicators of memory impairment and impaired concentration, could indicate the achievement of anabolic, neurotrophic, and bioenergetic effects. A significantly significant decrease in the level of liver transaminases indicates the hepatoprotective effect, while normalization of elevated pro-inflammatory markers (ferritin, IL-6, CRP) may indicate anti-inflammatory and immuno-regulatory effects. Based on these findings, course prescriptions targeting pro-inflammatory markers and hepatoprotection can be recommended for use in complex non-drug rehabilitation to increase its clinical effectiveness and improve subjective indicators of the quality of life of patients with post-COVID syndrome [20].

Biomarker-guided nutritional rehabilitation has shown promise in anorexia nervosa (AN). Anorexia nervosa is a severe psychiatric disorder characterized by profound nutritional deficits and significant alterations in body composition, cellular integrity, and hydration. Nutritional rehabilitation is critical not only for weight restoration but also for improving body composition and metabolic functions. However, optimal strategies for integrating caloric and protein intake to achieve balanced recovery remain underexplored. Research has aimed to evaluate the interactions between caloric/protein intake and time on quantitative (weight and BMI) and qualitative (body composition and cellular health) outcomes, and to identify markers that predict recovery trajectories and guide

personalized nutritional interventions [26]. Findings have shown that caloric intake predominantly influenced early fat mass recovery, while protein intake was crucial for preserving lean tissues and promoting cellular regeneration. Interaction effects between caloric/protein intake and time revealed dynamic changes in body composition, underscoring the need for adaptive strategies.This highlights the importance of a dynamic, marker-based approach to nutritional rehabilitation in AN, where integrating caloric and protein intake with advanced body composition and hydration markers enables personalized interventions and balanced recovery, shifting treatment toward a focus on qualitative improvements over weight restoration alone [26].

In cardiac rehabilitation, biomarkers have been used to monitor progress and predict outcomes. Heart-type fatty acid-binding protein (H-FABP) is a non-invasive bio-marker with high sensitivity and specificity, capable of pointing out myocardial injury and predicting major adverse cardiovascular events (MACE). Cardiac rehabilitation programs, through complex and sustained post-interventional management, play an important role in reducing the plasma levels of H-FABP [27]. In a study of post-coronary artery bypass (CABG) patients, H-FABP values decreased both in diabetics and in non-diabetics between two phases of cardiac rehabilitation, 6 months apart from CABG. More than half of the patients had an important reduction of H-FABP at 6 months after the onset of the CR program, with diabetic patients showing a more noticeable reduction. Ischemic lesion during open heart surgery is linked to high levels of H-FABP and with an occurrence risk of postoperative atrial fibrillation, highlighting the importance of metabolic control as a target of the complex management in cardiac rehabilitation [27].

Limitations and Challenges

Despite the promising advances in biomarker-guided rehabilitation strategies, several limitations and challenges persist. Biomarker-driven rehabilitation faces challenges such as standardization, ethical considerations, and technological demands [2]. These challenges are multifaceted and require consideration in the development and implementation of biomarker-guided approaches.

One significant challenge is the heterogeneity in biomarker assessment methodologies and the lack of standardization. In the context of neuroimaging biomarkers for cognitive recovery after stroke, comparison of studies is limited by heterogeneity in cognitive assessments, and for all modalities, current findings need replication in larger samples [12]. This lack of standardization makes it difficult to compare results across studies and establish clear clinical guidelines.

The limited understanding of the relationship between biomarkers and functional outcomes represents another challenge. Evidence suggests that injuries in the nervous system disturb the stability between inhibition and excitability essential for the recuperation process of neuroplasticity. However, the mechanisms involved in this balance are not completely understood, and despite advancement in the field, the knowledge has had a low impact on the rehabilitation practice [16].

The technical complexity and cost of certain biomarker assessment technologies also pose challenges to widespread clinical implementation. Challenges such as cost, accessibility, and the need for interdisciplinary collaboration remain critical considerations in the integration of laboratory diagnostics into physical therapy practices [1]. This is particularly relevant for advanced neuroimaging techniques and genetic testing, which may not be readily available in all rehabilitation settings.

The translation of research findings into clinical practice remains a significant challenge. Patients, clinicians, researchers, and payers are seeking to understand the value of using genomic information to inform clinical decision-making. However, challenges exist to widespread clinical implementation of genomic medicine, a prerequisite for developing evidence of its real-world utility [28]. Similar challenges exist for other types of biomarkers in rehabilitation settings.

Finally, there is a need for more robust evidence on the effectiveness of biomarker-guided rehabilitation strategies compared to conventional approaches. Although no neuroimaging tool is ready for use as a biomarker at this stage, studies suggest a clinically meaningful role for neuroimaging in predicting post-stroke cognitive recovery [12]. More research is needed to establish the clinical utility and cost-effectiveness of biomarker-guided approaches in various rehabilitation contexts.

Future Directions and Research Gaps

The field of biomarker-guided rehabilitation strategies is rapidly evolving, with several promising directions for future research. One of the main hypotheses in current research is that the level of intracortical inhibition is related to functional deficits. By developing a better understanding of the neuroplasticity mechanisms involved in rehabilitation, researchers expect to build neurophysiological "transdiagnostic" biomarkers, especially markers of inhibition, which will have great relevance in the scientific and therapeutic improvement in rehabilitation [16].

There is a growing need for large-scale, longitudinal studies to validate the predictive value of biomarkers in rehabilitation outcomes. The Deficit of Inhibition as a Marker of Neuroplasticity study (DEFINE) is following four groups (stroke, spinal cord injury, limb amputation, and osteoarthritis) to understand the neuroplasticity mechanisms involved in motor rehabilitation. With a plan to recruit 500 subjects (including 100 age- and sex-matched controls), this study employs a battery of neurophysiological assessments to assess plasticity on the motor cortex before and after rehabilitation [16]. Such comprehensive studies are essential for establishing the utility of biomarkers in guiding rehabilitation strategies.

The integration of multiple biomarkers into predictive models represents another important direction. A combination of CCL5, IL-1Ra and IL-10 at week 1 may predict patient outcomes in COVID-19 [3]. This suggests that examining combinations of biomarkers, rather than individual markers, may provide more robust predictive value for rehabilitation outcomes across various conditions.

The development of point-of-care testing for biomarkers in rehabilitation settings is another area for future research. Technology used for assessing EEG biomarkers can be easy to use, low-cost, and present valid measurements for the recommended oscillatory frequencies, implying possible use in rehabilitation by collecting data in real-time during therapeutic interventions and assessments [8]. Advances in wearable sensors and portable diagnostic devices may facilitate the real-time monitoring of biomarkers during rehabilitation, allowing for more responsive and adaptive interventions.

Personalized rehabilitation strategies based on individual biomarker profiles represent a promising direction. Early diagnosis of a patient's cognitive and psycho-emotional functions using neuropsychological markers can be useful in further personalized management of rehabilitation treatment using virtual reality technologies [29]. The integration of biomarker assessment with emerging technologies such as virtual reality and telemedicine may enable more personalized and accessible rehabilitation approaches.

There is also a need for research on the cost-effectiveness of biomarker-guided rehabilitation strategies. Research comparing HRV-guided training with standard HIIT in stroke patients could evaluate outcomes in terms of cardio-respiratory fitness, heart rate variability, functional parameters, body composition, quality of life, inflammatory markers, and cognitive function, as well as assess the feasibility of patients undertaking an 8-week cardiac rehabilitation program, evaluating its safety and their adherence. Such comprehensive assessments could determine whether biomarker-guided approaches offer advantages in terms of both clinical outcomes and resource utilization [9].

CONCLUSION

Biomarker-guided rehabilitation strategies represent a promising frontier in personalized rehabilitation medicine, offering the potential to optimize interventions, predict outcomes, and enhance recovery across various conditions. This review has examined the diverse types of biomarkers being utilized in rehabilitation contexts, including inflammatory markers, neurophysiological indicators, and other physiological parameters. These biomarkers provide valuable insights into disease processes, recovery potential, and response to interventions, enabling more tailored and effective rehabilitation approaches.

The application of biomarker-guided strategies has shown particular promise in neurological conditions such as stroke and spinal cord injury, musculoskeletal conditions like osteoarthritis, and emerging areas such as post-COVID syndrome. Across these contexts, biomarkers have demonstrated utility in predicting recovery trajectories, guiding intervention intensity, monitoring progress, and evaluating outcomes.

A variety of methodological approaches and technologies have been employed to identify and utilize biomarkers in rehabilitation, including neuroimaging techniques, wearable sensors, and advanced computational approaches. These diverse methodologies reflect the multifaceted nature of rehabilitation and the need for comprehensive assessment of patient status and progress.

Despite significant advances, several challenges persist, including the heterogeneity in biomarker assessment methodologies, limited understanding of the relationship between biomarkers and functional outcomes, technical complexity and cost of certain assessment technologies, and the need for more robust evidence on effectiveness compared to conventional approaches.

Future research directions should focus on large-scale longitudinal studies, integration of multiple biomarkers into predictive models, development of point-of-care testing, personalized rehabilitation strategies based on individual biomarker profiles, and cost-effectiveness analyses. By addressing these research gaps, the field of biomarker-guided rehabilitation can continue to evolve and enhance patient outcomes through more precise, personalized, and effective interventions.

The evolution of biomarker-guided rehabilitation strategies represents a significant paradigm shift from standardized protocols toward precision medicine in rehabilitation. By leveraging objective biological indicators to inform clinical decision-making, this approach has the potential to optimize rehabilitation outcomes, reduce healthcare costs, and improve quality of life for patients across a wide range of conditions.

REFERENCES

1. Alqahtani, M. F., Alqahtani, A. S., Asiri, A. Y., Alqahtani, R., Arishi, A. A., & Alqahtani, S. Y. (2024). The intersection of laboratory testing and physical therapy: implications for patient rehabilitation – a systematic review. Journal of Ecohumanism. https://doi.org/10.62754/joe.v3i8.5576
2. Mathur, N. & Mathur, S. (2025). The use of biomarkers in physiotherapy for personalized medicine. PARIPEX-INDIAN JOURNAL OF RESEARCH. https://doi.org/10.36106/paripex/6300176
3. Zhao, Y., Qin, L., Zhang, P., Li, K., Liang, L., Sun, J., Xu, B., Dai, Y., Li, X., Zhang, C., Peng, Y., Feng, Y., Li, A., Hu, Z., Xiang, H., Ogg, G., Ho, L., McMichael, A., Jin, R., … Zhang, Y. (2020). Longitudinal covid-19 profiling associates il-1ra and il-10 with disease severity and rantes with mild disease.. JCI Insight. https://doi.org/10.1172/jci.insight.139834
4. Idzik, M., Poloczek, J., Skrzep-Poloczek, B., Dró d , E., Che mecka, E., Czuba, Z., Jochem, J., & Stygar, D. (2022). The effects of 21-day general rehabilitation after hip or knee surgical implantation on plasma levels of selected interleukins, vegf, tnf- , pdgf-bb, and eotaxin-1. Biomolecules. https://doi.org/10.3390/biom12050605
5. Kurmyshev, M., Zozulya, S., Zakharova, N. V., Barkhatova, A., Nikiforova, I., & Klyushnik, T. (2022). Markers of systemic inflammation in assessing the effectiveness of neurocognitive rehabilitation in aged patients with mild cognitive impairment. Psikhiatriya. https://doi.org/10.30629/2618-6667-2022-20-3-47-56
6. Assenza, G. & Lazzaro, V. D. (2015). A useful electroencephalography (eeg) marker of brain plasticity: delta waves. Neural Regeneration Research. https://doi.org/10.4103/1673-5374.162698
7. Simis, M., Camsari, D. D., Imamura, M., Filippo, T. R., Souza, D. R. D., Battistella, L., & Fregni, F. (2021). Electroencephalography as a biomarker for functional recovery in spinal cord injury patients. Frontiers in Human Neuroscience. https://doi.org/10.3389/fnhum.2021.548558
8. Toledo, F. & Thaler, M. (2020). Gamma frequencies as a predictor for the accomplishment of a motor task guided through the action observation network. NeuroRehabilitation (Reading, MA). https://doi.org/10.3233/NRE-201508
9. Carrasco-Poyatos, M., Granero-Gallegos, A., López-García, G., & López-Osca, R. (2022). Hrv-guided training for elders after stroke: a protocol for a cluster-randomized controlled trial. International Journal of Environmental Research and Public Health. https://doi.org/10.3390/ijerph191710868
10. Moyal, A. J., VanBibber, H. D., Geletka, B. J., Seshadri, D. R., Calcei, J., & Voos, J. E. (2024). Poster 309: wearable muscle oxygen saturation sensor to guide return to play post-aclr. Orthopaedic Journal of Sports Medicine. https://doi.org/10.1177/2325967124s00276
11. Romero-Dapueto, C. & Castillo, R. (2021). Oxidative stress markers in copd patients admitted to pulmonary rehabilitation. The Open Respiratory Medicine Journal. https://doi.org/10.2174/1874306402115010068
12. Tahmi, M., Kane, V. A., Pavol, M., & Naqvi, I. (2022). Neuroimaging biomarkers of cognitive recovery after ischemic stroke. Frontiers in Neurology. https://doi.org/10.3389/fneur.2022.923942
13. Wang, D., Wang, J., Zhao, H., Liang, Y., Zhang, W., Li, M., Liu, H., Hu, D., Zhang, S., Xing, E., Su, Y., Yu, W., Sun, J., & Yang, A. (2023). The relationship between the prefrontal cortex and limb motor function in stroke: a study based on resting-state functional near-infrared spectroscopy. Brain Research. https://doi.org/10.2139/ssrn.4209858
14. Wang, Y., Huang, X., Liu, J., Zhao, X., Yu, H., & Cai, Y. (2019). A systems analysis of the relationships between anemia and ischemic stroke rehabilitation based on rna-seq data. Frontiers in Genetics. https://doi.org/10.3389/fgene.2019.00456
15. Sravanthi, U. N. S., Dadi, K., Bapi, R. S., Sylaja, P., Kesavadas, C., Pr, S., & Paul, R. (2023). Application of graph theoretic measures for assessing efficacy of stroke rehabilitation. IEEE International Joint Conference on Neural Network. https://doi.org/10.1109/IJCNN54540.2023.10191122
16. Simis, M., Imamura, M., Melo, P. S. D., Marduy, A., Battistella, L., & Fregni, F. (2021). Deficit of inhibition as a marker of neuroplasticity (define study) in rehabilitation: a longitudinal cohort study protocol. Frontiers in Neurology. https://doi.org/10.3389/fneur.2021.695406
17. Lacerda, G. J. M., Camargo, L., Imamura, M., Marques, L., Battistella, L., & Fregni, F. (2024). Eeg oscillations as neuroplastic markers of neural compensation in spinal cord injury rehabilitation: the role of slow-frequency bands. Brain Science. https://doi.org/10.3390/brainsci14121229
18. O'Sullivan, O., Behan, F., Coppack, R., Stocks, J., Kluzek, S., Valdes, A., Bennett, A., & O'Sullivan, A. M. O. (2023). Osteoarthritis in the uk armed forces: a review of its impact, treatment and future research. BMJ Military Health. https://doi.org/10.1136/military-2023-002390
19. Wojdasiewicz, P., Poniatowski, L. A., & Szukiewicz, D. (2014). The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators of Inflammation. https://doi.org/10.1155/2014/561459
20. Yurova, O., Konchugova, T., Apkhanova, T. V., Gilmutdinova, I., Vasileva, V. A., Kulchitskaya, D., Marchenkova, L., Glazachev, O., Dudnik, E. N., & Ansokova, M. A. (2024). Evaluation of the clinical effectiveness of the drug laennec in complex rehabilitation of patients with post-covid syndrome: a randomized trial. Bulletin of Rehabilitation Medicine. https://doi.org/10.38025/2078-1962-2024-23-1-38-48
21. P chalska, M., Goldberg, E., Góral-Pó rola, J., & Morga, R. (2025). Neurotherapy in long neuro-covid parkinson's-like syndrome. Acta Neuropsychologica. https://doi.org/10.5604/01.3001.0055.0198
22. Zozulya, S., Yastrebova, V., Solokhina, T., & Klyushnik, T. (2021). Assessment of the effectiveness of psychosocial rehabilitation in schizophrenia patients using biological markers. European psychiatry. https://doi.org/10.1192/j.eurpsy.2021.1350
23. Narain, N., Kiebish, M., Vishnudas, V., Tolstikov, V., Miller, G., Gesta, S., Granger, E., & Sarangarajan, R. (2021). Csao-1. interrogative biology: unraveling insights into causal disease drivers by use of a dynamic systems biology and bayesian ai to identify the intersect of disease and healthy signatures. Neuro-Oncology Advances. https://doi.org/10.1093/NOAJNL/VDAB070.001
24. Paquette, S., Gouin, S., & Lehmann, A. (2023). Utilizing auditory emotion biomarkers, the underpinning of emotion perception improvement in cochlear implant users. Journal of the Acoustical Society of America. https://doi.org/10.1121/10.0018863
25. Ceglia, A., Bailly, F., & Begon, M. (2023). Moving horizon estimation of human kinematics and muscle forces. IEEE Robotics and Automation Letters. https://doi.org/10.1109/LRA.2023.3291921
26. Dozio, E., Alonge, M., Tori, G., Caumo, A., Russo, R. G., Scuttari, E., Fringuelli, L.,

& Terruzzi, I. (2025). Dynamic nutrition strategies for anorexia nervosa: marker-based integration of calories and proteins. Nutrients. https://doi.org/10.3390/nu17030560

27. Namat, R. A., Felea, M., Costache, I., Aursulesei, V., Petri , A., Mitu, O., Constantin, M., Sorodoc, V., Sorodoc, L., Miftode, I., Miftode, R., Namat, N. A., Namat, D. A., Luta, A., Ion, A., Mihalcia, M. M., Ciocoiu, M., Tinic , G., & Mitu, F. (2018). Heart-type fatty acid-binding protein (h-fabp) in patients with type 2 diabetes beneficiaries of rehabilitation program post coronary artery bypass grafting. Revista de Chimie. https://doi.org/10.37358/rc.18.10.6608
28. Weitzel, K., Alexander, M., Bernhardt, B., Calman, N., Carey, D., Cavallari, L., Field, J., Hauser, D., Junkins, H., Levin, P. A., Levy, K. D., Madden, E. B., Manolio, T., Odgis, J. A., Orlando, L., Pyeritz, R., Wu, R. R., Shuldiner, A., Bottinger, E., ... Network, O. B. O. T. A. (2015). The ignite network: a model for genomic medicine implementation and research. BMC Medical Genomics. https://doi.org/10.1186/s12920-015-0162-5
29. Tynterova, A., Barantsevich, E., Khoymov, M., Shusharina, N. N., & Rozhdestvensky, A. (2023). Personalized approach in neurocognitive rehabilitation of patients in the acute period of ischemic stroke using virtual reality technologies. 2023 7th Scientific School Dynamics of Complex Networks and their Applications (DCNA). https://doi.org/10.1109/dcna59899.2023.10290552.