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Neurorehabilitation in neurotrauma: Treating traumatic brain and spinal cord injuries

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Neurorehabilitation in neurotrauma: Treating traumatic brain and spinal cord injuries

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Editorial: Neurorehabilitation in neurotrauma: treating traumatic brain and spinal cord injuries

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rehabilitation research, neurological rehabilitation, brain injuries, traumatic brain injury, spinal cord injury

Editorial on the Research Topic
Neurorehabilitation in neurotrauma: treating traumatic brain and spinal cord injuries

Traumatic Brain Injury (TBI) and Spinal Cord Injury (SCI) represent significant global public health challenges. The World Health Organization (WHO) estimates that about 69 million individuals suffer from TBI annually, and between 250,000 and 500,000 new cases of SCI occur each year (World Health Organization, 2019). These injuries have severe consequences on the lives and social reintegration of affected individuals, highlighting the need for innovative and effective interventions to promote functional recovery (Areas et al., 2019). Neurological rehabilitation, however, encounters major obstacles due to the heterogeneity of neurological injuries, which leads to variable treatment responses and hinders the development of standardized protocols. Additionally, the complexity of these disorders often requires multidisciplinary approaches that are challenging to coordinate and resource-intensive (Ponsford et al., 2000; Turner-Stokes, 2009). Limited access to specialized care and the high costs of advanced rehabilitation technologies further exacerbate these challenges, particularly in resource-constrained settings (Chrysafides et al., 2019).

Recent advancements in rehabilitation technologies have greatly expanded treatment options. Innovations such as deep brain stimulation, virtual reality, and robotic devices are transforming traditional therapeutic approaches (Holtzheimer and Mayberg, 2011; Hidler et al., 2009; Laver et al., 2017). Deep brain stimulation has shown potential in modulating neural circuits to enhance motor and cognitive functions in TBI and SCI patients (Holtzheimer and Mayberg, 2011). Virtual reality offers immersive rehabilitation environments that enhance motor learning and patient engagement (Laver et al., 2017). Robotic devices facilitate repetitive task practice and precise movements, which are crucial for neuroplasticity and functional recovery (Hidler et al., 2009). These technologies have demonstrated promising efficacy in improving motor and cognitive functions, significantly enhancing quality of life of patients (Kleim and Jones, 2008; Alvareza et al., 2018; Hillyard and Näätänen, 2018; Edgerton et al., 2019). The ongoing development of these technologies, along with

personalized rehabilitation approaches, continues to advance the field and offer innovative support for improved outcomes. In addition to these advancements, early rehabilitation efficacy is well-supported by evidence, but obstacles such as the lack of ideal predictive models and disparities in access to technologies persist, hindering progress (Kreuter and Højlund, 2020). Recent research has significantly contributed to the better understanding of these conditions.

In their scientific study, Sudhakar et al. examined psychiatric and medical comorbidities associated with mild TBI using data from the national TBI Model Systems (TBIMS) database. Their findings revealed a high prevalence of psychiatric comorbidities, including anxiety, depression, and post-traumatic stress disorder (PTSD), alongside chronic pain and cardiovascular comorbidities among survivors of mild TBI. Additionally, Xu et al. conducted a network meta-analysis to evaluate the efficacy of five Chinese medicine monomers in functional recovery in animal models of SCI. Their review of 59 studies indicated that all monomers exhibited positive effects, with tanshinone IIA (TIIA) demonstrating efficacy in early recovery and resveratrol (RSV) in later stages. The study calls for further research to enhance the standardization and clinical application of these findings. another important study developed by Castellani et al. performed a multicenter retrospective study to assess the incidence of healthcare-associated infections (HAIs) and multidrug-resistant HAIs in patients with severe acquired brain injury (sABI). Their research involving 134 participants revealed significantly higher rates of HAIs and multidrug-resistant HAIs in semi-intensive units compared to other settings. In the field of exercise-centered neurological rehabilitation, Gorgey et al. investigated the combined effects of neuromuscular electrical stimulation-resistance training (NMES-RT) and functional electrical stimulation-cycling of the lower limbs (FES-LEC) vs. passive movement training (PMT) and FES-LEC in adults with chronic SCI. The study found a trend toward increased $\dot{V}O_2$ peak and reduced visceral fat in the NMES-RT + FES group compared to the PMT + FES group, although FES-LEC did not significantly enhance muscle cross-sectional area. However, in his scientific research, Snowden et al. conducted a systematic review of aerobic exercise as an intervention for TBI survivors. The review highlighted the effectiveness of aerobic exercise, particularly for adolescents and adults, and identified the need for additional studies focused on children and the elderly to adapt treatment guidelines for these specific populations.

An innovative study within a current context of global relevance carried out by Keleman et al. assessed the impact of the COVID-19 pandemic on early rehabilitation outcomes for TBI patients in Bosnia and Herzegovina. Analysis of data from 174 patients in 2021 indicated that the pandemic did not negatively affect clinical outcomes. Early rehabilitation remained effective, resulting in significant improvements in Glasgow Coma Scale, Barthel Index, and Functional Independence Measure scores. A clinical study performed by Zhi et al. at West China Hospital of Sichuan University was performed aiming to evaluate the efficacy and safety of acupuncture as a complementary therapy for Prolonged Disorders of Consciousness (pDOC). With 110 participants, the study aims to provide robust evidence regarding the efficacy and safety of acupuncture for pDOC, potentially informing clinical practices and future research. Eilfort et al. investigated the role of neuroplasticity in the reticulospinal (RS) and corticospinal (CS) systems in functional recovery following unilateral spinal cord injury, focusing on a patient with Brown-Séquard-plus Syndrome. Using the StartReact paradigm and transcranial magnetic stimulation (TMS), they observed a significant increase in ipsilateral RS activation in the biceps brachii, suggesting that elbow flexion recovery is primarily driven by the RS system. Eliason et al. evaluated the effectiveness of non-invasive brain stimulation (NIBS), including TMS and tDCS, both as standalone interventions and in combination with neurorehabilitation therapies. The review of 22 studies involving 657 participants revealed that while two studies found NIBS ineffective, the majority reported improvements in neuroplasticity and ABI-related symptoms.

These studies underscore the critical importance and substantial impact of neurorehabilitation research in understanding the effects of traumatic events on mortality in young individuals, years of life lost, and high incidence of disability. The breadth of interdisciplinary research in neuroscience highlighted in this editorial reflects the commitment of numerous researchers to developing effective interventions for global communities. Collectively, these studies emphasize the necessity of addressing neurological disorders as a significant public health issue, requiring targeted attention from researchers and policymakers. It is crucial that, in addition to the progress already made, ongoing research continues to tackle emerging questions to better guide efforts and investments in neurotrauma research. The significant impact of these conditions particularly on young adult mortality, years of life lost, and disability rates justifies increased allocation of resources and support. Future research is essential for deepening understanding and enhancing therapeutic strategies, and only through sustained and amplified investment can we effectively confront these challenges and reduce their associated consequences.

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FA: Conceptualization, Writing – original draft, Writing – review & editing. WD: Writing – original draft. GA: Writing – original draft. HJ: Writing – review & editing.

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Prevalence of comorbidities post mild traumatic brain injuries: a traumatic brain injury model systems study

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Traumatic brain injury (TBI) is associated with an increased risk of long-lasting health-related complications. Survivors of brain trauma often experience comorbidities which could further dampen functional recovery and severely interfere with their day-to-day functioning after injury. Of the three TBI severity types, mild TBI constitutes a significant proportion of total TBI cases, yet a comprehensive study on medical and psychiatric complications experienced by mild TBI subjects at a particular time point is missing in the field. In this study, we aim to quantify the prevalence of psychiatric and medical comorbidities post mild TBI and understand how these comorbidities are influenced by demographic factors (age, and sex) through secondary analysis of patient data from the TBI Model Systems (TBIMS) national database. Utilizing self-reported information from National Health and Nutrition Examination Survey (NHANES), we have performed this analysis on subjects who received inpatient rehabilitation at 5 years post mild TBI. Our analysis revealed that psychiatric comorbidities (anxiety, depression, and post-traumatic stress disorder (PTSD)), chronic pain, and cardiovascular comorbidities were common among survivors with mild TBI. Furthermore, depression exhibits an increased prevalence in the younger compared to an older cohort of subjects whereas the prevalence of rheumatologic, ophthalmological, and cardiovascular comorbidities was higher in the older cohort. Lastly, female survivors of mild TBI demonstrated increased odds of developing PTSD compared to male subjects. The findings of this study would motivate additional analysis and research in the field and could have broader implications for the management of comorbidities after mild TBI.

KEYWORDS

traumatic brain injury, comorbidities, prevalence, psychiatric, mild TBI, rehabilatation, medical complications

Introduction

Traumatic brain injury (TBI) constitutes one of the major global health challenges across the world (Gururaj, 2002; Langlois et al., 2006; Lawrence et al., 2016; Rao et al., 2018). TBI is known to be associated with several health-related complications both in the acute and chronic phases and progressively affects the quality of life of the patient population (Brooks et al., 1986; Shoumitro et al., 1999; Hibbard et al., 2000). Treating TBI and TBI-related comorbidities are challenging to the healthcare systems given the

number of people affected in civilian and military settings and the myriad of symptoms and comorbidities that ensue following the injury (Brooks et al., 1986; Hibbard et al., 2000; Gururaj, 2002; Langlois et al., 2006; Dean and Sterr, 2013; Lawrence et al., 2016; Danna-Dos-Santos et al., 2018). As a result, TBI and associated comorbidities could impose a severe financial burden on both the patient population and governments worldwide (Gururaj, 2002; Langlois et al., 2006; Kayani et al., 2009; Lee et al., 2021). Furthermore, numerous clinical trials to find a cure for TBI have failed to produce the desired benefit in the patient population (Ye et al., 2009; Stein, 2015; Sudhakar et al., 2019; Sudhakar, 2023). Existing treatment options focus on preventing secondary brain damage through careful clinical management of patients (Jacobi et al., 2002; Armitage-Chan et al., 2007; Flower and Hellings, 2012; Vella et al., 2017; Dash and Chavali, 2018; Ripley et al., 2019).

TBI can be categorized as mild, moderate, and severe injury types based on the scores of the patients reported using the Glasgow coma scale (GCS) (Robert Laskowski et al., 2015; Jain and Iverson, 2022). Mild TBI can occur as a result of concussion in sports activities, falls in elderly subjects, injuries on the battlefield, and whiplash injuries (Kraus and McArthur, 1996; Cassidy et al., 2004; Rutland-Brown et al., 2006; Robert Laskowski et al., 2015). While moderate-severe TBIs are responsible for a majority of death and disability (Kraus and McArthur, 1996; Cassidy et al., 2004; Rutland-Brown et al., 2006; Robert Laskowski et al., 2015), it has been reported that the incidence of mild TBI is higher compared to moderate-severe ones (Langlois et al., 2006). In addition to that, the incidence of mild TBI cases is often underreported in the literature because these estimates often do not encompass subjects who don't seek medical attention or in-patient hospitalization (Robert Laskowski et al., 2015). Mild TBI has often been termed a "silent epidemic" because the sign and symptoms of the injury don't usually manifest immediately leading to difficulties in diagnosis. Understanding the long-term health complications (Dean and Sterr, 2013; Danna-Dos-Santos et al., 2018) in the mild TBI population could lead to better disease management in the absence of any visible problems immediately after the injury (Robert Laskowski et al., 2015). Further adding to the woes of clinical TBI is the heterogeneity of injury types. Heterogeneity is an inherent component of TBI owing to several factors including the type and severity of the injury, the affected brain region(s), different pathoanatomical correlates, illness history, age, and sex, etc (Saatman et al., 2008; Maas, 2016). Heterogeneity is also widespread in mild TBI where distinct clusters of the patient population were reported across multiple datasets based on demographics, injury-related information, and laboratory metrics (Si et al., 2018a,b; Pugh et al., 2021). In addition to an incomplete understanding of the activation of cellular and molecular cascades post mild TBI (Werner and Engelhard, 2007; Schwab et al., 2022), the presence of widespread heterogeneity (Saatman et al., 2008; Maas, 2016; Si et al., 2018a,b) has made it quite challenging to come up with a drug to stop secondary brain injuries from happening (Ye et al., 2009) resulting in low success rates of numerous clinical trials (Ye et al., 2009; Stein, 2015; Sudhakar, 2023). When effective therapeutic options become limited for TBI, properly planned patient care (Vella et al., 2017; Dash and Chavali, 2018) along with proactive disease prevention measures could vastly improve patient experiences.

Several research studies have indicated that individuals with TBI exhibit an increased risk of developing a plethora of medical and mental-health comorbidities (Bryant et al., 2010; Bryant, 2011; Yeh et al., 2013; Jain et al., 2014; Katzenberger et al., 2015; Hammond et al., 2019; Stein et al., 2019). These conditions which severely affect the life of the patients fall under a wide umbrella of diseases that include the following: psychiatric and neurological impairments (Bryant et al., 2010; Bryant, 2011; Yeh et al., 2013; Jain et al., 2014; Hammond et al., 2019; Stein et al., 2019), cardiovascular ailments (Liao et al., 2014; Hammond et al., 2019), gastrointestinal (Katzenberger et al., 2015), and lastly those diseases that interfere with endocrine functioning (Tanriverdi et al., 2008). While these studies are very informative in providing information about the post-traumatic development of comorbidities, systematic studies exploring the prevalence of various health-related comorbidities at a discrete time point(s) post injury are required in the field. A previous TBIMS study quantified the prevalence of TBI comorbidities at a 10-year follow-up time period following the index injury (Hammond et al., 2019). This study elegantly reports the prevalence of 44 comorbidities collected using a survey method called Medical and Mental Health Comorbidities Interview (MMHCI) (Hammond et al., 2019). MMHCI was modelled based on National comorbidity survey replication for the mental health conditions and National Health and Nutrition Examination Survey (NHANES) (Center for Disease Control, National Center for Health Statistics, 1999) and was administered to a section of subjects in the TBI Model Systems (TBIMS) national database (Traumatic Brain Injury Model Systems Program, 2021), a neurotrauma registry consisting of longitudinal patient data collected from multiple trauma centres in the United States. While the study was very informative in reporting the prevalence of a list of 44 comorbidities for individuals with moderate-severe TBI, there is a larger need in the field to perform a similar analysis for subjects with mild TBI and understand how the prevalence of comorbidities post brain trauma depends on demographics and injury-specific variables. Our view was emphasized in a recent review of research studies (Tso et al., 2021) that have utilized the TBIMS database (Traumatic Brain Injury Model Systems Program, 2021), where the authors have pointed out that the comorbidity analyses that were performed using the database are quite sparse and the subject remains relatively unexplored.

We in this study employ a multidimensional approach in quantifying the prevalence of 26 comorbidities at 5- years post mild TBI. Using TBIMS national database (Traumatic Brain Injury Model Systems Program, 2021), we estimated the prevalence of comorbidities as a function of demographic variables (age and sex) from the data of subjects who received inpatient rehabilitation. Our results indicate individuals with mild TBI are confronted with various health-related ailments the prevalence of which is also influenced by age and sex, the two demographic variables included in the analysis.

Materials and methods

We performed an extensive analysis of patient data using the TBIMS national database

(Traumatic Brain Injury Model Systems Program, 2021) and quantified the prevalence of medical and mental health comorbidities at 5-years post mild TBI. In addition to that, we quantify the prevalence of comorbidities as a function of the age and biological sex of the subjects. The analysis of various psychiatric and medical comorbidities was performed using the public version of the TBIMS national database (Traumatic Brain Injury Model Systems Program, 2021). A request to access the public version of the database was placed in November 2021 and the request was approved a few days later (Traumatic Brain Injury Model Systems Program, 2021). Altogether, the TBIMS database contains information about 17,932 subjects (Traumatic Brain Injury Model Systems Program, 2021). Information about the comorbidities was collected using the National Health and Nutritional Examination Survey (NHANES) (Center for Disease Control, National Center for Health Statistics, 1999) where the subjects were asked a series of questions regarding the presence/absence of each comorbidity and their onset (before, at the same time, and after the index injury) at multiple follow up time point (1, 2, 5, 10, 15, 20, and 25 years). If a particular condition was found to be positive at the previous administration, the same item was refrained from asking again. Self-diagnosis was not accepted and only diagnosis originating from a doctor or a certified healthcare professional was included in the database. More information on NHANES administration can be found in the TBIMS data dictionary (Traumatic Brain Injury Model Systems Program, 2021). The public version of the database (Traumatic Brain Injury Model Systems Program, 2021) has information about 26 medical and mental health comorbidities of the subjects at multiple follow-up time points (Traumatic Brain Injury Model Systems Program, 2021). In this study, only data collected at 5-year follow-up was considered for analysis.

The database (Traumatic Brain Injury Model Systems Program, 2021) consists of subjects with a minimum age of 16 years and hence the same inclusion criteria were applied to our analysis. We grouped the subjects into three categories based on the severity of the index TBI: mild, moderate, and severe. The severity of TBI was determined using the Glasgow coma scale (GCS) (Jain and Iverson, 2022). All analyses in this study were performed on mild TBI subjects whose GCS scores fell between 13 and 15 (Jain and Iverson, 2022). Data analysis was performed using the Python programming language. Custom Python scripts were written and executed using the Google Collaboratory application (https://colab.research.google.com/). Patient data was read using the pandas python library (https://pandas.pydata.org/) and analysis of the prevalence of the comorbidities was performed thereafter. All scripts used in the study and data generated as a result of this study will be made available to the scientific community upon request.

Statistical analysis

All statistical analyses in this study were performed on mild TBI subjects. For each comorbidity, we computed the total number of mild TBI subjects who have the condition with onset at the same time or after the index injury at 5-year follow-up time point. Next, the percentage of subjects with a specific comorbidity was computed as the ratio of the number computed in the previous step to the total number of subjects with and without the condition. This number represents the observed prevalence of each comorbidity at a given follow-up time point (Hammond et al., 2019). We also computed the percentage of subjects with the condition and onset before the index TBI in the same manner. We computed the prevalence using two different descriptions of onset so as to provide maximum information to the medical practitioners as each of these definitions could provide vital insights for designing foresighted patient care programs.

We established statistical significance between the prevalence of comorbidities for young vs old subjects, and male vs female subjects. Subjects whose age at follow-up (5-years post TBI) is less than or equal to 50 years were categorized as young and those with age at follow-up greater than 50 years were categorized as old. For estimating the statistical significance of young vs old subjects, we first computed the odds ratio (McHugh, 2009; Steven and Hoffman, 2022) using the following formula,

$$Odds\ ratio\ (OR) = \frac{a^{*}d}{b^{*}c} \tag{1}$$

where 'a' represents the percentage of cases (prevalence) with the comorbidity in the older cohort at 5-year follow-up, 'b' represents the percentage of cases in the older cohort without the comorbidity at the same follow-up time period. Similarly, 'c' represents the percentage of cases (prevalence) with the comorbidity in the younger cohort at 5-year follow-up and 'd' represents the percentage of cases in the younger cohort without the comorbidity at the same follow-up time period. This ratio represents the odds of observing a comorbidity in older subjects compared to the odds in the younger cohort. Similarly, the odds ratio capturing the relative prevalence in female vs male subjects in the cohort was computed to determine the sex dependence of post-traumatic prevalence of comorbidities. After computing the odds ratio, statistical significance was established using Fisher's-Exact test (95% confidence interval) (McHugh, 2009). The probability 'p' for Fisher's-Exact test was calculated using the following formula,

$$p = \frac{(a+b)!\ (c+d)!\ (a+c)!\ (b+d)!}{a!\ b!\ c!\ d!\ n!} \tag{2}$$

where a, b, c, and d represent the same metrics as mentioned above for the odds ratio and n represents the sum of all four variables. Confidence intervals (McHugh, 2009; Steven and Hoffman, 2022) for the odds ratio were computed using the below formula,

$$\begin{aligned} u &= e^{\left[\ln(OR) + 1.96 * \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}\right]} \\ l &= e^{\left[\ln(OR) - 1.96 * \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}\right]} \end{aligned} \tag{3}$$

where u and l are upper and lower bounds of the confidence interval.

To determine if a confounding effect (Jager et al., 2008; Jose et al., 2008) of age at follow-up or effect modification was present in the association between the prevalence and biological sex of the subjects, the following procedure was followed: Two strata were created representing subjects <= 50 years of age and subjects > 50 years of age at 5-year follow-up corresponding to two different values of the confounder. For each stratum, we calculated the odds

ratio of the relative prevalence of comorbidities in female subjects compared to male subjects (OR_1 and OR_2). We next determined if the stratum-specific odds ratios (OR_1 and OR_2) were similar to each other using the Breslow-Day-Tarone test (BDTT) for homogeneity (95% confidence interval) (Breslow and Day, 1980; Breslow, 1996). If the odds ratios were found to be significantly different from each other ($p < 0.05$), we report the stratum-specific odds ratio for the comorbidity in question (effect modification).

If the odds ratios were similar ($p >= 0.05$), we utilized the Mantel-Haenszel test (MHT) (Kuritz et al., 1988; Jose et al., 2008; Tripepi et al., 2010) to determine if there is an association between sex and prevalence of the comorbidity in question (95% confidence interval). Additionally, we report Mantel-Haenszel odds ratio (OR_{MH}) (Kuritz et al., 1988; Jose et al., 2008; Tripepi et al., 2010) adjusted for age at follow-up (and magnitude of confounding) which is calculated from the stratum-specific numbers using the following formula,

$$OR_{MH} = \frac{\sum \frac{a_i * d_i}{n_i}}{\sum \frac{b_i * c_i}{n_i}} \quad (4)$$

where a_i, b_i, c_i, and d_i represent the same as explained above (for odds ratio) in the ith stratum of the confounder (age at follow-up) and n_i is computed by adding all four variables a_i, b_i, c_i, and d_i in the same stratum.

Lastly, the magnitude of confounding (CM) was calculated using the following formula,

$$Magnitude\ of\ confounding\ (CM) = \frac{OR_{crude} - OR_{MH}}{OR_{MH}} \quad (5)$$

where OR_{MH} represents the adjusted odds ratio obtained using the Mantel-Haenszel formula (Kuritz et al., 1988) and OR_{crude} represents the crude (unadjusted) odds ratio.

Results

From the TBIMS national database, we first grouped the subjects into mild, moderate, and severe TBI groups based on the GCS scores collected at the time of admission to the hospital (see section "Materials and methods"). Out of the 17,932 subjects in the TBIMS national database, 4,915 subjects belong to the mild category, 2,642 subjects belong to the moderate group and 3,007 subjects are severe TBI subjects. The remaining subjects were either chemically sedated or paralyzed or intubated or their GCS score was missing or unknown. Out of the 10,564 subjects from whom the GCS score was measured, 46.5 % belong to the mild category. We then computed the mean values of age at onset, GCS, and post-traumatic amnesia (PTA) for mild TBI subjects. The average age at injury onset for subjects with mild TBI is 55.47 ± 0.28 (mean ± sem) years. The mean values of PTA and GCS for the same group are 10.38 ± 0.21 days, 14.6 ± 0.007 respectively.

Prevalence of comorbidities at 5 years following mild TBI

We next sought to understand the prevalence of various comorbidities at 5 years following the index TBI. The presence or absence of various medical and behavioural comorbidities was collected through a patient survey modelled based on NHANES (Center for Disease Control, National Center for Health Statistics, 1999). The 26 comorbidities that were covered in the NHANES interview were grouped under the following 8 categories: cardiovascular, neurological, musculoskeletal and rheumatologic, ophthalmological, endocrine, gastrointestinal, respiratory and psychiatric/mental health (**Table 1**). For each condition, we estimated the prevalence by counting the total number of subjects with the condition at the same time or after acquiring the index TBI and dividing this number by the total number of subjects who responded to the question (those with the presence and absence of the condition). We did the same to obtain the numbers for the prevalence of each condition with onset before acquiring TBI.

The final number of mild TBI subjects that took part in the NHANES survey at 5-years post injury is 223-228. Out of this, 149-153 belong to the older cohort of patients and 69-71 belong to the younger cohort. 163-166 are males and 59-62 are female subjects. The prevalence of all 26 comorbidities for individuals with mild TBI at 5-year follow-up time point is given in **Table 1**. Using this data, we compiled a list of the top 10 comorbidities ranked according to their prevalence (at the same time or after TBI) at 5-year follow-up time point for subjects with mild TBI (**Table 2**). All further analyses in the study (old vs young and female vs male subjects) were performed for this list of highly prevalent comorbidities on subjects with mild TBI. A close inspection of **Table 2** reveals that individuals with mild TBI are confronted with psychiatric conditions which include anxiety, depression, post-traumatic stress disorder (PTSD), and panic attacks (PA) at 5 years post injury. In addition to psychiatric comorbidities, cardiovascular comorbidities (hypertension (HT) and high blood cholesterol (HBC)) were also prevalent among subjects with mild TBI in the TBIMS national database. Lastly, the list includes other comorbidities like chronic pain (CP), osteoarthritis (OA), cataracts, and sleep disorder (SD). From these results, it becomes clear that subjects with mild TBI are confronted with a myriad of health-related issues at 5 years following the injury.

Prevalence of comorbidities in young and old subjects

We next sought to determine if the prevalence of the top 10 medical and mental health comorbidities at the same time or after TBI differ between young and old subjects with mild TBI. Subjects were classified as young or old based on an age threshold of 50 years (see section "Materials and methods"). We asked the question if older subjects in the cohort exhibited increased odds of developing a particular set of comorbidities compared to younger subjects. To do this, we computed the OR for the top 10 prevalent comorbidities (compiled in the previous step) and established its significance using the Fisher's-Exact test (see section "Materials and methods"). Our results indicate that psychiatric comorbidities (depression, anxiety, PTSD, and PA) exhibit an increased prevalence in the younger compared to an older cohort of subjects at the same time or after TBI. However, statistical significance was obtained only for the odds ratio of depression (OR = 0.37 and $p = 0.026$,

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TABLE 1 Prevalence of psychiatric and medical comorbidities for mild TBI patients at 5-year follow-up time point.

Comorbidity	Before TBI		Same time or after TBI	
	X/N	%	*X/N*	%
Cardiovascular				
Hypertension	77/228	33.77	32/228	14.04
Congestive heart failure	11/226	4.87	5/226	2.21
Myocardial infarction	17/227	7.49	4/227	1.76
Other heart conditions	20/225	8.89	13/225	5.78
Stroke	9/226	3.98	13/226	5.75
High blood cholesterol	50/224	22.32	23/224	10.27
Endocrine				
Diabetes	33/226	14.60	13/226	5.75
Gastrointestinal				
Liver disease	10/228	4.39	7/228	3.07
Musculoskeletal and Rheumatologic				
Rheumatoid arthritis	8/224	3.57	6/224	2.68
Osteoarthritis	26/225	11.56	14/225	6.22
Chronic pain	26/223	11.66	35/223	15.70
Neurologic				
Sleep disorder	20/223	8.97	19/223	8.52
Movement disorder	1/224	0.45	2/224	0.89
Dementia	6/223	2.69	11/223	4.9
Ophthalmologic				
Cataracts	26/224	11.61	21/224	9.38
Psychiatric/Mental health				
Alcoholism	15/224	6.70	2/224	0.89
Drug addiction	10/223	4.48	3/223	1.35
Anxiety	29/223	13.00	36/223	16.14
Obsessive-compulsive disorder	2/223	0.089	3/223	1.35
Panic attacks	12/224	5.36	19/224	8.48
Post-traumatic stress disorder	8/224	3.57	25/224	11.16
Depression	35/223	15.70	35/223	15.70
Bipolar disorder	7/224	3.13	6/224	2.68
Attention deficit disorder/Attention deficit hyperactivity disorder	13/224	5.80	7/224	3.13
Respiratory				
Emphysema	15/228	6.58	9/228	3.95
Pneumonia	17/224	7.60	13/224	5.80

'X' represents the number of subjects with a specific comorbidity (before, same time or after TBI) and 'N' represents the total number of subjects with the presence and absence of the comorbidity.

Table 3). The prevalence of all other comorbidities (rheumatologic, ophthalmological, and cardiovascular) at the same time or after TBI was higher in the older cohort compared to the younger cohort. For example, subjects with age at follow-up > 50 years were 9.79 times more likely to experience OA compared to subjects with age at follow-up <= 50 years. Altogether, our results reveal a unique pattern of comorbidity dynamics in younger vs older individuals with mild TBI.

Prevalence of comorbidities according to the biological sex of the subjects

We next sought to understand if the prevalence of comorbidities at the same time or after TBI was dependent on the biological sex of the subjects in the cohort. For this, we first computed the prevalence for the set of top 10 medical and psychiatric comorbidities at the same time or after TBI for male

TABLE 2 Summary of top 10 most prevalent comorbidities for mild TBI subjects at 5-year follow-up.

Comorbidity	Prevalence (%)
Anxiety	16.14
Depression	15.7
Chronic pain	15.7
Hypertension	14.04
Post-traumatic stress disorder	11.16
High blood cholesterol	10.27
Cataracts	9.38
Sleep disorder	8.52
Panic attacks	8.48
Osteoarthritis	6.22

and female subjects in the cohort (**Table 4**). Since female subjects have a longer lifespan and tend to outlive men (Ginter and Simko, 2013), we reasoned that age could be a confounding factor in the association between sex and the prevalence of comorbidities. In order to control for confounding, we resorted to stratified analysis (see section "Materials and methods") (Jager et al., 2008; Jose et al., 2008). Briefly, we created two strata of the confounder (age at follow-up): subjects with age at follow-up > 50 years and subjects with age at follow-up <= 50 years. Stratum-specific odds ratio was computed for each stratum of the confounder. Based on the results from BDTT (Breslow and Day, 1980; Breslow, 1996), either effect modification or possible confounding was established. If effect modification was observed, stratum-specific odds ratios were reported while if confounding was observed unconfounded (adjusted) odds ratio (OR_{MH}) (Kuritz et al., 1988; Jose et al., 2008; Tripepi et al., 2010) and magnitude of confounding (CM) was reported. Odds ratios reflect the odds of observing the comorbidity in female subjects compared to the odds in male subjects.

Strong effect modification was observed for comorbidities such as depression, CP, SD and OA ($p < 0.005$ in the BDTT). Female subjects with age at follow-up <= 50 years exhibited decreased odds for depression compared to male subjects at 5-year follow-up ($OR_2 = 0.18$, **Table 5**). Additionally, female subjects with age at follow-up > 50 years exhibited increased odds of developing CP compared to male subjects at 5-year follow-up ($OR_1 = 2.84$, **Table 5**).

Possible confounding was observed for anxiety, HT, PTSD, HBC, and PA (**Table 6**). However, the magnitude of confounding was less than 10% for the above-mentioned comorbidities except for HBC. Female subjects demonstrated increased odds of developing PTSD compared to male subjects at 5-year follow-up ($OR_{MH} = 1.88$, **Table 6**). Our results, therefore, revealed interesting patterns in the association between biological sex and the prevalence of comorbidities post mild brain trauma.

Discussion

We studied the longstanding comorbidities of acquiring mild TBI using patient data from the TBIMS national database. We did so by computing the prevalence of medical and mental health comorbidities at 5 years post index TBI. Our secondary aim is to understand how the prevalence of various comorbidities post mild TBI is influenced by a subset of patient demographics (sex, and age). Our analysis indicates the presence of interesting dynamics in the development of medical and mental-health comorbidities post TBI which could be useful to devise foresighted programs for the patient community. Our work hopes to contribute to the sparse body of literature concerning the prevalence of various comorbidities post mild TBI.

The findings in this study are similar to those that have been previously reported in the literature. A number of studies have reported that individuals with TBI exhibit an increased risk of developing psychiatric problems (Schwarzbold et al., 2008; Bryant et al., 2010; Bryant, 2011; Gould et al., 2011; Mallya et al., 2015; Stein et al., 2019) and demonstrate an impaired cognitive and oculomotor function (Dean and Sterr, 2013; Danna-Dos-Santos et al., 2018) compared to the general population. In our study, the most commonly manifested psychiatric disorders for individuals with mild TBI were anxiety and depression. Other frequently reported psychiatric conditions were PTSD, and PA. The prevalence of obsessive-compulsive disorder (OCD), bipolar disorder (BD), and attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) following TBI were far less common compared to other psychiatric conditions in our analysis. Confirming our results, depression, and generalized anxiety disorder were the two most common psychiatric conditions reported in a cohort of subjects with mild TBI from trauma centres in Australia (Bryant et al., 2010). Similarly, an increased risk prevalence of depression (and PTSD) was reported in a previous prospective study (Stein et al., 2019) of more than 1,000 individuals with mild TBI. Increased prevalence of anxiety and comorbid anxiety with depression have also been reported following TBI in the same study (Stein et al., 2019). These results have enormous clinical implications for the mild TBI community in post-traumatic disease management. For example, foresighted clinical programs could be implemented to screen the presence of depression, anxiety, and PTSD at multiple time points post acquiring mild TBI. Further, relatives of mild TBI survivors could be involved to watch out for symptoms of the above-mentioned psychiatric conditions in their family members.

We found that PTSD is highly prevalent in individuals with mild TBI (**Table 2**) and more so in female subjects (**Tables 4**, **6**). Interestingly, in a previous TBIMS study (Hammond et al., 2019) that quantified the prevalence of comorbidities in individuals with moderate-severe TBIs, PTSD did not find itself in the list of top 10 comorbidities that were highly prevalent. Although the existence of PTSD after both mild (Middelboe et al., 1992; Bryant and Harvey, 1998; Bryant, 2011) and severe (Mcmillan, 1991, 1996; Bryant, 1996, 2011; Bryant et al., 2000) forms of TBI has been established in the literature, it's possible that stronger PTA and loss of consciousness could retard the encoding of trauma-related experiences and prevent them from being re-experienced later (Bryant, 2011; Mallya et al., 2015). As a consequence, the risk of developing PTSD could be higher in mild cases of TBI compared to severe ones (Bryant, 2011; Mallya et al., 2015). Confirming this observation, a few studies have reported that the risk of developing PTSD is elevated in mild TBI compared to severe

TABLE 3 Comparison of the prevalence of comorbidities according to the age of the subjects at 5-year follow-up.

Comorbidity	>50 years at 5-year follow-up		<= 50 years at 5-year follow-up		OR [CI]	*p*-value
	X/N	%	*X/N*	%		
Anxiety	22/149	14.76	14/70	20	0.71 [0.34–1.47]	0.46
Depression	17/150	11.33	17/69	24.63	0.37 [0.17–0.8]	0.016
Chronic pain	21/150	14	13/69	18.8	0.69 [0.33–1.47]	0.45
Hypertension	27/153	17.6	5/71	7.04	2.91 [1.16–7.33]	0.03
Post-traumatic stress disorder	14/150	9.3	11/70	15.71	0.52 [0.22–1.24]	0.2
High blood cholesterol	21/150	14	2/70	2.8	5.26 [1.46–18.9]	0.009
Cataracts	20/150	13.3	0/70	0	Inf	0.0001
Sleep disorder	14/150	9.3	5/69	7.2	1.31 [0.47–3.7]	0.79
Panic attacks	11/150	7.3	8/70	11.4	0.61 [0.23–1.64]	0.46
Osteoarthritis	13/151	8.6	1/70	1.4	9.79 [1.2–78.8]	0.018

'*X*' represents the number of subjects with a specific comorbidity (same time or after TBI) and '*N*' represents the total number of subjects with the presence and absence of the comorbidity. OR, odds ratio; CI, confidence interval. The *p*-value was obtained using the Fisher's - Exact test.

TABLE 4 Comparison of the prevalence of comorbidities according to the biological sex of the cohort at 5-year follow-up.

Comorbidity	Female		Male	
	X/N	%	*X/N*	%
Anxiety	11/59	18.6	25/164	15.2
Depression	7/60	11.67	28/163	17.2
Chronic pain	13/59	22.03	11/164	13.4
Hypertension	8/62	12.9	24/166	14.45
Post-traumatic stress disorder	10/60	16.67	15/164	9.1
High blood cholesterol	5/60	8.33	18/164	10.97
Cataracts	7/60	11.67	14/164	8.5
Sleep disorder	4/60	6.67	15/163	9.2
Panic attacks	6/60	10	13/164	7.9
Osteoarthritis	7/61	11.47	7/164	4.3

'*X*' represents the number of subjects with a specific comorbidity (same time or after TBI) and '*N*' represents the total number of subjects with the presence and absence of the comorbidity.

cases (Bombardier et al., 2006; Zatzick et al., 2010; Mallya et al., 2015).

With respect to cardiovascular comorbidities, we find that HT and HBC are quite common after mild TBI (**Tables 1**, **2**). In line with our results, there are a few studies in the literature that associate TBI with an increased risk of cardiovascular comorbidities (Ahmadi et al., 2015; Wang et al., 2018; Nyam et al., 2019; Turner et al., 2021; Izzy et al., 2022). In a longitudinal study of individuals with TBI up to 10 years post injury, the authors found that cardiovascular and neurological comorbidities (Izzy et al., 2022) are highly prevalent in mild TBI as well as moderate-severely injured subjects. According to another study (Nyam et al., 2019) involving 16211 subjects who were followed up to 5 years post injury, TBIs are associated with an increased risk of developing cardiovascular comorbidities. In addition to that, TBIs are associated with an elevated risk of developing cardiovascular conditions such as arrhythmias and cardiomyopathies, and atherosclerosis (Ahmadi et al., 2015; Wang et al., 2018).

We also determined if the prevalence of comorbidities at the same time or after TBI exhibits differential patterns as a function of sex and the age of the participants at follow-up. Younger subjects (<= 50 years at follow-up) in our study were prone to developing depression compared to older participants who exhibited increased odds of developing cardiovascular (HT and HBC) comorbidities, cataracts, and OA (**Table 3**). Similar results were also seen in a previous study (Chan et al., 2017) where the younger cohort (<65 years old) was characterized by a high prevalence of psychiatric comorbidities whereas the older cohort (>65 years old) was characterized by the presence of cardiovascular, metabolic, and endocrine-related comorbidities. Such differential presence of comorbidities post TBI was also confirmed in a previous TBIMS study (Hammond et al., 2019).

With respect to the association between sex and prevalence of comorbidities, our results revealed that for a certain set of comorbidities, the association depends on the age at follow-up of the participants (effect modification) (**Tables 5**, **6**). While depression was highly prevalent in young males compared to young females, the latter group exhibited increased odds of developing post-traumatic chronic pain (**Table 5**). Also, female subjects with mild TBI were more prone to developing PTSD compared to their male counterparts (**Table 6**). Women in general are more susceptible to developing PTSD (Olff, 2017), musculoskeletal conditions like OA (Zhang and Jordan, 2010), and anxiety disorders (McLean et al., 2011). In the TBI population, prior results have established that musculoskeletal (OA) and cardiovascular comorbidities are common in females compared to male subjects irrespective of age (Chan et al., 2017). Similarly, women TBI survivors are at an increased risk of developing PTSD, and depression (Kim et al., 2018) and were shown to exhibit an elevated severity in anxiety and depression (Mikolić et al., 2021).

TABLE 5 Comorbidities for which effect modification was observed in female vs male subjects stratified by age at follow-up of 5-years.

Comorbidity	Prevalence in S1 (%)		Prevalence in S2 (%)		OR_1 [CI]	OR_2 [CI]	p_{BDTT}	p_1	p_2
	F	M	F	M					
Depression	13	10	7	29	1.34 [0.56–3.23]	0.18 [0.08–0.44]	0.001	0.66	7.4e-5
Chronic pain	24	10	15	20	2.84 [1.28–6.31]	0.71 [0.34–1.47]	0.01	0.01	0.46
Sleep disorder	9	9	0	9	1 [0.38–2.6]	0	8e-3	1	0.003
Osteoarthritis	15	6	0	2	2.76 [1.03–7.45]	0	0.036	0.06	0.5

S1 represents stratum 1 (age at follow-up of 5 years > 50 years), S2 represents stratum 2 (age at follow-up of 5 years <= 50 years), OR_1 and OR_2 represent the odds ratio of female vs male subjects in S1 and S2 respectively, p_{BDTT} represents the p-value obtained using the Breslow-Day-Tarone test (BDTT), p_1 and p_2 represents the p-value of odds ratio in S1 and S2 respectively obtained using Fishers-Exact test. F, female; M, male; CI, confidence interval.

TABLE 6 Comorbidities effect modification was not observed in female vs male subjects stratified by age at follow-up of 5-years.

Comorbidity	Prevalence in S1 (%)		Prevalence in S2 (%)		p_{BDTT}	OR_{crude}	OR_{MH}	p_{MHT}	CM
	F	M	F	M					
Anxiety	18	13	21	20	0.54	1.33	1.23	0.43	8.35
Hypertension	15	18	7	7	0.75	0.92	0.86	0.64	6.5
PTSD	15	7	21	14	0.55	2.07	1.88	0.03	10
High blood cholesterol	11	15	0	4	0.11	0.7	0.54	0.12	30.5
Panic attacks	9	7	14	11	0.99	1.28	1.31	0.41	-2.9

S1 represents stratum 1 (age at follow-up of 5 years > 50 years), S2 represents stratum 2 (age at follow-up of 5 years <= 50 years), OR_1 and OR_2 represent the odds ratio in S1 and S2 respectively, p_{BDTT} represents the p-value obtained using the Breslow-Day-Tarone test (BDTT), OR_{crude} represents the crude (unadjusted) odds ratio, OR_{MH} represents the adjusted (unconfounded) odds ratio computed using the Mantel-Haenszel formula, p_{MHT} represents the p-value obtained using Mantel-Haenszel test (MHT) and CM represents the magnitude of confounding. F, female; M, male.

Limitations of the study and future work

The subjects in this study were those who received in-patient rehabilitation for mild TBI in one of the TBIMS centres (Traumatic Brain Injury Model Systems Program, 2021). These subjects were typically characterized by the presence of intracranial pathology and/or PTA (Traumatic Brain Injury Model Systems Program, 2021). Sufficient caution should be exercised while generalizing the results of the study to the mild TBI population as a whole since this population might also comprise subjects who were treated in less sophisticated hospitals/outpatient clinics or may even include subjects who may not seek medical attention. Further, our aim in this study is not to establish any sort of causal relationship but to elucidate the most frequently manifested psychiatric and medical problems in individuals with mild TBI. Future studies could incorporate a control group of non-TBI subjects for comparison and establishing causal inference. Lastly, the study could potentially suffer from ascertainment bias as it's possible that some comorbidities that were diagnosed post TBI could have been persistent and undiagnosed prior to acquiring the injury due to lack of medical attention or some other reasons.

Another potential limitation of our study could be related to smaller sample sizes at each follow-up time point. For example, even though the TBIMS database consists of information pertaining to 4,915 mild TBI subjects, only 223-228 subjects enrolled in the NHANES study at 5-year follow-up time period. This could become problematic especially when comparing the prevalence between different patient subgroups where sample size could further diminish. As the TBIMS national database expands in the future with an increasing number of subjects, the current analysis could be repeated to see if there is any effect of sample size on the prevalence and statistical significance. Lastly, future administration of patient surveys/questionnaires (NHANES) could be expanded to cover other medical conditions.

This study is a preliminary excursion into the various factors that influence the development of comorbidities post mild TBI. In the future, we intend to build upon this work to study pairwise disease co-occurrences at scale using graph networks and network analysis (Fotouhi et al., 2018; Ljubic et al., 2020; Lee and Park, 2021). In doing so, a larger avenue of analysis is opened to visualize and understand disease comorbidities as differences in network structures across scales (Fotouhi et al., 2018; Ljubic et al., 2020; Lee and Park, 2021). Comorbidities are understood as unique spatial organisations of statistically significant interconnected disease nodes with varying depths of connectedness (Fotouhi et al., 2018; Kim et al., 2018; Lee and Park, 2021). Network structural properties will be compared across time, TBI severity, and demographic conditions. The significance of this approach is an intuitive visualisation of diseases in terms of their co-occurrences, and clusters of diseases can be identified for unique TBI severity and demographic conditions that could inform proactive post-TBI healthcare. The current literature on using disease networks to study comorbidity relationships in subjects with TBI is sparse and we seek to contribute to that body of knowledge. Finally, as the incidence of mild TBI is frequent in the general population, future excursions of the work could include understanding the comorbidity dynamics as a function of the number of impacts experienced by the subjects.

Conclusion

Our study indicates that individuals who have sustained mild TBI could develop serious long-term medical and psychiatric comorbidities which could affect their pace of recovery. The results of this study could motivate further investigation regarding the prevalence of health-related problems in the mild TBI population and encourage the development of foresighted programs and patient care for post-traumatic management of comorbidities. The findings reported in the paper have wider implications for prognosis, patient management, and treatment of various comorbidities after TBI.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.tbindsc.org.

Ethics statement

This study is secondary data analysis of a publicly available dataset. The original studies involving human participants were reviewed and approved by Krea Institutional Review Board. Written informed consent to participate in the original study was provided by the participants' legal guardian/next of kin.

Author contributions

SS: conceptualization, methodology, investigation, writing—review and editing. SC: Conceptualization, investigation, writing—review and editing. KP: investigation, writing—review and editing. KM: methodology, writing—review and editing. SKS: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project management, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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Comparative efficacy of five most common traditional Chinese medicine monomers for promoting recovery of motor function in rats with blunt spinal cord injury: a network meta-analysis

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Objective: This research employed a network meta-analysis (NMA) to examine the effectiveness of five traditional Chinese medicine (TCM) monomers for promoting motor function recovery in rats with blunt spinal cord injury (SCI).

Methods: Wangfang, China National Knowledge Infrastructure, Web of Science, Embase, Chinese Scientific Journal Database, PubMed, and the Chinese Biomedical Literature Databases were searched for retrieving relevant articles published from their inception to December 2022. Two reviewers performed screening of search results, data extraction, and literature quality assessment independently.

Results: For this meta-analysis, 59 publications were included. Based on the recovery of motor function at weeks 1, 2, 3, and 4 in NMA, almost all TCM groups had significantly increased positive effects than the negative control animals. In terms of cumulative probability, the tanshinone IIA (TIIA) group ranked first in restoring motor function in the first week after blunt SCI, and the resveratrol (RSV) group ranked first during the last 3 weeks.

Conclusion: The NMA revealed that TCM monomers could effectively restore motor function in the rat model of blunt SCI. In rats with blunt SCI, TIIA may be the most effective TCM monomer during the first week, whereas RSV may be the most effective TCM monomer during the last 3 weeks in promoting motor function recovery. For better evidence reliability in preclinical investigations and safer extrapolation of those findings into clinical settings, further research standardizing the implementation and reporting of animal experiments is required.

Systematic Review Registration: https://inplasy.com/, identifier INPLASY202310070.

KEYWORDS

animal studies, traditional Chinese medicine, monomer, spinal cord injury, motor function, network meta-analysis

1. Introduction

Spinal cord injury (SCI) is a kind of disease that affects the central nervous system and is linked to a significant risk of disability and death. In addition, the incidence of SCI is increasing (1–3). Of all the factors that contribute to SCI, trauma is the most common causal factor observed in clinical cases. SCI can broadly be categorized into two injuries: primary and secondary. Primary injury is caused by direct external force on the spinal cord during the trauma. After the primary injury, the activity of factors such as inflammation, oxidative stress, autophagy, and apoptosis gradually expands across the spinal tissue, causing secondary injuries. Such injuries cause extensive and sustained damage, leading to permanent loss of motor and sensory function (4–6). The current treatment options for SCI include decompression surgery, medication, and physical therapy; irrespective, there are no satisfactory treatments for SCI (7, 8). As a result, the treatment of SCI remains a major challenge. Many injury models have been used in the study of SCI, among which these blunt injury models, where the spinal cord is compressed or contused, imitate common human injuries and offer an excellent setting for research into secondary pathophysiological processes that take place immediately following injury in a more precise manner (9, 10). Furthermore, in experimental animals, the pathophysiology of SCI is considerably similar in rats and humans (11). Rats are also less expensive and more standardized than other animal species, making them the most commonly used model for studying SCI (12, 13).

In the quest to explore effective treatments for blunt SCI, a few studies have demonstrated the neuroprotective role of traditional Chinese medicine (TCM) monomers (14, 15). At present, more than ten TCM monomers are available for the treatment of blunt SCI, five of which have been extensively studied: curcumin (CUR), tetramethylpyrazine (TMP), resveratrol (RSV), ginsenoside (GS), and tanshinone IIA (TIIA). CUR is a hydrophobic polyphenol that is the biologically active component of turmeric (16, 17). TMP is a monomer alkaloid that is extracted from the dried rhizome of *Ligusticum chuanxiong*, a Chinese herbal medicine (18, 19). RSV is a polyphenol found in berries and wine that is used in TCM (20, 21). GSs are steroid glycosides and triterpene saponins obtained from *Panax ginseng*, a plant that has been historically used for medicinal purposes (22, 23). Almost all GSs have anti-inflammatory and antioxidant properties and thus their medicinal potential is often analyzed together (24). TIIA is a monomer obtained from the liposoluble extract of *Salvia miltiorrhiza* Bunge (25, 26). Animal studies have demonstrated that these five TCM monomers assume a neuroprotective role in blunt SCI through several mechanisms to promote the recovery of motor function. Irrespective, it is still unclear which of these monomers is the most suitable for motor function recovery after blunt SCI. Therefore, the present study aimed to assess data from rat studies on the use of TCM monomers for treating blunt SCI. Subsequently, a network meta-analysis (NMA) was employed to examine the effectiveness of five TCM monomers for promoting motor function recovery in rats with blunt (SCI). The results obtained will provide a theoretical basis for the treatment of blunt SCI using TCM monomers and lay a foundation for future research, which can promote the use of animal data in clinical research.

2. Materials and methods

2.1. Registration

The guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed throughout this investigation (27). The research protocol was submitted to INPLASY for registration (registration number: INPLASY202310070).

2.2. Search strategy and selection criteria

The following databases were searched: Chinese Biomedical Literature, Wanfang, Chinese Scientific Journal, China National Knowledge Infrastructure, Web of Science, Ovid-Embase, and PubMed (inception to December 2022). Potentially eligible papers were identified using the following terms as topic words, keywords, free-text terms, or Medical Subject Heading terms: "curcumin," "turmeric yellow," "curcumin phytosome," "ginsenoside," "panaxosides," "resveratrol," "trans-resveratrol," "cis-resveratrol," "tanshinone," "tanshinone IIA," "tetramethylpyrazine," "ligustrazine," "chuanxiongzine," "spinal cord injuries," "spinal cord injury," "spinal injury," "spinal cord trauma," and "spinal cord contusion." An individualized database-specific approach was used for each search. Methods of blinding, languages used, and publishing dates were unrestricted. The detailed search strategy of each database is provided in Supplementary Table S1.

All enrolled studies followed the criteria: (1) Animals: rat with blunt SCI (contusion and compression model); (2) Intervention: five TCM monomers (CUR, TMP, RSV, GS, and TIIA); (3) control: placebo or no treatment; (4) Outcome: Weekly Basso-Beattie-Bresnahan (BBB) Locomotor Rating scale scores over 4 weeks. (5) Study type: control studies. Studies were excluded if (1) SCI was induced by other means, such as complete transverse SCI, hemisection SCI, and spinal cord ischemia/reperfusion injury; (2) BBB scores were not reported; (3) studies were duplicated; and (4) if complete raw data were not provided or if data could not be extracted.

2.3. Data collection and quality assessment

Two trained researchers were involved in selecting articles and extracting data from eligible studies in full compliance with the criteria for inclusion/exclusion as well as in cross-checking them. Disagreements were resolved by a third researcher. Relevant data were extracted according to a standard checklist, which included two major parameters: basic data (author [s], publication year, country, study design; species, age, sex, weight, size of the sample, animal modeling methods, type of TCM monomer, dose, and route) and outcomes (BBB score).

Using SYRCLE's Risk of Bias tool for animal research, the reviewers conducted independent assessments of the quality of the articles that were included in the analysis (28). The following ten criteria were used to assess possible bias in the enrolled studies: (1) sequence generation, (2) baseline characteristics, (3) allocation concealment, (4) random housing, (5) blinded animal intervention, (6) random outcome assessment, (7) blinded outcome assessment, (8) incomplete outcome data, (9) selective outcome reporting, and (10) other types of bias. A third reviewer was consulted to settle any disagreements of opinion that may have arisen. Each study was graded to either be of "low," "high," or "unclear" risk.

2.4. Statistical analysis

All variables included in our study were continuous variables. These variables were retrieved for NMA using STATA version 16, and the standardized mean difference (SMD) and the respective 95% confidence interval (CI) were calculated. Subsequently, the evidence network diagram was created to compare the five TCM monomers and allow a visual assessment of the relationship between each monomer and sample size. The thickness of the line segment indicated the number of studies that examined both interventions, whereas the size of the circles indicated the sample sizes used. Various intervention probabilities were ranked using SUCRA (surface under the cumulative ranking area). The SUCRA scores varied from 0 to 100%, reflecting the gradual increase from the poorest to the best treatments (29). Publication bias and small-sample effects were assessed using funnel plots.

3. Results

3.1. Literature search

The search of the relevant literature yielded a total of 1827 articles, with 958 of them being written in Chinese and 869 in English. Following the removal of duplicates and publications that did not fulfill the criteria for inclusion, 59 articles (29 English and 30 Chinese) assessing the efficacy of TCM monomers in SCI were finally included. Figure 1 provides an in-depth description of the screening process.

3.2. Basic study characteristics

In total, 56 randomized controlled trials (RCTs) and three controlled studies were included. Animals used in these investigations were either SD rats (55 articles) or Wistar rats (4 articles), see Figure 2A. In total, 27 publications used only male rats, 21 used only female rats, and 8 comprised equal numbers of male and female rats; In three of the research studies, the rat's sex was not specified. Overall, rats varied in age between 6 weeks and 36 weeks, in weight between 180 g and 350 g, and in sample size between 4 and 54. Contusion (46 research articles) and compression (13 articles) were the two modes of modeling used, see Figure 2B. Regarding the TCM monomers, 17, 21, 8, 9, and 4 studies evaluated the efficacy of CUR, TMP, RSV, GS, and TIIA, respectively, see Figure 2C. The monomers were administered intraperitoneally (49 studies), intramuscularly (1 study), intrathecally (1 study), intraperitoneally + intramuscularly (1 study), intraperitoneally + intrathecally (1 study), intravenously (2 studies), orally (2 studies), or epidurally (1 study); the route of administration was not reported in 1 study, see Figure 2D. Supplementary Table S2 displays the included publications' baseline characteristics.

3.3. Risk of bias

The assessment results showed a medium quality for all the included literatures. Only five of the 56 RCTs (8.5%) that were examined provided evidence that randomization was carried out with the aid of a random number table or a computer. However, in these publications, the use of concealed grouping was not reported at any point. Overall, 98.3% of the articles (58 out of 59) indicated that the subjects' baseline characteristics, including age, sex, and body weight, were matching. Moreover, the random allocation of rats throughout the experiment was indicated by 55.9% (33/59) of the reports. Since the included publications only provided a limited amount of information, it was not possible to obtain blinding information from those publications. However, only 15.3% of studies (9/59) indicated they randomly selected animals for measuring outcomes. Blinding of outcome assessors was applied in 57.6% (34/59) of studies. In 96.6% (57/59) of the studies, all rats were included in the final analysis. The purity of TCM monomers has not been reported in any studies. All expected results were clearly reported, but not all studies provided access to the protocol. Therefore, there is a high risk of performance bias in literature quality assessment. Figure 3 provides a comprehensive summary of the methods used to evaluate the potential for bias across studies.

3.4. Network meta-analysis

3.4.1. First week after treatment with TCM monomers

A total of 57 studies were included for network meta-analysis. The evidence network showed there was no direct comparison between all types of TCM monomers. At the same time, the number of studies on TMP was the largest, see Figure 4A. The results of NMA indicated that rats had significantly higher BBB scores in TCM monomer groups compared to negative controls. However, the differences in BBB scores of rats between the five types of TCM monomers were not statistically significant, see Table 1. Rank ordering and SUCRA value results showed that TIIA might be the most effective TCM monomer for SCI, see Figure 5A and Supplementary Table S3. The comparison-correction funnel plot was basically symmetrical, suggesting that there was less possibility of publication bias, see Figure 6A.

3.4.2. Second week after treatment with TCM monomers

A total of 54 studies were included for network meta-analysis. The evidence network showed there was no direct comparison between all types of TCM monomers. At the same time, the number of studies on TMP was the largest, see Figure 4B. The results of NMA indicated that rats had significantly higher BBB scores in TCM monomer groups compared to negative controls. However, the differences in BBB scores of rats between the five types of TCM monomers were not statistically significant, see Table 2. Rank ordering and SUCRA value results showed that RSV might be the most effective TCM monomer for SCI, see Figure 5B and Supplementary Table S4. The comparison-correction funnel plot was basically symmetrical, suggesting that there was less possibility of publication bias, see Figure 6B.

3.4.3. Third week after treatment with TCM monomers

A total of 36 studies were included for network meta-analysis. The evidence network showed there was no direct comparison between all types of TCM monomers. At the same time, the number

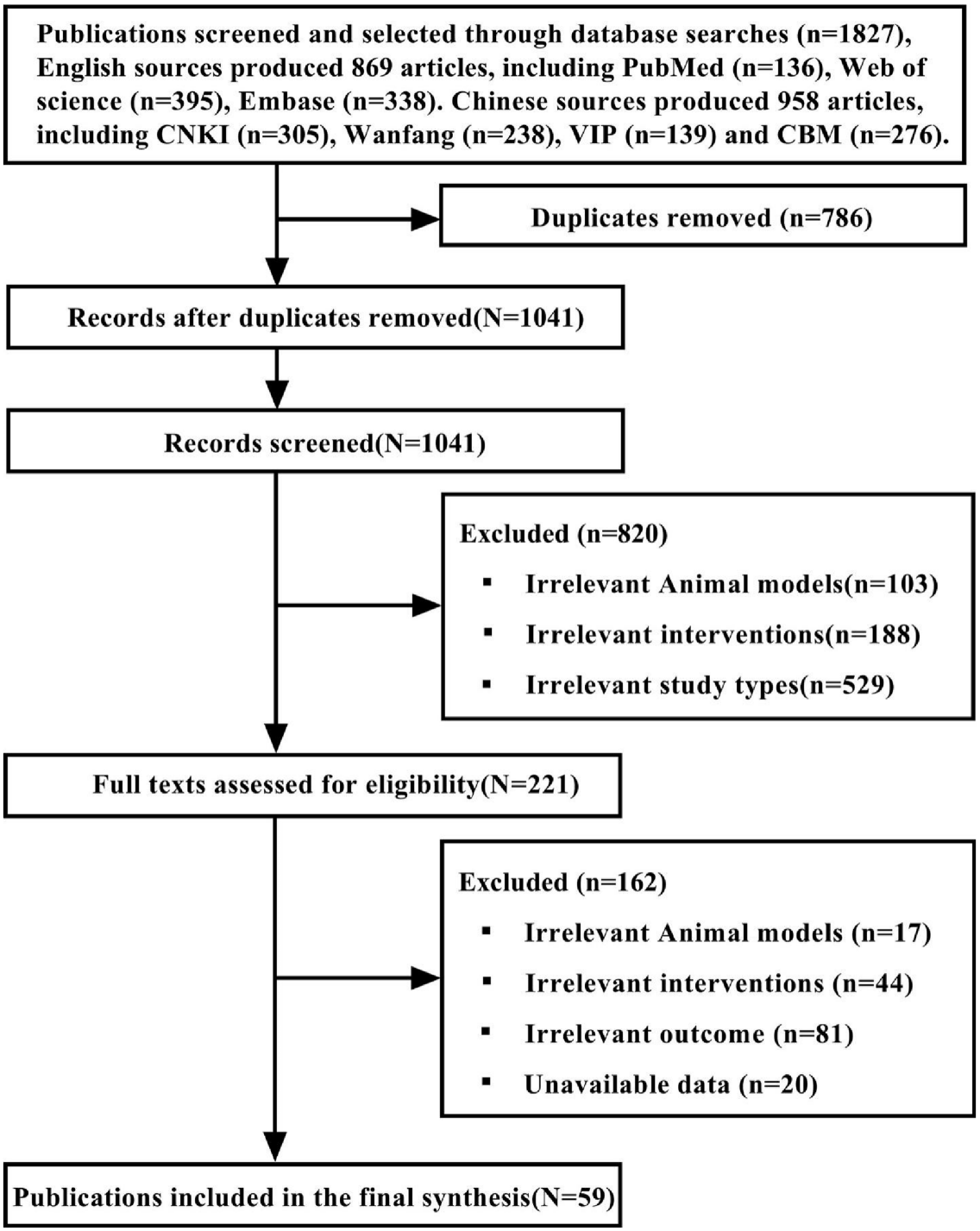

FIGURE 1
Flowchart of references - screening process.

of studies on TMP was the largest, see Figure 4C. The results of NMA indicated that rats had significantly higher BBB scores in TCM monomer groups compared to negative controls. However, the differences in BBB scores of rats between the five types of TCM monomers were not statistically significant, see Table 3. Rank ordering and SUCRA value results showed that RSV might be the most effective TCM monomer for SCI, see Figure 5C and Supplementary Table S5. The comparison-correction funnel plot was basically symmetrical, suggesting that there was less possibility of publication bias, see Figure 6C.

3.4.4. Fourth week after treatment with TCM monomers

A total of 32 studies were included for network meta-analysis. The evidence network showed there was no direct comparison between all types of TCM monomers. At the same time, the number

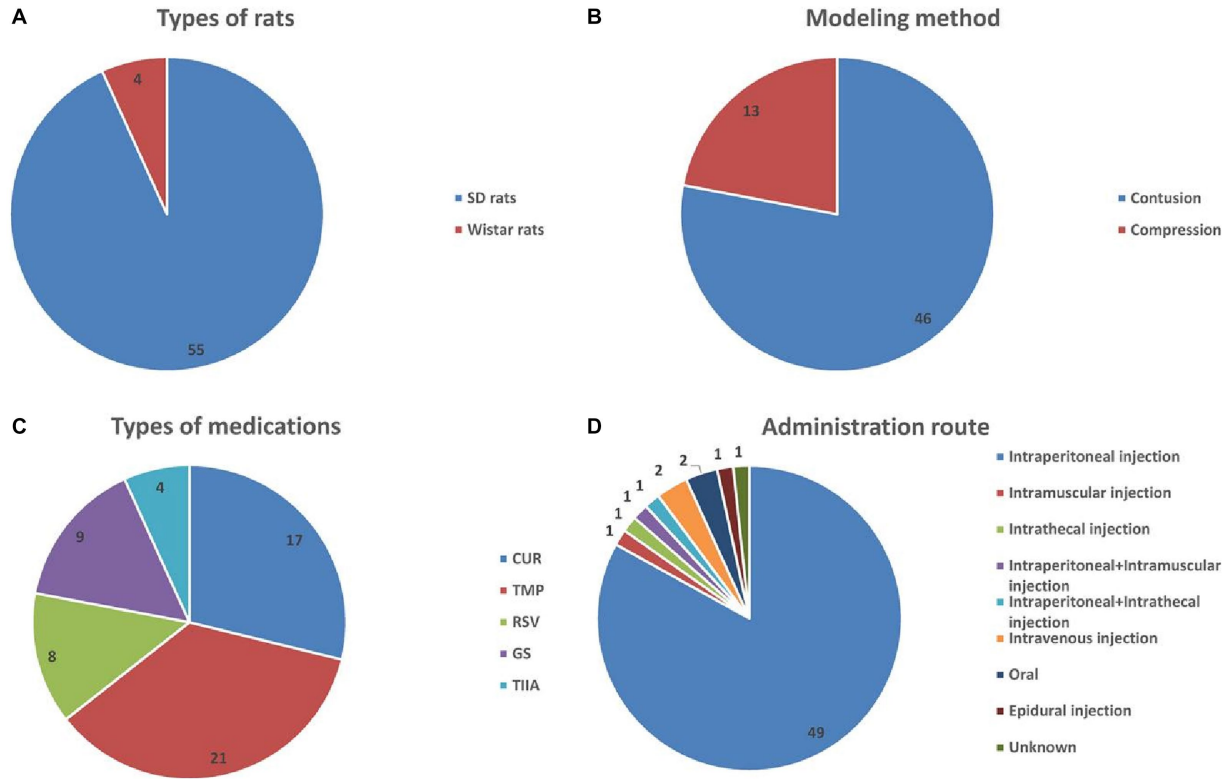

FIGURE 2
Basic information for inclusion in the study. **(A)** Types of rats; **(B)** modeling method; **(C)** types of medications; **(D)** administration route.

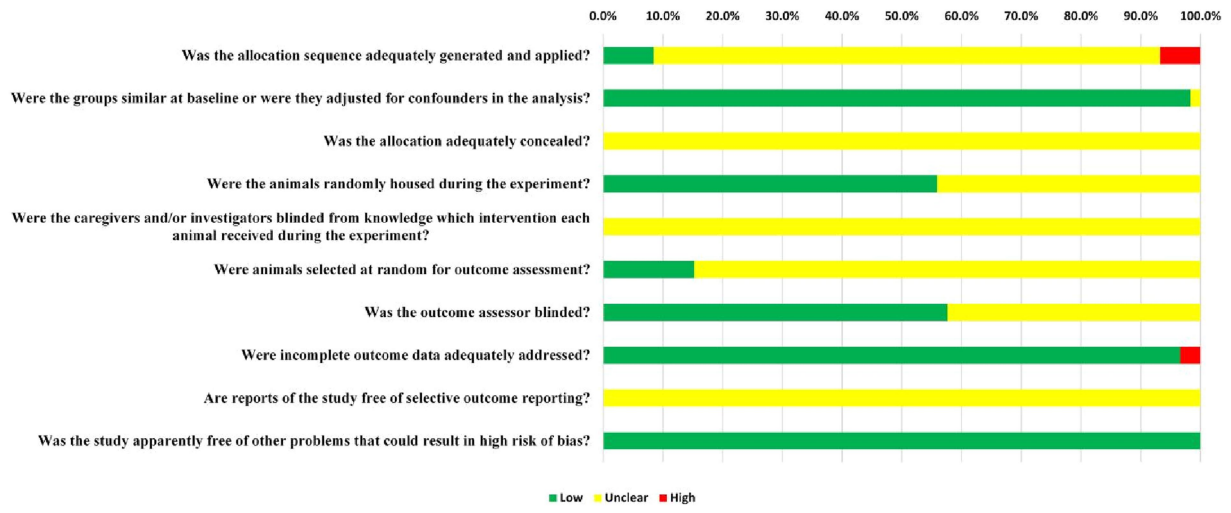

FIGURE 3
The results of the risk of bias assessment.

of studies on CUR was the largest, see Figure 4D. The results of NMA indicated that rats had significantly higher BBB scores in TCM monomer groups compared to negative controls. Except for the CUR and RSV, the differences in BBB scores of rats between other types of TCM monomers were not statistically significant, see Table 4. Rank ordering and SUCRA value results showed that RSV might be the most effective TCM monomer for SCI, see Figure 5D and Supplementary Table S6. The comparison-correction funnel plot was basically symmetrical, suggesting that there was less possibility of publication bias, see Figure 6D.

4. Discussion

As far as we know, this is the first NMA that evaluates the motor function recovery in rat blunt SCI models following treatment with

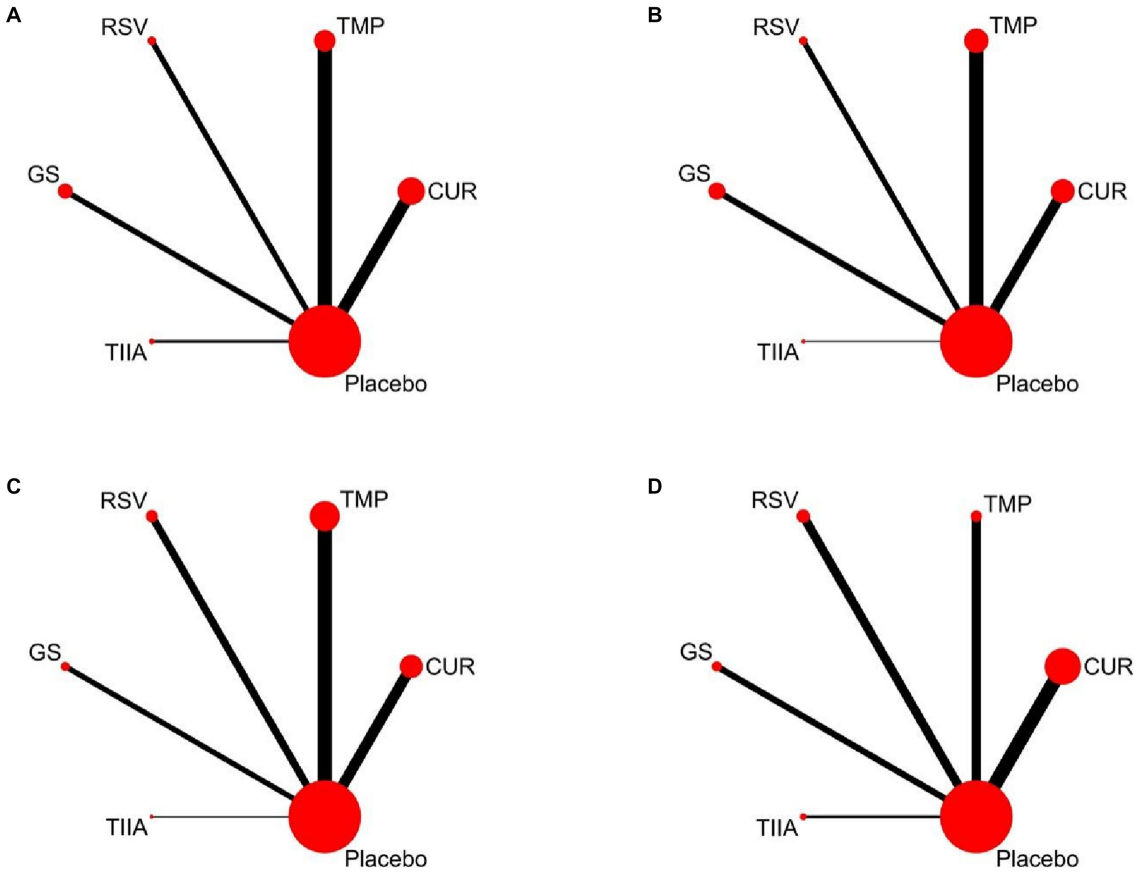

FIGURE 4
Evidence network diagram Circle size represents sample size involved; thickness of the line segment represents the number of studies involving both interventions. **(A)** The first week; **(B)** the second week; **(C)** the third week; **(D)** the fourth week.

TABLE 1 Network meta-analysis results 1 week after treatment with TCM monomers.

CUR					
−0.53 (−1.58,0.52)	TMP				
−1.28 (−2.67,0.10)	−0.75 (−2.13,0.62)	RSV			
−0.89 (−2.25,0.47)	−0.36 (−1.71,0.98)	0.39 (−1.23,2.02)	GS		
−1.67 (−3.41,0.07)	−1.14 (−2.87,0.59)	−0.38 (−2.34,1.57)	−0.78 (−2.71,1.16)	TIIA	
1.75 (1.00,2.50)	**2.28 (1.55,3.01)**	**3.04 (1.87,4.20)**	**2.64 (1.51,3.77)**	**3.42 (1.85,4.99)**	Placebo

Bold values are significant pairwise comparisons.

TCM monomers The BBB Locomotor Rating scale (score range: 0–21; complete flaccid paraplegia to normal function) is a sensitive measure of motor function recovery. Accordingly, this tool was used for assessing motor function recovery in SCI rat models (30–32). According to NMA, almost all TCM monomers significantly improved motor function recovery when compared with the negative control group at weeks 1, 2, 3, and 4. This finding indicates the considerable potential of TCM monomers in treating SCI. Although the lack of statistical significance in the BBB scores of the five TCM monomer groups at weeks 1, 2, and 3 may be attributed to the small sample size, the results based on rank ordering and SUCRA values still indicate that in the first week after SCI, the TIIA group showed the best recovery of motor function, while the RSV group exhibited the best recovery of motor function in the last 3 weeks. Therefore, we can consider TIIA may be the most effective TCM monomer during the first week, whereas RSV may be the most effective TCM monomer during the last 3 weeks in promoting motor function recovery. In the future, further studies with larger sample sizes are needed to validate our findings.

Several key conclusions emerge from the studies evaluated in this meta-analysis. TIIA may have a better effect on early recovery of motor function than the other monomers. This conclusion has been supported by a few various researchers. Our team established in a previous research report that TIIA has great potential in remodeling the spinal pathway and exhibits neuroprotective effects in the early stage of SCI (33). In addition, TIIA can relieve histopathological damage, rescue microvessels, and reduce blood–brain barrier permeability to protect motor neurons through the Notch signaling pathway (34). In SCI, an increase in the number of activated astrocytes and glial scarring both lead to decreased neurological function. Treatment with TIIA can thus effectively ameliorate these biological changes leading to a satisfactory

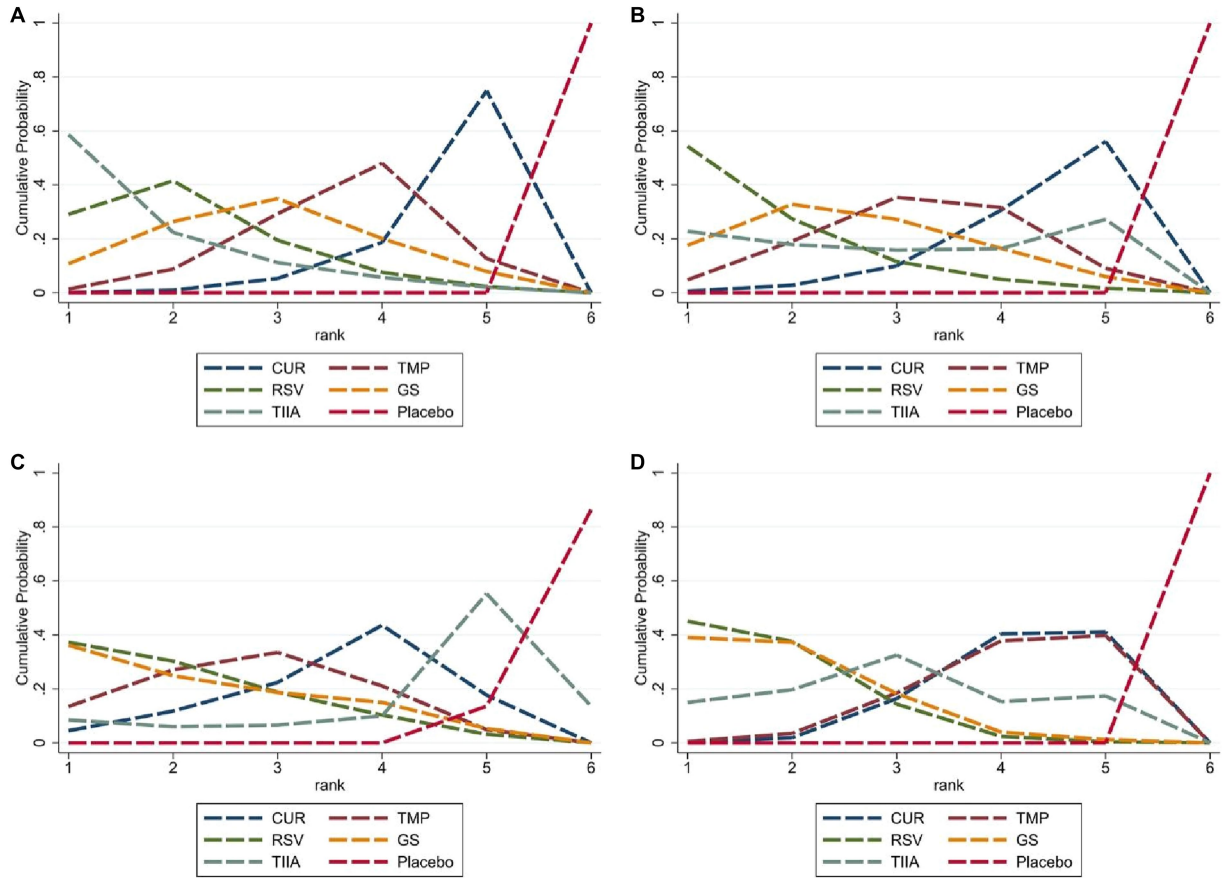

FIGURE 5
Cumulative probability ranking curve. The vertical axis represents cumulative probabilities, while the horizontal axis represents ranks. **(A)** The first week; **(B)** the second week; **(C)** the third week; **(D)** the fourth week.

functional recovery (35). Therefore, TIIA exhibits neuroprotective activity and promotes recovery of motor function in the early stage of SCI. However, caution should be exercised in assessing whether the early therapeutic effect of TIIA in SCI is the most optimal among the five TCM monomers, as this study only included four eligible studies on TIIA treatment for SCI. Further relevant literature is still needed to validate this conclusion.

In addition, according to the findings of this investigation, RSV could be the TCM monomer that is most efficient in promoting the restoration of motor function in rats with blunt SCI during the last 3 weeks of treatment. Secondary injury, including inflammation, oxidative stress responses, and neuronal apoptosis, occurring after the initial SCI results in further neurological damage. This pathophysiological status is alleviated by RSV owing to its ability to relieve inflammation, inhibit oxidative damage, and prevent apoptosis. Furthermore, previous studies have demonstrated that RSV suppresses the inflammatory response in SCI by upregulating the SIRT-1 signaling pathway and downregulating the NF-κB signaling pathways (36, 37). SCI is associated with the generation of free radicals, which cause oxidative degradation of lipids (38). Therefore, malondialdehyde (MDA) and superoxide dismutase (SOD) are often used as indices of oxidative injury in SCI (39). Prior studies have found that RSV is a good biological antioxidant that can reduce secondary oxidative stress-induced cell injury after SCI. It mediates this activity by increasing the SOD level and decreasing the MDA level in serum (40). A few studies have found that treatment with RSV is associated with significant upregulation of the anti-apoptotic gene Bcl-2 as well as significant inhibition of neuronal apoptosis (41, 42). These findings have boosted the potential of RSV as a treatment for SCI. The results of this study further support these findings that RSV is a promising drug for promoting motor function recovery after blunt SCI.

The other three TCM monomers (CUR, TMP, and GSs) can also play an indispensable function in SCI treatment. Studies have shown that CUR inhibits the overactivation of microglia by regulating the expression of microglia TLR4, thereby reducing inflammation-induced neuronal injury (43). In addition, CUR activates the Nrf2 signaling pathway and upregulates the Nrf2/HO-1 signaling pathway, which promotes free radical antioxidant properties (44). Thus, CUR has demonstrated efficacy in alleviating inflammation and oxidative damage associated with central nervous system damage in mammals (45). Similarly, *in vivo* data have shown that TMP regulates the spinal cord microenvironment (46). In a rat model of acute SCI, TMP decreases the expression of migration inhibitory factors, which may play a role in repairing damaged tissue (47). A few studies have suggested that TMP inhibits the expression of IL-18, IL-1β, TNF-α, NF-κB, and neutrophil infiltration and increases the level of NF-κB inhibitor and IL-10. These activities reduce the inflammatory response after SCI and exert a neuroprotective activity (48, 49). Similarly, the efficacy of GSs in treating SCI has been demonstrated. By inducing neurotrophic factors for astroglia, GSs have demonstrated enhancement of scratch wound healing in cell cultures; moreover, GSs have shown improvement in nerve function

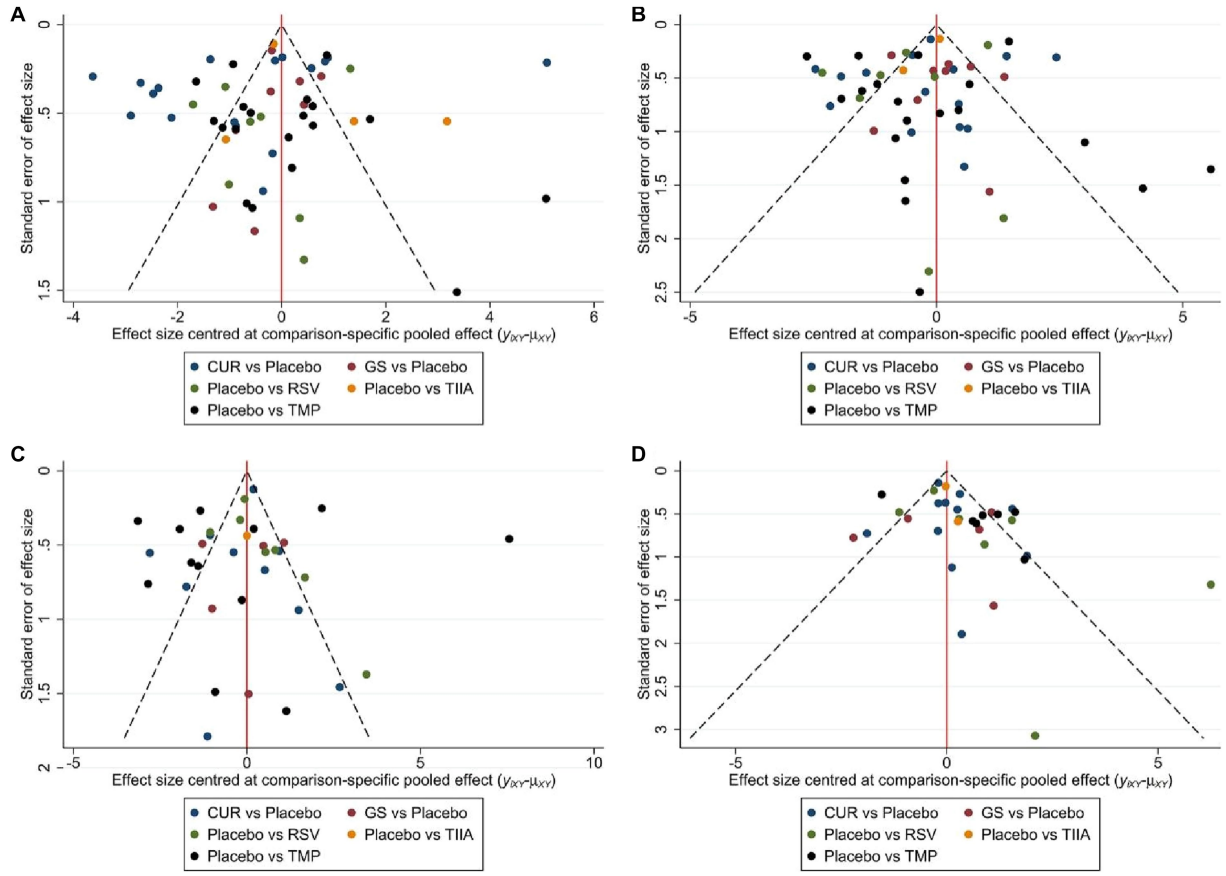

FIGURE 6
The comparison-correction funnel plot **(A)** The first week. **(B)** The second week. **(C)** The third week. **(D)** The fourth week.

TABLE 2 Network meta-analysis results 2 week after treatment with TCM monomers.

CUR					
−0.49 (−1.47,0.49)	TMP				
−1.15 (−2.39,0.10)	−0.66 (−1.88,0.56)	RSV			
−0.73 (−1.89,0.43)	−0.24 (−1.38,0.90)	0.42 (−0.96,1.79)	GS		
−0.53 (−2.47,1.41)	−0.04 (−1.97,1.88)	0.61 (−1.45,2.68)	0.20 (−1.82,2.22)	TIIA	
2.89 (2.17,3.60)	**3.37 (2.70,4.05)**	**4.03 (3.01,5.05)**	**3.62 (2.70,4.54)**	**3.42 (1.62,5.22)**	Placebo

Bold values are significant pairwise comparisons.

recovery in animal models of SCI (45, 50). In addition, GS can effectively inhibit the SCI-induced activation of the MAPK signaling pathway, thus alleviating secondary injury after SCI (51). These findings can well explain the mechanism of the three TCM monomers promoting motor function recovery following blunt SCI, which can lay a foundation for future research.

TCM monomers thus exhibit neuroprotective activity and could remarkably enhance motor function in rats with blunt SCI, especially TIIA, and RSV. Furthermore, combining multiple therapeutic approaches would benefit spinal cord functional recovery; these include the use of two or more TCM monomers and the use of TCM monomers combined with molecular therapy, cell therapy, or tissue engineering. Therefore, in the future, TCM monomers will be an important focus in the quest for blunt SCI treatment.

5. Limitations

This research faced several shortcomings. Firstly, the data that are now available on TCM monomers and the decline in motor function linked to SCI are inadequate because of the restricted number of rats involved in each trial, the limited sample sizes, and the insufficient examination of the data on BBB scores. Secondly, We only considered the BBB score since it is the most common and best shows the impact of TCM monomers treatment; however, we failed to assess any further outcome measures due to few reports. Thirdly, we were unable to determine where the heterogeneity originated in an accurate manner. Therefore, in our investigation, we used a model with random effects, which resulted in highly conservative findings. Fourth, this study compared five TCM monomers that are commonly used for the treatment of SCI;

TABLE 3 Network meta-analysis results 3 week after treatment with TCM monomers.

CUR					
−0.53 (−2.33,1.26)	TMP				
−0.97 (−3.04,1.10)	−0.44 (−2.40,1.52)	RSV			
−0.91 (−3.25,1.42)	−0.38 (−2.62,1.86)	0.06 (−2.40,2.53)	GS		
1.38 (−2.88,5.65)	1.92 (−2.29,6.13)	2.36 (−1.98,6.69)	2.29 (−2.17,6.76)	TIIA	
3.69 (2.34,5.04)	**4.23 (3.05,5.41)**	**4.67 (3.10,6.23)**	**4.60 (2.70,6.51)**	2.31 (−1.73,6.35)	Placebo

Bold values are significant pairwise comparisons.

TABLE 4 Network meta-analysis results 4 week after treatment with TCM monomers.

CUR					
−0.03 (−1.23,1.17)	TMP				
−1.33 (−2.62,-0.04)	−1.30 (−2.68,0.08)	RSV			
−1.26 (−2.66,0.14)	−1.23 (−2.73,0.27)	0.07 (−1.50,1.64)	GS		
−0.63 (−2.43,1.17)	−0.60 (−2.48,1.27)	0.70 (−1.24,2.63)	0.63 (−1.39,2.65)	TIIA	
3.17 (2.41,3.92)	**3.20 (2.27,4.12)**	**4.50 (3.46,5.54)**	**4.43 (3.25,5.61)**	**3.80 (2.16,5.43)**	Placebo

Bold values are significant pairwise comparisons.

thus, the potential therapeutic role of other TCM monomers may have been overlooked. Fifth, drug dose and administration route may have affected the recovery of motor function. However, subgroup analyses were not performed owing to a smaller number of included studies. Sixth, the purity of TCM monomer is closely related to the therapeutic effect and dosage, but it has not been reported in any study, which may bring a certain risk of bias; In addition, the number of animals in different studies varies, and the quality of the literature included in the studies needs to be carefully evaluated.

6. Conclusion

The NMA revealed that TCM monomers could effectively restore motor function in the rat model of blunt SCI. TIIA may be the most effective TCM monomer to improve motor function recovery in the first week of rats with blunt SCI, and RSV may be the most effective TCM monomer during the last 3 weeks.

The existing animal experiments on the use of TCM monomers for SCI still encounter various difficulties with blinding, allocation concealment, randomization, and reporting of results, according to a systematic review of the included research. Because of these limitations, animal research may not provide reliable findings. The quality of evidence in preclinical investigations may be improved by standardizing the implementation and reporting of animal experiments, and the risk of extrapolating preclinical findings into clinical settings can be reduced.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LX conceived the study. LX, YY, WZ, WL, CL, ZG, and XY contributed to the study design. LX drafted the manuscript. YY and XY edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1165076/full#supplementary-material

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Healthcare-associated infections and antimicrobial resistance in severe acquired brain injury: a retrospective multicenter study

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Background: Recent studies underscore that healthcare-associated infections (HAIs) and multidrug-resistant (MDR) HAIs affect rehabilitation outcomes and hospital length of stay (LOS) for severe acquired brain injury (sABI).

Objective: This study aimed to estimate HAI incidence in different sABI rehabilitation settings and determine risk factors and HAI impact on neuromotor and cognitive recovery.

Methods: We conducted a retrospective multicenter study in two semi-intensive units (SICUs), two high-specialty post-acute units (PAUs), and one long-term care (LTC) rehabilitation facility. Data extraction was performed by experienced clinicians, using a structured Excel file and they agreed upon criteria for case definitions of healthcare. The main outcome measures were the HAI and MDR HAI incidence and the LOS, the functional recovery was measured using the Level of Cognitive Functioning and Disability Rating Scale.

Results: There were 134 sABI participants. The calculation of the probability level was adjusted for three pairwise comparisons among settings ($0.05/3 = 0.017$). The HAI and MDR HAI incidences were significantly higher in SICU (3.7 and 1.3 per 100 person-days) than in other settings (LTC: 1.9, $p = 0.034$ and 0.5, $p = 0.026$; PAU: 1.2, $p < 0.001$ and 0.3, $p < 0.001$). HAI and MDR HAI risk variables included older age, an increased number of devices, and carbapenemase-producing Enterobacteriaceae (CPE) colonization, while a high prealbumin plasma value seemed to have a protective effect.

Conclusion: HAIs are related to longer LOS, and colonization is associated with poor prognosis and poor functional outcomes with reduced ability to achieve the cognitive capacity of self-care, employability, and independent living. The need to ensure the protection of non-colonized patients, especially those with severe disabilities on admission, is highlighted.

KEYWORDS

rehabilitation outcome, brain injuries, infections, multidrug resistance, carbapenemase-producing Enterobacteriaceae

Introduction

Healthcare-associated infections (HAIs) are a severe threat to patient safety in Europe. The European Center for Disease Prevention and Control (ECDC) surveys estimated an HAI prevalence of 6.5% in acute care hospitals and 3.9% in long-term care facilities (1). Patients hospitalized with a neurological diagnosis, especially those with severe acquired brain injury (sABI), are more likely to develop HAI (2) because of their immunodeficiency. It has only recently been realized that the impairment of the relationship between the central nervous system and the immune system caused by injury leads to secondary immunodeficiency (CNS injury-induced immunodepression, CIDS) and infection (3). In addition, medical devices, mental health problems, severe clinical conditions, and poor nutritional status (4) may contribute to further impairing their immune defenses.

Recent studies underscore that HAI and multidrug-resistant (MDR) HAIs affect rehabilitation outcomes and the hospital length of stay (LOS) for sABI patients (5). Research on HAIs and MDR HAIs, especially in rehabilitation and neurorehabilitation settings, is scant (6). The HAI prevalence among patients admitted to Rehabilitation Units in Europe has been reported to be approximately 8 to 15% (7). Respiratory tract infections, urinary tract infections (UTIs), ventilator-associated pneumonia, surgical site infections, surgical procedure-related infections, meningitis, and sepsis are common in intensive care units, especially if the length of stay exceeds 6 days (8). A recent study focused on MDR organism (MDRO) management in European rehabilitation facilities through a questionnaire. The prevalence is high, and the management of MDRO colonization is variable without any MDRO screening protocol, despite the increasing prevalence of CPE in healthcare facilities across Europe (9). An MDR pathogen organism is defined as non-susceptibility to at least one agent in three or more antimicrobial categories (10). The most common infections in this population are predominantly due to multiple pathogen germs and MDR germs, in particular: *Acinetobacter baumannii*, Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (11).

Data on the impact of carbapenemase-producing Enterobacteriaceae (CPE) colonization, which is the main risk factor for severe infection and high environmental spread (12), are also lacking.

The primary aim of the study was to estimate the HAI incidence and their etiology, distinguishing MDR and non-MDR infections, in sABI patients treated in inpatient rehabilitation settings such as semi-intensive care units (SICU), post-acute units (PAU), and long-term care (LTC) facilities. The secondary aims were to identify potential risk factors for HAI development and estimate the impact of HAIs on patients' recovery and LOS.

Methods

Study design and setting

This observational, retrospective multicenter study was conducted in four hospitals that comprise five different rehabilitation settings: two SICUs, two high-specialty PAUs, and one LTC facility. These wards are part of a clinical care pathway for sABI patients, encompassing the acute and rehabilitation phases up to discharge at home or to community facilities. All those settings are subjected to similar prevention and infection control measures according to the clinical care pathway. The two SICUs interact with the intensive care unit and neurosurgery to ensure a timely neurorehabilitation approach. They define the diagnosis, begin the rehabilitation process, and once patients are stabilized, they are directed to the next level of care. The two PAUs provide comprehensive care for sABI patients, offering separate units for disorders of consciousness with a long-term rehabilitation process. Based on the clinical stability and recovery of the patients, the trajectories of the rehabilitation path could differ. The possible trajectories were only SICU→ PAU ($N = 49$), SICU→ LTC ($N = 2$), SICU→ PAU→ LTC ($N = 1$), and PAU→ LTC ($N = 1$). Unique trajectories were only SICU ($N = 22$), PAU ($N = 39$), and LTC ($N = 20$).

Patients not eligible for intensive rehabilitation treatment are directed to the LTC (13). All five wards use the same diagnostic and treatment approach with an individually customized rehabilitation plan that also involves the patients' families.

The study was approved by the local Ethics Committee (protocol No. 609-2019-OSS-AUSLIM) and did not receive funding. Informed consent was obtained when possible or waived in accordance with the General Authorization of the Privacy Guarantor No. 09/2016 on observational retrospective studies.

Participants

Data on patients hospitalized in 2018, including patients admitted in 2017 and discharged by 31 December 2018, were extracted from medical records.

Data extraction was made by experienced clinicians, including some of the authors (GBC, AB, and EB), who entered the data extracted in a structured Excel file, using agreed criteria on case definitions of healthcare-associated infections based on ECDC Codebook (14) and are summarized in Supplementary Table S1.

During the study, some patients were admitted to more than one setting. In these cases, data were collected from both settings. Inclusion criteria were as follows: age $\geq$18 years, sABI of any etiological origin (traumatic, non-traumatic hemorrhagic, anoxic, infective, neoplastic, or toxic-metabolic), Glasgow Coma Scale $\leq$ 8 for at least 24 h, and impairments of physical, neurocognitive, and/or psychological function that involve a severe disability.

Infection diagnosis

The number and etiology of infections occurring during hospitalization were collected. The diagnostic criteria of HAI were based on the ECDC Codebook (14) and are summarized in Supplementary Table S1. The most common infections are bloodstream infections (BSIs), UTIs, and pneumonia.

Other infections were considered if reported in medical records. They included *Clostridium difficile* infection, otitis,

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TABLE 1 Characteristics of the study sample at baseline and by rehabilitation setting.

Variables	Study sample at admission $N = 134$	SICU $N = 90$	PAU $N = 74$	LTC $N = 24$
Male, *n* (%)	89 (66.4)	60 (66.7)	52 (70.3)	13 (54.2)
Female, *n* (%)	45 (33.3)			
Age, mean ± SD	53.3 ± 18.2	51.1 ± 18.6	50.6 ± 16.1	69.8 ± 14.4
Etiology, *n* (%)				
Traumatic	54 (40.3)	39 (43.3)	33 (44.6)	4 (16.7)
Associated trauma*	21 (38.9)	33 (84.6)	27 (81.8)	1 (25.0)
Non-traumatic hemorragic	68 (50.7)	32 (35.6)	30 (40.5)	11 (45.8)
Other	12 (9.0)	19 (21.1)	11 (14.9)	9 (37.5)
Time since injury (days), median [IQR]	34.5 [18.7–79]	28 [15–45]	62.5 [35–94]	106 [28–148]
Comorbidity, *n* (%)	33 (24.6)	17 (18.9)	13 (17.6)	15 (62.5)
Pre-admission surgery, *n* (%)				
No	79 (59.0)	58 (64.4)	30 (40.5)	13 (54.2)
Neurosurgery	39 (29.1)	20 (22.2)	31 (41.9)	8 (33.3)
Other	16 (11.9)	12 (13.3)	13 (17.6)	3 (12.5)
LCF upon admission, median [IQR]	3 [2.25–5]	4 [3–5]	5 [3–6]	-
LCF at discharge, median [IQR]		5 [4–6]	6 [5–7]	-
DRS upon admission, mean ± SD	19 [16–23]	19 [15–22]	18 [14–20]	-
DRS at discharge, mean ± SD		16 [7–20]	11 [6–17]	-
Proteins (g/dL) upon admission	6.4 ± 1.4	6.5 ± 1.5	6.4 ± 0.8	6.2 ± 1.3
Albumin (g/L) upon admission	25.9 ± 11.9	31.1 ± 5.0	32.4 ± 5.7	28.3 ± 5.9
Prealbumin (mg/dL) upon admission	17.9 ± 6.8	17.9 ± 6.4	19.9 ± 6.3	17.2 ± 7.9
Transfers, *n* (%)		12 (13.3)	22 (29.7)	2 (8.3)
Surgery during hospitalization, *n* (%)				
No	113 (84.3)	83 (92.2)	54 (73.0)	22 (91.7)
Neurosurgery	11 (8.2)	2 (2.2)	16 (21.6)	0
Other	10 (7.5)	5 (5.6)	4 (5.4)	2 (8.3)
Ward shift caused by worsening, *n* (%)		6 (6.7)	8 (10.8)	0
CPE colonization, *n* (%)				
No	84 (62.7)	66 (73.3)	40 (54.0)	12 (50.0)
Upon admission	29 (21.6)	14 (15.6)	22 (29.7)	7 (29.2)
During hospitalization	21 (15.7)	10 (11.1)	12 (16.2)	5 (20.8)
Complications, *n* (%)	48 (35.8)	10 (11.1)	46 (62.2)	23 (95.8)
Length of stay (days), median [IQR]		20.5 [13–42]	103 [55–203]	47.5 [9–169]
Medical devices				
Indwelling catheter, *n* (%) days, median [IQ range]		78 (86.7) 21.5 [10–55]	44 (59.5) 55 [19–101]	24 (100) 43.5 [9–156]
Central venous catheter, *n* (%) days, median [IQ range]		40 (44.4) 14 [7–33]	18 (24.3) 24.5 [6–53]	3 (12.5) 45 [8–164]
Tracheostomy tube, *n* (%) days, median [IQ range]		65 (72.2) 32 [17–70]	46 (62.2) 99 [30–200]	13 (54.2) 42 [10–148]
PEG or PEJ, *n* (%) days, median [IQ range]		29 (32.2) 44 [17–76]	32 (43.2) 225 [110–285]	13 (54.2) 98 [42–173]

*Among patients with traumatic etiology; continuous data are reported as mean ± SD or median and [interquartile range, IQR]; categorical variables are reported as count (n) and column percentages (%). SICU, semi-intensive care unit; PAU, post-acute unit; LTC, long-term care facility; LCF, levels of cognitive functioning; DRS, disability rating scale; CPE, carbapenemase-producing Enterobacteriaceae; PEG, percutaneous endoscopic gastrostomy.

cellulitis, ventriculitis, phlebitis, epididymo-orchitis, skin and soft tissue infections, and intra-abdominal infections.

We omitted fewer common infections.

Infections were classified as non-MDR HAI or MDR HAI according to the organism found and based on the international expert proposal of Magiorako et al. (10) study.

Outcome variables

The primary outcome was the incidence of HAIs and MDR HAIs. Secondary outcomes included LOS and functional recovery measured using the Disability Rating Scale (DRS) (15) and the Level of Cognitive Functioning Scale (LCF) (16), which are routinely administered in SICU and PAU settings. These functional assessment scales were not administered in the LTC setting.

LCF is a well-established tool to assess cognitive functioning in post-coma patients, validated in an Italian study (17). Patients are classified into eight levels, from 1 (non-responders) to 8 (purposeful-appropriate person); the higher the value, the better the cognitive function.

DRS is a 30-point scale measuring eight areas of functioning: eye-opening, verbalization, motor response, level of cognitive ability for daily activities of feeding, toileting, and grooming, overall level of dependence, and employability (18). Scores in each area (rated from 0 to 3 or 0 to 4 or 0 to 5) are summed to yield a total score between 0 and 30, with a higher score denoting lower functioning.

Independent variables

The predictors of HAIs were classified into pre-admission characteristics, inpatient indicators, clinical parameters, and device-related data. Pre-admission variables were socio-demographic characteristics, history of previous diseases, type of injury, and any previous surgery. We added the condition of associated trauma for traumatic patients (Table 1) for those who suffered other traumatic lesions such as thoracic, skeletal, abdominal, or spinal cord. We also collected comorbidities, meaning specifically the presence of coexisting or additional pathologies with respect to brain damage with an infectious impact.

Inpatient indicators included the time between injury and admission, any transfers to other departments, any surgery during hospitalization, and any ward shifts caused by clinical worsening.

Clinical parameters were CPE colonization on admission or during rehabilitation and nutritional parameters (protein, albumin, and prealbumin assay) on admission. Moreover, clinical conditions with a potential negative impact on the functional outcome not directly related to HAIs (cardiovascular complications, osteoarticular problems, wound onset, and dystonia) were collected.

Devices included an indwelling urinary catheter, a central venous catheter, a tracheotomy tube, and a percutaneous endoscopic gastrostomy. The number of medical devices used for each patient was collected.

Statistical methods

Continuous variables were summarized using mean and standard deviation (±SD) when normally distributed, and median and interquartile range [IQR] otherwise; categorical variables were summarized using frequencies.

The incidence of HAIs and MDR HAIs per 100 person-days was calculated using the length of hospital stay as the exposure time. HAI incidence was compared between the three settings. In case of a significant difference, the rehabilitation setting was included as an adjustment variable in the subsequent analyses.

A negative binomial regression analysis was used to identify the risk factors associated with HAI and MDR HAI incidence. Significant variables were included in a multivariable model. The results were reported as an incidence rate ratio (IRR) and 95% confidence interval (95% CI). All the significance levels reported refer to comparisons of regression coefficients in the Poisson and negative binomial models. When more than two groups were compared, a Bonferroni correction to the probability level was applied. The adjustment for the rehabilitation setting is obtained by including the rehabilitation setting in the model as two dummy variables, one for PAU and one for LTC, and using SICU as the reference category.

In a secondary analysis, including data from SICU and PAU settings only, patients were classified into three mutually exclusive groups: no infection, at least one HAI (non-MDR), and at least one MDR HAI.

These groups were compared on LOS and the rehabilitation outcomes (DRS and LCF scores at discharge), using negative binomial regression and linear regression, respectively. The results on LOS were reported as predicted LOS (in weeks) with 95%CI. In linear regression analysis, a model adjusted for rehabilitation setting and functional score on admission was initially estimated, then a multivariable model adjusted for other factors was obtained. Regression coefficients were reported with 95%CI.

The backward stepwise variable selection procedure was applied to obtain parsimonious multivariable models (p for removal=0.05). Robust standard errors were estimated using a clustered sandwich estimator to take into account repeated measurements (i.e., admissions in different settings) on the same individual. Bonferroni's correction was applied for multiple comparisons. The Bonferroni correction consists of adopting a significance level adjusted for the number of comparisons when the groups compared are more than 2.

In this case, the probability level was adjusted for three pairwise comparisons among settings ($0.05/3 = 0.017$). The statistical software (Stata), when the Bonferroni correction is requested, provides already adjusted p-values. For instance, if the p-value of a test is 0.002, it is provided in the output as $0.002^*3 = 0.006$. All the p-values in our results are adjusted p-values when they refer to comparisons of the three settings.

Statistical analyses were carried out using Stata version 15 (StataCorp, College Station, TX). The significance level was set to a p-value of < 0.05.

TABLE 2 HAI and MDR HAI incidence in each rehabilitation setting.

	Num. HAI	HAI incidence per 100 person-days	95%CI		Num. MDR HAI	MDR HAI incidence per 100 person-days	95%CI
SICU	115	3.74	2.50–4.99		41	1.33	0.82–1.85
PAU	122	1.23	0.92–1.55		32	0.32	0.17–0.48
LTC	43	1.93	1.03–2.83		12	0.54	0.20–0.88

SICU, semi-intensive care unit; PAU, post-acute unit; LTC, long-term care facility; HAI, healthcare-associated infections; MDR, multidrug-resistant.

Results

Patients' characteristics

The analysis included 188 records of 134 patients admitted to at least one of the four hospitals. During the study period, 49 patients were transferred from SICU to PAU, 2 patients from SICU to LTC, 1 patient from PAU to LTC, and 1 patient crossed all three settings (Supplementary Figure S1). Overall, the analysis included the data of 90 patients hospitalized in SICU, 74 patients hospitalized in PAU, and 24 patients hospitalized in LTC. Patients' characteristics by setting are reported in Table 1. The mean age was 53.3 ±18.2 years, and 66.5% of patients were male. Traumatic etiology accounted for 40.4% of cases, and 23.9% of patients had comorbid conditions. In LTC, the sample was older on average, had more comorbidities, and had a lower frequency of traumatic etiology. The median LOS was 21 days [13–42] in SICU, 103 days [55–203] in PAU, and 48 days [9–169] in LTC.

HAI incidence

The HAI incidence ranged from 1.2 per 100 person-days in PAU to 1.9 in LTC and up to 3.7 in SICU (Table 2). The incidence in SICU was significantly higher than in the other settings ($p < 0.001$ SICU vs. PAU; $p = 0.034$ SICU vs. LTC). MDR HAI incidence was 0.3 per 100 person-days in PAU, 0.5 in LTC, and 1.3 in SICU. The incidence in SICU was significantly higher compared to the other two settings ($p < 0.001$ SICU vs. PAU; $p = 0.026$ SICU vs. LTC).

Supplementary Figure S2 reports the HAI and MDR HAI incidence in each rehabilitation setting, according to the infection etiology. Overall and MDR bloodstream infections (BSIs) had a significantly higher incidence in the SICU as compared to the other settings. The overall UTI incidence was higher in SICU (0.68, 95%CI: 0.33–1.03) than in LTC (0.45, 95%CI: 0.11–0.78) and PAU (0.20, 95%CI: 0.10–0.31), but only the difference between SICU and PAU was significant ($p = 0.017$). On the other hand, the overall incidence of pneumonia was similar in SICU (1.01, 95%CI: 0.46–1.55) and LTC (0.94, 95%CI: 0.37–1.52), while it was significantly lower in PAU (0.36, 95%CI: 0.21–0.52). MDR pneumonia incidence had a similar trend. A low incidence of MDR UTIs, skin and soft tissue infections, and intra-abdominal infections was observed in all three settings. The incidence of other infections was higher in SICU as compared to the other two settings. Overall, 280 infections occurred; the most frequent pathogens involved were *P. aeruginosa* (15.7%), *K. pneumoniae* (14.3%), *E. coli* (10%), *P. mirabilis* (7.4%), *Candida* spp. (4.8%), *E. faecalis* (4.3%), and *A. baumannii* (3.9%). In 26.1% of cases, the pathogen was not identified.

Among the 280 HAIs, 85 were identified as MDR (30.3%). The MDR frequency on certain isolates was higher than 50%, specifically: *K. pneumoniae* (55%, $N = 33$), *A. baumannii* (89%, $N = 9$), methicillin-resistant *S. epidermidis*, MRSE ($N = 8$), methicillin-resistant *S. aureus*, MRSA ($N = 6$), and *E. cloacae* (100%, $N = 4$).

Factors associated with HAI incidence

Table 3 shows the factors associated with HAI and MDR HAI incidence. In the regression analysis adjusting for rehabilitation setting only, older age, any comorbidities, lower LCF and higher DRS scores upon admission, higher number of devices, and CPE colonization were all significantly associated with HAI development during inpatient rehabilitation. Conversely, a high prealbumin plasma value on admission was associated with a decreased likelihood of developing HAI. In the multiple regression analysis, older age, an increased number of devices, and CPE colonization remained significant. Older age and CPE colonization were also significant risk factors for MDR HAI incidence.

Association between HAI and rehabilitation outcomes

In the SICU setting, LOS was significantly higher in the HAI group compared with the no-infection group (4.7 vs. 2.6 weeks, $p = 0.008$) and even higher in the MDR HAI group (10.2 weeks, $p = 0.003$) (Figure 1A). In the PAU setting, LOS was on average 11 weeks in the no-infection group and approximately 25–26 weeks in the HAI and MDR HAI groups. After adjusting for the number of devices, surgery during rehabilitation, and complications, the differences between the three groups remained significant (Figure 1B).

In a regression model adjusted for admission score and rehabilitation setting, being in the MDR HAIs group was significantly associated with higher DRS and lower LCF scores at discharge (Table 4). However, these associations were no longer significant after adjusting for the number of devices, surgery during rehabilitation, and complications. Notably, in the presence of CPE colonization and complications, disability at discharge increased as the time from injury to hospitalization increased. Similarly, the LCF score at discharge was lower for patients with an increased time from injury to hospitalization, patients who

TABLE 3 Factors associated with HAI and MDR HAI incidence: results of bivariate and multiple negative binomial regression models, adjusted for rehabilitation setting.

	Overall HAI				MDR HAI			
	Bivariate model		Multiple model		Bivariate model		Multiple model	
	IRR (95%CI)	p-value	IRR (95%CI)	p-value	IRR (95%CI)	p-value	IRR (95%CI)	p-value
Male	0.91 (0.60–1.38)	0.653			1.27 (0.63–2.55)	0.508		
Age	1.02 (1.01–1.03)	**<0.001**	1.02 (1.01–1.03)	**0.006**	1.03 (1.01–1.05)	**0.010**	1.03 (1.00–1.05)	**0.042**
Etiology Traumatic (ref.) Vascular Other	1.00 1.40 (0.91–2.16) 1.44 (0.95–2.20)	0.208			1.00 1.22 (0.56–2.65) 2.03 (0.91–4.52)	0.263		
Pre-admission surgery No (ref.) Neurosurgery Other	1.00 0.85 (0.58–1.26) 0.91 (0.48–1.74)	0.753			1.00 0.79 (0.41–1.52) 1.00 (0.32–3.09)	0.805		
Comorbidity	1.69 (1.16–2.47)	**0.007**			1.48 (0.76–2.88)	0.249		
LCF upon admission	0.85 (0.75–0.96)	**0.010**			0.79 (0.65–0.96)	**0.016**		
DRS upon admission	1.05 (1.02–1.09)	**0.002**			1.09 (1.02–1.16)	**0.008**		
Proteins upon admission	0.94 (0.78–1.13)	0.511			0.85 (0.63–1.15)	0.303		
Albumin upon admission	0.98 (0.94–1.03)	0.381			0.95 (0.88–1.03)	0.199		
Prealbumin upon admission	0.96 (0.93–0.99)	**0.011**			0.93 (0.86–0.99)	**0.029**		
Number of medical devices	1.51 (1.28–1.79)	**<0.001**	1.34 (1.15–1.55)	**<0.001**	1.33 (0.98–1.81)	0.065		
CPE colonization	2.14 (1.45–3.15)	**<0.001**	1.65 (1.09–2.48)	**0.017**	4.20 (1.89–9.33)	**<0.001**	3.78 (1.67–8.58)	**0.001**
Transfers	0.81 (0.55–1.19)	0.286			0.86 (0.44–1.67)	0.655		
Surgery during hospitalization	0.72 (0.47–1.09)	0.121			0.61 (0.26–1.41)	0.247		
Ward shift caused by worsening	1.23 (0.77–1.96)	0.385			2.10 (1.08–4.09)	**0.029**		
Complications	1.29 (0.83–1.99)	0.254			1.04 (0.50–2.18)	0.906		

Nutritional parameters, baseline LCF, and baseline DRS scores were excluded from multiple model estimation because of missing data; significant factors are given in bold. HAI, healthcare-associated infections; MDR, multidrug-resistant; LCF, levels of cognitive functioning; DRS, disability rating scale; CPE, carbapenemase-producing Enterobacteriaceae.

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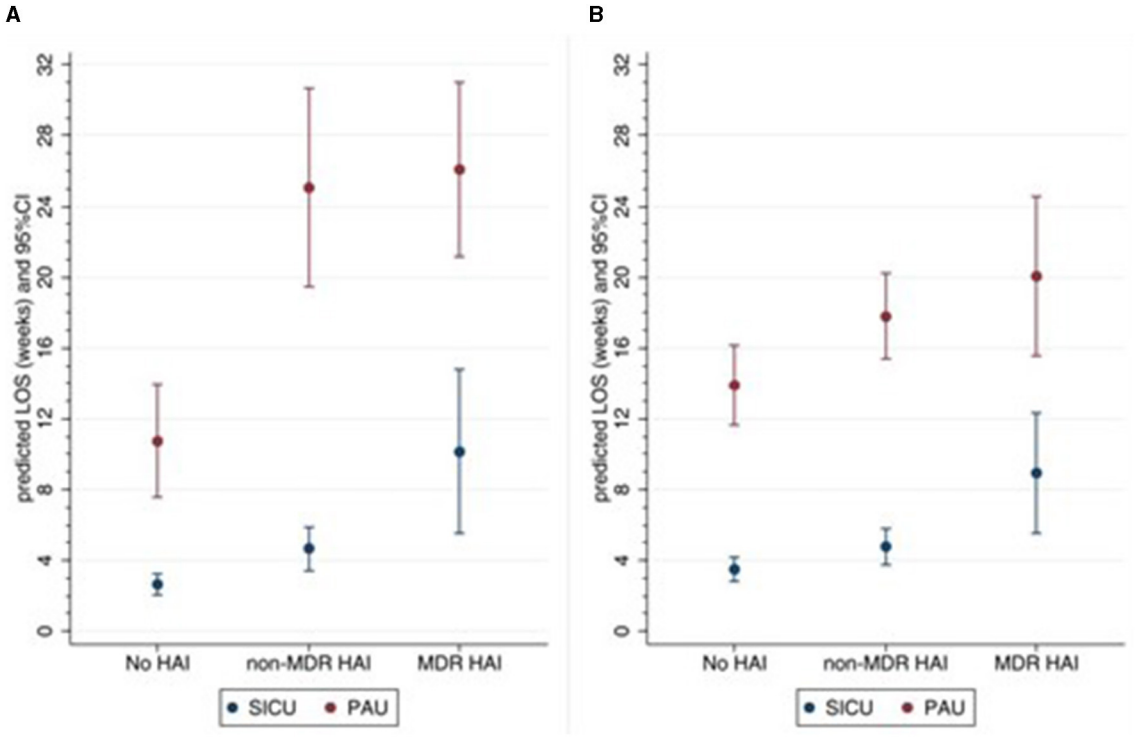

FIGURE 1
Predicted LOS according to setting and HAI groups. **(A)** Unadjusted, **(B)** adjusted for number of medical devices, surgery during rehabilitation, any complications. HAI, healthcare-associated infections; MDR, multidrug-resistant; SICU, semi-intensive care unit; PAU, post-acute unit; LOS length of stay.

underwent neurosurgery before rehabilitation, and those with an etiology other than traumatic or vascular.

Discussion

In this study, we investigated and compared HAI incidences among sABI patients in different settings. We found that in SICU HAIs and MDR HAIs, the incidence was higher than in other settings, especially for BSIs. Pneumonia and UTIs were also more frequent in SICU and LTC settings than in PAU.

According to the ECDC and a previous study (8), intensive care units are the hospital wards with the highest prevalence of HAIs associated with the use of invasive devices and prolonged hospitalization. Moreover, in the intensive care unit setting, the burden of antimicrobial resistance is high due to the severity of the clinical condition of the patients, the frequent use of antibiotics, and varying infection prevention and control practices (19). In addition, it is established that central nervous system injury is an independent risk factor for increased susceptibility to infections (20). In fact, injury leads to secondary immunodeficiency, causing a disturbance of the interplay between the immune system and the central nervous system (3). Dziedzic et al. (20) investigated the clinical significance of the immune status in the development of nosocomial infections in brain-injured patients, where the critical abnormalities include an overall reduction in helper and regulatory T-cell frequencies, reduced proliferation of cytotoxic T cells, reductions in NK and B cell numbers, and increased production of IL-6 and IL-10 from monocytes.

Interestingly, as underscored by Meisel et al. (3), the predominantly proinflammatory response in the CNS is in contrast to the well-organized anti-inflammatory response by the peripheral system. Injury-induced compensatory anti-inflammatory response system may prove to be beneficial as it could control excessive systemic inflammation; however, this response may also be triggered in the absence of a systemic stimulus, i.e., in the case of a TBI, resulting in a detrimental anti-inflammatory dominant response that causes systemic immune system shutdown. This involves the release of immunomodulators from the injured brain into the circulation, which in turn instigates a state of imbalance between pro- and anti-inflammatory mediator cascades, which further weakens the systemic immune defense system. For these reasons, it would be appropriate to increase the attention and control level during the earliest stages of rehabilitation when the patient is more fragile and subjected to invasive devices, as we found in the SICU setting. Close attention is required to adhere to hand hygiene and contact precautions.

The secondary goals of the study included the identification of potential risk factors for HAI development. We found that higher age, CPE colonization, and a higher number of devices are significant risk factors for HAI, with the first two also being significant factors for MDR HAI. Conversely, a high prealbumin plasma value on admission was associated with a lower risk of HAI and MDR HAI occurrence.

TABLE 4 Association between HAI groups and DRS and LCF scores at discharge: results from multiple linear regressions.

	DRS				LCF			
	Model 1		Model 2		Model 1		Model 2	
	b (95%CI)	p-value	b (95%CI)	p-value	b (95%CI)	p-value	b (95%CI)	p-value
HAI groups No HAI (ref.) HAI non–MDR HAI MDR	– 0.30 (−1.25–1.84) 2.35 (0.61–4.09)	0.703 0.009	– −0.59 (−2.06–0.89) 0.28 (−1.91–2.47)	0.432 0.802	– −0.14 (−0.50–0.22) −0.58 (−1.08 to −0.09)	0.430 0.022	– 0.04 (−0.32–0.40) −0.20 (−0.75–0.35)	0.825 0.478
Score upon admission	0.93 (0.83–1.02)	<0.001	0.90 (0.80–1.00)	<0.001	0.82 (0.72–0.93)	<0.001	0.75 (0.65–0.86)	<0.001
SICU (ref.) PAU	– −2.22 (−3.58 to −0.87)	0.001	– −3.66 (−5.05 to −2.28)	<0.001	0.49 (0.16–0.82)	0.004	0.65 (0.34–0.97)	<0.001
Time between injury and rehabilitation (weeks)			0.08 (0.03–0.12)	0.001			−0.02 (−0.04 to −0.01)	0.002
CPE colonization			1.88 (0.33–3.45)	0.018				
Any complication			1.54 (0.17–2.92)	0.028				
Pre–admission surgery No (ref.) Neurosurgery Other							– −0.50 (−0.88 to −0.13) 0.06 (−0.32–0.45)	0.008 0.741
Etiology Traumatic (ref.) Vascular Other							– 0.06 (−0.31–0.42) −0.74 (−1.24 to −0.24)	0.757 0.004

Model 1 includes HAI groups, the score at admission, and the rehabilitation setting; Model 2 includes, in addition, other factors associated with the score at discharge. HAI, healthcare-associated infections; MDR, multidrug-resistant; LCF, levels of cognitive functioning; DRS, disability rating scale; SICU, semi-intensive care unit; PAU, post-acute unit; CPE, carbapenemase-producing Enterobacteriaceae.

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Elderly patients are at high risk of HAIs due to the age-related decline of the immune system, known as immunosenescence. Comorbid conditions can often complicate infections, diminishing the ability to treat them effectively (21). We included all the comorbidities with an infectious impact, and we observed that cardiologic and endocrine-metabolic were the most frequent, according to Bellaviti et al. (5) study.

Devices predispose to infection by damaging or invading epithelial and mucosal barriers and by supporting the growth of biofilms implicated in the development of medical device-related infections (22). sABI patients frequently require several intensive therapy measures that involve devices, such as tracheotomy with assisted breathing, bladder catheterization, and parenteral nutrition.

As to CPE colonization, previous studies found a peculiar CPE epidemiology in long-term acute rehabilitation facilities with high rates of cross-transmission in sABI patients (23). CPE is a dangerous MDRO because most of the carbapenemase-encoding genes are located on transferable genetic elements associated with other antibiotic resistance genes, leading to their rapid transfer and the spread of uncontrollable superbugs (24). Indeed, CPE is among the major causative agents of nosocomial infections (25). In Europe, *K. pneumoniae* is a common cause of BSI, UTIs, and respiratory tract infections, and it is easily transmitted between patients, resulting in nosocomial outbreaks and high rates of morbidity and mortality, reaching 70% in some countries, with attributable mortality for BSI of 50% (26).

The protective effect of a high prealbumin value confirms the importance of nutritional status in contrast to MRDOs. Unfortunately, sABI patients can develop potential severe complications with high protein expenditures, such as pressure sores and muscular weakness, which significantly increase the risk of infection. Boselli et al. (4) reported that the supplementation of essential amino acids may reduce the occurrence of HAI in sABI patients and that low levels of prealbumin and high levels of c-reactive protein are predictors of infections (4). Another study identified serum albumin and prealbumin as predictors for unfavorable outcomes in traumatic brain injury, but in the subgroup of sABI patients, just serum albumin remained significant (27). We can assume, hence, that the prealbumin level can be used as a marker of frailty and that one goal of SICU and rehabilitation settings is to reach or maintain a good nutritional status in sABI patients.

Regarding the impact of HAIs on patient recovery, MDR HAIs seemed associated with a worse outcome (higher DRS and lower LCF), but when other factors (e.g., time to rehabilitation, CPE colonization, and complications) were taken into account, the association was no longer significant.

However, the study by Rollnik showed that in patients in early neurological rehabilitation, the improvement achieved was comparable between patients with and without MDROs (28). On the contrary, in a recent Italian study (29) on sABI patients admitted to three neurorehabilitation centers, those with infections showed a significantly lower improvement in physical function, a higher LOS, and a higher rate of mortality than subjects without infection or colonization.

In line with Bartolo et al. (6), our results indicate that CPE colonization was a significant risk factor for higher disability (higher DRS score) at discharge. This result highlights the importance of minimizing the risk of CPE colonization during inpatient rehabilitation. This can be done by means of appropriate infection prevention practices, such as hand hygiene, environmental cleaning, favoring single-room accommodations, the use of surveillance cultures to identify unrecognized carriers, contact precautions, and isolation, as well as enhanced antimicrobial stewardship to prevent the emergence of resistance. However, the implementation of infection prevention practices is particularly difficult in rehabilitation facilities because of the nature of inpatient care, which by definition is of a longer duration than that in acute care hospitals and in many cases may involve the facility becoming the patient's home environment (26). The availability of appropriate single rooms and MDRO screening appear to be a major infrastructural deficit (30) and the isolation of patients with MDROs presents a serious disadvantage for the rehabilitation outcome (31). The common prevention and infection control practices in our clinical care pathway might improve the management and safety of patients.

We found no significant difference between traumatic, vascular, or other etiologies with respect to the incidence of HAIs (Table 3). Therefore, we found a lower frequency of traumatic etiology in LTC, and the LCF score at discharge was lower for those who had an etiology other than traumatic or vascular.

Finally, we investigated the hospital LOS and found that patients with HAI had a longer LOS; moreover, in SICU, MDR HAI was associated with a higher LOS as compared to HAI. The significantly higher LOS for infected patients was also reported in other studies (5, 6).

Taken together, the results on rehabilitation outcome and LOS indicate that in our clinical pathway, HAI impact on rehabilitation determines a prolonged LOS rather than a worse outcome at discharge. The absence of association between infections and outcomes can be explained by considering that the clinical pathway aims at discharging patients once their best possible outcome is reached, based on personalized goals.

Furthermore, the relationship between infections and LOS can also be interpreted in the opposite direction [34]: As the length of hospitalization increases, the risk of infection increases. Thus, clinicians need to direct their efforts to minimize hospital LOS, taking all the possible preventive measures to reduce the risk and rate of infection on the one hand and improving the efficiency of the rehabilitation process to reduce the risk of complications on the other. This multifactorial approach can improve the health of patients and the costs of the healthcare system.

Limitations

Due to the retrospective study design, information on nutritional parameters and LCF and DRS scales was missing or not available in the LTC setting, and the identification of infectious events was sometimes difficult. Indeed, data were

retrieved from clinical records, and some information on infections was inferred from antibiotic therapies, requests for consultation with an infectious disease specialist, and any other report related to infection. As a result, the infection rate could have been underestimated.

Conclusion

Our study suggests that the management of HAIs and antimicrobial resistance risk is crucial to exploiting the potential for recovery of sABI across all stages of the rehabilitation pathway. Neglecting or underestimating this problem may delay or prolong the rehabilitation process and frustrate patients, caregivers, and healthcare professionals' efforts. The key finding is that HAIs are related to longer LOS, and colonization is associated with poor prognosis and outcomes. Hence, we underscore the need to ensure the protection of non-colonized patients, especially those with severe disabilities on admission.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

GC, EB, and AB contributed to conception and design of the study. EM and GL organized the database. EM performed the statistical analysis. GC, EM, and GL wrote the first draft of the manuscript. EB, AB, ST, and FT wrote sections of the manuscript. RP and PV reviewed the final version. All authors contributed to manuscript revision, read and approved the submitted version.

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In memoriam

During the preparation of this paper Dr. Elisa Maietti prematurely died. She was a brilliant statistician and an unforgettable joyful, radiant, generous and supportive colleague. This paper is dedicated to her memory.

Conflict of interest

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1219862/full#supplementary-material

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Effects of two different paradigms of electrical stimulation exercise on cardio-metabolic risk factors after spinal cord injury. A randomized clinical trial

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Objective: To examine the combined effects of neuromuscular electrical stimulation-resistance training (NMES-RT) and functional electrical stimulation-lower extremity cycling (FES-LEC) compared to passive movement training (PMT) and FES-LEC in adults with SCI on (1) oxygen uptake (VO_2), insulin sensitivity and glucose disposal in adults with SCI; (2) Metabolic and inflammatory biomarkers; (3) skeletal muscle, intramuscular fat (IMF) and visceral adipose tissue (VAT) cross-sectional areas (CSAs).

Materials and methods: Thirty-three participants with chronic SCI (AIS A-C) were randomized to 24 weeks of NMES-RT + FES or PMT + FES. The NMES-RT + FES group underwent 12 weeks of evoked surface NMES-RT using ankle weights followed by an additional 12 weeks of progressive FES-LEC. The control group, PMT + FES performed 12 weeks of passive leg extension movements followed by an additional 12 weeks of FES-LEC. Measurements were performed at baseline (BL; week 0), post-intervention 1 (P1; week 13) and post-intervention 2 (P2; week 25) and included FES-VO_2 measurements, insulin sensitivity and glucose effectiveness using the intravenous glucose tolerance test; anthropometrics and whole and regional body composition assessment using dual energy x-ray absorptiometry (DXA) and magnetic resonance imaging to measure muscle, IMF and VAT CSAs.

Results: Twenty-seven participants completed both phases of the study. NMES-RT + FES group showed a trend of a greater VO_2 peak in P1 [$p = 0.08$; but not in P2 ($p = 0.25$)] compared to PMT + FES. There was a time effect of both groups in leg VO_2 peak. Neither intervention elicited significant changes in insulin, glucose, or inflammatory biomarkers. There were modest changes in leg lean mass following PMT + FES group. Robust hypertrophy of whole thigh muscle CSA, absolute thigh muscle CSA and knee extensor CSA were noted in the NMES-RT + FES group compared to PMT + FES at P1. PMT + FES resulted in muscle hypertrophy at P2. NMES-RT + FES resulted in a decrease in total VAT CSA at P1.

Conclusion: NMES-RT yielded a greater peak leg VO_2 and decrease in total VAT compared to PMT. The addition of 12 weeks of FES-LEC in both groups

modestly impacted leg VO_2 peak. The addition of FES-LEC to NMES-RT did not yield additional increases in muscle CSA, suggesting a ceiling effect on signaling pathways following NMES-RT.

Clinical trial registration: identifier NCT02660073.

KEYWORDS

neuromuscular electrical stimulation, functional electrical stimulation, resistance training, spinal cord injury, rehabilitation

1. Background

Cardio-metabolic risk factors are considered among all-cause mortality in persons with spinal cord injury (SCI). These factors have been well described and characterized by diminished cardiovascular performance, insulin resistance, dyslipidemia and increased visceral adipose tissue (VAT) that leads to central obesity (1, 2). Recent guidelines supported by systematic reviews and randomized clinical trials reported the efficacy of two different approaches of electrical stimulation to train paralyzed muscles in persons with SCI (3–5). The first approach is recognized as functional electrical stimulation (FES) and commonly used for lower extremity cycling (FES-LEC) (4, 6). The second approach, surface neuromuscular electrical stimulation-resistance training (NMES-RT) (7–9), relies on activation of a single muscle group by progressively lifting ankle weights to evoke muscle hypertrophy. Both techniques yield a spectrum of improvements in cardio-metabolic profile in persons with SCI (8–15). Furthermore, a recent systematic review highlighted the superior effect of NMES-RT in inducing skeletal muscle hypertrophy after SCI (16).

In the last three decades, several problems have been identified during applications of FES-LEC. FES-LEC induced premature fatigue of trained muscles resulting in a reduction of torque output and overall cycling performance (17, 18). Premature fatigue affects cycling performance which may interfere with training intensity and subsequently limit cardio-metabolic benefits (19). This may also be explained by a short duty cycle (i.e., on/off time) for each muscle group which results in less tension than required to induce conditioning of the paralyzed muscles (20). As a result, the VO_2 peak of untrained individuals with SCI may not exceed 0.4 L/min suggesting a very low exercise intensity from using FES-LEC (17). Another concern is that FES-LEC predominately relies on carbohydrate as a source of energy with less reliance on fat (21). Reliance mainly on glycolysis during exercise for 30–60 min is inefficient and may contribute to pre-mature fatigue during FES-LEC (22). After SCI, muscle fiber types transform from slow-oxidative to fast fatigable glycolytic fibers (23); which is accompanied by mitochondrial dysfunction (24). Because of the COVID-19 pandemic, several rehabilitation programs have utilized secure telehealth systems to reduce travel time, waiting lists and risk of hospital acquired infections. However, most persons with SCI do not have access to FES-LEC for home use. Additionally, previous trials reported that adherence dropped remarkably after 8 weeks of home use of expensive FES-LEC ergometers (25). Therefore, it is empirical to provide a rehabilitation approach that can address these limitations of FES-LEC and may serve as an alternative approach in persons with SCI.

Surface NMES-RT has been safely used in home-settings in individuals with chronic SCI (7, 26). In addition, NMES-RT combined with testosterone treatment (TT) resulted in increased fiber cross-sectional area (CSA), citrate synthase a biomarker of mitochondrial density and succinate dehydrogenase in persons with SCI (27). Another study demonstrated increase knee extensor specific tension after 16 weeks of NMES-RT and TT. The peak torque of the trained extensor increased by 48% accompanied with 17% slowness in the rise time (28). Knee extensor muscle group may provide 80% of the driving power during FES-LEC (29). The knee extensor muscle group atrophied by 50% compared to the pre-injury size after SCI (30); which may impact the performance during FES-LEC. A previous randomized clinical trial demonstrated that FES-LEC combined with progressive RT for 12 weeks resulted in greater muscle size and peak torque compared to FES-LEC only in persons with incomplete SCI (31). Therefore, these findings suggest that addition of NMES-RT may attenuate several of the limitations of FES-LEC and potentially enhance the effects of FES-LEC on cardiometabolic risk factors.

The overall objectives of the current trial are to determine the impact of evoking skeletal muscle hypertrophy using surface NMES-RT prior to conducting FES-LEC on oxygen uptake, insulin sensitivity and glucose effectiveness (primary outcome variables) compared to those who underwent passive movement and FES-LEC training only. We hypothesized that 12 weeks of NMES-RT prior to FES-LEC may result in greater skeletal muscle hypertrophy, decreasing IMF and VAT, and further enhance gains in aerobic fitness and insulin sensitivity observed during a subsequent 12-week training of FES-LEC.

2. Methods

2.1. Study design

A 5 years, 2015–2020, two-site, randomized controlled study was conducted to investigate the efficacy of NMES-RT + FES versus PMT + FES (control group) on cardio-metabolic risk factors after SCI. A detailed study protocol was previously published that highlighted the primary objectives of the work (32). After signing an

Abbreviations: ASIA, American Spinal Injury Association (ASIA); AIS, ASIA Impairment Scale; BL, baseline; BMI, body mass index; CSA, cross-sectional area; CRP, C-reactive protein; DXA, dual energy x-ray absorptiometry; FES, functional electrical stimulation; FES-LES, functional electrical stimulation-lower extremity cycling; FM, fat mass; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; IMF, intramuscular fat; IGF-1, insulin growth factors-1; IGFBP-3, insulin growth factors binding protein-3; IVGTT, Intravenous Glucose Tolerance Test; MRI, magnetic resonance imaging; NMES, neuromuscular electrical stimulation; NMES-RT, neuromuscular electrical stimulation-resistance training; PMT, passive movement training; P1, post-intervention 1; P2, post-intervention 2; RPM, revolution per minute; SAT, subcutaneous adipose tissue; SCI, spinal cord injury; TT, testosterone treatment; VAT, visceral adipose tissue; VO_2, oxygen uptake.

approved informed consent, each participant underwent a detailed physical examination, including neurological assessment, and International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). Using block randomization, participants were randomized into either 12 weeks of NMES-RT followed by 12 weeks of FES-LEC or PMT for 12 weeks followed by 12 weeks of FES-LEC. The entire duration of the study is 27 weeks (3 weeks of measurements and 24 weeks of training). Measurements were conducted at bassline (BL; prior starting any intervention), post-intervention 1 (P1; 12 weeks after intervention) and post-intervention 2 (P2; 24 weeks after intervention). Preliminary results from the current trial were previously published (9, 33).

Thirty-three individuals, with chronic (≥1-year post injury) SCI were randomized into either NMES-RT + FES ($n = 17$) or PMT + FES ($n = 16$; Table 1). Study inclusion and exclusion criteria were previously listed. Briefly, participants were between 18 and 65 years old, men/women, greater than 1-year post SCI, with BMI ≤ 30 kg/m^2. Participants with motor complete or incomplete C5-L2 level of injury, the American Spinal Injury Association (ASIA) Impairment Scale (AIS) classification A, B, or C were considered for the trial. Participants with pre-existing chronic medical conditions [cardiovascular disease, uncontrolled type II DM, uncontrolled hypertension, insulin dependence, pressures injuries stage 3 or greater, hematocrit above 50%, urinary tract infection, or participants with neck of femur or total body osteoporosis (T-score equal or worse than −2.5 SD) and bone mineral density of distal femur and proximal tibia (less than 0.6 gm/cm^2) to reduce the likelihood of fracture during training] were excluded from the trial (32).

3. Interventions

3.1. NMES-resistance training

A video publication providing full details on the NMES-resistance training (NMES-RT) protocol was previously published (34). Briefly, NMES-RT was applied for 12 weeks to the knee extensor muscles via surface electrodes to induce concentric-eccentric actions. Two 8 ×10 cm^2 adhesive carbon electrodes were placed on the skin over the knee extensor muscle group. After placement of the electrodes, NMES parameters were adjusted at a frequency of 30 Hz, biphasic pulses of 450 µs with interpulse interval of 50 µs and amplitude of current sufficient to evoke knee extension. Training was performed twice weekly, separated by at least 48 h, for 12 weeks with the first week of the NMES-RT performed without ankle weights to ensure that the knee extensor muscles can extend the weight of the lower leg against gravity. The training session consisted of 4 sets of 10 repetitions that were alternated between the right and left knee extensors and separated by 2 min of rest following each set. Once full knee extension was achieved in a sitting position, an increment of 2 lbs. was gradually added per leg on a weekly basis. The increase in ankle weights was only considered when full knee extension was achieved (7, 8, 15).

3.2. Passive movement training for the control group

Passive ROM was applied for 12 weeks prior to FES-LEC (9, 32). A member of the research team supported the leg proximal to the ankle joints and moved it from 90° knee flexion close to full knee extension. The leg was maintained up for 5 s and returned down for 5 s. The passive movements were repeated in the same fashion described in NMES-RT protocol: 10 reps for the right leg followed by 10 reps for the left leg for total of 4 sets × 10 reps.

3.3. Functional electrical stimulation-lower extremity cycling

A video publication providing full details on the functional electrical stimulation-lower extremity cycling (FES-LEC) protocol was previously published (34). FES-LEC was conducted for 12 weeks, twice weekly, for each participant. Rectangular adhesive conductive electrodes were placed on the skin of the knee extensor, hamstrings, and gluteus maximus muscle groups. Pulse frequency was set at 33.3 Hz, pulse duration at 350 µs and resistance was adjusted every 10 min to maintain a speed of 40–45 revolutions per minute (RPM). Resistance of the bike was increased in 0.5 Nm increments per 10-min stage over the course of 12 weeks. The progression in resistance was customized based on the subject's performance riding the FES-LEC ergometer over 12 weeks. The progression of FES-LEC was previously described in details [see Table 3 in (32)]. The fatigue threshold was set at 18 RPM; if RPM falls below 18 RPM; the bike was set to automatically shift from active to passive cycling (cool-down). During the three-minute cool-down period, participants passively cycled with no electrical stimulation. The cool down period was then followed by 5 min of recovery, during which the participant was still connected to the bike but in a complete resting position while constantly monitoring blood pressure and heart rate.

3.4. Dietary recalls

Each participant met with a dietitian at the start of the study and was asked to maintain a weekly 3 to 5-day food dietary log to monitor their caloric and liquid intake for the duration of the study (15, 32). Dietary logs were administered to ensure controlling for the caloric intake and macronutrients. No nutritional advice was given on portion size of the food. However, based on participants' basal metabolic rate, the dietitian recommended the percentage of macronutrients at 45% carbohydrates, 30% fat and 25% total protein. Dietary logs were analyzed on a weekly basis using a nutritional software package (Nutrition Data System for Research version 2014) under the supervision of a registered dietitian. After the analysis was completed, the average caloric intake (kcal) and percentage macronutrients (carbohydrates, fats and proteins) were calculated, and monthly feedback was provided via phone call (15, 32).

4. Measurements

4.1. Metabolic profile variables

4.1.1. Leg oxygen uptake using FES-LEC

One week prior to the intervention (week 1), post-intervention 1 (P1; week 14) and post-intervention 2 (P2; week 27), peak oxygen uptake (VO_2) was measured using a COSMED K4b2 (COSMED USA, Chicago, IL) portable metabolic unit (9, 17). After calibration, subjects

TABLE 1 Demographic, physical and SCI characteristics of 33 participants who were randomized into 24 weeks of NMES-RT + FES or PMT + FES.

Particip. ID	Group	Sex	Age (yrs.)	Ethne.	Weight (kg)	Height (cm)	BMI (kg/m^2)	NLI	AIS	TSI (yrs.)	CLASSIF.	Range of lifted weights (lbs)	Total missed visits
001–10,123	PMT + FES	M	48	AA	95.2	183.2	28.4	T4	A	17	Paraplegia	N/A	1
002–10,187	PMT + FES	M	61	C	75.2	182.5	22.6	L1	B	34	Paraplegia	N/A	0
006–10,142	PMT + FES	M	25	AA	60.6	174.5	19.9	C8	A	2	Paraplegia	N/A	8
010–10,177	PMT + FES	M	51	AA	84.6	169.1	29.6	T5	B	9	Paraplegia	N/A	2
011–10,064	PMT + FES	M	30	C	61.8	176.2	19.9	T10	A	5	Paraplegia	N/A	4
016–10,140	PMT + FES	M	21	C	52.6	178.3	16.5	T4	A	7	Paraplegia	N/A	3
017–10,178	PMT + FES	M	36	AA	66.8	179.7	20.7	T5	A	7	Paraplegia	N/A	1
018–10,154	PMT + FES	M	25	AA	52.3	184.2	15.4	C6	C	1	Tetraplegia	N/A	1
022–10,130	PMT + FES	F	51	AA	69.4	164.1	25.8	C6	A	13	Tetraplegia	N/A	2
023–10,113	PMT + FES	M	51	C	83.2	181.3	25.3	T5	A	1.75	Paraplegia	N/A	0
027–10,148	PMT + FES	M	57	C	71.9	182.4	21.6	C5	A	35	Tetraplegia	N/A	0
030–10,019	PMT + FES	M	25	C	58.0	185.4	16.9	C7	B	2	Tetraplegia	N/A	4
033–10,052	PMT + FES	F	46	C	73.8	163.0	27.8	T1	A	8	Paraplegia	N/A	1
036–10,063	PMT + FES	M	57	AA	60.3	167.0	21.6	T11	C	1.5	Paraplegia	N/A	5
038–10,166	PMT + FES	F	32	AA	51.3	151.1	22.5	T4	B	1	Paraplegia	N/A	4
039–10,106	PMT + FES	F	55	C	76.7	166.7	27.6	C5	A	14	Tetraplegia	N/A	5
Mean	16	12 M:4F	41.9	8AA:8C	68.4	174.3	22.6	C5-L1	10 A: 4B:2C	9.9	6 T: 10 P		2.6
SD			13.8		12.8	9.8	4.4	6 T: 10 P		10.8			2.3
003–10,122	NMES-RT + FES	M	34	AA	68.1	182.2	20.5	T12	B	1.5	Paraplegia	0–20	4
004–10,006	NMES-RT + FES	F	50	C	73.4	153.7	31.1	T3	B	29	Paraplegia	0–20	0
005–10,128	NMES-RT + FES	M	53	C	89.7	178.7	28.1	C6	A	26	Tetraplegia	0–0	6
007–10,179	NMES-RT + FES	M	41	C	59.3	172.4	20.0	T4	B	25	Paraplegia	0–22	1
009–10,135	NMES-RT + FES	M	48	C	63.8	174.0	21.1	T8	A	20	Paraplegia	W	6
012–10,181	NMES-RT + FES	M	20	C	83.8	185.9	24.2	C5	B	3	Tetraplegia	0–18	0
014–10,149	NMES-RT + FES	M	27	C	61.0	185.5	17.7	T6	A	4	Paraplegia	0–22	3
015–10,089	NMES-RT + FES	M	41	AA	106.3	173.5	35.3	T11	A	3	Paraplegia	0–2 (R)/ 0–8 (L)	2
019–10,034	NMES-RT + FES	M	33	AA	90.3	172.2	30.5	T8	C	11	Paraplegia	0–22	1
020–10,176	NMES-RT + FES	M	23	C	58.0	178.8	18.1	T6	A	1.58	Paraplegia	0–2	0
024–10,186	NMES-RT + FES	M	44	C	53.5	183.0	16.0	C7	A	13	Tetraplegia	0–0	6

(Continued)

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TABLE 1 (Continued)

Particip. ID	Group	Sex	Age (yrs.)	Ethne.	Weight (kg)	Height (cm)	BMI (kg/m^2)	NLI	AIS	TSI (yrs.)	CLASSIF.	Range of lifted weights (lbs)	Total missed visits
028–10,092	NMES-RT + FES	M	20	AA	45.2	178.7	14.2	C6	B	1.83	Tetraplegia	0–8	4
029–10,180	NMES-RT + FES	M	55	AA	76.4	171.7	25.8	C5	A	30	Tetraplegia	0–12	3
032–10,160	NMES-RT + FES	M	31	AA	70.4	169.4	24.5	T6	A	8	Paraplegia	0-2(L)	6
035–10,098	NMES-RT + FES	F	24	C	72.2	171.3	24.6	T12	C	4	Paraplegia	0–0	2
037–10,039	NMES-RT + FES	M	54	AA	95.0	178.9	29.7	T11	C	4	Paraplegia	0–18	3
040–10,077	NMES-RT + FES	M	46	C	44.8	160.2	17.5	C6	A	20	Tetraplegia	W	3
Mean	17	15 M:2F	37.9	7AA:10C	71.2	174.7	23.5	C5-T12	9A: 5B:3C	12.1	6 T: 11P		2.9
SD			12.3		17.4	8.5	6.0	6 T:11P		10.6			2.2

AA, Afro-American; AIS, American Spinal Cord Injury Impairment Scale; BMI, body mass index; C, Caucasians; CLASSIF, classifications; Ethne, ethnicity; L, Left Leg; N/A, not applicable; NLI, neurological level of injury; P, paraplegia; R, right leg; T, tetraplegia; TSI, time since injury; W, withdrawn.

were asked to place the mask on their face to monitor oxygen (VO_2) and carbon dioxide production. A three-minute resting phase allowed the subject to get used to breathing with the mask while on the RT-300 bike. After the resting phase, VO_2 was measured during a three-minute warm-up phase, the resistance of the bike was gradually increased by 2 Nm every 2 min until fatigue. During testing, the servo motor was tuned off, and the cool-down phase was followed by the recovery phase.

VO_2 and VCO_2 were monitored throughout exercise to determine total energy expenditure using the Weir equation. Five minutes of recovery was recorded to determine the efficacy of each intervention on energy expenditure and substrate utilization. Heart rate (via polar HR monitor) was recorded every 30 s and blood pressure (COSMED 740) was recorded before, every 2 min during cycling, and for another 5 min after cycling to ensure full recovery to baseline.

4.1.2. Intravenous glucose tolerance test (primary outcome variables)

A standard intravenous glucose tolerance test (IVGTT) was used to determine insulin sensitivity and glucose effectiveness. Each subject underwent an IVGTT before (BL), and 12 weeks after interventions (P1and P2). After a 10–12-h fast, an indwelling catheter with an intravenous saline drip (0.9% NaCl) was placed. Following 20 min of glucose injection, a bolus of insulin (0.02 U/kg) was injected to determine insulin sensitivity. Plasma glucose was measured by the Autoanalyzer glucose oxidase method and plasma insulin concentrations was determined by commercial radioimmunoassay. The S_I (glucose disposal rate per unit of secreted insulin per unit time; i.e., insulin sensitivity) and S_G (glucose mediated glucose disposal rate) were calculated from a least-squares fitting of the temporal pattern of glucose and insulin throughout the IVGTT using the MINMOD program (14, 35).

4.1.3. Serum total, free testosterone, IGF, FFA

Total Testosterone measurements were performed by radioimmunoassay after sample extraction and column chromatography. The interassay coefficient of variation (CV) is 12.5% or less for all quality control samples analyzed. Plasma IGF-I and IGFBP-3 concentrations were measured by immunoluminometric assay (Quest Diagnostics, Madison, NJ) and RIA (Diagnostics Systems Laboratories Inc., Webster, TX), respectively. Ten ml of blood was collected from the indwelling venous catheter and lipid profile (HDL-C, LDL-C, total cholesterol, and TG) were determined using standard analyses procedures (15).

4.1.4. Inflammatory biomarkers

Before starting the intravenous glucose tolerance test (IVGTT) and following a 12-h fast, blood was collected from the indwelling venous catheter and CRP, IL-6, TNF-α, and free-fatty acids (FFA) were determined by the Virginia Commonwealth University Clinical Research Center Laboratory using available enzyme-linked immunosorbent assay kits (15).

4.2. Body composition

4.2.1. Body mass index and anthropometrics

Each participant was asked to empty their bladder and then propel onto a wheelchair weighing scale to evaluate weight in kg. The wheelchair was measured separately, and the difference taken for the

final weight. The height of each participant was determined with the subject on his/her right side in the supine position. Two smooth wooden boards were placed at the participant's head and heels and the distance between them determined the height in nearest cm. The Body mass index (BMI) (Kg/m^2) was calculated as weight (kg)/height^2 (m^2). Anthropometrics were determined in duplicate by identifying the narrowest region of the trunk from sitting and lying positions. After normal expiration, a tape measure was used around the participant's trunk to measure waist circumference (WC) (35–37).

4.2.2. Dual energy x-ray absorptiometry (DXA)

Total body and regional (lumbar spine, proximal femur, and forearm) DXA scans were performed using a GE Lunar iDXA (Lunar Inc., Madison, WI) bone densitometer DXA was used to measure body composition in SCI individuals, specifically regional and total fat mass (FM) and fat-free mass (FFM). at the Hunter Holmes VAMC hospital. All scans were performed and analyzed using Lunar software version 10.5. After scanning, total and regional % FM and FFM were determined using DXA software. The longitudinal precision of total and regional body composition using DXA as well as the percentage error compared to the gold-standard body composition technique were previously determined in persons with SCI (34, 35). Body composition assessment of the upper extremity serves as an internal control for repeated measure longitudinal trial (34).

4.2.3. Magnetic resonance imaging

Skeletal muscle CSAs were determined before (baseline), and twice after 12-week interventions (post-intervention 1 and post-intervention 2) using a 1.5 Tesla GE magnet (9, 15). Transaxial images, 0.8 cm thick and 1.6 cm apart, were taken from the hip joint to the knee joint (thigh) and from knee to the ankle (leg) using the whole-body coil. T1-weighted imaging was performed using a fast spin-echo sequence to capture visceral fat images. To measure visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), transverse slices (0.8 cm thickness) are acquired every 0.4 cm gap from the xyphoid process to the femoral heads. Images were acquired in a series of two stacks with L4-L5 used as a separating point. Participants were asked to take a deep breath in and hold their breath for 10–15 s to reduce the respiratory-motion artifact associated with magnetic resonance imaging (MRI) for the abdominal region (36, 37). For analysis purpose, VAT-SAT slices were classified according to the distribution across different anatomical regions into $VAT_{L\text{-}K}$ or $SAT_{L\text{-}K}$ [between liver (L) and kidneys (K)], $VAT_{K\text{-}Um}$ or $SAT_{K\text{-}Um}$ [between the kidneys and umbilicus], $VAT_{IC\text{-}F}$ or $SAT_{IC\text{-}F}$ [between iliac crests and femoral heads] and VAT_{total} or SAT_{total} [the average of the entire multi-axial slices from the liver to femoral heads]. Finally, VAT: SAT ratio was calculated across different anatomical regions as well as for the total trunk region.

4.3. Statistical analyses

Using a block randomization, a 2 × 2 design was developed in which participants were matched based on level of injury (tetraplegia vs. paraplegia) and time since injury (less versus more than 10 years). Randomization was conducted using n-query computer program at the baseline prior enrollment in the trial. A Supplementary Table S1 was included to highlight the entire procedure for randomization for the trial. Allocation into either PMT + FES or NMES-RT + FES groups was based in the order of enrollment in the trial.

All data were tested for normality using the Shapiro–Wilk tests. Outliers were detected using normal Q-Q plots at different time points (BL, P1, P2) for each group. If normality was not assumed ($p < 0.05$), the examined variable was then log-transformed before conducting any statistical analyses. Independent T-tests were conducted to examine physical characteristics (age, weight, height, BMI, time since injury) between both groups (NMES-RT + FES and Passive + FES). To account for baseline variabilities on the dependent variables (body composition and metabolic variables), multivariate analysis of covariance (MANCOVA) was conducted to statistically analyze the primary (VO_2, Si, Sg) and secondary variables of the study. The baseline measurement served as the covariate, both the post-intervention 1 and 2 measurements served as the dependent variables and the group assignments (NMES-RT + FES vs. Passive + FES) served as a fixed factor. If the assumptions of MANCOVA was violated, mixed model analysis of variance (MANOVA) was then used to determine whether there a time effect (baseline, post-int1 and post-int 2), between group effects or interaction. If there is a time effect, repeated measure ANOVA was then used after applying the split data function. Independent *t*-tests were also conducted if the MANOVA revealed an interaction. When appropriate, a Bonferroni post-hoc adjustment for multiple comparisons was performed to control for type II error. Linear regression analyses were used to test the association between body composition variables and different metabolic variables. The study was powered based on preliminaryVO_2 peak data following NMES-RT and yielded an effect size of 0.432 and a power of 99.82%. Partial eta squared (η^2_p) measurements were reported for the primary outcome variables. SPSS missed data function was used to estimate missing values for the primary outcome variables (VO_2, Si and Sg) only when participants completed BL and P1 assessment visits (only for 4 participants). Although 33 participants were enrolled at baseline, statistical analyses were only conducted for 27 participants (82%). The other 6 participants were withdrawn after being randomized at different phases through the trial. Statistical analyses were performed using IBM-SPSS version 29.0 (SPSS, Chicago, IL). Statistical significance was set at alpha level of 0.05 and all values are presented as mean ± SD.

5. Results

Originally, 40 participants were enrolled in the trial. Five participants were considered screen failure and 2 participants withdrew immediately after sinigang a consent form without any intervention. Thirty-three participants were enrolled and randomized in the trial in which 6 of them withdrew at different phases of the trial. Of the 6 participants, 4 participants competed P1 in the PMT + FES group and two participants withdrew from the NMES-RT + FES group in weeks 5 and 11 because of problems with transportation and COVID19 pandemic, respectively. Therefore, data analyses were based on the 27 participants who completed the entire study.

Participant demographics and injury characteristics are presented in Table 1. There were no differences in participants' physical and SCI characteristics between the NMES-RT + FES and PMT + FES groups ($p > 0.05$). Recruitment of the study was discontinued in February 2020 because of the COVID-19 pandemic. Two active participants

were asked to discontinue training because of the fear of contracting COVID-19 (ID# 039 and ID# 40). Their data were not included in the trial. Figure 1 illustrates the number of missed visits across the trial and the primary factors that contributed to these missed visits. The total number of missed visits were not different between groups ($p = 0.63$; Table 1). On average, the number of missed visits did not exceed 2 visits before P1 (1.35 ± 1.66) and P2 (1.93 ± 1.77) in the NMES-RT + FES group. On contrary, the average number of missed visits was 0 and 2 before P1 (0.38 ± 0.62) and P2 (2.33 ± 1.91), respectively, in the PMT + FES group.

The average caloric intake and percentage macronutrients are presented in Table 2. Compared to PMT + FES group, NMES-RT + FES group showed a trend of greater % protein intake in P1 (19.5 ± 4.4 vs. 17.2 ± 3.6%, $p = 0.06$). Additionally, there was a trend of lower %fat intake in the NMES-RT + FES compared to PMT + FES group.

5.1. Power and resistance of FES-LEC

Power and resistance data of FES-LEC were not normally distributed and did not meet the assumption of normality after being log-transformed. Non-parametric Mann–Whitney U was used to analyze the difference between group. The PMT + FES group induced a greater resistance at P1 compared to the NMES-RT + FES group (5.1 ± 4.6 vs. 3.6 ± 1.9 Nm, $p = 0.027$). NMES-RT + FES showed a trend of increase in power (6.0 ± 3.5 to 13 ± 12.5 W, $p = 0.08$) and resistance (31 ± 1.1 to 6.6 ± 6.5 Nm, $p = 0.06$) in P2 compared to BL.

5.1.1. Metabolic profile variables

5.1.1.1. Effects of NMES-RT + FES vs. PMT + FES on FES-LEC VO_2 peak

The data for VO_2 peak (Table 2) was normally distributed ($p = 0.086$–0.23). MANCOVA demonstrated that NMES-RT + FES ($n = 13$) had a trend towards a greater FES-LEC VO_2 peak in P1($p = 0.08$; $\eta^2_p = 0.12$) but not in P2 ($p = 0.25$) compared to PMT + FES ($n = 14$). Mixed model ANOVA revealed that there was a time effect ($p = 0.001$; $\eta^2_p = 0.23$). Pairwise comparisons revealed that that PMT + FES elicited a trend in VO_2 peak following P2 compared to P1 ($p = 0.078$); whereas NMES-RT + FES resulted in changes in VO_2 peak following P2 compared to BL ($p = 0.0005$) but not after P1 ($p = 0.11$).

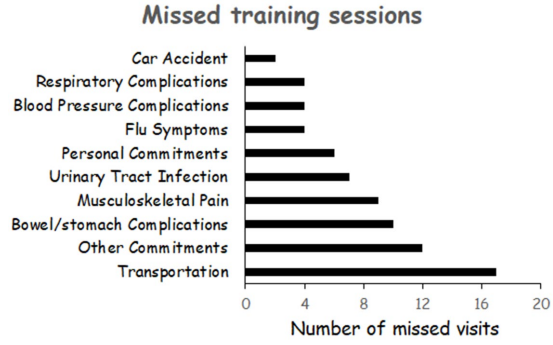

FIGURE 1
Primary factors that contributed to missed visits across the entire trial for both groups.

There was no difference in relative VO_2 between groups at P1 ($p = 0.14$) and at P2 ($p = 0.57$). Repeated MANOVA showed a time effect ($p = 0.007$; $\eta^2_p = 0.18$) in relative VO_2. Pairwise comparisons demonstrated that PMT + FES resulted in difference following P2 compared to P1 ($p = 0.042$) but not compared to BL ($p = 0.16$). Pairwise comparisons showed that NMES-RT + FES increased ($p = 0.034$) relative VO_2 in P2 compared to baseline (Table 2).

5.1.1.2. Effects of NMES-RT + FES vs. PMT + FES on metabolic profile

There was no difference between groups in fasting plasma glucose at either P1 ($p = 0.93$) or P2 ($p = 0.80$) or fasting plasma insulin at P1 ($p = 0.9$) or P2 ($p = 0.6$). Additionally, there was no difference between both groups on Sg [P1; $p = 0.3$ and P2; $p = 0.42$] and log-transformed values of Si at [P1; $p = 0.23$ and P2; $p = 0.3$]. Finally, log-transformed values of HOMA-B and HOMA-IR were not different between groups (Table 2).

There were no differences in BMR between both groups at P1 ($p = 0.27$) and P2 ($p = 0.87$). Basal metabolic rate adjusted to total body lean mass was not different between groups at P1 ($p = 0.9$) and P2 ($p = 0.5$). Similarly, respiratory exchange ratio (RER) did not yield differences between both groups at P1 ($p = 0.3$) and P2 ($p = 0.8$).

5.1.1.3. Effects of NMES-RT + FES vs. PMT + FES on lipid profile

There were no differences between groups in TG, LDL-C, HDL-C, TC after P1 ($p = 0.37$; $p = 0.36$; $p = 0.7$; $p = 0.53$; $p = 0.4$, respectively) or P2 ($p = 0.6$; $p = 0.62$, $p = 0.18$, $p = 0.7$, $p = 0.7$, respectively; Table 2). There was time effect in LDL-C ($p = 0.02$; $\eta^2_p = 0.15$) within groups. Pairwise comparison indicated that NMES-RT + FES resulted in LDL-C reduction in P2 compared to P1 (12%, $p = 0.031$) but not compared to BL ($p = 0.38$). Non-HDL-C showed a time effect ($p = 0.023$; $\eta^2_p = 0.15$); pairwise comparison indicated that there was a trend ($p = 0.07$) in P2 compared to P1 following NMES-RT + FES but not following PMT + FES (Table 2). There was a trend of a within group effect in TC ($p = 0.07$; $\eta^2_p = 0.10$). Finally, there was a time effect in TC: HDL-C ratio ($p = 0.01$; $\eta^2_p = 0.17$) as well as a trend of between group effect ($p = 0.08$). Pairwise comparisons indicated a trend ($p = 0.07$) in P2 compared to BL following PMT + FES (Table 2).

5.1.1.4. Effects of NMES-RT + FES vs. PMT + FES on anabolic biomarkers

Anabolic biomarkers were not analyzed for the last 8 participants (4 participants per group) because of funding constraints. There were no differences in the anabolic biomarkers (serum testosterone, IGF-1 and IGFBP-3) between the two intervention groups (Table 2).

5.1.1.5. Effects of NMES-RT + FES vs. PMT + FES on inflammatory biomarkers

Inflammatory biomarkers were not analyzed for the last 8 participants (4 participants per group) because of funding constraints. Data were logged transformed for IL6, CRP and FFA before running statistical analyses. There were no differences in the inflammatory biomarkers between the two groups. There was interaction between both groups on log-transformed values of CRP ($p = 0.048$; $\eta^2_p = 0.16$). There was time effect in log-transformed FFA ($p = 0.031$; $\eta^2_p = 0.20$) within groups (Table 2).

TABLE 2 Effects of 24 weeks of PMT + FES compared to NMES-RT + FES on primary and secondary outcome variables of the metabolic profile in persons with spinal cord injury.

		PMT + FES			NMES-RT + FES		
		Baseline	Post-Int1	Post-Int 2	Baseline	Post-Int1	Post-Int 2
Dietary Records & Macronutrients	Caloric intake (kcal)	1,718 ± 857	1,728 ± 759	1,745 ± 692	1,693 ± 623	1,674 ± 403	1,804 ± 547
	%Fat	35 ± 6.0	34 ± 6.0	36.0 ± 5.0	37 ± 7.3	33.0 ± 7.0	33.0 ± 6.0
	%Carbohydrate	46 ± 8.0	48 ± 6.0	46 ± 8.0	42 ± 9.0	47 ± 8.0	47 ± 8.0
	%Protein	18.5 ± 4.0	17 ± 4.0	18 ± 4.0	19 ± 5.0	19.5 ± 4.0	18 ± 4.0
Oxygen uptake (VO_2)	FES-LEC VO_2 (l/min)	0.49 ± 0.24 (n = 14)	0.48 ± 0.19 (n = 14)	0.57 ± 0.27 (n = 14)	0.48 ± 0.15 (n = 13)	0.58 ± 0.20[#] (n = 13)	0.62 ± 0.23 (n = 13)
	Relative VO_2 (ml/kg/min)	7.7 ± 4.7 (n = 14)	7.4 ± 3.6 (n = 14)	9.0 ± 5.1 (n = 14)	6.5 ± 2.5 (n = 13)	8.1 ± 4.0 (n = 13)	8.3 ± 4.0 (n = 13)
Carbohydrate Profile	Fasting Plasma glucose (mg/dl)	96.6 ± 21.4 (n = 14)	91.5 ± 7.0 (n = 14)	96.0 ± 22.0 (n = 14)	90.0 ± 13.0 (n = 12)	90.0 ± 15.0 (n = 12)	93.0 ± 16.0 (n = 12)
	Fasting Plasma insulin (μU/ml)[L]	6.1 ± 5.0 (n = 16)	5.7 ± 3.3 (n = 16)	8.2 ± 9.1 (n = 16)[M]	7.1 ± 5.7 (n = 15)	5.7 ± 3.3 (n = 15)	8.3 ± 5.7 (n = 15)[M]
	Sg (min^{-1})	0.048 ± 0.08 (n = 14)	0.022 ± 0.01 (n = 14)	0.024 ± 0.016 (n = 14)	0.083 ± 0.23 (n = 12)	0.02 ± 0.01 (n = 12)	0.021 ± 0.01 (n = 12)
	Si[L]	4.4 ± 3.0 (n = 11)[O]	6.2 ± 5.0 (n = 11)	7.2 ± 6.6 (n = 11)[M]	6.6 ± 6.0 (n = 13)[O]	5.7 ± 4.9 (n = 13)	5.6 ± 5.0 (n = 13)[M]
Energy expenditure	BMR ($kcal.day^{-1}$)	1,410 ± 173 (n = 13)	1,370 ± 3,170 (n = 13)	1,408 ± 118 (n = 13)	1,524 ± 211 (n = 11)	1,519 ± 138 (n = 11)	1,569 ± 234 (n = 11)
	BMR.lean $mass^{-1}$ (kcal/g)	0.033 ± 0.004 (n = 13)	0.032 ± 0.004 (n = 13)	0.032 ± 0.003 (n = 13)	0.032 ± 0.004 (n = 11)	0.032 ± 0.003 (n = 11)	0.033 ± 0.004 (n = 11)
	Respiratory exchange ratio (RER)	0.85 ± 0.05 (n = 14)	0.85 ± 0.04 (n = 15)	0.84 ± 0.07 (n = 12)	0.82 ± 0.05 (n = 13)	0.84 ± 0.05 (n = 13)	0.86 ± 0.03 (n = 12)
Lipid profile	TG (mg/dl)[L]	95.5 ± 46.0 (n = 14)	103.0 ± 59.0 (n = 14)	92.0 ± 47 (n = 14)	110 ± 59 (n = 12)	97 ± 41 (n = 12)	94 ± 44.5 (n = 12)
	LDL-C (mg/dl)	86 ± 20 (n = 14)	82 ± 23 (n = 14)	79 ± 26 (n = 14)	112 ± 32 (n = 12)	117 ± 40* (n = 12)	103 ± 28* (n = 12)
	HDL-C (mg/dl)	42 ± 10 (n = 14)	42 ± 10 (n = 14)	44 ± 11 (n = 14)	39 ± 7 (n = 12)	38 ± 6 (n = 12)	38 ± 7 (n = 12)
	Non-HDL-C (mg/dl)	105 ± 23 (n = 14)	103 ± 25 (n = 14)	97 ± 30 (n = 14)	134 ± 48 (n = 12)	137 ± 43*[ŧ] (n = 12)	122 ± 31*[ŧ] (n = 12)
	Total cholesterol (TC; mg/dl)	147 ± 23 (n = 14)	145 ± 21 (n = 14)	142 ± 29 (n = 14)	173 ± 39 (n = 12)	175 ± 43 (n = 12)	160 ± 30 (n = 12)
	TC: HDL-C	3.7 ± 1.3 (n = 14)	3.7 ± 1.4 (n = 14)	3.4 ± 1.3*[ŧ] (n = 14)	4.5 ± 1.2 (n = 12)	4.6 ± 1.2 (n = 12)	4.3 ± 1.1 (n = 12)
Anabolic profile	Serum testosterone (ng/dl)	291 ± 214 (n = 14)	296 ± 222 (n = 14)	284 ± 233 (n = 14)	364 ± 215 (n = 11)	376 ± 197 (n = 11)	381 ± 214 (n = 11)
	IGF-1[L] (ng/ml)	138 ± 54 (n = 10)	128 ± 52 (n = 10)	134 ± 59 (n = 10)	148 ± 57 (n = 9)	147 ± 47 (n = 9)	138 ± 49 (n = 9)
	IGBP-3 (ng/dl)	1,897 ± 424 (n = 10)	1,850 ± 392 (n = 10)	1,822 ± 368 (n = 10)	1,840 ± 389 (n = 8)	1,854 ± 409 (n = 8)	1,779 ± 330 (n = 8)
Inflammatory biomarkers	TNFα (pg/ml)	21.5 ± 4.1 (n = 10)	24.0 ± 4.5 (n = 10)	22.6 ± 2.5 (n = 10)	22.5 ± 4.0 (n = 9)	22.4 ± 5.1 (n = 9)	21.3 ± 5.7 (n = 9)
	IL6 (pg/ml)[L]	6.9 ± 12.0 (n = 9)	7.0 ± 9.6 (n = 9)	4.9 ± 5.0 (n = 9)	5.7 ± 4.7 (n = 5)	12.0 ± 21 (n = 5)	410.0 ± 15.0 (n = 5)
	CRP (ng/ml)[L,X]	15,946 ± 27,023 (n = 10)	12,523 ± 12,827 (n = 10)	5,459 ± 8,607 (n = 10)	14,704 ± 13,055 (n = 10)	10,868 ± 14,688 (n = 10)	19,502 ± 39,703 (n = 10)

(Continued)

TABLE 2 (Continued)

		PMT + FES			NMES-RT + FES		
		Baseline	Post-Int1	Post-Int 2	Baseline	Post-Int1	Post-Int 2
	FFA (μg/ml)[L]	7.1 ± 6.1 (n = 10)	5.4 ± 4.4 (n = 10)	5.0 ± 4.7* (n = 10)	5.0 ± 1.7 (n = 8)	4.7 ± 1.7 (n = 8)	3.6 ± 2.1* (n = 8)

[#]A trend toward difference in VO_2 between groups; L: data were logged transformed before running statistical analysis, because the data did not meet the assumption of normality; O: outliers resulted in omission of the data. *Pairwise comparison difference indicating a time effect within a group. *[?]A trend towards pairwise comparisons. [x]Interaction between groups, $p = 0.048$. [M]Missing values were considered in Post-Int 2.

5.1.2. Body composition variables

5.1.2.1. Anthropometrics

The interventions had no effects on anthropometric variables as demonstrated in Table 3.

5.1.2.2. DXA

Repeated measure analysis indicated that there is a significant decline in upper extremity lean mass ($p = 0.009$). Pairwise comparison showed that there was 433 g decline (6.4%) in the NMES-RT + FES ($p = 0.012$). There was a total decline in total mass of the upper extremity mass ($p = 0.04$); pairwise comparison indicated that there was a trend of decline in total mass ($p = 0.08$) following P1 in the NMES-RT + FES (Table 3).

Mixed model analysis indicated increases ($p = 0.012$) in leg lean mass (g) in the PMT + FES group. Pairwise comparison showed a 0.76 kg increase in P 2 compared to P1 (6%, $p = 0.041$). MANCOVA revealed significant difference in leg bone mineral content ($p = 0.038$) between the groups following P1 (Table 3).

5.1.2.3. Magnetic resonance imaging

Table 4 highlights the changes in muscle and IMF CSAs following PMT + FES and NMES-RT + FES. Muscle CSA was presented in the forms of whole or absolute CSA (i.e., after subtracting IMF) for whole thigh and knee extensor muscle group. Table 4 denoted the changes in muscle hypertrophy in the whole muscle CSA and knee extensors, respectively.

The entire data for VAT, SAT and VAT: SAT ratio did not meet the assumption of normality and had to be log-transformed (Table 5). There was a trend of 16% decrease in $VAT_{L\text{-}K}$ following NMES-RT compared to baseline ($p = 0.054$). $VAT_{K\text{-}Um}$ and $VAT_{IC\text{-}F}$ showed a trend of lower CSA in the NMES-RT + FES compared to PMT-FES following P1 ($p = 0.06$) and P2 ($p = 0.084$), respectively. Finally, VAT_{total} was 26.7 and14.2% lower in the NMES-RT + FES compared to PMT-FES following P1 ($p = 0.023$) and P2 ($p = 0.050$), respectively.

$SAT_{IC\text{-}F}$ decreased in the PMT + FES ($p = 0.018$) but not in the NMES-RT + FES group. Pairwise comparisons showed a trend between P2 and P1 ($p = 0.077$) in the PMT-FES group. Finally, there was no changes in the VAT: SAT ratio between both groups.

6. Discussion

Several important findings were noted in the current study that are likely to expand our knowledge about the interaction or complementary effects between NMES-RT and FES-LEC. The addition of 12 weeks of FES-LEC following 12 weeks of NMES-RT did not result in additional increase in muscle size. There was an increase in muscle mass after adding 12 weeks of FES-LEC to PMT; however, it was obviously non-significantly greater following NMES-RT. The addition of FES-LEC resulted in recognized gains in power and resistance only in P2 in the NMES-RT + FES; however, the gains in both variables was only noted following P1in the PMT + FES group. Similar to our recent findings (9), NMES-RT managed to increase leg VO_2 peak compared to PMT; however, the addition of FES-LEC resulted in increasing VO_2 and relative VO_2 in P2 compared to P1 in both groups. It is interesting to note that NMES-RT + FES resulted in a 12% decrease in the LDL-C level as well as total trunk VAT CSA. Finally, based on the current findings, home-based training may overcome several of the barriers that emerged during the course of the training, such as missing visits and study discontinuation as a result of the COVID-19 pandemic.

6.1. Significance and rationale of the work

Recent studies and guidelines have recommended both aerobic and resistance training to evoke muscle hypertrophy, strength or increasing aerobic capacity, respectively, in persons with SCI (3, 4, 31). We aimed to evoke muscle hypertrophy prior application of FES-LEC training to attenuate several of its existing limitations and to maximize the benefits on cardio-metabolic variables (18, 29). The addition of progressive FES-LEC training as described in this protocol following NMES-RT did not evoke further muscle hypertrophy (see below). However, we demonstrated increased muscle strength as measured by the resistance and power of the FES ergometer bike. The current findings suggest a clear dissociation in musculoskeletal adaptations versus neuromuscular adaptations in the current trial. Previous research indicated that neuromuscular adaptations via increasing neural drive commonly precede muscle hypertrophy (38–40); especially when resistance training is applied for a short period of 4–6 weeks (41). Based on the current findings, progressive FES-LEC enhanced neuromuscular adaptations without evoking muscle hypertrophy in the NMES-RT + FES group. Surprisingly, the PMT + FES group experienced both muscle hypertrophy and increased strength after 12 weeks of just PMT compared to NMES-RT; suggesting a training specificity. It is possible to speculate the evoking muscle hypertrophy may have attenuated the recognized effects of FES-LEC on muscle strength in the NMES-RT + FES compared to the PMT + FES group following P1. Previous work indicated that when aerobic training (AT) preceded RT, the performance of RT was diminished up to 8 h in the muscles that were involved in aerobic training (42). A previous meta-analysis concluded that concurrent AT and RT may attenuate gains in explosive strength; however, the report stressed the need for AT and RT to improve physical fitness and health (43).

TABLE 3 Effects of 24 weeks of PMT + FES compared to NMES-RT + FES on body composition variables in persons with spinal cord injury.

		PMT + FES-LEC			NMES-RT + FES		
		Baseline	Post-Int1	Post-Int 2	Baseline	Post-Int1	Post-Int 2
Anthropometrics	Supine WC	81 ± 13.4 (n = 14)	81.5 ± 13.0 (n = 14)	83.0 ± 15 (n = 14)	86 ± 14.0 (n = 12)	85.5 ± 15.0 (n = 12)	86.4 ± 13 (n = 12)
	Supine AC	81 ± 14.0 (n = 14)	81 ± 15.0 (n = 14)	82.0 ± 16 (n = 14)	87.5 ± 15 (n = 13)	88 ± 17.0 (n = 13)	87.5 ± 16.5 (n = 13)
	Supine Hip circumference	94 ± 12.0 (n = 14)	95 ± 13.0 (n = 14)	96.0 ± 12 (n = 14)	98 ± 10 (n = 13)	99 ± 10 (n = 13)	100 ± 0.0 (n = 13)
	Waist to Hip ratio	0.86 ± 0.06 (n = 14)	0.85 ± 0.08 (n = 14)	0.86 ± 0.06 (n = 14)	0.88 ± 0.08 (n = 13)	0.87 ± 0.08 (n = 13)	0.87 ± 0.06 (n = 13)
	Supine Thigh circumference	46 ± 6.0 (n = 14)	47 ± 7.0 (n = 14)	48.0 ± 7.0 (n = 14)	50 ± 10 (n = 13)	50.5 ± 8.0 (n = 13)	50 ± 08.0 (n = 13)
	Seated Calf circumference	30 ± 3.0 (n = 14)	30.5 ± 3.0 (n = 14)	30.0 ± 3.1 (n = 14)	32.0 ± 4.0 (n = 13)	32 ± 4.1 (n = 13)	32 ± 4.0 (n = 13)
Body composition-DXA							
Upper Extremity	Fat mass (g)	2,270 ± 1,422 (n = 14)	2,225 ± 1,221 (n = 14)	2,146 ± 1,277 (n = 14)	2,231 ± 1,182 (n = 13)	2,247 ± 1,062 (n = 13)	2,247 ± 1,190 (n = 13)
	%Fat mass	25.5 ± 15 (n = 14)	26.3 ± 14 (n = 14)	25.5 ± 15 (n = 14)	24.5 ± 9 (n = 13)	25.6 ± 11.0 (n = 13)	26.5 ± 11.0 (n = 13)
	Lean mass (g)	6,167 ± 2,358 (n = 14)	5,956 ± 2,318 (n = 14)	6,023 ± 2,356 (n = 14)	6,739 ± 1,480 (n = 13)	6,222 ± 1,776 (n = 13)	6,306 ± 1,716 (n = 13)
	BMC (g)	437 ± 114 (n = 14)	436 ± 120 (n = 14)	437 ± 120 (n = 14)	445 ± 78 (n = 13)	432 ± 81 (n = 13)	432 ± 82 (n = 13)
	Total mass (kg)	8.8 ± 2.7 (n = 14)	8.6 ± 2.7 (n = 14)	8.6 ± 2.7 (n = 14)	9.5 ± 2.1 (n = 13)	8.9 ± 2.2 (n = 13)	9.2 ± 2.3 (n = 13)
Lower extremity	Fat mass (g)	6,562 ± 3,355 (n = 14)	6,877 ± 3,575 (n = 14)	6,674 ± 3,871 (n = 14)	7,711 ± 3,870 (n = 13)	7,420 ± 3,625 (n = 13)	7,905 ± 3,574 (n = 13)
	%Fat mass	25.5 ± 15 (n = 14)	33 ± 13 (n = 14)	31 ± 13 (n = 14)	32.0 ± 9.0 (n = 13)	32.0 ± 9.4 (n = 13)	32.5 ± 10.0 (n = 13)
	Lean mass (g)	12,643± 2,622 (n = 14)	12,342± 2,687 (n = 14)	13,104 ± 2,519 (n = 14)	14,351 ± 2,561 (n = 13)	14,183± 3,207 (n = 13)	14,854± 3,140 (n = 13)
	BMC (g)	789.5 ± 217	788 ± 207	759 ± 203	823 ± 194	791 ± 215[#]	811 ± 223
	Total mass (kg)	20 ± 3.6	20 ± 3.8	20.5 ± 4.2	23 ± 5.5	22.4 ± 5.8	23.6 ± 5.4
Trunk	Fat mass (g)	11,246 ± 7,154 (n = 14)	11,627 ± 7,563 (n = 14)	11,475 ± 7,632 (n = 14)	13,773 ± 7,707 (n = 13)	14,382 ± 8,253 (n = 13)	13,971 ± 7,736 (n = 13)
	%Fat mass	31.4 ± 16.0 (n = 14)	32.0 ± 16.0 (n = 14)	31.3 ± 17.0 (n = 14)	34.3 ± 12.0 (n = 13)	35.1 ± 14.0 (n = 13)	35.4 ± 14.0 (n = 13)
	Lean mass (g)	20,835 ± 3,643 (n = 14)	20,783 ± 3,413 (n = 14)	21,089 ± 3,116 (n = 14)	22,757 ± 2,831 (n = 13)	22,676 ± 1,776 (n = 13)	21,974 ± 2,846 (n = 13)
	BMC (g)	824 ± 219 (n = 14)	808 ± 234 (n = 14)	832 ± 231 (n = 14)	904 ± 221 (n = 13)	879 ± 221 (n = 13)	864 ± 167 (n = 13)
	Total mass (kg)	33 ± 8 (n = 14)	33 ± 8 (n = 14)	33 ± 8 (n = 14)	37 ± 10 (n = 13)	38 ± 10 (n = 13)	37 ± 9 (n = 13)
Total	Fat mass (g)	21,133 ± 11,334 (n = 14)	21,927 ± 12,006 (n = 14)	21,465 ± 12,577 (n = 14)	24,890 ± 11,551 (n = 13)	25,222 ± 12,058 (n = 13)	25,357 ± 11,953 (n = 13)
	%Fat mass	30 ± 13 (n = 14)	30.7 ± 13 (n = 14)	29.6 ± 14 (n = 14)	31.5 ± 9.4 (n = 13)	32 ± 11 (n = 13)	32.3 ± 11.0 (n = 13)

(Continued)

TABLE 3 (Continued)

		PMT + FES-LEC			NMES-RT + FES		
		Baseline	Post-Int1	Post-Int 2	Baseline	Post-Int1	Post-Int 2
	Lean mass (g)	43,629 ± 8,167 (n = 14)	43,282 ± 7,114 (n = 14)	44,181 ± 7,226 (n = 14)	47,644 ± 5,959 (n = 13)	47,464 ± 6,089 (n = 13)	46,892 ± 6,808 (n = 13)
	BMC (g)	2,724 ± 467 (n = 14)	2,713 ± 458 (n = 14)	2,679 ± 470 (n = 14)	2,781 ± 466 (n = 13)	2,710 ± 481 (n = 13)	2,690 ± 466 (n = 13)
	Total mass (kg)	67.5 ± 12.7 (n = 14)	68 ± 13 (n = 14)	68 ± 14 (n = 14)	75 ± 16 (n = 13)	75 ± 16 (n = 13)	75 ± 15 (n = 13)

[#]Difference between groups.

6.2. Muscle hypertrophy is attenuated in the NMES-RT + FES group

Based on the current report, there is a hiking effect on the signaling pathway involved in evoking muscle hypertrophy in the NMES-RT group. Following 12 weeks of NMES-RT, the hypertrophy signaling pathway attained a ceiling effect. We and others have noted the abundance of protein following either NMES-RT or FES-LEC (26, 44, 45). The paralyzed muscles have intact signaling pathway that can be upregulated when the appropriate stimulation pattern is delivered (44, 45). We have recently studied the primary predictors of muscle hypertrophy between high and low responders with SCI (33). We noted that high responders may experience great Akt protein expression with concomitant increase IGFBP-3 without a recognized changes in circulating IGF-1. Furthermore, mRNA analysis revealed upregulation in IRS-1, Akt, mTOR with concomitant downregulation in myostatin, MurF-1 and PDK4 compared to the low responders (33). Therefore, changing the stimulation paradigm from NMES-RT to FES-LEC did not trigger upregulation or downregulation or signaling pathways to evoke additional muscle hypertrophy. On contrary, the addition of FES-LES to PMT resulted in muscle hypertrophy; however, it deemed less comparable to NMES-RT.

6.3. Effects of training on cardio-metabolic risk factors

The current findings support recognized benefits of training on cardio-metabolic risk factors (1). The noticeable change was recognized in VO_2 peak and predominantly in the NMES-RT + FES group. Furthermore, the NMES-RT + FES resulted in improvement in the LDL-C profile and decrease in total VAT CSA. We have previously demonstrated a 14% increase in FES-LEC VO_2 peak (i.e., leg VO_2 peak) following 12–16 weeks of NMES-RT compared to PMT (9). The increases in whole thigh muscle and knee extensor muscle CSAs were associated with increase in VO_2 peak (9). A recent randomized clinical trial showed that in 76 adolescents adding RT to either moderate continuous AT or to high intensity AT resulted in increasing VO_2 peak by 4.4 and 5.5%, respectively (46). In the current trial, we noticed 12% increase in VO_2 peak in adults with SCI. The difference in VO_2 between groups was non-significantly noted in P1 but was further enhanced in P2 especially in the NMES-RT + FES group. Although statistically different, it is still unclear the clinical implications of these findings for the SCI population. Another randomized clinical trial recommended combination exercise of RT and AT for 5 days per week compared to either RT or AT only in improvement of cardio-respiratory fitness in overweight and obese individuals (47). Additional benefits included decrease in VAT CSA and LDL-C profile. The association of VAT to cardio-metabolic risk factors have been well studied and this has been shown to mediated via increasing inflammatory cytokines and negatively impacting circulating testosterone and mitochondrial activity (48).

The question that remains to be addressed is whether the preceding NMES-RT attenuated the effects of 12 weeks FES-LEC on cardio-metabolic outcomes. Several trials demonstrated the efficacy of FES-LEC on enhancing the cardio-metabolic profile (10, 11, 14). Training drives improvement in cardio-metabolic health is primarily mediated by increasing muscle mass (9) and accompanied with increased mitochondrial density and activity after SCI (27). This will result in subsequent increase in fatty acid oxidation and hence increase insulin sensitivity and enhanced metabolic flexibility. The decrease in VAT CSA as well as LDL-C following NMES-RT + FES supported previous findings. However, the addition of FES-LEC to NMES-RT did not induce additional muscle hypertrophy. This can be explained by possible antagonistic physiological adaptations of AT and RT; which may interfere with each other when the two types of training are performed serially (49). The combination of both RT and aerobic training has been shown to be superior in weight loss to either intervention alone in obese elderly able-bodied persons (49).

6.4. Limitations

Several of the current findings were trended towards statistical insignificance. Spinal cord injury is a heterogenous population with wide range of level of injuries and time since injuries. The results of the current trial may serve as important clinical findings towards mitigating cardio-metabolic risk factors after SCI. Contrary, statistical differences in lean mass and BMC may not be of clinical significance and are considered within the error of repeated measures as previously highlighted (34). It is possible that the frequency of training (2x per week) of FES-LEC was ineffective in enhancing cardio-metabolic benefits. Previous trials recommended a frequency of 3x per week. Gater et al. recently demonstrated that 5x per week for 16 weeks of FES-LEC resulted in decreasing percentage body fat in 6 individuals with motor complete SCI (35). We chose a frequency of 2x per week to increase adherence and compliance. Dolbow et al. previously indicated that the adherence following 8 weeks home use of FES-LEC decreased from 72 to 63% (25). We originally powered the study based on VO_2 change to recruit 48 individuals with SCI (24 per group); however, the 5-year trial resulted only in 33 participants. The small sample size may have possibly impacted the overall findings on the

TABLE 4 Effects of 24 weeks of PMT + FES compared to NMES-RT + FES on muscle CSA and intramuscular fat (IMF) in persons with spinal cord injury.

		PMT + FES						NMES-RT + FES					
		Right			Left			Right			Left		
		BL	P1	P2	BL	P1	P2	BL	P1	P2	BL	P1	P2
Whole Muscle CSA	Proximal	101 ± 22 (n = 15)	97 ± 22 (n = 12)	107 ± 23* (n = 13)	98 ± 22 (n = 14)	90 ± 25 (n = 12)	113 ± 25** (n = 11)	95 ± 33 (n = 15)	114 ± 32$^{\#\#}$*** (n = 14)	117 ± 34* (n = 12)	96 ± 33 (n = 15)	113 ± 30$^{\#}$*** (n = 14)	122 ± 31** (n = 12)
	Middle	89 ± 22 (n = 15)	87 ± 25 (n = 12)	96 ± 24* (n = 13)	88 ± 23 (n = 14)	89 ± 27 (n = 12)	102 ± 27** (n = 11)	85 ± 33 (n = 15)	104 ± 31$^{\#\#}$*** (n = 14)	109 ± 33** (n = 12)	87 ± 32 (n = 15)	104 ± 31** (n = 14)	113 ± 31** (n = 12)
	Distal	70 ± 17 (n = 15)	71 ± 21 (n = 12)	81 ± 21** (n = 13)	72 ± 19 (n = 13)	72 ± 22 (n = 12)	83 ± 22** (n = 11)	70 ± 26 (n = 15)	81 ± 22$^{\#}$* (n = 14)	86 ± 23* (n = 12)	70 ± 25 (n = 15)	81 ± 22* (n = 14)	83 ± 21* (n = 11)
	Average	87 ± 19 (n = 15)	86 ± 22 (n = 12)	94 ± 22* (n = 13)	88 ± 21 (n = 14)	87 ± 24 (n = 12)	101 ± 24* (n = 11)	84 ± 30 (n = 15)	100 ± 27$^{\#\#}$*** (n = 14)	104 ± 29** (n = 12)	85 ± 29 (n = 15)	100 ± 26$^{\#}$*** (n = 14)	108 ± 28** (n = 12)
ABS Whole Muscle CSA	Proximal	84 ± 23 (n = 15)	76 ± 26 (n = 12)	84 ± 27 (n = 13)	84 ± 26 (n = 14)	79 ± 25 (n = 12)	90 ± 24 (n = 12)	84 ± 29 (n = 15)	101 ± 31$^{\#}$* (n = 14)	102 ± 30* (n = 12)	84 ± 28 (n = 15)	99 ± 26$^{\#}$* (n = 14)	106 ± 27* (n = 12)
	Middle	73 ± 22 (n = 15)	68 ± 32 (n = 12)	74 ± 23 (n = 13)	73 ± 23 (n = 14)	69 ± 22 (n = 12)	79 ± 24 (n = 12)	72 ± 27 (n = 15)	86 ± 30* (n = 14)	92 ± 29* (n = 12)	72 ± 27 (n = 15)	86 ± 25$^{\#}$* (n = 14)	90 ± 25 (n = 12)
	Distal	53 ± 17 (n = 15)	48 ± 17 (n = 12)	51 ± 22 (n = 13)	60 ± 20 (n = 14)	47 ± 20* (n = 12)	55 ± 23 (n = 12)	52 ± 19 (n = 15)	56 ± 19 (n = 14)	63 ± 20 (n = 12)	49 ± 18 (n = 15)	57 ± 19$^{\#}$ (n = 14)	60 ± 18 (n = 11)
	Average	71 ± 19 (n = 15)	65 ± 21 (n = 12)	71 ± 23 (n = 13)	73 ± 20 (n = 14)	67 ± 20 (n = 12)	76 ± 22 (n = 12)	70 ± 24 (n = 15)	82 ± 24$^{\#}$ (n = 14)	86 ± 24* (n = 12)	69 ± 23 (n = 15)	82 ± 21$^{\#}$* (n = 14)	85 ± 22* (n = 11)
KE Muscle CSA	Proximal	45 ± 13 (n = 15)	41 ± 14 (n = 12)	50 ± 15* (n = 13)	43 ± 14 (n = 14)	42 ± 15 (n = 12)	52 ± 16** (n = 12)	40 ± 13 (n = 15)	53 ± 14$^{\#\#}$*** (n = 14)	53 ± 15** (n = 12)	40 ± 13 (n = 15)	52 ± 14$^{\#}$** (n = 14)	55 ± 14** (n = 12)
	Middle	41 ± 13 (n = 15)	40 ± 16 (n = 12)	46 ± 15* (n = 13)	40 ± 14 (n = 14)	40 ± 16 (n = 12)	49 ± 17** (n = 12)	38 ± 14 (n = 15)	50 ± 14$^{\#\#}$*** (n = 14)	52 ± 15** (n = 12)	38 ± 13 (n = 15)	49 ± 15** (n = 14)	53 ± 15** (n = 12)
	Distal	32 ± 9 (n = 15)	33 ± 12 (n = 12)	36 ± 12* (n = 13)	32 ± 10 (n = 14)	33 ± 13 (n = 12)	39 ± 13** (n = 12)	30 ± 11 (n = 15)	38 ± 10$^{\#}$*** (n = 14)	40 ± 10* (n = 12)	30 ± 12 (n = 15)	37 ± 10.5$^{\#}$* (n = 14)	36 ± 9$^{\#}$* (n = 11)
	Average	40 ± 11 (n = 15)	39 ± 13 (n = 12)	45 ± 14* (n = 13)	39 ± 12.3 (n = 14)	39 ± 14.4 (n = 12)	47 ± 15** (n = 12)	37 ± 12 (n = 15)	47 ± 11$^{\#\#}$*** (n = 14)	49 ± 13** (n = 12)	36 ± 12 (n = 15)	46 ± 12** (n = 14)	49 ± 13.3** (n = 11)

(Continued)

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TABLE 4 (Continued)

		PMT + FES						NMES-RT + FES					
		Right			Left			Right			Left		
		BL	P1	P2	BL	P1	P2	BL	P1	P2	BL	P1	P2
ABS KE Muscle CSA	Proximal	40 ± 13 (n = 15)	34 ± 15 (n = 12)	39 ± 18 (n = 13)	38 ± 15 (n = 14)	36 ± 14 (n = 12)	43 ± 17 (n = 12)	38 ± 13 (n = 15)	47 ± 15#* (n = 14)	47 ± 15 (n = 12)	36 ± 12 (n = 15)	47 ± 14#** (n = 14)	49 ± 15* (n = 12)
	Middle	36 ± 12 (n = 15)	32 ± 14 (n = 12)	36 ± 15 (n = 13)	35 ± 14 (n = 14)	34 ± 14 (n = 12)	39 ± 16 (n = 12)	34 ± 12 (n = 15)	41 ± 16 (n = 14)	45 ± 14 (n = 12)	32 ± 12 (n = 15)	41 ± 14#** (n = 14)	43 ± 14* (n = 11)
	Distal	26 ± 8 (n = 15)	23 ± 10 (n = 12)	25 ± 13 (n = 13)	25 ± 11 (n = 14)	22 ± 12 (n = 12)	27 ± 14 (n = 12)	24 ± 9 (n = 15)	27 ± 12 (n = 14)	29 ± 11 (n = 12)	22 ± 9 (n = 15)	27 ± 12 (n = 14)	27 ± 10 (n = 11)
	Average	34 ± 10 (n = 15)	30 ± 13 (n = 12)	34 ± 15 (n = 13)	34 ± 13 (n = 14)	31 ± 13 (n = 12)	37 ± 15 (n = 12)	32 ± 11 (n = 15)	39 ± 13 (n = 14)	41 ± 12 (n = 12)	30 ± 10 (n = 15)	39 ± 12#** (n = 14)	39 ± 12* (n = 11)
Whole Thigh IMF	Proximal	16 ± 12 (n = 15)	21 ± 18 (n = 12)	24 ± 22 (n = 13)	15 ± 11 (n = 14)	18.6 ± 13.6 (n = 12)	21 ± 17 (n = 12)	10 ± 8 (n = 15)	13 ± 9 (n = 14)	14 ± 10 (n = 12)	12 ± 12 (n = 15)	12 ± 9 (n = 14)	16 ± 14 (n = 12)
	Middle	16 ± 11 (n = 15)	19 ± 13 (n = 12)	22 ± 20* (n = 13)	14 ± 8 (n = 14)	18 ± 12 (n = 12)	21 ± 17 (n = 12)	13 ± 10 (n = 15)	18 ± 14 (n = 14)	17 ± 13 (n = 12)	15 ± 11 (n = 15)	16 ± 10 (n = 14)	17 ± 14 (n = 12)
	Distal	18 ± 12 (n = 15)	24 ± 14 (n = 12)	25 ± 21 (n = 13)	19 ± 11 (n = 14)	26 ± 15 (n = 12)	26 ± 19 (n = 12)	18 ± 13 (n = 15)	25 ± 16 (n = 14)	22 ± 17 (n = 12)	20 ± 14 (n = 15)	23 ± 10 (n = 14)	23 ± 13 (n = 11)
	Average	16 ± 11 (n = 15)	21 ± 14 (n = 12)	23 ± 20* (n = 13)	16 ± 8 (n = 14)	20 ± 13 (n = 12)	22 ± 17 (n = 12)	14 ± 10 (n = 15)	19 ± 13 (n = 14)	18 ± 12 (n = 12)	15.7 ± 11 (n = 15)	17 ± 9# (n = 15)	18 ± 13 (n = 12)
Whole Thigh % IMF	Proximal	17 ± 13 (n = 15)	22 ± 18 (n = 12)	19 ± 16 (n = 12)	17 ± 14 (n = 14)	19 ± 15 (n = 12)	19 ± 16 (n = 12)	11 ± 7 (n = 15)	12 ± 9 (n = 14)	13 ± 9 (n = 12)	13 ± 8 (n = 15)	11 ± 8 (n = 14)	13 ± 10 (n = 12)
	Middle	18 ± 13 (n = 15)	22 ± 15 (n = 12)	20 ± 15 (n = 12)	17 ± 11 (n = 14)	21 ± 14 (n = 12)	20 ± 15 (n = 12)	15 ± 8 (n = 15)	18 ± 13 (n = 14)	15 ± 11 (n = 12)	17 ± 11 (n = 15)	16 ± 8 (n = 14)	15 ± 11 (n = 12)
	Distal	25 ± 16 (n = 15)	33 ± 16 (n = 12)	29 ± 19 (n = 12)	24 ± 14 (n = 14)	36 ± 21 (n = 12)	32 ± 21 (n = 12)	25 ± 12 (n = 15)	30 ± 17 (n = 14)	25 ± 17 (n = 12)	28 ± 14 (n = 15)	30 ± 11(n = 14)	27 ± 14 (n = 11)
	Average	19 ± 13 (n = 15)	25 ± 15 (n = 12)	22 ± 15 (n = 12)	19 ± 10 (n = 14)	24 ± 14 (n = 12)	23 ± 16 (n = 12)	17 ± 8 (n = 15)	19 ± 12 (n = 14)	17 ± 10 (n = 12)	19 ± 10 (n = 15)	18 ± 8 (n = 14)	17 ± 11 (n = 12)
KE IMF	Proximal	5.5 ± 4.8 (n = 15)	8.4 ± 11 (n = 12)	10.9 ± 13.2* (n = 13)	4.8 ± 4.0 (n = 14)	6.2 ± 6.1 (n = 12)	8.9 ± 10.4 (n = 12)	2.9 ± 2.1 (n = 15)	5.6 ± 5.4 (n = 14)	6.2 ± 5.7 (n = 12)	4.5 ± 5.1 (n = 15)	4.5 ± 3.5# (n = 14)	6.1 ± 6.8 (n = 12)
	Middle	5.0 ± 4.8 (n = 15)	7.7 ± 8.7 (n = 12)	10.7 ± 12.9* (n = 13)	5.2 ± 3.7 (n = 14)	6.2 ± 5.6 (n = 12)	9.1 ± 9.4 (n = 12)	4.5 ± 3.9 (n = 15)	9.2 ± 9.5 (n = 14)	7.6 ± 7.4 (n = 12)	6.0 ± 5.8 (n = 15)	7.4 ± 5.4 (n = 14)	7.4 ± 7 (n = 12)
	Distal	5.4 ± 4.5 (n = 15)	9.9 ± 8.7 (n = 12)	11.3 ± 12.9 (n = 12)	6.2 ± 4.2 (n = 14)	10.3 ± 8.2 (n = 12)	11.7 ± 10.5 (n = 12)	5.9 ± 4.6 (n = 15)	11.1 ± 9.6 (n = 14)	9.8 ± 9.4 (n = 12)	8.3 ± 7.2 (n = 15)	10.0 ± 5.6# (n = 14)	9.1 ± 6.1 (n = 11)
	Average	5.2 ± 4.5 (n = 15)	8.5 ± 9.1 (n = 12)	10.9 ± 12.5* (n = 13)	5.4 ± 3.4 (n = 14)	7.4 ± 5.8 (n = 12)	9.8 ± 9.9 (n = 12)	4.4 ± 3.2 (n = 15)	8.6 ± 8 (n = 14)	7.9 ± 6.8 (n = 12)	6.2 ± 5.7 (n = 15)	7.3 ± 4.8 (n = 14)	7.2 ± 6 (n = 12)

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TABLE 4 (Continued)

		PMT + FES						NMES-RT + FES					
		Right			Left			Right			Left		
		BL	P1	P2	BL	P1	P2	BL	P1	P2	BL	P1	P2
KE % IMF	Proximal	12.4 ± 10.3 (*n* = 15)	19.6 ± 21.1 (*n* = 12)	22.2 ± 23.5* (*n* = 13)	13 ± 12.3 (*n* = 14)	15.2 ± 14 (*n* = 12)	17.7 ± 19.9 (*n* = 12)	7.8 ± 6.6 (*n* = 15)	11.8 ± 12.8 (*n* = 14)	12.3 ± 13.2 (*n* = 12)	11.0 ± 11.6 (*n* = 15)	9.2 ± 7.6 (*n* = 14)	11.8 ± 13.6 (*n* = 12)
	Middle	11.8 ± 9.9 (*n* = 15)	18.7 ± 15.4 (*n* = 12)	21.9 ± 20.8 (*n* = 13)	14.0 ± 10.5 (*n* = 14)	15.8 ± 11.6 (*n* = 12)	18.8 ± 17.3 (*n* = 12)	11.9 ± 9.0 (*n* = 15)	18.9 ± 20.2 (*n* = 14)	14.5 ± 14.1 (*n* = 12)	15.9 ± 14.1 (*n* = 15	15.9 ± 10.8 (*n* = 14)	15.2 ± 14.2 (*n* = 12)
	Distal	17.2 ± 12.5 (*n* = 15)	28.7 ± 17.8 (*n* = 12)	31.3 ± 24.1 (*n* = 13)	20.9 ± 15.2 (*n* = 14)	32.2 ± 22.8 (*n* = 12)	30.7 ± 23.6 (*n* = 12)	19.5 ± 11.2 (*n* = 15)	29.4 ± 24.6 (*n* = 14)	23.7 ± 22.2 (*n* = 12)	25.0 ± 17.3 (*n* = 15)	29.5 ± 16.5 (*n* = 14)	26.8 ± 20.1# (*n* = 11)
	Average	13.3 ± 10.0 (*n* = 15)	21.7 ± 17.0 (*n* = 12)	24.3 ± 21.8* (*n* = 13)	15.3 ± 9.9 (*n* = 14)	19.9 ± 13.1 (*n* = 12)	21.6 ± 19.8 (*n* = 12)	12.8 ± 7.6 (*n* = 15)	19.7 ± 18.7 (*n* = 14)	16.7 ± 13.8 (*n* = 12)	17.1 ± 13.3 (*n* = 15)	17.7 ± 10.9 (*n* = 14)	17.0 ± 14.4 (*n* = 12)

Proximal CSA represent the first 4 MRI slices starting with the first one just at the inferior border of the gluteus maximus muscle; middle CSA represents the 4 slices of the mid-thigh; distal CSA represents the average of the 4–6 slices towards the knee joints. Average CSA represents the average of the entire 12–14 slices per right or left leg.

**Between group differences $p < 0.001$.

#Between group differences $p < 0.001$–$p \leq 0.049$.

**Time effect within group, $p < 0.001$.

*Time effect within group, $0.001 < p \leq 0.043$.

primary outcome variables. Additionally, the COVID-19 pandemic resulted in early discontinuation of the study. Similar to other studies and pre-planned design, the IVGTT was performed 5–7 days following the last training session. It is possible that a shorter window of 36–48 h might have better demonstrated training effects. In addition, unreported changes in dietary habits may have influenced or masked the effects of training on Sg and Si.

7. Summary/Conclusion

In conclusion, this is the first randomized clinical trial that examined the effects of evoking muscle hypertrophy via NMES-RT on maximizing the benefits of FES-LEC on cardio-metabolic risk factors in persons with chronic SCI. The use of FES-LEC following 12 weeks of NMES-RT modestly influence cardio-metabolic risk factors and evoked additional muscle hypertrophy as hypothesized. The findings support that VO_2 peak is the primary factor that appears to be responsive to both training paradigms especially following NMES-RT + FES. The evidence supports the notion that both NMES-RT and FES-LEC may have different training effects on musculoskeletal and neuromuscular adaptions. Evoking muscle hypertrophy may attenuate the elicited neuromuscular adaptations during FES-LEC. Neuromuscular adaptations are further enhanced by FES-LEC suggesting a training specificity. Additionally, there is further mitigation of cardio-metabolic risk factors as noted by improvement in the lipid profile and decrease in VAT after NMES-RT. The inclusion of PMT did not impact any of the examined cardio-metabolic outcomes. We believe that compared to the expensive FES-LEC ergometers, NMES-RT may provide an alternative, simple and cheap rehabilitation approach either in clinical settings or for home-use that may overcome transportation problems, a primary impediment to utilization of proven interventions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation after obtaining necessary approvals from Richmond Inst. for Veterans Research.

Ethics statement

The studies involving humans were approved by Richmond Inst. for Veterans Research IRB. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. RK: Data curation, Supervision, Writing – review & editing. WC: Conceptualization, Data curation, Methodology, Writing – review & editing. BB: Writing – review & editing. RG:

TABLE 5 Effects of 24 weeks of PMT + FES compared to NMES-RT + FES on central obesity variables (VAT, SAT, VAT: SAT ratio) in persons with spinal cord injury.

		PMT + FES-LEC			NMES-RT + FES		
		Baseline	Post-Int1	Post-Int 2	Baseline	Post-Int1	Post-Int 2
Visceral adipose tissue (VAT)[L]	$VAT_{L\text{-}K}$ (cm^2)	68.2 ± 74 (n = 14)	67 ± 78 (n = 12)[!]	73.3 ± 86 (n = 13)	55.2 ± 59 (n = 13)	46.2 ± 57 (n = 12)	58.1 ± 60 (n = 11)
	$VAT_{k\text{-}Um}$ (cm^2)	89.2 ± 81 (n = 14)	94 ± 98 (n = 12)	93.4 ± 92 (n = 13)	80.2 ± 90 (n = 13)	69 ± 84[#?] (n = 12)	87.5 ± 97 (n = 11)
	$VAT_{IC\text{-}F}$ (cm^2)	54.2 ± 40 (n = 14)	53 ± 38 (n = 12)	58.6 ± 53 (n = 12)	52.8 ± 40 (n = 13)	41.4 ± 27 (n = 12)	46.6 ± 34[#?] (n = 11)
	VATtotal (cm^2)	70 ± 60 (n = 14)	71.8 ± 68 (n = 12)	75.4 ± 73 (n = 13)	62.1 ± 61 (n = 13)	52.6 ± 57[#] (n = 12)	64.7 ± 66[#] (n = 11)
Subcutaneous adipose tissue (SAT)[L]	$SAT_{L\text{-}K}$ (cm^2)	76.7 ± 61 (n = 14)	69.8 ± 57 (n = 12)	81.7 ± 72 (n = 13)	111.8 ± 92 (n = 14)	96.6 ± 81 (n = 13)	104.1 ± 78 (n = 12)
	$SAT_{k\text{-}Um}$ (cm^2)	143.3 ± 102 (n = 14)	136.3 ± 105 (n = 12)	147.5 ± 115 (n = 13)	193.7 ± 139 (n = 14)	181.9 ± 138 (n = 13)	191.8 ± 132 (n = 12)
	$SAT_{IC\text{-}F}$ (cm^2)	166.5 ± 116 (n = 14)	161.7 ± 129 (n = 12)	146.3 ± 113* (n = 12)	196 ± 124 (n = 14)	191.4 ± 138 (n = 13)	191.1 ± 136 (n = 12)
	SATtotal (cm^2)	130.1 ± 94 (n = 14)	125.2 ± 99 (n = 12)	128.8 ± 98 (n = 13)	167.7 ± 119 (n = 14)	160.3 ± 121 (n = 13)	164 ± 113 (n = 12)
VAT:SAT ratio[L]	$VAT:SAT_{L\text{-}K}$	0.75 ± 0.3 (n = 13)	0.77 ± 0.3 (n = 11)	0.8 ± 0.5 (n = 12)	0.87 ± 0.7 (n = 14)	0.91 ± 0.8 (n = 13)	0.71 ± 0.5 (n = 11)
	VAT: $SAT_{k\text{-}Um}$	0.6 ± 0.3 (n = 13)	0.6 ± 0.4 (n = 11)	0.65 ± 0.4 (n = 12)	0.6 ± 0.5 (n = 14)	0.6 ± 0.5 (n = 13)	0.53 ± 0.4 (n = 11)
	VAT: $SAT_{IC\text{-}F}$	0.33 ± 0.2 (n = 13)	0.4 ± 0.2 (n = 11)	0.4 ± 0.2 (n = 11)	0.33 ± 0.2 (n = 14)	0.33 ± 0.2 (n = 13)	0.33 ± 0.2 (n = 11)[#?]
	VAT:SATtotal	0.55 ± 0.3 (n = 13)	0.57 ± 0.3 (n = 11)	0.6 ± 0.3 (n = 12)	0.6 ± 0.4 (n = 14)	0.61 ± 0.5 (n = 13)	0.57 ± 0.4 (n = 11)

[L]Entire data of VAT, SAT, and VAT: SAT ratio were logged transformed for failing to meet the assumption of normality. [#]Difference between groups (p = 0.023–0.05); #?, a trend of between group difference (p = 0.06–0.084). *Difference within PMT + FES group (p = 0.018). Pairwise comparison suggested difference between P2 and P1 timepoints (p = 0.077). L, liver; K, kidneys; IC, iliac crests; F, femoral heads. [!]MRI scan of one of the participants was not analyzed because interference of the intrathecal baclofen with the field of view of VAT and SAT.

Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. RK: Data curation, Investigation, Methodology, Writing – review & editing. LG: Conceptualization, Data curation, Investigation, Writing – review & editing. TL: Conceptualization, Investigation, Supervision, Writing – original draft. AS: Formal analysis, Investigation, Methodology, Writing – review & editing. RA: Conceptualization, Data curation, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1254760/full#supplementary-material

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Outcome of early rehabilitation of patients with traumatic brain injury during COVID-19 pandemic in The Republic of Srpska, Bosnia and Herzegovina

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Introduction: The COVID-19 pandemic has placed a tremendous burden on the healthcare system. Patients with traumatic brain injury (TBI) have to get fast track treatment which is independent of environmental conditions. The aim of this study was to investigate epidemiological and clinical outcomes of early rehabilitation and compare it with the literature data during the non-COVID-19 period.

Materials and methods: A retrospective study included 174 patients with TBI, average 57 ± 19.08 years. They all underwent treatment in the University Clinical Center, Republic of Srpska, Bosnia and Herzegovina during the period January-December 2021. We have analyzed the epidemiological data and clinical course in 174 patients as well as the outcome of early rehabilitation in 107 patients. In clinical evaluation were used: Glasgow Coma Score (GCS), Functional Independence Measure (FIM) and Barthel Index on admission and at discharge, as well as Glasgow Outcome Scale (GOS) at discharge. ANOVA, SPANOVA, Student *t*-test and Pearson correlation coefficient were used in statistical analysis. The value ($p < 0.05$) was used for statistical significance.

Results: A total of 174 patients with TBI were included in this study. Most of the patients ($n = 94$) were older than 60, male ($n = 125$) and the most frequent cause of TBI was falling over ($n = 88$). About a half ($n = 92$) had a mild TBI, almost one third of the sample had moderate ($n = 52$), while only 30 patients had severe TBI. Total of 139 (80.3%) patients had the improved outcome, the worsening was registered in 2 (1.2%), while the fatal outcome was reported with 33 (18.5%) patients. When comparing the scores on admission and at discharge, the improvement of mean parameter values was reported for GCS (9.9 vs. 14.1), for Barthel Index (57.25 vs. 86.85), and for FIM (67.35 vs. 105.15), ($p < 0.001$). A complete recovery at discharge was found in 63.79%, a mild deficit in 8.62%, while serious deficit was found with 6.32%, and vegetative state with 2.29% patients.

Conclusion: The COVID-19 pandemic had a significant effect on the epidemiological data but not on the clinical outcome of patients with TBI. Early rehabilitation proved to be effective and to contribute to positive treatment outcome.

KEYWORDS

traumatic brain injury, COVID-19 pandemic, epidemiology, early rehabilitation, clinical outcome

1. Introduction

Traumatic brain injury (TBI) is one of the leading causes of morbidity, disability and mortality in all age groups, placing a significant burden on healthcare systems. There are more than 50 million people experiencing a brain injury in the world on the annual basis. The incidence of TBI in Europe is 47.3–694 per 100,000 inhabitants per year, while the mortality rate is 9–28.1/100,000 (1). The direct and indirect costs of TBI treatment in the USA amount to 90 billion dollars, and in the Netherlands 383.81 million Euro (2, 3). TBI is classified according to the mechanism of injury, location and severity of the injury. Regarding TBI severity, the Glasgow Coma Scale (GCS) is most often used on admission. According to this scale, brain injuries are divided into mild (GCS $\geq$ 13), moderate (GCS 9–12) and severe (GCS $<$ 9). There is currently no specific therapy for TBI. Patients with moderate and severe brain injury require complex treatment and rehabilitation involving a multidisciplinary approach (4). However, even patients with a mild brain injury can develop a severe clinical picture, which is why a prognostic model is necessary to plan their early rehabilitation. Unfortunately, there is still no ideal predictive model that would include clinical outcomes or biomarkers (5).

TBI leads to physical, cognitive, social, emotional and behavioral disorders. This is why in recent years there has been more and more interest in the effectiveness of early rehabilitation in reducing these disorders (6–8). Outcomes after TBI can range from full recovery to permanent disability or death. Even mild TBI can impair neuronal integrity, alter brain metabolism, and increase cell membrane renewal, which can cause long-term neurodegeneration (9).

Early rehabilitation can begin very early, after the patient has been stabilized. Early neurorehabilitation aims to improve motor and functional recovery while preventing secondary complications (pneumonia, atelectasis, muscle atrophy, decubitus ulcers, deep vein thrombosis, contractures). The intensity and duration of early rehabilitation are recommended to be individually dosed depending on the patient's general condition and abilities, and the approach should be multidisciplinary (10).

Measuring rehabilitation treatment outcomes after TBI is particularly challenging due to the variety and severity of impairments that remain after hospitalization and the post-acute period. The following scales are most commonly used: Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Functional Independence Measurement (FIM) and Barthel Index (11, 12). The COVID-19 pandemic has led to severe health challenges with major socioeconomic consequences around the world. Due to COVID-19 healthcare systems had to adapt quickly to the increased influx of patients, as well as the increased need for respiratory and intensive care. Due to the exponential admission to hospitals and intensive care units, it was necessary to redistribute staff, and to change the usual working practices. Due to the maximum occupancy of the intensive care units (ICU) and the increased need for mechanical ventilation, the operating theaters were converted into improvised intensive care units (13). To date, it remains unclear to what extent the pandemic and the measures implemented have affected the treatment and outcome of patients suffering from brain injury, especially due to the fact that moderate and severe brain injuries require hospitalization in ICU. The first case of COVID-19 infection in the Republic of Srpska was registered on 5 March 2020, vaccination started on 9 March 2021, and a lockdown was introduced on 21 March 2020 (14). The epidemiology of TBI was largely influenced by the changes in daily routine. The results of studies conducted in Austria, Italy, France, Finland and Switzerland have shown a reduced number of TBI cases compared to the years before the pandemic (15–19). According to a recent meta-analysis, underdeveloped and medium-developed countries were the most affected, where mortality due to TBI increased (20). Despite the lockdowns, the number of traffic accidents in some countries was reported to paradoxically increase (21). According to our information, in Bosnia and Herzegovina has been no research on the outcome of early rehabilitation of the patients suffering from TBI to date. Two studies on epidemiological and clinical characteristics of TBI have been published in Bosnia and Herzegovina. One hundred and forty one patients suffering from severe TBI, during the period 2002–2004 were described in the study Dizdarević et al. (22). A multi-center study on TBI, published in 2007, compared the epidemiological characteristics, treatment and outcome of the severe TBI in the European countries with various economic statuses, whereby Bosnia and Herzegovina was among less developed countries (23). The aim of this study was to investigate epidemiological and clinical outcomes of early rehabilitation and compare it with the literature data during non COVID-19 period.

2. Materials and methods

In our research we conducted a retrospective study that included all patients suffering from TBI admitted to the Intensive Care Unit and Neurosurgery Clinic of the Republic of Srpska University Clinical Center, Banja Luka, Bosnia and Herzegovina during the period from 1 January 2021 to 31 December 2021. About 1,170,000 inhabitants live in the region covered by the Republic of Srpska University Clinical Center, which is the reference institution (24). The inclusion criteria implied the patients suffering from TBI, Covid-19 negative. 174 patients whose epidemiological data and treatment outcome were analyzed were included in the study. The excluding criteria for early rehabilitation were: the patients who died during the first 5 days of being hospitalized ($n = 13$), length of stay $<$ 3 days ($n = 34$) and Covid-19 positive patients ($n = 0$). 20 patients died during early rehabilitation, so that the outcomes of early rehabilitation were analyzed with 107 patients (Figure 1).

We analyzed the following parameters: sex, age, mechanism and type of injury, number of surgical procedures, number of patients on mechanical ventilation, number of total days of hospitalization, outcome and implementation of early rehabilitation. The mentioned variables represent independent research variables. The kinesiotherapy implementation plan included positioning, an anti-decubitus program, passive and actively assisted exercises to maintain and increase the range of motion in all segments of the upper and lower extremities, as well as respiratory kinesiotherapy. Early rehabilitation began after stabilization of the patients, on the second day at the earliest, and on the tenth day after admission at the latest. It was conducted twice a day for 30 min, 7 days a week. Dependent variables relate to the outcome of the treatment measured by the

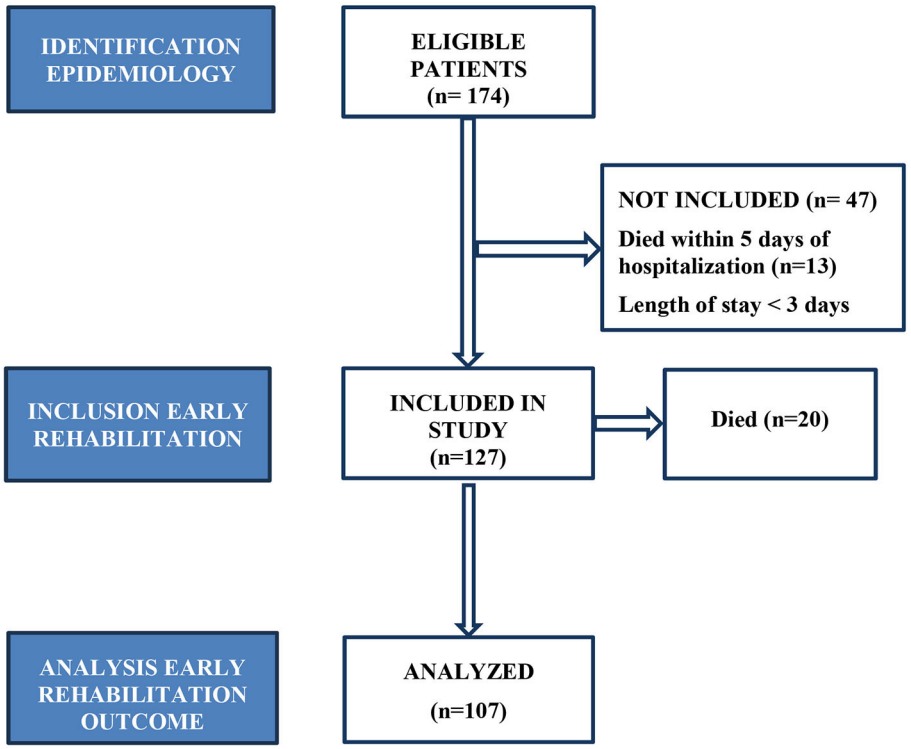

FIGURE 1
Flow diagram representing study design with inclusion and exclusion criteria.

following methods: Glasgow Coma Scale (GCS) on admission and discharge, Glasgow Outcome Scale (GOS) on discharge, Functional Independence Measurement (FIM) on admission and discharge, and Barthel's Index on admission and discharge. The GCS is a point-based pathophysiological score that determines the level of consciousness after a brain injury by assessing verbal and motor responses as well as eye opening. It is expressed in points, with the lowest score being 3, which indicates deep coma or death, and the highest being 15, which indicates that the central nervous system function of a patient has been preserved. Considering the total number of GCS, all brain injuries are divided into mild GCS (≥13), moderate (GCS 9–12) and severe (GCS< 9) (10). The Glasgow Outcome Scale (GOS) is used to assess disability after brain injury. Five outcome categories were distinguished: death, vegetative state, severe deficit, mild deficit and complete recovery (12). The functional independence index measures the motor and cognitive functioning of the patient, and includes 18 parameters for the assessment of physical, psychological and social functions. The parameters are divided into six groups: self-care, sphincter control, mobility, motor skills, communication and social cognition. Each of the 18 items is rated from 1 (complete assistance) to 7 (complete independence). The maximum number of points is 126 (complete independence), and the minimum number of points is 18 (complete dependence). According to the score, the patients are categorized into seven categories: 1. Full assistance, 2. Maximum assistance, 3. Medium assistance, 4. Minimal assistance, 5. Supervision, 6. Partial independence and 7. Complete independence (2). Barthel's Index serves to assess the functional status in the daily life activities. The Barthel Index assesses personal hygiene, bathing, toileting, climbing stairs, dressing, stool and urination control, transfer from chair to bed, mobility and wheelchair mobility. Based on the obtained results, the patients are assessed as completely independent (100), slightly dependent (91–99), moderately dependent (61–90), severely dependent (21–60) and completely dependent (0–20) (25, 26).

3. Statistical analysis

The incidence of individual groups, as well as their share in percentages was calculated for all independent research variables: gender, age (years), mechanism of injury, type of injury, surgery, mechanical ventilation, early rehabilitation, total hospitalization days, outcome. All listed independent variables are categorical: The Kolmogorov–Smirnov (K-S) test was used to test the normality of the distribution of numerical variables, while Skewness and Kurtosis were also used as the measures of distribution asymmetry, for the following variables: Barthel index at admission, Barthel index at discharge, FIM at admission, FIM at discharge, GCS at admission, GCS at discharge as well as GOS. The psychometric properties of the tests were examined, whereby Cronbach α was used to examine internal consistency. The value of the test $\alpha \geq 0.7$ is considered as the acceptable test reliability. Of descriptive indicators, median (Me) with interquartile range (IQR), arithmetic mean (M) with standard deviation (SD) as well as a range (Minimum - Maximum) were shown.

In order to determine whether there were statistically significant differences in the prominence of dependent variables, while taking into account the independent variables (gender, age categories, mechanism of injury, type of injury, surgical procedure, mechanical ventilation, early rehabilitation, number of hospitalization days and outcome), Student's *t*-test and ANOVA were used. Both tests are two-tailed tests for the possibility of an effect in two directions—positive and negative. Split-plot ANOVA (SPANOVA) was used to investigate the effects of independent variables on repeated measures. In other words, the influence of sex, age, mechanism of injury, type of injury, presence of surgeries, mechanical ventilation and early rehabilitation on the outcome of treatment was examined, measured by the Barthel scale, FIM and GCS. SPANOVA test was also used to test a separate recovery, i.e., the difference at the beginning and at the end of measuring of Barthel test, FIM and GCS. Wilks' λ and its statistical probability (p) were shown for the influence of the interaction of independent and dependent variable (e.g. whether the change of the result on Barthel test is equal for men and women). Partial η^2 was used to measure the size of the effect of independent variables on the change of the results at the beginning and at the end of measurement for the Barthel test, FIM and GCS. According to Cohen criterion, the influence can be small (Partial $\eta^2 = 0.01$), medium (Partial $\eta^2 = 0.06$) and large (Partial $\eta^2 = 0.14$). Wilks' λ is also an indicator of a separate influence of time, i.e. the difference at the beginning and at the end for the measured parameters. Correlations between numerical variables were tested by the Pearson correlation coefficient and displayed using a Scatter Plot. The level of statistical significance was set at $p < 0.001$. IBM SPSS Statistics version 25 was used for data analysis.

4. Results

A total of 174 patients with TBI were included in the research, of which 28.2% were female. A total of 4.6% of these patients were under 20 years of age, 14.9% were 21 to 40 years old, 26.4% of patients were 41 to 60 years old, while more than a half of the patients were over 60 years old (54.0%). Falling over was the cause of half of the TBI, or 50.6%. Subdural hematoma (SDH) was present in 38.5%, contusion in 35.6%, epidural hematoma (EDH) in 14.9%, subarachnoid hemorrhage (SAH) in 8.6%, while 2.3% of patients suffered from intracerebral hematoma (ICH). One third (33.3%) of patients with TBI during the COVID-19 pandemic underwent a surgery, while 20.7% of patients were on mechanical ventilation. According to the GCS, 92 (52.87%) had a mild brain injury, 52 (29.88%) had a moderate brain injury, and 30 (17.25%) had a severe brain injury. Due to the general condition of 127 (73.0%) patients early rehabilitation was possible. Improvement was recorded in 80.3% of patients, symptoms worsened with 1.2%, while death was recorded in 18.5% of patients. Worsening and improvement were defined based on the clinical condition of the patient at discharge. General data of these patients are shown in Table 1. Table 2 shows the differences in functional scores in the examined patient sample in relation to epidemiology, injury mechanism and treatment outcome.

TABLE 1 General data on patients with traumatic brain injury.

	$N = 174$
Gender	
Male	125 (71.8%)
Female	49 (28.2%)
Age (years)	
0–20	8 (4.6%)
21–40	26 (14.9%)
41–60	46 (26.4%)
>60	94 (54.0%)
Mechanism of injury	
Traffic trauma	23 (13.2%)
Fall	88 (50.6%)
Other cases	55 (31.6%)
No data	8 (4.6%)
Type of injury	
Contusion	62 (35.6%)
Epidural haematoma	26 (14.9%)
Subdural haematoma	67 (38.5%)
Subarachnoid hemorrhage	15 (8.6%)
Intracerebral haematoma	4 (2.3%)
Surgery	
Yes	58 (33.3%)
No	116 (66.7%)
Mechanical ventilation	
Yes	36 (20.7%)
No	138 (79.3%)
Early rehabilitation	
Yes	127 (73.0%)
No	47 (27.0%)
Total days of hospitalization	
0–3	34 (19.5%)
4–7	57 (32.8%)
8–10	31 (17.8%)
>11	52 (29.9%)
Outcome	
Improved	139 (80.3%)
Deceased	33 (18.5%)
Worsening	2 (1.2%)

Worsening and improvement were defined based on the clinical condition of the patient at discharge.

Descriptive statistics of all measured tests and the psychometric characteristics of the questionnaire, as well as the Kolmogorov-Smirnov test and Cronbach's α coefficient are

TABLE 2 Differences among the functional scores in patients with traumatic brain injury regarding the epidemiology, mechanism of injury and outcome of treatment.

	BA	BD	FIMA	FIMD	GCSA	GCSD	GOS
Gender (*p*-value)[a]	0.055	0.087	0.016	0.097	0.014	0.164	0.161
Male	50.9 (32.2)	83.1 (23)	60 (29.1)	101 (25.8)	9.3 (3.4)	13.8 (2.1)	1.6 (1)
Female	63.6 (24)	90.6 (5.4)	74.7 (22.9)	109.3 (10.2)	10.9 (1.3)	14.4 (1)	1.3 (0.6)
Age (years) (*p*-value)[b]	0.226	0.765	0.128	0.679	0.001	0.464	0.51
0–20	57 (29.5)	90.3 (4.6)	66.7 (25.3)	113.8 (2)	9.5 (3.3)	14.8 (0.4)	1 (0)
21–40	44.7 (36.4)	83.3 (23.4)	53 (30.4)	100.9 (27)	7.9 (4)	13.7 (2.3)	1.6 (1)
41–60	49.2 (32.3)	82.9 (23.1)	59.2 (29.8)	102 (25.5)	8.8 (3.3)	13.7 (2.1)	1.5 (0.9)
>60	60 (27.3)	86.5 (18.4)	69.8 (26.1)	103.5 (21.3)	10.8 (1.9)	14.2 (1.8)	1.5 (0.9)
Mechanism of injury (*p*-value)[b]	0.208	0.864	0.555	0.603	0.292	0.704	0.457
Traffic injury	56.3 (28.8)	89.8 (6.1)	65.8 (26.2)	114.7 (0.5)	9.3 (3.2)	14.8 (0.4)	1 (0)
Fall	59.1 (29.8)	85.6 (20.6)	66.8 (27.2)	102.3 (23.6)	10.1 (3)	14 (2)	1.6 (0.9)
Other causes	46.6 (29.9)	83.1 (22)	59.2 (29.4)	102.3 (24.4)	9.3 (2.6)	13.9 (2)	1.5 (0.9)
No data	40 (46.2)	87.5 (8.7)	54 (41.6)	108.8 (12.5)	7.5 (5.2)	14.3 (1.5)	1.3 (0.5)
Type of injury (*p*-value)[b]	0.007	<0.001*	0.009	0.002	<0.001*	0.002	0.032
Contusion	65 (24.3)	91.4 (5.9)	71.7 (24.5)	108.2 (11.6)	10.3 (2.7)	14.3 (1.1)	1.4 (0.7)
EDH	39.1 (35.4)	80.3 (27.5)	49 (29.2)	100.3 (29.8)	7.6 (3.8)	13.7 (2.4)	1.6 (1)
SDH	53.1 (29.6)	84.4 (19.3)	64 (28.1)	101.9 (22.7)	10.3 (2.3)	14 (1.9)	1.6 (0.9)
SAH	66.5 (24.7)	89.2 (11)	77.3 (22.6)	110 (15.8)	10.4 (2.8)	14.5 (1.6)	1.2 (0.6)
ICH	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Surgery (*p*-value)[a]	<0.001*	0.003	0.001	0.006	0.002	0.032	0.014
Yes	39.2 (31.8)	78 (26.3)	53.2 (30.4)	95.7 (29.5)	8.6 (3.7)	13.5 (2.5)	1.8 (1.1)
No	64.1 (25.6)	89.8 (13.1)	70.9 (24.5)	108.1 (15.8)	10.4 (2.3)	14.3 (1.4)	1.3 (0.7)
Mechanical ventilation (*p*-value)[a]	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Yes	14.3 (29.6)	66.4 (35.2)	28.7 (23.8)	80.2 (36.1)	5.9 (4.2)	12.2 (3)	2.4 (1.1)
No	63.5 (22.4)	89.4 (11.2)	72.1 (22.3)	108.6 (14.4)	10.6 (1.8)	14.4 (1.2)	1.3 (0.7)
Early rehabilitation (*p*-value)[a]	0.621	0.812	0.689	0.914	0.715	0.994	0.994
Yes	54.1 (30.8)	85.1 (20.3)	64.1 (28.4)	103.2 (23.1)	9.7 (3.1)	14 (1.9)	1.5 (0.9)
No	65 (14.1)	88.5 (5)	56 (22.6)	105 (14.1)	10.5 (0.7)	14 (1.4)	1.5 (0.7)
Total days of hospitalization (*p*-value)[b]	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
0–3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
4–7	65.9 (21.6)	91.4 (5.3)	72.7 (22.4)	110.8 (9.5)	10.8 (1.7)	14.6 (0.8)	1.2 (0.5)
8–10	62.2 (23.7)	90.4 (5.5)	73.9 (23.1)	110.8 (10)	10.4 (2.3)	14.6 (0.8)	1.2 (0.5)
>11	38.2 (35.1)	75.7 (29.6)	49.2 (30.4)	91.1 (31.5)	8.3 (3.9)	13 (2.6)	2 (1.1)
Outcome (*p*-value)[b]	0.541	0.001	0.958	<0.001*	0.549	0.002	0,001
Improved	54.1 (30.8)	86 (18.5)	63.9 (28.3)	104.3 (21.4)	9.7 (3.1)	14.1 (1.8)	1.5 (0.8)
Deceased	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Worsening	67.5 (17.7)	40 (56.6)	65 (35.4)	46.5 (40.3)	11 (1.4)	10 (2.8)	3.5 (0.7)

[a]Student's t-test was performed.

[b]ANOVA was performed.

EDH, epidural haematoma; SDH, subdural haematoma; SAH, subarachnoid hemorrhage; ICH, intracerebral haematoma. BA, Barthel admission; BD, Barthel discharge; FIMA, Functional Independence Measurement admission; FIMD, Functional Independence Measurement discharge; GCSA, Glasgow Coma Score admission; GCSD, Glasgow Coma Score Discharge; GOS, Glasgow Outcome Scale.

n/a, not applicable. The values were shown as Mean (Std. Deviation).

*Means statistically significant.

TABLE 3 Descriptive statistics and psychometric characteristics of the questionnaire.

Total scores	Min-Max	Me	IQR	M	SD	Skewness	Kurtosis	K-S	*p*	α
BA	0–80	60.00	25.00	54.32	30.59	−1.06	−0.51	0.284	<0.001*	0.732
BD	0–95	92.00	10.00	85.12	20.11	−3.61	12.98	0.315	<0.001*	0.718
FIMA	18–95	75.00	50.00	63.96	28.21	−0.74	−1.08	0.220	<0.001*	0.813
FIMD	18–120	115.00	20.00	103.25	22.90	−2.60	6.83	0.307	<0.001*	0.858
GCSA	3–15	11.00	2.00	9.69	2.96	−2.28	5.18	0.313	<0.001*	0.860
GCSD	7–15	15.00	1.00	13.96	1.87	8.51	83.56	0.452	<0.001*	0.893
GSO	1–4	1.00	1.00	1.50	0.87	1.59	1.38	0.419	<0.001*	0.776

Me, Median; IQR, Inter-quartile range; M, Mean; SD, Std. Deviation; K-S, Kolmogorov–Smirnov test; p, statistical significance; α, Cronbach's alpha; BA, Barthel admission; BD, Barthel discharge; FIMA, Functional Independence Measurement admission; FIMD, Functional Independence Measurement discharge; GCSA, Glasgow Coma Score admission; GCSD, Glasgow Coma Score Discharge; GOS, Glasgow Outcome Scale. *, statistically significant.

TABLE 4 Outcomes of early rehabilitation of patients with traumatic brain injury.

	Wilks' Lambda	*F*	Hypothesis df	Error df	*p*	Partial Eta^2
Barthel index	0.438	135.814	1	106	<0.001*	0.562
Barthel index × gender	0.993	0.779	1	105	0.379	0.007
Barthel index × age	0.971	1.015	3	103	0.389	0.029
Barthel index × mechanism of injury	0.957	1.547	3	103	0.207	0.043
Barthel index × type of injury	0.944	1.510	4	102	0.205	0.056
Barthel index × surgery	0.945	6.161	1	105	0.015	0.055
Barthel index × mechanical ventilation	0.858	17.328	1	105	<0.001*	0.142
Barthel index × early rehabilitation	0.999	0.144	1	105	0.705	0.001
FIM	0.280	271.955	1	106	<0.001*	0.720
FIM × gender	0.986	1.455	1	105	0.230	0.014
FIM × age	0.943	2.061	3	103	0.110	0.057
FIM × mechanism of injury	0.955	1.610	3	103	0.192	0.045
FIM × type of injury	0.917	2.309	4	102	0.063	0.083
FIM × surgery	0.988	1.229	1	105	0.270	0.012
FIM × mechanical ventilation	0.943	6.398	1	105	0.013	0.057
FIM × early rehabilitation	0.997	0.314	1	105	0.576	0.003
GCS	0.217	382.336	1	106	<0.001*	0.783
GCS × gender	0.958	4.577	1	105	0.035	0.042
GCS × age	0.807	8.200	3	103	<0.001*	0.193
GCS × mechanism of injury	0.916	3.163	3	103	0.028	0.084
GCS × type of injury	0.834	5.087	4	102	0.001	0.166
GCS × surgery	0.952	5.240	1	105	0.024	0.048
GCS × mechanical ventilation	0.822	22.740	1	105	<0.001*	0.178
GCS × early rehabilitation	0.998	0.236	1	105	0.628	0.002

F, F-test; p, statistical significance; FIM, Functional Independence Measurement; GCS, Glasgow Coma Score. *Means statistically significant.

shown in Table 3. We tested the normality of the distribution using the Kolmogorov-Smirnov test, since it is recommended to use it for large samples (≥50). Statistically-wise, the distribution of all variables deviates significantly from normal. All scales have high or very high reliability (0.718–0.893) Cronbach's α coefficient.

An improvement was found at discharge measured by Barthel's index in patients with TBI [Wilks' $\lambda = 0.438$, F (1.106) = 135.814, $p < 0.001$, Partial $\eta^2 = 0.562$]. η^2 accounts for 56.2% of the variance which is classified as a large effect. The influence of early rehabilitation on the value of the test was not recorded, and the same applied to sex, age, mechanism of injury and type of injury. The presence of surgery shows a statistically significant influence on the change in the value of Barthel's Index [Wilks' $\lambda = 0.945$, F (1.105) = 6.161, $p = 0.015$, Partial $\eta^2 = 0.055$], as well as mechanical ventilation [Wilks' $\lambda = 0.858$, F (1.105) = 17.328, $p < 0.001$, Partial $\eta^2 = 0.142$]. The size of the effect of surgery is medium (5.5% variance), and of mechanical ventilation high (14.2% variance). Patients who did not have surgery and who were not on mechanical ventilation had a higher score on the Barthel Index at discharge. The FIM is better at discharge M = 103.25 (22.90) than at admission [M = 63.96 (28.21), Wilks' $\lambda = 0.280$, F (1.106) = 271.955, $p < 0.001$, Partial $\eta^2 = 0.720$]. The size of effect of FIM is high (72.0% of variance). The value of the FIM test is influenced by mechanical ventilation [Wilks' $\lambda = 0.943$, F (1.105) = 6.398, $p = 0.013$, Partial $\eta^2 = 0.057$]. Mechanical ventilation has a medium effect size on FIM, i.e. it accounted for 5.7% FIM based on mechanical ventilation. Recovery measured by the FIM test is lower in patients who were on mechanical ventilation.

A total of 30 patients (17.24%) had a severe brain injury measured by the GCS. The outcome measured by the GCS is influenced by: gender [Wilks' $\lambda = 0.958$, F (1.105) = 4.577, $p = 0.035$, Partial $\eta^2 = 0.042$], age [Wilks' $\lambda = 0.807$, F (3.103) = 8.200, $p < 0.001$, Partial $\eta^2 = 0.193$], mechanism of injury [Wilks' $\lambda = 0.916$, F (3.103) = 3.163, $p = 0.028$, Partial $\eta^2 = 0.084$], type of injury [Wilks' $\lambda = 0.834$, F (4.102) = 5.087, $p = 0.001$, Partial $\eta^2 = 0.166$], surgery [Wilks' $\lambda = 0.952$, F (1.105) = 5.240, $p = 0.024$, Partial $\eta^2 = 0.048$] and mechanical ventilation [Wilks' $\lambda = 0.822$, F (1.105) = 22.740, $p < 0.001$, Partial $\eta^2 = 0.178$]. Age, mechanical ventilation, type of injury and mechanism of injury have a high impact on GCS, accounting for 19.3% of the variance, 17.8% of the variance, 16.6% of the variance and 8.4% of the variance of the dependent variable, in that sequence. Surgery, accounting for 4.8% of the variance and gender accounting for

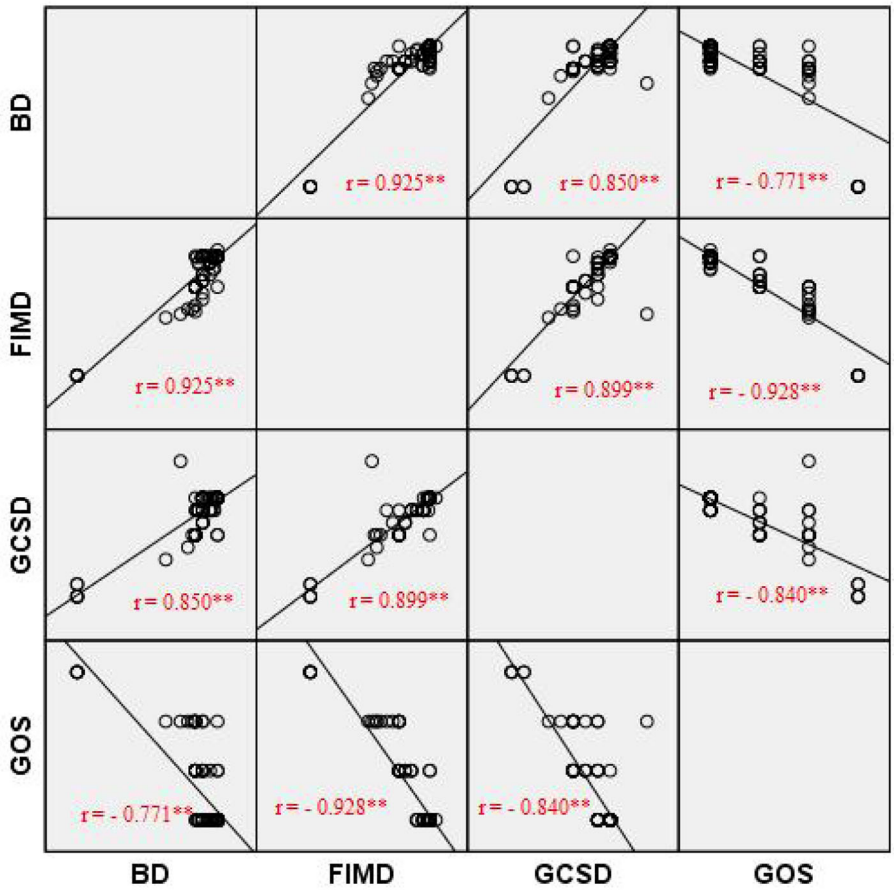

FIGURE 2
Graph representing correlation between GCS, GOS and Barthel Index. BA, Barthel admission; BD, Barthel discharge; FIMA, Functional Independence Measurement admission; FIMD, Functional Independence Measurement discharge; GCSA, Glasgow Coma Score admission; GCSD, Glasgow Coma Score Discharge; GOS, Glasgow Outcome Scale. Pearson Correlation was performed. **Correlation is significant at the 0.01 level (2-tailed).

4.2% of the variance of the dependent variable, have medium-sized impact on GCS. Better progress measured by measuring by GCS showed better progress in women, the youngest (0–20 years), then in patients whose injuries were caused by traffic trauma, then patients with SAH, and those who did not have surgery and were not on mechanical ventilation. As for the level of consciousness, the results on the GCS showed an improvement in the total sample at discharge compared to admission [Wilks' $\lambda = 0.217$, F (1.106) $= 382.336$, $p < 0.001$, Partial $\eta^2 = 0.562$]. The results are shown in Table 4.

Figure 2 shows the relationship between the outcomes studied (BD, FIMD, GCSD and GOS). All correlations are high. GOS negatively correlates with BD ($r = -0.771$, $p \leq 0.01$), FIMD ($r = -0.928$, $p \leq 0.01$), GCSD ($r = -0.849$, $p \leq 0.01$). All correlations between BD, FIMD and GCSD are very high, positive and statistically significant at the $p \leq 0.01$ level.

5. Discussion

The importance of the TBI problem is underestimated due to the lack of research and quality data. We conducted a retrospective study of the patients who sustained TBI and were treated at the Republic of Srpska University Clinical Center, Banja Luka, the largest tertiary center in the Republic of Srpska.

In our study, we determined with statistical significance that TBI had been more common in men 125 (71.8%). The mean age of the respondents was 57 ± 19.08. According to the age structure, TBI was most prevalent in the group of patients over 60 years of age, 94 (54%). The mean age was 33.4 ± 8.9 in the study by Dizdarević et al. and 29 years in a multi-center clinical research (22, 23). The age distribution of TBI in various studies showed that moderate and severe injuries mainly affected young men, most often due to a traffic trauma (27). Falling over is the most common cause of TBI, in 88 (50.6%) patients, and traffic trauma in 23 (13.2%) of patients. Based on the studies conducted for Bosnia and Herzegovina, the most common cause of TBI included traffic trauma and falls (53 vs. 28) (22). According to the multi-center study, violence (both blunt and penetrating) was considerably a more frequent cause of TBI in the low middle-income economies (12%) (23). Possible causes of falls as the leading mechanism of injury in our study included the following: social isolation, anxiety, alcoholism, lock-down, reduced use of public transport. Falling over by the elderly people can also be explained by lack of balance and coordination, poorer vision, the presence of comorbidities, as well as lower availability of the health system in terms of postponing check-ups in all areas.

Changes in the mechanism of TBI during the pandemic differ among countries and are most likely to reflect their socioeconomic status. For example, in Austria during the lockdown there were no TBI reported caused by skiing; at the same time an increased frequency of TBI due to traffic accidents was registered in New York (15, 21). In Italy, no differences in the TBI mechanism were found compared to the period before the pandemic (16). Despite restrictive measures to control the COVID-19 pandemic, the incidence of TBI remained high during the second wave of the pandemic.

In our research, it was determined that subdural hemorrhage was the most common injury, occurring in 67 (38.5%) patients, followed by brain contusion 62 (35.6%). Surgical intervention (craniotomy) was performed in 58 (33.3%) patients, which is less compared to the results of other studies (37–67%) (28). 36 (20.7%) patients required mechanical ventilation. According to the results of this study, surgery and mechanical ventilation are associated with a worse outcome, which is consistent with the results of other studies (29, 30). The average length of hospitalization was 10.86 days (1–61 days). The outcome of TBI was affected by the pandemic in a number of countries. Published studies most frequently investigated the incidence and severity of TBI, but only few studies have shown the impact of the COVID-19 pandemic on the outcome of TBI (31). Therefore, we can only partially compare the results of our study with any other research.

The incidence of moderate or severe TBI before and during the COVID-19 pandemic varies among studies. A large multi-center study by Grassner et al. concluded that the number of patients requiring neurosurgical intervention was lower during the pandemic compared to previous years (19). A recent meta-analysis found no significant differences in frequency of moderate and severe TBI before and during the pandemic (20).

With 139 (80.3%) patients the outcome was improved, deterioration occurred with 2 (1.2%) patients, while 33 (18.5%) patients died. Reported death rates from TBI vary widely. In the USA, mortality due to TBI was 17.1 per 100,000 people in 2010, while in China, mortality after TBI in 2013 was 13.0 per 100,000 people. Based on Eurostat data from 25 European countries, the mortality rate in 2012 was 11.7/100,000 people (95% CI 9.9–13.6), however ranging widely from 3.6 per 100,000 people in Turkey to 21.8 per 100,000 people in Switzerland (32). In the pre-pandemic period, mortality caused by TBI was 9–28.1/100,000 (12). In a multicentre study conducted in Bosnia and Herzegovina, the mortality from severe TBI was lower than expected: mortality in the ICU was 46%, and according to another study, mortality from severe TBI was 50% to 76.9%, depending on the mechanism of injury in the study by Dizdarević et al. (22, 23).

The mean value of GCS at admission was 9.9, and at discharge 14.1. According to the results of the multi-center study, the mean value of GCS at discharge from ICU was 9.6 (23). In the study conducted by Fan et al. higher GCS was measured in patients who underwent an early intensive rehabilitation program compared to the control group (33). A study by Hankemeier et al. showed that the GCS at discharge in the group of subjects undergoing early rehabilitation was significantly higher compared to the group that did not go through early rehabilitation (25). The mean value of the Barthel Index on admission was 57.25, and at discharge 86.85. In a study that included 623 patients, Hankemeier, et al. showed that a poor outcome was correlated with a Barthel Index of <50 (25). The average value of the FIM at admission was 67.35, and at discharge 105.15. The study by MacDonald et al. which included 5.582 patients with TBI in the period 2011–2016 showed an increase in FIM values during hospitalization and early rehabilitation of patients (34). Complete recovery at discharge measured by the GOS was reported for 111 (63.79%) patients, mild deficit for 15 (8.62%), severe deficit for 11 (6.32%), vegetative state for 4 (2.29) and death

for 33 (18.5%) patients. Steiner et al. found that early rehabilitation was associated with better recovery, based on the GOS (35).

The main advantage of our study is in the size of the sample. The analyzed data were from the relatively long period of COVID-19, which included lockdown and restrictions imposed on movement and social life. Compared to previous studies, we paid special attention to the impact of COVID-19 on the outcome of TBI treatment.

Nevertheless, this study also had some limitations. We conducted a retrospective study in one center. Our center covers approximately 30% of the population with mild TBI and about 90% with moderate and severe TBI. Therefore, we did not fully extend our results to the general population. Most cases of mild TBI were treated in other hospitals. On the other hand, all moderate and severe TBI were referred to our institution. We did not compare the results of early TBI rehabilitation with studies conducted in Bosnia and Herzegovina, because according to our knowledge, such studies have not yet been implemented.

6. Conclusion

COVID-19 has imposed many challenges for healthcare professionals in terms of treating TBI patients during the pandemic. According to the results of our study, the COVID-19 pandemic had a significant effect on the epidemiological data rather than on clinical outcome in patients with TBI, because throughout the pandemics, the patients with TBI continued being treated as the highest priority. Early rehabilitation proved to be effective and to contribute to the positive treatment outcome.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethical Board of University Clinical Center of The Republic of Srpska, Banja Luka, Bosnia and Herzegovina. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

NK: Conceptualization, Investigation, Methodology, Writing—original draft. RK: Conceptualization, Methodology, Supervision, Writing—review and editing. AM: Conceptualization, Methodology, Supervision, Writing—review and editing. DD-C: Methodology, Investigation, Supervision, Writing—review and editing.

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Brain changes: aerobic exercise for traumatic brain injury rehabilitation

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Introduction: Traumatic Brain Injury (TBI) accounts for millions of hospitalizations and deaths worldwide. Aerobic exercise is an easily implementable, non-pharmacological intervention to treat TBI, however, there are no clear guidelines for how to best implement aerobic exercise treatment for TBI survivors across age and injury severity.

Methods: We conducted a PRISMA-ScR to examine research on exercise interventions following TBI in children, youth and adults, spanning mild to severe TBI. Three electronic databases (PubMed, PsycInfo, and Web of Science) were searched systematically by two authors, using keywords delineated from "Traumatic Brain Injury," "Aerobic Exercise," and "Intervention."

Results: Of the 415 papers originally identified from the search terms, 54 papers met the inclusion criteria and were included in this review. The papers were first grouped by participants' injury severity, and subdivided based on age at intervention, and time since injury where appropriate.

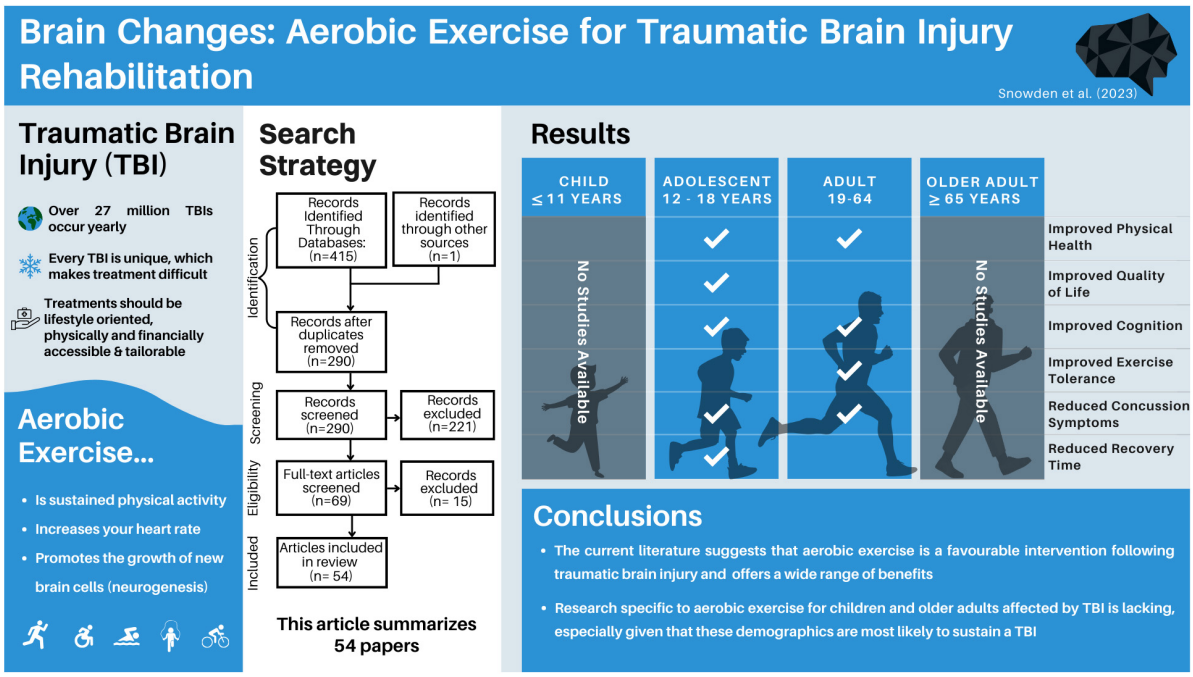
Discussion: Aerobic exercise is a promising intervention for adolescent and adult TBI survivors, regardless of injury severity. However, research examining the benefits of post-injury aerobic exercise for children and older adults is lacking.

KEYWORDS

traumatic brain injury, aerobic exercise, TBI intervention, aerobic intervention, concussion

1 Introduction

Traumatic brain injuries are a global health issue, with more than 27 million treated injuries being reported yearly (James et al., 2019). To put this figure in context, the number of reported head injuries is greater than the entire population of some countries, like Australia (25.69 million) (Australian Bureau of Statistics, 2023). Despite this being a global health issue, treating individuals with traumatic brain injury (TBI) remains challenging. TBIs are often



GRAPHICAL ABSTRACT
A graphical representation of the study design and findings.

called snowflake injuries due to their unique etiology, severity, affected population, and the burden they place on families and the health care system in any country. Given how unique each TBI can be, finding the best course of treatment for individuals remains challenging. Ideal treatments should be lifestyle oriented, physically and financially accessible, tailorable, and easily implementable. While aerobic exercise may meet many of these criteria, it is currently unknown how effective it is as a treatment for TBI across age and injury severity.

Aerobic exercise can be defined as low-to-vigorous-intensity, repetitive physical exercise performed for extended periods, that produce an elevation in heart rate. The term "aerobic" highlights how the body uses oxygen to meet energy requirements through aerobic metabolism (McArdle et al., 2006; Plowman and Smith, 2007). Both subjective measures (relative perceived exertion, talk tests) and objective measures (heart rates, oxygen intake/output) are common ways of assessing an aerobic exercise prescription, with the gold standard being a maximal oxygen consumption test (Lee and Zhang, 2021). The current Government of Canada recommends that healthy adults aged 18–64 get at least 2.5 h per week of physical activity, focusing on aerobic activity in 10 + min sessions (Government of Canada, 2018). While these guidelines are helpful for general fitness, very few standardized recommendations exist for aerobic exercise following TBI, and most of the graded recommendations are based on mild TBI (Parachute, 2017).

It is worth exploring aerobic exercise as a rehabilitation method for brain injury for a number of reasons. First, it promotes physical health, and cardiovascular fitness. Additionally, it has been shown to promote cognitive and mental health (Ruegsegger and Booth, 2018), both of which can be impacted by TBI (Langlois et al., 2006; Haarbauer-Krupa et al., 2021). Aerobic exercise is a potentiator of neuroplasticity, the brain's ability to rewire, reorganize and form new neural connections. In animal models, it has been extensively studied as a means to stimulate neurogenesis, the brain's ability to form and integrate new neurons (van Praag et al., 1999; Farmer et al., 2004; Nokia et al., 2016). It has been shown to improve cognitive functions commonly impacted by TBI, including improving attention, memory and processing speed in children and adults (Khan and Hillman, 2014; Young et al., 2015), as well as reducing levels of depression and anxiety (Carek et al., 2011). Given that TBI-survivors have a higher likelihood of poverty (Young and Hughes, 2020) and disability (Hyder et al., 2007), the low cost and adaptable nature of aerobic exercise makes it an appealing therapeutic option.

An important consideration for brain injury interventions is that TBI outcomes can differ depending on the age at which the injury was sustained. Children are more likely to show initial improvements, only to later have disrupted brain development leading to cognitive and behavioral issues that manifest over time, potentially impacting academic performance and social relationships (Anderson et al., 2009). Adolescent children aged 12 to 17 may have a more complicated TBI experience, as this is a period of complex cognitive, hormonal and physical growth. For example, studies focused on TBI in adolescents have observed significant risks of further mental and physical health challenges (Ilie et al., 2014) and impaired socially adapted decision capacity, compared to non-brain-injured peers (Beauchamp et al., 2019). For adults, especially as they reach middle-to-older age, post-TBI challenges can span from difficulties with the return to work, early cognitive decline, and slowed recovery timelines (Rabinowitz et al., 2021). Despite these complexities, developing brains tend to have greater

neuroplastic potential, and may be more receptive to post-injury intervention. Given these age-associated TBI outcomes and risks, it is essential to consider the affected individual's age, as the injury's implications and recovery trajectories differ across age groups.

Previous systematic review papers on the effects of aerobic exercise following traumatic brain injury have been limited by focusing on the severity of injury [i.e., concussion (Howell et al., 2019; Langevin et al., 2020)] or specific outcome measures [i.e., quality of life (O'Carroll et al., 2020) and cognition (McDonnell et al., 2011)]. To better understand how aerobic exercise may be used as a treatment following TBI, this systematic scoping review aims to encapsulate the literature examining aerobic exercise-based interventions following TBI, separated by injury severity and age. Given the diversities of the injury and the intervention, a scoping review was deemed an appropriate methodology to synthesize the vast body of evidence in this field. The aim is to present a comprehensive review of the literature on aerobic exercise as a post-TBI intervention, in order to better determine what interventions are supported and which areas require more investigation.

2 Methods

2.1 Registration

This scoping review was conducted in accordance with the Preferred Reporting for Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) (Tricco et al., 2018) and was guided using pre-determined frameworks for scoping reviews (Arksey and O'Malley, 2005; Levac et al., 2010; Tricco et al., 2018). An overview of this framework includes: identifying the research question, relevant studies, study selection, data extraction/data charting, and summarizing and presenting the results. This review's objectives, eligibility criteria, preliminary study characteristics, and indicator papers were determined before starting the study. In accordance with PRISMA-ScR, the protocol was not registered; however, is available by request.

2.2 Research question

What is the evidence surrounding aerobic exercise to improve cognitive, mental and physical health following all severities of traumatic brain injury in children, adolescents and adults?

2.3 Eligibility criteria

Inclusion and exclusion criteria were determined *a priori* and selected to capture focused results related to the research question (**Supplementary Table 1**).

2.4 Information sources

Three databases (i.e., Web of Science, PubMed, PsychInfo) were selected as digital search engines for this review paper. These databases were selected based on their missions to deliver quality clinical and medical materials. The first search occurred on May 01, 2023, and a final search was conducted on August 01, 2023. Two authors (TS and JM) conducted these searches individually and compared search results to ensure the reliability of the search terms.

2.5 Search

To identify eligible articles, four search term blocks were used (**Supplementary Table 2**). Four search blocks were used, each to assist in finding related articles: Traumatic Brain Injury, Aerobic Exercise, Intervention, Review. The first three blocks used AND modifiers between, while the fourth block used a NOT modifier to reduce the number of review papers included in the search results.

2.6 Selection of sources of evidence

The first and second authors individually exported the results into Zotero citations manager for screening and selection. To start, duplicate titles were removed, then titles and abstracts were screened for initial eligibility. The remaining papers were read in entirety, and full eligibility was assessed, as determined by the *a priori* inclusion criteria. The first and second author compared their final papers for inclusion, and any discrepancies were resolved by consensus. The number of papers at each step is available in **Figure 1**.

2.7 Data charting

Data charting was split between team members (TS, JM, MB, EE, CA, EG, HR, JB), and overseen and confirmed by TS and JM. Google Sheets was used to chart data, and specific variables of interest were identified before data charting. In addition to the standard variables (e.g., type of study, participant demographics, time since injury, intervention details), a notes and considerations section was added such that the charter was able to make note of anything pertinent in the study that was not immediately captured in the primary data charts. The results tables are simplified versions of the complete data charting used in this review.

2.8 Data items

The specific data items and rationale used in the data charting can be found in **Supplementary Table 3**.

2.9 Synthesis of results

Following the data charting, TS reviewed all charting and papers to ensure their alignment with the goals of the paper. While data charters made notes about considerations for each study, the authors did not conduct any formal critical appraisals or

bias scoring in alignment with PRISMA-ScR protocols. However, should this scoping review inspire systematic reviews, the authors encourage including bias scoring or other critical metrics of the included data. Upon completion of data charting, papers were grouped based on participant age and severity of TBI, and a narrative summary was composed.

3 Results

3.1 Selection of sources as evidence

The first and second authors individually searched Web of Science, PubMed and PsychInfo databases, and found a total of 415 articles. After removing duplicate items, 290 articles were screened. After screening the title and abstract of each paper, 69 papers remained for full-text reading. Of the 69 papers, five were excluded due to wrong injury type, eight were excluded for not including an aerobic intervention, one was excluded as it did not contain primary research data, and one was excluded for not including any health-related outcome measures, leaving 54 papers in this review (Figure 1).

3.2 Characteristics of sources of evidence

Of the included articles, three overarching research designs emerged, including case series, randomized controlled trials, and non-randomized pre-post intervention studies. All citations were presented as primary, peer-reviewed articles, as defined in the inclusion and exclusion criteria. In studies encompassing multiple pre-defined age groups, the results were reported separately within each respective category if separate age-based analyses were conducted. However, if the age groups were combined, the study findings would be reported based on the category that corresponds to the mean age of the participants. Therefore, while thirty-four of the studies included adults (aged 18 +), 23 included adolescents (aged 12–17, inclusive), and five included children under 12, the main grouping of TBI severity could only be sub-sectioned into

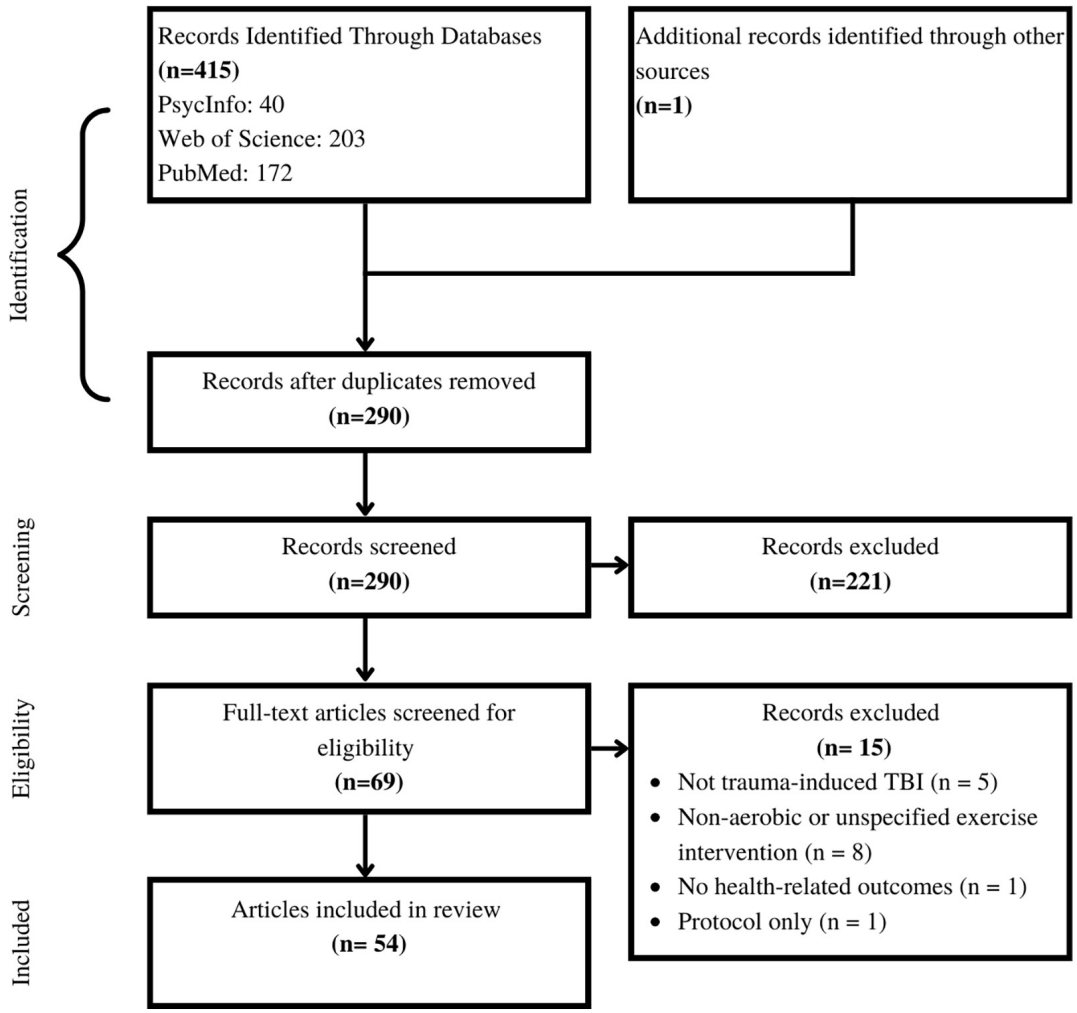


FIGURE 1
Selection of sources of evidence. The authors started with 415 papers. Following systematic duplication removal, screening, and eligibility assessment 54 papers were included in this review.

adults (n = 32) and adolescents (n = 22), given that all studies reported a mean age above 12.

3.3 Results of individuals sources of evidence

The following sections are divided by reported severity of injury (severe, mixed, mild, unspecified) and further subdivided by reported age group (adult, adolescent). Studies with similar outcome measures (mental health, physical health, cognitive health) are presented within these subcategories. **Figure 2** provides an overview of the selected included articles.

3.4 Severe brain injury

Six of the included studies exclusively studied individuals with severe brain injuries. Five papers examined adults (Hassett et al., 2009; Corral et al., 2014; Chanpimol et al., 2017; Curcio et al., 2020; Wender et al., 2021), while one presented a case report on an adolescent female (Tiwari et al., 2018). Full results are presented in **Table 1**.

3.4.1 Adults

All studies included at least two time points (pre- and post-interventions). In most cases, individuals were adults when they sustained their TBI, with time since injury ranging across studies from unspecified inpatient admissions (Hassett et al., 2009) to 27 years post injury (Wender et al., 2021), however, most interventions occurred within 1–2 years post-injury. Intervention timelines ranged from 4-weeks to 12-weeks, typically 3 times per week for 30–60 min. Engagement in aerobic activity varied between studies; two used recumbent cycling for their aerobic component (Corral et al., 2014; Wender et al., 2021), one used a virtual reality platform (Chanpimol et al., 2017), one used aquatic therapy (Curcio et al., 2020), and the last used walking and jogging (Hassett et al., 2009). All studies were conducted in a clinic or otherwise supervised setting, and Hassett et al. (2009) also included a home-based exercise group.

Outcomes of interest across these studies included fitness, balance, quality of life, mental health, as well as brain structure and functions. Hassett et al. (2009), Corral et al. (2014), and Chanpimol et al. (2017) all observed improvements in measures of cardiovascular fitness across their interventions. Curcio et al. (2020) observed improvements in multiple measures of balance, and quality of life, while Wender et al. (2021) found large effects of exercise on measures of verbal memory and processing speed as compared to a stretching/toning control group. Additionally, Wender et al. (2021) reported greater increases in left hippocampal and right thalamic volumes, however this study included 2–3 individuals per group.

Some considerations of these studies include the limited definitions of aerobic or cardiovascular activity; only two studies included target heart rate or effort zones (Corral et al., 2014; Wender et al., 2021). Only one study included a home-based intervention and found decreased adherence in that group compared to clinic-based interventions. It is also important to consider the sample sizes in terms of adequate power and statistical analyses.

3.4.2 Adolescents

One case report examined the effects of aerobic exercise on a 17-year-old female who sustained their TBI in adolescence (2 years post-injury) (Tiwari et al., 2018). The home-based intervention

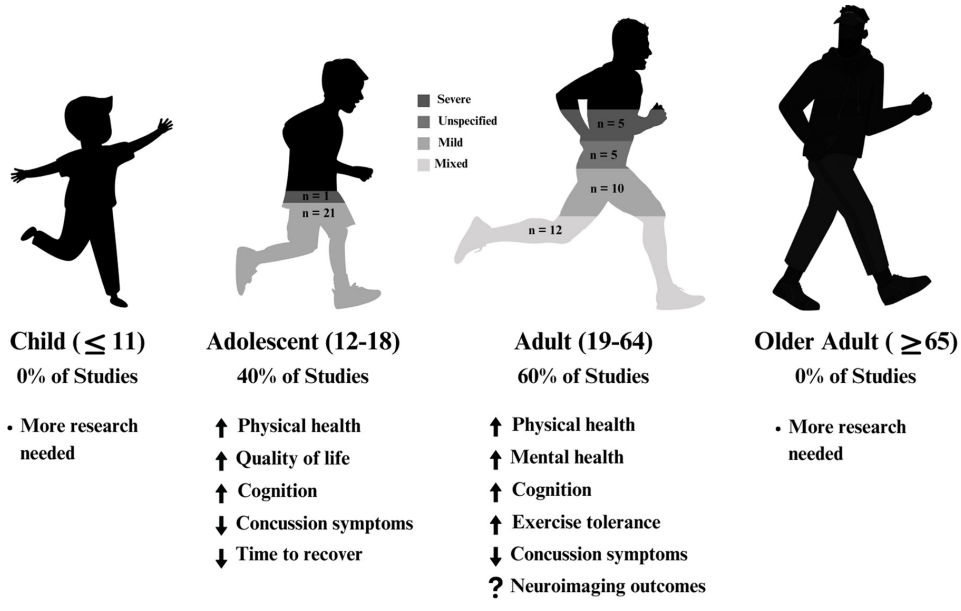


FIGURE 2
A summary of results across age within the included articles. A majority of studies focussed on adults (aged 19–64), and the remaining studies focussed on adolescents (aged 12–18). 57% of studies solely examined mild traumatic brain injury.

TABLE 1 Summary of the effects of aerobic exercise intervention following severe traumatic brain injury.

Refe-rences	Study Design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Interven-tion location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Chanpimol et al., 2017	Case series	To evaluate the effects of a Kinect-based virtual reality (VR) intervention using commercially available motion capture games on balance outcomes for an individual with chronic TBI and to assess the feasibility of this intervention for eliciting cardiovascular adaptations	$n = 1$; adult aged 37; male	11 years	2x sessions for 50–60 min per week for 8 weeks	VR training would consist of mini games which would adress domains of dynamic balance, static balance, and cardiovascular fitness that were appropriate for the participant based on clinical judgment. Rest breaks were allowed as required.	Clinic-based	Mini supervised VR games to challenge cardiovascular systems	The single participant completed the intervention	Balance; cardiovascular health	Dynamic Gait Index (DGI), Functional Reach Test (FRT), Limits of stability (LOS) test, resting HR (RHR); HR at end (HRe)	Significant decline in HR at end and time in training range with an increase in total activity time; improved dynamic balance
Corral et al., 2014	Pre-post intervention study	To determine if exercise in people with TBI can increase circulating progenitor cells and if there are any accompanying physical or psychological benefits of such intervention.	Exercise electro-stimulation group: $n = 5$; cycling program group: $n = 5$; adults aged 35 ± 7; males	At least 1 year	Exercise electro-stimulation group: 3 sessions per week for approximately 8 weeks; cycling program: 3 days per week for 12 weeks	Exercise electro-stimulation group intervention was not defined. Cycling program: warm up with 5 min of abdominal work and cycling until reaching 60% of maximum workload, followed by 3 × 12 min of interval work at 60–80% max workload, 3 min of active recovery at 60%, ending with gently cycling for 5 min and stretching.	Exercise electro-stimulation group: University Exercise Physiology Unit (3 sessions/week) and at home (2 sessions/week); cycling group: not specified	Exercise electro-stimulation group: not specified, but participants engaged in endurance, resistance, and proprioceptive exercises; cycling program: cycling, with a focus on endurance	2/5 participants completed the exercise electro-stimulation group; 5/5 participants completed the cycling group; 5/6 participants completed the intermittent hypobaric-hypoxia and muscle electro-stimulation group; 4/5 participants completed the control group	Aerobic capacity; circulating progenitor cell levels; physical stress; psychological stress	VO2 uptake; CDC34 + quantification in peripheral blood by staining and flow cytometry assay; Verbal Memory-RAVLT; Trail Making Test (TMT A and B); Stroop Test; Wechsler Adult Intelligence Scale (WAIS III); Tower of London tests; Reduced Paced Auditory Serial Addition Test (PASAT-G);	Exercise electro-stimulation group: improved aerobic capacity and increased circulating progenitor cell levels in peripheral blood in the last 3 weeks of intervention; cycling group: PASAT-G test improvement and significant increase in VO2 uptake

(Continued)

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TABLE 1 (Continued)

References	Study Design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Curcio et al., 2020	RCT	To examine the effects of aquatic training on balance, gait, activities of daily living, and quality of life in severe TBI survivors	Aquatic intervention: $n = 10$; adults aged 37.4 ± 15.3; males and females; land control: $n = 10$; adults aged 43.0 ± 14.1; males and females	Acquatic intervention: 5.8 ± 2.6 months; land control: 4.8 ± 2.7 months	3×45 min sessions per week for 4 weeks	In the pool, participants did a warm up for 5 min consisting of breathing exercises and arm movements, followed by 20 min of a repetitive exercise sequence, and 20 min of step exercises.	Rehabilitation hospital	Acquatic therapy	22 participants initially; 2 dropped out (1 from intervention group and 1 from control group) before assessment	Balance (main outcome measure); disability; gait; quality of life; spasticity	Berg balance scale (BBS); modified Barthel index (MBI); Disability Rating Scale (DRS); Tinetti Gait Balance Scale (TBG); Quality of Life After Brain Injury (QOLIBRI); Modified Ashworth Scale (MAS)	Significantly increased scores for BBS, MBI, BBG, and QOLIBRI after intervention compared to baseline

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TABLE 1 (Continued)

References	Study Design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Hassett et al., 2009	RCT	To compare the effects of supervised fitness center-based exercise with unsupervised home-based exercise on cardiorespiratory fitness and psychosocial functioning in people with TBI	Fitness center group: $n = 32$; adults aged 35.4 ± 14.6; home-based group: $n = 30$; adults aged 33 ± 11.8	Not reported; but participants recruited from inpatient admissions	3×1 h sessions per week for 12 weeks	5 min warm up; 20 min strength training for 6 muscle groups (quadriceps, plantar flexors, abdominals, pectorals, triceps, back extensors) 2 sets of 15 reps or 3 sets of 10 reps (total 180 reps); 30 min continuous cardiorespiratory fitness training that was symptom limited and moderate intensity (breathing hard but able to talk); 5 min cool down; walking/jogging exercise for at least 1 fitness session per week.	Fitness center and home-based	Walking or jogging	Adherence defined as $\geq$36 sessions over 12 weeks; better adherence in fitness center group (72 SD 25) vs. home-based 44 SD 42 (higher percentage of completed sessions)	Cardiorespiratory fitness; psychosocial functioning	Primary physical: maximal velocity; distance; peak HR; % HR max; secondary physical: BMI; waist to hip ratio (WHR); waist circumference; goal attainment: #goals set; %goals achieved; psychological: depression; anxiety; stress; vigor; tension-anxiety; depression-dejection; anger-hostility; fatigue; confusion-bewilderment. Outcomes measured at baseline; at completion of intervention; and 3 months-post intervention using modified 20-m shuttle test (walk/jog along 20-m track with increasing speed).	Both groups improved in fitness as measured by distance and velocity; no differences between fitness center and home-based groups; no differences in psychosocial functioning; both interventions equally effective at improving cardiorespiratory fitness

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TABLE 1 (Continued)

Refe-rences	Study Design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Interven-tion location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Tiwari et al., 2018	Case series	To examine the effects of home based circuit training on gait, energy expenditure, and functional performance following TBI	$n = 1$; adolescent aged 17; female	2 years	35 min sessions 4x per week for 4 weeks	5 min warm up; 30 min circuit training; 10 exercises, 10 reps each in 1 circuit. Repeat in same order for 30 min; number of circuits performed progressed over the 4 weeks; Exercises (in order performed): lateral walking with elastic resistance bands, lunges, lateral lunge, sideways walking with squats, sit to stand transitions from a chair, squats, tall kneeling with arm raises, tall kneeling proprioceptive neuromuscular facilitation D-2 pattern, marching, hamstring and calf stretches	Home-based	Circuit training	100%	Balance; mobility; strength	6-Min Walk Test (6MWT); physiological cost index (PCI = HR walking-HR resting/walking speed); gait speed (meters/second); Canadian Occupational Performance Measure (COPM) performance score and satisfaction score	Improved distance in 6MWT; increased PCI score; decreased resting HR; improved gait speed; improved COPM; improved COPM satisfaction suggesting improved self-perception of occupational performance

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TABLE 1 (Continued)

Refe-rences	Study Design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Interven-tion location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Wender et al., 2021	RCT	To determine the feasibility of an aerobic exercise intervention for severe TBI survivors, and assess how aerobic exercise impacts neuropsychological function and brain structure	Exercise: $n = 2$; active control: $n = 3$; adults aged 27–49; males and females	1–27 years	3 × 30 min sessions for 12 weeks	TBI participants were randomly assigned to an aerobic exercise (recumbent cycling) or active control (stretching) group. The aerobic exercise group maintained at least 60% of their maximal HR during the sessions.	Clinic-based	Recumbent cycling	100%	Cardiorespi-ratory fitness; magnetic resonance Imaging; neuropsy-chological testing	Rey Auditory Verbal Learning Test; Symbol Digit Modalities Test; hippocampal and thalamic brain volume; peak oxygen consumption using the incremental exercise test	No between group differences on any measure; large effects of exercise were observed on the RAVLT and SDMT; exercise condition was associated with larger increases in left hippocampal and right thalamus volumes

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included 4 × 35-min weekly sessions, for 4 weeks. This circuit-style intervention included a mixture of resistance exercises and cardiovascular training. Similar to adults with severe TBIs, researchers found improved cardiovascular health, quality of life, and increased gait speed.

3.5 Mixed injury severity

Twelve studies included mixed severities of mild, moderate and/or severe in their aerobic intervention studies (Bhambhani et al., 2005; Brown et al., 2005; Schwandt et al., 2012; Wise et al., 2012; Bellon et al., 2015; Chin et al., 2015, 2019; Weinstein et al., 2017; Morris et al., 2018; Ding et al., 2021; Romanov et al., 2021; Tomoto et al., 2022), all of which reported on adults aged 18–65. Full results can be found in **Table 2**.

3.5.1 Adults

Eleven of twelve studies employed aerobic interventions at chronic time points post-injury, ranging from 6 months to 23 years (Bhambhani et al., 2005; Brown et al., 2005; Schwandt et al., 2012; Wise et al., 2012; Bellon et al., 2015; Chin et al., 2015, 2019; Weinstein et al., 2017; Ding et al., 2021; Romanov et al., 2021; Tomoto et al., 2022), while one study looked at individuals within 3 months of injury (Morris et al., 2018). Intervention timelines ranged between 4 to 14 weeks, with a minimum of two 15-min weekly sessions (Brown et al., 2005), and a maximum of daily activity (Bellon et al., 2015). Most studies employed supervised interventions, with only three involving a home-based component (Wise et al., 2012; Bellon et al., 2015; Ding et al., 2021). Half of the studies used walking or jogging as the aerobic intervention, typically done on a treadmill (Brown et al., 2005; Bellon et al., 2015; Chin et al., 2015, 2019; Weinstein et al., 2017; Romanov et al., 2021). Depending on the study and participant abilities, some interventions offered physical supports (i.e., walking poles, weight assistance). The other half of the studies used multiple types of exercise or allowed participants to choose their aerobic activity based on abilities and preferences (Bhambhani et al., 2005; Schwandt et al., 2012; Wise et al., 2012; Morris et al., 2018; Ding et al., 2021; Tomoto et al., 2022). Nine of twelve studies tracked participants' heart rates to ensure aerobic zone adherence, all of which aimed for 60–80% of participants' maximal heart rates.

Outcomes of interest varied between studies and included measures of mental health, physical health and abilities, cognition, quality of life, carotid arterial compliance, and feasibility of intervention. Eight studies included at least one measure of physical health or ability, all of which reported improvements across their respective interventions, most commonly improvements in VO2 max and heart rates (Bhambhani et al., 2005; Brown et al., 2005; Schwandt et al., 2012; Chin et al., 2015, 2019; Romanov et al., 2021; Tomoto et al., 2022). Six studies included measures related to mental health, with a majority (5/6) reporting improvements in their study-specific measures of stress, depression, quality of life and mood (Schwandt et al., 2012; Wise et al., 2012; Bellon et al., 2015; Weinstein et al., 2017; Chin et al., 2019; Ding et al., 2021). Of note, some studies used self-report for these metrics, while others used standardized inventories (see **Table 2**). Three studies included cognition-related measures, with Chin et al. (2015) reporting improvements in working memory performance and Romanov et al. (2021) finding improvements in attention. However, Chin et al. (2015) found no changes in cognitive performance across various other cognitive measures from pre- to post-intervention.

These studies should be reviewed with several considerations. First, it is hard to extrapolate if different effects of intervention would be observed if the studies focused on one severity of brain injury, given the heterogenous needs of adults with mild TBI compared to severe TBI. Many studies in this group were pilot studies, and were likely underpowered (Bhambhani et al., 2005; Brown et al., 2005; Schwandt et al., 2012; Chin et al., 2015, 2019; Weinstein et al., 2017; Morris et al., 2018; Ding et al., 2021; Tomoto et al., 2022), requiring follow-up with full studies. Further, several studies did not include control groups at all timepoints (Schwandt et al., 2012; Wise et al., 2012; Bellon et al., 2015; Chin et al., 2015; 2019; Weinstein et al., 2017; Morris et al., 2018; Ding et al., 2021). Intervention adherence also seemed to be a challenge, with adherence rates near 50% in two studies (Bhambhani et al., 2005; Bellon et al., 2015).

3.6 Mild brain injury

Ten studies specifically looked at aerobic interventions post-concussion in adults (Leddy et al., 2010; Leddy and Willer, 2013; Polak et al., 2015; Clausen et al., 2016; Adams and Moore, 2017; Dobney et al., 2017; Snyder et al., 2021; Varner et al., 2021; Hutchison et al., 2022; Langevin et al., 2022), and 21 studies focused on adolescents (Gagnon et al., 2016; Imhoff et al., 2016; Chrisman et al., 2017, 2021; Kurowski et al., 2017; Yuan et al., 2017; Chan et al., 2018; Hunt et al., 2018; McGeown et al., 2018; Micay et al., 2018; Bailey et al., 2019; Gladstone et al., 2019; Leddy et al., 2019a,b, 2021; Willer et al., 2019; Dobney et al., 2020; Howell et al., 2021, 2022; Chizuk et al., 2022; Shore et al., 2022). Results for adults are presented in **Table 3**.

3.6.1 Adults

Individuals were adults when they sustained their TBIs, with time since injury ranging from 48 h to 2.7 years. Five studies had set intervention lengths (ranging from 1 to 12 weeks), whereas the other studies took an individualized approach to the aerobic intervention duration. The type of aerobic modality performed was only specified in five of the ten studies. Aerobic modalities included recumbent cycling, elliptical and treadmill (Polak et al., 2015; Adams and Moore, 2017; Dobney et al., 2017; Snyder et al., 2021). Participants were assigned a target heart rate in eight of the ten studies, which ranged from 60–80% of maximum. Involvement of a home-based intervention was present in over half of the studies (6/10) (Leddy et al., 2013; Polak et al., 2015; Adams and Moore, 2017; Dobney et al., 2017; Varner et al., 2021; Hutchison et al., 2022), and the majority of studies included supervision throughout the interventions.

All ten studies examined concussion symptoms as an outcome measure. Other outcome measures varied between studies and included return to activity, exercise tolerance, cervical range of motion, head/neck questionnaires, diffusion tensor imaging, cognition, fMRI activity, sleep, and postural stability. Post-concussion symptoms were reduced following aerobic intervention

TABLE 2 Summary of the effects of aerobic exercise intervention following mixed-severity traumatic brain injury.

References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Bellon et al., 2015	RCT	To determine the efficacy of a 12-week walking program for TBI survivors	$n = 69$; adults aged 43.7 ± 15.8; males and females	Mild $n = 10$; moderate $n = 10$; severe $n = 35$; unknown $n = 13$	Mean 100.5 ± 119.9 months	Daily walking for 12 weeks	Participants were given pedometers to count steps. Participants completed a 1-week baseline to establish a baseline step count. Participants were encouraged to increase their weekly steps by 5% each week, until they reached a 40% increase at week 8, and maintained that level for the remaining 4 weeks.	Home-based	Walking	Not reported, but of 123 enrolled participants, 69 completed all three time-points (baseline, 12-, 24-weeks).	Perceived depression; perceived stress	Perceived Stress Scale; Centre for Epidemiological Studies-Depression	Increased walking over 12-weeks; reduced depressive symptoms; reduced perceived stress
Bhambhani et al., 2005	Pre-post intervention study	To examine time course of body composition and cardiovascular changes following routine TBI rehabilitation and circuit training	$n = 14$; adults aged 18–52; males and females	Moderate and severe TBI	17.2 ± 17 months	3x circuit training sessions per week for 12 weeks	Each session included 5–10 min warm up, followed by 45 min of circuit training (15–20 min of cycling, arm cranking or treadmill walking, 15–20 min of resistance training, 5 min cool down). Participants aimed to keep their HR at 60% of their HRR.	Clinic-based	Recumbent cycling, arm cranking, treadmill walking	Not reported, but of 26 enrolled participants, 14 completed the circuit program and 5 test trials.	Body composition; peak cardiorespiratory response	Body Mass Index;% Body Fat; Basal Metabolic Rate; Echocardiogram	No significant changes on body composition; improved cardiorespiratory response (peak power, oxygen uptake and ventilation rate)

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TABLE 2 (Continued)

Refe-rences	Study design	Aim/ objective	Participant details	TBI demo-graphics	Time since injury	Interven-tion timeline	Intervention details	Interven-tion location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Brown et al., 2005	RCT	To compare body weight support treadmill training to conventional over ground gait training	*n* = 20; adults aged 20–57; males and females	Moderate and severe TBI	7–23 years	2x body weight support treadmill training for 15 min per week for 14 weeks	Starting speed was the fastest participants could handle and was increased as tolerated over the course of 3 months. If a rest was needed, the clock was stopped and continued when participants resumed.	Residential rehabilitation center	Body weight supported treadmill training	Not reported	Walking and stepping ability	Functional Ambulation Category; functional reach; Timed Up and Go; gait velocity; step width; step length differential using instrumented gait mat	Increased walking for both training; significant improvement in step length differential for conventional over ground gait training

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TABLE 2 (Continued)

References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Chin et al., 2015	Pre-post intervention study	To examine cognitive function in individuals with TBI prior to and after participation in an aerobic exercise training program	$n = 7$; adults aged 33.3 ± 7.9; males and females	Chronic, non-penetrating; mild $n = 4$; moderate $n = 3$; $n = 5$ injuries due to falls	4.0 ± 5.5 years	3×30 min per session of a vigorous intensity exercise on treadmill per week for 12 weeks	Participants completed neuropsychological assessments and self-report questionnaires prior to performing a treadmill cardiopulmonary exercise test to volitional exhaustion. The target HR for exercise training was 70–80% of the participants' HRR and was calculated as based on the HR response from the baseline cardiopulmonary exercise test. Speed and/or grade were adjusted as needed to maintain the exercising HR within the target range. An additional 5–10 min of warm-up and cool-down were also performed within each training session.	Clinic-based	Vigorous-intensity exercise on treadmill	Not reported	Cardiorespiratory fitness; cognitive function; depression; sleep quality	Trail Making Test Part A (TMT-A); Trail Making Test Part B (TMT-B); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory; version 2 (BDI-II); oxygen consumption rate; work rate	Improvements in cognitive function were observed with greater scores on the TMT-A, TMT-B, and RBANS total scale; no changes in measures of the PSQI and BDI-II which tested sleep quality and depression; magnitude of cognitive improvements was strongly related to the gains in cardiorespiratory fitness

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TABLE 2 (Continued)

References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Chin et al., 2019	Pre-post intervention study	To examine the effect of aerobic exercise training on oxygen uptake on-kinetics during treadmill walking in individuals with TBI	$n = 7$; adults aged 33.3 ± 7.9; males and females	Chronic, non-penetrating; mild $n = 4$; moderate $n = 3$; $n = 5$ injuries due to falls	4.0 ± 5.5 years	3×30 min per session of a vigorous intensity exercise on treadmill per week for 12 weeks	Participants were initially evaluated for exercise test by performing two square-wave bouts of exercise at moderate intensity that was separated by 8 min of active recovery. The target HR for exercise training was 70–80% of the participants' HRR and was calculated as based on the HR response from the baseline cardiopulmonary exercise test. Speed and/or grade were adjusted as needed to maintain the exercising HR within the target range. An additional 5–10 min of warm-up and cool-down were also performed within each training session.	Clinic-based	Vigorous-intensity exercise on treadmill	Not reported	Oxygen uptake on-kinetics; performance fatigability	HR; speed/grade on the treadmill	Faster oxygen uptake on-kinetics observed for both the absolute and relative intensity; suggesting improved performance in individuals with TBI

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References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Ding et al., 2021	RCT	To investigate the feasibility of a community-based aerobic exercise intervention for people with TBI	$n = 9$; adults aged 18–65; males and females	Diagnosed mild to severe TBI; mild $n = 6$, moderate to severe $n = 3$	20 ± 22 months	3 months of aerobic exercise training; 20 min × 3 days for first week, increase to 30 min × 5 days or 50 min × 3 days by end of fourth week and for the remaining 8 weeks	Participants wore HR monitors. A total of 5 min warm up and cool down before and after each aerobic training session. Exercise intensity gradually increased training from 50–60% of max HR to 70–80% of max HR. First aerobic training session was conducted with a certified trainer, the rest from home or a local fitness center.	Home-based or community fitness center	Not specified; participants chose any modality preferred	Participant compliance (ratio of completed to prescribed exercise sessions that participants achieved their target HR) in aerobic exercise training (AET) group was 40% to 91% (median = 76%). Attrition: initially 10 participants in the AET group, but 1 withdrew because of fatigue and muscle pain.	Cardiorespiratory fitness; cognitive function; health status	Peak oxygen uptake (VO2peak); Flanker Inhibitory Control and Attention Test; List Sorting Working Memory Test; Picture Sequence Memory Test; Dimensional Change Card Sort Test; Pattern Comparison Processing Speed Test; Picture Vocabulary Test; Oral Reading Recognition; Patient-Reported Outcomes Measurement Information System	AET group had a trend of improved VO2peak (8%) compared to stretching and toning group (−4%); 7 of 9 AET participants had improved VO2peak (6% to 28%) after the 3 month intervention; no significant improvement in cognitive assessment performance; small, but significant improvement in depression, anxiety, and anger

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TABLE 2 (Continued)

References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Morris et al., 2018	Case series	To examine the feasibility of introducing aerobic physical exercise programs to those with severe TBI, which includes computerized cognitive training	$n = 5$; adults aged 19–56; males	Moderate or severe TBI; 3–8 or 9–13 on the GCS; no previous history of moderate or severe TBI; no aphasia, amnesia had resolved	24–91 days	8 weeks	Aerobic exercise occurred 3x per week for 8 weeks at 50–70% HRR for 45–60 min, including a 10 min warn up and cool down.	Hospital	Active/ passive exercise trainer or recumbent cycling, dependent on patient ability (changed over the course of the study based on recommendation by physical therapist)	2 of 5 participants were only able to complete about half of the sessions, but percent adherence was calculated to be 87–100% in any given patient.	Feasibility outcomes; neuropsychological testing (mentioned in methods but not results)	Number of adverse events reported; adherence to the aerobic exercise program (session durations and number of session attended)	Weak correlation between ratings of perceived effort and HRR; no serious adverse events occurred in participants undergoing intervention

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References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Romanov et al., 2021	RCT	To compare how an adapted physical exercise program including endurance, strength, balance, stretching, and cognitive exercises influences muscular ability, attention process and general workability in TBI patients	$n = 25$; adults aged 41.1 ± 9.7; males	Moderate to severe TBI	2 years	8 weeks	Regular Rehab program: 5 days a week (Monday to Friday), morning exercise (45 min each day), and brain gymnastics (45 min, only Tuesday and Thursday). Morning exercise included: endurance exercises to improve circulation, strength exercises to empower body, and stretching exercises to improve flexibility. Adapted Physical Exercise: 90 min, 2x per week (in addition to regular rehab program), 30–40 min, nordic walking with gymnastic rod.	Center for people with acquired brain injury	Nordic walking with gymnastic rods	100%	Attention process; motor and functional ability	Chair Stand Test; Bicep Curl Test; Chair Sit and Reach Test; 6-min Walk Test; Berg's Balance Scale; Standardized d2 Test (tests attention process)	Both groups showed improvements across all tasks; experimental group showed greater improvements than Regular Rehab Program but differences were not significant; experimental group showed statistically significant improvement on Standardized d2 Test, indicating improved attention compared to other group

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TABLE 2 (Continued)

Refe-rences	Study design	Aim/ objective	Participant details	TBI demo-graphics	Time since injury	Interven-tion timeline	Intervention details	Interven-tion location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Schwandt et al., 2012	Pre-post interven-tion study	To determine the effectiveness of an aerobic exercise program on depression symptoms following TBI	*n* = 4; adults aged 19–48; males and females	Moderate to severe TBI	11 months–7.2 years; mean 2.6 years	3x per week for 12 weeks	Each session included a: 10 min warm up, 30 min at predetermined power output, and 10 min cool down. Participant predetermined power output was 208–(0.7 × age). Participants raised their HR above 70% of age-predicted maximum HR, and had a perceived exertion of 5 or 6 on Borg Scale, with systolic blood presure not >220 mm Hg. Training intensity was maintained 5–10 W below peak workload achieved on baseline testing.	Physio gym at rehabilitation hospital	Cycle ergometry, treadmill, or recumbent step machine; choice made by participant and researcher based on physical limitations, safety, and ability to reach certain thresholds	76–81%, mean = 78%	Aerobic capacity; depressive symptoms; program perception questionnaire; self-esteem	Hamilton Rating Scale for Depression; Rosenberg Self-Esteem Scale; Borg Scale of perceived exertion; Peak power output; HR at fixed power output	Increased peak power output; decreased HR; decreased perceived exertion on Borg Scale; lower scores on Hamilton Rating Scale for Depression (i.e., less depressed); improved Rosenberg Self Esteem Scale scores (i.e., increased self-esteem)

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TABLE 2 (Continued)

References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Tomoto et al., 2022	Pre-post intervention study	To determine if aerobic exercise improves carotid arterial compliance in adults with chronic TBI	TBI: $n = 19$; control: $n = 19$; adults aged 26–61; males and females	Mild, moderate, and severe TBI; mild $n = 11$; moderate to severe $n = 8$	6 months–6 years	3 × 20 min sessions for the first week, followed by 3 × 50 min Or 5 × 30 min sessions for the remaining 11 weeks	TBI participants were split into an Aerobic Exercise Training (AET) group, and a Stretching and Toning (SAT) group. The intensity, frequency and duration of the AET program was based on an individuals maximal HR, and progressively increased as participants adapted to the workload. Week 1: 50–60% maximal HR; Week 2–12: 70–80% maximal HR. Participants started with a 5 min warm up, followed by the aerobic component, and then a 5 min cool down.	One session in clinic, remaining sessions in the community	Any mode of aerobic activity, as long as the HR goals were maintained	3 of 19 participants did not complete the intervention (1 lost to follow-up, 1 had surgery, 1 had muscle pain); compliance in the AET group ranged from 40–91%	Carotid arterial compliance (CAC); cerebral blood flow (CBF); cerebrovascular resistance (CVR)	CAC: tonometry and ultrasonography at the common carotid artery; CBF: ultrasonography at the bilateral internal carotid and vertebral arteries; pulsatile CBF: transcranial Doppler ultrasonography at the middle cerebral arteries; CVR: calculated as mean arterial pressure divided by total CBF	Increased CAC; improved $VO2_{max}$ and decreased systemic blood pressure was observed following AET compared to SAT, but not statistically significant; increases in CAC were associated with decreased pulsatile CBF

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TABLE 2 (Continued)

References	Study design	Aim/ objective	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Weinstein et al., 2017	Pre-post intervention study	To examine if 12-weeks of aerobic exercise changes mood in adults with chronic TBI symptoms	$n = 10$; adults aged 32.9 ± 6.5; males and females	Mild, moderate, and severe TBI; mild $n = 11$; moderate to severe $n = 8$	At least 6 months; mean 6.6 years	3 × 30 min sessions for 12 weeks	Participants were allowed 5–10 min of warm up and cool down. Participants aimed to have their HR between 70 and 80% of their maximum. Aerobic walking was performed supervised on a treadmill.	In clinic	Treadmill walking	12 participants were enrolled, 10 participants completed the program	Mood	Profile of Mood States Short Form	Less mood disturbances at week 12 compared to baseline
Wise et al., 2012	Pre-post intervention study	To determine the effect of exercise on exercise maintenance, depression, quality of life and mental health in adults with TBI and depression	$n = 40$; adults aged 18–55; males and females	Mild, moderate and severe TBI with at least a mild level of depressive symptoms	6 months–5 years	5 × 30 min sessions for 10 weeks	1x per week, participants completed a supervised in-clinic exercise session including warm up and cool down. A total of 4x per week, participants performed aerobic exercise on their own or in the community. Participants were asked to maintain 60–80% of their maximal HR.	In clinic and at home	Unspecified	Not reported	Exercise maintenance; mental health; mood; quality of life	Beck Depression Inventory; Medical Outcomes Study 12-Item Short-Form Health Survey; Perceived Quality of Life Scale; 7-day physical activity recall	Depression-like symptoms decreased at 10-weeks, and maintained 6-months later; nearly half of the participants maintained their new activity levels; participants who exercised more had lower depression scores and higher mental health and quality of life

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in nine studies (Leddy et al., 2010; Leddy and Willer, 2013; Polak et al., 2015; Clausen et al., 2016; Adams and Moore, 2017; Dobney et al., 2017; Snyder et al., 2021; Hutchison et al., 2022; Langevin et al., 2022). Varner et al. (2021) found no significant change in post-concussion symptoms after 1 month of daily aerobic exercise that began 48 h post-injury compared to the control group. The two studies that examined exercise tolerance found an improvement in participants' ability to exercise without symptom exacerbation post-intervention (Leddy et al., 2010; Clausen et al., 2016). In relation to brain imaging, Leddy et al. (2013) reported fMRI activation in TBI survivors after exercise to be the same as healthy exercise controls, and Polak et al. (2015) found no correlation between post-intervention symptom reduction and DTI metrics. Of note, both of the aforementioned reports were pilot studies ($N = 4$ concussed individuals in the intervention group), which must be considered when interpreting these data.

Considerations include inadequate comparison groups in some studies (Clausen et al., 2016; Adams and Moore, 2017; Dobney et al., 2017; Langevin et al., 2022). One study provided insufficient details on the aerobic exercise paradigm, and half of the studies did not specify the modality of aerobic exercise performed, affecting their reproducibility.

3.6.2 Adolescents

Most individuals were adolescents (12–18 years) upon sustaining their injury, with time since injury as short as three days up to 2.8 years post-injury (Hunt et al., 2018; Leddy et al., 2019a). Five studies included children (younger than 12 years) (Imhoff et al., 2016; Hunt et al., 2018; Dobney et al., 2020; Leddy et al., 2021; Howell et al., 2022), and two included adults (19 years and older) (McGeown et al., 2018; Howell et al., 2022), but since the average age within the study was in the adolescent range, and no age-separated analyses were done, results are presented in the adolescent section. Studies examining aerobic exercise interventions in adolescents post-concussion can be divided into two categories: early intervention (within 2 weeks post-injury), and chronic intervention for persistent symptoms (4 weeks or longer post-intervention). Due to the large number of studies in this section, the authors sub-grouped and presented the studies based on the above. Full results are presented in **Tables 4**, **5**, respectively.

3.6.2.1 Adolescents—Acute timepoint

Nine studies assessed adolescents with mTBI within 2-weeks of injury (Micay et al., 2018; Leddy et al., 2019a,b, 2021; Willer et al., 2019; Dobney et al., 2020; Howell et al., 2021, 2022; Chizuk et al., 2022). Intervention timelines ranged from 4 to 8 weeks; however, several studies discontinued the intervention once return-to-play status was assumed. Most commonly, studies had participants engaging in daily aerobic exercise for 20 min (Leddy et al., 2019a,b, 2021; Willer et al., 2019), or 20-min sessions 5 days per week (Howell et al., 2021, 2022). The remaining studies examined 6x per week, 3x per week, 2x per week or personalized frequency for 15–20 min per session (Micay et al., 2018; Dobney et al., 2020; Chizuk et al., 2022). All studies tracked heart rate and had participants exercising at 60–90% of their max heart rates during the exercise sessions. Eight studies allowed participants to choose their aerobic modality, if heart rate targets were met; most commonly participants engaged in jogging, walking or recumbent cycling. Micay et al. (2018) had participants exclusively use recumbent cycling as an aerobic activity.

These particular studies showcased a distinct set of outcome measures. All studies were primarily centered on recovery from concussion, frequently evaluating parameters such as the duration of recovery, concussion symptoms, time taken to return to play, and participants' ability to tolerate exercise. Of the eight studies that evaluated recovery time, seven found that implementing early exercise interventions reduced time to recover compared to standard care (Leddy et al., 2019a,b, 2021; Willer et al., 2019; Dobney et al., 2020; Howell et al., 2021; Chizuk et al., 2022). Additionally, Howell et al. (2022) reported that the early exercise group was less likely to develop persistent post-concussion symptoms compared to the usual treatment group.

Adherence to the exercise interventions ranged from 61 to 100% across studies, and interestingly, Chizuk et al. (2022) reported that adherent participants recovered faster than non-adherent participants, supporting the benefits of early exercise post-mTBI. While this set of studies represents the most cohesive group, most studies focus on sport-related concussions, therefore, these results may not be generalizable to wider populations.

3.6.2.2 Adolescents—Chronic timepoints

Twelve studies examined aerobic exercise for adolescents at least 1 month post injury who were experiencing at-least one persistent post-concussion symptom (Gagnon et al., 2016; Imhoff et al., 2016; Chrisman et al., 2017, 2021; Kurowski et al., 2017; Yuan et al., 2017; Chan et al., 2018; Hunt et al., 2018; McGeown et al., 2018; Bailey et al., 2019; Gladstone et al., 2019; Shore et al., 2022). A majority of these studies offered a mix of in-clinic and at-home interventions for 6 weeks (Chan et al., 2018; Hunt et al., 2018; Bailey et al., 2019; Chrisman et al., 2021; Shore et al., 2022), with up to an additional two weeks, making an 8-week intervention (Kurowski et al., 2017; Yuan et al., 2017; Gladstone et al., 2019). One study consisted of a four-week intervention (McGeown et al., 2018). In contrast, the remaining three studies offered the intervention until symptom resolution occurred (Gagnon et al., 2016; Imhoff et al., 2016; Chrisman et al., 2017). Intervention frequency ranged from 3 times per week (15–45 min) to 20 min daily. Ten studies included effort-based measures (e.g., Borg scale) or physiological measures (i.e., heart rate) to gauge aerobic status during exercise (Gagnon et al., 2016; Imhoff et al., 2016; Chrisman et al., 2017, 2021; Kurowski et al., 2017; Yuan et al., 2017; Chan et al., 2018; Bailey et al., 2019; Gladstone et al., 2019; Shore et al., 2022). Recumbent cycling was the exclusive aerobic modality in five studies (Imhoff et al., 2016; Kurowski et al., 2017; Yuan et al., 2017; McGeown et al., 2018; Gladstone et al., 2019), while five studies offered participants their choice of activity (Gagnon et al., 2016; Chan et al., 2018; Hunt et al., 2018; Chrisman et al., 2021; Shore et al., 2022). Two studies had participants engage in treadmill-based walking or running (Chrisman et al., 2017; Bailey et al., 2019).

While nine of twelve studies in this set examined concussion-related symptoms, many included additional measures of mental health, mood, cognition, intervention experience, balance, saliva-based protein analysis, illness perception and structural connectivity. A total of 100% of studies that examined concussion-related symptoms found improvements post-intervention; however, only five of these studies included appropriate comparison groups (Gagnon et al., 2016; Imhoff et al., 2016;

TABLE 3 Summary of the effects of aerobic exercise intervention following mild traumatic brain injury in adults.

References	Study design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Adams and Moore, 2017	Case series	To explore changes in outcome measures and return to meaningful life activities in six individuals who had persistent dizziness for at least 9-months post-concussion	$n = 6$; adults aged 18–55; males and females	At least 9 months with dizziness (266–974 days)	Ranging from 14–27 aerobic sessions that occurred for 30 min 3–5x per week; individualized based on participant needs and clinician expertise	60–80% of maximal HR (based on sub-maximal symptom test) aerobic exercise was performed for 30 min 3–5x per week.	Supervised home program	Recumbent cycling	Not reported	Balance; concussion symptoms; dizziness; return to activity; return to work/study	Rivermead Post-concussion Questionnaire Symptoms; Psychosocial impact; Dizziness Handicap Inventory; Activities-specific Balance Confidence Scale; Functional Gait Assessment	Improved Return to work outcomes; all six participants improved their physical activity levels, reduced concussion symptoms, improved dizziness and balance confidence

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TABLE 3 (Continued)

References	Study design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Clausen et al., 2016	Pre-post-intervention study	To evaluate control of cerebral blood flow (CBF) during exercise in females with post-concussion syndrome	$n = 6$; adults aged 23 ± 6; females	6–12 weeks	5–6 × 20 min sessions per week for 12 weeks	HR monitored subsymptom threshold aerobic exercise treatment program at 80% maximum HR from treadmill test.	University concussion clinic	Not specified	Not reported	Concussion symptoms; exercise tolerance	Blood pressure; end-tidal CO2; cerebral bloodflow velocity; minute ventilation; treadmill test; Post-concussion Symptom Scale	Improved exercise tolerance so that symptoms were not exacerbated on the treadmill test; symptoms improved and were not significantly different than the healthy reference group; participants with PCS still had higher HR at onset of exercise than the healthy reference group; PCS participants could only exercise to 90% of their predicted VO2 max even after the intervention; significant increase in min ventilation (Ve) and significant decrease in CO2 partial pressure (PetCO2); significant decrease in CBF velocity

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TABLE 3 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Dobney et al., 2017	Pre-post-interven-tion study	To test the effectiveness of an active rehabilitation program for children and adolescents with persistent post-concussive symptomologies	Aquatic intervention: $n = 10$; adults aged 37.4 ± 15.3; males and females; land control: $n = 10$; adults aged 43.0 ± 14.1; males and females	Pre-intervention appointment: 28 ± 3.3 days; then in-person visit: 40 ± 7.4 days	Daily; number of sessions is dependent on being asymptomatic for 7 days or return to work/play.	Active Rehabilitation protocol. Aerobic activity: stationary bike or treadmill used to reach a target HR zone (50–60%). Resistance is modified until target HR is acquired. Patient exercises for 15 min in target zone.	Location unclear but assumed physiotherapy clinic and home	Stationary bike or treadmill	Not reported	Post-concussion symptoms in four domains: cognitive, emotional, sleep, and physical	Post-concussion Symptom Scale (PCSS) from Sport Concussion Assessment Tool 2 and 3	Active rehabilitation reduced total PCSS score and in all specific domains (cognitive, emotional, sleep, and physical)

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TABLE 3 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Hutchison et al., 2022	RCT	To examine the effect of a structured aerobic exercise program on days to recovery vs. usual care exercise in adolescents and young adults with sports-related concussion	Structured aerobic exercise: $n = 20$; usual care exercise: $n = 19$; adolescent aged 16–22; males and females	3 days	11 sessions over 28 days	Structured exercise program group: 8 × 20 min sessions; 2 days of exercise followed by 1 day rest. Intensity and duration increased each session. Intensity was determined by calculating target HR (progressed 60–75% of age-predicted max HR). Usual care exercise group: followed instructions from sport med physician; subjects advised to increase intensity gradually with minimal head movement then exercises included progression of head movements, visual/cognitive burdens, sport-specific activities, heavy resistance.	Exercise laboratory and at-home; Fitbit monitoring	Stationary bike with limiting movement to head; elliptical or treadmill jogging as alternatives	Not reported but mentioned 6 participants lost to follow up; analyzed $n = 19$ structured exercise group and $n = 19$ usual exercise group	Asymptomatic status; medical clearance; symptom severity	Sport Concussion Assessment Tool 5 (SCAT5); current/premorbid baseline function and objective assessments by physician	Similar symptom severity and total symptom scores at enrollment, but structured aerobic exercise group had lower symptom severity at subsequent assessments vs. usual care group; structured exercise group had faster time to asymptomatic status and earlier medical clearance

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TABLE 3 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Langevin et al., 2022	RCT	To determine if cervicovesti-bular rehabilitation in addition to an aerobic exercise program would reduce mTBI-associated symptoms, as compared to an exercise intervention alone	$n = 60$; adults aged 18–65; males and females	3–12 weeks; mean 39 ± 15 days	Individualized; 8 sessions (30–45 min) over 6 weeks, and asked to continue to follow the program from weeks 6–12	No specific details on the type of aerobic intervention.	Clinic-based; supervised by a kinesiologist	Not specified	Dropout rate was 6.7%; mentioned that "adherence and home exercise was recorded using a self-filled booklet," but no other mention	Cervical range of motion; clearance to return to function; concussion symptoms; head/neck questionnaires	Post-concussion Symptoms Scale (PCSS); Neck Disability Index (NDI); Headache Disability Inventory (HDI); Dizziness Handicap Inventory (DHI); Numerical Pain Rating Scale (NPRS); Global Rating of Change (GRC); Flexion-Rotation Test (FRT); vestibular/Ocular Motor Screening (VOMS); Head Impulse Test (HIT); cervical segmental motion/sensitivity	Decrease in PCSS, DHI, HDI and BDI; no difference from group receiving cervicovestibular intervention (although this group had better scores on FRT, HIT, range of motion)
Leddy et al., 2010	Case series	To determine if exercise intervention would decrease post-concussion symptoms in a safe manner	$n = 12$; adults aged 27.9 ± 14.3; males and females	6–40 weeks; mean 19 weeks	5–6 days per week for an individualized amount of time (previous treadmill test) or until symptoms increased; treatment was continued until they could complete the treadmill test without increased symptoms	Aerobic exercise at 80% of target HR.	Unclear location; with supervision	Not specified	Not reported, but states compliance was determined by trainer (for athletes) and symptom reports (non-athletes)	Ability to exercise; concussion symptoms, time to recovery	Graded symptom checklist; HR; blood pressure	Decreased symptom score; increased amount of time able to exercise; increased peak HR and systolic blood pressure without symptom increase

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TABLE 3 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Leddy et al., 2013	Pre-post-interven-tion study	To determine if exercise intervention in individuals with post-concussion syndrome would cause a decrease in symptoms, and if their fMRI activity would differ from controls	Concussed: $n = 8$; control: $n = 4$; adolescents and adults aged 17–33; males and females	At most 12 months	20 min per day; 6 days a week; until able to perform at 80% of age-predicted max HR without symptoms	Aerobic exercise at 80% of HR.	At-home or in a gym	Not specified	Not reported	Concussion symptoms; functional magnetic resonance imaging (fMRI) activity; HR	fMRI with math processing test; Post-concussion scale	Increased maximum HR; decreased symptoms; no change in math processing; fMRI activation same as controls with exercise

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TABLE 3 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Polak et al., 2015	Pre-post-interven-tion study	To investigate diffusion tensor imaging characteristics in patients with post-concussion syndrome who received exercise and placebo stretching treatments compared with a group of healthy controls	Control: $n = 15$; adults aged 26.2 ± 1.7; exercise: $n = 4$; adults aged 25.2 ± 5.7; stretching: $n = 4$; adults aged 22.8 ± 6.2; males and females	Exercise: 66 ± 6.6 days; stretching: 170 ± 118.8 days	8 weeks	Controlled and progressive aerobic treadmill test targeted at 80% of this HR, and this program was modified as the HR for symptom aggravation increased. Placebo patients were given instructions for a low-impact breathing and stretching regime and were instructed to keep their HR below 50% of their age predicted maximum. Had to go to Leddy *et al.* to find methods: 20 min per day, 6 days per week.	At-home or in a gym	Treadmill	100%	Diffusion tensor imaging (DTI)	DTI; tract-based spatial stats; potholes	No significance for potholes; reduced number of PCS symptoms and increased maximum HR, but this was not correlated with DTI metrics

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TABLE 3 (Continued)

References	Study design	Aim/ objective	Participant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Snyder et al., 2021	RCT	To examine adherence, symptom response and key functional outcomes immediately following intervention and at 3 month follow up	$n = 38$; adolescents and adults aged 18–32; males and females	14–25 days	Daily for 7 days; single rest day taken after 3 or 6 days	5 min warm up; 20 min bike at moderate intensity; 5 min break; 20 min bike at moderate intensity; 5 min cool down. Moderate intensity exercise: maintaining 65–75% of estimated HR max, HR max: 208–0.7 × age.	In-person with research staff	Lode Corival stationary bike	Aerobic group attrition: 7.7%; non-aerobic group attrition: 0%	Mood; neurocognition; postural stability; sleep; symptom report	Sport Concussion Assesment Tool 3 (SCAT3); Medical Outcome Scale (MOS); self-reported measure of sleep quality; Beck Depression Inventory (BDI-II); State Trait Anxiety Inventory (STAI); Balance Error Scoring System (BESS); Weschler Adult Intelligence Scale, 3rd ed (WAIS-III); Weschler Memory Scale, 3rd ed; Paced Auditory Serial Addition Test (PASAT); Ruff 2 and 7; DKEFS Trail Making Test; California Verbal Learning Test, 2nd ed (CVLT-II); Letter-number Sequencing; Wisconsin Card Sorting Test; Controlled Oral Word Association	Reduced symptom severity scores; full symptom recovery by 3 month follow up, this did not differ from TBI + non-aerobic group; neurocognitive index scores improved, this did not differ from TBI + non-aerobic group at post-intervention or 3 month follow up; positive changes for depression, state anxiety, sleep, and postural stability, not statistically significant between groups

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TABLE 3 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Varner et al., 2021	RCT	To determine if light exercise could prevent post-concussion symptoms at 30 days post injury	Exercise: $n = 183$; control: $n = 184$; adults aged 18–64; males and females	Immediately	48 h of physical rest following the mTBI, followed by daily 30 min aerobic exercise for 1 month	Upon presentation to the emergency room, participants were randomly assigned into a control group, or prescribed light exercise group. Participants were prescribed 30 min of daily aerobic exercise of their choice for 30 days	Home-based	Not specified	Control group: 13 participants withdrew; exercise group: 5 participants withdrew	Post-concussion symptoms	Rivermead Post-concussion Symptoms Questionnaire	No between group differences observed between exercise group and control group on post-concussion symptoms at 30 days, or change in post-concussion symptoms

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TABLE 4 Summary of the effects of aerobic exercise interventions within two-weeks following mild traumatic brain injury in adolescents.

References	Study design	Aim/ objective	Participant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Chizuk et al., 2022	RCT	To examine whether there is a direct relationship between adherence to a personalized exercise prescription and recovery, or if initial symptom burden affects adherence to the prescription	$n = 62$; adolescent athletes aged 15.77 ± 1.6; males and females	6×20 min of aerobic exercise of choice (walking, jogging, stationary cycling) per week for 4 weeks.	Each week, until recovered, participants received a new training target HR based on reassessment of exercise tolerance on the Buffalo Concussion Treadmill Test (BCTT). If a participant did not recover by the 4th week, a more comprehensive form of treatment was initiated. When exercising, participants were prescribed to perform at least 20 min of aerobic exercise of their choice (walking, jogging, stationary cycling) daily for 6 days out of 7, at 90% HR (but this fluctuated). Participants were instructed to stop exercise if their symptoms increased by 2 or more points on a 1- to 10-point visual analog scale when compared with their pre-exercise value.	Home-based	Aerobic exercise of choice (walking, jogging, stationary cycling)	Adolescent adherence rates ranged from 10% to 88%, depending on the week of the intervention; using the definition of completing at least two-thirds of the prescribed volume of aerobic exercise, 31 out of 51 (61%) of the participants were adherent	Cardiorespiratory response; concussion symptoms	HR; Buffalo Concussion Treadmill Test (BCTT); Post-concussion Symptom Inventory (PCSI)	Those who were adherent were more symptomatic and were more exercise intolerant at their initial visit, yet recovered faster than those who were not adherent; decrease in recovery time as exercise tolerance increased

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TABLE 4 (Continued)

References	Study design	Aim/ objective	Participant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Dobney et al., 2020	RCT	To examine the feasibility of an active rehabilitation (AR) program for youth with concussion symptoms lasting 2 weeks after injury and compare early AR to usual AR	Early AR: $n = 10$; usual care AR: $n = 10$; children and adolescents aged 9–17; males and females	8 week study period; mean of 3.7 days per week for early AR and 4.2 days per week for usual care AR; mean reported exercise duration of 18.5 ± 11.4 min for early AR and 21.2 ± 21.2 min for usual care AR	Same intervention for early and usual care AR groups. Aerobic exercise at 60% max HR predicted for their age for 15 min.	Home-based with supervision (check-ins after 1-week of intervention)	Aerobic exercise of choice (most common: walking, jogging, stationary cycling)	Participants were more adherent to exercise duration and frequency recommendations; participants were less adherent to the frequency of exercise sessions prescribed (7 days per week)	Concussion symptoms	Post-concussion Symptom Inventory (PCSI)	Symptom severity as measured by PCSI improved over time in both the early and usual care AR groups; 15 of 20 participants had reduced or same symptom severity scores as baseline; early AR group had symptoms that were considered at "normal" (comparable to baseline levels in healthy youth) levels by 4 weeks post-injury, whereas usual care group had normal symptoms at 6-weeks post-injury

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TABLE 4 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Howell et al., 2021	RCT	To examine the effects of a prescribed aerobic exercise program on symptom severity and exercise volume	*n* = 41; adolescents and adults aged 14–21; males and females	8 week aerobic exercise; 5x per week; 20 min at target HR	Provided aerobic exercise prescription (intervention group: intensity, duration, frequency) within 14 days of injury. At baseline, participant aerobic fitness was determined and initial exercise prescription was based on results; individualized target HR, frequency (5x per week); 20 min at target HR. At 4-weeks post-enrollement underwent aerobic exercise test and prescription intensity was adjusted as needed but same volume (20 min per day, 5x per week) and symptoms were assessed. Standard-of-care group adhered to physician recommended physical activity. Modes of exercise were left to participant preference. Weekly log of aerobic activity; reported symptom severity at 1-and 2-months post-enrollement. Subjects were given HR monitor to ensure exercised at prescribed intensity and to monitor daily activity.	Unreported; implied gym/home or other since mode of exercise was left up to participant	Not specified	41 enrolled; 37 included in analysis; 4 excluded because they did not complete >50% of exercise diaries	Exercise volume; symptom severity	Post-concussion Symptom Inventory (PCSI); exercise volume (average min/week); must have completed >50% of exercise diaries	No significant differences in symptom severity between prescription vs. standard-of-care groups; exercise volume was also similar; greater exercise volume was associated with lower symptom burden after 1 month (i.e., those with <100 min/week exercise had higher symptom severity regardless of group); exercise volume of >160 min/week was associated with symptom resolution after 1 month

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TABLE 4 (Continued)

References	Study design	Aim/ objective	Participant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Howell et al., 2022	RCT	To determine the proportion of adolescents at moderate or high risk of PPCS that develop PPCS when prescribed early aerobic exercise vs. standard-of-care and examine exercise volume	*n* = 16; children and adolescents aged 10–18; males and females	Five × 20 min sessions per week for four weeks	Early aerobic exercise group: individualized target intensity (80% of HR at end of exercise test) and uniform volume (5x/week for 20 min/day). Standard-of-care group: adhere to physician's recommendations on physical activity; symptom limited activity without specific exercise recommendation.	Unreported; implied at-home	Not-specified	100%	PPCS; exercise volume and intensity	Post-concussion Symptom Inventory (PCSI) at 1-month post-concussion; Average min/week recorded aerobic exercise, Average HR and max HR recorded during each session	Smaller proportion of early aerobic exercise group developed PPCS compared to standard-of-care group. Exercise volume and intensity were not significantly different.
Leddy et al., 2019a	RCT	To determine if daily exercise would decrease the time to recovery and symptoms following a sports-related concussion in adolescent athletes	*n* = 103; adolescent athletes aged 13–18; males and females	Daily for 20 min or until symptoms increased; intervention was until they recovered from their injury as determined by the physician, or after 30 days	Aerobic exercise at 80% of target HR; participants were not allowed to stretch before or after exercise.	At-home or in a gym; with supervision	Stationary bike; treadmill; walk/jog	89% of daily reports included completion of exercise intervention that day; 7 participants were removed because they missed 3 days in a row or completed less than 75% of daily symptom reports	Concussion symptoms; days to recovery	Post-concussion Symptom Scale	Exercise decreased the time to recovery; no significant change in symptoms
Leddy et al., 2019b	Pre-post-intervention study	To determine if exercise intervention would decrease the time to recovery and concussion-related symptoms in male adolescent athletes	*n* = 54; adolescent athletes aged 13–18; males	Daily for 20 min or until symptoms increased for 14 days	Aerobic exercise at 80% of target HR; 5 min warm-up and 5–10 min of cool-down.	At home or in a gym; with supervision	Stationary bike; treadmill	93.2% of daily symptom scores were completed (6.8% absent)	Concussion symptoms; days to recovery	Post-concussion Symptom Scale	Exercise decreased recovery time from first visit and symptom scores after 14 days

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TABLE 4 (Continued)

References	Study design	Aim/ objective	Participant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Leddy et al., 2021	RCT	To determine if exercise intervention would reduce recovery time and symptoms from a sport-related concussion, including safety and adherence	Adolescents: *n* = 38; aged 9–18; males and females; parents: *n* = 38	Daily for 20 min for up to 4 weeks or until recovery	Aerobic exercise at up to 90% of target HR.	Home-based	Walking; jogging; stationary bike	Exercise: 65%; control: 50%	Concussion symptoms; exercise ability; recovery time	Post-concussion Symptom Inventory; HR	Exercise decreased recovery time and resulted in fewer symptoms; increased HR during exercise and amount of time exercising per day
Micay et al., 2018	RCT	To examine the feasibility of implementing a standardized aerobic exercise intervention in the post-acute stage of sport-related concussion recovery in a sample of adolescent students with sport-related concussion compared with usual care	Intervention: *n* = 8; control: *n* = 7; adolescents aged 14–18; males	Approximately 4–6 weeks until time to clearance of return to sport	8 sessions proceeding in a stepwise fashion with respect to duration and intensity using the Velotron Racermate Pro stationary cycle ergometer; 50–70% age-predicted max HR (intensity increased over sessions). A total of 20 min sessions.	University concussion clinic	Recumbent cycling	100%; 1 participant excluded because she was the only female	Return to play; symptom severity	Efficacy of the intervention; symptom status (Post-concussion Symptom Scale); time to medical clearance	No change in time to clearance; significant correlation between acute symptom severity and overall time to medical clearance
Willer et al., 2019	Pre-post-intervention study	To compare outcomes of adolescents with concussion who were prescribed rest, aerobic exercise or stretching	Exercise: *n* = 52; stretching: *n* = 51; rest *n* = 48; adolescents aged 13–18 years; males and females	Daily 20 sessions for 4 weeks or until recovery, whichever came first	Participants warmed up for 5 min, performed aerobic exercise (walking, jogging or biking), for 20 min, and cooled down for 5 min. Participants were told to stop exercising if their symptoms got worse. All exercise was sub-threshold, calculated as 80% of the HR achieved at symptom exacerbation or voluntary exhaustion.	At-home or in-clinic	Aerobic exercise of choice	7 participants lost to follow up; 10 participants removed because they did not report daily symptoms; 1 participant had influenza and was removed	Concussion symptoms; days to recovery	Sport Concussion Assessment Tool 3 (SCAT3); Post-concussion Symptom Scale	Exercise group recovered faster than the rest group by an average of 3 days; no between group differences in delayed recovery; female participants in the rest group showed an acute increase in symptoms compared to the other groups

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Chrisman et al., 2017, 2021; Kurowski et al., 2017; Yuan et al., 2017; Chan et al., 2018; Bailey et al., 2019; Shore et al., 2022). In terms of cognition, Gladstone et al. (2019) found that exercise increased crystallized and fluid cognition composite scores, Gagnon et al. (2016) reported improved processing speed and no differences in balance, while Imhoff et al. (2016) reported improvements in multiple memory tasks and balance. McGeown et al. (2018) examined salivary brain-derived neurotrophic factor (BDNF), but did not find any improvements post-exercise. However, the authors suggest this can be attributed by the large variance in baseline levels and the variable intervention length. One study examined functional connectivity and found that participants in the exercise group had increased global efficiency and decreased normalized path length (Yuan et al., 2017). Only one study assessed attitudes and feasibility of the exercise intervention; 100% of the participants reported that the active rehabilitation was effective (Hunt et al., 2018).

Many considerations are prudent when assessing this group of studies. First, the sample sizes in ten of the twelve studies are below 30 individuals, which may indicate that a majority of these studies are underpowered. Additionally, only five studies included control or comparison groups, which helps determine effects related to the intervention.

3.7 Unspecified

Five studies did not specify the severity of traumatic brain injury in participants undergoing aerobic interventions, but referred to trauma-induced brain injury (Hoffman et al., 2010; Esquenazi et al., 2013; Kolakowsky-Hayner et al., 2017; Pennington et al., 2022; Tefertiller et al., 2022). Full results are presented in **Table 6**.

All participants in these studies were adults, with time since injury ranging from 6 months to 5 years. Aerobic exercise interventions spanned from 4 to 12 weeks. Two of these interventions included home-based components and the other three were clinic-based. Aerobic modalities varied amongst studies, including the use of treadmills, stationary cycling, rowing machines, stair-steppers, indoor tracks, and outdoor walking. Four studies used a single modality of aerobic exercise, three of which had participants walking (two on the treadmill, one with home-based walking) and one study used stationary cycling (Esquenazi et al., 2013; Kolakowsky-Hayner et al., 2017; Pennington et al., 2022; Tefertiller et al., 2022). The study using stationary cycling also involved a combined intervention with virtual reality (Pennington et al., 2022).

Outcome measures assessed in these studies were gait, severity of depression, fatigue, balance, mobility, neuropsychological assessments, alcohol use, and post-concussion symptoms. Esquenazi et al. (2013) found that participants improved their mobility, along with self-selected and maximum velocity on the treadmill after the aerobic exercise intervention. Hoffman et al. (2010) found an improvement in pain after the exercise intervention, and lower post-intervention depression scores for the high-activity exercise group compared to the low-activity group. Participant fatigue was reduced after intervention in Kolakowsky-Hayner et al. (2017) and Tefertiller et al. (2022) found improved balance and mobility post-intervention which persisted at the 4-week follow-up. Improved cognitive inhibition was reported by Pennington et al. (2022); however, they found no change in alcohol use or post-concussion symptoms post-intervention.

It should be noted that there was low adherence to the home-based intervention in Kolakowsky-Hayner et al. (2017), with almost a third of participants discontinuing the intervention. Pennington et al. (2022) only had 53% of participants fully complete their in-person study, which included an 8-week follow-up. Additionally, target heart rate zones were only assigned to participants in one of the five studies (Hoffman et al., 2010).

4 Discussion

Fifty-four studies were included in this review, and first divided based on injury severity (i.e., severe, mixed, mild, unspecified), then subdivided based on age (i.e., adult, adolescent), and time since injury (i.e., acute, chronic) when applicable. The purpose of this review was to describe the breadth of aerobic interventions used to improve health-related outcomes post-TBI across the lifespan. However, it is worth noting that no studies exclusively examined aerobic exercise following moderate TBI, nor in children younger than 12, and therefore these groups are absent from the present review.

For adults, aerobic exercise post-TBI is a promising intervention, especially as no studies reported adverse effects for participants. However, it is worth considering how the impact of aerobic exercise may be influenced by factors such as the severity of the injury and time since injury. In studies focusing on severe brain injury, aerobic exercise seems to be effective at improving cardiovascular health and balance in TBI survivors, and shows promise for improving cognitive functions, like memory, which is supported by increased hippocampal volume post-intervention. In mixed and unspecified injury severity groups, again, aerobic exercise shows benefits related to cardiovascular and physical and fitness, cognition, and mental health. The studies focused on mild TBIs, including concussions, showed more consistent benefits for aerobic exercise interventions, particularly in symptom reduction and exercise tolerance. However the lesser-studied effects of these interventions on cognitive and neuroimaging measures are mixed. Overall, the body of evidence generally supports aerobic exercise as a safe, easily implementable intervention for adults post-TBI.

In adolescents, 21 studies examined aerobic exercise post-mild traumatic brain injury, and one study presented a case study post-severe TBI. From this cohort of studies, aerobic exercise is a safe and beneficial intervention for post-concussion adolescents, and can be effectively implemented as early as one-week post-injury. Overall, early implementation seems to promote recovery compared to standard care, and chronic implementation is effective at reducing concussion-related symptoms and supporting cognition and fitness.

While these findings are promising, there are several notable limitations in the present study and existing research. In the present study, while we aimed to conduct a comprehensive review, we could not include papers that did not have an official English translation. In the literature, although many studies showed positive results of aerobic exercise, an individual's time since injury

TABLE 5 Summary of the effects of aerobic exercise interventions implemented four weeks or longer following mild traumatic brain injury in adolescents.

References	Study design	Aim/ objective	Participant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Bailey et al., 2019	RCT	To describe a model multidisciplinary concussion management and explore management methods in the acute and post-acute settings	Intervention: $n = 7$; control: $n = 8$; adolescents aged 14–18; males and females	Daily 20 min sessions per week for 6 weeks	80% of individual maximum HR threshold.	3 supervised clinic sessions per week, and home-based exercise between clinic days	Treadmill running	Not reported	Concussion symptoms; neuropsychological; postural stability	Post-concussive Scale Revised (PCS-R); Beck Depression Inventory	Participants in the exercise group had less symptoms at follow-up
Chan et al., 2018	RCT	To examine the safety and tolerability of an active rehabilitation program for adolescents who are slow to recover from a sport-related concussion	Intervention: $n = 10$; control: $n = 9$; adolescents aged 15.9 ± 1.66; males and females	Mean 3.4 sessions per week for 6 weeks (not including at home exercise program)	Consisted of submaximal aerobic training, light coordination and sport-specific exercises, visualization and imagery techniques, and a home exercise program.	Outpatient concussion clinic and home-based	Not specified; mentioned light aerobic exercise	100%	Cognitive performance; fatigue; measures of health-related quality of life; mood; self-reported post-concussion symptoms	Post-concussion Symptom Scale (PCSS); Patient-Reported Outcomes Measurement Information System; Beck Depression Inventory for Youth–Second Edition; Pediatric Quality of Life Multidimensional Fatigue Scale; Teen Report Standard Version; Balance Error Scoring System; Immediate Post-concussion Assessment and Cognitive Test	Statistically significant treatment effect on post-concussion symptoms; no adverse effects when compared with control group

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TABLE 5 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Chrisman et al., 2017	Pre-post-intervention study	To examine the safety of a Sub-Symptom Threshold Exercise Program (SSTEP) in youth and determine if there is a correlation with concussion symptom improvement	$n = 87$; children and adolescents aged 14.9 ± 2.3; males and females	Daily sub-threshold physical activity for the same time they could perform physical activity during the initial treadmill testing (or for a maximum of 20 min). A total of 1–2 week follow up and continued the exercise intervention until they could complete the Balke treadmill test without worsening symptoms	Initial evaluation with the Balke treadmill test to obtain a heart-rate threshold above which they report increased symptoms. Prescribed an at home sub-threshold exercise program (at a HR 80% of that that causes symptoms).	Home-based	Treadmill for the initial determination of HR threshold; no specific details on the prescribed at-home component	142 patients referred to SSTEP program; 83 underwent treatment meeting inclusion criteria	Concussion symptoms	Sport Concussion Assessment Tool 2 (SCAT2)	SCAT2 scores decreased exponentially over time after beginning the intervention; no participant had symptoms worsen after beginning SSTEP; monitored exercise from the SSTEP program was safe for youth and there was a correlation with improvement in concussion symptoms
Chrisman et al., 2021	Pre-post-intervention study	To assess feasibility and acceptability of a telehealth delivered exercise intervention for concussion, the Mobile Subthreshold Exercise Program (MSTEP), and collect pilot data regarding efficacy	$n = 19$; adolescents aged 14.2 ± 2.2; males and females	7x exercise (at home choice) per week for 6 weeks	Initial goal was set at 10 min at a HR of 120. Individuals could choose the type of exercise they completed. If symptoms worsened during exercise, youth were instructed to take a break and decrease the HR goal utilized until they were able to tolerate 10 min of exercise. Goals were advanced weekly as tolerated to a maximum of 60 min of physical activity per day at a HR of 140. Participants would wear Fitbits and fill out surveys.	Home-based	Aerobic exercise of choice at home, as long as HR was increased to goal (120 or 140)	1 individual withdrew from the study at 3 weeks due to increasing headaches; participants wore the Fitbit on 80% of days and completed 94% of surveys and 96% of Zoom calls	Concussive symptoms; health-related quality of sleep; symptoms of anxiety and depression	Health and Behavior Inventory; Pediatric Quality of Life Inventory; Fear of pain questionnaire (adapted for concussive symptom); Patient Health Questionnaire-9; Generalized Anxiety Disorder Scale-7; Adolescent Sleep Wake Scale-10 item	Concussive symptoms improved significantly from baseline to weeks 3 and 6; health-related quality of life improved

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TABLE 5 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Gagnon et al., 2016	Pre-post-intervention study	To investigate an active rehabilitation (AR) program in adolescents who experienced persistent post-concussive symptomo-logies following sports related concussion	$n = 10$; adolescents aged 14–18; males and females	Daily; number of sessions dependent on being asymptomatic for 7 days; treatment lasted 6.8 ± 4.7 weeks post-injury	15 min of aerobic training at 60% of maximal capacity.	Clinic-based and home program	Stationary bike or treadmill	Not reported	Post-concussion symptoms	Post-concussion Scale; mood (Beck Depression Inventory); energy level (Pediatric Quality of Life Multidimensional Fatigue Scale); balance and coordination (body coordination component of Bruininks-Oseretsky test of motor proficiency); cognitive function (ImPACT)	(Reduced post-concussion symptoms on the post-concussion scale); increased processing speed (ImPACT); no changes on other measures
Gladstone et al., 2019	RCT	To determine the if subsymptom aerobic exercise improves quality of life and cognition following mild TBI	$n = 30$; adolescents aged 12–17; males and females	6–8 weeks; 5–6 sessions a week	At baseline participants Borg rate of perceived exertion of 11 (resistance level of 2) for 5 min. Perceived exertion was increased every 5 min for 30 min; during intervention participants exercised 5–6 times per week at 80% of the level that exacerbated symptoms. Exercise levels were modified with 6 visits.	At-home and in-clinic	Upright exercise bike	Participants completed 4.42 ± 1.95 sessions per week	Cognition; quality of life	NIH toolbox Cognition Battery (Fluid and Crystalized Cognition Composite Score); PedsQL Generic Core	Increased Fluid and Crystalized Cognition Composit scores; Increased PedsQL scores

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TABLE 5 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Hunt et al., 2018	Pre-post-intervention study	To identify key components in an active rehabilitation program and receive perspective from youths with mTBI and their parents	Adolescents: $n = 38$; aged 9–18; males and females; parents: $n = 38$	6 week active rehabilitation program; 1x daily	Prescribed home program tailored to individual. A total of 4 components: (1) low intensity aerobic exercise for 15 min (treadmill or stationary bike), (2) sport specific coordination drills (max 10 min), (3) relaxation (deep breething, visualization) for 5 min, (4) concussion education/support (initial 1 h session and ongoing support/reinforcement through phone calls). Education topics included: concussion awareness, sleep, nutrition, energy management, return to school and return to play.	Home-based	Treadmill or stationary bike	38 youth and 36 parents completed post-intervention survey	Parent experience; youth experience	Survey measured whether active rehabilitation program was helpful; which strategy aided in concussion recovery; which strategy they'd recommend to a friend; program adherence	100% youth reported active rehab was helpful; top 3 helpful strategies reported were: energy management strategies (47.4%); aerobic exercise (31.6%), and sports drills (21.1%); key ingredients: learning energy management, physical activity, seeking help; 100% parents would recommend program; key ingredients: encouraging recovery through structured activities, youth accountability, patience/accepting uncertain timelines
Imhoff et al., 2016	Pre-post-intervention study	To identify if active rehabilitation intervention influences recovery of slow-to-recover mTBI patients	$n = 18$; youth aged 10–17; males and females	3 × 15–45 min sessions per week for an unlimited amount of weeks until symptom-free status was reached (48 ± 88 days)	The intervention had 3 components: (1) progressive sub-maximal low- to high-intensity (based on rate of perceived exertion) aerobic cycling for up to 20 min; (2) low intensity sport specific coordination exercises up to 10 min; (3) therapeutic balance exercises.	Supervised home programme	Recumbent cycling	85% ± 20%	Balance; coordination; concussion symptoms; neuropsychological; return to play	Neuropsychological: RAVLT; Verbal Fluency; Digit Span; SDMT; CPTII	Decreased concussion symptoms; improved verbal memory; semantic fluency and working memory; improved balance

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TABLE 5 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
										Coordination and Balance: SCAT3; Biosway; BOT2	
Kurowski et al., 2017	RCT	To examine the effects of aerobic training for the management of prolonged symptoms in adolescents with mTBI	Aerobic training: $n = 15$; stretching: $n = 15$; adolescents aged 12–17; males and females	5–6 days per week for at least 6 weeks (+ up to 2 weeks); participants that did not return to preinjury symptom level continued in their program for up to two additional weeks	Cycling group: tailored sub-symptom exacerbation aerobic exercise program based on aerobic cycling test performance at baseline; 80% of the duration that exacerbated symptoms at baseline assessment. Reassessment performed weekly and aerobic program adjusted accordingly. Stretching group: full-body stretching program that targeted upper and lower extremities and mid-section; rotated on biweekly basis.	Home-based	Cycling	Adherence lower in aerobic training group (4.42 times per week) vs. stretching (5.85 times per week)	Symptom severity	Post-concussion Symptom Inventory (PCSI); self-ratings considered primary outcome (pre-injury; pre-intervention), at interval visits, and after run-out period	Greater rate of improvement based on self-reported PCSI in aerobic training group vs. stretching
McGeown et al., 2018	Pre-post-intervention study	To evaluate the effect of exercise-based rehabilitation on symptom scores, brain-derived neurotrophic factor (BDNF), cognitive functions and static balance in a sample of participants with post-concussion syndrome	$n = 9$; adolescents and adults aged 14–21; males and females	4 weeks (3 sessions per week)	Warm-up followed by, stationary cycling, static balance training, and then cool down exercises requiring approximately 40–60 min for each session. Balance exercises included the same three positions performed during the balance error scoring system (BESS) protocol; DS with feet side by side and touching; SL while standing on one leg; and TS with the heel of one foot directly in front of the toes of the other foot. Participants completed three sets of each exercise, with a one min rest between each exercise.	University concussion clinic?	Recumbent cycling	100%, but some participants took up to 78 days to complete the study because a session would be stopped if it exacerbated their concussion symptoms	Balance; cognitive function; concussion symptoms; salivary-BDNF levels	Salivary BDNF	No statistically significant differences for resting HR, resting systolic BP, resting diastolic BP, or for salivary-BDNF concentrations following the aerobic and balance exercise program; no other significant results mentioned related to aerobic exercise

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TABLE 5 (Continued)

Refe-rences	Study design	Aim/ objective	Partici-pant details	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Shore et al., 2022	Pre-post-intervention study	To explore the feasibility of a newly developed, remote accessible active rehabilitation program (Tele-Active Rehabilitation) that was designed for adolescents with concussion	*n* = 3; adolescents aged 14–17; males and females	3 days per week for 6 weeks	10–30 min of subsymptom threshold activity, progressed throughout the program. Started 10 min at level 4 Pictorial Children's Effort Rating Table (PCERT), if tolerated progressed to no more than 30 min at level 6 PCERT.	Gym or at-home	Walking; running; cycling; swimming	77–100%	Illness perception; occupational performance; post-concussion symptoms; program satisfaction	Post-concussion Symptom Inventory (PCSI)–adolescent version; Brief Illness Perception Questionnaire (BIPQ); Canadian Occupational Performance Measure (COPM); Client Satisfaction Questionnaire (CSQ)	Decreased post-concussion symptoms (PCSI); most pronounced symptom reduction from week 0 to week 3; lower BIPQ scores indicating more favorable perception of their condition; 2 of 3 participants reached clinically significant change in COPM score (other approached clinical significance) indicating better occupational performance
Yuan et al., 2017	RCT combined with case-control comparison	To determine structural connectivity changes after aerobic exercise training in adolescents with persistent symptoms after mTBI	Exercise: *n* = 8; stretching: *n* = 9, case-control participants selected from pediatric functional neuroimaging research network; mean age 15.45 ± 1.72; males and females	5–6 days per week for at least 6 weeks (+ up to 2 weeks); participants that did not return to preinjury symptom level continued in their program for up to two additional weeks.	Cycling group: tailored sub-symptom exacerbation aerobic exercise program based on aerobic cycling test performance at baseline; 80% of the duration that exacerbated symptoms at baseline assessment. Reassessment performed weekly and aerobic program adjusted accordingly. Stretching group: full-body stretching program that targeted upper and lower extremities and mid-section; rotated on biweekly basis.	Home-based	Cycling	Not reported	Concussion symptoms; structural connectivity	Global efficiency; mean local efficiency; modularity; normalized clustering coefficient; normalized characteristic path length; small-worldness; Post-concussion Symptom Inventory score	Increased global efficiency and decreased normalized characteristic pathlength in exercise group; improved concussion symptoms were correlated with increase global efficiency in the aerobic group

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TABLE 6 Summary of the effects of aerobic exercise interventions following unspecified-severity traumatic brain injury.

References	Study design	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Esquenazi et al., 2013	RCT	Robotic-assisted: $n = 8$; adults aged 37.1 ± 10.6; manually assisted: $n = 8$; adults aged 41.9 ± 16.8; males and females	Severity not specified but participants had issues with ambulation as the result of a TBI	At least 1 year	6–8 weeks; 3x per week for 18 sessions; 45 min each session	Gait Mat with self-selected velocity and maximal velocity set at 10–20% of body weight support. Every 3rd session the self-selected velocity and maximal velocity were assessed and if either measure improved the training speed was increased (maximum of 10%). Manually assisted locomotor therapy group used a Lite Gate body weight support system and therapist support. The robotic-assisted locomotor therapy group with a Lokomat.	Clinic-based	Treadmill	1 participant from manually assisted treadmill group withdrew	Gait parameters	Self-selected velocity and maximal velocity; secondary gait measurements with the 6-Min Walk Test and the mobility domain of Stroke Impact Scale	Self-selected velocity and maximal velocity increased in both robotic-assisted and manually assisted treadmill training groups; no differences between the two groups; for 6-Min Walk Test no change in robotic-assisted therapy but an increase in manually assisted therapy; for stroke impact scale, increase in both groups

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TABLE 6 (Continued)

References	Study design	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Hoffman et al., 2010	RCT	Control $n = 40$; treatment $n = 40$; adults aged 37–40; males and females	Self-reported TBI severe enough to require medical intervention/ hospital admission; score of 15 on Patient questionnaire-9; must report at least mild depression severity at baseline	6 months–5 years	10 weeks; 1x per week	Each session included 15 min warm-up (stretching and walking); 30 min aerobic exercise (incline treadmill, stair-stepper, rowing machine, stationary bike, indoor track). Exercise intensity was adjusted to reach HR goal that was 60% estimated maximum HR (220-age), which would have participant exercise approx 50% of their aerobic capacity and reach perceived exertion of 12 on a 20-point scale; 15 min of cool down (stretching, slow walking). Participants were also asked to perform additional 30 min of aerobic exercise 4x per week at home.	Community gym and additional aerobic exercises at-home	Treadmill; stair-stepper; rowing machine; stationary bike; indoor track	84 enrolled; 4 did not attend sessions after enrollment; 76 participants completed 10-week assessment; unable to contact 4 subjects for 10 week assessment; mean number of sessions attended was 5.88 where more than half exercise group attended 7 or more sessions	Severity of depression	Beck Depression Inventory (BDI); physical symptoms of depression/ health; pain; fatigue; Brief Pain Inventory (BPI); Pittsburgh Sleep Inventory; Head Injury Symptom checklist; SF-12 Health Survey	No significant differences on the BDI (severity of depression) in treatment vs. control; exercise group had less pain interference and greater improvement on BPI compared to control; no improvement on increasing min of exercise, head injury symptoms, perceived quality of life, sleep, general health, HR, or ability to walk; high activity sub-group (greater than 90 min exercise per week) had lower depression scores than low activity group; high activity group also reported more community activity, better quality of life, better general mental health.

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TABLE 6 (Continued)

References	Study design	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Kolakowsky-Hayner et al., 2017	RCT	Walking first: $n = 62$; nutrition first: $n = 63$; adults aged 42.7 ± 15.5; males and females	TBI at least 6 months prior that required medical attention; must be able to ambulate; use of orthotics, cane/walker permitted	6 months	36 weeks total; 12 weeks exercise period; 12 weeks nutrition period; 12 weeks washout	Use pedometer to track steps; total number of steps, aerobic steps, calories burned, and miles walked. Assigned coach set time, weight and stride length. Goal of 5% increase over individual baseline in daily steps for first week. Subsequent weeks, step goal was increased until reached 40% incease in week 8 and maintained in last 4 weeks.	Home-based	Walking	Poor adherence; almost a third discontinued intervention	Fatigue	Global Fatigue Index (GFI); the Barrow Neurological Institute (BNI) Fatigue Scale Overall Severity Index Score; and the Multidimensional Fatigue Inventory (MFI); domains of fatigue: severity, distress, impact on activity, and timing of fatigue	Exercise-first and nutrition-first groups increased number of steps over time; less fatigue (GFI, BNI total and MFI general score) after walking intervention, whereas nutrition intervention had little impact on fatigue; less fatigue after 24 weeks (active part of intervention) and wash out period (36 weeks)
Tefertiller et al., 2022	RCT	$n = 31$; adults aged 18–65; males and females	Chronic TBI with self-reported and objective balance deficits, completed inpatient rehabilitation at single TBI specialized rehabilitation hospital	At least 1 year	1 h sessions; 3x per week for 4 weeks	5 min of balance training; >35 min of mobility training; Virtual Reality + Treadmill Training (VRTT) group: Treadmill training with feedback on gait in the form of VR games; Treadmill Training (TT) group: Treadmill training only.	Clinic-based; supervised by physiotherapist	Motek C-Mill Treadmill	100%	Balance; mobility	Community Balance and Mobility Scale (CB and M); 10 meter walk test (10MWT); 6 min walk test (6MWT); Timed Up and Go (TUG); HR; perceived exertion; Physical Activity Enjoyment Scale (PACES)	Improved CBand M; nominal increases 10MWT; increased 6MWT; nominal improvements in TUG; VRTT and TT groups had greater PACES score indicating more enjoyment of the program compared to standard care group; no significant differences relating to aerobic exercise and current standard of care; all groups had improved balance and mobility after 12 week intervention and at 4 week follow up

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TABLE 6 (Continued)

References	Study design	Participant details	TBI demographics	Time since injury	Intervention timeline	Intervention details	Intervention location	Aerobic modality	Participant adherence	General outcome measures	Specific outcome measures	Results related to aerobic exercise
Pennington et al., 2022	Pre-post-intervention study	Exercise only: $n = 13$; gameplay control: $n = 12$; VR-EFT: $n = 18$; males and females	Not reported, but all had alcohol use disorder	At least 6 months	8 weeks	Used a recumbent bicycle, a set of gameplay controllers mounted on the recumbent bicycle handlebars, and an Oculus Rift VR headset. A total of 3 sessions of control (exercise or game) per week for 3 weeks, 1 week rest, 3 weeks combined game while on bike, 3x per week.	San Francisco Veterans Affairs Health Care System	Recumbent cycling	7/30 lost to follow up for various reasons; 7/30 did not do 8 week follow up (mostly due to COVID); 23/30 included in analysis; overall 53% completed the study	Neuropsychological testing; PCS; alcohol use and craving	Working memory; visual scanning; cognitive flexibility; cognitive inhibition; cognitive inhibition-switching; processing speed; auditory-verbal immediate recall; auditory-verbal delayed recall; visuospatial immediate recall; visuospatial delayed recall; exploratory analyses: within group change in alcohol use, craving and post-concussive symptoms; drinks per week; Obsessive Compulsive Drinking Scale (OCDS) total; OCDS Obsessive Subscale; OCDS Compulsive Subscale; Neurobehavioral Symptom Inventory	Combined exercise and game had improvement in cognitive inhibition switching and visual scanning; significant improvement in cognitive inhibition associated with the exercise-only condition; no changes in alcohol consumption following the combined intervention; no changes in post-concussion symptoms in any intervention group.

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should be considered. Time since injury can play a role in physical recovery. For example, with severe brain injury, multiple physical injuries are common activity-limiting comorbidities (Chan et al., 2017). Several studies included assisted-physical activity, by use of walking supports, physical therapists present, and including non-balance dependent exercise (e.g., hand cranking), demonstrating that aerobic exercise is possible amongst other physical challenges. Neurologically, the post-TBI timeline is complex and may differ by injury severity. TBIs can cause cytotoxic cell death, neuronal damage, neural metabolic crisis, gliotic scarring, inflammation, and an increase in reactive oxygen species, all contributing to adverse outcomes. However, the post-injury timeline is also known to be one of neuroplasticity. It is suggested that neuroplasticity may occur in three phases post-injury (Sophie Su et al., 2016). During the first few days post-injury, increased cell death, neurometabolic strain and decreased cortical inhibitory pathways may signal for neuronal cells and glial cells to replace damaged ones and facilitate recovery, and the utilization of new neuronal networks (Burda and Sofroniew, 2014; Giza and Hovda, 2014; Sophie Su et al., 2016). In the weeks post-injury, synaptogenesis and axonal sprouting assist in the process (Sophie Su et al., 2016), while neural metabolism begins to stabilize (Wieloch and Nikolich, 2006). However, these previous perturbations from the brain's typical state may induce "negative plasticity," a perpetuating cycle of reduced brain plasticity, which can persist years after the injury (**Figure 3**; Tomaszczyk et al., 2014). This negative plasticity has been attributed to lack of use, reduced efficiency in processing sensory and perceptual information, and impaired control over neuromodulation, and is hypothesized to underlay long-term TBI-induced neurodegeneration (Tomaszczyk et al., 2014). Given that aerobic exercise promotes neuroplasticity, it seems especially important to include it in rehabilitation programs at all stages post injury, but it may have the largest benefits at more acute timepoints. It could also be possible that interventions implemented at chronic timepoints should occur at higher frequency, and for longer, to counteract the hypothesized negative plasticity.

Common limitations in this cohort of studies include inadequate comparison groups, lack of details about the exercise programs, small sample sizes, and low adherence rates. While comparison groups are especially important for intervention-based studies, we recognize the many challenges that can occur in this population that can make having these groups challenging (e.g., recruitment windows, scheduling, participants engaging in multiple therapeutic interventions). The importance of adequate comparison groups (e.g., active control, wait-list control) allows us to draw more definitive conclusions about the intervention's effects, which is especially important post-injury, given that time is an important factor in recovery. Studies which only include one group, or have small sample sizes are still valid and beneficial, and can lead to areas for future research, but they should be interpreted with discretion. Several studies in this review reported adherence rates near 50%, which may indicate challenges with study design, participant interest, feasibility, and accessibility of the intervention. In this set of studies, a mix of clinic-based and home-based studies reported low adherence, therefore, it may be important to offer both in-person and at-home options, such that participants can determine what would be best for them. Given these adherence challenges, it would be worthwhile to conduct feasibility studies in this area to better understand the contributing factors to this low adherence. Another challenge in this set of studies included limited details on aerobic activity, for example, unclear reporting of modality, duration, and frequency of sessions, and if participants had specific effort or heart rate targets. Accurate reporting of interventions allows future researchers to repeat and expand study designs that show promise. While these studies offer valuable insights, the common limitations underscore the necessity for well-structured, detailed research protocols, and robust adherence strategies.

TABLE 7 Recommendations for future researchers using aerobic exercise as a post-traumatic brain injury intervention.

Item	Recommendation
Study design	• Randomized controlled trial with a minimum of two groups (intervention, control) and two timepoints (baseline, post-intervention)
	• *A priori* power analysis conducted to determine appropriate sample size
Intervention	• Includes a pre-defined aerobic goal (e.g., 80% maximal heart rate)
	• Objective measurement of aerobic goal to assess compliance
	• Any type of aerobic activity
	• At-least 3 × 30 min per week for 12-weeks
	• Supervised activities may increase compliance
Accessibility	• Physical supports and modified activities enhance accessibility
	• Offer in-person and at-home activities
Reproducibility	• Published studies should clearly detail their aerobic methodology such that future studies can build from the work
	• Publish all intervention materials including exercise videos, participant hand-outs to could facilitate future research

This scoping review serves as a foundation for the application of post-traumatic brain injury aerobic exercise. Based on this review, we propose a methodological framework and a number of suggestions and areas for future research (**Table 7**). A key finding of this scoping review is the clear lack of research for children aged 12 years and younger, and elderly adults, aged 65 and over. Across all TBI severities, not one study exclusively studied children or elderly adults, despite the fact that these age groups are most at risk for TBIs (Government of Canada, 2020). Interventions at these time points are critical, as children are going through robust neurological development, while older adults typically fare worse after TBI than younger adults (LeBlanc et al., 2006; Araki et al., 2017). TBIs are one of the greatest causes of death and disability in these groups, and adapted aerobic exercise is a promising, and understudied research area. Physical abilities may play a role in this understudied area, but just because someone has reduced or different mobility, does not mean that aerobic exercise should be avoided. Weight-assisted walking, walking poles, water activities and hand cranking are some of the many ways in which researchers could accommodate younger and older age groups into the current body of literature. Another lacking area of research is specific to moderate TBI, or TBIs with a Glasgow Coma Scale rating of 9–13. While individuals with moderate

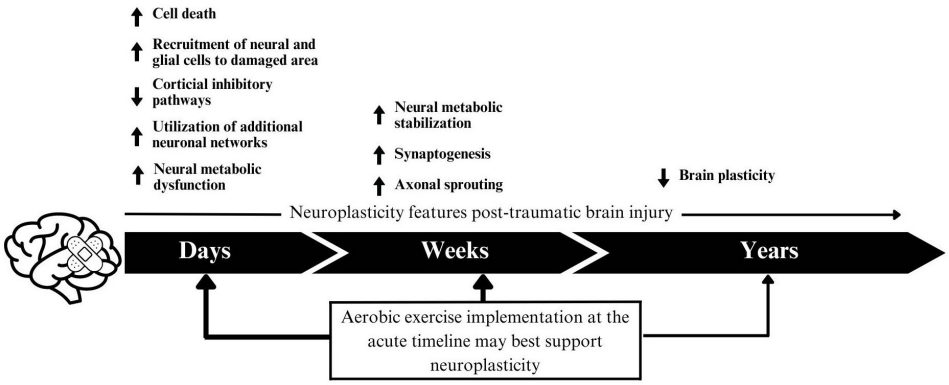

FIGURE 3
A proposed schematic of negative plasticity following traumatic brain injury. Arrow thickness indicates the proposed impact of intervention within that timeframe.

TBIs were included in the research presented, they were either grouped in with severe TBI survivors or their injury severity was unspecified. By definition, moderate TBIs present uniquely upon examination, and survivors deserve tailored and specific research to support their recovery. One recommendation is to include severity-based sub-analyses of research to elicit any severity-specific findings.

5 Conclusion

In conclusion, this scoping review presented the array of aerobic interventions used post-TBI across different life stages. It seems that while aerobic exercise post-TBI is a promising intervention area, it is influenced by various factors such as injury severity and the timing of the injury. Moreover, while this review suggests general consensus on the safety and effectiveness of aerobic exercise as a rehabilitative strategy post-TBI, it also highlights some significant gaps and limitations in the current research landscape.

Among these limitations, the inadequacy of comparison groups, small sample sizes, vague reporting on exercise programs, and low adherence rates emerged as key challenges. Despite these hurdles, it's essential to acknowledge that studies with such limitations can still fuel future research and contribute to our understanding, albeit requiring careful interpretation.

Based on the present review, we suggest several avenues for future research. These include detailed and clear reporting of intervention design and execution, providing both in-clinic and at-home options for participants, and emphasizing the importance of power analysis in determining sample sizes. Furthermore, a focus on age-specific research is paramount given the glaring lack of studies on children aged 12 and under and elderly adults over 65. It is crucial to develop research strategies that are inclusive and accommodate individual abilities across the lifespan, especially considering the high risk of TBIs in these age groups. Also, more specific research on moderate TBIs, often overlooked in studies, is needed to ensure recovery support tailored to this group.

As such, this scoping review serves as a critical cornerstone for future research into the use of aerobic exercise post-TBI. By addressing the noted limitations and gaps in the existing body of knowledge, we can enhance our understanding of this field and optimize recovery strategies for TBI survivors across different ages and injury severities.

6 Transparency, rigor, and reproducibility

This review is part of a series of systematic reviews of Brain Changes Initiatives' Brain Pillars of Health project. This scoping review was conducted according to PRISMA-ScR methodology and guidelines, and our findings are reported according to the PRISMA-ScR checklist. Our review was conducted by a multidisciplinary team including clinical experts in the field of brain injury, researchers and a survivor of brain injury. As reported in this scoping review, a range of aerobic exercise interventions exists for traumatic brain injury rehabilitation, however, there is a paucity of data specifically for children and older adults. Further, we assess intervention methods and study designs currently in use, and suggest standardization practices for future research. The search strategy is detailed in full in this manuscript. Full data charting sheets are available upon request.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

TS: Conceptualization, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review and editing. JM: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review and editing. MB: Formal analysis, Investigation, Writing – review and editing. EE: Formal analysis, Investigation,

Writing – review and editing. CA: Formal analysis, Investigation, Writing – review and editing. EG: Investigation, Writing – review and editing. HR: Investigation, Writing – review and editing. JB: Investigation, Writing – review and editing. MG: Conceptualization, Funding acquisition, Resources, Writing – review and editing. JG: Conceptualization, Writing – review and editing. BC: Conceptualization, Funding acquisition, Resources, Writing – review and editing.

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Author disclosure

MG and Brain Changes Initiative (BCI)

MG is a physician, the founder of BCI, and a TBI survivor. In 2013, MG endured a critical motor vehicle accident, resulting in a severe traumatic brain injury. Following immediate life support, MG faced notable cognitive and physical impairments, casting doubt on returning to his previous medical schooling and active lifestyle. Through concerted efforts, including acute care and admittance to Toronto Rehabilitation Institute, he embarked on a profound recovery process, including Physiotherapy, Occupational Therapy, and Speech-Language Pathology. After his discharge, MG's extensive research on neurogenesis and neuroplasticity helped structure a tailored rehabilitation program. With unwavering hard-work and commitment, he triumphantly completed his medical degree and residency at Western University's Schulich School of Medicine. Now a licensed physician, MG has inaugurated Brain Changes Initiative, targeting transformative research, support, and advocacy in TBI, aiming to revolutionize the standard of care in Canada and worldwide. This initiative underscores the importance of tailored rehabilitation and continuous research in shaping a promising path for TBI survivors. To learn more about the Brain Changes Initiative's story, research and funding opportunities visit: https://www.brainchanges.org/.

This review is the first commissioned piece in a series of systematic reviews for Brain Changes Initiative, focused on BCI's six pillars of brain health: Aerobic Exercise, Cognitive Training, Sleep Hygiene, Mindfulness, Nutrition, and Limiting Harmful Exposures. MG is the founder of BCI and BRC and JG sit on BCI's scientific advisory board. TSR is a volunteer for BCI.

Conflict of interest

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1307507/full#supplementary-material

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Evidence for reticulospinal plasticity underlying motor recovery in Brown-Séquard-plus Syndrome: a case report

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Brown-Séquard Syndrome (BSS) is a rare neurological condition caused by a unilateral spinal cord injury (SCI). Upon initial ipsilesional hemiplegia, patients with BSS typically show substantial functional recovery over time. Preclinical studies on experimental BSS demonstrated that spontaneous neuroplasticity in descending motor systems is a key mechanism promoting functional recovery. The reticulospinal (RS) system is one of the main descending motor systems showing a remarkably high ability for neuroplastic adaptations after incomplete SCI. In humans, little is known about the contribution of RS plasticity to functional restoration after SCI. Here, we investigated RS motor drive to different muscles in a subject with Brown-Séquard-plus Syndrome (BSPS) five months post-injury using the StartReact paradigm. RS drive was compared between ipsi- and contralesional muscles, and associated with measures of functional recovery. Additionally, corticospinal (CS) drive was investigated using transcranial magnetic stimulation (TMS) in a subset of muscles. The biceps brachii showed a substantial enhancement of RS drive on the ipsi- vs. contralesional side, whereas no signs of CS plasticity were found ipsilesionally. This finding implies that motor recovery of ipsilesional elbow flexion is primarily driven by the RS system. Results were inversed for the ipsilesional tibialis anterior, where RS drive was not augmented, but motor-evoked potentials recovered over six months post-injury, suggesting that CS plasticity contributed to improvements in ankle dorsiflexion. Our findings indicate that the role of RS and CS plasticity in motor recovery differs between muscles, with CS plasticity being essential for the restoration of distal extremity motor function, and RS plasticity being important for the functional recovery of proximal flexor muscles after SCI in humans.

KEYWORDS

Brown-Séquard Syndrome, spinal cord injury, reticulospinal tract, corticospinal tract, StartReact, motor recovery, neural plasticity, mirror activity

1 Background

Brown-Séquard Syndrome (BSS) and Brown-Séquard-plus Syndrome (BSPS) are uncommon conditions occurring in 2–4% of patients with traumatic spinal cord injury (SCI) (1, 2). A pure form of BSS is extremely rare and characterized by a confined unilateral spinal lesion that results in ipsilesional hemiplegia and loss of proprioception, as well as loss

of pain and temperature sensation on the contralesional side below the level of injury (3). Most observations of Brown-Séquard-like syndromes correspond to the less pure form of the syndrome termed BSPS. The BSPS consists of a predominantly unilateral spinal lesion that leads to a characteristic asymmetric presentation of paresis and hypalgesia (2, 3). Patients with BSS and BSPS generally have a good prognosis for motor recovery and for a return to near pre-injury lifestyles (3, 4).

An important driver for functional recovery after incomplete SCI is spontaneous neuroplastic adaptation within the central nervous system (CNS) (5). The predominant impairment of descending fibers on one side, and sparing of fibers on the other, renders the BSS an interesting model to study neuroplasticity and functional recovery. Fiber sprouting and synaptic rewiring of descending motor tract systems lead to enhanced motor drive in spinal cord areas below the lesion, inducing functional recovery. This has been extensively demonstrated for the corticospinal (CS) system (4, 6). However, neuroplasticity has also been shown in other descending motor systems such as the phylogenetically conserved, functionally relevant reticulospinal (RS) system. Besides the CS system, the RS system is considered a main descending motor system for movement control (7). Recent preclinical studies revealed that the RS system shows a high potential for neuroplastic adaptations upon incomplete SCI: Preserved RS fibers showed remarkable compensatory sprouting, with axons crossing the midline of the sublesional spinal cord, innervating the ipsilesional (i.e., denervated) hemicord (8, 9). Additionally, other preclinical BSS studies identified significant regenerative sprouting of severed RS fibers above the level of injury forming new synapses onto propriospinal neurons bypassing the lesion site (10). Recently, Asboth and colleagues found that, after a severe experimental SCI transecting the CS tract in mice, fibers from the motor cortex synapsed onto sprouting descending RS fibers, thereby forming a cortico-reticulospinal detour pathway (11). The mentioned studies indicate that RS plasticity is a key mechanism driving functional recovery in experimental SCI models. There is growing evidence that RS plasticity might also play an essential role in the restoration of motor function in humans with SCI (12, 13).

The most common approach to assess RS drive non-invasively is the StartReact paradigm (14). In this paradigm, the reaction time of movements is shortened when movement initiation is paired with loud acoustic stimuli (LAS) compared to moderate acoustic stimuli (MAS). Although the mechanisms underlying the StartReact effect are not fully understood, there is compelling evidence from preclinical (15) and clinical studies (13, 16) that the RS system plays a key role in the reaction time shortening. Indeed, the degree of reaction time shortening is hypothesized to reflect the extent of the RS drive (12, 15, 17). The StartReact paradigm has previously been used to assess RS plasticity in neurological patients (13, 16).

Compared to the CS system, RS projections are more diffuse, often innervating spinal interneurons and motor neurons of both ipsi- and contralateral sides (18). Previous studies have demonstrated that single RS neurons drive bilateral muscle activation (19–21). Upregulation of the RS system has been associated with mirror movements, describing involuntary synchronous movements of one limb during voluntary movements of the other limb (22, 23). Mirror movements are often reported in stroke patients, and are usually observed in the less impaired extremity, during voluntary activation of the more impaired extremity (23, 24). Mirror movements quantified by electromyographic (EMG) recordings are typically referred to as mirror activity.

This study aimed at examining neuroplasticity in the two principal desending motor systems, i.e., the CS and RS system, in a patient with BSPS. We hypothesized that RS plasticity is present in proximal muscles after SCI, resulting in enhanced RS drive on the ipsilesional side that might underlie motor recovery and mirror activity.

2 Case presentation

The subject is a 58-year-old male, who presented with an incomplete tetraplegia (ASIA impairment scale (AIS) D) due to a right-sided SCI at neurological level C1, after a bicycle accident. T2-weighted magnetic resonance imaging (MRI performed at day 35 post-injury) showed a high-cervical spinal lesion primarily affecting the right hemicord (Figures 1A,B). Sensory function as measured by the International standards for neurological classification of SCI (ISNCSCI) assessment score showed that mechano-sensation (light touch) was reduced on both sides, indicating partial spinal damage of the contralesional dorsal column. Pain sensation (pinprick) was reduced on the ipsilesional side, and nearly absent contralesionally. The subject showed motor symptoms reflecting a BSS with ipsilesional paresis being more pronounced in the upper compared to the lower extremities (Figure 1C). The patient's syndrome conforms to BSPS resulting from a mainly unilateral spinal lesion.

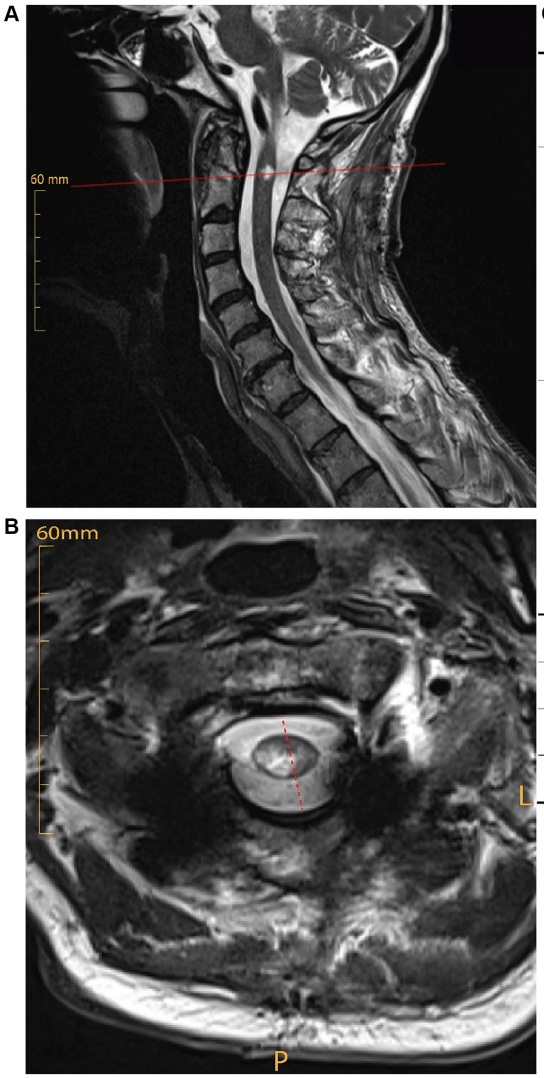
The subject showed a substantial degree of functional recovery: He regained the ability to walk independently seven weeks post-injury. Five months after injury, most key muscles of the upper and lower extremities showed full strength according to the ISNCSCI motor examination (Figure 1C). The subject was discharged from inpatient rehabilitation five months post-injury with some persisting motor impairments in the upper ipsilesional extremity.

2.1 Functional assessments

Clinical data were assessed during the acute phase (one-month post-injury) as well as five months post-injury, thus allowing to monitor functional recovery over time. The ISNCSCI motor score was used to assess the strength of upper and lower extremity muscles. The ISNCSCI motor score rates muscle strength on a scale from 0 (no strength) to 5 (full strength). Walking function was assessed by standardized clinical tests including the Timed Up and Go test, the 10-meter walk test, and 6-min walk test.

2.2 Neurophysiological assessments

RS drive to the ipsi- and contralesional cord was assessed by the StartReact paradigm at five months post-injury. The subject sat in a chair placed 0.3 m in front of a speaker box (ElectroVoice, ELX200, United States). Sound intensity was adjusted with a high-precision sound level meter (Cirrus research, CR162B). First, the subject was presented with five LAS (120 dB, 50 ms, 1,000 Hz) to get familiarized with the loud startling tones. This was followed by a paradigm of 30 stimuli with a randomized order of 19–21 MAS (82 dB, 50 ms, 1,000 Hz) and 9–11 LAS. Varying numbers of LAS



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ASIA Motor Score		Acute (AIS D)		5 m. post-injury (AIS D)	
		R	L	R	L
UE	Elbow flexors	0	5	5	5
	Wrist extensors	0	4	5	5
	Elbow extensor	0	5	4	5
	Finger flexor	0	4	5	5
	Finger abductors	0	4	4	5
LE	Hip flexors	4	5	5	5
	Knee extensors	5	5	5	5
	Ankle dorsiflexor	3	5	5	5
	Long toe extensors	3	5	5	5
	Ankle plantar flexors	3	5	5	5

Gait Assessments	Acute	5 m. post-injury
Timed Up and Go [s]	91	7
10 meter walk test [s]	56	4
6 min. walk test [m]	-	600

FIGURE 1
(A) Saggital and **(B)** axial T2-weighted magnetic resonance images of the cervical spine acutely (i.e., 35 days) post injury, showing a mainly right-sided spinal lesion. **(C)** Functional recovery over five months post-injury. Clinical measures of muscle strength (ISNCSCI motor score), and walking function (timed-up and go test, 10-meter walk test, 6-min walk test) show substantial initial impairments that are pronounced on the ipsilesional side. All functional tests demonstrate a strong functional recovery over time. AIS, AISA impairment scale; L, left; LE, lower extremities; m., months; P, posterior; UE, upper extremities.

and MAS were used to prevent anticipation of the imperative stimulus towards the end of the blocks. Each stimulus was preceded by a warning stimulus (92 dB, 50 ms, 500 Hz) with varying time intervals between the warning stimulus and LAS or MAS (1500–3,000 ms). Acoustic stimuli were generated using a custom-made Simulink application (Matlab R2021b, Mathworks Inc., Natick, United States). The subject was instructed to perform different movements as fast as possible upon LAS or MAS. There was no instruction on the extent of movement. In total, the patient performed six experimental StartReact blocks [elbow flexion (left & right), elbow extension (left & right), and ankle dorsiflexion (left & right)]. Surface EMG signals were recorded bilaterally from the sternocleidomastoid, biceps brachii, triceps brachii, and tibialis anterior muscles using bipolar Ag-AgCI surface EMG Electrodes (H124SG, Kendall). The EMG signal was sampled at 2000 Hz and recorded using a wireless EMG system (Myon Aktos, Cometa Systems, Bareggio, Italy). Acutely and six months post-injury, a clinical neurophysiological assessment was performed. Transcranial magnetic stimulation (single-pulse TMS at 100% stimulator output with double cone coil, Magstim BiStim^2, The Magstim Co Ltd., Whitland, UK) was performed one and six months post-injury in the framework of clinical routine assessments, and therefore deviates from classical research protocols. MEPs were assessed to probe CS drive to biceps brachii and tibialis anterior muscles on the ipsi- and contralesional side. To evoke MEPs in the biceps brachii, the coil was placed at the vertex, and 4 cm laterally to the left (for ipsi-) or right (for contralesional biceps). For MEPs in the tibialis anterior, the coil was placed at the vertex. MEPs were applied without muscle pre-contraction. Per muscle and time point, two to six stimulations were applied.

2.3 Data analysis

EMG muscle onset was defined as EMG activity surpassing baseline EMG activity ± two standard deviations (SD). Baseline EMG activity was measured 100 ms before stimulus release. Motor reaction time was calculated from the time between stimulus onset and muscle onset. The StartReact effect was calculated by subtracting the median reaction time of LAS trials from the median reaction time of MAS trials. MEPs were bandpass filtered from 10 to 500 Hz and rectified.

Mirror activity was analyzed based on EMG activity during StartReact trials. Specifically, EMG activity was assessed in homologous muscles of the contralateral side during a task on the affected side. The time point of muscle onset in the voluntary muscle was determined (T_{onset}). The mean area under the curve (AUC) for 100 ms after T_{onset} was calculated in the EMG signal of the mirror muscle (AUC_{mirror}). Background EMG activity was defined as AUC in the time window of 1 s before T_{onset} in the EMG signal of the mirror muscle ($AUC_{background}$). AUC values were time normalized. Mirror activity was expressed as ratio of AUC_{mirror} to $AUC_{background}$ in percent [adapted from Cincotta et al. (25)]. Values above 100% indicate the presence of mirror activity in the muscle contralateral to the voluntary movement.

2.4 Statistical analysis

Statistical analysis was performed using R (Version 4.2.3, RStudio, Inc.), with the level of significance set at $p < 0.05$ for all statistical tests. Given the non-normal data distribution of reaction time values (assessed with a Shapiro–Wilk-Test), the Mann–Whitney *U* test was performed to compare reaction times in response to MAS and LAS for each task. StartReact effects were quantified by the Wilcoxon signed-rank test after randomized down-sampling of MAS trials to the number of LAS trials. Cohen's d effect sizes were calculated.

Mirror activity was compared between LAS and MAS using the Mann–Whitney *U* test. Due to a lack of a significant difference, MAS and LAS trials were combined for the analysis of mirror activity. Mirror activity for the contralesional muscles was analyzed during tasks of the homologous ipsilesional muscles. Mirror activity values were compared using a Kruskal-Wallis test. A pairwise comparison was performed using a Bonferroni-corrected Dunn's test and Hedges's g effect sizes were calculated.

3 Results

3.1 Functional assessments

All clinical tests demonstrated a substantial functional recovery of the subject over five months post SCI (Figure 1C). The ISNCSCI motor score demonstrateda complete paralysis of the upper extremity muscles and a partial paresis of lower extremity muscles on the ipsilesional side acutely post-injury. In contrast, muscle strength on the contralesional side was well preserved. Whereas muscle strength of the ipsilesional elbow flexors and ankle dorsiflexors recovered completely, persisting deficits occurred in the ipsilesional elbow extensor and finger abductor (M. abductor digiti minimi) at five months post-injury. Light touch sensation was reduced bilaterally (ipsi-: 25/56 points; contralesional: 25/56 points) acutely post-injury, and only showed minor recovery over time (ipsi-: 26/56 points; contralesional: 28/56 points). Pain sensation was disproportionally reduced on the contra- (4/56 points) vs. ipsilesional side (36/56 points) acutely, and did not recover over a period of five months (ipsi-: 27/56 points; contralesional: 0/56 points). Clinical gait measures demonstrated obvious walking impairments in the acute phase after injury, which recovered substantially over five months (Figure 1C).

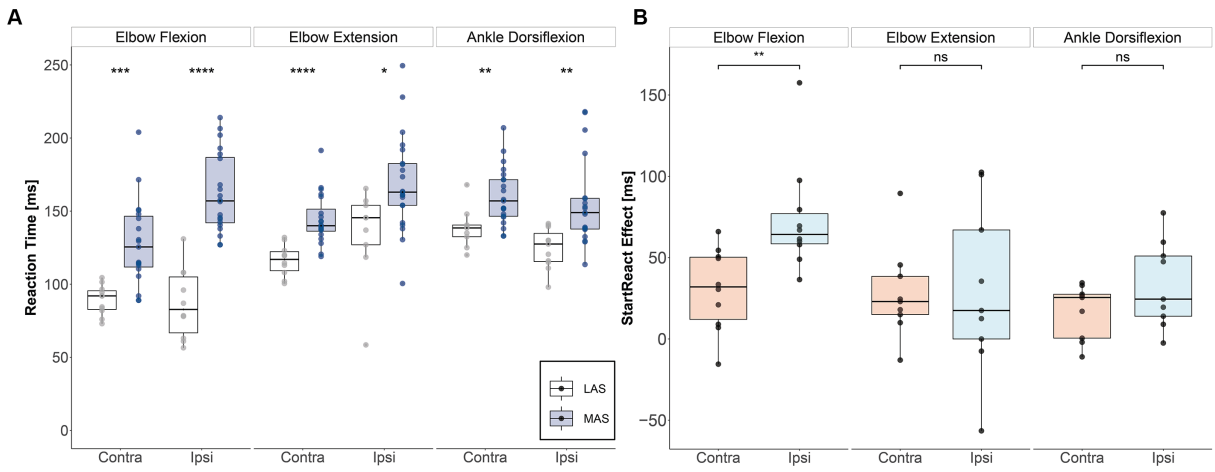

FIGURE 2
StartReact effects for upper and lower extremity muscles. **(A)** Median reaction times for each task and side for moderate acoustic stimuli (MAS) and loud acoustic stimuli (LAS). (Significance levels of Mann–Whitney *U* test: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$). **(B)** StartReact effects as measured by the difference in reaction time between MAS and LAS trials for each task and side. There was an enhanced reticulospinal gain in the ipsi- vs. contralesional biceps brachii muscle five months after SCI. Contra, contralesional; Ipsi, ipsilesional; LAS, loud acoustic stimuli; MAS, moderate acoustic stimuli.

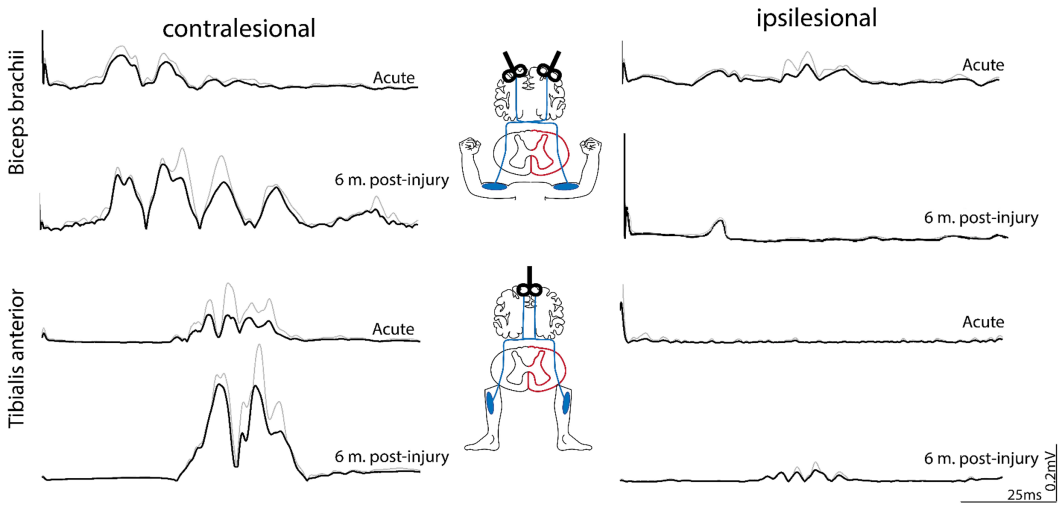

FIGURE 3
Motor-evoked potentials (MEPs) assessing corticospinal drive to biceps brachii and tibialis anterior muscles. Transcranial magnetic stimulation (TMS) was applied over the relative cortical representation of the arm and leg for both the ipsi- and contralesional side. Acutely after injury (1 month post-injury), MEPs were observed in the contralesional biceps and tibialis anterior. Low-amplitdue MEP occurred in the ipsilesional biceps, whereas no MEPs were observed in the ipsilesional tibialis anterior. Six months post-injury, MEPs were enhanced in the contralesional muscles, whereas the ipsilesional biceps brachii did not reveal enhanced MEPs compared to acute time points. In contrast to acute time points, MEPs re-occurred in the ipsilesional tibialis anterior 6 months post-inury, indicating restoration of CS drive to this muscle. MEP responses represent grand averages (black) + standard deviations (gray) of multiple stimulations (two to six per muscle). m, month(s).

3.2 StartReact

The subject demonstrated significant StartReact effects in all assessed muscles on both sides (Figure 2A). Accordingly, reaction times were significantly faster in response to LAS than MAS (biceps brachii left (contralesional): $U = 17$, $p < 0.001$, $d = 1.61$; biceps brachii right (ipsilesional): $U = 2$, $p < 0.001$, $d = 2.87$; triceps brachii left: $U = 11$, $p < 0.001$, $d = 1.82$; triceps brachii right: $U = 39$, $p = 0.013$, $d = 1.06$; tibialis anterior left: $U = 31.5$, $p = 0.005$, $d = 1.2$; tibialis anterior right: $U = 34$, $p = 0.003$, $d = 1.23$; Mann–Whitney U tests).

Figure 2B shows that the StartReact effect, which reflects RS drive, was substantially enhanced on the ipsilesional compared to the contralesional side for the biceps brachii ($V = 1$, $p = 0.004$, $d = 1.37$). In contrast, the StartReact effect did not differ between the ipsi- vs. contralesional side in the triceps brachii ($V = 21$, $p = 0.91$, $d = 0.04$) nor in the tibialis anterior ($V = 8$, $p = 0.098$, $d = 0.58$; Wilcoxon signed-rank test). Cortical motor-evoked potentials (MEPs):

3.3 Cortical motor-evoked potentials (MEPs)

Acutely after injury, MEP latencies were delayed in biceps brachii muscles bilaterally [contralesional: 17.1 ms; ipsilesional: 18.2 ms; cutoff pathological latency: 12 ms (26)] and in the contralesional tibialis anterior [33.6 ms; cutoff pathological latency: 32.5 ms (26)]. No MEPs could be evoked in the ipsilesional tibialis anterior acutely post-injury (Figure 3). MEP latencies after six months post-injury were similar to the acute values in biceps brachii muscles (contralesional: 14.2 ms; ipsilesional: 19.5 ms) and the contralesional tibialis anterior (33.7 ms). Compared to the acute phase, MEP amplitude was unchanged in the ipsilesional biceps (acute: 0.05 mV; 6 months: 0.06 mV), but slightly enhanced on the contralesional side (acute: 0.11 mV; 6 months: 0.19 mV). MEP amplitude in the contralesional tibialis anterior was increased after six months compared to acutely post-injury (acute: 0.1 mV; 6 months: 0.33 mV; Figure 3). Interestingly, MEP responses were observed in the ipsilesional tibialis anterior six months post-injury (latency: 33.8 ms; amplitude: 0.04 mV), indicating partial restoration of CS drive to ipsilesional lumbar motoneuron pool of the tibialis anterior. Motor nerve conduction velocity of the ulnaris and tibialis nerves were not impaired acutely and six months post-injury, implying that there was no impairment of the peripheral nervous system.

3.4 Mirror activity

Mirror acitivity was examined on the contralesional side during the voluntary contraction of the homologous muscles on the right ipsilesional side (Figure 4). Mirror activity was observed only in the biceps brachii muscles, but not the triceps brachii and tibialis anterior (Figure 4A). The amount of mirror activity was different across muscles ($H(3) = 65.7$, $p < 0.001$, $\eta 2 = 0.5$; Kruksal-Wallis Test), with biceps brachii showing higher values than the other muscles (biceps left vs. triceps left: $z = -7.0$ $p < 0.001$, Hedges's $g = 2.5$; biceps left vs. tibialis anterior left: $z = -6.9$, $p < 0.001$, Hedges's $g = 2.55$; Mann–Whitney U Test; Figure 4B).

4 Discussion

The subject presented with a BSPS, with severe initial motor impairment on the ipsilesional side. The subject showed substantial motor recovery over five months post-injury. Superior recovery of biceps brachii vs. triceps brachii function agrees with earlier reports (27). Recent findings by Sangari and Perez (13) provide evidence that increased RS drive to the biceps brachii, but not the triceps brachii might be the

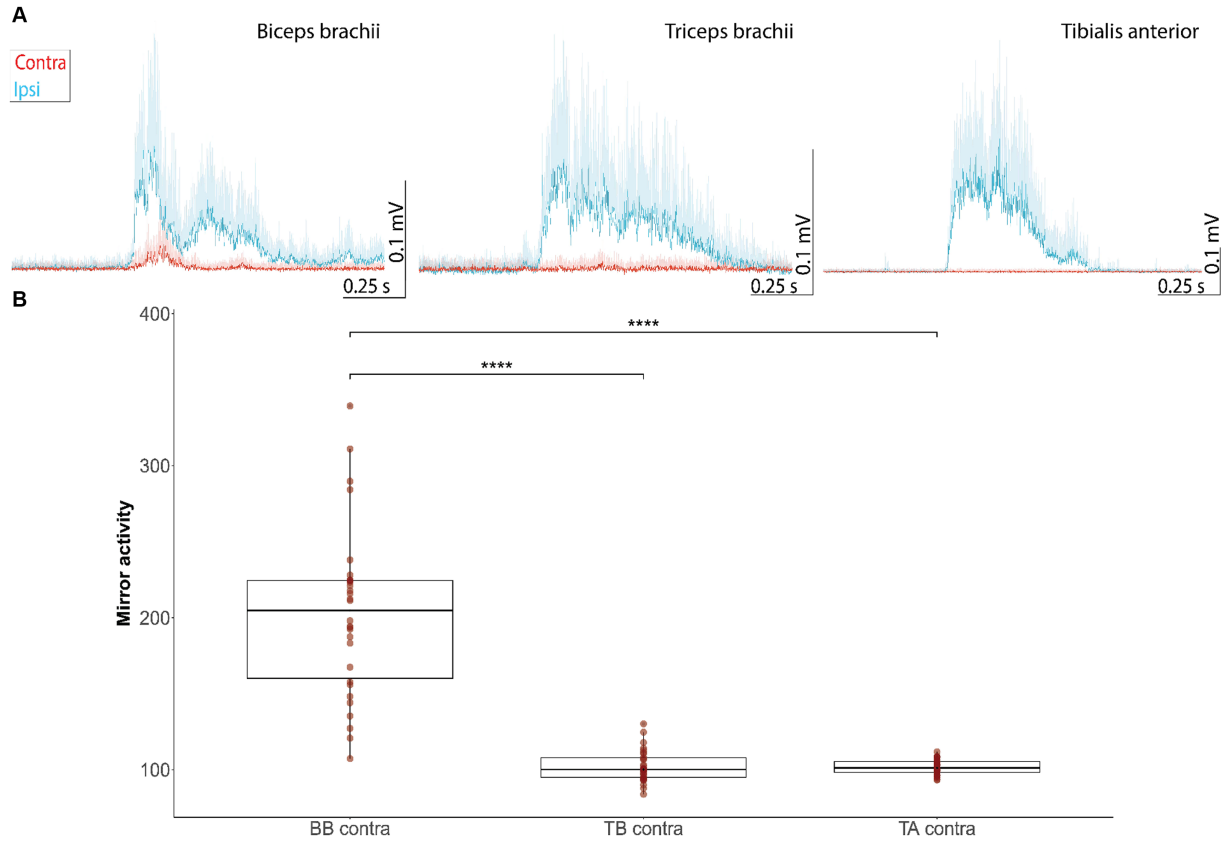

FIGURE 4
Mirror activity in muscles of the contralesional side evoked by movements of homologous muscles on the more impaired, ipsilesional side. **(A)** EMG responses represent grand averages + standard deviations of the ipsi- (blue line) and contralesional muscles (red curve) during movements of the ipsilesional joints. Mirror activity is observed in the contralesional biceps brachii, but not triceps brachii and tibialis anterior muscle. EMG traces were offset corrected to the baseline EMG signal before muscle onset (−1,000 ms to −1 ms before muscle onset). **(B)** Mean AUC of the contralateral EMG during 100 ms after muscle onset in the voluntary muscle, expressed as a percentage of the mean background AUC level in the contralateral muscle. Values <100% indicatemirror activity (significance levels of Dunn-Bonferroni-Test: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$). AUC, Area under the curve; BB, biceps brachii; contra, contralesional; TA, tibialis anterior; TB, triceps brachii.

underlying mechanism for the better recovery of elbow flexion vs. extension in subjects with cervical incomplete SCI. Indeed, preclinical and clinical findings point towards a strong RS drive to elbow flexors (13, 17, 20, 28). Our data provide supportive evidence for the role of RS plasticity in the functional recovery of ipsilesional biceps brachii function by showing enhanced RS drive to the ipsi- vs. contralesional biceps brachii. The fact that MEPs in the ipsilesional biceps brachii did not normalize over time suggests that recovery of elbow flexion is not caused by CS plasticity, supporting earlier reports (29). Interestingly, MEP normalization was observed in the ipsilesional tibialis anterior, which is in line to previous findings in patients with BSS (30). In contrast, only moderate left-to-right difference in the StartReact effects was present in this muscle. The novel findings from this participant with BSPS suggest that recovery of ipsilesional ankle dorsiflexion is predominantly driven by CS plasticity. This is in line with reports demonstrating that the tibialis anterior is under strong CS control (31, 32) and that CS plasticity promotes recovery of ankle dorsiflexion (33). Our findings indicate that the neuroplastic mechanisms underlying motor recovery may differ between various muscles, and that the neuroplastic potential of the RS system might be pronounced in proximal flexor muscles (34). Combinatory neurophysiological assessments including StartReact and MEPs will be required to further disentangle the role of neuroplasticity in descending motor systems for functional recovery after CNS injury.

Our findings support the idea of meaningful contributions of the RS system to functional recovery in incomplete SCI reported in preclinical (8–10) and clinical studies (12, 13). While the StartReact paradigm does not allow to differentiate between compensatory or regenerative plasticity, our data imply that RS drive is enhanced for particular muscles on the largely denervated ipsilesional side and that this neuroplastic adaption is associated with functional recovery in individuals with SCI. The presence of a notable StartReact effect on the ipsilesional side five months after a half-sided spinal lesion might be explained by the high proportion of bilateral RS projections to the spinal cord, including numerous midline-crossing projections both above and below the lesion (9). This diffuse projection pattern allows the RS system to convey motor drive to the ipsilesional spinal cord below the injury. Additionally, enhanced StartReact effects in the ipsi- vs. contralesional biceps brachii suggests neuroplastic adaptions in the RS system over time. However, as there is no available data on the StartReact effect acutely post-injury, the underlying mechanisms of augmented RS drive remain unknown. MEPs have been examined in the framework of routine clinical assessments and, therefore, have not been performed for triceps brachii. We are, therefore,

not able to discuss the role of CS plasticity on the functional recovery of this muscle.

Beneficial effects of RS plasticity on motor recovery partially contrast findings in stroke patients where RS plasticity is sometimes associated with maladaptive phenomena such as associated movements or spasticity (35–37). This negative association, however, might also be driven by the fact that both RS plasticity and maladaptive features are related to the severity of corticospinal tract damage (38). The discrepant effects of RS plasticity in stroke and SCI might be explained by the deviating extent of loss in cortical motor control: Patients with stroke often show hyperexcitability of the reticular formation which is triggered by cortico-reticular disinhibition (39). In contrast, regulation of the reticular formation by cortical structures is preserved in patients with SCI, which might allow the RS system to contribute to meaningful recovery in SCI patients (12, 29).

Increased RS drive to biceps brachii motoneurons in the ipsilesional hemicord was accompanied by the occurrence of mirror activity in the contralesional biceps. Mirror activity has previously been linked to an upregulated RS drive in response to CS tract damage (36). Ejaz et al. (23) demonstrated that the occurrence of mirror activity in the biceps provides supporting evidence for an enhanced bilateral RS drive to spinal motoneurons. Interestingly, mirror activity only occurred in the muscle revealing the highest StartReact effect, which further supports that mirror activity is, at least in part, mediated by the RS system.

There are some limitations regarding this report. In contrast to the clinical routine assessments (such as gait assessments, TMS etc.), StartReact measurements have not been performed acutely post-injury, because our research team was not aware of this patient case at this stage. However, considering the complete paralysis of ipsilesional biceps and triceps brachii muscles acutely after injury, RS drive to these muscles (as measured by the StartReact paradigm) can likely be assumed to be absent at this time. Another limitation concerns the accuracy of the unilateral spinal lesion. Although sensory assessments and MEPs indicate that the syndrome does not conform to a pure BSS, the canonical motor features of the BSS, which are of main interest for this report, are present in a form which is rare. Despite signs of weak contralesional CS tract damage, CS impairment seems clearly more pronounced on the ipsi- than contralesional side as indicated by strongly reduced or absent MEP amplitudes in the ipsilesional biceps brachii and tibialis anterior acutely post-injury. This is in line with neuroimaging data indicating a high-cervical, primarily right-sided spinal lesion. Therefore, the functional, electrophysiological, and neuroimaging findings suggest an asymmetric, largely one-sided spinal lesion that mimics several sensorimotor features of the BSS.

5 Conclusion

The findings of this case report suggest that RS plasticity occurring after incomplete SCI can be assessed by the StartReact paradigm. The BSPS provides a unique opportunity to compare neuroplastic adaptations in the RS system between the largely spared (contralesional) and impaired (ipsilesional) side. The data imply that enhanced RS drive is mainly found in the ipsilesional biceps brachii where it is related to motor recovery and the occurrence of mirror activity. Further research is needed to gain more insights into the contribution of the RS and CS system to functional recovery and to disentangle the beneficial and maladaptive effects of RS plasticity in human SCI and other neurological conditions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The study was approved by the Ethics Committee of the Canton Zurich. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from the individual for the publication of any data included in this article.

Author contributions

AE: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. MR: Investigation, Writing – review & editing. BZ: Investigation, Writing – review & editing. AC: Investigation, Writing – review & editing. LF: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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.

Publisher's note

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Acupuncture-assisted therapy for prolonged disorders of consciousness: study protocol for a randomized, conventional-controlled, assessor-and-statistician-blinded trial

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Background: Acupuncture is a promising non-pharmaceutical complementary therapy in treating prolonged Disorders of consciousness (pDOC), but solid evidence to support its effectiveness and safety is still lacking. Thus, the purpose of this study is to investigate the efficacy and safety of acupuncture-assisted therapy for pDOC patients.

Methods: A single-center, prospective, randomized, conventional-controlled, assessor-and-statistician-blinded trial has been designed and is being conducted at West China Hospital of Sichuan University. A total of 110 participants will be randomly assigned to the experimental group and the control group in a 1:1 allocation ratio and evaluated using Coma Recovery Scale-Revised (CRS-R) at 8 a.m., 12 p.m., and 4 p.m. on 2 consecutive days before enrollment to determine the consciousness level. The experimental group will receive acupuncture combined with conventional treatment, while the control group will receive only conventional treatment during the trial observation period. The treatment duration of both groups will be 20 days. Among them, the frequency of acupuncture-assisted therapy is once a day, with 10 consecutive sessions followed by a day's rest for a total of 24 days. Data will be collected separately during baseline and after the final treatment. For data analysis, both Full Analysis Set (FAS) and Per Protocol Set (PPS) principles will be performed together by applying SPSS 27.0 software. The primary outcome measures are the changes of CRS-R before and after treatment, while the secondary outcome measures are the changes of Full Outline of Unresponsiveness Scale (FOUR), the changes of Nociception Coma Scale-Revised (NCS-R), the changes of Disability Rating Scale (DRS), the changes of Mismatch Negativity (MMN) and P300 before and after treatment, respectively.

Discussion: This trial aims to rationally assess the consciousness level from multiple 2 perspectives through subjective evaluation and objective detection by selecting several standardized clinical scales combined with Event-Related Potential (ERP) detection technology. In this way, we will be able to reduce the

subjectivity of consciousness assessment and objectively evaluate the clinical efficacy of acupuncture-assisted therapy for pDOC. The study, if proven to be effective and safe enough, will provide a favorable evidence to guide medical decision-making choices and future researches.

Clinical trial registration: https://www.chictr.org.cn/, identifier ChiCTR2300076180.

KEYWORDS

acupuncture, prolonged disorders of consciousness, randomized controlled trial, effectiveness and safety, study protocol

1 Introduction

Disorders of consciousness (DOC) is a persistent state of loss of consciousness usually caused by structural damage or dysfunction of the neural systems that regulate wakefulness and awareness (1, 2). The main mechanism is related to brain cell metabolic malfunction attributed to cerebral ischemia, hypoxia, insufficient glucose supply, and abnormalities in enzyme metabolism, which leads to impaired reticular function and low brain function (3). When this state lasts longer than 28 days, these patients will be diagnosed with prolonged disorders of consciousness (pDOC) (4), which mainly include vegetative state (*VS*)/unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS) (5). Patients with *VS*/UWS retain the sleep–wake cycle, can open their eyes voluntarily, and remain awake, but are unable to perceive and respond accordingly to their own or environmental stimuli (6). In contrast, patients with MCS who also retain the sleep–wake cycle can show minimal but definite signs of awareness of themselves or the environment, which can include eye movements that track objects, show purposeful responses to stimuli, or cannot be interpreted as purely reflexive movements (2).

It has been reported that the prevalence of pDOC patients in the United States approaches 100,000–300,000 (7). Meanwhile, the prevalence of pDOC patients in Europe ranges from 0.2 to 6.1 cases per 100,000 individuals (8). Although there is no reliable data in China in terms of prevalence for pDOC, it is undeniable that the number of pDOC patients is increasing with the improvement of medical resuscitation techniques (9). Due to pDOC patients need long-term and continuous medical expenses as a support for their lives, which creates a severe burden and pressure on both families and society. The main goal of rehabilitation for pDOC patients is to improve their consciousness level and functional recovery. Currently, owing to the limited number of available therapies and their effectiveness in promoting wakefulness, it is meaningful to find a safe and effective long-term adjuvant therapy for pDOC patients.

Acupuncture, as a specialty therapy of Traditional Chinese Medicine (TCM) with a history of thousands of years, has been widely used to treat various ailments as a safe and effective therapy (10, 11). Preliminary studies have indicated that acupuncture not only promotes the recovery of consciousness, speech, and limb functions, reducing the disease duration but also improves the long-term quality of life for DOC patients, effectively reducing mortality and disability (12–14). Meanwhile, the efficacy of acupuncture-assisted therapy may be related to the mechanisms that acupuncture enhances blood supply and oxygenation in the lesion area, reduces the occurrence of edema developmental changes in the necrotic area, and rescues some neurons on the verge of loss of function, thus further promoting self-repairing of the damaged brain tissues and reconstruction of neural networks (15–17). To date, however, it appears from the results of our literature study that there have been no RCTs conducted on pDOC alone. Compared with DOC patients, pDOC patients suffer from the effects of more severe brain damage, more complications, and greater difficulty in promoting awakening. Consequently, a first investigation of the efficacy and safety of acupuncture-assisted treatment of pDOC is necessary. In addition, acupuncture has fewer side effects and low cost, which greatly improves the usefulness of acupuncture. Therefore, acupuncture may be a better complementary therapy for pDOC patients.

At present, behavioral assessment, based on patients' motor and cognitive behaviors, is the main modality used in clinical practice to evaluate the consciousness level of pDOC patients. However, the misdiagnosis rate for this method of assessing consciousness state for patients with pDOC through the use of scale scores has been high, at approximately 40% (18, 19). In order to minimize the misdiagnosis rate and to objectively reflect the clinical efficacy of acupuncture-assisted therapy for pDOC. In this study, we selected several standardized clinical scales closely related to the consciousness level, and combined them with indicators for the detection of Event-Related Potentials (ERP), which together serve as indicators of efficacy evaluation, aiming to reasonably judge the clinical efficacy of acupuncture-assisted treatment of pDOC from the perspectives of subjective assessment and objective detection.

2 Methods and analyses

2.1 Design and setting

A single-center, prospective, randomized, conventional-controlled, assessor-and-statistician-blinded trial is being performed at West China Hospital of Sichuan University (Sichuan, China). A total of 110 eligible participants will be randomly assigned to the experimental group and the control group in a 1:1 allocation ratio. Acupuncture combined with conventional treatment will be compared to conventional treatment in patients with pDOC. The study was approved by the ethics committee of West China Hospital of Sichuan

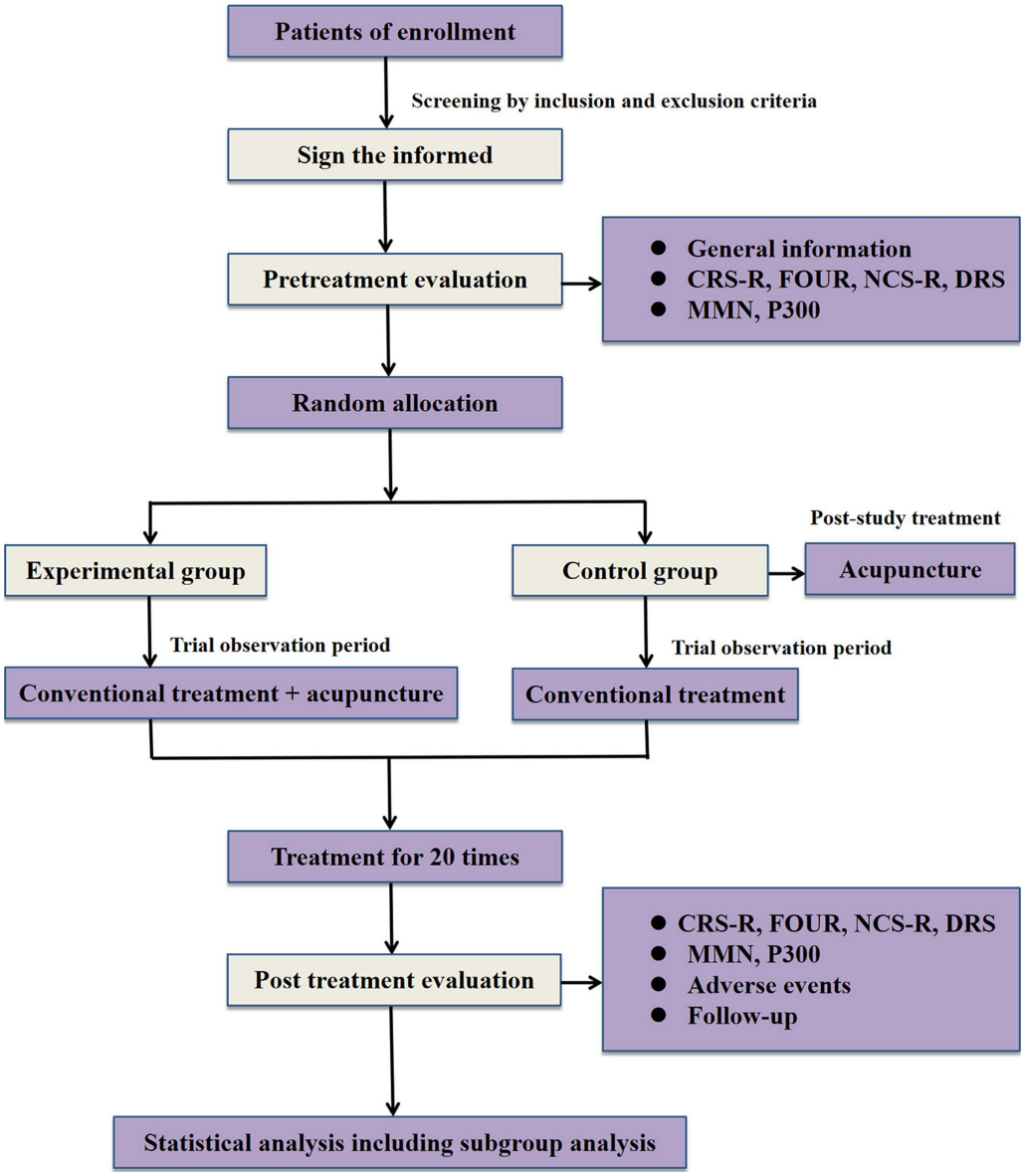

FIGURE 1
Experimental flow chart.

University under the ethical approval number 2022 review (1622), and registration was completed in the China clinical trial registry under the registration number ChiCTR2300076180. Also, this trial is implemented strictly conforms to Standard Protocol Items, such as Recommendations for Interventional Trials (SPIRIT) 2013 statement (20) and the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (21). The process and details of this study will be demonstrated in Figure 1 and Table 1.

2.2 Patients

2.2.1 Recruitment strategies

This trial will be advertised for recruitment between January 2023 and October 2024 via WeChat, the hospital's official website, and the outpatient waiting hall. Subjects with pDOC were required to participate in our trial only after their family members and (or) legal representatives were informed, consented and signed an informed consent form. Meanwhile, they will be informed that patients with pDOC are free to withdraw from this trial at any time and that there will be no negative impact on their future treatment. Additionally, all personal information about the patient will be well protected and not casually disclosed.

2.2.1.1 Diagnostic criteria

Based on the 2020 edition of the European guidelines for the diagnosis of coma and other DOC published by the European Academy of Neurology and the 2018 edition of the American practice guidelines for DOC published jointly by the American Academy of Neurology and the American academy of rehabilitation medicine (18, 22), we can know that patients with DOC more than 28 days will be diagnosed as pDOC.

TABLE 1 Schedule of enrolment, interventions, and assessments.

Time point	Study period				
	Screening	Baseline	Intervention	Post-treatment	Follow up
Enrollment					
Eligibility screen	√	√			
Informed consent	√				
Medical history		√			
Random allocation		√			
Demographic data		√			
Intervention					
Conventional treatment + acupuncture ($n = 55$)			√		
Conventional treatment ($n = 55$)			√		
Assessments					
CRS-R		√		√	
FOUR		√		√	
NCS-R		√		√	
DRS		√		√	
MMN		√		√	
P300		√		√	
Others					
Adverse events			√	√	
Where pDOC patients go after being discharged from the hospital					√

CRS-R, the Coma Recovery Scale-Revised; FOUR, the Full Outline of Unresponsiveness Scale; NCS-R, the Nociception Coma Scale-Revised; DRS, the Disability Rating Scale; MMN, the Mismatch Negativity; pDOC, prolonged Disorders of Consciousness.

2.2.1.2 Inclusion criteria

Patients with pDOC meeting all of the following criteria will be enrolled in this trial. Otherwise, they will be excluded.

1 Patients who met the above diagnostic criteria for pDOC will be included only in the *VS*/UWS and MCS stages;
2 Those who have a first sudden onset of impaired consciousness with a clear etiology and a complete case history;
3 No significant hydrocephalus and no severe cerebral atrophy, 28 days < disease duration ≤6 months;
4 Age is between 18 and 80 years old and gender is not limited;
5 Those without significant cognitive impairment, hearing impairment, or visual impairment before onset;
6 Those who were able to communicate accurately in Chinese before the onset of the disease and who had no significant neurologic or psychiatric history;
7 Those with stable medical conditions, relatively stable vital signs, and not enrolled in another study within the last 3 months;
8 Informed consent was obtained from the subject's legal representative, and the subject's legal representative voluntarily cooperated and signed the informed consent form.

2.2.1.3 Exclusion criteria

Patients with pDOC meeting any one of the following criteria will be excluded from our study.

1 Those with a combination of intracranial tumors, episodes of intracranial infections, or brain death and/or other occupying diseases that significantly affect the results of the study;
2 Those with a history of drug use prior to illness;
3 Those with deep vein thrombosis;
4 Those with severe endocrine-metabolic disorders or with persistent status epilepticus;
5 Pregnancy, combined multiple trauma, limb fractures, or large skin defects.

2.2.1.4 Criteria for termination

Included pDOC patients meeting any one of the following criteria will be terminated from our trial.

1 Those whose vital signs were unstable due to changes in their condition during the observation period or who were advised by the managing physician that they could not continue to participate in this clinical study;
2 Those who require reoperation or die during observation;
3 Those who had a serious adverse reaction during the observation period and should not continue to participate in the study;
4 The legal representative does not cooperate with the study and repeated explanations by the clinician are not effective.

2.2.1.5 Criteria for withdrawal, dropout, and removal

Included pDOC patients meeting any one of the following criteria will be withdrew, dropped out, and removed from our study.

1 Patients who did not meet the inclusion criteria and were included in error;
2 Subjects with poor compliance by legal representatives who withdrew on their own during the study;
3 Combined use of treatments prohibited by this program, or those who change treatments midway on their own;
4 Those who are unfit to continue in the study due to major changes in the family.

2.2.1.6 Handling of exclusion and dropout cases

For pDOC patients who are kicked out and dislodged, we will take the following.

corresponding measures as appropriate to the situation to handle them appropriately.

1 In cases of dislodgement, the supervising physician should contact the subject's family or legal representative by visiting the home, scheduling a phone call, or sending an email, as much as possible, to inquire about the cause of the dislodgement, to keep a detailed record of when the last treatment was given, and to complete as many of the evaluation items as he or she is able to;
2 If a person withdraws due to adverse reactions or ineffective treatment, the supervising physician shall take appropriate measures to deal with the subject according to his/her actual situation;
3 Complete the Case Report Form (CRF) "Treatment Completion Summary" and "Clinical Trial Completion";
4 Once a pDOC patient is enrolled for observation, detailed records should be kept regardless of subsequent diagnosis and completeness of treatment;
5 The researcher should keep a detailed record of the reason and time of withdrawal from the study;
6 All rejected and dislodged cases were analyzed in the Full Analysis Set (FAS) at the end of the trial.

2.2.1.7 Supplementary explanation

To fully consider the safety of the subjects and the real reliability of the data in the course of this trial, this study only collected relevant data from subjects who met the requirements of the ERP technology test, and the rest of the participants only underwent clinical evaluation and treatment.

ERP technology testing requirements: ① subjects quiet, not agitated, and able to complete the test; ② skull intact, and no other factors affected.

2.3 Intervention

2.3.1 Conventional treatment in both groups

This study was divided into two groups, i.e., control group and experimental group. Subjects in both groups who participated in this trial will receive conventional clinical treatments with pDOC, including rehydration, anti-infection, seizure prevention, neurotrophic, acid-suppressing and gastric protection, mechanically assisted sputum evacuation, medication to resolve sputum, hyperbaric oxygen combined with transcranial direct current stimulation (tDCS) to promote awakening, physical rehabilitation, nutritional support, and other symptomatic treatments. Details of conventional treatment will be recorded carefully on the CRF to which the patient belongs, noting any change and the reasons promptly. The formulation of conventional treatment plans is mainly based on the "Chinese Expert Consensus on the Diagnosis and Treatment of pDOC" (23), closely related to the patient's clinical condition, combined with the recommendations and opinions of experts in the field, and referred to the clinical pathway medication guidance of West China Hospital of Sichuan University.

The following are the details of the clinical conventional treatment plan for pDOC patients: Renen 400 mL via gastric tube once a day; Ambroxol hydrochloride injection 30 mg intravenous drip combined with inhalation of acetylcysteine solution nebulized inhalation once a day; piperacillin sodium tazobactam sodium for injection 4.5 g IV drip every 8 h; omeprazole sodium 80 mg, 0.9% saline diluted in 100 mL of IV drip, once a day; Depakene 5 mg/kg dissolved in 100 mL saline IV drip within 1 h, every 8 h; Odekin 0.8 g IV drip, once a day. Hyperbaric oxygen therapy: Set the pressure of the hyperbaric oxygen chamber to 0.2 MPa, slowly and continuously pressurize for 20 min, wear a mask to inhale oxygen for 30–40 min per time, a total of two times, with a 10 min interval between each time, during which the air inside the chamber is sucked. After the two oxygen breaths are completed, slowly reduce the pressure and exit the chamber, once a day. tDCS therapy: The dorsolateral left prefrontal lobe was chosen as the anode, and the dorsolateral right prefrontal lobe was chosen as the cathode, with a stimulation intensity of 1 ~ 2 mA and a duration of 20 min, once a day, and with enhanced limb rehabilitation, bed standing and other treatments.

2.3.2 The experimental group

In the 20-day treatment phase, participants that allocated to the experimental group will receive acupuncture treatment in addition to conventional treatment. The frequency of acupuncture treatment will be once a day, with 1 day of rest after 10 consecutive treatments, for a total of 20 treatments. The distribution of observation time regarding the participation of pDOC patients in our trial was shown in Figure 2. The selection of acupoints in this study was mainly based on the results of data mining and consisted of acupoints that were selected a high number of times in the current application of clinical acupuncture-assisted therapy for DOC patients (24). Meanwhile, all acupoints will be localized according to the Chinese standard "Names and Localization of Meridian Points" (GB/T12346-2021), and the acupuncture manipulation techniques are mainly based on the "International Technical Operation Standards for Traditional Chinese Medicine - Xingnao Kaiqiao Acupuncture Method for the Treatment of Stroke," which was released and implemented by the World Federation of Traditional Chinese Medicine Societies on December 16, 2021, as the main guideline (25, 26).

Among all selected acupoints, Shuigou (GV26) and bilateral Neiguan (PC6) were the main points, and the remaining acupoints

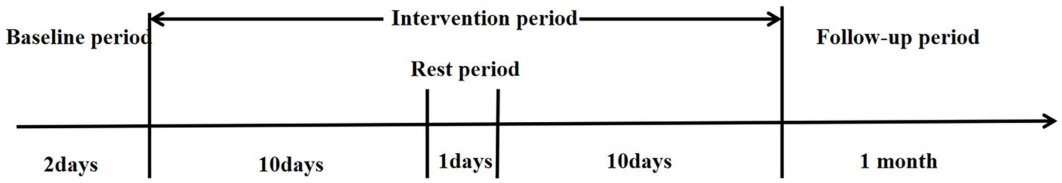

FIGURE 2
Time allocation chart.

were all supporting points, including Baihui (GV20), double Fengchi (GB20), double Jiquan (HT1), double Chize (LU5), double Hegu (LI4), double Laogong (PC8), double Houxi (SI3), double Zusanli (ST36), double Yinlingquan (SP9), double Sanyinjiao (SP6), double Taixi (KI3), double Yongquan (KI1), and double Taichong (LR3). The details of acupoint localization are shown in Table 2.

2.3.3 The control group

At the end of the study observation, all participants in the control group will be entitled to 20 free acupuncture intervention treatments as in the experimental group, and if all of them cannot be completed during their first hospitalization, the subject's entitlement will remain in effect for future hospitalizations at our institution until the 20th acupuncture treatment is completed.

2.3.4 Acupuncture operation process

All acupuncture operators have at least 5 years of clinical experience in acupuncture therapy and have obtained the doctor's qualification certificate. Their acupuncture manipulation has undergone unified standardized training and reached the qualification standard. During the acupuncture operation, the operator wears isolation clothing and strictly follows the principle of using a separate set of isolation clothing for each pDOC patient to avoid cross infection of drug-resistant bacteria among patients.

2.3.4.1 Sterilize

Before applying the needles, the acupuncture operator brushes and cleans his/her hands with soapy water and then wipes them with a 75% alcohol cotton ball. Next, they used 75% alcohol cotton balls to disinfect the skin of the needling site in a circular manner from the acupoint area to the periphery.

2.3.4.2 Needle insertion and needle travel

We choose the appropriate needle insertion technique based on the different injection sites, and strictly follow the acupuncture operation requirements corresponding to the acupoints to perform acupuncture techniques. The acupuncture operation is based on Shi's twisting tonic and diarrhea technique, when twisting, small amplitude, high frequency (twisting amplitude less than 90°, frequency of 120 ~ 160 times/min) for the tonic method. On the contrary, large amplitude, low frequency (twisting amplitude of more than 180°, frequency of 60 ~ 90 times/min) for the diarrhea method (25, 26).

2.3.4.3 Acupuncture manipulation

In the process of acupuncture manipulation, it is worth noting that when needling GV26, the needle tip should be obliquely inserted toward the nasal septum by 0.3–0.5 inches, and then acupuncture operations such as lifting and twisting should be performed. The intensity of stimulation should be measured by the patient's tears or moist eyeballs. Next, when needling PC6, the tip of the needle should be perpendicular to the skin into the needle about 0.5-1inches, and then use the lifting and inserting twisting and diarrhea method, and continue to travel the needle for 1 min. Meanwhile, it should be emphasized that in addition to the need to cause twitching of the upper limbs when needling the HT1, it is also necessary to avoid its adjacent axillary artery as a means of avoiding acupuncture accidents, and needling the LU5, LU5 should be positioned by bending the elbow at an internal angle of 120°, and the operator should hold the wrist joint of the affected limb with his hand, stabbing 0.5 ~ 0.8 inches straight, using the lift-and-insert diarrhea method, to make the needle sensation pass from the elbow joint to the fingers or to manually externally rotate the hand, and to externally rotate the hand and twitch it for 3 times as a criterion. In addition, SP6 should be stabbed obliquely along the medial edge of the tibia at an angle of 45° to the skin, and the needle should be advanced about 0.5 to 1 inch so that the tip of the needle is stabbed deeply into the position of the original SP6, and then the lifting and inserting method of tonic is used to the extent that the affected limb twitches three times. GV20 should be stabbed backward flatly for 1 inch, and then perform flat tonic and flat diarrhea maneuvers, and twist rapidly for 1 min. When needling GB20, the needle tip should be directed towards the opposite side of the eyeball and stabbed directly for 1–1.5 inches. A small amplitude and high-frequency twisting and turning method should be applied for 1 min. Additionally, when needling LI4, for patients with finger dysfunction, the acupoint on the affected side should be taken, and then the needle should be inserted with one hand, and the needle tip should be stabbed obliquely in the direction of the San Jian (LI3) for 1 ~ 1.5 inches, and then the lifting and inserting and cathartic methods should be used, to the extent that the patient's tightly clenched finger naturally stretches out or the index finger involuntarily jerks three times. Lift and insert the laxative method, to the extent that the patient's thumb twitches 3 times; for patients without finger dysfunction, the bilateral LI4 is subjected to the acupuncture maneuver of flat tonic and flat laxative. When needling KI1, we used a combination of lifting, inserting and twisting until the limb twitched. Finally, the needle penetration depth for PC8, SI3, ST36, SP9, KI3, and LR3 should be between 0.3–2 inches.

2.3.4.4 Retaining needle

The acupuncture manipulation were performed once every 10 min to maintain the needle sensation, a total of 2 times, and the needles were left for 30 min.

TABLE 2 The details of acupoint localization.

Acupoints	Anatomical location
Shuigou (GV26)	On the face, at the junction of the upper 1/3 and lower 2/3 of the manubrium sulcus.
Neiguan (PC6)	In the anterior region of the forearm, 2 inches above the transverse stripe on the distal part of the palmar side of the wrist, between the tendon of the palmaris longus and the tendon of the radial flexor carpi radialis.
Baihui (GV20)	On the head, 5 inches straight up from the center of the front hairline.
Fengchi (GB20)	In the posterior region of the neck, below the occipital bone, in the depression between the upper end of the sternocleidomastoid muscle and the upper end of the trapezius muscle.
Jiquan (HT1)	In the center of the axilla, where the axillary artery pulsates, the acupuncture point in this study was Lower Polar Spring, in the anterior region of the arm, on the line connecting the Polar Spring and the Shao Hai, 1 ~ 2 inches below the Polar Spring, avoiding the axillary hairs, and at the point where the muscles are plentiful.
Chize (LU5)	In the elbow region, on the transverse elbow stripe, in the radial depression of the biceps tendon.
Hegu (LI4)	On the back of the hand, between the 1st and 2nd metacarpals, at the midpoint of the radial side of the 2nd metacarpal.
Laogong (PC8)	In the metacarpal region, transverse to the proximal end of the 3rd metacarpophalangeal joint, favoring the 3rd metacarpal between the 2nd and 3rd metacarpals.
Houxi (SI3)	In the depression between the red and white flesh at the proximal end of the ulnar side of the 5th metacarpophalangeal joint of the hand.
Zusanli (ST36)	On the lateral side of the lower leg, 3 inches below the calf's nose, 1 transverse finger outside the anterior crest of the tibia, on the line between the calf's nose and Xiexi.
Yinlingquan (SP9)	On the medial side of the lower leg, in the depression between the lower edge of the medial tibial condyle and the medial border of the tibia.
Sanyinjiao (SP6)	On the medial side of the lower leg, 3 inches above the tip of the inner ankle, behind the medial border of the tibia.
Taixi (KI3)	In the ankle region, in the depression between the tip of the inner ankle and the Achilles tendon.
Yongquan (KI1)	On the sole of the foot, the center of the foot is most concave in the center of the foot when flexing the foot and curling the toes (when the webbing edge of the 2nd and 3rd toes on the sole of the foot meets the intersection of the anterior 1/3 and posterior 2/3 of the line connecting the heel of the foot).
Taichong (LR3)	On the dorsum of the foot, between the 1st and 2nd metatarsals, in the depression anterior to the union of the metatarsal bottoms, or where the arterial pulsation is palpable.

2.3.4.5 Needle output

The acupuncture operator uses their left thumb and forefinger to hold a disinfectant dry cotton swab and lightly press it onto the needle site. With their right hand, they hold the needle and twist it slightly before slowly lifting it to the subcutaneous area. Wait for a moment before releasing the needle. After the needle is pulled out, immediately press the needle hole again with a sterilized dry cotton ball to prevent bleeding.

2.4 Outcome measures

2.4.1 Primary outcome measures

The Coma Recovery Scale-Revised (CRS-R) can comprehensively assess the consciousness state in terms of auditory, visual, motor, speech, communication, and arousal levels (27). It was also the most sensitive indicator for clinical differentiation of the state of consciousness in patients with pDOC, and has an important reference value in identifying patients with coma, *VS*, MCS, and Emergence from Minimally Conscious State (EMCS), and was therefore considered to be the gold standard for clinical assessment of the level of consciousness (28, 29). Meanwhile, its reliability in monitoring states of consciousness has been commonly recognized. The CRS-R has a full score of 23, and the treatment was considered effective when the CRS-R score at the end of the trial session was greater than or equal to 3 points from the baseline period score (30). Due to the non-constant nature of the state of consciousness of pDOC patients (31), to provide a more reasonable response to the level of consciousness of pDOC patients, we will assess patients' CRS-R score at 8:00 am, 12:00 pm, and 4:00 pm on 2 consecutive days at baseline and at the end of the experimental observation, respectively, and take the highest value as the data participating in the final statistical analysis.

2.4.2 Secondary outcome measures

The Full Outline of Unresponsiveness Scale (FOUR) is another clinical scale widely used to assess the level of consciousness in patients with pDOC and consists of items such as ocular responses, motor responses, brainstem reflexes, and respiratory status (32). This tool can supplement the CRS-R with assessments such as brainstem reflexes and breathing patterns (33). Also, the higher the score, the better the patient's level of consciousness. The evaluation time is synchronized with the CRS-R.

The Nociception Coma Scale-Revised (NCS-R) can be used to assess the changes in sensitivity to painful stimuli during treatment in pDOC patients (34), which is a nociceptive behavioral observation tool developed specifically for patients with DOC due to (acquired) brain injury and has good clinical reliability, especially for patients with *VS*/UWS and MCS (35). The scale consists of three items (motor function, verbal function, and facial expression), each with a score range of 0–3. Of note, the presence of pain is indicated when the total NCS-R score is greater than or equal to 4; and the higher the score, the more pronounced the pain response.

The Disability Rating Scale (DRS) can be used to assess the degree of impairment of life functioning in post-traumatic pDOC patients in the domains of awareness (i.e., eye-opening, communication skills, motor responses), cognition (i.e., eating, toileting, and grooming), overall level of functioning, and employability. This study was combined with assessment scales such as CRS-R, FOUR, and NCS-R, which were assessed in several different periods to comprehensively determine the level of consciousness of pDOC patients, aiming to minimize the influence due to fluctuations in the patient's state of consciousness and the assessor's subjective experience to ensure the accuracy of the data.

Despite strengths as mentioned above for these standardized clinical scales, it is undeniable that there is always a certain subjectivity in behavioral evaluation. In comparison, the ERP detection technology captures the electrical signals generated by brain activity and has the advantages of high temporal resolution and the ability to assess the information processing capacity of pDOC patients without obvious behavioral manifestations, thus facilitating the discovery of hidden conscious activities in the areas of attention, sensation, emotion, and memory in pDOC patients (36). As a result, we chose the MMN, which reflects the processing of novel events by the brain (37), and P300, an endogenous component that reflects the advanced processing of sensation (38), as the final test indexes.

It has been shown that MMN has a good prognostic value for recovery of consciousness in severely impaired patients (39). For *VS* patients in particular, *VS* patients may have the same ability to be able to process target sound stimuli as MCS patients, suggesting that late-stage DOC patients without motor/behavioral responses still have a cerebral cortex activated by latent stimuli, thus facilitating the discovery of covert conscious activity in pDOC patients (40).

P300 is another ERP testing indicator that correlates with recovery of consciousness and prognosis. It has been suggested that improved awareness may be associated with improved allocation of attentional resources, which can be captured by the P300 amplitude (41). Therefore, in our study, the included pDOC patients will be tested for MMN and P300 at the baseline period and the end of the observation course, respectively, to rationally assess the clinical efficacy of acupuncture-assisted therapy for pDOC.

2.5 Sample size

In this trial, CRS-R changes will be regarded as a primary evaluation index. According to our previous pilot study, the changes of CRS-R before and after treatment in the experimental group was shown to be 3.07 ± 2.87 points ($n = 14$), and that in the control group was 1.14 ± 3.80 points ($n = 14$). Hence, sample size calculation was performed using G*Power 3.1.9.7 software (Heinrich-Heine-University Dvsseldorf, Dvsseldorf, Germany) with a significance level ($\alpha = 0.05$) of a 2-sided 2-sample *t*-test and 80% power to detect a difference between the 2 groups. Therefore, a total of 110 participants will be required allowing for 10% of attrition, with 55 cases in each group.

2.6 Randomization and allocation concealment

This study was conducted by an independent statistician who generated random numbers by applying Statistical Analysis System (SAS) 9.4 software programming (North Carolina State University, USA). All included pDOC subjects will be randomly assigned to the experimental group and control group. The specific implementation process is as follows: an independent random number administrator is responsible for the management and allocation of all random numbers. For subjects who meet the inclusion criteria and sign informed consent, the researcher in charge of recruitment will first contact the random number administrator by phone or WeChat, and report the basic information of the subjects to him/her before requesting the corresponding random number and grouping, and record them on the subject's CRF promptly. The randomization number administrator was required to back up the subject's randomization number, grouping, enrollment time, and basic information. In this trial, the implementation of random grouping and allocation concealment was ensured by the above method.

2.7 Blinding

This study was evaluated in a blinded fashion, with a third party who was unaware of the subgroups performing the clinical assessment and efficacy evaluation of all subjects. Blinded statistical analysis was used in the data summarization phase, with triple separation of the investigator, the outcome assessors, and the statistics analyzer of the data.

2.8 Informed consent

The subject's family and (or) legal representative will be informed of the details of this study, including the purpose of the study, potential benefits, and risks, other alternative treatment options available, as well as the rights that the subject has and the obligations that need to be fulfilled. They will also be informed that they will only sign the completed informed consent form before the patient is enrolled in our study. If a subject withdraws from the trial, the relevant assay data will be retained for final analysis of the results.

2.9 Safety monitoring

All adverse events occurring during the study period, regardless of whether they are related to acupuncture or not, must be recorded and reported in detail on the corresponding CRF forms of the subjects, mainly including the time of appearance of the adverse events, symptoms, signs, degree, duration, laboratory test indexes, treatments and results, aftermath, follow-up, etc., and analyze the reasons for the appearance of the adverse events. In addition, subjects must be treated promptly and appropriately until they return to normal. The incidence of adverse events will be considered for safety measurements, such as local hematoma, needle twisting, breaking, and bleeding. Also, the investigator is required to keep the subject's legal representative informed and to ask them to truthfully respond to any changes in the patient's condition after receiving the treatment. Further, any serious adverse events related to the trial must be reported immediately to the principal investigator, and its cause determined, its relevance to needling analyzed, and an appropriate solution proposed.

2.10 Follow-up

Considering that the participants in this study are pDOC patients who are categorized as clinically critical illnesses, they need to receive long-term and continuous clinical treatment as a guarantee to maintain their condition and promote their recovery. In this pilot study, since the observation time of pDOC patients is limited by the duration of hospitalization and patients still need to receive other treatments after discharge, in order to ensure the completeness of the trial implementation, we only followed up the destination of pDOC patients within 1 month of discharge from hospital without assessing or retesting the outcome indexes to ensure the reliability of the data.

2.11 Data collection and management

In this study, a CRF specially designed in advance will be applied to collect all the raw data from the subjects and backed up to the corresponding electronic database. Also, there were three examiners in our study, all of whom were trained in a uniform, specialized normative consciousness assessment, and their intraclass correlation coefficient was 0.8, which suggests a high degree of interstudy agreement, thus ensuring the reliability of the measurement data. Furthermore, all subjects who met the criteria for ERP testing were tested by the same one experienced and specialized neurophysiological technologist. Only members of the research team will have access to these data until published in a peer-reviewed journal.

3 Statistical analysis

In this study, all collected data will be statistically analyzed by 2 independent professional statisticians applying IBM SPSS Statistics 27.0 software for Windows (Stanford University, USA). Measurement data will be expressed as mean ± standard deviation ($\bar{x} \pm s$) and count data will be expressed as several cases or percentages. Statistical analysis of the measurement data will be done by performing normality and variance chi-square tests, for data that meet the normality and variance chi-square tests, paired samples t-tests will be used for intra-group comparisons, and independent samples t-tests for inter-group comparisons. As for data that do not meet the normality and variance chi-square tests, non-parametric tests will be used. In contrast, the chi-square test will be mainly used for statistical analysis of count data, while the Wilcoxon rank-sum test will be applied when two groups of hierarchical data are compared. For correlation analysis, Pearson's correlation analysis will be used if the variables conformed to a normal distribution, otherwise Spearman's correlation analysis will be used. A statistically significant difference or correlation will be indicated when $p < 0.05$. Eventually, all data collected will be analyzed in subgroups by *VS* and MCS populations.

Additionally, in order to evaluate the clinical efficacy and safety of acupuncture-assisted therapy for pDOC patients as comprehensively and rationally as possible, we plan to perform FAS and Per Protocol Set (PPS) analyses, respectively, on all the data eventually collected after comprehensively considering the strengths and weaknesses of the FAS and PPS analysis principles. In terms of the safety evaluation, we will perform statistical analyses based on the Safety Set (SS) principle, aiming to provide study conclusions with a high degree of credibility.

4 Quality control

To ensure the reliability of the results, all researchers participating in this trial will receive uniform standardized training and obtain a certificate of competence. To ensure consistency across participants, our group will develop a complete set of clinical management protocols. The above measures can be used to ensure the feasibility and safety of the clinical study.

5 Trial status

Patient enrollment for this study began on January 1, 2023, and the study is still ongoing. Protocol version number and date: V3.0, 25/04/2024. Patient enrollment is expected to be completed by October 2024.

6 Discussion

PDOC is considered to be a rare neurological disorder (42), and there is a lack of empirical guidance and strong evidence-based medical evidence for clinical diagnosis, treatment, evaluation, and related research. Indeed, it has been demonstrated that the available therapies, such as hyperbaric oxygen, tDCS, transcranial magnetism, and amantadine have limited efficacy to DOC patients (4, 43). In addition, as early as 2000 years ago in the famous ancient Chinese book" The Historical Records," there are medical records of acupuncture to promote the awakening of DOC. For these reasons, it is promising to improve the clinical wakefulness-promoting efficacy of existing therapies through the combination of acupuncture. Thus, the tDCS and hyperbaric oxygen therapies were included in the conventional treatment of this protocol. Meanwhile, considering the misdiagnosis rate may caused by behavioral evaluation, we selected several standardized clinical scales combined with ERP indicators jointly assess the consciousness level of pDOC patients before and after treatment, aiming to comprehensively evaluate the efficacy of acupuncture-assisted therapy for pDOC patients from the perspective of subjective evaluation combined with objective detection. Additionally, the implementation of this trial will be carried out in strict compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines and will be reported following the Consolidated Standards for Reporting of Trials and the Standards for Reporting Interventions in Controlled Trials of Acupuncture. Meanwhile, for the duration of the pilot study, patients in both groups will continue to receive standard conventional treatment for pDOC to ensure that there is no delay or exacerbation of the patient's condition as a result of participation in this study.

Nonetheless, some non-negligible limitations should be considered. Firstly, it is undeniable that our study is a single-center study, and there may be limitations in terms of underpowered and poorly generalizable experimental design and implementation, so the final findings should be treated with caution. Secondly, due to the

limitation of hospitalization time for pDOC patients in this study, our trial protocol was set up with only 20 acupuncture interventions, which may increase the risk of negative results as a result of short treatment time, but this does not negate the clinical effectiveness of acupuncture-assisted therapy for pDOC. Therefore, in the future, when conditions permit, we should extend the duration of acupuncture treatment as much as possible to improve the credibility of the research results.

Above all, our findings may not only provide useful clinical decision-making options for the rehabilitation of pDOC patients, but also indicate directions for improvement and enhancement in future clinical research.

Ethics statement

The study was approved by the Ethics Committee of West China Hospital of Sichuan University. In addition, all family members and (or) legal representatives of pDOC patients participating in this trial voluntarily signed an informed consent form, and the results of this trial will be submitted to a peer-reviewed journal for publication.

Author contributions

NZ: Conceptualization, Software, Writing – original draft. NS: Conceptualization, Software, Writing – original draft. PH: Software, Writing – original draft. L-yY: Software, Writing – original draft. C-xG: Software, Writing – original draft. JX: Software, Writing – original draft. Y-wL: Project administration, Resources, Supervision, Writing – review & editing. HZ: Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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.

Publisher's note

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Is non-invasive neuromodulation a viable technique to improve neuroplasticity in individuals with acquired brain injury? A review

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Objective: This study aimed to explore and evaluate the efficacy of non-invasive brain stimulation (NIBS) as a standalone or coupled intervention and understand its mechanisms to produce positive alterations in neuroplasticity and behavioral outcomes after acquired brain injury (ABI).

Data sources: Cochrane Library, Web of Science, PubMed, and Google Scholar databases were searched from January 2013 to January 2024.

Study selection: Using the PICO framework, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) randomized controlled trials (RCTs), retrospective, pilot, open-label, and observational large group and single-participant case studies were included. Two authors reviewed articles according to pre-established inclusion criteria.

Data extraction: Data related to participant and intervention characteristics, mechanisms of change, methods, and outcomes were extracted by two authors. The two authors performed quality assessments using SORT.

Results: Twenty-two studies involving 657 participants diagnosed with ABIs were included. Two studies reported that NIBS was ineffective in producing positive alterations or behavioral outcomes. Twenty studies reported at least one, or a combination of, positively altered neuroplasticity and improved neuropsychological, neuropsychiatric, motor, or somatic symptoms. Twenty-eight current articles between 2020 and 2024 have been studied to elucidate potential mechanisms of change related to NIBS and other mediating or confounding variables.

Discussion: tDCS and TMS may be efficacious as standalone interventions or coupled with neurorehabilitation therapies to positively alter maladaptive brain physiology and improve behavioral symptomology resulting from ABI. Based on postintervention and follow-up results, evidence suggests NIBS may offer a direct or mediatory contribution to improving behavioral outcomes post-ABI.

Conclusion: More research is needed to better understand the extent of rTMS and tDCS application in affecting changes in symptoms after ABI.

KEYWORDS

transcranial electrical stimulation, transcranial magnetic stimulation, brain injuries, cerebral stroke, neurological rehabilitation

Introduction

Acquired brain injury (ABI) includes traumatic brain injury (TBI) and non-traumatic brain injury (nTBI). TBIs are caused by an external event (e.g., motor vehicle accident), while an nTBI results from an internal process leading to cerebral damage (e.g., stroke) (Assecondi et al., 2020; Goldman et al., 2022). In the United States, approximately 1.5 million people survive an ABI each year (Georges, 2023), and 30% of survivors will continue to experience symptoms that may disrupt everyday activities (Allonsius et al., 2023). The sustained trauma disrupts neural connections, leading to physical impairments (e.g., movement deficits and pain), somatic symptoms (e.g., fatigue), neuropsychological dysfunction (e.g., impaired executive function (EF), memory loss, and arousal), and neuropsychiatric dysfunction (e.g., social and mental health). Physical therapy (PT), occupational therapy (OT), and cognitive therapy (CT) are rehabilitation techniques that have improved outcomes for individuals with ABI (Scherer, 2007; Cernich et al., 2010; Ustinova et al., 2015; Mikolić et al., 2019). When combined with OT and PT, CT addresses aspects of behavioral function to produce a synergistic effect on neuroplasticity (Embrechts et al., 2023). While these broadly recognized therapies hold a central place in neurorehabilitation for their value, the effectiveness of many neurological interventions varies significantly due to temporal constraints, personal factors, financial feasibility, and other barriers (Clayton et al., 2016; Dang et al., 2017; Hofer and Schwab, 2019; Diaz et al., 2023). For example, constraint-induced movement therapy (an effective intervention for ABI; CIMT) requires intensive dosage (e.g., 6 h) to facilitate effective extremity function (Cimolin et al., 2012; Reiss et al., 2012; Pedlow et al., 2014). Due to some of these barriers, many strongly supported interventions have not been widely incorporated into clinical practice (Fleet et al., 2014). Thus, a critical need remains for a neurorehabilitation treatment approach that integrates therapeutic approaches to extend neurorehabilitation treatment's efficacy, dosage, and number of responders.

There is a growing interest in the efficacy of non-invasive brain stimulation (NIBS) as a complement or supplement intervention to current approaches in ABI recovery to address bottom-up implications, including inflammation, edema, disruption of the blood–brain barrier (BBB), white matter destruction, excitotoxicity, and damage to vasculature as well as top-down implications including cognitive deficits, mood dysregulation, and occupational performance deficits (Villamar et al., 2012; Pope and Miall, 2014; Wessel et al., 2015; Clayton et al., 2016; Dang et al., 2017; Hofer and Schwab, 2019; Cha and Hwang, 2022; Nousia et al., 2022; Diaz et al., 2023). By modulating neural activity in specific brain regions, NIBS may promote synaptic and structural neuroplasticity by decreasing cortical hyperexcitability, enhancing long-term synaptic plasticity to avoid maladaptive consequences, facilitating the formation of new neural connections, and facilitating promoting cortical reorganization and consolidation of learning when coupled with physical, cognitive, or behavioral therapies (Bolognini et al., 2009; Schlaug et al., 2011; Villamar et al., 2012; Fregni et al., 2015).

The NIBS methods such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) involve using magnetic or electrical fields to modulate neural activity in specific brain regions. rTMS delivers a series of magnetic pulses to the same brain region over time and can be divided between high frequency (HF-rTMS) using ≥ 5 Hz and low frequency (LF-rTMS) using ″ 1Hz. tDCS applies low-level direct electrical current to the scalp to modulate cortical excitability through anodal (a-tDCS), widely associated with an excitatory response, or cathodal (c-tDCS), which is associated with an inhibitory response (Goldman et al., 2022).

Despite NIBS' use to address ABI-related mechanisms of injury for over a decade, a mechanistic model for neuroplasticity has yet to be established. Many recent studies, commentaries, and literature reviews being published report only on the physical symptom and behavioral impact of NIBS (Giordano et al., 2017; Schwertfeger et al., 2023; Zotey et al., 2023; Galimberti et al., 2024) or rationalize the mechanism of change to singular mechanisms such as the specific montage and polarity of tDCS electrodes (anode or cathode) to provide either an excitatory or inhibitory impact (Asloun et al., 2008; Bikson et al., 2010; Calderone et al., 2024), the ability for tDCS to influence resting membrane potential of the neuron (Chang et al., 2023; Calderone et al., 2024), and the inhibitory or excitatory impact of rTMS based on frequency and duration of exposure (Eldaief et al., 2013; Chang et al., 2023; Evancho et al., 2023; Calderone et al., 2024). Although these principles serve as an essential foundation for the study of NIBS post-ABI, anodal and cathodal stimulation in tDCS (Giordano et al., 2017) and duration and frequency of exposure in rTMS (Huang et al., 2005) are not synonymous with excitatory and inhibitory stimulation concerning their effects on neural function and human behavior (Giordano et al., 2017), nor do these rationales provide a potential model for uniformity among future study designs related to NIBS.

Many variables impact stimulation response, including pathological characteristics and pathogenesis of the primary diagnosis (e.g., type of injury, location of injury, and time since injury), person-specific variables (e.g., individual neuroanatomy, genetic factors, and current medication), and NIBS methodology (e.g., dosing parameters, electrode size, duration of the stimulation, current density, and simultaneous activities being performed with NIBS) (Zettin et al., 2021). These many considerations make it imperative to establish a model of neuroplasticity that communicates the pathophysiological complexities of NIBS' impact on cortical and subcortical structures and allows for an improved understanding of its mechanism of action within the brain and its effect on behavior. We propose hormesis-based neuroplasticity as a potential mechanistic model to guide and support the application of NIBS post-TBI.

Hormesis is a biphasic dose–response (DR) model that explains the physiological process whereby cells can respond to targeted, low-level environmental challenges (i.e., tDCS and rTMS) in a manner that subsequently increases their capacity for resilience and functional abilities, resulting in an improved ability to respond in ways that prepare them to resist and recover better from future challenges, including brain damage (Mattson and Leak, 2024). The hormetic dose–response curve typically includes both beneficial effects at low doses and detrimental effects at high doses. In the context of ABI, the focus is on the beneficial adaptations that occur within the 'hormetic zone' (Mattson and Leak, 2024). These adaptations, often called "stress-modulated, enhanced metabolic states of cells, involve improved energy, material, and information processing" (Leak et al., 2018). In particular, information processing has been suggested as a primary symptom of mild TBI (mTBI) sequelae (Senathi-Raja et al., 2010; Dymowski et al., 2015). This concept has been extensively studied in ischemia research, where mild ischemic episodes can

improve biological defenses and reduce damage from subsequent severe ischemic events (Stetler et al., 2014; Mattson and Leak, 2024).

Post-ABI, TMS, and tDCS can intermittently challenge the brain, promoting adaptive plasticity without overwhelming it. This controlled stimulation can mitigate maladaptive processes such as chronic neuroinflammation and excitotoxicity, common in TBI, thereby creating a supportive environment for brain repair and adaptation (Calderone et al., 2024; de Macedo Filho et al., 2024). Hormetic principles can elucidate the mechanistic underpinnings of NIBS through its focus on (1) establishing an optimal stimulatory dose (including frequency, intensity, duration, and pulse characteristics) for each individual, (2) identifying the specific brain sites and networks to be targeted, and (3) establishing an understanding of specific cellular components that mediate the stimulatory response (Giordano et al., 2017).

Considering hormetic principles of neuroplasticity and the critical need to develop an understanding of the mechanistic underpinnings of NIBS, the goals of this review are fivefold: (1) Consider hormesis-based neuroplasticity as a potential mechanism of action enhancing neuroplasticity with NIBS; (2) examine cortical excitability, regional cerebral blood flow (rCBF), and white matter integrity as key factors substantiating the use of NIBS as a viable and effective approach for enhancing positive alterations in neuroplasticity; (3) consider differences between NIBS as a standalone treatment and when combined with neurorehabilitation therapies to impact behavioral outcomes (coupled); (4) explore NIBS' candidacy as the primary mechanism of change affecting behavioral outcomes post-ABI while identifying barriers mitigating this potential and finally; and (5) offer direction for future research.

Materials and methods

Study selection

We used the Cochrane Library, Web of Science, PubMed, and Google Scholar databases to identify studies from January 2013 to January 2024. To cast a wide net, a set of key search terms was employed, including "Neuroplasticity," "Brain Injury," "Acquired Brain Injury," "Brain Injury rehabilitation," Non-invasive brain stimulation," "TMS," and "tDCS." The search was conducted following the PICO framework. It included 'P' (patient/problem), i.e., people with ABI, 'I' (intervention) with NIBS, 'C' (comparison) standalone intervention versus NIBS coupled with other neurorehabilitation therapies, and 'O' (outcome) with positive alterations in neuroplasticity and behavioral outcomes (Schardt et al., 2007). The inclusion criteria were as follows: (1) English language, (2) using NIBS as a standalone or coupled intervention, and (3) inclusion of neuroplasticity and behavioral outcomes. The exclusion criteria were as follows: (1) review articles and meta-analyses, (2) case studies without quantitative data, (3) book chapters, and (4) abstracts.

Quality assessment

The quality of literature was critically analyzed according to Strength of Recommendation Taxonomy (SORT) guidelines where Level 1 is assigned the letter 'A' (consistent and good quality patient-oriented evidence), Level 2 is assigned the letter 'B' (inconsistent or limited quality and patient-oriented evidence), and Level 3 is assigned the letter 'C' (consensus, usual practice, opinion, disease-oriented evidence, and case series of diagnosis and treatment) (Ebell et al., 2004).

Data extraction

The following results were independently extracted by two authors: (1) metadata (publication date and authorship); (2) participant characteristics (sample size and diagnosis); (3) methods (study design, whether NIBS was used as a standalone treatment or coupled with an additional neurorehabilitation therapy, any outcome measure evaluating treatment efficacy); (4) characteristics of NIBS (current intensity, duration, current type, electrode placement, and number of sessions); and (5) information related to mechanisms of change of NIBS and other mediating and confounding variables.

Results

Study characteristics

Of the initial 41 articles identified, 22 were selected according to inclusion criteria. Utilizing PICO, ('P'), all studies included individuals diagnosed with an ABI; ('I') 11 studies investigated tDCS, whereas 11 studies investigated rTMS; ('C') 11 studies on tDCS included 264 participants where 10 used a coupled design and 1 used a standalone approach. 11 studies on rTMS included 393 participants, where 4 articles used a coupled intervention and 7 articles used a standalone intervention. (See Table 1); ('O') all studies reviewed outcomes of either neuroplasticity or behavioral measures (Rushby et al., 2021; Ulrichsen et al., 2022). Level 1 included 12 randomized controlled trials (RCTs). Level 2 included two retrospective studies, one pilot study, one open-label, prospective case series investigation, and one large group case study with control. Level 3 included two case reports. A total of four non-interventional studies, two explanatory articles, six pre-clinical animal studies, five literature reviews or meta-analyses, and one abstract were eliminated according to exclusion criteria.

Repetitive transcranial magnetic stimulation (rTMS)

Four studies utilized a coupled approach of rTMS spanning 11–15 days to affect change in neuropsychological symptoms (Hara et al., 2016, 2017), motor function (Hara et al., 2016; Luk et al., 2022), and brain perfusion (Hara et al., 2017). One of these studies, a retrospective study, of those with either left ($n = 10$) or right ($n = 15$) post-stroke unilateral upper limb hemiparesis used LF-rTMS over the primary motor cortex (M1) combined with intensive OT (iOT) for 15 days. The results found right LF-rTMS had significant increases in motor and cognitive skills: Fugyl–Meyer Assessment (FMA) categories A–C scores ($p < 0.05$) and Trail Making Test (TMT) ($p < 0.05$), but left LF-rTMS did not have significant results (Hara et al., 2016). Another study investigated two distinct cases. The first case study (diffuse axonal injury (DAI))

TABLE 1 Study characteristics.

	#	Modality	Structure	Design	SORT	Participants with ABI
Middleton et al. (2014)	1	tDCS	Coupled	Consideration-of-concept pilot study	B	$n=5$
Kurtin et al. (2021)	2	tDCS	Coupled	Large group case study with control	B	$n=33$
Rushby et al. (2021)	3	tDCS	Coupled	Single-blind, randomized, within-group, cross-over design	A	$n=30$
Ulam et al. (2015)	4	tDCS	Standalone	Randomized double-blind trial	A	$n=26$
McCambridge et al. (2018)	5	tDCS	Coupled	Double-blinded and session order randomized.	A	$n=10$
Ulrichsen et al. (2022)	6	tDCS	Coupled	A randomized sham-controlled trial combining tDCS with computerized cognitive training	A	$n=74$
Sacco et al. (2016)	7	tDCS	Coupled	Randomized Control Trial	A	$n=32$
Eilam-Stock et al. (2021)	8	tDCS	Coupled	Case Study: open label tDCS protocol testing	C	$n=1$
Quinn et al. (2022)	9	tDCS	Coupled	Double blind, randomized control Trial	A	$n=34$
Lima et al. (2023)	10	tDCS	Coupled	Double blind, CONTROLLED study	B	$n=1$
Lefebvre et al. (2013)	11	tDCS	Coupled	Randomized, crossover, placebo controlled, double-blind trial	B	$n=18$ tDCS=264
Neville et al. (2019)	12	rTMS	Standalone	Randomized double-blind trial	A	$n=30$
Hara et al. (2017)	13	rTMS	Coupled	Case report	C	$n=2$
Hara et al. (2016)	14	rTMS	Coupled	Retrospective study; no control	B	$n=25$
Rodrigues et al. (2020)	15	rTMS	Standalone	A post-hoc analysis of a randomized clinical trial	A	$n=27$
Siddiqi et al. (2019)	16	rTMS	Standalone	Randomized, controlled, double-blinded pilot study	A	$n=15$
Rao et al. (2019)	17	rTMS	Standalone	A randomized sham-controlled pilot study	A	$n=30$
Leung et al. (2016)	18	rTMS	Standalone	Randomized controlled study	A	$n=24$
Franke et al. (2022)	19	rTMS	Standalone	Randomized controlled study	A	$n=28$
Zhou et al. (2021)	20	rTMS	Coupled	Retrospective study; with controls	A	$n=166$
Moussavi et al. (2019)	21	rTMS	Standalone	Randomized, placebo controlled, double-blind study	A	$n=22$
Luk et al. (2022)	22	rTMS	Coupled	Double-Blind randomized controlled trial	A	$n=24$ rTMS=393

used HF-rTMS over the anterior cingulate cortex (ACC). In contrast, the second case study (middle cerebral artery infarction) used LF-rTMS over the dorsolateral prefrontal cortex (DLPFC) and parietal cortex (Hara et al., 2017). Both case studies observed improvements across measures (Schardt et al., 2007) (see Supplementary Table S1), as well as an increase in regional cerebral blood flow (rCBF) over stimulated areas (Hara et al., 2017). The remaining seven RCTs ($N=175$) used a standalone approach over 5 to 20 consecutive days. Only one study investigating chronic DAI using HF-rTMS over left DLPFC ($n=30$) failed to find significant improvements across fine motor and neuropsychological testing (Neville et al., 2019). In three rTMS studies over the DLPFC, two used HF-rTMS and one used LF-rTMS to improve neuropsychological and neuropsychiatric symptoms (Rao et al., 2019; Rodrigues et al., 2020; Franke et al., 2022). Although they did not have significant changes in anxiety scores, Rodrigues et al. (2020) found there was a significant change in depression scores ($p=0.002$) and EF index ($p=0.001$)(Rodrigues et al., 2020). In an RCT with a crossover design ($n=28$), there were no significant neuropsychological improvements, but a significant improvement in all neuropsychiatric-related symptoms [e.g., neurobehavioral symptom inventory ($p=0.030$)] was noted (Franke et al., 2022). The study utilizing LF-rTMS provided mixed results favoring the sham treatment for overall improvement of neuropsychiatric assessments and neuropsychological assessments for delayed recall, cognitive flexibility, and processing speed, whereas the treatment group was favored for neuropsychological tests assessing immediate recall and inhibited automated responses. In this same study of 30 participants, 26 underwent structural magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) sequences preintervention to assess changes in white matter (WM) connectivity; 19 of those 26 underwent postintervention imaging. The pre–post-comparison of fractional anisotropy (FA) revealed little difference in WM between the groups (Rao et al., 2019). An RCT investigating a major depressive episode secondary to TBI ($n=15$) used bilateral stimulation for 20 sessions where the initial stimulation targeting the DLPFC node was conducted with left-sided HF-rTMS (4,000 pulses at 10 Hz frequency with 5-s trains and 20-s inter-train interval) followed by right-sided LF-rTMS (a single train of 1,000 pulses with 1 Hz frequency); the antidepressant response was negatively correlated with baseline functional connectivity (FC) between the right-sided stimulation site and the subgenual ACC (sgACC) ($p=0.04$) within the active group (Siddiqi et al., 2019). Finally, another RCT ($n=24$) investigated the ability of HF-rTMS over the left motor cortex to decrease neuropsychiatric symptoms, such as headaches, and improve attention (Leung et al., 2016). A

higher percentage of the subjects in the active stimulation group (58.3%) significantly showed at least a 50% headache intensity reduction ($p = 0.035$) at post-treatment 1-week assessment compared with the sham group (16.6%)(Leung et al., 2016).

Transcranial direct current stimulation (tDCS)

Ten tDCS studies used a coupled approach. One double-blinded TBI study ($n = 26$) used a standalone method to investigate whether a-tDCS (1 mA x 20 min) over the left DLPFC would improve attention and memory as measured by alterations in delta and theta waves observed on an electroencephalogram (EEG) over 10 consecutive days (Ulam et al., 2015). Statistically significant results found alterations in theta, delta, and alpha waves with treatment. The delta wave was significantly correlated with improved performance on neuropsychological batteries, such as elevator count with reversal ($p = 0.006$) in the a-tDCS group, compared to no significant changes in the sham group (Ulam et al., 2015). One RCT study of chronic stroke participants ($n = 10$) investigated corticomotor excitability and motor function using a-tDCS (1 mA x 15 min) over the contralesional M1 coupled with a circling task over three sessions; a-tDCS increased corticomotor excitability of both hemispheres trending toward improved paretic intralimb coordination, whereas c-tDCS had no effect (McCambridge et al., 2018). Two RCTs and one case study used a coupled approach with patients diagnosed with a TBI using a-tDCS over the left DLPFC (Sacco et al., 2016; Eilam-Stock et al., 2021; Quinn et al., 2022). Another RCT ($n = 32$) provided a-tDCS (2 mA x 20 min) followed by divided attention (DA) training 2x/day for 5 consecutive days. For both RCTs, active a-tDCS significantly improved reaction time ($t = 3.41$; $p = 0.004$), and fewer omission errors ($t = 4.49$; $p < 0.0001$) were observed in the experimental group on the divided attention (DA) subtest for the examination of attention (TEA), which was maintained after 1 month, compared to no significant improvement in control (Sacco et al., 2016). Another study ($n = 34$) provided a-tDCS (2 mA x 30 min) with simultaneous cognitive training for 10 consecutive weekdays and found both active and control groups demonstrated improvements in EF and post-traumatic symptoms from baseline to 1 month. Anodal tDCS was associated with greater improvements in working memory compared to control ($p = 0.007$) (Quinn et al., 2022). The case study applied a-tDCS (2 mA x 20 min) with simultaneous computerized cognitive training over 20 daily sessions (4 weeks) and found significant post-treatment improvements across neuropsychological and neuropsychiatric measures (Eilam-Stock et al., 2021). Two single-session studies (85 participants) used a-tDCS (1.8 mA-2.0 mA) with simultaneous cognitive therapy. One used an n-Back test (Rushby et al., 2021), and the other used the choice reaction test (Kurtin et al., 2021; Rushby et al., 2021). One study used a tDCS-fMRI (functional MRI) paradigm combining TBI patients and health controls to determine the influence of WM structure on the physiological effects of stimulation using DTI. It concluded that in the absence of task, neither anodal nor cathodal stimulation influenced dorsal anterior cingulate cortex (dACC)/pre-supplementary motor area (preSMA) FA on brain activity. Conversely, during task performance, there was an inverse relationship between WM structure and brain network activity with tDCS; as FA increased, there was more left IFG deactivation ($rs = 0.433$, $p = 0.001$)(Kurtin et al., 2021). The other study found significant correlations between a-tDCS, decreased arousal and reaction time, diminished performance on a 1-back task, and no effects on the Hospital Anxiety and Depression Scale (HADS), Fatigue and Alertness Scales, nor three Profile of Mood States (POMS) subscales: Vigor, Fatigue, and Depression (all $p > 0.05$)(Rushby et al., 2021). Two studies investigated tDCS efficacy in stroke survivors (n = 59) (Middleton et al., 2014; Ulrichsen et al., 2022). One of these studies used a-tDCS over the ipsilesional motor cortex and c-tDCS over the contralesional cortex (both 1.5 mA x 15 min) with guided motor-based activities over 24 sessions. Results found a clinically meaningful difference in the FMA assessment (mean change = 7.6, effect size = 0.47) (Middleton et al., 2014), and the other of these studies used a-tDCS over DLPFC and c-tDCS over the occipital cortex (both 1 mA x 20 min) with concurrent cognitive training over six sessions. A significant reduction in depression and fatigue symptoms over time was noted, with no significant immediate changes ($p = 0.021$) (Ulrichsen et al., 2022).

Discussion

Hormesis-based neuroplasticity and brainstem involvement in NIBS post-ABI

One possible mechanistic model of neuroplasticity that explains the efficacy of NIBS to promote positive physiological changes within cortical and subcortical structures and behavioral impact after ABI is brainstem activation in response to low-grade, targeted stimulation (Mattson and Leak, 2024). Dominant theories of TBI have historically considered the brainstem a primary site of injury because even mild acceleration/deceleration forces can cause a loss of consciousness (LOC), implicating the role of the brainstem in such events (Ward, 1958; Ward, 1964). Even without LOC or notable changes in the cortex, diffuse degeneration of white matter secondary to the shearing of neurons and blood vessels has been observed in other regions, including the brainstem (Strich, 1961; Crompton, 1971; Zimmerman et al., 2023). This degeneration impacts neurotransmitter-producing nuclei like the raphe nuclei (responsible for serotonin production), locus coeruleus (LC) (responsible for norepinephrine production), and pedunculopontine nucleus (PPN), and laterodorsal tegmental nucleus (LTN) (responsible for acetylcholine production) (Parvizi and Damasio, 2003; Valko et al., 2016). These neurotransmitters have a modulatory impact on synaptic behavior within glutamatergic (excitatory) and GABAergic (inhibitory) neurons (Zotey et al., 2023; Mattson and Leak, 2024). They can negatively impact the function of brain systems and networks essential for occupational performance (Giordano et al., 2017).

One implicated system is the reticular activating system (RAS), which receives sensory inputs from various sources and is primarily responsible for arousal, wakefulness, and attention (Ward, 1958). ABI can lead to changes in neurotransmitters such as acetylcholine and serotonin levels, which are crucial for the functioning of the RAS (Sachs, 1957). Increased acetylcholine and serotonin levels in the cerebrospinal fluid post-concussion (Bornstein, 1946; Sachs, 1957) might disrupt normal neurotransmission within the RAS, contributing to the block of sensory conduction. This phenomenon can result in commonly experienced symptoms post-ABI, including attention deficits, low arousal, and fatigue (Zhou et al., 2021), often concomitant

with delayed information processing speed and working memory impairments in this population (Sacco et al., 2016). Hormesis-based neuroplasticity offers a potential mechanistic model to explain these adaptations. Specifically, one theory of adaptation suggests that a decrease in RAS function leads to a greater reliance on classical lemniscal pathways, which are less vulnerable to injury. These pathways are more resilient to damage originating at the cortical level, allowing them to continue transmitting sensory impulses to the thalamus and sensory cortex (Foltz and Schmidt, 1956).

Recently, attention has been given to the influence of anodal tDCS (a-tDCS) on the locus coeruleus (LC) via the trigeminal nerve, which is responsible for transmitting sensory information from the face, including touch, pain, temperature, and proprioception (Tramonti Fantozzi et al., 2021). The LC is located in the dorsal–rostral pons and contains neurons that densely innervate the thalamus and amygdala and sparsely innervate the neocortex, hippocampus, cerebellum, and spinal cord with unmyelinated projections (Levitt and Moore, 1978; James et al., 2021). When organically or electrically stimulated, one of the resulting actions is the co-release of norepinephrine (NE) and dopamine (DA) from the LC terminals in the hippocampus, which enhances sustained attention (e.g., vigilance) by modulating neural excitability mood by regulating neurotransmitter balance, and memory consolidation by amplifying long-term potentiation to promote an essential component of working memory, spatial memory formation (Baddeley, 2012; Lemon and Manahan-Vaughan, 2012; Mather and Harley, 2016; James et al., 2021).

Future research should consider stimulating key cortical regions that send significant signals to the LC when activated by tDCS or rTMS, resulting in subcortical activation and modulation. These regions include the DLPFC, which influences executive function, attention, and working memory (Ulam et al., 2015; Sacco et al., 2016; Moussavi et al., 2019; Neville et al., 2019; Siddiqi et al., 2019; Rodrigues et al., 2020; Eilam-Stock et al., 2021; Franke et al., 2022; Quinn et al., 2022; Ulrichsen et al., 2022); the prefrontal cortex (PFC), including the dorsal medial PFC (dmPFC) and orbitofrontal cortex (OFC), which are crucial for attentional control and impulsivity; the ACC which plays a part in error recognition, arousal, and stress response (Hara et al., 2017); and the trigeminal nerve pathway, which when stimulated, has been shown in animal models to impact attention, mood, and memory through hippocampal pathways (Majdi et al., 2023a,b; Chen et al., 2024). Thus, a combined understanding of hormesis, cortical target sites of NIBS, and brainstem behavior (e.g., RAS and LC) explain the improvement of attention, mood, and memory post-ABI (Giordano et al., 2017).

NIBS as a viable and effective approach for enhancing positive alterations in neuroplasticity through cortical excitability, rCBF, and white matter integrity

Neuroplasticity can be neuronal and non-neuronal and synaptic or non-synaptic and is impacted by the activity being used during stimulation (Middleton et al., 2014), unique pathophysiology of ABI (Rodrigues et al., 2020), cortical excitability (Ulam et al., 2015), total brain volume (Neville et al., 2019), rCBF (Hara et al., 2017), and structural integrity of WM (Kurtin et al., 2021; Zhou et al., 2021). Studies incorporating diagnostic imaging provide evidence that NIBS is an effective approach for enhancing positive alterations in neuroplasticity.

In particular, the degree of cortical activity and related outcomes is significantly impacted by NIBS' target site; i.e., structures directly under stimulation were most sensitive to neuromodulation, and the montage of electrode placement impacted the overall effect (Ulam et al., 2015; Hara et al., 2017; McCambridge et al., 2018; Siddiqi et al., 2019; Franke et al., 2022; Quinn et al., 2022). With effects similar to synaptic long-term potentiation (LTP) (i.e., a natural brain mechanism that uses repeated signaling to strengthen communication between neurons, making it central to overall cognitive function), rTMS may enhance brain state in a partially predictable manner after ABI by either increasing or reducing connectivity dependent on target site(s) and modulatory intention (Siddiqi et al., 2019; Franke et al., 2022). For example, after reducing the connectivity between the rDLPFC and sgACC, there was greater connectivity in the default mode network (DMN) and dorsal attention network (DAN), indicating frequency is a primary consideration based on the desired outcome (Siddiqi et al., 2019).

Although there was little evidence that rTMS impacted WM connectivity to improve neuroplasticity (Rao et al., 2019), rTMS was found to impact the interhemispheric imbalance of rcBF (Hara et al., 2017). Specifically, HF-rTMS reduced perfusion (i.e., the passage of fluids) directly under the stimulation site. LF-rTMS had a cross-hemispheric impact on a large area within the affected brain hemisphere by increasing perfusion around the rTMS target contralesionally (Hara et al., 2017). These findings may indicate that partnering HF and LF-rTMS may promote a balanced response to the cascade of internal injury post-ABI. While HF managed intracranial pressure by reducing inflammation over the ipsilesional region, LF simultaneously increased circulation contralesionally, which helped redistribute fluids, improve oxygenation to healthy tissues, and support overall neuroplasticity.

Due to the alterations and reorganization of neural communication post-ABI, an individual may find cognitive functions taking more effort (Sacco et al., 2016; Quinn et al., 2022). The brain may reside in a state of chronic overactivity, resulting in significant increases in activity (hyperactivation) when required to complete a task, resulting in decreased performance due to increased energy expense. Evidence suggests coupling tDCS with neurorehabilitation therapies is a potential solution to address this hyperactivation (Ulam et al., 2015; Sacco et al., 2016; Quinn et al., 2022).

Depending on neurorehabilitation coupling, stimulation protocol, and montage, tDCS can impact the strength of connections between brain regions and increase or decrease perfusion immediately following treatment and after a follow-up period, potentially impacting neural activity in the targeted areas (Quinn et al., 2022). Furthermore, both anodal and cathodal stimulation amplify the underlying patterns of brain network activity set by the current cognitive brain state (Kurtin et al., 2021). Similar to rTMS, cortical excitability from tDCS may not be restricted to the location of the anodal electrode but extends to the cathodal site, indicating an interhemispheric effect (Ulam et al., 2015). This far-reaching capability of NIBS may create more opportunities for holistic interventions targeting both hemispheres simultaneously post-ABI. When a task was coupled with tDCS, FA increased, and reduced connectivity was observed in the targeted structures, demonstrating cortical reorganization and improved WM connectivity, which may amplify cognitive efficiency during task performance (Kurtin et al., 2021).

Finally, a-tDCS can alter theta, delta, and alpha waves, causing cumulative cortical excitability and resulting in the possibility of both immediate and positive changes over time (Ulam et al., 2015).

Behavioral outcomes using NIBS as a standalone or coupled intervention

Using a Coupled tDCS is more prevalent than rTMS, though both methods are efficacious in improving neuropsychological (Ulam et al., 2015; Sacco et al., 2016; Hara et al., 2017; Rodrigues et al., 2020; Eilam-Stock et al., 2021; Rushby et al., 2021; Franke et al., 2022; Quinn et al., 2022), neuropsychiatric (Sacco et al., 2016; Hara et al., 2017; Rao et al., 2019; Siddiqi et al., 2019; Rodrigues et al., 2020; Eilam-Stock et al., 2021; Rushby et al., 2021; Quinn et al., 2022; Ulrichsen et al., 2022), somatic (Eilam-Stock et al., 2021; Quinn et al., 2022; Ulrichsen et al., 2022), and motor outcomes (Middleton et al., 2014; Hara et al., 2016; McCambridge et al., 2018). In all cases, improved motor function resulted from coupled NIBS (Middleton et al., 2014; Hara et al., 2016; McCambridge et al., 2018), and outcomes were impacted by lateralization, contralesional or ipsilesional target site, and coupled intervention. All tDCS and rTMS studies coupled with cognitive therapy used computer-assisted programs (CAPs) for cognitive training (7 studies) (Sacco et al., 2016; Hara et al., 2017; Eilam-Stock et al., 2021; Kurtin et al., 2021; Rushby et al., 2021; Quinn et al., 2022; Ulrichsen et al., 2022). Using CAPs leads to greater motivation, better performance, and overall greater effect than offline paradigms (de Luca et al., 2014; Hill et al., 2016). Although there is an effect of CAPs as a standalone intervention (Kaldoja et al., 2015; Han et al., 2018), the efficacy of a-tDCS with CAPs on working memory (Sacco et al., 2016; Eilam-Stock et al., 2021; Quinn et al., 2022), EF (Sacco et al., 2016; Eilam-Stock et al., 2021), somatic function (e.g., fatigue, somatization) (Eilam-Stock et al., 2021; Quinn et al., 2022; Ulrichsen et al., 2022), and mental health (Sacco et al., 2016; Hara et al., 2017; Eilam-Stock et al., 2021; Quinn et al., 2022; Ulrichsen et al., 2022) supports a coupled intervention approach. rTMS is more widely used as an efficacious standalone approach for ABI (Leung et al., 2016; Hara et al., 2017; Neville et al., 2019; Rao et al., 2019; Siddiqi et al., 2019; Rodrigues et al., 2020; Franke et al., 2022). Like coupled tDCS, standalone rTMS has improved many symptoms post-treatment, resulting in a near-effect on neuropsychological, neuropsychiatric, and physical symptoms (Asloun et al., 2008; Bikson et al., 2010; Eldaief et al., 2013; Chang et al., 2023; Evancho et al., 2023; Zotey et al., 2023; Calderone et al., 2024). Similarly, studies measuring the longevity of intervention noted that EF, mental health, and somatic symptoms were maintained or improved by the follow-up period (between 1 week and 1 month) (Leung et al., 2016; Rodrigues et al., 2020; Franke et al., 2022). This improvement may be due to the far effect of rTMS on delta power, which is strongly correlated to EF and depression (Franke et al., 2022). These findings support using standalone rTMS to improve symptoms with both a near and far effect. Two studies investigating rTMS on DAI denied significant effects on neuropsychological and neuropsychiatric outcomes, regardless of standalone or coupled status (Hara et al., 2017; Neville et al., 2019). Although this could have been due to frequency and target site, it is worth considering that progressive atrophy resulting from primary and secondary axotomy and microhemorrhages associated with DAI impacts the effectiveness of rTMS as opposed to other ABI (Neville et al., 2019).

NIBS potential as the primary mechanism of change and future directions

Though NIBS has been investigated for decades, the change mechanism is not yet fully understood. To support comprehensive research on neuromodulation's influence on behavior, alternative explanations for change should be determined to improve understanding and establish future directions. This section explores the capacity of NIBS as the direct mechanism of change while considering that the mechanisms of action underlying stimulation may not be sufficient for explaining behavior outcomes and there may be other coexisting variables influencing behavioral change post-stimulation, including (1) depression, (2) attention, (3) placebo effect, and (4) widespread activation within cortical modules beyond the target site.

Improvement of depression

Depression and anxiety impact working memory, attention, speed of information processing, and executive function (Priyamvada et al., 2015; Uiterwijk et al., 2022), thus generating the possibility that improving mood symptoms may result in improved behavioral outcomes. However, many tDCS and rTMS studies have found positive isolated effects of NIBS on short—and long-term behavioral outcomes after accounting for depression and anxiety (Ulam et al., 2015; Leung et al., 2016; Rodrigues et al., 2020; Franke et al., 2022). One study investigated a-tDCS over the left DLPFC and controlled for symptoms of depression and anxiety and concluded that statistically significant favorable results on clinical outcomes were due to the modification of electrophysiological frequencies (i.e., increased alpha waves and decreased delta and theta waves) (Ulam et al., 2015). Another coupled tDCS study used two anodal leads on bilateral DLPFC with cognitive training to investigate the effects of tDCS on divided attention. This study excluded patients with neuropsychiatric illness The study found statistically significant results for divided attention while the change on the depression scale was insignificant ($p = 0.305$) (Sacco et al., 2016).

Currently, the data are limited to draw substantial conclusions regarding NIBS's ability as the primary mechanism of change; however, emerging studies have shown that NIBS has the potential to engage the primary target if the stimulation protocol is being followed properly e.g., correct cortical positioning of the electrode using brain mapping systems (Antal et al., 2017) and the confounding variables such as depression/anxiety are accounted for either at the study design or the analysis level. Future research should take measures to control for the presence of mood symptoms and incorporate neuroimaging assessments to enhance confidence in NIBS's ability to act as the primary mechanism of change.

Improvement of attention

Attention is often the first function to be addressed in cognitive therapy following ABI due to its influence on other neuropsychological functions (i.e., concentration, short-term memory, vigilance, and working memory) and its mediating role between information processing and language (Lee et al., 2023). Evidence suggests these functions can be improved by cognitive therapy, NIBS, or both (Leung et al., 2016; Hara et al., 2017; Quinn et al., 2022; Lee et al., 2023). Still,

the mechanism of change to support these outcomes continues to be explored through improved understanding of target specificity and cortical excitability.

Many rTMS and tDCS studies investigate the effectiveness of neuromodulation to improve attention, working memory, and other neuropsychological functions that may be impacted following an ABI by attempting to specifically target the dorsal regions of the ACC and DLPFC for their role in selective attention, working memory, performance reappraisal, and monitoring (Clarke et al., 1969; Ochsner et al., 2012; Leung et al., 2016; Hara et al., 2017; Kurtin et al., 2021; Quinn et al., 2022). However, the barrier to target specificity is confounded by the complexities of attention and its relationship to other neuropsychological functions, making it difficult to know which function most influences overall outcomes (Lee et al., 2023).

Kurtin et al. (2021) suggest the improvement of cognitive efficiency and behavioral outcomes is a byproduct of NIBS' ability to improve cortical organization and WM connectivity (Kurtin et al., 2021). This is substantiated by Hebbian theory, which suggests that sustained application of stimulus for more than several minutes leads to increased synaptic activity, thereby improving the receptiveness of the second area to respond to input from the first area (i.e., improvement of LTP) (Siddiqi et al., 2019; Korai et al., 2021; Pitcher et al., 2021; Barbati et al., 2022; Franke et al., 2022). Although intricacies are involved in directly mapping the role of NIBS on behavioral outcomes in studies involving attention, determining neural correlates of attention modulation may provide insight into NIBS capacity as a primary or mediatory agent of change(Nani et al., 2019). Additionally, studies seeking to elucidate the role of attention in improved performance after NIBS should consider specific contributions and mechanisms of action of attention to other neuropsychological functions to better understand its influence on outcomes.

Placebo effect

A placebo effect is a psychobiological phenomenon occurring in the brain after administering an inert substance or sham physical treatment (Price et al., 2008; Benedetti et al., 2011). Some studies have investigated this effect as the primary reason for positive outcomes after NIBS to account for inconsistencies among active and sham stimulation groups (Conforto et al., 2014; Braga et al., 2021). For example, one study using tDCS over the left DLPFC used neuropsychological tests to assess working memory, attention, and general executive function and discovered that both active and sham groups experienced significant improvements (Ulam et al., 2015). A possible explanation for this phenomenon is expectation and reward motivation (Ballard et al., 2011).

The expectancy theory suggests that non-volitional responses such as pain perception, emotional reactions, and other sensations can be self-confirming (Kirsch, 1985); that is, the mere suggestion that NIBS is effective can elicit or enhance the occurrence of those desired results (Kirsch, 1985). Expectations (i.e., the belief in the likelihood of something happening) can modulate a variety of cognitive processes, including perception (de Lange et al., 2018), motor control (Weinberg et al., 1979), and working memory (Bollinger et al., 2010). One coupled study combining tDCS and motor training investigated the likelihood of a placebo effect in tDCS and whether the participants' beliefs about tDCS impacted this effect (Haikalis et al., 2023). The active and sham tDCS groups showed more improvement on the motor task than the control group, indicating a significant placebo effect of tDCS on motor learning ($p = 0.007$); furthermore, those with higher beliefs and expectations of tDCS improved more than those with lower beliefs and lower expectations (Haikalis et al., 2023).

Expectation also has a psychobiological effect on cortical activation and dopaminergic distribution, which may impact neuropsychological and physical symptoms following ABI (Conforto et al., 2014; Braga et al., 2021). In one study, both active and control groups demonstrated improvements in executive function and post-traumatic symptoms from baseline to 1 month, which significantly correlated with the degree of connectivity change between the right DLPFC, which influences the physiology supporting motivated behavior, attention, and memory(Ballard et al., 2011), and the left anterior insula which has a primary role in the representation of natural rewards and their integration with attention and emotions ($p = 0.02$) (Haaranen et al., 2020). As seen in post-traumatic migraines, the placebo effect does not only impact neuropsychological functions but may also influence physical improvements. Ebell et al. (2004) found that sham rTMS over the DLPFC for 8 weeks induced a greater amelioration of post-concussive headaches compared to active rTMS, with a decrease in the number of headache days greater than 50% in the sham group, suggesting a powerful placebo response. Just as the impact or reward motivation on the mesocortical dopaminergic regions (Ballard et al., 2011), this sham treatment may have potentiated placebo analgesia by increasing patients' expectations, thereby inducing dopamine release (Conforto et al., 2014; Braga et al., 2021).

The placebo effect produces physiobiological results, which may indicate it can be exploited for clinical benefit while also accounting for improvements among active and sham groups (Annoni, 2013). Future studies may support this role by analyzing expectation priming (Rabipour et al., 2018), silencing the expectation mechanism by optimizing the placebo parameters (Benedetti et al., 2011), and using specific assessments to quantify participants' prior beliefs and expectancies related to NIBS at varying points throughout the assessment, intervention, and follow-up periods (Braga et al., 2021).

Target specificity

Finally, a challenge in establishing the clear effectiveness of neuromodulation to improve behavioral outcomes arises from the variability in how it impacts both proximal and distal brain areas relative to the target site. Neuromodulation may indirectly modulate other unnecessary or antagonistic cortical modules, thereby confounding NIBS's true mechanism of action to influence behavioral change (Morya et al., 2019). Improvements in technology and electrophysiological understanding may offer a solution to improving target specificity.

Due to its ability to indirectly measure the brain's neural activity and allow for millimeter precision in establishing target sites through its high spatiotemporal resolution (Kim et al., 2021), structural MRIs are used to design participant-specific tDCS or TMS protocols (Rezai et al., 2016; Sacco et al., 2016; Chudy et al., 2018; McCambridge et al., 2018; Rao et al., 2019; Siddiqi et al., 2019; Kurtin et al., 2021; Raguž et al., 2021; Quinn et al., 2022). Although initially using fMRI is shown to improve stimulation site specificity, functional connectivity and EEG may be used to establish a more optimized intervention design, including electrode placement, frequency, dose, and duration (Boes et al., 2018).

The phenomenon of ephaptic coupling and the use of the Ephaptic Modulation Index (EMOD) can explain the mechanisms of action underlying low-focality and broad neuromodulatory impact of NIBS while also offering a potential solution for optimizing future preliminary assessment, stimulation protocols, and positioning (Morya et al., 2019; Ruffini et al., 2020). Ephaptic coupling postulates that when populations of neurons synchronize their activity, it produces substantial electric fields (Ruffini et al., 2020). These fields can influence the excitability of appropriately oriented neurons, regardless of distance (Jefferys, 1995). Neuronal circuits are sensitive to weak endogenous or exogenous low-frequency (0–100 Hz) electric fields (> 0.1 V/m) (Ruffini et al., 2020). tDCS delivers these weak current waveforms and thus is expected to produce spatially extended electric fields throughout the brain (Ruffini et al., 2013, 2020). For example, Ulam et al. (2015) used tDCS, resulting in brain activations that extended from the anodal to cathodal electrodes across hemispheres (Ulam et al., 2015). The same is true for rTMS, as seen in a study that demonstrated the long-term impact of inhibitory LF-rTMS targeting the contralesional motor cortex post-stroke. The results indicated increased cortical excitability on the ipsilesional site, leading to statistically significant improvement in upper limb performance on the box and block test ($p = 0.049$) and MEP amplitude of both paretic ($p = 0.002$) and non-paretic ($p = 0.035$) hands (Luk et al., 2022).

EMOD can support future studies as it accounts for endogenous electric field strength, neuronal excitability, brain topography, spatial relationships, and frequency of neuronal activity within each cortical module (Ruffini et al., 2020). Behavioral modification by tDCS and rTMS depends on the relationship between neuronal signals required for a particular task and the noise generated by the stimulus (i.e., neuronal activity non-specific for the cortical module being targeted or the activity being conducted) (Miniussi et al., 2013; Braga et al., 2021). By accumulating knowledge of the natural state of electrical fields within each cortical module during the assessment period, future researchers in this area may better understand neuronal qualities and neuromodulation response potential (Ye et al., 2022), design protocols based on informed knowledge of potential summation of endogenous and exogenous fields, and which modules may have reduced impact potential based on ephaptic communication (Ruffini et al., 2020). More research is needed in ephaptic coupling and EMOD as it relates to NIBS in ABI to demonstrate its capacity to improve target site selection and stimulation application.

Strengths and limitations

This review has several strengths, including the representation of current research exploring the efficacy of NIBS in both standalone and coupled designs, the discussion on the potential of NIBS as the primary mechanism of change, and the exploration of a potential mechanistic model of neuroplasticity to explain the impact of NIBS on attention, memory, and mood. Additionally, it examines alternative explanations for the positive outcomes associated with NIBS and provides future recommendations that may benefit clinicians and researchers using NIBS in clinical trials. To the best of our knowledge, this is the only review that has addressed multiple aspects of NIBS including mechanism and efficacy within a single article. Moreover, while the review focuses on ABI, the explanation of the NIBS mechanism could also be helpful for other neurological disorders.

The limitations of this review could be addressed in future studies, including a more detailed exploration of the locus coeruleus concerning TBI and NIBS as well as further research based on cognitive science methodologies to understand common post-ABI symptoms such as information processing, attention, and working memory, and how these relate to the mechanisms of action presented.

Conclusion

rTMS and tDCS may improve neuroplasticity and behavioral outcomes after ABI. Although rTMS is used more widely as an efficacious standalone intervention, tDCS has emerged as another non-invasive approach to couple with neurorehabilitation therapies. The mechanistic model of neuroplasticity for NIBS suggests that these techniques promote synaptic plasticity and modulate neural network activity through controlled, low-level stimulation, which can induce beneficial neurochemical and structural changes in the brain. More research is needed to better understand the role of NIBS as the primary mechanism of change and its potential to positively alter symptoms after ABI.

Author contributions

ME: Data curation, Formal analysis, Methodology, Writing – original draft. PK: Data curation, Formal analysis, Methodology, Writing – original draft. GS: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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Supplementary material

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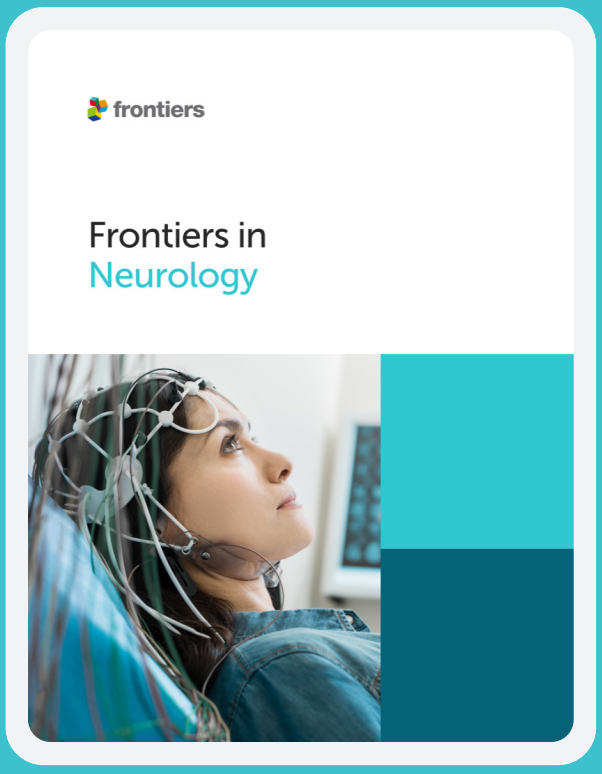

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